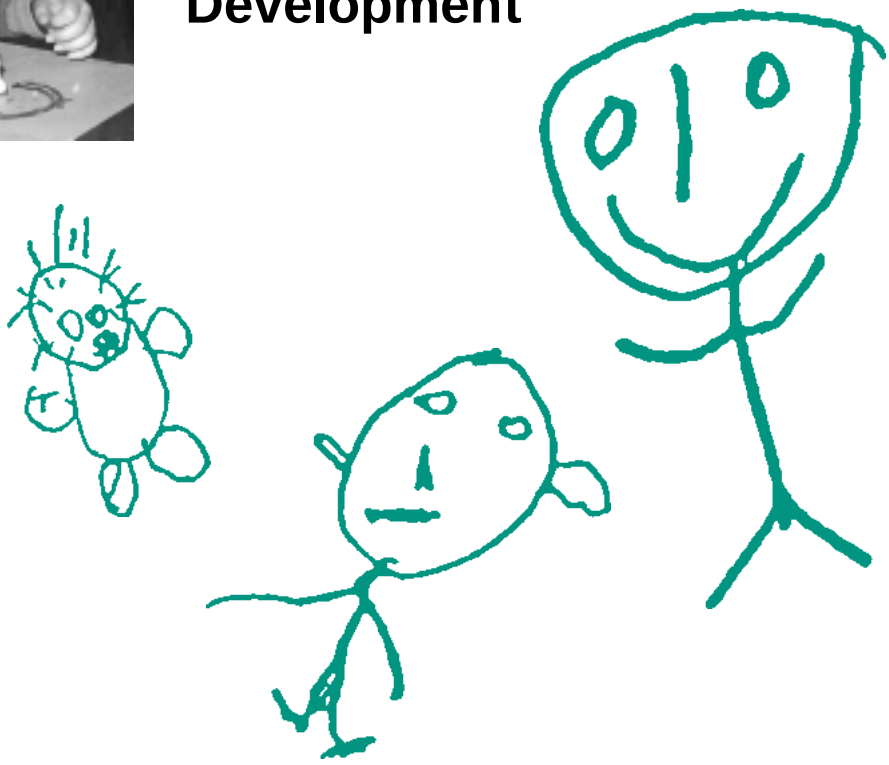
In Harm's Way:

Toxic Threats to Child Development



A REPORT BY

Greater Boston Physicians for Social Responsibility

Prepared for a Joint Project with Clean Water Fund

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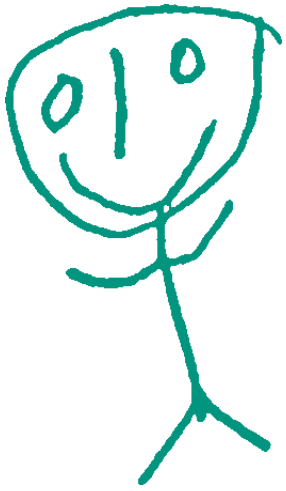

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PRODUCTION

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ORGANIZATIONS

Greater Boston Physicians for Social Responsibility (GBPSR) is an affiliate of Physicians for Social Responsibility, a national organization of over 15,000 physicians, health care professionals and supporters who are committed to the elimination of nuclear and other weapons of mass destruction, the preservation of a sustainable environment, and the reduction of violence and its causes. PSR is the national affiliate of International Physicians for the Prevention of Nuclear War, recipient of the 1985 Nobel Peace Prize. GBPSR's Human Health and the Environment Project (HHEP) was one of the first in the organization nationally to focus on the public health consequences of environmental pollution. Since 1992 the HHEP has been active in educating the medical community on the linkages between environmental exposures and health, activating members to work to protect public health, assisting grassroots groups with technical and scientific issues relating to human health and environment issues, and participating in public policy debates. In addition to *In Harm's Way: Toxic Threats to Child Development*, current projects include *Generations at Risk: Reproductive Health and the Environment*; the *Boston Sustainable Hospitals Project* of *Health Care Without Harm*, an organization that is working internationally to prevent pollution and the use of toxic products in the health care industry; and *No Room to Breathe*, focusing on the health effects of air pollution. For information on other reports and materials available from GBPSR, please see our web site at http://www.igc.org/psr/

Clean Water Fund (CWF) is a national nonprofit research and educational organization, with locally staffed environmental and health protection programs serving communities in over twenty states. CWF's mission is to develop strong grassroots environmental leadership and to bring together diverse constituencies to work cooperatively for changes that improve their lives, focused on health, consumer, environmental and community problems. Since 1978, CWF has helped people campaign successfully for cleaner and safer water, cleaner air, and protection from toxic pollution in our homes, neighborhoods and workplaces. Organizations and coalitions formed and assisted by CWF have worked together to improve environmental conditions, prevent or clean up health-threatening pollution in hundreds of communities and to strengthen policies locally and nationally. CWF's programs build on and complement those of Clean Water Action, a 700,000-member national organization which has helped develop, pass, strengthen and defend the nation's major water and toxics laws such as the Clean Water Act, Safe Drinking Water Act, Superfund and others, including their state-level counterparts.

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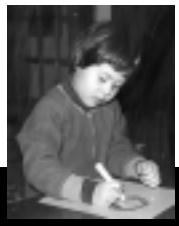

Foreword

The intersection between environmental chemicals and child development is a new area of public health science. It is only in the past few years that we have begun to grasp the potential health effects of even slight disturbances in child development. So much hinges on understanding the effects of environmental chemicals on these processes: developmental disabilities, including attention deficit/hyperactivity disorder, autism, and related neurodevelopmental diseases, affect millions of American children. The consequences of these disorders are often tragic. The familial, societal and economic costs are immense, and the disabilities can be life-long.

In the last two decades there has been an explosion of neurobiological research into attention, memory and other cognitive functions. In addition, the patterns and stages of normal brain development are now well understood. This new knowledge has given us a better understanding of the special vulnerability of the developing nervous system to the internal chemical environment. It is now clear from studies of animals and children that subtle changes in the concentrations of normally occurring chemicals such as hormones—as well as the presence of toxic agents like lead, mercury or PCBs—can produce profound and permanent changes in the developing nervous system. These changes can lead to decrements in mental performance and alterations of the reproductive system.

A picture is unfolding supported by a variety of laboratory, clinical and epidemiological research that suggests that neurotoxic chemicals in the environment may play a role in developmental disabilities. The implications of this notion are profound. If we can understand the role of environmental chemicals in neurodevelopmental disorders, we can take concrete steps toward the prevention of these disorders. By reducing and eliminating exposures to specific environmental chemicals through the use of regulatory bans, development and promotion of alternative agents and exposure minimization, we may, in time, be able to reduce the occurrence of neurodevelopmental disability. We may even be able to prevent some disabilities from ever again limiting a child's potential, an extraordinary prospect.

Yet such potential is often obscured by a voluminous and at times confusing scientific literature. *In Harm's Way* is an analysis of that literature. Ted Schettler and his co-authors have prepared a text on neurodevelopmental disorders and environmental chemicals that makes a complex body of scientific information accessible to health professionals and the scientifically literate general public.

The authors elucidate the evidence for specific scientific claims and help readers understand what is known and what is conjectured. They begin with two linked observations: (1) that developmental disabilities are common in American children; and (2) that the causes of these disabilities are largely unknown. *In Harm's Way* presents an elegant discussion of normal brain development and explores why these developmental processes are so vulnerable to environmental insult. It goes on to highlight a series of case studies describing chemicals in the environment that are known to disrupt brain development in laboratory animals and in children.

One of the difficulties in talking about neurodevelopmental disabilities is that these disorders are not easily defined. They do not lend themselves to simple diagnostic tests like blood sugar in diabetes or the EEG in epilepsy. They are defined in loose clinical or behavioral terms and often present as a range or spectrum of behaviors. At what point is difficulty learning diagnosed as a learning disability? When does inattention qualify as attention deficit hyperactivity disorder? While clinicians have devised ways of answering these and other similar questions, the labeling problem remains at the heart of efforts to understand patterns of neurobehavioral disabilities. The most basic of public health research efforts—a simple count of the number of cases—persists as a stumbling block, fraught with contested assumptions and rival criteria.

As one example of its eminently trenchant analysis, *In Harm's Way* carefully reviews the labeling problem such that clinicians, basic scientists, policy makers, advocates, and parents can forge shared understanding. Such is the usefulness of *In Harm's Way*. Throughout, it identifies some of the areas of greatest confusion in this new field, and delineates the underlying logic and lines of evidence. As a result, this book is sure to inform discussions among representatives of widely varying disciplines.

We stand at the brink of an era that will almost certainly see the identification of the causes of a wide range of neurobehavioral disorders. It will also enable preventive measures to be taken. *In Harm's Way* has clarified a starting point for this next era of environmental health.

Not-for-profit health advocacy organizations are now major players in health and environmental policy making. The successful passage of the Clean Air Act Reauthorization in 1996 was

achieved by the efforts of advocacy groups supporting the EPA. The same organizations, known in the United Nations as non-governmental organization (NGOs), are now participants in international treaty negotiations. Previously excluded from environmental health discussions in the UN and the World Health Organization, NGOs in the last 10 years have achieved a place at the negotiating table. To accomplish this, the not-for-profit advocacy organizations have become more effective politically and more professional scientifically.

The best of these organizations are able to provide scientifically credible information as an alternative point of view to government and industry. They can synthesize and review data in what are often emerging fields with contradictory signposts. Nowhere are the benefits of this capability more evident than in the field of environmental health. Experts from advocacy organizations now sit as scientific peers with representatives of government, academia and industry, as, for example, on the EPA's recently concluded Endocrine Disruptor Screening and Testing Advisory Committee.

Physicians for Social Responsibility (PSR) is an NGO at the forefront of efforts to establish for both the public and for policy makers the present state of the science in environmental health. In 1994, PSR released *Critical Condition: Human Health and the Environment*, edited by Eric Chivian, which gave a broad overview of the connection between health and global environmental change. In 1999, Ted Schettler and Maria Valenti, along with Gina Solomon and Annette Huddle, authored *Generations at Risk: Reproductive Health and the Environment*, in which they analyzed the science of reproductive health damage by chemical pollution. In other professional capacities physicians associated with PSR have participated in scientific analysis of the health effects of global warming and reemerging infectious disease as well as of biodiversity and species loss. With *In Harm's Way*, PSR lends its characteristic clarity to the field of children's environmental health. PSR—both the Greater Boston Chapter and its National Office—is to be commended for commissioning this important work.

The present situation of environmental health argues for precaution. We have apparently increasing incidence of significant

developmental disabilities. We have plausible biological mechanisms connecting environmental toxicants with health effects, as demonstrated in laboratory animals. We have accumulating evidence of neurotoxic damage to children by environmental agents, such as lead and PCBs. The authors of *In Harm's Way* provide compelling, scientifically documented arguments laying out the next steps we as a society must take: we must increase our understanding of the neurotoxicity of chemical agents now in the environment, and we must adopt public health policies that limit the exposure of fetuses and children to environmental chemicals.

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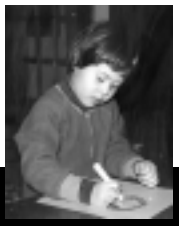


Executive Summary

This report examines the contribution of toxic chemicals to neurodevelopmental, learning, and behavioral disabilities in children. These disabilities are clearly the result of complex interactions among genetic, environmental and social factors that impact children during vulnerable periods of development. Toxic exposures deserve special scrutiny because they are *preventable* causes of harm.

Toxic exposures deserve special scrutiny because they are preventable causes of harm.

1. An epidemic of developmental, learning, and behavioral disabilities has become evident among children.

- It is estimated that nearly 12 million children (17%) in the United States under age 18 suffer from one or more learning, developmental, or behavioral disabilities.
- Attention deficit hyperactivity disorder (ADHD), according to conservative estimates, affects 3 to 6% of all school children, though recent evidence suggests the prevalence may be as high as 17%. The number of children taking the drug Ritalin for this disorder has roughly doubled every 4-7 years since 1971 to reach its current estimate of about 1.5 million.
- Learning disabilities alone may affect approximately 5-10% of children in public schools.
- The number of children in special education programs classified with learning disabilities increased 191% from 1977-1994.
- Approximately 1% of all children are mentally retarded.
- The incidence of autism may be as high as 2 per 1000 children. One study of autism prevalence between 1966 and 1997 showed a doubling of rates over that time frame. Within the state of California, the number of children entered into the autism registry increased by 210% between 1987 and 1998.

These trends may reflect true increases, improved detection, reporting or record keeping, or some combination of these factors. Whether new or newly recognized, these statistics suggest a problem of epidemic proportion.

2. Animal and human studies demonstrate that a variety of chemicals commonly encountered in industry and the home can contribute to developmental, learning, and behavioral disabilities.

Developmental neurotoxicants are chemicals that are toxic to the developing brain. They include the metals lead, mercury, cadmium, and manganese; nicotine; pesticides such as organophosphates and others that are widely used in homes and schools; dioxin and PCBs that bioaccumulate in the food chain; and solvents, including ethanol and others used in paints, glues and cleaning solutions. These chemicals may be directly toxic to cells or interfere with hormones (endocrine disruptors), neurotransmitters, or other growth factors.

Lead

- Increases in blood lead levels during infancy and childhood are associated with attention deficits, increased impulsiveness, reduced school performance, aggression, and delinquent behavior.
- Effects on learning are seen at blood lead levels below those currently considered "safe."

Mercury

- Large fetal exposures to methylmercury cause mental retardation, gait and visual disturbances.
- Smaller fetal exposures, such as those resulting from regular maternal fish consumption, have been implicated in language, attention, and memory impairments that appear to be permanent.

Manganese

- Unlike many other metals, some manganese is essential as a catalyst in several critically important enzymatic processes. However, several studies report a relationship between excessive childhood levels of manganese exposure and hyperactivity or learning disabilities.

Nicotine

- Children born to women who smoke during pregnancy are at risk for IQ deficits, learning disorders, and attention deficits.
- Children born to women who are passively exposed to cigarette smoke are also at risk for impaired speech, language skills, and intelligence.

Dioxins and PCBs

- Monkeys exposed to dioxin as fetuses show evidence of learning disabilities.
- Humans and animals exposed to low levels of PCBs as fetuses have learning disabilities.
- Children exposed to PCBs during fetal life show IQ deficits, hyperactivity, and attention deficits when tested years later.

Pesticides

- Animal tests of pesticides belonging to the commonly-used organophosphate class of chemicals show that small single doses on a critical day of development can cause hyperactivity and permanent changes in neurotransmitter receptor levels in the brain.
- One of the most commonly used organophosphates, chlorpyrifos (Dursban), decreases DNA synthesis in the developing brain, resulting in deficits in cell numbers.
- Some pyrethroids, another commonly used class of pesticides, also cause permanent hyperactivity in animals exposed to small doses on a single critical day of development.
- Children exposed to a variety of pesticides in an agricultural community in Mexico show impaired stamina, coordination, memory, and capacity to represent familiar subjects in drawings.

Solvents

- Exposure to organic solvents during development may cause a spectrum of disorders including structural birth defects, hyperactivity, attention deficits, reduced IQ, learning and memory deficiencies.
- As little as one alcoholic drink a day by a mother during pregnancy may cause her offspring to exhibit impulsive behavior and lasting deficits in memory, IQ, school performance, and social adaptability.
- Animal and limited human studies show that exposures to common chemicals like toluene, trichloroethylene, xylene, and styrene during pregnancy can also cause learning deficiencies and altered behavior in offspring, particularly after fairly large exposures.

3. A deluge of highly technical information has created communication gaps within the field of child development.

Some pyrethroids cause permanent hyperactivity in animals exposed to small doses on a single critical day of development.

- The recent explosion of research in the many sciences related to child development has produced a glut of highly technical information not readily understood by those outside the field in which the research was performed.
- A communication gap has resulted, dividing fields of research and separating the domains of research, clinical practice, and the public.
- Behavior and cognition can be described using clinical disorders, such as ADHD or Asperger's syndrome, which are categorical and qualitative. Alternatively, behavior and cognition can be described using abilities/traits, such as attention and memory, which are continuous and quantitative. Abilities/traits cluster into disorders in various ways and are emerging as an important bridge among the scientific disciplines focusing on child development.

Breast-fed infants are exposed to levels of dioxin that exceed adult exposures by as much as a factor of 50.

4. Although genetic factors are important, they should not be viewed in isolation.

Certain genes may be susceptible to or cause individuals to be more susceptible to environmental "triggers." Particular vulnerability to a chemical exposure may be the result of a single or multiple interacting genes. For example:

- Gene-coding for certain enzymes can influence how chemicals are metabolized or stored in the body, or increase a person's susceptibility to a chemical. For example, a gene coding for the enzyme, delta aminolevulinic acid dehydratase (ALA-D), can influence lead metabolism, bone storage of lead, and blood lead levels.
- Two genes increase susceptibility to organophosphate pesticides. One, carried by 4% of the population, results in lower levels of acetylcholinesterase, the target enzyme of organophosphates. The other, carried by 30-40% of the population, results in reductions in paroxonase, an enzyme that plays an important role in breaking down organophosphate pesticides.
- Antibody reactions to infections is another important gene-environment interaction. For example, studies suggest that "PANDAS" (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection), that may affect patients with obsessive compulsive disorder, Tourette's syndrome and tics, result from streptococcal antibodies that cross react with critical brain structures in genetically susceptible children.

5. Neurotoxicants are not merely a potential threat to children. In some instances, adverse impacts are seen at current exposure levels.

- According to EPA estimates, about 1.16 million women in the U.S. of childbearing years eat sufficient amounts of mercury-contaminated fish to risk damaging brain development of their children.
- Breast-fed infants are exposed to levels of dioxin that exceed adult exposures by as much as a factor of 50. Dioxin exposures of this magnitude have been shown to cause abnormal social behavior in monkeys exposed before birth through the maternal diet. (While breast milk contaminants may compromise some of the cognitive benefits of breast feeding, breast milk remains strongly preferred over infant formula due to numerous important benefits to infant health.)
- Prenatal exposure to PCBs at ambient environmental levels adversely affects brain development, causing attention and IQ deficits, which remain detectable years later and may be permanent.
- Neurotoxicants that appear to have trivial effects on an individual have profound impacts when applied across populations. For example, a loss of 5 points in IQ is of minimal significance in a person with an average IQ. However a shift of 5 IQ

points in the average IQ of a population of 260 million increases the number of functionally disabled by over 50% (from 6 to 9.4 million), and decreases the number of gifted by over 50% (from 6 to 2.6 million).

6. Vast quantities of neurotoxic chemicals are released into the environment each year.

- Of the top 20 chemicals reported by the Toxics Release Inventory as released in the largest quantities into the environment in 1997, nearly three-quarters are known or suspected neurotoxicants. They include methanol, ammonia, manganese compounds, toluene, phosphoric acid, xylene, n-hexane, chlorine, methyl ethyl ketone, carbon disulfide, dichloromethane, styrene, lead compounds, and glycol ethers. Over a billion pounds of these neurotoxic chemicals were released directly on-site by large, industrial facilities into the air, water, and land.
- Vast quantities of neurotoxic chemicals are also used in industrial processes and incorporated into products. For example, according to 1997 data from the Massachusetts Toxics Use Reduction Act, over half of the top twenty chemicals in use (over 500 million pounds), and half of those incorporated into products in Massachusetts, are known or suspected neurotoxicants.
- Use of lead in manufacturing increased 77% in Massachusetts between 1990-1997.

- An additional 1.2 billion pounds of registered pesticide products are intentionally and legally released each year in the United States.
- Mercury contamination of our waterways is so widespread that 40 states have issued one or more health advisories warning pregnant women or women of reproductive age to avoid or limit fish consumption. Ten states have issued advisories for every lake and river within the state's borders.

7. Environmental releases often lead to human exposures with potential for harm.

Dispersion of these chemicals is global.

- One million children in the US exceed the currently accepted threshold for blood lead level exposure that affects behavior and cognition (10 micrograms/dl). Updating the toxic threshold in keeping with the results of the most

recent studies would further lower this threshold, resulting in the addition of millions children to the roles of those impaired by lead exposure.

- A metabolite of the pesticide chlorpyrifos is present in the urine of over 80% of adults and 90% of children from representative population samples.
- Inuit mothers in the Arctic, far from sources of industrial pollution, have some of the highest levels of PCBs in their breast milk as a result of a diet rich in marine mammal fat.

8. The historical record clearly reveals that our scientific understanding of the effects of toxic exposures is not sufficiently developed to accurately predict the impact of toxicants, and that our regulatory regime has failed to protect children.

a. As testing procedures advance, we learn that lower and lower doses are harmful.

The historical record shows that "safe thresholds" for known neurotoxicants have been continuously revised downward as scientific knowledge advances. For example, the initial "safe" blood lead level was set at 60 micrograms/deciliter (ug/dl) in 1960. This was revised down to 10 ug/dl in 1990. Current studies suggest that lead may have no identifiable exposure level that is "safe." The estimated "toxic threshold" for mercury has also relentlessly fallen, and like lead, any level of exposure may be harmful.

Such results raise serious questions about the adequacy of the current regulatory regime, which, by design, permits children to be exposed up to "toxic thresholds" that rapidly become obsolete.

b. Most chemicals are not tested for their general toxicity in animals or humans, not to mention toxicity to a child's developing brain specifically.

Nearly 75% of the top high production and volume chemicals have undergone little or no toxicity testing. However, the EPA estimates that up to 28% of all chemicals in the current inventory of about 80,000 have neurotoxic potential. In addition:

- Complete tests for developmental neurotoxicity have been submitted to EPA for only 12 chemicals - nine pesticides and three solvents – as of December 1998.
- Testing for developmental neurotoxicity is not required even in the registration or re-registration of pesticides, one of the strictest areas of chemical regulation

c. Even when regulated, the risks from chemical exposure are estimated for one chemical at a time, while children are exposed to many toxicants in complex mixtures throughout development. Multiple chemical exposures often interact to magnify damaging effects or cause new types of harm.

With the exception of pesticides used on the food supply, current regimes regulate only one chemical at a time and do not take into account the potential for interactions. Since real world

exposures are to multiple chemicals, current regulatory standards, based on single chemical exposures, are inherently incapable of providing adequate margins of safety.

- New studies in humans and in the laboratory show that PCBs and mercury interact to cause harm at lower thresholds than either substance acting alone.
- A recent 5-year pesticide study suggests that combinations of commonly used agricultural chemicals, in levels typically found in groundwater, can significantly influence immune and endocrine systems, as well as neurological function, in laboratory animals.

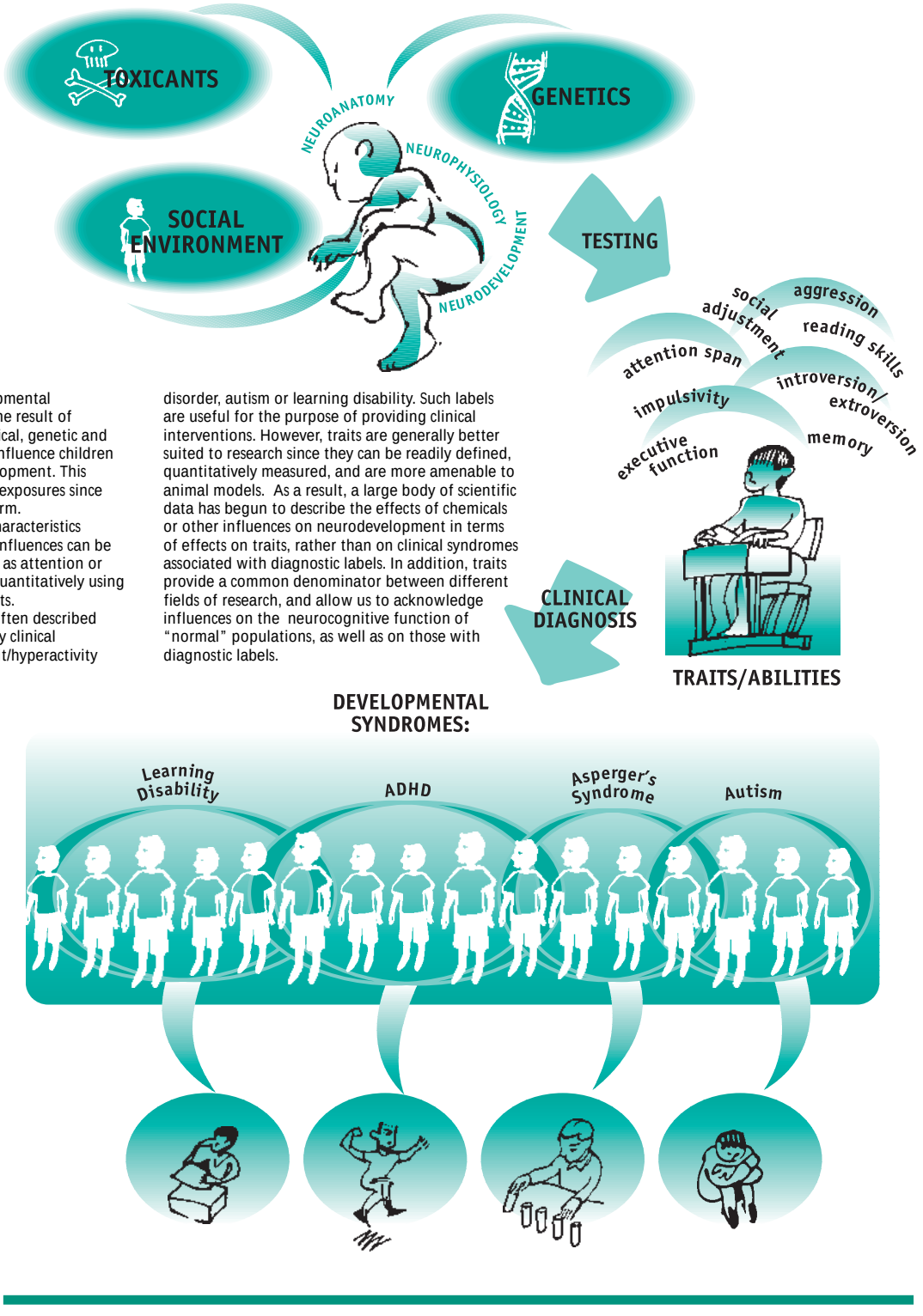
d. Animal studies generally underestimate human vulnerability to neurotoxicants.

- Animal studies of lead, mercury and PCBs each underestimated the levels of exposures that cause effects in humans by 100-10,000-fold.
- Regulatory decisions that rely largely on toxicity testing in genetically similar animals under controlled laboratory conditions will continue to fail to reflect threats to the capacities and complexity of the human brain as well as important gene-environment interactions.

9. Protecting our children from preventable and potentially harmful exposures requires a precautionary policy that can only occur with basic changes in the regulatory process.

- The inability of the current regulatory system to protect public health is not surprising, considering the disproportionate influence of special interests in the regulatory process. When there is evidence for serious, widespread and irreversible harm, as described in this report, residual scientific uncertainties should not be used to delay precautionary actions. Actions should include reduction and or elimination of exposures as well as further scientific investigation of developmental neurotoxicity.

Framework for Understanding

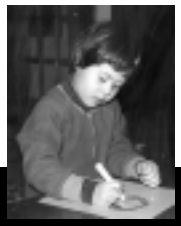


Learning, behavior, and developmental disabilities in children are clearly the result of complex interactions among chemical, genetic and social-environmental factors that influence children during vulnerable periods of development. This report focuses on the role of toxic exposures since they are a preventable cause of harm.

The cognitive and behavioral characteristics that result from these interacting influences can be described as traits or abilities, such as attention or memory, which can be measured quantitatively using a variety of neuropsychological tests.

Aggregates of these traits are often described using diagnostic labels that identify clinical syndromes, such as attention deficit/hyperactivity disorder, autism or learning disability. Such labels are useful for the purpose of providing clinical interventions. However, traits are generally better suited to research since they can be readily defined, quantitatively measured, and are more amenable to animal models. As a result, a large body of scientific data has begun to describe the effects of chemicals or other influences on neurodevelopment in terms of effects on traits, rather than on clinical syndromes associated with diagnostic labels. In addition, traits provide a common denominator between different fields of research, and allow us to acknowledge influences on the neurocognitive function of "normal" populations, as well as on those with diagnostic labels.

Chapter 1



Nature of the Problem

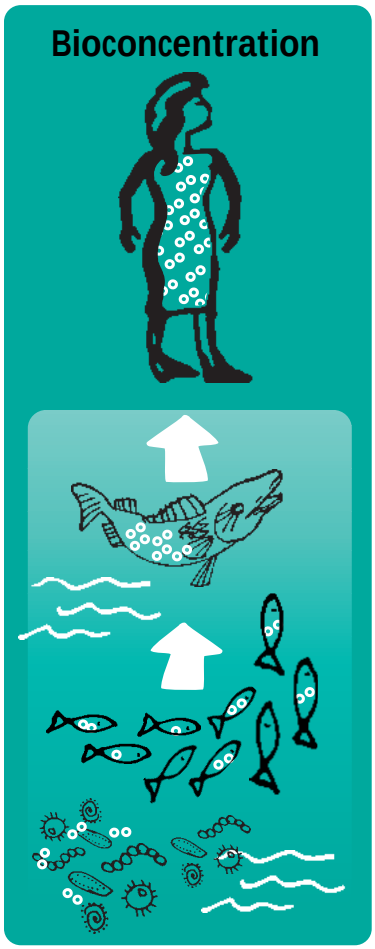
Children today face extraordinary challenges in the effort to succeed in an increasingly complex and demanding world. Parents, teachers, psychologists, and social workers know all too well that in the context of a high-tech, fast-paced world, many children are failing to meet fundamental challenges of daily life. In particular, the expectation to learn, exercise self-control, and participate respectfully in social groups has become for many a daunting challenge. These children are sometimes labeled as having learning disabilities, attention deficits, hyperactivity, autism spectrum disorders, or any one of a range of other developmental problems, depending on the mix and severity of their symptoms.

This report begins to examine the contribution of toxic chemicals to the origins of these disorders. We focus specifically on how neurotoxic chemicals contribute to developmental delays, hyperactivity, memory loss, attention deficit, learning disabilities, and aggressive behavior. Unlike an adult, the developing child exposed to neurotoxic chemicals during critical developmental windows of vulnerability may suffer from lifelong impacts on brain function.

Lead, mercury, alcohol, other solvents, some commonly used pesticides, dioxins, and PCBs interfere with normal brain development, with long term consequences for brain function. Some of these chemicals are used extensively in manufacturing and are emitted annually in the millions of pounds into the environment. Some bioaccumulate in the food chain and end up in our bones, blood, fat, urine, breast milk, ovaries, and sperm. They may then be passed to the developing child across the placenta, through breast milk, or in food. Many are so widely dispersed globally that Inuits in the Arctic, far from sources of industrial pollution, carry a large body burden of some of these chemicals. We believe that we can no longer ignore the mounting evidence that chemical exposures contribute to the epidemic of developmental disabilities.

Unlike an adult, the developing child exposed to neurotoxic chemicals during critical developmental windows of vulnerability may suffer from lifelong impacts on brain function.

It is equally important that we understand why, with few exceptions, this connection has not been widely and openly discussed—a serious failure, since environmental exposures are eminently preventable. The reasons are complex,



At one point, it was thought that "the solution to pollution is dilution". But we have found that certain persistent toxins do not stay dispersed. Through the process of bioconcentration they are reconcentrated in the food chain. They are appearing in dangerous concentrations in food, especially in meat, fish, and dairy products.

varying from the differing historical interests of professional disciplines to the corporate influence on regulation of toxic materials. For decades various scientific disciplines have carved out their sovereign territories within which they work. Geneticists, toxicologists, sociologists, educators, and healthcare providers do not seem to communicate easily or frequently enough with one another. A broader perspective looks across professional boundaries and recognizes that interactions among genetic inheritance and social and physical environmental factors challenge a more simplistic understanding of each alone. Meanwhile, the chemical manufacturing industry continues to wield enormous influence in Congress and the regulatory system. Requests for neurodevelopmental toxicity testing of marketed pesticides are ignored and data are virtually absent for all but a few of the industrial chemicals in widespread use.

In this brief report, we review evidence for chemical contributions to some neurological developmental disabilities and explore reasons for the relative silence that surrounds this issue. Some readers may find the material too technical, others too simplistic. Our goal, however, is simply to help advance and inform the discussion so that we might begin to remove our children out of harm's way.

The Magnitude of the Problem

The impact of children's developmental disorders on children and families is immense. Parents, teachers, school administrators, and communities spend increasing amounts of time, money, and energy trying to help children acquire skills that once came more naturally. Afflicted children risk early school drop-out, teen parenting, drug abuse, crime, institutionalization and suicide. A constant, consuming struggle at the verge of failure is known all too well by the children, their families, and providers. The struggle to pull these kids out of the river, or keep them from falling in, is so consuming that we have little time to consider the disturbing question of what put them in this precarious state in the first place.

The number of children known to be affected by developmental disabilities is staggering and appears to be increasing.

- It is estimated that nearly 12 million children (17%) in the United States under age 18 suffer from one or more developmental disabilities, (defined as deafness, blindness, epilepsy, stuttering or other speech defects, cerebral palsy, delay in growth and development, emotional or behavioral problems, learning disabilities).[1] [2]
- Learning disabilities alone may affect approximately 5-10% of children in public schools.[3] [4]
- The number of children in special education programs classified with learning disabilities increased 191% from 1977-1994.[5]

- Attention deficit hyperactivity disorder (ADHD), according to conservative estimates, affects 3 to 6% of all school children, though recent evidence suggests the prevalence may be as high as 17%. [6] [7] The number of children taking the drug Ritalin for this disorder has roughly doubled every 4-7 years since 1971 to reach its current estimate of about 1.5 million.[8]
- The incidence of autism may be as high as 2 per 1000 children. [9] One study of autism prevalence between 1966 and 1977 showed a doubling of rates over that time frame.[10] Within the state of California, the number of children entered into the autism registry increased by 210% between 1987 and 1998.[11]
- Approximately one percent of all children are mentally retarded.[12]

These statistics suggest problems of epidemic proportions. The proliferation of agencies, organizations, networks, and special education programs dedicated to assisting children and families affected by developmental disabilities underscores the magnitude of concern. The cost of remedial programs, though not fully known, clearly places a heavy burden upon the limited resources of educational and social service organizations.

The Origin of the Problem

A variety of explanations have been offered in response to these trends. One line of thought holds that the epidemic is more apparent than real - a product of better detection and record keeping, increased reporting, or a result of rising demands of an increasingly technologic society that places a high premium on the ability to perform more complex tasks at younger ages. While these explanations may be partially correct, they are not convincing for teachers, providers, and parents of affected children. Many who are closest to these children doubt that disabilities of the observed magnitude and incidence can be fully explained by rising expectations, and they can not imagine that such disabilities escaped notice in the past.

Although there is little doubt that many aspects of learning and development are genetically influenced, for the vast majority of these disorders there is no evidence that genetic factors are the predominant cause. In fact, the few syndromes that appear to be exclusively genetic (i.e. Lesh Nyhan, Tay-Sachs, Fragile X etc.) are fleetingly rare. Studies of adopted children and twins shed light on the degree to which genetic and environmental factors contribute to neurodevelopmental outcomes. Although our understanding is incomplete, we are now certain that complex interactions among genetic and environmental factors play extremely important roles. It is no longer in keeping with the state of scientific understanding to attribute the bulk of these developmental disabilities to genetic inheritance. Rather, we now understand that the outcomes are the result of interacting factors, among which are exposures to environmental contaminants that are preventable.

Information about the potential neurotoxicity or developmental neurotoxicity of most of these chemicals is virtually absent.

In this report we review important findings from developmental neurotoxicology, a science dedicated to the study of the impact of chemicals on the developing human brain. It is well beyond the scope of this report to address this topic exhaustively. Rather, we provide a brief overview of the process of brain development, how it may be disrupted by chemical exposures during periods of vulnerability, and concentrate on several common exposures or contaminants. We emphasize that information about the neurotoxic potential of many other chemicals and pollutants is woefully inadequate. We embed this discussion in a larger framework that acknowledges the interactions among chemical, genetic, and socioeconomic factors in the origins of developmental disorders. While the disciplines of biology, environmental sciences, psychology, and sociology are typically separated by distinct methods, concepts, and traditions, an integrated perspective of child development is likely to be much more valid and informative. The child, at the center of this disciplinary fragmentation, will particularly benefit from an integrated perspective that takes advantage of advances in each field.

Chemical Proliferation, Exposures, and Inadequate Toxicity Testing

About 80,000 chemicals are in commercial use in the United States.[13] The great majority of these compounds have been synthesized since World War II and are, therefore, new to the human environment in the evolutionary time frame. Documented and potential exposures are substantial, as indicated by the presence of chemicals in humans (biomonitoring), environmental monitoring, and chemical use and release information. From the moment of conception until reaching adulthood, children are regularly exposed to large numbers of metals, solvents, pesticides and other industrial substances, alone and in complex mixtures.

The degree to which these exposures disrupt development of humans and wildlife is a question of considerable importance and concern. Yet, of the chemicals on the EPA's inventory, even basic toxicity information is missing from publicly available sources for nearly 75% of the top 3000 high production volume substances.[14] Information about the potential neurotoxicity or developmental neurotoxicity of most of these chemicals is virtually absent. For the relatively few chemicals that have undergone developmental neurotoxicity testing, animal tests are used to predict risks of human exposure. Yet, considered in the absence of human data, our experience with lead, mercury, and polychlorinated biphenyls (PCBs) shows that animal tests often grossly underestimate risks to human neurological development. For most chemicals, even animal data are totally missing, and no systematic effort is in place to examine the neurodevelopmental consequences of exposure to mixtures of compounds that characterize the real world.

In summary, large numbers of chemicals are widely used in consumer products and regularly discharged to the environment, resulting in widespread exposures. Our limited understanding of their full neurotoxic potential, has one particularly unsettling implication: What we already know about neurodevelopmental toxic threats to children is likely to be only the tip of an iceberg.

How This Report is Organized

In the following chapters we review the intersection of several disciplines. We discuss the tightly orchestrated, intricate cascade of processes that unfold during brain development, many of which are vulnerable to disruption by environmental factors. We discuss the spectrum of developmental disabilities, their public health impacts, and what is known about their multifactorial origins, including genetics and gene-environment interactions. We review documented links between exposure to a selection of neurotoxic chemicals and traits that appear during child development or in animal testing. In addition, we present evidence of widespread exposure to some neurotoxic chemicals and note the failure of the regulators to require adequate testing for health effects in order to protect vulnerable populations. We also present evidence that developmental neurotoxic effects are not merely a potential threat, but that, for some chemicals, they occur at commonly encountered exposure levels. Finally, an appendix provides a summary of the clinical syndromes addressed throughout the report.

Cautions

As is almost always the case when considering conditions with multiple, interacting causative factors, understanding the cause(s) of a particular child's neurological developmental disability is extraordinarily difficult. This is particularly true when much of the research that identifies risk factors like, for example, elevated lead levels, is based on epidemiological rather than individual studies. Although we can conclude with certainty that, across a population, elevated lead levels during child development will impair cognition and alter behavior, we can never say with any certainty the degree to which those functions are impaired in a particular child because of lead exposure. This is because cognition and behavior are the result of complex interactions among genetic, social, and physical environmental factors. Those interactions are virtually never understood in detail in a single individual, and although it is tempting to attribute a particular outcome in a particular person to one or another factor, such a conclusion is rarely possible. Rather, we must learn what we can from available population-based information, prevent potentially harmful exposures whenever possible, and accept the limits of our ability to assign causes in individuals.

Our understanding of the benefits of treatment after a disability is detected is limited. For example, even though we know that low-level lead exposures will impact brain development, it is difficult to predict the degree to which an individual child will benefit from lowering elevated

lead levels by chelation therapy. However, environmental remediation designed to eliminate ongoing exposures is obviously a sensible first step.

This report is intended to summarize and interpret important research, much of which is largely unknown to the public. The benefits of prudently avoiding exposure to known, suspected, or potential neurotoxicants are clearly implied. The implications of these findings for therapeutic medicine, however, are separate, complex issues that we do not address.

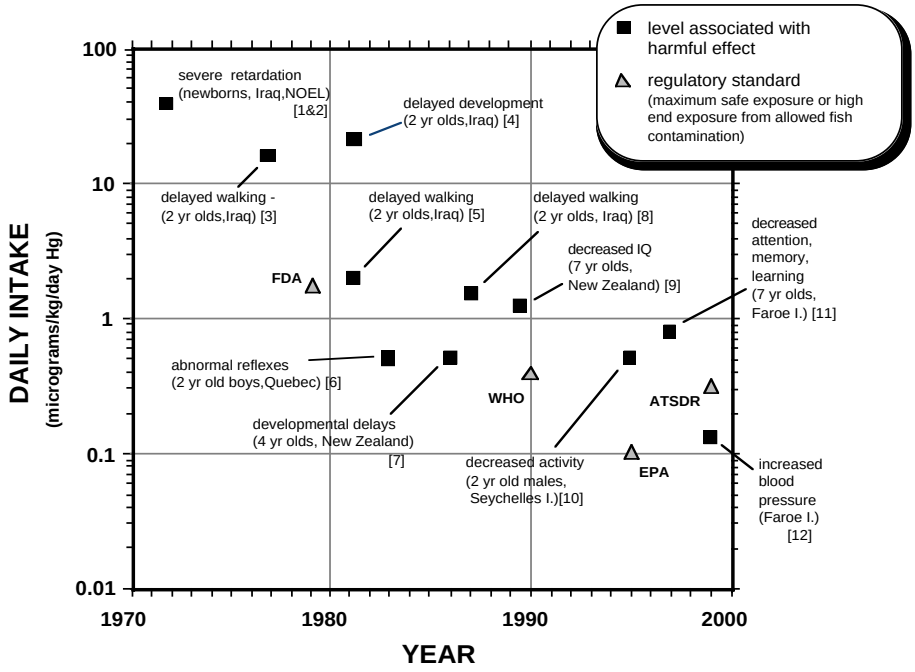
Historical Lessons

Placing our current understanding of these matters in an historical context is, as usual, a worthwhile exercise. The historical record clearly reveals that what are considered "safe thresholds" for known neurotoxicants have been continuously revised downward as scientific knowledge advances. For example, the initial "safe" level of blood lead levels was set at 60 microgm/dl in 1960. This was revised to 10 microgm/dl in 1990 when neurodevelopmental effects became clear at lower levels of exposure during critical windows of vulnerability. Now we know that neurodevelopmental effects occur at even lower levels of exposure, and many neurotoxicologists believe that there is no exposure, no matter how small, that is without impact on the developing brain. Updating the toxic threshold for lead with this new information would result in the addition of millions of children to the roles of those impacted by lead exposure – in addition to the one million currently recognized. Similarly, over the past 30 years, the recognized threshold for harm from mercury exposure has also relentlessly fallen. Recent studies suggest that, like lead, mercury may have no threshold below which adverse effects do not occur.

These observations raise serious questions about the adequacy of the current regulatory regime, which permits exposures up to "toxic thresholds" that eventually become obsolete only after more and more children are injured. What more do we really need to know before concluding that we must take the steps necessary to avoid contaminating food with mercury if we want to protect the developing brain?

It is also important to recognize that the implications of a small shift in some measure of neurological function differ for individuals and populations. For example, lead-related shifts in IQ or other neurobehavioral endpoints may be relatively small on an individual basis, but impacts at a population level are highly significant with broad ramifications. A 5- point decrease in the average IQ in a population of 260 million will increase the number of functionally disabled individuals by over 50 percent (those with IQ's of 70 or less), from 6 to 9.4 million, and simultaneously decrease the number of gifted individuals by over 50 percent (those with IQ's of 130 or greater), from 6 to 2.4 million. This shift translates into increased needs for special education and services as well as a significantly diminished intellectual capacity within the population as a whole.

Declining Threshold of Harm for Mercury



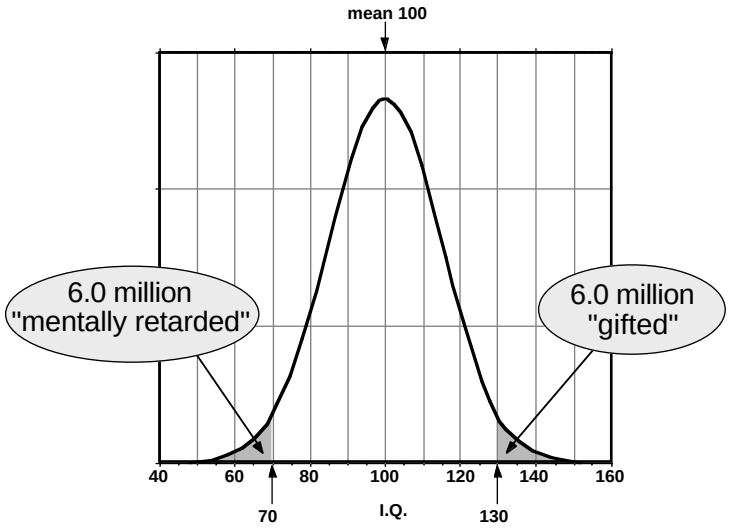
The proven threshold of harm tends to decrease as knowledge is accumulated. This figure shows the trend for one neurotoxicant: mercury. Scientific understanding of mercury's developmental neurotoxicity began with studies of the 1972 epidemic of mercury poisoning in Iraq. At that time case reports of infants severely retarded at birth identified an apparent toxic threshold for mercury exposure of greater than 34 ug/kg/d.[1] [2] (This appeared to be a "no effect level", or NOEL, for severe retardation at birth.) Within a few years, however, it became apparent that many children exposed prenatally to lower levels of mercury were delayed in learning to walk and talk, in spite of apparently "normal" development in infancy.[3] Subsequently, a variety of studies on diverse populations have established progressively lower thresholds for mercury effects by using increasingly sensitive measures of neurological function, and better statistical methods.[4] [5] [6] [7] [8] [9] [10] [11] [12]

A large, recent study has identified deficits in language, memory and attention that occur at prenatal mercury exposures under 0.85 ug/kg/d. This level is less than 3% of the toxic threshold identified in the initial observations from the Iraqi epidemic. The presence of a "discernible insidious effect" on language, memory and attention was noted, however, below even this low level[13] of 0.85 ug/kg/d, suggesting that the recognized threshold for neurological toxicity will continue declining as research methods improve.

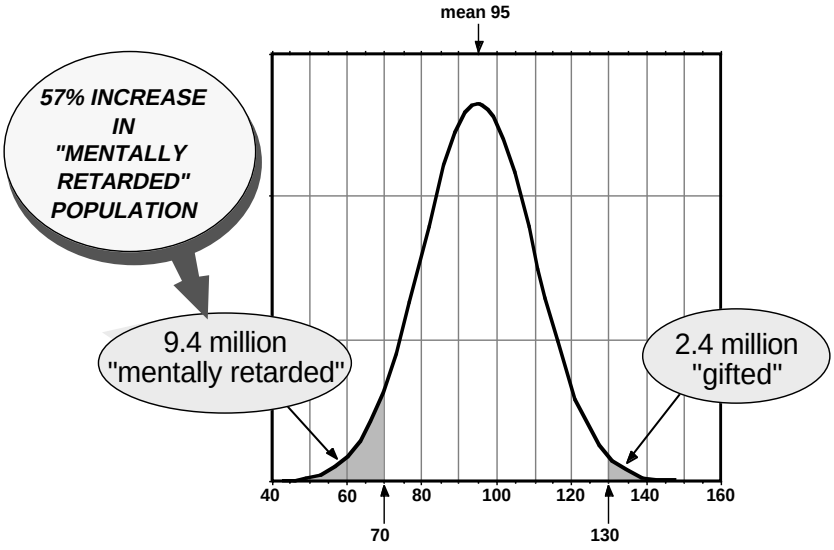
The black squares on the graph represent prenatal mercury exposures associated with adverse neurodevelopmental outcomes. The grey triangles represent World Health Organization (WHO), EPA, and Agency for Toxic Substances and Disease Registry (ATSDR) recommended limits for human mercury exposure. The standard issued by the FDA, it should be noted, regulates the level of mercury in fish, rather than in people. As a result, a wide variety of exposures may occur within the FDA regulatory limit, depending on how much and how often one eats fish, and the mercury level of the fish consumed. The indicated exposure is that of a 60 kg woman eating at the high end of fish consumption (100gm/d, the 95-97th percentile),[14] eating fish which are contaminated at the FDA permitted limit. In this worst case scenario, the woman is exposed to 1.65 ugm/kg/d, or about 16.5 times EPA's recommended safe limit.

Notes- 1.) Studies of the neurodevelopmental effects of mercury generally use hair or blood levels as markers of exposure, since these are more accurate indicators of exposure than dietary surveys. Health-based guidelines, however, are expressed as recommended limits of dietary exposure. For the purpose of comparing data between studies, and for comparing effects levels with regulatory guidelines, exposures as indicated by hair and blood levels of mercury have been converted to approximate equivalent dietary exposures. The quantitative relationships between food intake, hair and blood levels of mercury are described in the ATSDR Toxicological Profile for Mercury.[15] 2.) Study results that identified a range of exposures within which an effect was observed have been shown at the mid point of that range. Due to differences in study methodology, results are not strictly comparable between studies, and shown here mainly to indicate general trends over time.

Original IQ Distribution



Effect of a 5 Point Shift in Average IQ



POPULATION EFFECTS OF A SMALL SHIFT IN AVERAGE IQ

- The upper chart shows the distribution of IQ scores in a population where the average IQ is 100, and the standard deviation is 15. The grey area under the left "tail" of the curve represents the 2.3% of the population with an IQ <70, the score used to define mental retardation. In a population of 260 million, about 6 million people would fall below this line.
- The lower chart depicts an IQ distribution that results from lowering the average IQ by 5 points from 100 to 95. Now, 3.2% of the population, or 9.4 million people have an IQ below 70. This represents more than a 50% increase in the numbers of mentally retarded. The numbers of gifted, defined as those with IQ's greater than 130, have declined by more than 50% from 6 million to 2.4 million. Thus a small shift in average IQ results in greatly increased need for special education and services, as well as diminished intellectual capacity within the population as a whole.[16]

Spotlight

Missing: National Registry for Developmental Disabilities

Public health surveillance systems, such as birth defect registries and programs to monitor exposures to toxic substances, provide opportunities to follow trends, identify clusters, study causes, and plan preventive and service programs. Historically, federal and state government surveillance systems have focused on structural birth defects rather than developmental disabilities. As we have noted, however, some developmental disabilities may be thought of as functional birth defects, though they are often not accompanied by more easily detected structural abnormalities. Although this report is concerned with neurological developmental disabilities, the immune, endocrine, reproductive, and other systems may also function abnormally as a result of interactions of environmental and genetic factors during development.

Public health agencies often consider developmental disabilities quite separate from birth defects, though there is considerable overlap between the two. For example, the Centers for Disease Control and Prevention (CDC) assigns birth defect and developmental disability surveillance to two separate departments, which organize their programs in different ways. Yet, according to the CDC, nineteen percent of those with developmental disabilities also have birth defects, and 6.6 percent of those with birth defects have developmental deficits.

Definitions of developmental disabilities vary from federal to state and state to state agencies, particularly for cognitive disorders, and learning disabilities. This variability makes it difficult to monitor incidence, prevalence, and trends on a regional or national scale.

continued

DEVELOPMENTAL DISABILITY AS A FUNCTIONAL BIRTH DEFECT

Physical abnormalities evident at or soon after birth are readily recognized as birth defects, and chemical exposures are among several known causes of these abnormalities. Familiar examples include the severe arm and leg deformities resulting from prenatal exposure to the therapeutic drug, thalidomide.

Just as chemical exposures can cause defects in the physical structure of a limb or an organ system, early-life exposures can also impair function, often for a lifetime. Although structural birth defects resulting from maternal exposure to some teratogens have been recognized for centuries, functional defects have only relatively recently been recognized as part of a continuum of injuries that can result from prenatal toxic chemical exposures. For example, lifelong changes in endocrine, immune, or neurological function may result from chemical exposures before birth. Functional defects are often less immediately obvious than structural abnormalities, but are no less important since they constitute permanent impairments in the ability of an organ system to perform its function.

Public Interest Concerns

Public health and public interest groups have expressed three major concerns about ongoing surveillance activities:

1. Exposure data lacking

Environmental monitoring databases may be the only information available and are sometimes used, though those data are even less accurate surrogates of exposure levels.

Monitoring or estimating exposures to environmental contaminants, as well as health outcomes, is essential to identifying environmental factors that may be responsible for unexplained birth defects and developmental disabilities. Even a well-designed and implemented birth defect registry will have limited value if exposure data are lacking. Exposure monitoring may be accomplished by biological sampling (biomonitoring) or less accurately, by maternal questionnaires. Biomonitoring may include testing umbilical cord or infant blood, maternal blood, or maternal hair samples for metals, and other chemicals. DNA sampling can be used not only to examine for genetic causes of abnormalities but also, in some instances, to examine for exposures, since some toxicants leave a chemical specific "DNA fingerprint." Environmental monitoring databases may be the only information available and are sometimes used, though those data are even less accurate surrogates of exposure levels.

2. Developmental disabilities not included

Although major structural birth defects certainly deserve attention, many functional defects or developmental disabilities, including cognitive and behavioral abnormalites, remain uninvestigated. Surveillance for developmental disabilities, other than mental retardation, cerebral palsy, hearing and visual impairment, and epilepsy, is largely non-existent on a meaningful scale. In part this reflects the difficulty and expense encountered in establishing a large surveillance system for other disorders, but may also signal a reluctance to pursue incidence and trend data too aggressively because of the economic implications of diagnoses with attached mandated services.

3. Privacy concerns

Programs that include banking DNA or other biological specimens raise concerns about privacy and confidentiality. Some analytic data are predictive of future health or disease and have profound implications for insurability or employability. Because of concerns about unauthorized disclosure of information, individuals are often reluctant to participate in public health research projects that include the collection of personally identifiable data. Study participants usually lack ultimate ownership and control of data, and efforts to protect the privacy of individuals do not necessarily overcome underlying fears of inappropriate disclosure. The need for limited access to medical information by insurance companies, potential employers, health maintenance organizations, and others is recognized, but what the limits should be and how they are to be enforced is widely debated.

Mohawk Women's Breast Milk Study: Community Based Research Model

The Mohawk women's breast milk study was a research project designed to address concerns about privacy and data ownership. Investigators wanted to study the relationship between fish consumption and PCB breast milk contamination among nursing Mohawk women at Akwesasne, along the St. Lawrence River. Previously, PCBs from a nearby General Electric facility had been dumped or spilled onto Native American lands or into the river, contaminating soils, sediments, and the food chain. Mohawk women were reluctant to agree to participate in a study of their breast milk, without fundamentally restructuring their relationship with investigators from the New York State Department of Health. Rather than allowing outside experts to conduct a study in which community members would be passive participants, Mohawk women insisted on a more co-equal relationship in which they would assist in study design as well as own and control the analytic data. The study and results have been published in peer-reviewed journals.[1] Community members are among the authors. Breast milk PCB levels declined in the last three years of the six-year study, perhaps as a result of more consistent attention to advisories recommending against consumption of local fish by pregnant and nursing Mohawk women. This experience may serve as a useful starting point for dealing with concerns about privacy, confidentiality, and control of data in other circumstances.

1 Fitzgerald E, Hwang S, Bush B, Cook K, Worswick P. Fish consumption and breast milk PCB concentrations among Mohawk women at Akwesasne. Am J Epidemiol 148(2):164-172, 1998.

Citizen Database Fills Government Void

(With information taken from a piece written by Betty Mekdeci, Executive Director of the Association of Birth Defect Children, for *Birth Gazette*, Fall, 1997, with additional information added from a presentation by Ms. Mekdeci in October 1999)

The modern study of teratology (the study of birth defects) was born out of a world tragedy that occurred in 1962—over 10,000 babies born deformed as a consequence of their mothers taking the drug thalidomide. The National Birth Defects Registry (NBDR) was born out of the frustration of mothers, educators and other concerned citizens that critical information about birth defects and developmental disabilities was not being collected in the United States. It was created and is sponsored by the Association of Birth Defect Children with Betty Mekdeci at the helm. For twenty years Mekdeci has led a crusade to unravel the mysteries of why birth defects occur. Her efforts have brought her into the halls of Congress and into the lives of thousands of parents.

Like a sleuth collecting clues, the NBDR compiles information directly from the parents of infants and older children with birth defects, including functional defects that may go unrecognized at birth. Over 10,000 questionnaires have been distributed to try to piece together the puzzle of what has caused abnormalities ranging from limb deformities to learning disabilities.

The database has recently been utilized to analyze disabilities in the children of Vietnam veterans, with some disturbing results.

The database has recently been utilized to analyze disabilities in the children of Vietnam veterans, with some disturbing results. The registry has revealed a pattern of functional problems in Vietnam vets' children that includes significant increases in learning and attention problems, chronic skin disorders, benign tumors and cysts, allergic disorders, growth hormone deficiency, chronic infections, emotional/behavioral problems, prolapsed heart valves, and a range of conditions that may be consistent with a malfunctioning immune system. This pattern of disabilities is consistent with other research suggesting prenatal effects of dioxin on the developing immune system. The Vietnam veterans data has been presented to Congress, and cited in the report "Veterans and Agent Orange" (dioxin is a constituent of Agent Orange, the defoliant used in Vietnam).

This is no amateur operation. The questionnaire used to compile these findings has been evaluated and endorsed by a seven-member advisory board of national experts in reproductive biology, epidemiology, endocrinology, biochemistry and environmental biology. It is designed to act as an alert practitioner on a grand scale by searching for the "fingerprints" of teratogens. The reporting parent is also asked about the pre-conceptual exposures of the mother, and the father and mother's exposure history during pregnancy. Data from questionnaires are entered into a customized computer format, and automatically entered into more than 20 separate tables that can be connected in multiple ways for data analysis.

A recent report by the Pew Environmental Health Commission entitled "Healthy From the Start: Why America Needs a Better System to Track and Understand Birth Defects and the Environment," outlines the deficiencies of the state and national data collection systems for these disabilities. This is not news to Betty Mekdeci and her colleagues in Florida, who have been listening to the cries of the disabled children for decades.

The Association of Birth Defect Children, Betty Mekdeci, Executive Director, can be contacted at 930 Woodcock Road, Suite 225, Orlando, FL 32803. 407-245-7035. www.birthdefects.org

Footnotes to diagrams

1 Amin-Zaki L, Elhassani S, Majeed MA, et al. Perinatal Methylmercury Poisoning in Iraq. Am J Dis Child 130, Oct 1976, 1070-8.

2 Amin-Zaki L, Elhassani S, Majeed MA, et al. Intra-uterine Methylmercury Poisoning in Iraq. Pediatrics 54(5) p.587-95, 1974.

3 Marsh D. Fetal methylmercury poisoning: new data on clinical and toxicologic aspects. Trans Am Neurol Assoc 102:69-71, 1977.

4 Marsh DO, Myers GJ, Clarkson TW et al. Fetal methylmercury poisoning: clinical and toxicological data on 29 cases. Ann Neurol 7:348-353, 1980.

5 Marsh DO, GJ Myers, Clarkson TW et al. Dose-Response Relationship for Human Fetal Exposure to Methylmercury. Clinical Toxicology, 18(11): 1311-1318, 1981.

6 McKeown-Eyssen GE, Ruedy J Neims A. Methyl mercury exposure in Northern Quebec II. Neurologic findings in children. American J of Epidemiology 118(4): 470-479, 1983.

7 Marsh DO, Clarkson TW, Cox C et al. Fetal Methylmercury Poisoning. Arch Neurol 1987;44:1017-1022.

8 Marsh DO, Turner MD, Smith JC et al. Fetal methyl mercury study in a Peruvian fish-eating population. Neurotoxicology 16(4):717-726, 1995.

9 Cox C, Clarkson TW, Marsh DO et al. Dose-response analysis of infants prenatally exposed to methylmercury: dan application of a single compartment model to single-strand hair analysis. Environmental research 49: 318-332, 1989.

10 Davidson PW, Myers GH, Cox C. Longitudinal neurodevelopmental study of Seychellois children following in utero exposure to methylmercury from maternal fish ingestion: outcomes at 19 and 29 months. Neurotoxicology 16(4):677-688, 1995.

11 WHO task group on environmental health criteria for methylmercury. Methylmercury, Environmental Health Criteria 101. World Health Organization, 1990.

12 Sorensen N, Murata K, Budtz-Jorgensen et al. Prenatal methylmercury exposure as a cardiovascular risk factor at seven years of age. Epidemiology 10(4):370-5,1999.

13 Grandjean P, Weihe P, White R. Cognitive Deficit in 7-year-old children with prenatal exposure to methylmercury. Neurotoxicology and Teratology 19(6):417-428.

14 EPA. Mercury Study Report to Congress. Volume I, p.3-39. EPA-452/R-97-003. 12/97.

15 ATSDR. Toxicologic Profile for Mercury. US Department of Health and Human Services. 1998.

16 Adapted from Weiss, B. Endrocrine dispruptors and sexually dimorphic behaviors; a question of heads and tails. Neurotox 18:581-6, 1997.

Footnotes to text

1 Boyle CA, Decoufle P, Yeargin-Allsopp M. Prevalence and health impact of developmental disabilities in US children.- Pediatrics March 93(3):399-403, 1994.

2 U.S. Census Bureau Population Estimates Program, Washington DC. www.census.gov/population/estimate/nation/inttfile2-1.txt

3 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. 1994.

4 Parrill M. Research implications for health and human services. In Learning Disabilities, Lifelong Issues. Cramer and Ellis, Eds. 1996. Pgs. 227-295.

5 Kavale KA, Forness RR. Co-variants in learning disability and behavior disorders:an examination of classification and placement issues. Advances in Learning and Behavioral Disabilities, 12:1-42, 1992.

6 Goldman L, Genel M, et al. Diagnosis and treatment of attention deficit hyperactivity disorder in children and adolescents. JAMA 279(14):1100-1107, 1998.

7 Rowland, A. Prevalence and Risk Factors for ADHD in a North Carolina County:Study Design and Preliminary Results. Environmental Influences on Children conference, New York Academy of Medicine, May 1999.

8 Safer D, Zito J, Fine E. Increased methylphenidate usage for attention deficit disorder in 1990s. Pediatrics 98(6):1084-1088, 1996.

9 Centers for Disease Control and Prevention, National Center for Environmental Health, Division of Birth Defects and Disability and Health, Developmental Disabilities Branch. http://www.cdc.gov/nceh/programs/CDDH/dd/ddautism.htm

10 Gillberg C, Wing L, Autism: not an extremely rare disorder. Acta Psychiatr Scand 99(6):339-406, 1999.

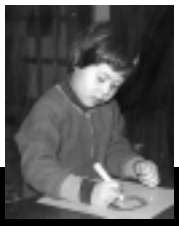
11 California Health and Human Services, Department of Development Services. Changes In the Population of persons with Autism and Pervasive Developmental Disorders in California's Developmental Services System:1987 through 1998. A Report to the Legislature, Mar 1999. http://www.autism.com/ari/dds/dds.html

12 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. 1994.

13 U.S. EPA. Office of Prevention, Pesticides and Toxic Substances. Endocrine Disruptor Screening and Testing Advisory Committee. Final Report. Washington DC. 1998.

14 Roe D, Pease W, Florini K, Silbergeld E. Toxic Ignorance: The Continuing Absence of Basic Health Testing for Top-Selling Chemicals in The United States. Environmental Defense Fund. 1997.

Chapter 2



Normal Brain Development and Developmental Toxicology

Normal Brain Development

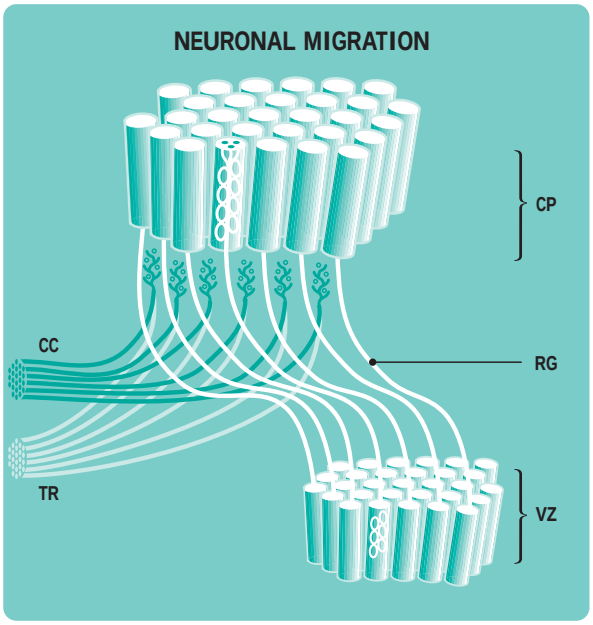
Brain development begins early in the child's first envir onment of the uterus and continues well beyond birth into adolescence. Normal brain development requires the intricate unfolding of a cascade of processes that do not occur during any other life stage. Consequently , developing fetuses and infants are uniquely vulnerable to disruption of these processes by environmental factors, including chemical contaminants and nutritional deficiencies. Cell proliferation, migration, differentiation, and synapse formation normally progress in a tightly programmed and orderly fashion. Subsequently , neural cir cuits ar e refined and consolidated through programmed cell death (apoptosis), a process that continues into childhood and adolescence. Interference with any stage of this cascade of events may alter normal progression of subsequent stages so that even short-term disruptions may have long-term effects later in life.

Neurons are the nerve cells in brain or peripheral nerves responsible for transmitting nerve impulses. Outgrowths from these cells, collectively called neurites, develop into long axons or shorter dendrites, each of which makes contact with neighboring neurons. Connections between neurons, called synapses, enable complex circuits to be established in the brain. Other cells, called glia, are responsible for the synthesis and maintenance of myelin, a coating around larger axons, which facilitates nerve transmission. Myelin consists largely of lipids (fats) with smaller amounts of protein. Some glial cells also provide scaffolding for the migration of neurons during development and help to maintain a normal biochemical environment.

Normal brain development requires the intricate unfolding of a cascade of processes that do not occur during any other life stage. Consequently, developing fetuses and infants are uniquely vulnerable to disruption of these processes by environmental factors, including chemical contaminants and nutritional deficiencies.

The timeline of normal brain development has been studied in detail in animals and to some degree in humans. Embryonic and early fetal development are characterized first by neuronal proliferation and migration.

Later, cellular dif fer entiation and synapse formation dominate. During normal development, neurons migrate to their final positions in a specific



During brain development neurons originate near the center of the brain (ventricular zone, VZ) and migrate along radial glial guides (RG) to their final location closer to the surface of the brain (cortical plate, CP). As the neurons migrate they intercept nerve fibers from other portions of the brain (thalamus, TR; the opposite side of the brain, CC). Later-developing neurons migrate to final positions closer to the brain surface, remaining in columns (outlined by cylinders) that correspond to columns from which they originated. (adapted from Rakic, 1988)

Rakic P. Specification of cerebral cortical areas. Science 241(4862):170-176, 1988.

sequence with those migrating to the cortex early forming the deepest layers while later arriving cells are more superficial. Proper positioning of the neurons is essential for establishing normal neural circuitry and brain function. Cell proliferation continues in the rat brain up to about 3 weeks after birth. In humans, neuron formation is largely complete at birth, and almost all neurons of the cerebral cortex have reached their final positions. Glia, however, continue to develop throughout life. Many synapses formed during the first two years of life are later eliminated as circuits are pruned. However, new synapses form throughout life, explaining how we can continue to learn and remember. Myelination continues well into the teenage years. [1]

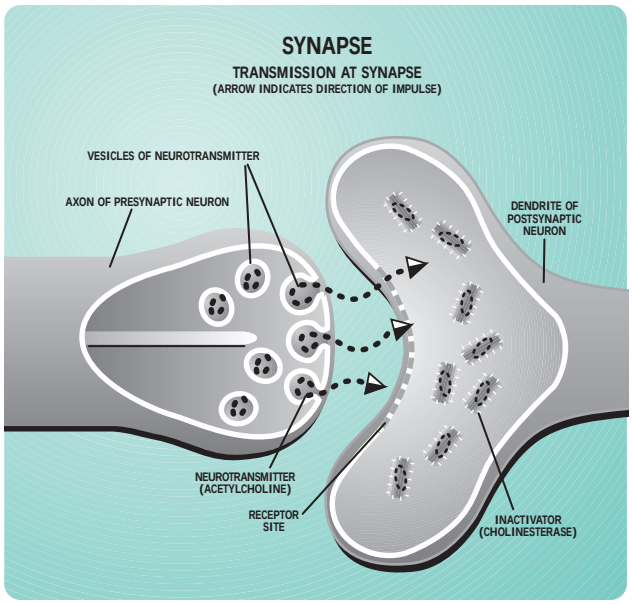
Development does not, however, progress uniformly in every area of the brain. For example, the cerebellum develops later than many other brain structures. Consequently, at any one time, some areas are undergoing cellular proliferation while others are undergoing primarily differentiation. Timing is, therefore, important when considering the potential effects of exposure to an environmental agent that disrupts specific developmental processes.

Neurotransmitters, hormones, neurotrophins, and growth factors orchestrate the intricate process of brain development. Neurotrophins are proteins that help regulate differentiation and survival of neurons. In the adult, neurotransmitters serve primarily to transmit nerve impulses from one neuron to another. In the developing brain, however, neurotransmitters serve an additional and very important role, helping to orchestrate the cascade of events necessary for normal brain development. Major neurotransmitters include acetylcholine (ACh), norepinephrine, dopamine, serotonin, gamma-amino butyric acid (GABA), glutamate, and aspartate. Growth, thyroid, steroid, and sex hormones also play important roles in brain development. Neurotransmitters, neurotrophins, and hormones exert their effects by attaching to specific cellular receptors, initiating a biological response. Receptor location and density are also determined during early brain development.

During prenatal life, neurotransmitters and their cellular receptors also develop on a specific timeline. For example, receptors for the neurotransmitter, acetylcholine, develop slowly from 16-20 weeks, followed by a lag time of about 4 weeks, and then rapid receptor formation during the last trimester of pregnancy.[2]

The class of neurotransmitters that includes dopamine and norepinephrine matures later.

The cholinergic neurotransmitter system, which utilizes acetylcholine as its chemical messenger, includes two types of receptors – muscarinic and nicotinic, so named because of their selective stimulation by muscarine (a chemical that can be extracted from certain mushrooms) and nicotine. Both types



of receptors are found in the central nervous system and their respective roles in brain development are gradually coming into focus, though considerable information is still missing. Normal development of muscarinic ACh receptors is important for later learning and cognition.[3] Initially, neurotransmitters promote DNA synthesis and cell proliferation.[4] Later, with increases in synaptic proliferation and nerve activity, the same transmitters promote differentiation of nerve cells into those with more specialized functions.

In general, cholinergic neurons frequently make contact with non-cholinergic structures, leading investigators to conclude that an important role is to modulate the activity of other types of neurons. For example, ACh released from one neuron, acting on the receptors of other neurons, modulates their release of norepinephrine, dopamine, GABA, serotonin, glutamate, and acetylcholine.[5]

The brain undergoes rapid structural and functional changes during late pregnancy and in the neonatal period.

The brain undergoes rapid structural and functional changes during late pregnancy and in the neonatal period. Cognitive functions and behavior arise from multiple sources and depend on more than one neurotransmitter and more than one portion of the brain. Attention, memory, language skills, learning capacity, and behavior result from integration of multiple structural and functional factors with cultural and social forces. These complex interactions make it exceedingly difficult to study the contribution of each factor independently. These complexities also make it difficult to study and understand when, if, or to what degree environmental factors play a role. Differing professional interests also help to explain the varying approaches of investigators from separate disciplines as they attempt to understand human behavior and cognitive abilities.

Developmental Neurotoxicology

Developmental neurotoxicants, including lead, mercury, pesticides, and others, may directly interfere with any of the processes required for normal brain development. Cell division, migration, differentiation, synapse formation, and apoptosis may be accelerated or delayed. Myelin formation may also be altered by toxic exposures or nutritional deficiencies. [6] Some neurotoxicants, like lead and alcohol, interfere with normal neurite development through a variety of mechanisms. Unique developmental processes, including myelination, synapse formation, and apoptosis continue under genetic and environmental control at least through puberty.[7] The timing, pattern, and level of toxic exposure largely determine which parts of the brain will be affected and to what degree. Various stages of development provide critical windows of vulnerability during which exposure to a chemical substance may have lasting adverse effects on brain function. Different learning or behavioral effects may result from exposure to the same agent at different times in brain development, depending on the location in the brain where susceptible neurodevelopmental events are taking place at the time of the exposure.

Some toxicants act indirectly by, for example, interfering with normal placental function, altering umbilical circulation, causing general growth retardation, or altering function or metabolism of hormones (endocrine disruptors). However, the distinction between direct and indirect toxicity is of no practical importance, since the child is still impaired. It is also critically important to keep in mind that neurotoxicants may interfere with brain development and subsequent function at exposure levels that have minimal, transient, or no effect on the adult brain.

The Role of Thyroid Hormone

Among the various growth factors and hormones necessary for normal brain development, thyroid hormone (thyroxine), which is essential for neuronal proliferation and differentiation, plays a particularly important role. [8] It appears that any toxicant that lowers thyroxine levels, or otherwise interferes with thyroid hormone action, even to a small degree, is likely to have an adverse impact on IQ and potentially other brain functions. Even transient decreases in thyroxine in the CNS during critical developmental periods may produce alteration in neuronal branching and cellular architecture in the brain.

It has long been known that maternal and fetal hypothyroidism, as determined by distinctly subnormal thyroxine levels, produce cognitive impairment in children. However, a recent study reports that even minor reductions in maternal thyroxine levels result in reduced performance on IQ tests in children. [9] In this study, elevated levels of thyrotropin, the pituitary hormone responsible for stimulating the thyroid to release thyroxine even when slightly decreased, predicted reduced performance on the Wechsler

Intelligence Scale for Children. IQ scores were 4 points lower in children of women with elevated thyrotropin levels compared to matched controls. Fifteen percent of the children had IQ scores of 85 or less compared to 5% of control children. Only some of the women with elevated thyrotropin also had low thyroxine levels.

Challenges to Identifying Neurotoxic Effects

One of the main problems encountered in studying the effect of chemical exposures on subsequent brain function is the possibility of a long latent period between the exposure and recognition of a functional deficit. For example, impaired language or reading skills may not become apparent until school age. Indeed, some investigators report that some chemicals administered during development have effects on brain function in subsequent generations. [10] Delays of this sort make it extremely difficult to attribute a functional brain abnormality to an earlier chemical exposure.

In addition, the symptoms of impaired brain function are not specific for each potential cause. That is, cognitive and behavioral disorders, or even mental retardation, may have multiple causes, including genetic and envir onmental factors. Mor eover , even a known neurodevelopmental toxicant, like alcohol, may cause a range of adverse ef fects including pr ematurity , cognitive disorders, mental retardation, and disturbances of sexual

differentiation of the brain. Lack of specificity of symptoms, multiple potential causes, and long latent periods between exposures and recognition of symptoms combine to ensure that establishing causal connections between symptoms and chemical exposures will be difficult.

Neurodevelopmental Toxicity Testing

Laboratory and epidemiological research over several decades has led to considerable insight into the capacity of a few neurodevelopmental toxicants to interfere with normal brain development, often with severe and lasting consequences. Unfor tunately , extensive information is available for only a few chemicals, though more neurodevelopmental data on many others are urgently needed. As new research is contemplated, an important question focuses on the degree to which

animal testing data predict neurological consequences of exposure in humans.

A retrospective look at the evolution of understanding of the neurodevelopmental toxicity of lead, mercury, and PCBs is instructive. In an historical review of this question, Rice et al. conclude that animal studies, particularly rodent studies, are disappointing in their ability to predict "safe" exposure levels, below which no human health effects are likely to occur.[11] Rodent studies often vastly underestimate the sensitivity of the developing human brain. For example, based on comparisons of animal and human data, animal studies of lead, mercury, and PCBs predict a "safe" exposure level in humans that is 2-4 orders of magnitude (100-10,000 fold) higher than levels that actually cause effects in humans. These sobering limitations must be kept in mind as we use the results of animal testing to estimate "safe" human exposure levels. *(see Chapter 7)*

1 Paus T, Zijdenbos A, Worsley K, et al. Structural maturation of neural pathways in children and adolescents: in vivo study. Science 283:1908-1911, 1999.

2 Ravikumar BV, Sastry PS. Muscarinic cholinergic receptors in human fetal brain: characterization and ontogeny of 3H-quinuclidinylbenzilate binding sites in frontal cortex. J Neurochem 44:240-246, 1985.

3 Ahlbom, J, Fredriksson A, Erikson P. Neonatal exposure to a type-1 pyrethroid (bioallethrin) induces dose-response changes in brain muscarinic receptors and behavior in neonatal and adult mice. Brain Res 645:318-324, 1994.

4 Lauder JM, Schambra UB. Morphogenetic roles of acetylcholine. Environ Health Perspect 109(suppl 1):65-69, 1999.

5 McGehee DS, Heath MJS, Gelber S, et al. Nicotine enhancement of fast excitatory synaptic transmission in CNS by presynaptic receptors. Science 269:1692-1696, 1995.

6 Wiggins RC. Myelination: a critical stage in development. Neurotoxicol 7:103-120, 1986.

7 Paus T, Zijdenbos A, Worsley K, et al. Structural maturation of neural pathways in children and adolescents: in vivo study. Science 283:1908-1911, 1999.

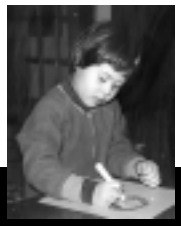
8 Porterfield SP. Vulnerability of the developing brain to thyroid abnormalities: environmental insults to the thyroid system. Environ Health Perspect 102(suppl 2):125-130, 1994.

9 Haddow JE, Palomaki GE, Allan WC, Williams JR, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 341(8):549-555, 1999.

10 Campbell JH, Perkins P. Transgenerational effects of drug and hormonal treatments in mammals: a review of observations and ideas. Prog Brain Res 73:chapter 33, 1988.

11 Rice D, Evangelista de Duffard A, Duffard R, et al. Lessons for neurotoxicology from selected model compounds: SGOMSEC joint report. Environ Health Perspect 104(suppl 2):205-215, 1996.

Chapter 3



The Clinical Spectrum of Developmental, Learning and Behavioral Disorders in Children

What's In a Label? - Working Definitions in Evolution

The disorders of learning, behavior and development cover a wide spectrum of disability, ranging from subtle to devastating. Distinguishing among the various syndromes, and the "normal" from the "abnormal" is a subject of considerable discussion and uncertainty.[1] The lack of consensus on these issues is reflected in the large number of alternate approaches to diagnosis and classification, and in the frequency with which old syndromes are redefined[2] and new ones appear. As a result, these disorders may be best characterized as works in progress, rather than rigid diagnostic entities.

The difficulties in diagnosis are not surprising, since learning, behavior, and developmental disorders lack specific markers - such as unique symptoms, blood tests or physical attributes. The limits of current scientific knowledge also prevent an understanding of biological underpinnings of these disorders. While gross brain structure usually appears normal, it is widely assumed that underlying problems exist at the level of neural circuitry, cellular and subcellular structure and function.[3] [4] [5] [6] Since most of these details lie beyond the current limits of science, the biological basis of these disorders remains poorly understood. Consequently, the developmental syndromes are defined by clinical symptoms, such as how children appear or behave. Since these defining symptoms are nonspecific, each symptom may occur as a part of many developmental, medical and psychiatric conditions, as well as in normal children.[7] [8]

Distinguishing among the various syndromes, and the "normal" from the "abnormal" is a subject of considerable discussion and uncertainty... these disorders may be best characterized as works in progress, rather than rigid diagnostic entities.

Developmental disorders are most often diagnosed according to a system of classification known as the DSM-IV, (The Diagnostic and Statistical Manual of Mental Disorders, Edition IV). As a categorical system of classification, the DSM-IV uses "clinically derived categories of classification based mostly on subjective consensus."[9] The DSM-IV enumerates criteria for diagnosing generally recognized mental health disorders. These criteria typically include

DIAGNOSTIC DILEMMAS

Consider the question of whether a fidgety, forgetful child has ADHD. According to the most recent, widely used definition, set by DSM IV in 1994, a child has ADHD if she/he exhibits at least six maladaptive, age-inappropriate symptoms in the areas of inattention or hyperactivity/impulsivity, with the added condition that these symptoms have been present for at least six months. The criteria symptoms, however, lack both specific definitions and thresholds for determining when a symptomatic behavior is occurring. Consider one of the DSM IV criteria symptoms: "fails to give close attention to details." How close is close, and at what level of detail? A 10 year old might fail to notice the name of the 5th president from the complete list of US presidents, the color of the teacher's shoes, or today's homework assignment written on the blackboard. And how often should the child have failed to pay close attention, 1%, 5%, or 50% of the time? Is a child failing to pay close attention to detail if s/he neglects to bring in his homework one, two, three or eight times a month? Clearly the conclusion that a child is "inattentive" is subjective and depends on the expectations and judgment of the observer.

DEFINITION - *Empirical:*

Derived from experience, observation or experiment.

symptoms, their durations, and exclusions. For a partial list of diagnostic criteria for development, learning and behavioral disorders, see the chart on page 35.

Observers have identified a number of drawbacks with this system of diagnosis, problems which are often associated with categorical classification. They include [10]:

1. Lack of empirical foundations;
2. Reliance on subjective-impressionistic criteria to derive individual categories;
3. Unsubstantiated assumptions regarding etiology;
4. Lack of objective, validated criteria for assigning diagnostic labels;
5. Failure to integrate the influence of context into diagnostic criteria;
6. Lack of demonstrated relevance to treatment;

The lack of a unifying, empirically-derived classification framework has several important consequences. The considerable impact on clinical practice was summarized by one observer as follows: "Looked at realistically, what this means is that after the elaborate procedures used in most clinics are completed, the child is placed in a category, which says exactly what we knew about him in the first place, that he has a problem."[11] In addition, as a result of the reliance on subjective diagnostic criteria, up to 30% of parents report their children have been labeled with three or more different diagnoses.[12]

The lack of a unifying framework also makes communication difficult among professionals, who may call similar disabilities by different names, or different disabilities by the same name. Research is also impaired when terms are ambiguous, since data from diverse sources cannot be readily compared. These concerns were summarized by two noted researchers, Achenbach and Edelbrock, in their observation that "the study of psychopathology in children has long lacked a coherent taxonomic framework within which training, treatment, epidemiology, and research could be integrated."[13]

Fortunately, much of the current research in learning and developmental disorders focuses on improving diagnosis and classification of childhood disabilities.[14] This will establish a more meaningful use of diagnostic labels. In addition, there is increasing recognition of the importance of integrating methods, vocabulary, concepts and knowledge across disciplines.[15] [16] This will ultimately improve research on underlying mechanisms, causes, treatments and prevention.

A Brief Overview of the Disorders of Learning, Behavior and Development

In spite of the limits to the current system of classification, the clinical syndromes commonly used to label children with developmental disabilities provide a set of management strategies. These strategies address the practical concerns of managing dysfunctional or inappropriate behavior in various settings.[17] In some cases labels also provide access to supportive services. These syndromes are described in detail in the appendix. As an introduction for readers not already familiar with them, we present here an abbreviated, admittedly oversimplified account of these disorders as currently defined. To organize this discussion, we use a pragmatic framework representing a composite of Wolraich, author of a widely used text in child development,[18] and the DSM-IV. While this framework differs slightly from the traditional DSM-IV, this approach is suited to the brief discussion offered here.

In spite of the limits to the current system of classification, the clinical syndromes commonly used to label children with developmental disabilities provide a set of management strategies.

OVERLAPPING SYNDROMES:

Percent of kids with ADHD that also have other developmental and social/psychiatric disorders[24]

- 10-30% have learning disabilities.
- 30-50% have language disability (a core symptom of autism when expressed in its extreme form.)
- 30-80% have oppositional disorder or conduct disorder.
- Frequently associated with other neurodevelopmental disorders: Asperger's, obsessive compulsive disorder, tic disorders, and mental retardation.
- May accompany social and psychiatric disorders: anxiety, depression, schizophrenia. (In the presence of a mental disorder, the diagnosis of ADHD cannot be made if the symptoms can be better accounted for by the accompanying social/psychiatric condition.)

As the scope of disability increases, problems tend to extend beyond the classroom setting. If several functions are impaired, a child is considered to have a "pervasive developmental disorder," or PDD.

1.Academic Disorders

Disorders predominantly expressed in the learning environment can be classified as "academic disorders." These include learning disabilities, such as the disorders of reading, math, and written expression. Attention deficit hyperactivity disorder, or ADHD, can also be considered an "academic disorder." Although problems must occur in more than one setting in order to meet diagnostic criteria, for most children the strongest expression of ADHD occurs in the school setting. ADHD consists of a mix of attentional problems, which are considered cognitive disabilities, and impaired impulse control. Impulse control is thought to be an expression of the ability to self-regulate, a trait technically referred to as "executive function."[19] Impairment in the ability to self-regulate is increasingly recognized as a unifying feature of ADHD. In the domain of motor activity, this is expressed as hyperactivity, for example by frequent fidgeting or the inability to sit still. In the domain of social behavior, impaired self-regulation is expressed in intrusive actions such as the inability to await one's turn, or recurrently intruding into conversations and games.

2. Pervasive Developmental Disorders

As the scope of disability increases, problems tend to extend beyond the classroom setting. If several functions are impaired, a child is considered to have a "pervasive developmental disorder," or PDD. The mildest pervasive developmental disorder, Asperger's syndrome, is characterized by impaired social interactions and restricted behavior and interests. Social impairment is characterized by lack of emotional reciprocity, impaired nonverbal exchanges such as eye-to-eye gaze and facial expressions, and disinterest in shared experience. Restricted, repetitive behaviors and interests are characterized by encompassing preoccupations, adherence to nonfunctional routines or rituals, or repetitive motor mannerisms such as hand flapping or finger twisting.

When language deficits compound social impairments and restricted/repetitive behaviors, a child is considered to have a more serious pervasive developmental disorder. Autism is the prototype of these serious PDDs, which in most cases are marked by loss of the capacity for self care as well. The serious PDD's may be characterized by more extreme restricted/repetitive behaviors, such as spinning, hand flapping, or head or body rocking. Interests are severely restricted in autism, as exemplified by the relative absence of pretend play. This is illustrated, for example, in the observation that autistic children, compared to control children, are more

likely to arrange objects into patterns or lines, or to shake or twirl toys rather than play imaginatively with them. [20]

Mental retardation and PDD's are both characterized by severe functional impairment, and many children with PDD's will also meet test criteria for mental retardation. PDD's are distinguished from mental retardation by the presence of repetitive, restricted behaviors, and social and communication impairments that are disproportionately impaired for a given IQ level. [21]

3. Behavioral Disorders

Behavioral disorders are also prominently expressed well beyond the classroom setting. Children are labeled with these disorders when their behavior is marked by the predominance of disruptive or aggressive features. When this behavior is directed mainly towards authority figures, the disorder is typically labeled as Oppositional Defiant Disorder (ODD). When disruptive/aggressive bevavior is more broadly directed, and of sufficient intensity to violate social norms and the rights of others, the problem is likely to be labeled Conduct Disorder (CD). [22] These disorders are distinguished from PDD's by the prominence of disruptive/aggressive behavior, by relatively normal verbal and nonverbal communication skills, and by the absence of repetitive/restricted behaviors and interests.

The clinical descriptions of behavioral disorders notably overlap with that of ADHD. This is not surprising considering the fine line between impaired impulse control and disruptive or aggressive behavior. The close relationship of these disorders is reflected in the fact that 30-80% of children diagnosed with ADHD are also felt to have ODD or CD [23]. The similarities of ADHD, ODD and CD are further reflected in the fact that ADHD is commonly classified not as an academic disorder, but rather as the mildest of the behavioral disorders.

For the sake of discussion in this report, learning and developmental disabilities can be organized in an admittedly over-simplified framework using three intersecting arrays of related disorders. Each array can be thought of

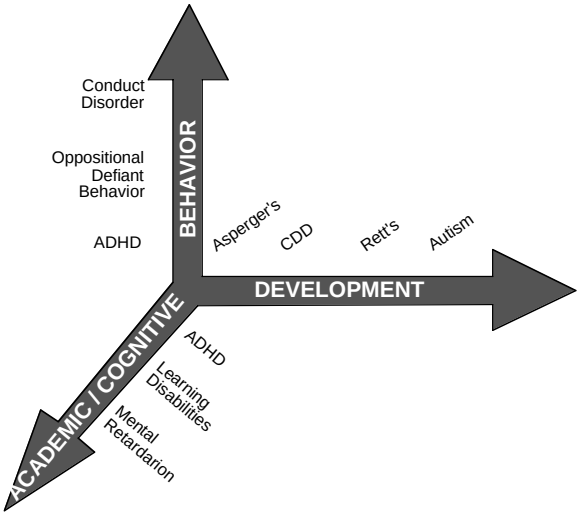
EXAMPLE OF SYMPTOM OVERLAP (OR NONSPECIFICITY): "STEREOTYPIES":

Restricted, repetitive patterns of behavior and interests, which characterize pervasive developmental disorders, are referred to as "stereotypies." Although

stereotypies are a necessary condition for making the diagnosis of a pervasive developmental disorder, they are not unique to pervasive developmental disorders. They are also present in mental retardation, schizophrenia, Parkinson's Disease and obsessive-compulsive disorder.[25]

Behavioral disorders are also prominently expressed well beyond the classroom setting. Children are labeled with these disorders when their behavior is marked by the predominance of disruptive or aggressive features.

Spectrum of Developmental Disorders



as a different dimension of function, along which the syndromes represent various degr ees of disability . From this perspective, Asper ger 's and autism represent increasing impairment along a developmental axis including social dysfunction, restricted behaviors, and impaired communication. On a second axis, ADHD, ODD and CD can be seen as progressive expressions of disr uptive/aggr essive behavior . On a third axis, ADHD, LD, and MR can be considered progressive expressions of cognitive dysfunction.

For the purpose of discussion, developmental disorders can be organized using a framework of intersecting arrays. Each array represents a different dimension of function, along which the syndromes represent varying degrees of disability. Each dimension can be seen as a spectrum of disability, in which there is considerable overlap between the various disorders.

DEFINITION - *Cognitive:*

Pertaining to the process of the mind, such as perceiving, thinking, or remembering.

Developmental Syndromes: Conventional Clinical Classifications

SYNDROME	DEFINITION	POSSIBLE COGNITIVE/ BEHAVIORAL EXPRESSIONS
"Academic" Disorders		
Learning Disorders - Including Disorders of Reading, Mathematics, Written Expression; and also Communication Disorders, including Disorders of Expressive Language, Mixed-Receptive Expressive Language, Phonological, Stuttering	Disorder in one or more of basic processes involved in understanding or using language including reading, writing and mathematical skills. Achievement on standardized tests significantly lower than expected for age, schooling and level of intelligence (2 standard deviations). Interfere with academic achievement or activities of daily life that require those skills.	Cognitive processing deficits Communication deficits
"Academic" and Behavioral Disorders		
Attention Deficit Hyperactivity Disorder (ADHD) Types: • Combined • Predominately Hyperactive • Predominately Inattentive	Persistent pattern of at least 6 symptoms of inattention and/or hyperactivity-impulsivity for at least 6 months that were present prior to age 7, that impair normal functioning, and that appear in 2 or more settings. Impairment in social, academic or occupational functioning.	Hyperactivity Impulsivity Inattention
Behavioral Disorders		
Conduct Disorders including those that are Mild, Moderate and Severe	A repetitive and persistent pattern of behavior in which the basic rights of others or major age-appropriate societal norms or rules are violated. At least three (or more) of following criteria (in past 12 months with one criterion in last 6 months): Aggression to people and animals, destruction of property, deceitfulness, theft, serious violation of rules. Little empathy/concern for well being of others. Childhood Onset Type and Adolescent Onset Type.	Aggression Fighting Stealing Vandalism Blaming others Low self-esteem Poor tolerance irritability, temper tantrums Lying Truancy Substance abuse

Developmental Syndromes: Conventional Clinical Classifications continued

SYNDROME	DEFINITION	POSSIBLE COGNITIVE/ BEHAVIORAL EXPRESSIONS
Behavioral Disorders		
Oppositional Defiant Disorder	Pattern of negativistic, defiant, disobedient and hostile behavior toward authority figures for at least 6 months. Onset usually prior to age 8, not later than early adolescence, with symptoms increasing with age. Must exhibit at least 4 of the following behaviors –loses temper, argues with adults, defies rules, deliberately annoys, blames others, angry, resentful, spiteful, overreactive.	Hostility Verbal aggression Anger
Developmental Delays		
Mental Retardation – Including Mild, Moderate, Severe, Profound, Unspecified	Significantly sub-average intellectual functioning (I.Q. 70 or below—at least 2 standard deviations below the mean) WITH significant limitation in adaptive functioning. Onset prior to age 18.	Mental retardation Deficits in a range of cognitive/behavior traits
Pervasive Developmental Disorders		
Asperger's Syndrome	Severe and sustained impairment in social interaction with restricted, repetitive patterns of behavior, interest and activities.	Motor delays, motor clumsiness Idiosyncratic or circumscribed interests Problems with empathy and modulation of social interaction
Autism	Impaired social interaction, impaired communications skills, restricted and stereotyped repertoire of activity and interests. Must have total of six characteristics in above 3 categories. Onset prior to age 3.	Abnormal non-verbal gestures Delay in or lack of spoken language with no other form of compensation Hyperactivity Attention deficit Aggression Violence to self Repetitive motor mannerisms

Developmental Syndromes: Conventional Clinical Classifications continued

SYNDROME	DEFINITION	POSSIBLE COGNITIVE/ BEHAVIORAL EXPRESSIONS
Pervasive Developmental Disorders		
Rett's Disorder	Regressive development physically and mentally after normal development in first-second year of life. Usually associated with severe or profound mental retardation. Onset usually prior to age 4. Reported only in females.	Deceleration of head growth Severe psychomotor retardation Cognitive deficits Motor dysfunction Impaired social interaction Stereotyped hand movements
Childhood Disintegrative Disorder	Regression in multiple areas of functioning after at least 2 years of apparently normal development. Loss of previously acquired skills in expressive or receptive language, social skills or adaptive behavior, bowel or bladder control, play, or motor skills. Usually associated with severe mental retardation. Onset between ages 3-4. More common in males.	Delay or lack of speech Repetitive and stereotyped behavior Cognitive deficits Motor dysfunction Impaired social interaction

Notes:

1. Definitions are those from the Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV), although definitions of learning disabilities as a general category may change from state to state and also as classified for funding for treatment purposes. See Appendix for references.

2. Many of the syndromes have overlapping traits with others. These have not been detailed.

Public Health Impact

Behavioral problems, learning disabilities and developmental delays have important public health effects in the United States, as demonstrated by the following statistics:

- It is estimated that 5% - 10% of the school age population have learning disabilities. [1] [2] 52% of all students in special education in public schools have learning disabilities. This equals about 2.25 million children. [3]

READING DISABILITY MAY HAVE CONSEQUENCES BEYOND SCHOOL[17]

"The eager third graders experiencing reading difficulties become, in turn, the frustrated ninth graders who drop out of school, the barely literate 25-year-olds who read at a fourth or fifth grade level, the thirty-something generation who are unemployed, and the defeated adults now raising families and needing public assistance."

- Nearly 40% of adults with learning disabilities have significant difficulties with employment or social adjustment. [4]
- Individuals with ADHD obtain less schooling and have poorer vocational achievement than their peers. [5] 62% of students with learning disabilities were unemployed one year after graduating high school. [6]
- 35% of all students identified as learning disabled drop out of high school. This is twice the rate of their peers without disabilities. [7]
- 50% of females with learning disabilities will be mothers (many of them single) within 3-5 years after leaving high school. [8]
- Up to 60% of adolescents in treatment for substance abuse have undetected learning disabilities. [9]
- Learning disabilities and substance abuse are the most common impediments to the employment of welfare clients. [10]
- 31% of adolescents with learning disabilities will be arrested 3-5 years after leaving high school. [11] The only adolescents with a higher arrest rate were those with emotional disturbance (57.6%). [12]
- Adolescents with learning disabilities are disproportionately involved with the juvenile justice system. 50% of juvenile delinquents tested were found to have undetected learning disabilities. The cost of juvenile incarceration is between $35,000 to $60,000 per year per person. [13]

Nearly 40% of adults with learning disabilities have significant difficulties with employment or social adjustment.

- Learning disabled individuals are more likely to be found delinquent in juvenile court, to be taken into custody by the police, and to receive more severe penalties because of their inability to effectively communicate or understand their situation. [14] [15]
- It is estimated that 42% of adults in correctional institutions were eligible for special education. [16]

Significant public funds and resources are spent each year on diagnosis, treatment and the study of these disorders. Implementation, design and adequate funding of appropriate treatment and prevention programs to best serve the children and public will require coordinated efforts on the part of parents, teachers, policy makers, researchers, and the government.

Social Impact

Children with learning disabilities, developmental delays, and behavioral disorders encounter a wide range of difficulties in learning, speaking, reading, writing, mathematics, attention, and behavior that put them at substantial risk for failure in the classroom or the workplace.[19] For many, these difficulties are lifelong and continue to cause hardships in adulthood. For example, according to employers, individuals with learning disabilities have a harder time keeping a job, learning new occupational skills, and getting along with co-workers.[20]

Children with these disorders may encounter a number of social, inter - personal, and emotional difficulties that are associated with their disability/ disabilities. For example, students with learning disabilities are often alienated,

LEARNING DISABILITIES WERE RECOGNIZED AS A FEDERALLY DESIGNATED HANDICAPPING CONDITION IN 1968

Public Law 94-142, the Education for all Handicapped Children Act of 1975, was reauthorized and amended several times and reenacted as the Individuals with Disabilities Education Act of 1990 (IDEA) (PL-476) and the Americans with Disabilities Act of 1990 (ADA) (PL101-336).[18]

Ever since the first effort to define learning disabilities in 1962 there has been controversy surrounding the diagnosis, interventions, and educational policies regarding learning disabilities. Some of the controversy can be attributed to the fact that definitions used by educators are not always the same as those used by mental health (psychological) professionals and/or those engaged in neurological research. Establishing a definition for a learning disability is important because governmental research, policy and funding, such as the number of children eligible for special education services and what these services will be, are based on the individual meeting the appropriate criteria. For example, it is not unusual for a learning disability condition or diagnosis to change when an individual moves from one state to another. *Definitions of Learning Disabilities are described in further detail in the Appendix.*

isolated, and misunderstood, which can lead to difficulties with social adjustment and life goal attainment. [21] They also are more likely to engage in substance abuse, become delinquent, commit crimes as adults, and have higher rates of suicide and mental illness than are other students. [22] The risk of these difficulties is enhanced if the individual is from a lower social economic status. Many of these same difficulties are associated with those children diagnosed with ADHD, as they are more likely to obtain less schooling, have poorer vocational achievement, and have a higher prevalence of mood disorders and anxiety disorders. [23]

There is also likely to be additional stress placed on the family of a child diagnosed with a learning, developmental, and/or behavioral disor der . Even if a developmentally delayed child lives at home, the additional costs of adequately caring for such a child can be staggering for the family . Depending on the level of disability , the child may need additional psychological, medical, and/or educational services, which may not be completely covered by medical insurance and/or other funding sources. In addition, parents or caretakers of developmentally delayed children may encounter difficulties such as a lack of programs to sustain their children in appropriate educational environments and/or supported living situations. Other difficulties, including lack of respite care and other support services, may occur in terms of funding and/or finding adequate living and work situations when their children become adults. Many quality of life issues are raised for children with the aforementioned disorders. Adequate funding of appropriate services is a public health concern that needs to be addressed.

Footnotes, Part 1

1 Mash EJ, Terdal LG. Assessment of child and family disturbance:a behavioral-system approach. In: Assessment of Childhood Disorders.Third Edition. Eds. Mash EM, Terdal LG. New York: Guilford Press, 1997, p.3.

2 Mann CC. Behavioral genetics in transition. Science 264:1686-1689, 1994.

3 Stone WL, Ousley OY. Pervasive developmental disorders: autism. In: Disorders of Development and Learning. Second Edition. Ed. Wolraich ML. St. Louis: Mosby, 1996, p.381.

4 Baumgaertel A, Copeland L, Wolraich ML. Attention deficit hyperactivity disorder. In: Disorders of Development and Learning. Second Edition. Ed. Wolraich ML. St. Louis: Mosby, 1996, p.432.

5 Coyle J. Foreward. Handbook of Developmental Neurotoxicology. Eds. Slikker W, Chang LW. San Diego: Academic Press, 1998, p. xv.

6 Taylor HG. Critical issues and future directions in the development of theories, models, and measurements for attention, memory, and executive function. In:Attention, Memory and Executive Function. Eds. Lyon GR, Krasnegor NA. Baltimore: Paul H. Brookes Publishing Co, 1996, p.405.

7 Stone WL, Ousley OY. Pervasive developmental disorders: autism. In: Disorders of Development and Learning. Second Edition. Ed. Wolraich ML. St. Louis: Mosby, 1996.

8 Baumgaertel A, Copeland L, Wolraich ML. Attention deficit hyperactivity disorder. In: Disorders of Development and Learning. Second Edition. Ed. Wolraich ML. St. Louis: Mosby, 1996.

9 Mash EJ, Terdal LG. Assessment of child and family disturbance:a behavioral-system approach. In: Assessment of Childhood Disorders.Third Edition. Eds. Mash EM, Terdal LG. New York: Guilford Press, 1997, p.17.

10 Mash EJ, Terdal LG ibid, p.16.

11 Dreger RM, Lewis PM, Rich TA et al. Behavioral classification project. Journal of Consulting Psychology 28:1-13, 1968. Cited in Assessment of Childhood Disorders.Third Edition. Eds. Mash EM, Terdal LG. New York: Guilford Press, 1997,p.16.

12 Gorham KA, DesJardins C, Page R. et al. Effect on parents. In: Issues in the Classification of Children, Ed. Hobbs N, Vol. 2, p. 154-188. San Francisco:Jossey-Bass, 1974. Cited in Assessment of Childhood Disorders.Third Edition. Eds. Mash EM, Terdal LG. New York: Guilford Press, 1997,p.16.

13 Achenbach TM, Edelbrock CS. The classification of child psychology: A review and analysis of empirical efforts. Psychological Bulletin 85:1275-1301. 1978. Cited in Mash ibid, p.16.

14 Mash EJ, Terdal LG. Assessment of child and family disturbance:a behavioral-system approach. In: Assessment of Childhood Disorders.Third Edition. Eds. Mash EM, Terdal LG. New York: Guilford Press, 1997.

15 Lyon GR. Preface. Attention, Memory and Executive Function. Eds. Lyon GR, Krasnegor NA. Baltimore: Paul H. Brookes Publishing Co, 1996

16 Taylor HG. Critical issues and future directions in the development of theories, models, and measurements for attention, memory, and executive function. In:Attention, Memory and Executive Function. Eds. Lyon GR, Krasnegor NA. Baltimore: Paul H. Brookes Publishing Co, 1996.

17 Wolraich ML. Ed. Disorders of Development and Learning. Second Edition. Ed.. St. Louis: Mosby, 1996.

18 Wolraich ML. Ibid.

19 Barkley RA. Attention-deficit/hyperactivity disorder. In: Assessment of Childhood Disorders.Third Edition. Eds. Mash EM, Terdal LG. New York: Guilford Press, 1997, p.77.

20 Stone WL, Ousley OY. Pervasive developmental disorders: autism. In: Disorders of Development and Learning. Second Edition. Ed. Wolraich ML. St. Louis: Mosby, 1996, p.389.

21 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition. Washington: American Psychiatric Association. 1994.

22 McMahon RJ, Estes AM. Conduct problems. In: Assessment of Childhood Disorders.Third Edition. Eds. Mash EM, Terdal LG. New York: Guilford Press, 1997.

23 Baumgaertel A, Copeland L, Wolraich ML. Attention deficit hyperactivity disorder. In: Disorders of Development and Learning. Second Edition. Ed. Wolraich ML. St. Louis: Mosby, 1996,p.428.

24 Baumgaertel A, Copeland L, Wolraich ML.ibid.

25 Ridley RM. The psychology of perseverative and stereotyped behavior. Prog Neurobiol Oct:44(2):221-31, 1994.

Footnotes, Part 2

1 American Psychiatric Association. Diagnostic and Statistical Manual, Fourth Edition. Washington, DC. 1994.

2 Parrill M. Research Implications for health and human services. In Cramer SC, Ellis E. Learning disabilities: Lifelong issues. Paul H. Brookes Publishing Company, Inc, Baltimore, 1996. Pgs. 277-293.

3 U.S. Department of Education. In Cramer SC, Ellis E (eds). Learning disabilities: Lifelong issues. Paul H. Brookes Publishing Company, Inc., Baltimore; 1996. P.xxx (introduction).

4 American Psychiatric Association. Diagnostic and Statistical Manual, Fourth Edition. Washington, DC. 1994.

5 American Psychiatric Association, Diagnostic and Statistical Manual. Fourth Edition. Washington, DC. 1994.

6 Wagner M, Newman L et al. In Cramer SC, Ellis E (eds). Learning disabilities: Lifelong issues. Paul H. Brookes Publishing Company, Inc., Baltimore; 1996.

7 Wagner M, Newman L et al. In Cramer SC, Ellis E (eds). Learning disabilities: Lifelong issues. Paul H. Brookes Publishing Company, Inc, Baltimore; 1996. p.xxx (introduction).

8 Wagner M, Newman L et al. In Cramer SC, Ellis E (eds). Learning disabilities: Lifelong issues. Paul H. Brookes Publishing Company, Inc., Baltimore; 1996. p.xxx (introduction).

9 Wagner M, Newman L et al. In Cramer SC, Ellis E (eds). Learning disabilities: Lifelong issues. Paul H. Brookes Publishing Company, Inc., Baltimore; 1996. p.xxx (introduction).

10 Office of the Inspector General. In Cramer SC, Ellis E (eds). Learning disabilities: Lifelong issues. Paul H. Brookes Publishing Company, Inc., Baltimore; 1996. p.xxx (introduction).

11 Wagner M, Newman L et al. In Cramer SC, Ellis E (eds). Learning disabilities: Lifelong issues. Paul H. Brookes Publishing Company, Inc., Baltimore; 1996. p.xxx (introduction).

12 Parrill M. Research Implications for health and human services. In Cramer SC, Ellis E (eds). Learning disabilities: Lifelong issues. Paul H. Brookes Publishing Company, Inc., Baltimore; 1996. Pgs. 277- 293.

13 McGee TP. Reducing school behavior and preventing criminal behavior. In Cramer SC, Ellis E (eds). Learning disabilities: Lifelong issues. Paul H. Brookes Publishing Company, Inc., Baltimore; 1996. Pgs. 229-233.

14 Eggleston CR. The justice system. In Cramer SC, Ellis E (eds). Learning disabilities: Lifelong issues. Paul H. Brookes Publishing Company, Inc., Baltimore; 1996. Pgs. 197-201.

15 Dickman GE. The link between learning disabilities and behavior. In Cramer SC, Ellis E (eds). Learning disabilities: Lifelong issues. Paul H. Brookes Publishing Company, Inc., Baltimore; 1996. Pgs. 215-228.

16 Eggleston CR. The justice system. In Cramer SC, Ellis E (eds). Learning disabilities: Lifelong issues. Paul H. Brookes Publishing Company, Inc., Baltimore; 1996. Pgs. 197-201.

17 Shaywitz SA, Shaywitz B. Unlocking learning disabilities: The neurological basis. In Cramer SC, Ellis E (eds). Learning disabilities: Lifelong issues. Paul H. Brookes Publishing Company, Inc., Baltimore; 1996. Pgs. 255-260.

18 Lyon GR. The state of research. In Cramer SC, Ellis E (eds). Learning disabilities: Lifelong issues. Paul H. Brookes Publishing Company, Inc., Baltimore; 1996. Pgs. 3-61.

19 Alexander D. Learning disabilities as a public health concern. In Cramer SC, Ellis E (eds). Learning disabilities: Lifelong issues. Paul H. Brookes Publishing Company, Inc., Baltimore; 1996. Pgs.249-253.

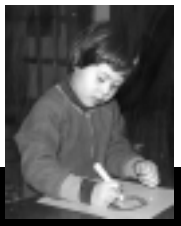
20 Alexander D. Learning disabilities as a public health concern. In Cramer SC, Ellis E (eds). Learning disabilities: Lifelong issues. Paul H. Brookes Publishing Company, Inc., Baltimore; 1996. Pgs.249-253.

21 Eggleston CR. The justice system. In Cramer SC, Ellis E (eds). Learning disabilities: Lifelong issues. Paul H. Brookes Publishing Company, Inc., Baltimore; 1996. Pgs. 197-201.

22 Dickman GE. The link between learning disabilities and behavior. In Cramer SC, Ellis E (eds). Learning disabilities: Lifelong issues. Paul H. Brookes Publishing Company, Inc., Baltimore; 1996. Pgs. 215-228.

23 American Psychiatric Association. Diagnostic and Statistical Manual, Fourth Edition. Washington, DC. 1994.

Chapter 4



The Long Road From Research to Real Life

The Widening Gap

In the past two decades, several disciplines have emerged that open exciting new perspectives in child development and learning. As summarized by G. Reid L yon, a noted researcher in child development, "An explosion of research activity in attention, memor y, and executive function has occurred since the mid-1980s. Unfor tunately , the literatur e relevant to these domains is so voluminous that the important converging trends in the data are sometimes difficult to identify and to apply to development and learning in children. This difficulty is exacerbated by the application of divergent theories, methodologies, and vocabularies that are used to identify and describe normal and atypical development…" [1]

While these comments were made in reference to particular areas of research, the problems they describe pervade the field of learning and development in general. W ith so much new information on so many fronts, clinicians and the public are hard pressed to absorb new developments.

This explosion of information in child development results from a variety of new technologies and methods. For example, developments in molecular biology revolutionized molecular genetics and molecular neur ochemistr y, permitting us to explore a variety of domains within the cell, including the human genome, and the processes of gene expression, neurotransmitter production, and cellular communication. Powerful new neuroimaging technologies, including magnetic resonance imaging and positron emission tomography (PET scans), vastly improved the understanding of brain structure. Because these technologies can selectively highlight regions of the brain that are mentally active at the time of testing, neuroimaging studies can now be used to explore the link between brain structure and function in real time.

Other critical improvements occurred in spectrometry and gas chromatography . These developments enabled scientists to measure unprecedented tiny concentrations of chemicals, permitting the identification and testing of previously unrecognized toxicants. In addition, the application of

DEFINITION - *Genome:*

The complete set of genetic information contained in the chromosomes..

new computer technologies to the study of cognition generated entirely new models for understanding how the brain processes information.

With the application of these new technologies, a variety of new, increasingly specialized fields have emerged. With increasing specialization, it is no surprise to see widening gaps between the disciplines of child development, and between the domains of research and clinical practice. Several factors may contribute to this unfortunate rift.

1. Much of the new information is so highly technical it is understood only by experts within the field from which the information originates.
2. Researchers and clinicians often have little contact. Consequently research agendas may not adequately reflect the concerns of clinicians or parents.
3. Research is often constrained by technical and methodologic concerns.
4. Funding sources may preferentially favor research with marketable technical applications rather than research relevant to less lucrative clinical concerns.
5. Busy clinicians may have limited interest in new academic topics lacking clear clinical applications.

By taking an interdisciplinary approach, this report attempts to narrow a part of the gap between research, clinical practice and public understanding. An interdisciplinary discussion on child development also supports the evolution of an over-arching bio-behavioral framework needed to integrate divergent perspectives on child development.[2]

We focus on recent findings in developmental neurotoxicology because this research readily translates into simple preventive measures to help protect children at risk. In addition to having practical applications, the research findings of developmental neurotoxicology are also of considerable academic interest. Since this research dovetails with research in other domains, particularly neuroscience and behavioral genetics, it furthers our understanding of the biological basis of development in general. In promoting a wider dialogue, we also hope to make research findings from the several "biological" domains more accessible to parents and clinicians.

Traits: A Bridge Between Divergent Disciplines (Neurotoxicology, Genetics and the Clinical Disorders)

Child development, like other behavioral sciences often uses categories to describe learning, behavior and development. [3] Categories focus on disease entities such as ADHD, autism, and other specific disorders. Categories are inherently dichotomous, meaning they imply only two possibilities: the child either has or does not have a particular disorder. Alternatively, behavior can be described using the concepts of abilities or traits, which vary as gradations along a continuum. [4] [5] Short term memory, impulsivity, and attentional ability are examples of traits relevant to learning, behavior and development. There is growing consensus that a better understanding of these traits is critical to understanding the clinical disorders. [6]

Deficits in traits/abilities appear to correspond to clinical syndromes, but relationships have not been clearly established. [7] For example, deficits in the trait attention appear to correspond to the clinical syndrome ADHD, however the relationship is not straightforward. For example, studies show that boys with ADHD perform poorly on measures of sustained attention, but are not impaired in the ability to selectively focus their attention. [8] [9] Other studies show that attention deficits in ADHD depend on the setting, and that the mere presence of an adult in the room at the time of testing improves attention measures. [10] While the relationship of traits and clinical syndromes is being explored, concurrent research is attempting to better define and understand the traits. [11]

Because traits are the subject of research in a variety of fields, they provide a basis for interdisciplinary dialogue. This was illustrated in the focus of a recent National Institute of Child Health and Human Development conference on attention, memory and executive function, three traits of central importance to development and learning. Focusing on traits permitted researchers and clinicians from a variety of domains, including psychology, neurology, pediatrics and special education, to exchange information on methods, concepts, and findings. Since a large body of genetic research has also focused on cognitive and behavioral traits, behavioral genetics can also be integrated into the larger discussion utilizing traits as a common denominator.

Because traits are the subject of research in a variety of fields, they provide a basis for interdisciplinary dialogue. Aside from linking the divergent disciplines of child development, traits/abilities are well suited to research because they can be tested and quantified as specific functions.

Traits As Useful Outcome Measures in Research

Aside from linking the divergent disciplines of child development, traits/abilities are well suited to research because they can be tested and quantified as specific functions. In toxicology, researchers increasingly

"examine specific functions and processes rather than milestones, accumulated knowledge or general abilities."[12] For example, the effects of in-utero cocaine exposure have been detected at various stages of infancy and childhood using tests of specific function such as visual recognition memory or attentional ability. In contrast, standardized tests of general cognitive ability, (such as the Bayley Scales of Infant Development, or the Stanford-Binet Intelligence Scale) have shown little differences between exposed and unexposed children.[13] Likewise, specific tests of attention, such as the Continuous Performance Test, are more sensitive than global assessments or neurological exam to low levels of prenatal mercury exposure. As a computer-assisted neuropsychological test, the Continuous Performance Test is sensitive to "minute differences in responses… [and] therefore statistically superior in detecting subtle neurobehavioral dysfunction."[14]

THE CONTINUOUS PERFORMANCE TEST: AN EXAMPLE OF A TEST FOR ATTENTIONAL ABILITY (from Grandjean[17])

In the Continuous Performance Test, children watch a series of animal silhouettes flashed on a screen. The child's task is to press a button every time a cat appears over a 4-minute interval. The test is scored by the number of missed responses and the average reaction time during the last three minutes. This test is considered to be a measure of vigilance, a particular kind of attention.

Clinical syndromes like ADHD or Asperger's syndrome, may be problematic in research because they are categorical rather than quantitative, and because their definitions continue to change over time.[15] In addition, clinical syndromes translate poorly into animal models which are often used to study the effects of toxicants on neurodevelopment. This is illustrated by the difficulties developing animal models for autism research. As summarized by Patricia Rodier, a leading researcher in the field, "..the behavioral criteria by which autism and related disorders are diagnosed…do not invite animal experiments…Much of our most specific behavioral information… relates to behaviors that probably are exclusive to humans, such as language, associative pointing, and imitation."[16]

For all these reasons, the effects of various factors on neurodevelopment are often measured on specific behavioral and cognitive abilities rather than on clinical syndromes or global measures of development or intelligence. Focusing on traits generally provides a common denominator between different fields of research, produces more reliable and sensitive measures, and allows us to study the effects of toxicants and genetics on the "normal" population as well as on those with diagnostic labels.

1 Lyon GR. Preface. Attention, Memory and Executive Function. Eds. Lyon GR, Baltimore: Paul H. Brookes Publishing Co., 1996, p.xv.

2 Taylor HG. Critical issues and future directions in the development of theories, models, and measurements for attention, memory, and executive function. In:Attention, Memory and Executive Function. Eds. Lyon GR, Krasnegor NA, Baltimore: Paul H. Brookes Publishing Co., 1996, p.400-401.

3 Mash EJ, Terdal LG. Assessment of child and family disturbance:a behavioral-system approach. In: Assessment of Childhood Disorders.Third Edition. Eds. Mash EM, Terdal LG. New York: Guilford Press, 1997, p.16-19.

4 Plomin R, DeFries JC. The genetics of cognitive abilities and disabilities. Scientific American, May, 1998:62-69.

5 McClearn GE, Volgler GP, Plomin R. Genetics and behavioral medicine. Behavioral Medicine, 22:93-101, 1996.

6 Taylor HG. Critical issues and future directions in the development of theories, models, and measurements for attention, memory, and executive function. In:Attention, Memory and Executive Function. Eds. Lyon GR, Krasnegor NA. Baltimore: Paul H. Brookes Publishing Co., 1996, p.401-405.

7 Taylor HG. Ibid. p.407.

8 Taylor HG. Ibid. p. 406.

9 Barkley RA. ADHD and the Nature of Self-Control. New York: Guildord Press, 1997, p. 10.

10 Barkley RA. Ibid, p.12.

11 Taylor HG. Ibid. p.401-405.

12 Fried PA. Behavioral evaluation of the older infant and child. In: Handbook of Developmental Neurotoxicology. Eds. Slikker W, Chang LW. San Diego: Academic Press, 1998, p.474-476.

13 Fried PA. Ibid, p. 476.

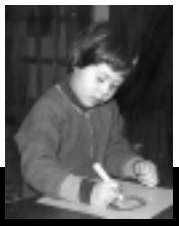
14 Grandjean P, Weihe P, White RF, et al. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. Neurotoxicology and Teratology 19(6):417-428, 1997.

15 Mann CC. Behavioral genetics in transition. Science 264:1686-1689, 1994.

16 Rodier PM. Neuroteratology of autism. In: Handbook of Developmental Neurotoxicology. Eds. Slikker W, Chang LW. San Diego: Academic Press, 1998, p.662.

17 Grandjean P, Weihe P, White RF, et al. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. Neurotoxicology and Teratology 19(6):417-428, 1997.

Chapter 5



Multiple Causes of Developmental, Learning and Behavioral Disability

Introduction

Diverse influences contribute to developmental, learning and behavioral disability. These influences are generally divided into two broad groups: genetic factors, determined by hereditary information contained in human chromosomes, and environmental factors, which include all non-genetic influences. Environmental influences can be further subdivided into several categories, including physical, chemical, infectious and social. Chemical factors, which are the focus of this report, are broadly defined as synthetic and naturally occurring substances to which an individual is exposed. Social-environmental factors are defined as encompassing family, cultural and socioeconomic variables.

It is widely recognized that influences from various domains interact in very complex ways,[1,2,3] though research has generally focused on one domain at a time. As a result, a truly over-arching framework and methodology have yet to be developed to examine the real-world interactions of these influences.

Genes or the Environment: An Outdated Dichotomy

Over the past 20 years, studies of twins and adopted children have clarified important genetic contributions to a variety of cognitive, behavioral and personality traits. Altogether these studies suggest that for many of these traits, heredity accounts for about 50% of the observed differences among individuals.[4,5] Some mistakenly take this as evidence that these traits are genetically determined. According to Robert Plomin, director of the Center for Developmental and Health Genetics at Pennsylvania State University, "research into heritability is the best demonstration…of the importance of the environment." If heredity accounts for 50% of the variability in a trait, the other 50% of variability must be due to environmental influences.[6,7] In other words, genetic and environmental influences seem to be roughly equal in determining many neurocognitive characteristics.[8]

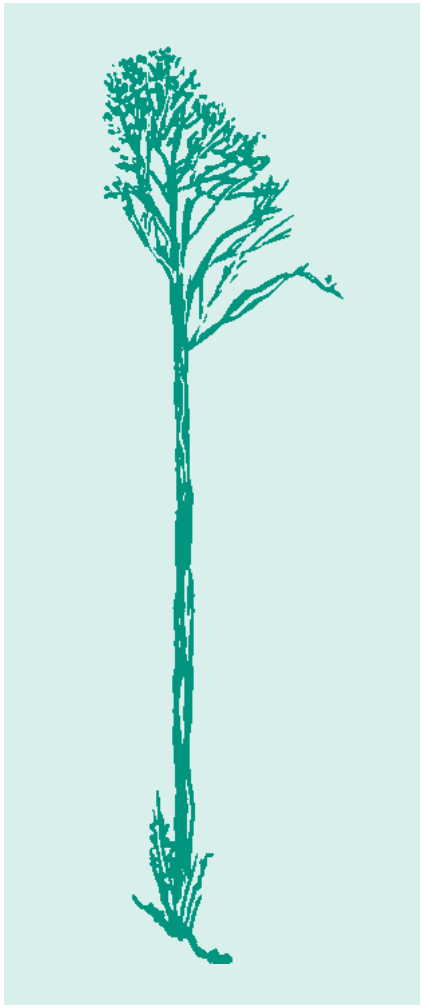
Genetic and environmental influences seem to be roughly equal in determining many neurocognitive characteristics.

DEFINITION - *Genotype:*

The genetic makeup of an individual.

PHENOTYPIC PLASTICITY

Genotype is a term that refers to the specific genetic makeup of an individual, whereas phenotype refers to the traits or characteristics of that individual as they actually appear. For many traits, phenotype is only partially a result of the genotype. Environmental factors encountered during fetal development, or even after birth, also affect the phenotype. The variability of phenotypes for a given genotype or within populations of genetically similar individuals is called phenotypic plasticity.



Among the most dramatic examples of phenotypic plasticity are the marked differences in genetically similar individuals in different environments. For example, in the illustration, the tall thin tree actually grew in a dense forest, where rapid vertical growth was essential in order to compete successfully for light. The genetically similar, short, branched tree grew on a south-facing open slope where there was no competition for light, allowing the tree to grow in a very different manner. In general, phenotypic plasticity is a result of

both the environmental cues that trigger the variable phenotypes and the individual's capacity to respond to those cues, based largely in the genotype. In other words, phenotypic plasticity is a result of gene-environment interactions.

Phenotypic plasticity is of two types.[1] One is the spectrum of phenotypes that may be expressed by a given genotype in a range of different but relatively stable environments. To study this, one would look for the appearance of different traits in genetically similar populations located in different environments. The other type of plasticity refers to the response of individual organisms to variations in a single environment. In this case, either the ability to adapt, or conversely, the susceptibility to adverse effects from even minor environmental fluctuations, particularly during development, reflects the plasticity of the individuals.

In this report, we are largely concerned with the second type of plasticity when we note that, at most, genotype accounts for about 40-60% of the variance in neurodevelopmental traits or disorders, while the remainder is more persuasively explained by environmental factors and gene-environment interactions.

1 Via S. The evolution of phenotypic plasticity: what do we really know? In: Ecological Genetics, Ed: Real L. Princeton University Press, Princeton NJ, 1994

Observers also point out that inferences from these studies are based on the simplistic assumption that genes and the environment have simple additive effects. [9] [10] In fact, current research shows that gene-environment interactions can be extremely complex. As summed up by Plomin and his colleague Gerald McClearn, also from the Center for Developmental and Health Genetics, in a recent review article: "simple approaches to complex phenotypes may lead to misleading or erroneous conclusions. Particularly inappropriate are questions couched in either -or ter ms: Is such and such a trait the result of genes or of environment? Unfor tunately , this type of thinking was promoted for decades by the natur e-versus-nur ture contr oversy , which convinced many academicians that they had to choose sides. W e hope that this brief overview has made apparent the intellectual bankruptcy of this either -or for mulation." [11]

Our approach to developmental disabilities can be informed by medical models for addressing other complex problems with multiple contributing factors. Atherosclerotic heart disease, the cause of heart attacks, is one example of a multifactorial problem in which modern medicine has had relatively good success, markedly reducing the incidence of the disease over the past several decades. [12] [13] [14] [15] Like developmental disability , ather oscler otic heart disease is influenced by a variety of factors, most of which have both genetic and environmental components.

The medical model for approaching atherosclerotic heart disease entails addressing all of the risk factors that are amenable to inter vention: obesity , smoking, elevated blood pressure and cholesterol, diabetes, diet and sedentary lifestyle. Identifying a genetic marker for risk of heart disease, (such as the apolipoprotein E4), does not as of yet trigger specific therapy , but it does indicate the need for more vigorous control of other risk factors. Applying such a model to learning and developmental disorders would argue for eliminating toxicant exposures, since they are readily preventable, and for improving the social environment of children at risk. While genes themselves cannot be altered, the environmental triggers for some genetic diseases can be reduced or eliminated. Clarifying genetic risks factors can also identify the children most in need of additional protection from toxicants and other adverse environmental factors, including social factors.

Rare Diseases Governed by Powerful "OGOD" Genes: the PKU Prototype

In 1984, for the first time, a gene associated with developmental disability was identified and localized within human chromosomes: the gene that causes phenylketonuria, (PKU), a rare disorder that occurs in 1 in 10,000 births. PKU is a prototype "single gene disor der." Such genes ar e also called OGOD genes, a term which stands for "one gene, one disor der."[16] The genetic component of a disease caused by an OGOD gene is controlled by one gene only, unlike the common developmental

DEFINITION - *Phenotype:*

The traits or characteristics of an individual as they actually appear. Phenotype results from the interaction of genotype and the environment.

DEFINITION - *Gene:*

The basic unit of heredity, consisting of a segment of DNA that codes for a particular product, such as an enzyme. Each gene occupies a certain location on a chromosome.

PHENYLKETONURIA (PKU)

In the past PKU was responsible for about 1% of cases of institutionalized mental retardation.[17] When a child inherits the PKU gene from each parent, the child cannot produce the enzyme phenylalanine hydroxylase, which is required to break down the amino acid phenylalanine.[18] This leads to the build up of phenylalanine in the blood, and, since high levels of phenylalanine are harmful to the developing brain, severe brain damage results. As another consequence of high blood phenylalanine levels, a related compound for which the disease is named, phenylketone, appears in the urine.

Simply by reducing phenylalanine in the diet, the build up of toxic metabolites is prevented, and neurologic development proceeds normally. Since phenylalanine, like other amino acids, is a building block of protein, it is found in all protein foods, particularly those high in protein such as fish, eggs, meat, cheese, and peanuts. By lowering the amount of protein in the diet, the trigger for the disease is removed, and the defective gene becomes harmless.

DEFINITION -
Amino acids:

Organic compounds, (marked by the presence of both an amino and a carboxyl group), which are the building blocks of proteins. 20 amino acids are used by the body for growth and metabolism. Some of these can be produced by the liver. The rest must be supplied in the diet.

disorders that are genetically influenced by the combined tiny contributions of a myriad of genes. Diseases that arise from single gene defects are in theory, at least, particularly amenable to intervention since they are associated with a single etiology.

Many rare disorders affecting neurodevelopment have been identified as OGOD disorders by a characteristic inheritance pattern. These rare disorders include other syndromes which, like PKU, are caused by the inability to metabolize various nutrients, including other amino acids and fatty acids. Like PKU, many of these disorders, as well as their developmental effects, are preventable if the problematic nutrient is reduced in the diet, beginning in early life. Specific genes responsible for many of these disorders have been identified. Dietary interventions to prevent these disorders, however, were developed on the basis of clinical studies long before the defective genes were identified. A newborn screening program for PKU, in fact, was in place in Massachusetts more than 20 years before the discovery of the PKU gene. Currently Massachusetts is piloting a newborn screening program that tests for 20 rare, metabolic diseases associated with developmental disability. Dietary interventions for these disorders also predated the identification of their respective OGOD genes.

While molecular genetics has allowed us to identify specific genes and to understand their chemical structure, it has not yet resulted in specific treatments for neurodevelopmental disability. Once a gene is identified, however, molecular genetics studies can begin to clarify how the gene causes disease. While no "quick fixes" have yet resulted from such investigations, it is believed the identification of genes will eventually lead to the development of specific preventions and treatments including environmental and pharmaceutical interventions.

Common Diseases Influenced by Multiple "Puny" Genes

In contrast to the powerful OGOD gene of PKU, genetic influence over the common disorders of learning and development appears to be controlled by the cumulative impact of innumerable genes. Such genes, which "act together in a probablistic fashion to influence a common trait" are referred to as "quantitative trait loci" (QTLs). The implication of this finding is that traits relevant to learning and development are influenced not by single genes, but by many genes, each of which makes a very small contribution towards the trait. In

the words of a prominent behavioral geneticist, each of these genes has a "puny effect on phenotype," that is, the trait as it's actually expressed. [19]

Gene-Environment Interactions: A Spectrum of Complexity

The complexities of gene-environment interactions in neurodevelopment are just beginning to be unraveled. However, it is already clear that there are an astounding variety of ways that genes and the environment can interact. PKU illustrates a straight forward "simple trigger" interaction involving one gene and one environmental factor. The three examples that follow illustrate more complex interactions.

Example 1: Complex Gene-Environment Interactions Mediate Some Effects of Organophosphate Pesticides

The gene-environment interactions that mediate the effects of organophosphate pesticides are extremely complex, and not yet completely understood. Some of the effects of organophosphate pesticides are mediated by at least five different enzymes, [20] some of which have been shown to be influenced by their own set of environmental and/or genetic factors. [21] [22] [23] [24] [25] [26] To illustrate the complexity of this interaction, we will focus on the two enzymes that have been most extensively researched to date: paraoxonase and acetylcholinesterase.

Since their development in the 1930s, organophosphate chemicals have been known to interfere with the function of acetylcholinesterase, an enzyme critical to the proper functioning of the nervous system. Acetylcholinesterase, which is found throughout the nervous system and the body in general,[27] is responsible for breaking down the neurotransmitter acetylcholine. Organophosphate pesticides (OPs), however, inhibit the enzyme and prevent it from performing this critical function.

ACUTE HIGH DOSE ORGANOPHOSPHATE POISONING, AN EXPRESSION OF MAJOR CHOLINESTERASE INHIBITION

Acetylcholinesterase inhibition has long been recognized in acute pesticide poisoning that follows high dose exposures to pesticides. This syndrome consists of over-activation and dysfunction of the considerable portion of the nervous system that uses the neurotransmitter acetylcholine. The consequences of this over-activation/dysfunction are comparable to the clinical effects of "nerve gas" agents designed for chemical warfare, chemicals from which some modern pesticides are derived. The grim picture of acute OP poisoning includes excessive secretions (salivation, tears and bronchial secretions), slowing of the respiratory rate, wheezing and respiratory distress, unstable pulse and blood pressure, muscle twitches followed by weakness or paralysis, vomiting and diarrhea, urinary and fecal incontinence, drowsiness, confusion and ultimately coma and death.[65]

DEFINITION - *Enzymes:*

Protein molecules, coded for by genes, that facilitate chemical reactions.

As a result, acetylcholine builds up at the junctions between nerve cells, first causing over-stimulation, and then complete dysfunction of the involved nerve pathway. At high exposures, this results in the characteristic symptoms of OP poisoning, which are identical to those caused by organophosphate chemical warfare agents.

While large exposures to OPs have long been recognized as causing the nerve gas syndrome, more recent animal studies have suggested that low dose exposures can cause more insidious injury to the developing fetus, and can do so at exposure levels that do not cause clinical symptoms in the mother. Concern about fetal toxicity arises from the fact that very small alterations in acetylcholinesterase function alter levels of acetylcholine in the developing brain. Because the multiplication and differentiation of brain cells are guided by local neurotransmitters, small changes in the concentration of acetylcholine caused by OP exposure may alter the developing architecture of the exposed brain, and impair a variety of behaviors later in life. (OPs also cause other forms of fetal neurotoxicity that are independent of the acetylcholinesterase mechanisms discussed here. See Chapter 6 for details.)

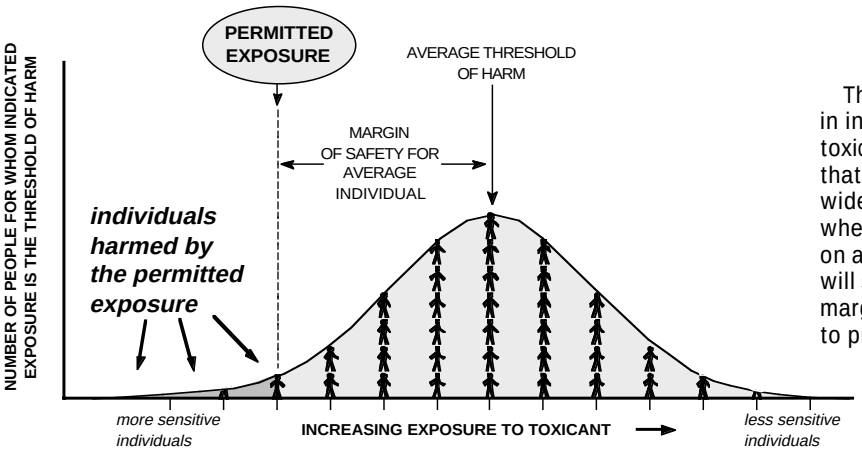
While large exposures to OPs have long been recognized as causing the nerve gas syndrome, more recent animal studies have suggested that low dose exposures can cause more insidious injury to the developing fetus, and can do so at exposure levels that do not cause clinical symptoms in the mother.

Genetic factors markedly modify these OP effects that are mediated through acetylcholinesterase. About 4% of the population carries a gene that produces a poorly functioning form of acetylcholinesterase.[28 29 30 31] This greatly increases an individual's vulnerability to cholinesterase inhibition by OPs, since the diminished reservoir of functioning enzyme is more easily overwhelmed by OPs. Cholinesterase levels are also affected by a variety of other factors including age, body weight, height, gender, pregnancy and liver disease.[32] Thus a host of antecedent factors, both environmental and genetic, interact to determine acetylcholinesterase levels, which in turn help determine the vulnerability of the fetal brain to environmental toxicants, in this case OPs.

Another genetically determined enzyme further modifies an individual's susceptibility to OP toxicity. This enzyme, paraoxonase, which is found in the blood, plays an important role in detoxifying several organophosphate pesticides.[33 34] For example, individuals vary 11-fold in the ability to deactivate the pesticide parathion depending on which gene they carry for this enzyme. Studies in mice show that low levels of paraoxonase increase susceptibility to chlorpyrifos (Dursban),[35 36] a pesticide to which the US population is widely exposed. High paraoxonase activity thus acts as a first line of defense against organophosphate effects. However, those with the relatively inactive form of paroxonase, an estimated 30%-38% of the population,[37 38] will be slower to break down these OPs and consequently more vulnerable to acetylcholinesterase inhibition. If in addition the individual has low levels of acetylcholinesterase, due to either genetic or environmental factors, the individual will have further increased susceptibility to acetylcholinesterase inhibition by organophosphate pesticides.

Thus, as demonstrated in animal studies, levels of OP exposure that are

Spectrum of Vulnerability



There is wide variation in individual sensitivity to toxicant exposure. This means that in a large population with widespread exposures, even when the dosage is acceptable on average, many people will still be hurt. A significant margin of safety is required to prevent such injuries.

well tolerated by some individuals may cause permanent alterations in brain development and behavior in those who are more vulnerable due to a complex mix of genetic, age-related and environmental factors.

Individual differences in vulnerability are widely recognized by scientists, but may be vastly under -estimated by r egulatory agencies. In chemical regulation, for example, EP A has typically used a standard tenfold uncertainty factor to account for all known and unknown human variability in susceptibility to that chemical, including differences between adults and childr en. Yet as pr eviously discussed, paraoxonase activity alone varies by a factor of 11. Since there are four other enzymes that mediate OP toxicity whose variability has not yet been characterized, individual differences in vulnerability to OPs may be several orders of magnitude greater than the 10-fold variation currently recognized by regulatory agencies.

Only after specific research on a particular chemical has been conducted to demonstrate greater differences in vulnerability will regulatory agencies consider implementing policies that are more protective than the standard practice. Unfortunately such "after the fact" regulation allows generations to be harmed in the time required to clarify the complex interactions that create vulnerability .

Example 2: Gene-Environment Interactions in "PANDAS," Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infection

Another important area of gene-environment interactions involve antibody reactions to infection. One example of this interaction has recently been recognized in subsets of patients with several neuropsychiatric disorders. These patients, whose symptoms markedly worsen following infections with Group A streptococcus, (the cause of "strep throat") are considered to have PANDAS. Post-str eptococcal exacerbations have been shown to occur in several disorders in which repetitive behaviors are a prominent feature. These include the neuropsychiatric

DEFINITION - *Obsessive compulsive disorder:*

A disorder characterized by recurrent and persistent thoughts or impulses that are experienced as intrusive and cause marked anxiety. May be accompanied by repetitive behaviors (such as hand washing, ordering, counting) the person feels compelled to do according to rigid rules.

DEFINITION - *Tics:*

Sudden, rapid, recurrent, stereotyped, involuntary motor movements or vocalizations. May include actions such as eye blinking, neck jerking, facial grimacing, stamping, and repeating words out of context. They are typically exacerbated by stress, and stop during absorbing activities and sleep.

DEFINITION - *Tourette's Disorder:*

A syndrome consisting of multiple motor and vocal tics causing significant impairment in social or occupational functioning.

DEFINITION - *Antigen:*

A protein or carbohydrate marker on the surface of a cell that identifies the cell as "self" or "non self".

syndrome obsessive-compulsive disorder (OCD), and two involuntary movement disorders, tics and Tourette's syndrome. [39] [40] While post-streptococcal exacerbations have not been documented in autistic children, limited immunologic data suggest that many autistic children have the same genetic susceptibility to post-streptococcal immune reactions. [41]

The clinical significance of PANDAS has not yet been clarified. However, several lines of evidence support an emerging consensus that PANDAS represents a valid diagnostic construct[42] and that PANDAS results from a unique gene-enviroment interaction. One line of evidence involves a series of immunologic studies. In these investigations, patients with PANDAS have been shown to carry an immune marker in the blood (B lymphocytes with D8/17 antigen), which has been previously identified as a marker of susceptibility to rheumatic fever, a serious inflammatory disease that occasionally follows streptococcal infection. A high incidence of OCD and involuntary movement disorders in rheumatic fever provides a second, clinical line of evidence supporting a link between streptococcal infection and neuropsychiatric disease.[43] [44]

There is also limited neuroimaging support for the PANDAS construct. This is provided by a case report in which serial magnetic resonance imaging (MRI) studies revealed acute enlargement in a particular area of the brain (basal ganglia) concurrent with post-streptococcal exacerbations of OCD. [45] And finally, the construct is supported by a recent National Institute of Health study that showed therapies that reduce immune reactions (plasma exchange and intravenous immunoglobulin) are effective in reducing symptom severity in children with post-streptococcal OCD, Tourette's syndrome and tic disorders. [46]

An autoimmune mechanism has been proposed that suggests PANDAS result from streptococcal antibodies that cross react with critical brain structures (basal ganglia) in genetically susceptible children. [47] [48] [49] [50] [51] This proposed mechanism as well as the clinical significance of the PANDAS syndrome will need to be further clarified by larger, more comprehensive prospective studies that track infectious, immunologic and neuropsychiatric events and outcomes.

Example 3: Gene-Environment Interactions Affecting Lead Metabolism

Gene-environment interactions have also been identified that affect the way the body handles lead. These interactions involve a gene coding for the delta ALA enzyme (delta aminolevulinic acid dehydratase), which has been shown to affect lead metabolism, bone storage and blood lead levels. While studies have begun to understand how the gene influences the way the body handles lead, the influence of the gene on the neurotoxicity of lead has not yet been clarified. [52] [53] [54] [55] [56] [57] [58] [59] [60]

The Role of the Social Environment

Toxicants and genetics have emerged as important influences in learning and development over the past two to three decades. The important role of the social environment in human development,

however, has been recognized for most of the 20th century.[61] A large body of research documents the associations between social environmental factors and developmental outcomes.[62] For instance, good parental mental health, social supports, education and parenting style characterized by reciprocity have all been associated with improved developmental outcomes. A large scale intervention study has also shown that social supports, parenting skills training and high quality early childhood education improve developmental outcomes in high risk children.[63] [64]

As a practical matter, the importance of the social environment is underscored by the fact that both the assessment of developmental disability as well as management interventions occur mainly in the domain of the social environment. The psychologists and educators who deal with the bulk of learning and developmentally disabled children are generally trained in behavioral traditions that focus on the social environment. In contrast, toxicology and genetics have not yet been routinely translated into the clinical domain, with the notable exception of medical screening programs that test infants for lead, PKU, hypothyroidism and a variety of rare metabolic diseases caused by gene defects.

The importance of the social environment is extensively addressed in other literature. We will therefore not discuss the social environment further in this report except to acknowledge its importance as both a causal factor and as a therapeutic modality in learning and developmental disabilities.

An autoimmune mechanism has been proposed that suggests PANDAS result from streptococcal antibodies that cross react with critical brain structures (basal ganglia) in genetically susceptible children.

1 Mash EJ, Terdal LG. Assessment of child and family disturbance:a behavioral-system approach. In: Assessment of Childhood Disorders.Third Edition. Eds. Mash EM, Terdal LG. New York: Guilford Press, 1997, p. 21-22.

2 Plomin R, Craig I. Human behavioral genetics of cognitive abilities and disabilities. BioEssays 19(12):1117-1124, 1997.

3 Taylor HG. Critical issues and future directions in the development of theories, models, and measurements for attention, memory, and executive function. In:Attention, Memory and Executive Function. Eds. Lyon GR, Krasnegor NA. Baltimore: Paul H. Brookes Publishing Co., 1996,p.401.

4 Bouchard TJ. Genes, environment, and personality. Science Vol. 264: 1700-1701, 1994.

5 Plomin R, Owen MJ, McGuffin P. The genetic basis of complex human behaviors. Science Vol. 264: 1733-1739, 1994.

6 Mann CC. Behavioral genetics in transition. Science 264:1686-1689, 1994.

7 Plomin R, DeFries JC. The genetics of cognitive abilities and disabilities. Scientific American, May, 1998:62-69.

8 Plomin R, Owen MJ, McGuffin P. The genetic basis of complex human behaviors. Science Vol. 264: 1733-1739, 1994.

9 Bailey RC. Hereditarian scientific fallacies. Genetica 99(2-1):125-133, 1997.

10 Mann CC. Ibid.

11 McClearn GE, Vogler GP, Plomin R. Genetics and behavioral medicine. Behavioral Medicine 22:93-102, fall, 1996.

12 Lilly, LS. Ischemic heart disease in Textbook of Primary Care Medicine, Second Edition, Ed. Noble J. St. Louis: Mosby, 1996, p.218.

13 Goldberg RJ, Yarzebski J, Lessard D et al. A two-decades (1975-1995) long experience in the incidence, in-hospital and long-term case-fatality rates of acute myocardial infaction: a community-wide perspective. Journal American College of Cardiology 33(6):1533-9, 1999.

14 Wilhelmsen L. ESC population studies lecture 1996. Cardiovascular monitoring of a city over 30 years. European Heart Journal 18(8):1220-30, 1997.

15 Pell S. Trends in the incidence of myocardial infaction and in associated mortality and morbidity in a large employed population, 1957-1983. New England Journal of Medicine 312(16):1005-11, 1985.

16 Plomin R, Owen MJ, McGuffin P. The genetic basis of complex human behaviors. Science Vol. 264: 1733-1739, 1994.

17 Plomin R, Owen MJ, McGuffin P. 1994. Ibid.

18 Plomin R, EdFries JC, McClearn GE et al. Behavioral Genetics, Third Edition. New York: WH Freeman and Company, 1997, p. 111.

19 McClearn GE, Vogler GP, Plomin R. Genetics and behavioral medicine. Behavioral Medicine 22:93-102, fall, 1996.

20 Mutch E, Blain PG, Williams FM. Interindividual variations in enzymes controlling organophosphate toxicity in man. Human and Experimental Toxicology 11(2):109-116, 1992.

21 Costa LG, Li WF, Richter RJ, Shih DM et al. The role of paraoxonase (PON1) in the detoxification of organophosphates and its human polymorphism. Chemico-Biological Interactions 119-120:429-38, 1999.

22 Clendenning JB, Humbert R, Green ED, et al. Structural organization of the human PON1 gene. Genomics 35(3):586-9, 1996.

23 Shih DM, Gu L, Xia YR, et al. Mice lacking serum paraoxonase are susceptible to organophosphate toxicity and atherosclerosis. Nature 394(6690):284-7, 1998.

24 Genc S, Gurdol F, Guvene S, Kargi Y. Variations in serum cholinesterase activity in different age and sex groups. European Journal of Clinical Chemistry and Clinical Biochemistry 35(3):239-40, 1997.

25 Trundle D, Marcial G. Detection of chilinesterase inhibition. The significance of cholinesterase measurements. Annals of Clinical and Laboratory Science 18(5):345-2, 1988.

26 Brock A, Brock V. Plasma cholinesterase activity in a healthy population group with no occupational exposure to known cholinesterase inhibitors: relative influence of some factors related to normal inter-and intra-individual variations. Scandinavian Journal of Clinical and Laboratory Investigation 50(4):401-8,1990.

27 Trundle D, 1988. Ibid.

28 Rosenman KD, Guss PS. Prevalence of congenital deficiency in serum cholinesterase. Archives of Environmental Health 52(1):42-4, 1997.

29 Pinto Pereira LM, Clement Y, Telang BV. Distribution of cholinesterase activity in the population of Trinidad. Canadian Journal of Physiology and Pharmacology 74(3):286-9, 1996.

30 Reiner E, Simeon-Rudolf V, Skrinjaric-Spoljar M. Toxicology Letters 82-83:447-52, 1995.

31 Trundle D, 1988. Ibid.

32 Brock A, Brock V, 1990. Ibid.

33 Costa LG, Li WF, Richter RJ, Shih DM et al, 1999. Ibid.

34 Furlong CE, Li WF, Costa LG et al. Genetically determined susceptibility to organophosphorus insecticides and nerve agents: developing a mouse model for the human PON1 Polymorphism. Neurotoxicology 19(4-5):645-50, 1998.

35 Furlong CE, 1998. Ibid.

36 Furlong CE, Richter RJ, Seidel SL, et al. Role of genetic polymorphism of human plasma paraoxonase/arylesterase in hydrolysis of the the insecticide metabolites chlorpyrifos oxon and paraoxon. American Journal of Human Genetics 43(3):230-8, 1988.

37 Furlong CE, Richter RJ, Seidel SL, 1988. Ibid.

38 Padungtod C, Niu T, Wang Z, Savitz DA, Christiani DC, et al. American Journal of Industrial Medicine 36(3):379-87, 1999.

39 Trifiletti RR, Packard AM. Immune mechanisms in pediatric neuropsychiatric disorders. Tourette's syndrome, OCD, and PANDAS. Child and Adolescent Psychiatric Clinics of North America 8(4):767-75, 1999.

40 Swedo SE, Leonard HL, Garvey M. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. American Journal of Psychiatry 155(2):264-71, 1998.

41 Hollander E, DelGiudice-Asch G, Simon L, et al. B lymphocyte antigen D8/17 and repetitive behaviors in autism. American Journal of Psychiatry 156(2):317-20, 1999.

42 Trifiletti RR, Packard AM, 1999. Ibid.

43 Asbahr FR, Negrao AB, Gentil V et al. Obsessive-compulsive and related symptoms in children and adolescents with rheumatic fever with and without chorea: a prospective 6-month study. American Journal of Psychiatry 155(8):1122-4, 1998.

44 Asbahr FR, Ramos RT, Negrao AB et al. Journal of the American Academy of Child and Adolescent Psychiatry 38(12):1522-5, 1999.

45 Giedd JN, Rapoport JL, Leonard HL, et al. Case study: acute basal ganglia enlargement and obsessive-compulsive symptoms in an adolescent boy. Journal of the American Academy of Child and Adolescent Psychiatry 35(7):913-5, 1996.

46 Perlmutter SJ, Leitman SF, Garvey MA, et al. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. Lancet 354(9185):1153-8, 1999.

47 Hollander E, DelGiudice-Asch G, Simon L, et al, 1999. Ibid.

48 Swedo SE, Leonard HL, Mittleman BB, et al. Identification of children with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections by a marker associated with rheumatic fever. American Journal of Psychiatry 154(1):110-2, 1997.

49 Garvey MA, Giedd J, Swedo SE. Journal of Child Neurology 13(9):413-23, 1998.

50 Asbahr FR, Negrao AB, Gentil V et al, 1998. Ibid.

51 Kurlan R. Neurology 50(6):1530-4, 1998.

52 Smith CM, Wang X, Hu H et al. A polymorphism in the delta-aminolevulinic acid dehydratase gene may modify the pharmacokinetics and toxicity of lead. Environmental Health Perspectives 103(3):248-53, 1995.

53 Bergdahl IA, Grubb A, Schutz A et al. Lead binding to delta-aminolevulinic acid dehydratase in human erythrocytes. Pharmacology and Toxicology 81(4):153-8, 1997.

54 Wetmur JG. Influence of the common human delta-aminolevulinate dehydratase polymorphism on lead body burden. Environmental Health Perspectives 102 Suppl 3:215-9, 1994.

55 Wetmur JG, Lehnert G, Desnick RJ. The delta-aminolevulinate dehydratase polymorphism: higher blood lead levels in lead workers and environmentally exposed children with the 1-2 and 2-2 isozymes. Environmental Research 56(2):109-19, 1991.

56 Claudio L, Lee T, Wolff MS, et al. A murine model of genetic susceptibility to lead bioaccumulation. Fundam Appl Toxicol 35(1):84-90, 1997.

57 Tomokuni K, Ichiba M, Fujisiro K. Interrelation between urinary delta-aminolevulinic acid, serum ALA, and blood lead in workers exposed to lead. Industrial Health 31(2):51-7,1993.

58 Schwartz BS, Lee BK, Stewart W et al. Delta-Aminolevulinic acid dehydratase genotype modifies four hour urinary lead excretion after oral administration of dimercaptosuccinic acid. Occupational and Environmental Medicine 54(4):241-6, 1997.

59 Sithisarankul P, Cadorette M, Davoli CT et al. Plasma 5-aminolevulinic acid concentration and lead exposure in children. Environmental Research 80(1):41-9, 1999.

60 Sithisarankul P, Schwartz BS, Lee BK et al. Aminolevulinic acid dehydratase genotype mediates plasma levels of the neurotoxin, 5-aminolevulinic acid, in lead-exposed workers. American Journal of Industrial Medicine 32(1):15-20, 1997.

61 Plomin R, DeFries JC. The genetics of cognitive abilities and disabilities. Scientific American, May, 1998:62-69.

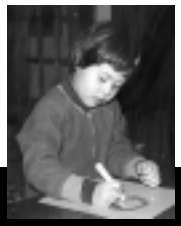
62 Taylor HG. Critical issues and future directions in the development of theories, models, and measurements for attention, memory, and executive function. In:Attention, Memory and Executive Function. Eds. Lyon GR, Krasnegor NA. Baltimore: Paul H. Brookes Publishing Co., 1996, p. 400-1.

63 Ramey CT, Bryant DM, Wasik BH et al. The infant health and development program for low birthweight, premature infants: program elements, family participation, and child intelligence. Pediatrics 89(454-65),1992.

64 Ramey CT, Ramey SL. Which children benefit the most from early intervention? Pediatrics 94(6 Pt 2):1064-6, 1994.

65 Ecobichon DJ. Toxic effects of pesticides. In: Casarett and Doull's Toxicology, Fifth Edition. Ed Klaasses CD. New York: McGraw-Hill, 1996.

Chapter 6



Known and Suspected Developmental Neurotoxicants

A large number of chemical compounds interfere with normal brain development, including heavy metals, alcohol and other solvents, nicotine, opiates, cocaine, marijuana, some pharmaceuticals, pesticides, and others. As described in Chapter 2, neurodevelopmental toxicants may alter brain development and function in specific and permanent ways. A few have been extensively studied (e.g. lead, mercury, alcohol), while most others have undergone minimal examination.

The following profiles summarize what is known about the neurodevelopmental toxicity of some commonly encountered solvents, pesticides, nicotine, metals, and persistent organochlorine compounds. We also briefly discuss important controversies over the potential neurodevelopmental toxicity of compounds that are intentionally added to drinking water and food – fluoride and certain food additives.

Experimental toxicity testing usually involves examining one chemical at a time. Although this approach provides important information, it fails to inform us about the neurodevelopmental effects of exposures to mixtures of many different compounds. Every human body contains mixtures of heavy metals and synthetic organic chemicals in blood, bone and other organs, fat, breast milk, sperm and expired air. Epidemiological research is complicated by the fact that there are no unexposed people to serve as controls for comparison purposes. These limitations should be kept in mind when reading the following toxicity profiles.

Every human body contains mixtures of heavy metals and synthetic organic chemicals in blood, bone and other organs, fat, breast milk, sperm and expired air.

Finally, although the references cited do not exhaustively review the available literature, they are representative and include areas of uncertainty and controversy. Importantly, many chemical compounds with known or suspected neurological toxicity have never been tested for their effects on brain development and function. For them, there are no data to review.

METALS

Lead

- Increases in blood lead levels during infancy and childhood are associated with attention deficits, increased impulsiveness, reduced school performance, aggression, and delinquent behavior .
- Effects on learning are seen at blood lead levels below those currently considered "safe."

Routes of Exposure

Since lead was removed from most of the nation' s gasoline supply , most current environmental exposures in the US come from lead paint, lead contaminated dust, and drinking water . Occupational and hobby exposures also contribute to the lead levels of some adults. Lead tends to be stored in bones, and during pr egnancy , accelerated maternal bone turnover results in mobilization of lead, leading to increased blood lead levels.

Human Studies

Lead easily crosses the placenta and enters the fetal brain where it interferes with normal development. Many studies report adverse neuro-developmental impacts resulting from fetal or infant exposures to lead, including lowered intelligence, hyperactivity, learning and attention disorders, and changes in behavior. (for example, see [1 2 3]) Here we summarize results from several of the larger epide-miological studies, omitting most of a large body of animal research because of the relative wealth of human data.

In the 1940s, the consequences of lead poisoning, including poor school per for mance, impulsive behavior , shor t attention span, and restlessness, were reported. [4] Since then neurodevelop-mental damage at lower levels of exposure has been well documented. In fact, there is no evidence of any threshold for lead-induced cognitive impairment resulting from early life exposures. [5]

In one of the earliest studies of lead effects on intelligence, investigators reported a 4-point difference in IQ, measured by the Wechsler Intelligence Scales for Children – Revised (WISC-R), between children with the highest and lowest deciduous tooth-lead levels.[6] Other studies have reached similar conclusions. In Boston, a cohort of children from middle and upper middle class homes has been followed for years.[7] [8] Reduced performance on the Bayley Mental Development Index (MDI) was associated with elevated umbilical cord blood lead levels. The difference in scores between the high (mean, 14.6 microgm/dl) and low (mean, 1.8 microgm/dl) blood lead levels was 4-7 points at 6, 12, and 24 months of age. When the children were re-tested at 10 years of age, a 10 microgm/dl increase in blood lead at 24 months of age was associated with a 5.8-point decline in IQ as measured by WISC-R. Other studies show similar results.[9]

In the Boston cohort, teachers reported behavioral changes in children that correlated with lead levels. Children with the higher levels were more distractible, dependent, impulsive, easily frustrated, not persistent, and unable to follow directions. Attention-deficit

disorder also correlates with hair lead levels.[10] Increased blood level in infancy and early childhood may be manifest in older children and adolescents as decreased attention span, reading disabilities, and failure to graduate from high school[11] Two studies report that lead exposure correlates with aggressive, destructive, and delinquent behavior.[12] [13]

Animal Studies

Animal studies support these conclusions from epidemiological data. Monkeys exposed to lead from birth, so that blood lead levels are maintained at about 15 microgms/dl, show increased distractibility , inappr opriate r esponses to stimuli, and difficulty adjusting response strategies. [14] A review of animal studies reports deficits in performance, learning, and attention associated with low-level lead exposures. [15]

Mechanisms of Neurotoxicity

Several neurodevelopmental processes are altered by lead exposure, leading to abnormal brain development. Intrauterine neurodevelopmental effects of lead affect both the cellular structure of the brain and its chemistry.[16] Structural effects include altered cell proliferation, differentiation, synapse formation, and programmed cell death. Neurochemical effects include altered neurotransmitter levels (acetylcholine, dopamine, glutamate) and altered dopamine receptor density in various parts of the brain.[17] Lead is also a potent inhibitor of the NMDA (glutamate) receptor. The fetal brain may be particularly sensitive not only because unique organizational processes are underway but also because of an immature blood-brain barrier. One study found greater uptake of lead in fetal brain during gestation than after birth in rats.[18]

Mercury

- Freshwater fish are sufficiently contaminated with methylmercury in most of the US to necessitate fish consumption advisories warning pregnant women or women of reproductive age to avoid or limit consumption because of threats to fetal brain development
- Large fetal exposures to methylmercury cause mental retardation, gait and visual disturbances
- Smaller fetal exposures may cause lasting impairment of language, attention, and memory
- Fetal mercury and PCB exposures interact to result in magnified effects on neurological development

Routes of Exposure

Mercury (Hg) may exist in a number of different chemical forms but is usually released into the environment as a metal or an inor ganic compound. The US EP A estimates that human activities are responsible for emissions of approximately 160 tons of mercury annually in the US.[19] Major sources are coal-fired power plants and municipal and medical waste incinerators. Atmospheric mercury often travels long distances before being deposited onto the ear th's sur face. Mer cury in sediments and water bodies is converted by bacteria into methylmer cury, which

How Much Mercury In My Tuna Sandwich?

The EPA sets "safe" reference doses for the chemicals we are exposed to through our air, water, and food. Yet it is difficult to translate those levels, expressed in micrograms and parts per million, into information that is meaningful for our daily lives. For instance, how can I determine how much mercury I am exposed to each time I eat a tuna sandwich? Some basic information on equivalencies and abbreviations will help you do the math so you can determine how much of a chemical you may be exposed to.

The first step in determining exposure is converting the various measures into equivalent units. In the United States we often express our body weight in pounds or the amount of food we eat in ounces. Environmental concentrations and exposures, however, are usually calculated using metric units (grams, kilograms). Note the following equivalencies:

- 1 kilogram (kg) = 2.2 pounds (lb)
- 1 pound = 16 ounces = 454 grams
- 1 ounce = 28 grams (gm)

Because we are often concerned about exposures to very small quantities of chemicals, it is helpful to know the following units of measure that represent tiny subdivisions of the gram (gm):

- Milligram (mg) = 1/1000 gm (thousandth)
- Microgram (ug or microgm) = 1/1,000,000 gm (millionth)
- Nanogram (ng) = 1,000,000,000 gm (billionth)
- Picogram (pg) = 1,000,000,000,000 gm (trillionth)

For example, there are 1,000 milligrams in 1 gram, or 1 million micrograms in that same gram.

We are generally exposed to chemicals that are contained within another medium such as air, water or food. In order to calculate exposure we must first calculate the **concentration**, or the amount of the chemical that is contained in the water we drink or the food we eat. For example, if 1 gram of fish contains, on average, 1 microgram (ug) of mercury, we would express the concentration as 1microgm/gm. Since there are a million micrograms in a gram, another way to express this concentration is 1 part per million, or 1 ppm. The following chart outlines the equivalencies:

- Gm/kg = mg/g = parts per thousand = ppthousand (1/1000)
- Mg/kg = microgm/g = parts per million = ppm (1/1,000,000)
- Microgram/kg = ng/gm = parts per billion = ppb (1/1,000,000,000)
- Ng/kg = picogm/gm = parts per trillion = ppt (1/1,000,000,000,000)

Since we have determined the concentration of mercury in the tuna fish, we can determine how much mercury an individual is exposed to when eating the fish. With a few basic calculations, we can calculate the mercury exposure of a woman who consumes 7 ounces of tuna per week, given an average tuna mercury level of 0.2 ppm (Assume she does not eat any other fish or shellfish, or have any other significant exposures to mercury).

How can I determine how much mercury I am exposed to each time I eat a tuna sandwich?

- First we convert the ounces into metric units:

  7 oz = 196 gms fish

- Then we multiply the amount of fish consumed/week with the concentration of mercury in the fish to determine the mercury exposure per week:

  196 gms fish/week x 0.2 microgm mercury /gm fish = 39.2 microgm mercury/week

  How much mercury is that per day?

- Divide by 7, since there are 7 days in a week:

  39.2 microgm of mercury /week = 5.6 microgm of mercury/day = daily mercury exposure

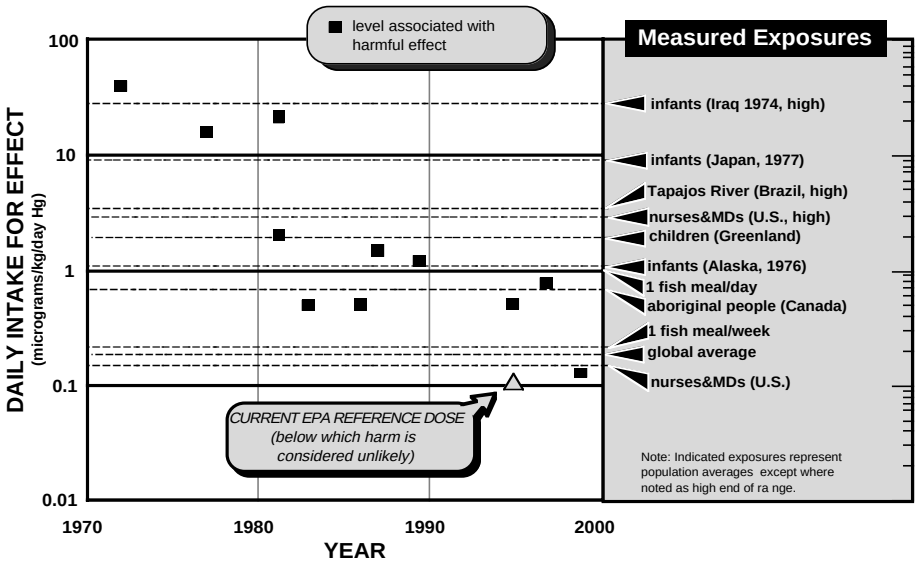
Typically we standardize exposures by dividing the total exposure by the body mass. Expressing exposure on a "per kilogram" basis allows us to compare exposures among individuals of different sizes. If we assume the woman eating the sandwich is of average weight, (132 pounds, or 60 kg), we divide the total exposure by 60 kilograms:

5.6 microgm/60 kg of mercury/day
= 0.093 microgm/kg

We have determined that the mercury exposure of a 132 lb woman (60 kg) eating 7 ounces (196 grams) of tuna per week is 0.093 microgms/kg/day. This level of exposure is just at the limit of EPA's "safe" reference dose of 0.1 microgrm/kg/day.

This calculation is based on the assumption that the woman weighs 132 lbs. What would the mercury exposure be if a 50 lb child consumed the same amount of tuna over the course of a week? The child would be exposed to approximately 0.243 microgms/kg/day of mercury.

Mercury: Inadequate Margin of Safety



Mercury exposures associated with harmful effects have been recognized at progressively lower levels over the past several decades as research meth ods have improved. EPA's current advised safe exposure limit, represented by the triangle, is exceeded by many groups. It is also exceeded by the global average mercury exposure. This average, based on a report of 559 hair samples from 32 locations around the world, reflects a cumulative average of levels of fish consumption, and degrees of fish contamination.[1 2 3 4 5 6 7 8 9 10 11] (All indicated exposures were assessed as hair or blood mercury levels, except US nurses and physicians, whose exposures were estimated by dietary survey.)

bioaccumulates as it passes up the food chain. As a result, fish consumed by pregnant women or women of reproductive age may be contaminated with methylmercury at levels that pose a threat to the uniquely vulnerable developing brain of the fetus. Forty states have issued fish advisories warning women of reproductive age to limit or avoid consuming fresh water fish because of mercury contamination. Large predator ocean fish, like swordfish and some tuna, may also be sufficiently contaminated to pose a risk, particularly when eaten regularly . According to EP A estimates, 1.16 million women of childbearing years eat sufficient amounts of mercury-contaminated fish to pose a risk of harm to their future children.

Animal Studies

Studies in animals confirm the developmental neurotoxicity of organic mer cury. Four-month-old rats, exposed to 0.008 mg Hg/kg/day on gestational days 6-9 show significantly impaired behavioral performance, as tested by rewarding for total lever presses. [20] Fifty-60-day-old monkeys born to mothers that received 0.04 or 0.06 mg methylHg/kg/day for an average of 168 or 747 days prior to mating show impaired visual recognition memor y.[21] Autopsy studies in developmentally exposed animals show smaller brain sizes, dilated ventricles, and distorted cellular architecture.

Human Studies

The devastating effects of methylmercury on the developing human brain after excessive exposure were tragically demonstrated in large-scale poisonings. In Minamata Bay , Japan, during the 1950' s, residents r egularly consumed fish contaminated with methylmer cury fr om an industrial plant' s ef fluent in the bay . Infants bor n in the late 1950's developed characteristic neurological findings including mental retardation, disturbances of gait, speech, sucking, and swallowing, and abnormal reflexes. [22] Mothers of affected children often showed no sign of mercury poisoning.

Another large scale poisoning occurred in Iraq in the 1970's when residents baked bread with grain intended for planting that had been treated with organic mercury as a fungicide. Unlike Minamata, this represented an acute rather than chronic poisoning. Symptoms were similar in the two circumstances, but visual disturbances in adults were more severe in Iraq with actual blindness in several instances. [23] The critical effect from prenatal exposure to methylmercury was psychomotor retardation with delays in learning to walk and an increased incidence of seizures. Using maternal hair mercury levels as a measure of prenatal exposure, investigators calculated that the lowest observed adverse effect level (LOAEL) for psychomotor retardation occurred when maternal hair levels of mercury were between 10-20 ppm. [24] Maternal hair mercury levels are thought to be a fairly accurate indicator of fetal mercury exposures during pregnancy.

More recently, epidemiological studies conducted in the Seychelle and Faroe Islands have attempted to identify more subtle developmental neurological effects of low-dose methylmercury exposure and to identify a threshold, if one exists, below which there is no discernable toxicity. These study populations were selected because their fish or marine mammal based diets regularly exposed them to low doses of methylmercury, and maternal hair levels of mercury in these populations bracketed the LOAEL identified in the Iraq study.

In the Seychelles, 738 children were followed with sequential detailed neurological testing. Maternal hair levels of mercury averaged 6.8 ppm. At age 2 years, more highly exposed boys scored significantly lower on activity level when tested by the Bayley Infant Behavior Record. [25] Among boys and girls combined, the effect of mercury on activity level was significant only at a maternal hair level greater than 12 ppm. Follow up testing at age 5 years showed no persistent effect of prenatal mercury exposure. [26] Neurological testing at 66 months of age included the McCarthy Scales of Children's Abilities, Preschool Language Scale, Woodcock-Johnson Applied Problems and Letter and Word Recognition Tests of Achievement, the Bender Gestalt Test, and the Child Behavior Checklist.

In the Faroe Islands, 917 newborn/mother pairs were tested at birth for maternal hair and umbilical cord blood mercury levels. Children whose mother's hair mercury levels were 10-20 ppm were compared with those whose hair levels were less than 3 ppm. Early examination of children showed that the most exposed children had subtle changes in the function of portions of the brain associated with hearing and motor skills. As they grew older, some deficits in learning capacity also became apparent. At age 7 years these children underwent extensive neurological testing including the Neurobehavioral Evaluation System (NES) Finger Tapping and Hand-Eye Coordination Test, Tactual Performance Test, NES

According to EPA estimates, 1.16 million women of childbearing years eat sufficient amounts of mercury-contaminated fish to pose a risk of harm to their future children.

Continual Performance Test, Wechsler Intelligence Scale for Children – Revised (WISC-R) Digit Spans, WISC-R Similarities, WISC-R Block Designs, Bender Gestalt Test, California Verbal Learning Test, Boston Naming Test, and the Nonverbal Analogue Profile of Mood States. [27] The studies showed a significant correlation between impairment in the areas of language, attention, and memory and prenatal mercury exposure.

The studies showed a significant correlation between impairment in the areas of language, attention, and memory and prenatal mercury exposure.

Investigators in each study controlled for many potentially confounding factors including socioeconomic status, quality of the home environment, and breast feeding status, among others. The differing results may be explained by several different factors. First, some neurological effects do not become apparent until later in childhood when certain neurological functions begin to develop. This, however, becomes less likely to explain the discrepant findings as the Seychellois children approach age 7 and continue to show no lasting deficits. Second, the testing techniques used in the Faroes may be more sensitive than those used in the Seychelles. The Faroe investigators included examination of some specific areas of neurocognitive performance that are more easily and accurately detected by detailed computer analysis. Third, the exposure pattern is likely to have differed in the two groups. In the Seychelles, fish are contaminated with methylmercury at a relatively low level and mercury exposure is the result of a constant diet of fish. In the Faroe Islands, however, mercury exposure results from intermittent ingestion of pilot whale meat that contains about 10 times the mercury concentration of ocean fish. Consequently, it is likely that the Faroese experience intermittent spikes of mercury exposure that are higher than the Seychellois. The neurodevelopmental consequences of these two exposure patterns may differ. Fourth, pilot whale blubber is also contaminated with PCBs and other organochlorine chemicals, which also affect neurological development. Though methylmercury is largely contained in the whale meat, some residents also eat whale blubber, resulting in concomitant PCB exposures. PCB levels were measured in the Faroe Island study, and investigators used analytical statistical techniques to control for co-contaminants as they looked for effects of prenatal mercury exposure. However, some critics believe that the other contaminants may explain at least some of the findings. The Faroe Islands study team strongly disagrees and argues that they successfully controlled for PCB co-contamination.[28] Finally, the Faroe Islands study identified a relationship between neurodevelopment and cord blood levels of mercury, rather than maternal hair. Umbilical cord blood levels may better reflect actual fetal exposures.

Additional studies also show developmental neurotoxicity after oral exposure of humans and non-human primates to low doses of organic mercury.[29] [30] [31] In a New Zealand study, maternal hair mercury levels of 15 microgms/gm were associated with poorer performance on the Wechsler Intelligence Scale for Children.

Based on the Seychelles study, the Agency for Toxic Substances and Disease Registry (ATSDR) has established a

minimum risk level for oral exposure to methylmercury at 0.5 microgm/kg/day. However, the EPA has set the level at 0.1 microgm/kg/day. Based on dietary surveys, the EPA estimates that about 7% of women in the US of childbearing age consume methylmercury in excess of the "safe" dose.[32] However, among women who eat any fish at all, 50% of those of childbearing age consume excess methylmercury.

The Food and Drug Administration (FDA) established an "action level" for mercury in fish at 1 ppm in 1979. [33] However , the FDA's action level is a non-binding informal guideline, is not legally enforceable, and only serves as discretionary guidance to FDA and to states when deciding when seafood might be adulterated. Fish consumption has increased in the US since 1979, and critics have argued that this action level is not health-protective. Indeed, FDA was quoted in a 1991 General Accounting Office report as stating that the agency failed to consider reproductive and developmental toxicity when establishing the guideline. [34] Also in 1991, the National Academy of Sciences noted that the FDA guideline did not adequately protect sensitive populations, including fetuses, babies and young children.[35] (see Spotlight)

Mechanisms of Neurotoxicity

Mercury has a high affinity for binding to specific chemical structures (e.g., sulfhydryl groups) on proteins, which is thought to explain many of its biological activities. [36] The result is diffuse alteration of cellular function, inhibition of protein synthesis, and formation of reactive oxygen species, which can damage DNA and disrupt cell division. [37] In the nervous system, mercury interferes with development of microtubules, which are small tubular structures in the neuronal skeleton. [38] Mercury also disrupts cell membrane integrity and alters the chemical characteristics of the surface of cells, making them more likely to adhere to one another . This may explain how cellular migration is affected during brain development. Mercury exposure also disrupts synaptic transmission.

In an in vitro study, methylmercury and polychlorinated biphenyls (PCBs) were reported to interact synergistically, with combined exposures resulting in lowering of dopamine levels in animal brain tissue to a greater degree than would have been predicted by adding the effects observed when the chemicals were used individually.[39] New data, as yet unpublished, from a long term ongoing study of children born to mothers consuming fish from Lake Ontario, show that prenatal PCB and mercury exposures also interacted to reduce performance of 3-year-old children on the McCarthy Scales of Children's Abilities.[40] Mercury exposures in this study were quite low, yet they combined with PCB exposures to increase adverse impacts on neuro-development. Together, these observations raise important questions about the adequacy of fish consumption advisories based on single chemical analyses. Freshwater fish in many areas of the US are contaminated with mercury, PCBs, dioxin, and other toxicants. Risk assessments or advisories that are based on single hazard analyses that define safe fish consumption limits are unlikely to be protective of public health.

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Manganese

- Unlike many other metals, some manganese is essential as a catalyst in several critically important enzymatic processes
- However , several studies r epor t a relationship between excessive childhood levels of manganese exposure and hyperactivity or learning disabilities

Unlike mercury and lead, which are not required for human health, the metal manganese is essential in trace amounts in order to promote several critical enzymatic reactions. Manganese deficiency may result in abnormalities of connective tissue, cartilage, and bone. In various species, too little dietary manganese causes impaired skeletal development and reproduction, abnormal carbohydrate and lipid metabolism, and movement disorders.

Routes of Exposure

In non-occupational settings, most manganese exposure comes from food. The National Research Council estimates a safe and adequate daily dietary intake of 2-5 milligrams. The ordinary adult dietary intake ranges from 0.52-5.33 milligrams daily with an average of 3 milligrams.[41] Infant dietary intake of manganese varies dramatically with the source of food. Human breast milk contains about 6 micrograms/liter. Infant formula contains about 77 micrograms Mn/liter if no manganese has been added and about 100 micrograms Mn/liter if it has been supplemented.[42] Soybean plants efficiently extract manganese from soil, and soy-based infant formula contains 200-300 micrograms Mn/liter.[43] Consequently, formula-fed infants ingest much more manganese than those who are breast-fed.

Formula-fed infants ingest much more manganese than those who are breast-fed.

Infants and young children absorb more and excrete less ingested manganese than adults.

An organic form of manganese, methylcyclopentadienyl manganese tricarbonyl (MMT), is used in a portion of the nation's gasoline supply as an octane enhancer. When burned, MMT-supplemented gasoline releases several inorganic manganese compounds into the atmosphere, causing small but widespread inhalation exposures, as well as land and water deposition. Animal studies show that inhaled manganese compounds may travel along the olfactory nerve directly into the brain, bypassing the general circulation and the blood-brain barrier.[44] The relevance of this pathway of exposure in humans is uncertain.

In adults, only about 3-5%, or approximately 100 microgms, of ingested manganese is absorbed into the circulation. Much of this is immediately excreted into the bile so that adults retain only about 30 microgms daily .[45] Animal studies show that young animals absorb much more ingested manganese than adults – about 70% in young rats compared to 1-2% in adults. [46] Manganese balance studies in humans also show that infants and young children absorb more and excrete less ingested manganese than adults. [47] Moreover , the blood brain bar rier, which keeps many blood-bor ne chemicals from entering the brains of older children and adults, is immature in infants, allowing proportionately more manganese to gain access to and lodge in the developing brain.

Animal Studies

Despite being an essential trace element, excessive exposures to manganese can be harmful to the brain, lungs, and reproductive system. Adverse reproductive effects, including testicular toxicity and reduced testosterone levels, occur in animals exposed to manganese during fetal development at levels that show no other toxic effects but that are considerably higher than normal human dietary intake. [48]

The more critical health effect, however, that may occur at much lower levels of exposure, is brain damage. Emerging evidence demonstrates that the brains of fetuses and newborns are more susceptible to the toxic effects of manganese than adults and that developmental exposures may result in unique neurological effects. A review of the published literature on manganese neurotoxicity in rodents identified seven studies in which animals were exposed during development. [49] Three studies investigated behavioral outcomes, and each reported increased activity levels in offspring.

Human Studies

Respiratory symptoms, pneumonia, or bronchitis occur in workers with large inhalation exposures to manganese. Obvious neurological effects of manganese were first noted in workers in manganese mines, refineries, and smelters. "Manganism" includes tremor and movement disorders, often preceded by "manganese madness," characterized by compulsive running, fighting, and singing. The movement disorder of manganism has some similarity to Parkinsonism, though there are distinct differences.

Several investigators have attempted to detect early signs of neurological damage from manganese exposure in adults. One describes a continuum of dysfunction due to manganese exposure, including behavioral and emotional effects in addition to the well-known movement disorder. [50] Another used behavioral methods to look for early signs of manganese neurotoxicity after low-level exposures and concluded that there are effects on response speed, motor functions, and memory. [51]

Several studies have reported a relationship between manganese hair levels in children and hyperactivity or learning disabilities. One found that the concentration of manganese in the hair of formula-fed infants increased from 0.19 micrograms/gm of hair at birth to 0.965 microgms/gm at six weeks, declining to 0.685 microgms/gm at four months of age. In breast-fed infants, hair levels increased only to 0.330 microgms/gm at four months of age. In this study, hair levels of manganese in hyperactive children were 0.434 microgms/gm as compared to levels of 0.268 microgms/gm in age-matched controls who were not hyperactive. [52] Another study reported hair manganese levels of 0.83 microgms/gm in hyperactive children compared with 0.58 microgms/gm in controls. [53] This study also found elevated lead levels in hyperactive children. A third study also reports higher hair manganese levels in children with attention deficit hyperactivity disorder than in controls. [54]

Emerging evidence demonstrates that the brains of fetuses and newborns are more susceptible to the toxic effects of manganese than adults and that developmental exposures may result in unique neurological effects.

Mechanisms of Neurotoxicity

Animals exposed to excessive manganese early in life show depressed levels of the neurotransmitters dopamine, norepinephrine, and serotonin.[55] One study shows that gestational serotonin depletion in rodents causes much more extensive structural change in the brains of offspring than similar depletions in adults, a result that is not surprising, in light of the important role of neurotransmitters in brain development.[56]

Some studies of children exposed to cadmium have shown hyperactivity and reduced verbal and performance IQ.

Conclusions

The susceptibility of the developing brain to manganese toxicity deserves further attention. Many infant formulas are regularly supplemented with manganese. Nutritional experts must have thought that human breast milk is deficient in this essential element and that supplements would not be harmful. Soy-based formulas contain even higher amounts of naturally-occurring manganese. But metabolic studies show that infants absorb more and excrete less manganese than adults. Furthermore, in infants, blood-borne manganese more readily enters the brain than in adults. Animal studies show that developmental exposures to manganese are associated with hyperactivity. Several studies show that hair manganese levels are higher in children with hyperactivity disorders than in controls. These observations call into question the wisdom of supplementing infant formulas with this metal or adding MMT to gasoline, and make the case for urgent research to clarify areas of outstanding uncertainties. As we learned from boosting

gasoline octane ratings with lead, population-wide exposures, however low-level they may be, sometimes have serious, unintended consequences.

Cadmium

- Studies of the neurological effects of developmental exposure to cadmium report mixed and sometimes conflicting results
- In animal tests, cadmium exposure causes a mixture of hyperactivity, reduced activity, and altered learning, depending on the timing, dose, route of exposure, and test methods
- Some studies of children exposed to cadmium have shown hyperactivity and reduced verbal and performance IQ

Routes of Exposure

Cadmium is a metal with no essential biological function, but it may interfere with normal neurological development through a variety of mechanisms. Cadmium is released to the environment from fossil fuel burning, mining and manufacturing operations, sewage sludge, phosphate fertilizers, and medical and municipal waste incinerators. Cadmium is used for a variety of industrial

purposes including metal plating, paint pigments, plastic stabilizers, and nickel-cadmium batteries.

The largest source of most human exposure to cadmium is dietary with an average adult daily intake of 10-30 microgms. Soil cadmium is readily taken up by leafy vegetables and grain crops, creating the potential for significantly increasing levels in crops grown on soil treated with sewage sludge containing cadmium from industrial sources. [57] Domestic and laboratory animals fed plants grown on sludge-amended soil may develop cadmium toxicity .[58] Cadmium also tends to concentrate in shellfish found in contaminated coastal waters. Another important source of cadmium is cigarette smoke; smokers have blood levels of cadmium approximately twice that of non smokers. [59]

Animal Studies

For several reasons studies of the neurological consequences of early life exposures to cadmium are more difficult to conduct than studies of lead, for example. Cadmium is rapidly removed from the blood and stored in the kidneys, liver, pancreas, and adrenal glands, making blood level measurements a poor indicator of exposure. Chronic cadmium exposure induces the production of a protein, metallothionein, which binds the metal and reduces its toxic effects. However, intermittent acute exposures to cadmium may escape this mechanism and lead to more severe toxic responses. In laboratory tests, even moderate levels of cadmium exposure may reduce animal weight gain, making it difficult to distinguish between direct cadmium toxicity and nutritional deficiencies from decreased food and water intake. Finally, the effect of cadmium on the fetus may be largely an indirect result of impairment of placental function, enzyme inhibition, or alteration of other essential trace metals in the brain rather than a direct toxic effect on fetal tissues. For example, metallothionein induced by cadmium may also bind zinc, an essential trace element, resulting in manifestations of zinc deficiency, which include birth defects. Indirect neurodevelopmental effects are also inferred from the observation that studies of cadmium exposure during pregnancy usually fail to find evidence of elevated cadmium levels in the fetal brain.[60]

Soil cadmium is readily taken up by leafy vegetables and grain crops, creating the potential for significantly increasing levels in crops grown on soil treated with sewage sludge containing cadmium from industrial sources.

In animals exposed to cadmium prenatally , a mixtur e of, and sometimes conflicting, neurological effects are noted. Mor eover , females seem to be more sensitive to neurodevelopmental effects than males, yet male animals are more often studied. Both hyperactivity and reduced activity are noted in offspring, depending on the exposure level, route of exposure, and tests used to measure activity levels. [61] [62] [63] The capacity of an animal to learn an avoidance task is also sometimes impaired. [64] In most cases, neurotoxicity is noted only when doses are sufficient to alter weight gain and growth. These studies have used maternal exposure levels in the range of 0.1-4.0 mg/kg daily during pregnancy via injection, diet, gastric lavage, or inhalation.

In contrast, neonatal exposure to cadmium is potentially more harmful than prenatal exposure because the

blood-brain barrier is not yet fully developed, and cadmium may have direct access to the developing brain. Microscopic studies show lesions in the brains of cadmium-treated neonatal rats that are not seen in the brains of treated adult rats, suggesting that the immature blood-brain barrier is an important factor in cadmium neurotoxicity. Here, too, animal studies show a mixture of hyperactivity, reduced activity, and altered learning in young animals, depending on test methods, dose, and route of exposure.

Human Studies

Several human studies have attempted to examine the neurological consequences of early exposures to cadmium. These are complicated by the correlation of lead and cadmium exposures, making it difficult to determine the relative contribution of each metal to observed effects. One study found a significant correlation between elevated hair cadmium and lead levels and hyperactivity in children.[65] Another study of a rural population of 149 children 5-16 years old found a correlation between hair lead and cadmium levels and reduced verbal and performance IQ when tested by the Wechsler Intelligence Scale for Children.[66] This study controlled for gender, age, race, and socioeconomic status. Interestingly, lead and cadmium seemed to affect different aspects of intelligence. Lead levels were more highly correlated with reduced performance IQ while cadmium levels correlated better with reduced verbal IQ.

In a prospective study, a hair sample was taken from 26 newborn children and their mothers and analyzed for lead and cadmium.[67] Six years later, the children were tested by the McCarthy Scales of Children's Abilities. Cadmium hair levels in children correlated with reduced perceptual and motor performance. Cadmium hair levels in mothers correlated with poorer child performance in general cognitive, perceptual, quantitative, and motor function. Lead levels also correlated with reduced perceptual performance, motor, and quantitative scores.

Mechanisms of Action

Cadmium may be directly or indirectly toxic to the brain of the developing child. During pregnancy, cadmium may interfere with placental and essential enzyme function or the availability of essential trace elements or other nutrients. Neonatal exposures alter neurotransmitter levels, including norepinephrine, dopamine, serotonin, and acetylcholine.[68] Cadmium exposure is also associated with increased free radical production in tissues resulting in cell membrane damage and changes in a variety of other physiological functions.

Tobacco Smoke and Nicotine

- Children born to women who smoke during pregnancy are at risk for IQ deficits, learning disorders, and attention deficits
- Children born to women who are passively exposed to cigarette smoke are also at risk for impaired speech, language skills, and intelligence

Routes of Exposure

Cigarette smoke and one of its components, nicotine, are among the most studied neurodevelopmental toxicants. Many animal studies are conducted with pure nicotine, which easily crosses the placenta, while human epidemiological studies examine the effects of exposure to the complex mixture of chemicals in tobacco smoke, including nicotine. Nicotine exposure in animals, however, produces some of the same effects in offspring as those seen in children whose mothers smoked during pregnancy, and nicotine is, therefore, likely to be a substantial contributor to the observed effects.

Animal Studies

In animals and humans, nicotine and tobacco smoke exposure cause growth retardation and other complications of pregnancy (prematurity, placental abnormalities, respiratory distress syndrome).[69] In order to examine for neurological effects of prenatal nicotine exposure that are due solely to toxic effects on the developing brain and not due to generally retarded growth, it is important to conduct animal testing at relatively low-levels of exposure. Larger doses that cause decreased oxygen delivery to the fetus may cause retarded growth and are less informative about exclusively neurotoxic effects. Therefore, animal studies done with low-dose infusion pumps that better mimic the level of human fetal exposure to nicotine due to maternal smoking give extremely relevant information.

In rats, prenatal nicotine exposure by maternal low-dose infusion, causes hyperactivity in young offspring.[70] The effect is most pronounced in males. Results of testing for effects on learning and memory are mixed. Normally rodents tend to show increasing interest in exploring novel environments as they age from infancy to adulthood. Rats exposed to low doses of nicotine in utero showed an opposite effect in that they tend to explore novel environments more readily in infancy but less after puberty.[71] Similar changes were seen in other maze tests.[72] These tests also show that complicating the task by changing the testing context sometimes uncovers nicotine-induced behavioral changes that would not otherwise be apparent.

Human Studies

A number of studies of children whose mothers smoked during pregnancy report adverse effects, including diminished intellectual capacity and achievement into adulthood.[73] [74] [75] [76] Effects are apparent immediately after birth. For example, one study reports that, using Brazelton Neonatal Behavioral Assessment Scales, infants born to smokers score significantly lower at 2, 3, and 14 days postpartum than unexposed infants.[77] Hearing seems to be particularly affected. Nicotine exposed infants were able to adapt to sounds normally but were less able to orient toward the source of the sound. This finding persisted at 2 weeks of age.

A large study of 12,000 children followed from birth to 11 years of age showed that those whose mothers

A number of studies of children whose mothers smoked during pregnancy report adverse effects, including diminished intellectual capacity and achievement into adulthood.

smoked more than 10 cigarettes daily during pregnancy were 3-5 months retar ded in general ability , reading and math skills at age 11. [78] Investigators corrected for socioeconomic and biological variables in the study population.

One study that followed a cohort of children into adulthood found that, by age 23, offspring of mothers who smoked during pregnancy had significantly lower academic achievement than unexposed children. [79] This study controlled for social class, size of family, and birth weight. It did not control for maternal academic achievement.

Maternal and/or childhood exposure to environmental tobacco smoke ("passive smoking") also seems to have adverse effects. [80] For example, after correcting for confounding variables, children at ages 6-9, tested for speech and language skills, intelligence, and visual/spatial abilities, whose mothers were exposed to passive cigarette smoke during pr egnancy , per for med intermediate between children of smoking mothers and those unexposed .[81] Investigators noted attention deficits and information processing problems in exposed childr en. Testing included the Wechsler Intelligence Scale for childr en with three-factor scores including verbal comprehension, perceptual organization, and fr eedom fr om distractibility . In an animal study of the effects of environmental tobacco smoke, rats exposed only post-natally and not pre-natally had reduced DNA content in their brains when compared to unexposed animals. [82]

Mechanisms of Neurotoxicity

Animal studies show that gestational exposure to nicotine at levels that do not cause growth retardation increases the number of cholinergic nicotinic neuroreceptor sites in the fetus and neonate, an effect that persists through the postnatal period of synapse formation. [83] Prenatal nicotine exposure also causes subnormal levels of the neurotransmitters dopamine and norepinephrine in the postnatal period. [84] Changes in norepinephrine utilization persist in some areas of the brain in adulthood.

A study of fetal and neonatal rats exposed to nicotine showed reduced DNA synthesis in the brain. [85] This was particularly marked in areas of the brain with higher concentrations of nicotinic receptors and in areas undergoing rapid cell division.

Cigarette smoke, however , is chemically complex and includes carbon monoxide and cyanide. In addition to the direct action of nicotine on the developing brain, other potential mechanisms of toxicity of smoke include low oxygen levels from carbon monoxide and impaired transfer of nutrients across the placenta, resulting in generally retarded fetal growth.

Conclusions

Tobacco smoke is a complex mixtur e of chemicals including nicotine, a neurotoxic substance with lasting effects on neurological function after fetal exposures. Offspring of animals and humans exposed to nicotine in utero are hyperactive and experience increased tremors and impaired auditory responsiveness. Children exposed to

nicotine and other contaminants of cigarette smoke during gestation show persistent intellectual impairment that affects performance on neurological testing and is associated with lower academic achievement. Environmental tobacco smoke ("passive smoking") also interferes with brain development.

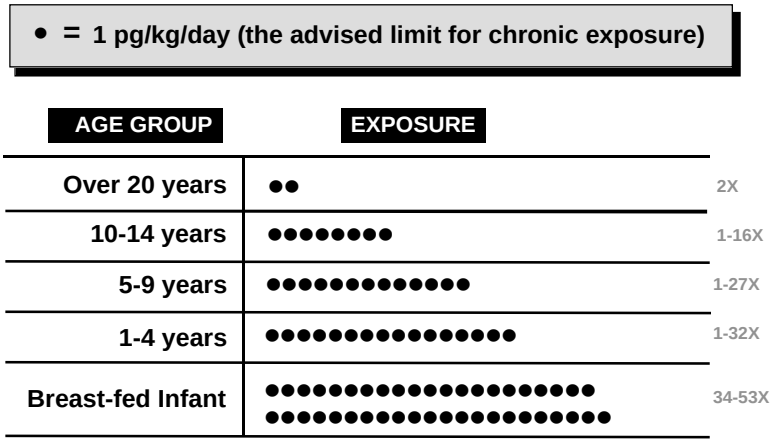
DIOXINS AND PCBS

- Monkeys exposed to dioxin as fetuses show evidence of learning disabilities
- Humans and animals exposed as fetuses to low levels of PCBs have learning disabilities
- Children exposed to PCBs during fetal life show IQ deficits, hyperactivity , and attention deficits when tested years later

Dioxins are a family of chemical compounds unintentionally produced during a variety of industrial processes, including municipal and medical waste incineration, secondary copper smelting, hazardous waste incineration, and chlorine-based pulp and paper bleaching, among others. Dioxins consist of two benzene rings, joined by two oxygen atoms, with varying numbers of chlorine atoms distributed ar ound the peripher y. The toxicity of a given dioxin molecule varies with the number and position of chlorine atoms. Most of the toxic manifestations of dioxin exposure are mediated through attachment of the dioxin molecule to a cellular receptor (the Ah receptor), although some neurodevelopmental effects may be unrelated to Ah receptor activation. Within the dioxin family of compounds, 2,3,7,8 – tetrachlorodibenzo-p-dioxin (with chlorine atoms in the 2,3,7,8 positions) has the highest affinity for the Ah receptor and is the most potent trigger of Ah r eceptor -mediated ef fects.

Polychlorinated biphenyls (PCBs) are industrial chemicals that were intentionally produced for many years and used for a variety of purposes including as lubricants, coatings, and insulating material in electrical transformers. In the US, and in most other countries, PCB production has been

Current Dietary Dioxin Exposures



* Based on a *minimal risk* level defined by ATSDR as a level at or below which adverse health effects are not expected to occur in humans. *Chronic exposure* is defined as an exposure lasting 1 year or longer.

Dioxin is concentrated in animal fat, and accumulates at higher levels in long-lived animals, and animals higher in the food chain. Because human food sources vary with age, dioxin intake also varies with age.[1] [2] Because dioxin is concentrated in breast milk, the intake of breast-feeding infants is highest, exceeding ATSDR's recommended limit for chronic exposure (one year or longer) by a factor of 34-53. This limit is exceeded to lesser degrees in all age groups. According to EPA, if one were to calculate, based on all human and animal data, a dioxin exposure limit that would protect against noncancer effects, (incorporating uncertainty factors to account for species differences and sensitive populations, such as the fetus), this exposure limit would be "on the order of 10 to 100 times below the current estimates of daily intake in the general population."[3]

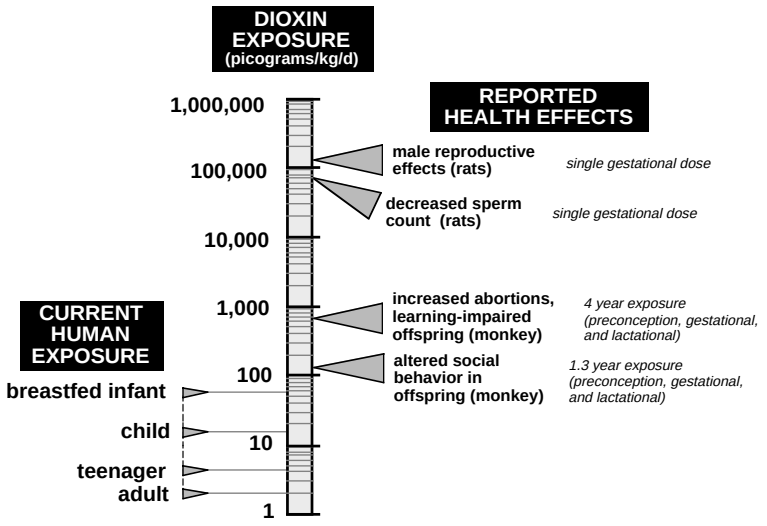
banned because of their environmental persistence, tendency to bioaccumulate, and toxicity. However, PCBs still exist in many electrical transformers, in landfills, and hazardous waste sites. PCBs are structurally similar to dioxins but lack the oxygen atoms between the benzene rings.

Routes of Exposure

Exposure to dioxins and PCBs is largely through dietary sources. Both dioxins and PCBs are environmentally persistent and tend to bioaccumulate in fatty tissue. Consequently, concentrations of each are highest at the top of the food chain, including beef, pork, dairy products, and fish. Breast milk contains among the highest levels of any human tissue because of its high fat content, which explains why a nursing infant is exposed to a substantial portion of a total lifetime dose of each of these families of chemicals during the first few months of life.

An adequate margin of safety requires several orders of magnitude between the range of human exposures and the lowest level of adverse health effects. Adverse health effects of dioxin,[1 2 3 4] however, have been demonstrated in animals at levels of exposure that approximate the upper range of human exposures. This demonstrates the urgent need to reduce human exposures by reducing or eliminating dioxin production and release.

Dioxin: Inadequate Margin of Safety

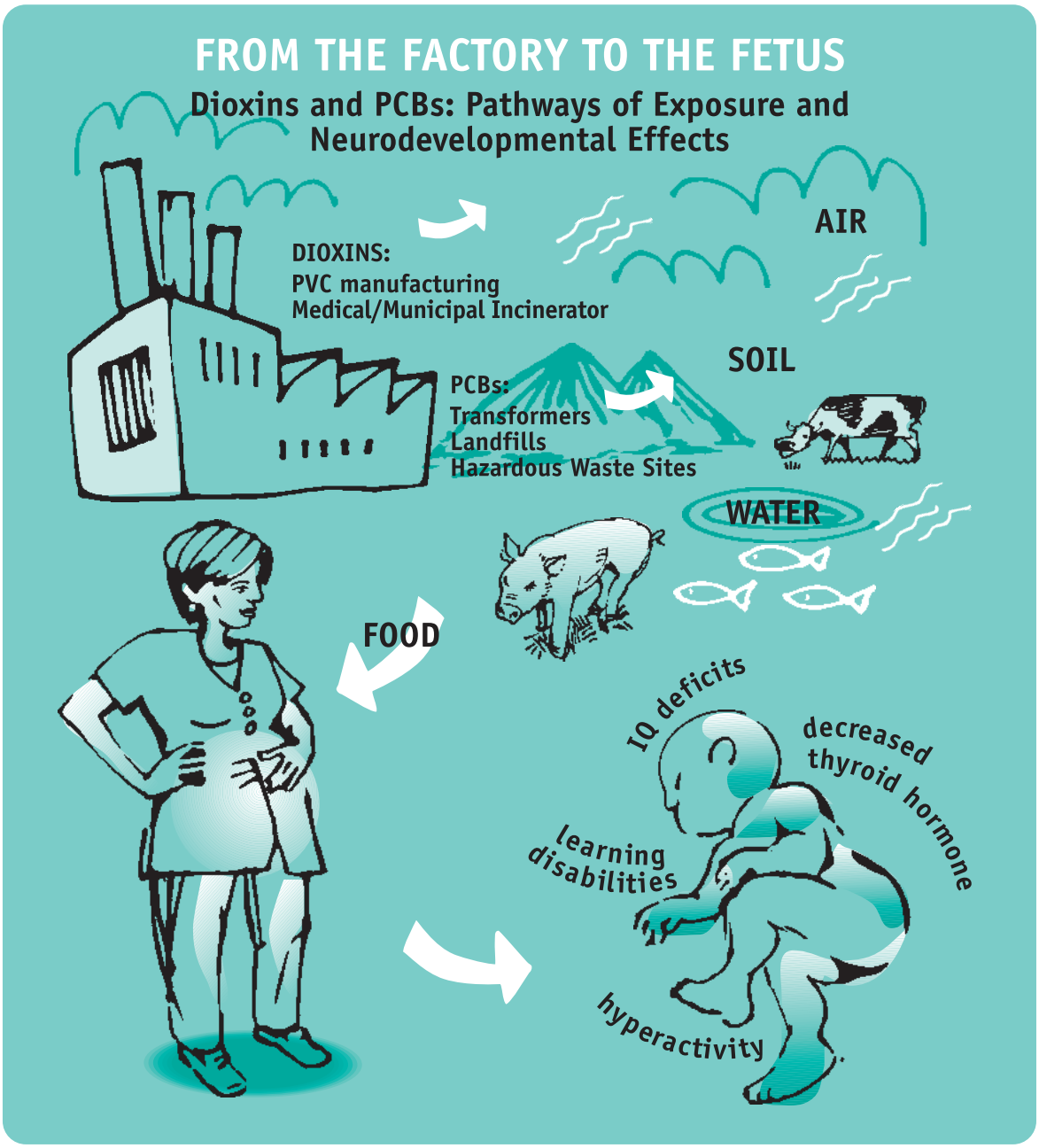


Animal Studies

Monkeys exposed gestationally to dioxin through a maternal diet containing 5-25 ppt dioxin, within the range of human breast milk contamination, show deficits in discrimination-reversal learning (retarded learning of shape reversals).[86] In this test, animals initially learn to respond correctly to a particular shape, form, color, or position. Then the correct answer is reversed so that the previous incorrect response now becomes correct. This requires changing a response strategy, a task more difficult than simply learning to discriminate initially.

Monkeys fed from birth to age twenty weeks with a PCB mixture and concentration representative of PCBs typically found in human breast milk showed significantly impaired learning and performance skills when tested between 2.5 and 5 years of age.[87] In addition to retarded learning, exposed monkeys showed perseverative behavior (constant repetition) and an inability to inhibit inappropriate responses.[88] The affected monkeys had blood PCB levels of 2-3 ppb, similar to levels in the general human population. Other investigators report similar effects on learning and behavior in monkeys exposed to PCBs shortly after birth, including hyperactivity.[89 90]

Rats exposed to PCBs prenatally show reduced visual discrimination, increases and decreases in activity level, and impaired learning.[91 92] Depending on the particular PCB(s) used in the study, effects are seen at maternal doses as low as 2 microgms/kg/day every second day from day 10-20 of gestation, with no no-effect level identified.



Dioxin is unintentionally produced in a variety of industrial processes, including municipal and medical waste incineration.[1] Once emitted into the air, dioxin often travels more than a thousand miles before settling on pastures and water bodies that produce the global food supply.[2] PCBs were produced predominantly from the 1920's to the 1980's, for use in a variety of products including transformers, capacitors, and lubricant oils.[3] While PCB production has been banned in most countries, approximately two-thirds of the total amount produced has not yet been released to the environment.[4] PCBs have been introduced into the environment through careless disposal, leakage from industrial facilities and waste disposal sites, and from products in use.[5] [6] PCBs introduced to land or water bind to soil and sediment particles, evaporate at various rates, and, like dioxin, undergo long range atmospheric transport. [7] [8]

Because of their similar chemical properties, PCBs and dioxin have similar patterns of long range atmospheric transport resulting in widespread deposition. Both accumulate in the cattle and fish feeding on contaminated vegetation, and concentrate further in species eating high on the food chain, including humans. PCBs and dioxin can remain in soil for many years. [9] [10] Laboratory studies in animals have demonstrated significant dermal absorption of PCBs, but not of dioxin, following contact with contaminated soil.[11] [12] [13] However, most human exposure to both PCBs and dioxins occurs through food consumption.[14] [15] Because dioxin and PCBs are carried by fat, they are passed during pregnancy from mother to fetus, the most vulnerable stage of human development, and continue to be transmitted during breast feeding. Dioxin and PCBs thus illustrate one of the unforeseen pathways by which industrial chemicals may travel from the factory to the fetus.

Human Studies

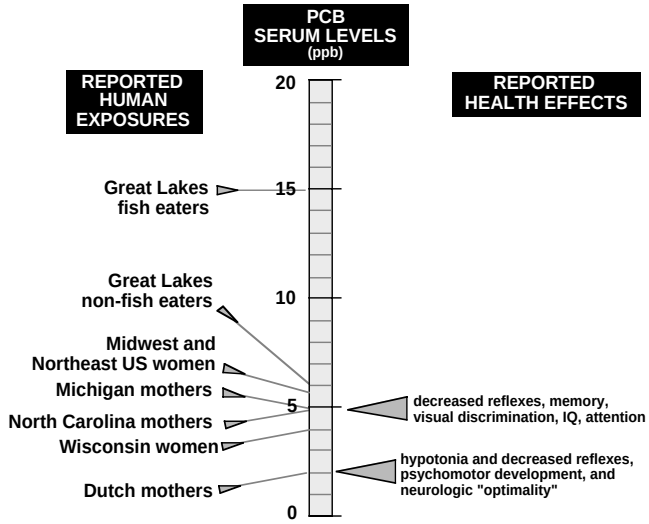
In the late 1960s and early 1970s two episodes of accidental human exposure to PCB-contaminated rice oil in Japan and T aiwan r esulted in tragic developmental effects in children born to exposed mothers. [93] The developing fetus was much more sensitive than mothers, and numerous abnormalities were observed including low birth weight, hyperpigmented skin, swollen gums and eyelids, and early tooth eruption. Neurological abnormalities were among the most significant findings, including mental retardation among some of the most highly exposed. Delayed brain development and behavioral abnormalities in the children persist for years after the incidents. Exposed children have deficits on IQ testing, and according to teachers, are hyperactive and exhibit more behavioral problems than those unexposed. [94]

Although these tragic incidents exposed children to obviously toxic amounts of PCBs, other studies have examined the neurodevelopmental effects of exposures to levels of PCBs found in the ambient environment. One group of 212 children in Michigan has been followed for years. Children were classified as offspring of fish-eating mothers if maternal Lake Michigan fish consumption was at least 6-8 oz/month. Some of the study families, however , were not fish eaters. In most cases, but not all, fetal and nursing PCB exposure correlated with maternal Lake Michigan fish consumption before and during pregnancy . The childr en most highly exposed to PCBs prenatally showed delayed or reduced psychomotor development and poorer performance on a visual recognition memory test. [95] These children have now been followed for more than 11 years. Prenatal PCB exposure remains associated with lower IQ scores after controlling for other factors, including socioeconomic status. [96] Compared with the low exposure group, the most highly exposed children were more than three times as likely to perform poorly on IQ tests and tests designed to measure their attention span. They were more than twice as likely to be at least two years behind in word comprehension in reading. According to the investigators, the most frequent manifestations of neurodevelopmental toxicity of PCBs are disturbances in neuromotor activity and attention (deficits in focused and sustained attention), impairments of higher cognitive functions and learning, and neurodevelopmental delays. These disturbances seem likely to persist throughout the school years.

Another group of children in North Carolina shows similar results. Higher fetal PCB exposures, as measured by PCB levels in maternal blood, were associated with lower scores on psychomotor development tests (Brazelton) at six and twelve months of age than those with lower exposures. [97]

In a New York study of several hundred newborn children whose mothers ate PCB-contaminated fish from Lake Ontario, those with the higher exposures showed abnormal reflexes and startle responses and

PCBs: Inadequate Margin of Safety



decreased visual recognition when compared with the less exposed. [98] Recently, investigators reported that, at 12 months of age, prenatal PCB exposure was associated with poorer performance on the Fagan Test of Infant Intelligence and at 3 years of age with poorer performance on the McCarthy Scales of Children's Abilities. [99]

The development of another group of 418 children has been studied prospectively for several years in the Netherlands, after measuring PCB/dioxin levels in maternal blood during the last month of pregnancy, in umbilical cord blood, and in breast milk. These exposures were all at ambient environmental levels and not the result of a large accidental exposure or of excessive fish consumption. Cognitive abilities were assessed in 395 of these children with the Kaufman Assessment Battery for Children at 42 months of age. [100] After adjustment for co-variables, maternal PCB blood levels were significantly associated with lower scores on the overall cognitive and sequential and simultaneous processing scales of this battery. Lactational exposures and current exposure to PCBs and dioxin were not related to 42-month cognitive performance, indicating that the adverse effect is the result of fetal exposure to PCBs.

The investigators also report that umbilical cord and maternal PCB blood levels are significantly associated with less time at high level play. Blood PCB levels in 42-month old children are associated with slower reaction times and more signs of hyperactivity as reported by parents. This study also reported small but significant reductions in thyroid hormone levels at 2 weeks and 3 months of age in the children with the highest PCB/dioxin fetal exposures. [101]

Prenatal exposure to background levels of PCBs has been shown to adversely effect reflexes, memory and neurological function as assessed by physical exam in infants and toddlers. Adverse effects on attention, memory, intelligence and reading comprehension have been demonstrated in children followed up to age 11.[1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22]

Mechanisms of Neurotoxicity

The mechanisms of action of dioxins and PCBs on early neurological development are incompletely understood. Dioxins and some PCBs share one mechanism of action but differ in others. However, because their chemical characteristics are similar, they tend to co-exist in biological tissues, making it difficult to distinguish between their toxic effects in human epidemiological studies.

Dioxins and dioxin-like PCBs (so-called coplanar or non-ortho PCBs) share a common mechanism of action by binding to the Ah receptor. This complex is then further processed and passes into the cell nucleus where it binds to DNA, influencing the production and metabolism of a variety growth factors, hormones, and hormone receptors. However, many non-coplanar or ortho-PCBs that do not readily attach to the Ah receptor also have biological activity, which substan-

tially contributes to their neurodevelopmental toxicity . At least some of this toxicity may result from interference with thyroid hormone function.

PCBs may interfere with thyroid hormone in a variety of ways. In animal tests, some PCBs displace thyroxine from its carrier protein, transthyretin, in the circulation. In many animals, thyroxine, attached to transthyretin, is the form by which thyroid hormone gains access to the fetal brain. Any chemical that interferes with this binding has the potential to alter normal brain development. However, in humans, another protein, thyroid binding globulin, is the main carrier protein for thyroxine, and their binding is less affected by PCBs.

Dioxin and PCBs may also interfere with thyroid hormone function by increasing the turnover of thyroxine through induction of an enzyme, which facilitates the metabolism and excretion of the hormone. [102] PCBs may also interfere with thyroid-hormone-mediated gene transcription. [103] A recent report, however , shows that, although pr enatal PCB exposure does reduce thyroxine levels, thyroid-dependent protein synthesis in the brain is not affected by the doses used. [104] This finding implies that the neurodevelopmental effects of prenatal PCB exposures are not exclusively due to decreased thyroid hormone levels.

Some PCBs also alter normal brain neurotransmitter levels, although the nature of change depends on PCB structure. [105] For example, ortho-PCBs decrease dopamine synthesis while non-ortho PCBs increase dopamine levels after in utero and lactational exposure in rats. [106] This effect may also be related to the neurodevelopmental delays described in humans exposed to PCBs in utero.

Conclusion

Dioxins and PCBs adversely affect brain development and function at ambient levels of exposure. The effects of prenatal exposure to PCBs appear to be permanent. Psychomotor developmental delays, attention deficits, changes in play behavior, and cognitive impairment, including IQ deficits, have been described in large human study populations. The mechanism(s) by which these chemicals exert their neurotoxic effects are not fully understood but probably include alterations in neurotransmitter levels and thyroid hormone function.

PESTICIDES

- Animal tests of pesticides belonging to the commonly used organophosphate class of chemicals show that small single doses on a critical day of development can cause permanent changes in neurotransmitter receptor levels in the brain and hyperactivity
- One of the most commonly used organophosphates, chlorpyrifos (Dursban), decreases DNA synthesis in the developing brain, resulting in deficits in cell numbers
- Some pyrethroids, another commonly used class of pesticides, also cause permanent hyperactivity in animals exposed to small doses on a single critical day of development

- Children exposed to a variety of pesticides in an agricultural community in Mexico show impaired stamina, coordination, memory, and capacity to represent familiar subjects in drawings

Many pesticides kill insects because they are neurotoxic. For example, the organophosphates and carbamates inhibit acetylcholinesterase, the enzyme responsible for breaking down the neurotransmitter acetylcholine. Other families of pesticides including pyrethroids, pyrethrins, and organochlorines also exert their toxic action by interfering with nerve cell function. Routes of exposure to pesticides are discussed in Chapter 7.

Organophosphates

Organophosphates are widely used for pest control in the home, on the lawn and garden, and on the commercial food supply.

Animal Tests

Studies in neonatal mice show that a single dose of an organophosphate pesticide (1.5 mg diisopropylfluorophosphate [DFP]/kg body wgt) on postnatal day 10 causes permanent decreases in muscarinic cholinergic receptors in the cerebral cortex and hyperactivity at 4 mos. of age. [107] Exposed animals showed persistently increased locomotion (horizontal movement) and total activity (all types of movement) when compared to untreated controls.

Chlorpyrifos (Dursban), one of the most heavily used organophosphates, also causes neurochemical and behavioral effects in rats exposed during gestation. Pregnant rats given chlorpyrifos (6.25, 12.5, or 25 mg/kg/day by injection, gestational days 12-19) had offspring with fewer muscarinic cholinergic receptors in their brains and markedly altered righting reflex and cliff avoidance tests. [108] When maternal rats are treated with 5 mg chlorpyrifos/kg/day by gavage from gestational day 6-postnatal day 11, offspring have a decreased auditory startle response and decreased brain weight. [109] (For comparison purposes, the current reference dose [RfD] for chlorpyrifos, the human dose below which no adverse effects are considered likely, is 3 microgm/kg/day)

Studies in neonatal mice show that a single dose of an organophosphate pesticide on postnatal day 10 causes hyperactivity at 4 mos. of age.

Another organophosphate, diazinon, was given to pregnant mice at 0, 0.18, or 9.0 mg/kg/day thoughout pregnancy, and the development of their offspring was evaluated. [110] Offspring of the mothers receiving the highest dose grew more slowly than those in the lower exposure groups. Although offspring of those receiving the lowest dose grew normally, behavioral testing revealed delays in development of the contact placing reflex and sexual maturity. Adult offspring of mothers exposed at either dose showed impaired endurance and coordination. The RfD for diazinon is under review by EPA.

Organochlorines

DDT is an organochlorine pesticide no longer used in the US but heavily used in some parts of the world both in agriculture and for disease vector control. DDT was banned in the US and

other countries because of toxicity to wildlife and its capacity to bioaccumulate and persist in the environment for years. DDT also exerts its toxic action by interfering with the stability of nerve cell membranes, resulting in overstimulation of the nervous system in exposed animals.

Animal Tests

Newborn mice were given a single dose of 0.5 mg DDT/kg on day 3, 10, or 19 of life and examined at 4 months of age for activity level and muscarinic cholinergic receptors in the brain cortex. [111] Those animals exposed to DDT on day 10 showed significant increases in activity level and decreases in receptor levels at that age. Mice exposed on days 3 or 19 did not show significant changes. These results highlight a short but significant window of vulnerability to a neurotoxic chemical when exposure may have lifelong effects on brain structure and function.

Human Studies

Reports of the neurological evaluation of children exposed to pesticides are few and are usually limited to the acute effects of exposures. However , a recent study of childr en in Mexico, who are regularly exposed to a mixture of pesticides in their largely agricultural community , suggests that many different brain functions may be impaired by pesticide exposure during child development. [112] Researchers compared two different groups of 4-5 year old children who came from very similar genetic, social, and cultural backgr ounds. However , one gr oup lived

in a community where pesticides were regularly used in agriculture whereas the other came from a community with a non-chemical agricultural system. A variety of organochlorine pesticides were measured in the umbilical cord blood and breast milk of individuals in the pesticide-exposed community , though exposure to other classes of pesticides wer e also likely .

Children in the exposed community showed significantly diminished stamina and coordination when asked to catch a ball, stand on one foot as long as possible, jump in place, and drop raisins into a bottle cap from a distance of 15 cm. Memory in the pesticide-exposed children was also impaired. They were less able to recall what they had been promised as a reward (a red balloon) before testing started. Exposed children were also impaired in their ability to draw recognizable representations of people and objects. When asked to draw a person, exposed children averaged 1.6 body parts/drawing in drawings considerably more distorted than those

of the unexposed children that averaged 4.4 body parts/drawing. Houses and trees drawn by pesticide exposed children were also more distorted and difficult to interpret. Exposed children appeared to be less creative in their play activity.

Pyrethroids

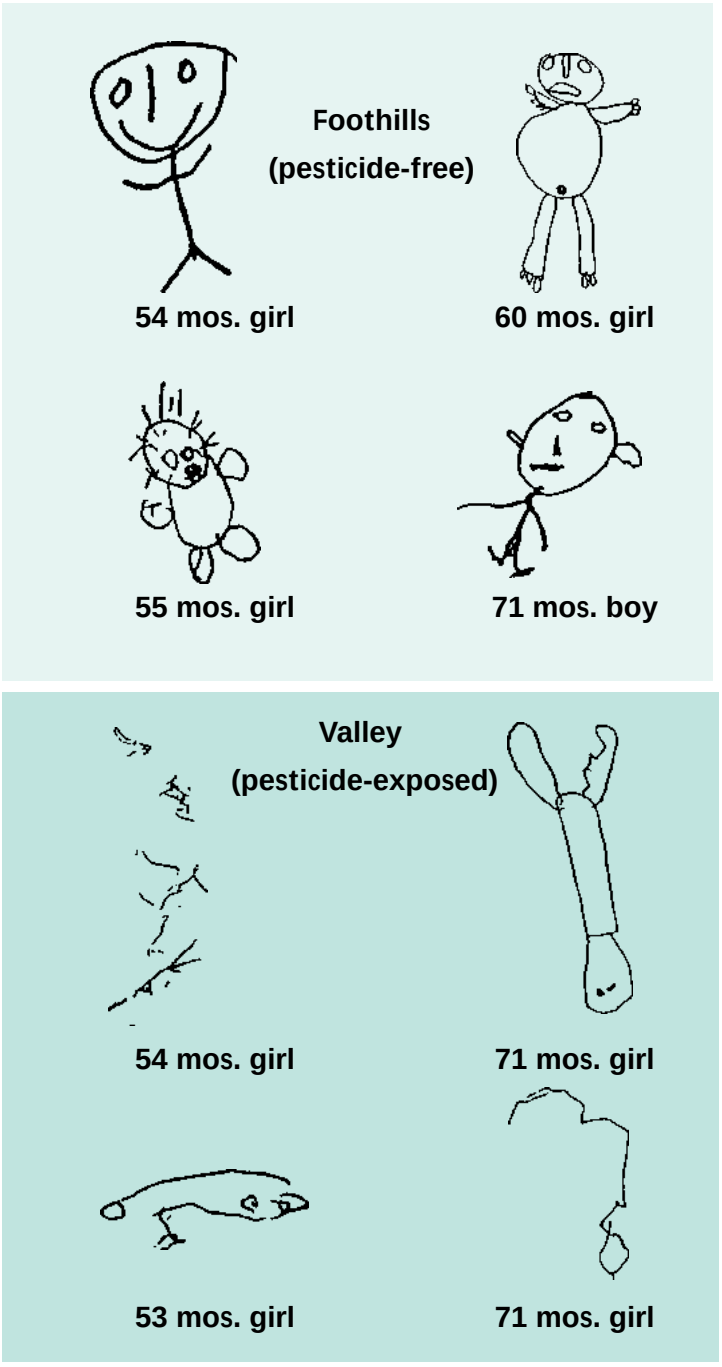
Naturally-occurring pyrethrins or synthetic pyrethroids are insecticides that also exert their toxic action by interfering with the electrical activity of nerve cells. They are sometimes divided into Type I and Type II compounds. Type I cause repetitive firing of nerve cells while Type II cause nerve inexcitability by blocking cell depolarization.

Animal Tests

Mice given small doses of bioallethrin (T ype I) or deltamethrin (Type II) on day 10 of life also show reduction in muscarinic cholinergic receptor levels in the brain cortex as adults, along with hyperactivity .[113] In an attempt to better define the dose-response curve, investigators used doses of bioallethrin at 0.21, 0.42, 0.70, and 42 mg/kg on day 10 of life. The hyperactivity of the mice as adults increased with increasing levels of exposure through the 0.70 mg/kg dose, but then fell sharply with the 42 mg/kg dose. This observation is particularly important for pesticide testing in that testing at higher doses of exposure may fail to identify an adverse effect seen only at lower levels of exposure. Current methods for dose selection for pesticide regulatory testing purposes may miss this effect and should be re-examined.

Drawings of a Person

by Yaqui children (by age and gender)



Illustrations are those by Mexican Yaqui Indian children drawn during a study of the effects of pesticide exposure on neurological development. The study was conducted by Elizabeth A. Guillette, PhD, University of Arizona. Illustrations used with permission.

Another study of two pyrethroids, fenvalerate and cypermethrin, examined the effect on neurotransmitter levels in offspring of rats after gestational and lactational exposures.[114] Alterations in levels of neurotransmitter enzymes (monamine oxidase and acetylcholinesterase) were noted. Dopamine receptor levels in the brain were decreased after exposure to each of the chemicals and muscarinic cholinergic receptor levels were markedly decreased only after cypermethrin.

Mechanisms of Neurotoxicity

The low concentrations of chlorpyrifos necessary to impair DNA synthesis and cell division are actually lower than exposure levels of children under some pesticide home-use conditions.

Organophosphates and carbamates inhibit acetylcholinesterase, the enzyme responsible for breaking down the neurotransmitter acetylcholine at nerve synapses or at the junction of nerves with muscles. The result is twofold. In the short term, the synapse or neuromuscular junction is overstimulated and clinical symptoms result. But in the developing organism, as previously noted, neurotransmitters also play important roles in orchestrating cell proliferation, migration, differentiation, synapse formation and apoptosis. Alterations in neurotransmitter levels during development have significant effects on the brain that do not occur after adult exposures.

Several different mechanisms help explain the neurodevelopmental effects of organophosphates. First, by altering neurotransmitter levels (acetylcholine and others secondarily) these chemicals interfere with cell replication and differentiation. Second, acetylcholinesterase itself appears to have a role in brain development, independent of its serving as an enzyme to break down the neurotransmitter, acetylcholine. Research shows that the enzyme facilitates neurite outgrowth from neurons and that deficiency of the enzyme reduces neurite outgrowth.[115] In addition, chlorpyrifos decreases DNA synthesis, independent of its cholinergic mechanism, resulting in deficits in numbers of cells in the developing brain.[116] [117] This latter observation is particularly important for two reasons. First, the potential for toxicity of organophosphates is often inferred from the degree of cholinesterase inhibition, but the effects of chlorpyrifos on DNA synthesis and cell numbers show that no general conclusions may be drawn from anticholinesterase activity alone. Neurotoxicity testing has not generally been designed to measure the effects of organophosphates on cell proliferation and differentiation. The presumption has been that cholinesterase inhibition is the most sensitive endpoint. Second, the low concentrations of chlorpyrifos necessary to impair DNA synthesis and cell division are actually lower than exposure levels of children under some pesticide home-use conditions.[118] [119]

Pyrethroids, pyrethrins, and organochlorines also exert their toxic action by interfering with nerve cell function. By modifying the permeability of nerve cell membranes to various ions they may either increase or decrease the excitability of nerve cells causing repetitive firing or prolonged inactivity. Studies done in developing animals show that each of these classes of insecticides

may also permanently alter neuroreceptor levels in portions of the brain and modify animal behavior as a result.

Conclusions

Several different classes of pesticides show unique neurodevelopmental toxicity in animals exposed during gestation or at particular windows of vulnerability in the neonatal period. Small exposures during those periods of susceptibility permanently alter brain neur oreceptor levels and cause hyper - activity in the animals as adults. These adverse effects are distinctly unlike those seen after adult animal exposures. It is important to note that the stage of brain development in rodents at age 10 days is similar to the same stage in humans during the last trimester of pr egnancy . These results, therefore, suggest the potential for similar effects in the offspring of women who are exposed to these types of chemicals during the latter par t of pr egnancy . One study of childr en exposed to a mixture of pesticides during development shows adverse impacts on a variety of neurological functions, including stamina, coor dination, memor y, and ability to conceptualize and draw . These r esults confirm the need for comprehensive neurodevelopmental testing of pesticides before they are licensed for commercial use. Under cur rent law , the US EP A is authorized to require such testing but, with rare exceptions, has failed to exer cise that authority . (see chapter 7)

SOLVENTS

- Exposure to organic solvents during development may cause a spectrum of disorders including structural birth defects, hyperactivity , attention deficits, reduced IQ, learning and memory deficiencies.
- As little as one alcoholic drink a day during pregnancy may cause impulsive behavior and lasting deficits in memor y, IQ, school performance, and social adaptability in offspring.
- Animal and limited human studies show that exposures to common chemicals like toluene, trichloro-ethylene, styrene, and xylene during pregnancy can also cause learning deficiencies and altered behavior in offspring, though fairly large exposur es may be necessar y.

Routes of Exposure

Organic solvents are widely used in consumer products, hobbies, and industry. Releases of some or ganic solvents to the environment from large industrial sources are reported on the Toxics Release Inventory (TRI). For example, in 1997 over 115 million pounds of toluene, 75 million pounds of xylene, 46 million pounds of styrene, and 21 million pounds of trichlor oethylene wer e released to air , water , and land by the lar gest industries required to report their toxic emissions. Ethanol is consumed in alcoholic beverages. Toluene and xylene ar e in gasoline and its vapors, as well as other consumer products. Trichlor oethylene is commonly used as a degreaser and is a common drinking water contaminant at low concentrations. Because many solvents are volatile, inhalation exposures are particularly important.

Clinical manifestations of fetal alcohol exposure include hyperactivity and attention deficit.

Ethanol (alcohol)

The neurodevelopmental effects of ethanol have been extensively studied. The term "fetal alcohol syndrome" (FAS) was first coined in 1973 to describe malformations in the offspring of chr onic alcoholic women. [120] However , the consequences of fetal alcohol exposure had been known long before. Affected children show a mixture of craniofacial, limb, and cardiovascular defects associated with growth and developmental delays, though the degree of impair ment can var y considerably . Cognitive functions may vary from normal to severely disrupted while physical features may independently vary from normal to obviously abnormal.

The Institute of Medicine of the National Academy of Sciences Committee to Study Fetal Alcohol Syndrome has proposed five diagnostic categories for fetal alcohol related abnor malities: [121] 1) diagnosis of F AS and a confirmed history of maternal alcohol exposur e, 2) diagnosis of F AS without a confirmed history of maternal alcohol exposur e, 3) par tial FAS with confirmed alcohol exposure, 4) alcohol related birth defects, 5) alcohol related neurodevelopmental disorders.

The spectrum of clinical abnormalities probably reflects differences in timing, duration, and level of alcohol exposure during gestation, although the timing of periods of vulnerability for each of the various disorders is not well known. First trimester exposure is probably necessary for the distinctive physical facial abnormalities seen in FAS.[122] Alcohol exposur e during the second and third trimester alters neuronal cir cuitr y. The thir d trimester is a particularly vulnerable time for brain injury as a result of alcohol exposure. [123] Alcohol's ef fects on the fetus ar e mor e related to the maternal peak blood alcohol level than to total alcohol consumed, so that binge drinking is likely to be more harmful than equal amounts consumed over a longer period of time. [124] One study finds a threshold effect at an average of 0.5 oz. absolute alcohol per day .[125]

Clinical manifestations of fetal alcohol exposure include hyperactivity and attention deficit.[126] Memory, speed of information processing, and arithmetic functioning are also

adversely affected.[127] Eating disorders, bedwetting, sleep disorders, speech delay, anxiety, depression, and psychotic symptoms may also occur. Although there is a higher likelihood of cognitive disorders and mental retardation in FAS children, mental function varies and may be normal.

A study of 16 pairs of twins heavily exposed to alcohol prenatally found concordance for fetal alcohol syndrome in five pairs of monozygotic twins and in 7 of 11 pairs of dizygotic twins.[128] Genetically-determined variations in maternal metabolism of alcohol also influence the likelihood of FAS in offspring, since one of the metabolites of alcohol, acetaldehyde, is thought to contribute substantially to the condition.[129] These observations demonstrate the interaction of genetic factors with a well-known neurodevelopmental toxicant.

One of the difficulties encountered in studying the results of fetal alcohol exposure is the frequent co-occurrence of poor maternal nutrition, delayed prenatal care, and other maternal substance abuse, including tobacco. These factors complicate efforts to tease out the clinical features that are solely due to alcohol. Moreover, eating and sleep disturbances, behavioral difficulties, and impaired cognitive functioning and attention often adversely impact the mother-infant relationship. Thus, it is difficult to know how much future disability is attributable to fetal alcohol exposure and how much is due to social factors during infancy and early childhood.

Mechanisms of Neurotoxicity

Animal studies show that fetal alcohol exposure causes reduction in brain weight, selective loss of certain cells, impaired maturation of cells, and retarded synaptic development.[130] [131] Several different mechanisms probably contribute to alcohol toxicity. They include disruption of cell-cell interactions by interfering with cell adhesion molecules[132], reduction of placental transport of amino acids, glucose, and other nutrients as a result of reduced oxygen supply[133], and abnormalities of synaptic transmission.[134]

Other Solvents

Human Studies

Compared to ethanol, much less is known about the effects of other solvents on brain development and function. Occupational exposures to solvents may cause both peripheral and central nervous system effects in adult workers and are also associated with birth defects, including abnormalities of the central nervous system, in their offspring.[135] [136] However, little information is available about the neurological development of children whose mothers were exposed to solvents during pregnancy. One study examined neurological development of children at an average age of 3 years whose mothers had been occupationally exposed to solvents during at least some portion of pregnancy.[137] No significant effect was found on evaluation for attention, behavior, sociability, activity, or learning. Developmental milestones were the same in exposed and unexposed groups, with

the exception of delayed onset of walking in the children exposed throughout pregnancy as compared to unexposed children. (13.3 mos. vs. 12.2 mos.) This finding is of uncertain significance since the children of mothers exposed for only the first or first and second trimesters of pregnancy actually began walking sooner than the unexposed. (10.8, 11.6 mos vs. 12.2) Maternal exposures in this study were not actually measured, and no attempt was made to correlate developmental outcomes with specific solvents. It may, therefore, be misleading to draw any firm conclusions from this single study.

Toluene is an organic solvent used in glues, inks, paints, cleaning agents, and gasoline. After large exposures, such as encountered with maternal glue sniffing during pregnancy, offspring may be born with craniofacial abnormalities resembling those of FAS.[138] Follow up studies show growth retardation and persistent deficits in cognition, speech, and motor skills. It is unknown whether or not a threshold level of exposure to toluene exists, below which no neurodevelopmental effects occur in humans. The developmental effects of toluene so closely resemble those of alcohol, that some investigators believe the mechanism of toxicity is similar.[139] As with alcohol, it may be the case that even relatively small exposures to toluene have subtle but important effects on neurocognitive development, though this has not been studied well in humans.

Animal Studies

Animal studies also show neurobehavioral consequences of intermittent large prenatal exposures to toluene. Pregnant mice were exposed to 200, 400, or 2000 ppm (parts per million) toluene by inhalation for 60 minutes, 3 times a day, on gestational days 12-17. Offspring from the highest exposure group performed more poorly on behavioral tests of righting reflex, grip strength, and inverted screen.[140] Rats exposed to 1800 ppm toluene 6 hrs/day by inhalation on days 7-20 gestation gave birth to offspring with impaired learning when tested in a Morris water maze.[141] Occupational safety limits for toluene in the US allow 200 ppm exposure for a 40 hr. work week. (Occupational safety limits may not be enforced. The values are presented here only for purposes of comparison to experimental data.) Mice supplied with drinking water containing 16, 80, or 400 mg. toluene/liter (ppm) during pregnancy and lactation gave birth to offspring with deficient motor skills (rotorod performance).[142] The highest exposed group showed decreased habituation in open-field activity. The EPA's maximum contaminant level (MCL) for toluene in drinking water is 1.0 mg/l (ppm).

The offspring of rats supplied with drinking water containing 312, 625, or 1250 mg trichloroethylene/liter (ppm) throughout gestation and lactation were studied.[143] Exploratory behavior was increased in 60- and 90-day old male rats exposed at any level. Locomotor

activity (running wheel) was higher in rats exposed to 1250 ppm trichlor oethylene. The EP A's drinking water MCL for trichloroethylene is 0.005 mg/l (ppm) The offspring of rats exposed to 1800 ppm trichloroethylene by inhalation 6 hr/day , 5 days per week for 2 weeks before mating had reduced body weight but no evidence of behavior abnormalities. [144] The offspring of those exposed throughout pregnancy had marginally reduced activity levels. Occupational safety limits in the US allow trichloroethylene exposure at 100 ppm for a 40 hr . work week.

Xylene exposure by inhalation at 500 ppm, 6 hrs/day , on gestational days 7-20 resulted in rat offspring with decreased brain weight and diminished motor performance (rotorod) and learning and memory (Morris water maze).[145] 500 mg/m3 xylene is equivalent to 115 ppm. In another study , the offspring of rats exposed to xylene at 500 mg /m3, 6 hrs/day , 5 days/wk, throughout pregnancy showed reduced horizontal movement in open field testing and structural changes in brain, hear t, liver , and kidneys. [146] At 50 mg/m3 offspring showed retarded growth and skeletal abnormalities. Occupational safety limits in the US allow xylene exposure at 100 ppm for a 40 hr . work week.

Young rats (1-48 days of age) exposed to styrene at 25 and 50 ppm 7 hrs/day , 6 days/wk. showed significant delays in weight gain, decreased activity in open field testing, and decreased avoidance behavior .[147] Occupational safety limits for styrene exposure in the US allow 50 ppm for a 40 hr . work week. Another study shows an important interaction between prenatal styrene exposure and dietary protein deficiency .[148] Rats given a pr otein deficient diet and styrene (100 mg/kg/day) during pregnancy gave birth to offspring with lower brain weights and a marked increase in amphetamine-induced hyperactivity when compared to controls, including those exposed to just styrene or only a low protein diet.

Conclusions

In summar y, many studies show that fetal exposure to relatively small amounts of alcohol disrupts normal brain development, resulting in hyperactivity , attention and lear ning disor ders, and impair ed memor y. The magnitude of risk of fetal alcohol syndrome depends on both genetic and environmental factors and their interactions. Large inhalation exposures to toluene during pregnancy (glue sniffing) also carries the risk of devastating effects on fetal brain development, as well as causing structural birth defects. The effects of smaller exposures on fetal brain development are unknown. Other solvents that may be encountered in the workplace or in consumer products have the potential for disrupting normal brain development but usually at relatively high exposur e levels. However , animal tests suggest that, at levels at or below those allowed in the workplace, xylene and styr ene may alter lear ning, behavior , motor skills, and activity levels after fetal exposure. Since volatile solvents are

Animal tests suggest that, at levels at or below those allowed in the workplace, xylene and styrene may alter learning, behavior, motor skills, and activity levels after fetal exposure.

often present in consumer products, excessive hobby and home exposures are possible, particularly when products are used in confined or poorly ventilated areas. Nutritional factors may also contribute to neurodevelopmental impacts of solvent exposure.

Additional Chemicals of Concern

Although assessments for developmental neurotoxicity are missing for many chemicals, two very different kinds of substances deserve particular mention because they are intentionally added to water or food, thereby exposing large populations on a lifetime daily basis. Whenever entire populations are exposed to any chemical substance through the food or water supply, exhaustive safety evaluations should be essential prior to initiation of exposure and as new data become available.

Fluoride

Since the 1950's, in many communities throughout the US and other areas of the world, fluoride has been added to community drinking water supplies with the intention of reducing tooth decay. Controversy about the safety of that practice centers around concerns about increased risks of tooth staining and brittleness (dental fluorosis), bone brittleness (skeletal fluorosis), bone cancer, hormone disruption (melatonin), premature puberty, and altered neurological developmental. In addition, some critics argue that fluoridating the water supply has a minimal impact on tooth decay. The practice has been staunchly defended by the American Dental Association and heralded by the Centers for Disease Control and Prevention as one of the major public health success stories of the 20th century. We do not intend to review the entire controversy here. Recent reviews are found elsewhere.[149] [150] [151] Rather, here we comment briefly on concerns about neurodevelopmental impacts of prenatal exposure to fluoride.

The US EPA sets a Recommended Maximum Contaminant Level of 4.0 ppm fluoride in drinking water. The National Institute for Dental Research considers fluoride at 1 ppm optimal for preventing dental caries. This level may be exceeded in some communities. Additional sources of fluoride, including topical fluoride treatments, fluoride tablets, and fluoride toothpaste, add to the total fluoride burden.

In an animal study, pregnant rats were given 0.13 mg sodium fluoride/kg by injection on 9 separate occasions from days 14-18 or 17-19 during pregnancy.[152] Offspring of treated animals and controls were monitored by videotape that was then computer-analyzed in order to quantify various behavioral characteristics. Offspring

exposed to fluoride on days 17-19 of pregnancy showed significant hyperactivity . They tended to move fr om one activity to another more frequently than unexposed animals. This study has been criticized for using excessive fluoride exposures. The authors respond by noting that the blood levels of fluoride in the treated animals were similar to the levels measured in people who are exposed through fluoridated water . Another criticism center ed on the lack of biological plausibility that the results would differ in the two groups exposed at similar times during pregnancy .[153] The authors, however , point out that vulnerable developmental stages change rapidly during this time window and argue that the findings are entirely plausible. [154]

Another study found that the offspring of rats given 5, 15, 50 ppm fluoride in drinking water during pregnancy and lactation had significantly elevated acetylcholinesterase levels when tested at 80 days of age. [155] Maternal acetylcholinesterase levels were also increased. Though not measured in this study , a likely r esult of elevated acetylcholinesterase activity is decreased acetylcholine levels. As we have noted, the enzyme, acetylcholinesterase, and the neur otransmitter , acetylcholine, play important roles in brain development. Changes in the concentrations of any neurotransmitter during development may have permanent neurological consequences. The largest effect was seen at 5 ppm, decreasing at the higher levels.

Two reports from China identify significantly lower childhood IQs in communities where fluoride exposure is elevated. In one community, where drinking water naturally contains 4.12 ppm fluoride, IQs were significantly lower than in a nearby community with fluoride levels at 0.91 ppm. (average IQ 98 vs. 105)[156] This difference persisted when the study population was controlled for parental educational level. The authors describe similar occupations, living standards, and social customs in the two communities. The ecologic design of this study imposes some limits on the conclusions that may be drawn since the exposure (fluoride) and outcome (IQ) were compared on a population-wide basis without any attempt to associate individual fluoride exposure levels with individual IQs. Nonetheless, an IQ shift of 7 points in an entire population has large population-wide implications, as well as impacting individual members, and these results deserve close attention.

In the other study, investigators used dental fluorosis and urinary fluoride levels to stratify children into four quartiles.[157] Elevated fluoride exposures were associated with decreased IQs in this population. That is, the distribution of IQ scores in children in each quartile of fluoride exposure shifted progressively downward as the fluoride exposures increased.

Conclusion

Studies in animals and human populations suggest that fluoride exposure, at levels that are experienced by a significant proportion of the

Studies in animals and human populations suggest that fluoride exposure, at levels that are experienced by a significant proportion of the population whose drinking water is fluoridated, may have adverse impacts on the developing brain.

population whose drinking water is fluoridated, may have adverse impacts on the developing brain. Though no final conclusions may be reached from available data, the findings are provocative and of significant public health concern. Perhaps most surprising is the relative sparseness of data addressing the central question of whether or not this chemical, which is intentionally added to drinking water, may interfere with normal brain development and function. Focused research should address this important matter urgently.

Food Additives

The potential for certain food additives to alter neurological development, behavior, and learning capacity has been the subject of lively debate and controversy for many years. Food additives of concern are 1) the amino acid, glutamate, present naturally in many proteins and added to many processed foods, 2) the artificial sweetener, aspartame, which is metabolized into the two amino acids, aspartate and phenylalanine, and 3) food colorings and dyes.

One focus of concern centers around the observation that glutamate and aspartate are the major excitatory amino acid neurotransmitters in the mammalian brain and that large amounts of glutamate administered to pregnant rhesus monkeys late in gestation result in damage to the fetal brain.[158] [159] Damage to the hypothalamus, the portion of the brain responsible for sending chemical messages to the underlying pituitary gland, and an essential link in hormonal regulatory processes, has been most extensively studied.

It is important to note that most of the adult brain is protected by the blood-brain barrier, whereas the blood-brain barrier is not complete in the developing human brain until about six months of age (3 weeks in rats, an important difference when considering the design of neurotoxicity testing). However, the hypothalamus is not protected by a blood-brain barrier at any time during life and remains in contact with any potentially neurotoxic substances circulating in the blood.[160] Destruction of hypothalamic cells would be expected to disrupt the intricate chemical messenger (hormonal) feedback loops among the hypothalamus, pituitary, and testes or ovaries.

Indeed, studies show that rats treated in the neonatal period with large doses of monosodium glutamate (MSG) have significantly smaller accessory sexual organs and lower concentrations of testosterone.[161] However, the doses of MSG used in these studies are often 2-5 gms/kg on several consecutive days, levels known to cause destruction of hypothalamic neurons, whereas the upper bound of human dietary daily intake of MSG is approximately 35 mg/kg.[162] [163] [164] However, Olney argues that blood glutamate levels, after an oral dose in adult humans, rise 20 times higher than a comparable dose in adult monkeys and five times higher than in mice.[165] Therefore, he says, the margin of safety is not what it appears from animal testing.

One study shows that the offspring of rats fed diets containing 2%, 4%, or 6% aspartame during pregnancy and lactation showed delays in eye opening, swimming, righting, startle response, and walking. [166] Effects were seen at each exposure level. Exposure during nursing had more effect than prenatal exposure. These exposures are approximately 3-9 gms/kg/day, which is about a thousand times higher than expected human exposure levels. However, it is important to remember the lessons from lead, mercury, and PCBs - that animal studies commonly underestimate human sensitivity to developmental neurotoxicants by 100-10,000 fold.

The second focus of concern centers on the apparent capacity of food dyes and additives to alter behavior in some children diagnosed with ADHD or other attentional disorders. In the 1970's, Benjamin Feingold sparked considerable interest when he linked food additives to behavior changes in children with hyperactivity, mood, and behavioral disorders.[167] Since then, the topic has remained highly controversial. A recent report from the Center for Science in the Public Interest reviewed 23 controlled studies, some of which were blinded, and found 17 with evidence that some children's behavior significantly worsens after they consume artificial colors or certain foods. [168] The authors also note that the National Institute of Mental Health largely dismiss diet as a treatment approach and that the Food and Drug Administration denies the effect of diet on behavior. This topic is an instructive intersection of published scientific studies, anecdotal reports, regulators, a publicly funded research institution, burdens of proof, and uncertainty.

Conclusions

For about 25 years considerable controversy has swirled around the degree to which food additives, including artificial sweeteners, flavor enhancers, colorings, and dyes, may influence children's brain function. Studies show that exposures substantially higher than those in the human diet are necessary to cause observable adverse effects in animals. Historical reviews show, however, that animal tests frequently underestimate the sensitivity of the human brain. Human studies also show that at least some children appear to be particularly sensitive to dietary exposures to these additives, with hyperactivity and decreased attention spans.

The degree to which these food additives contribute to attentional and behavioral disorders in the general population remains uncertain, though it seems clear that some children respond with behavioral changes recognized by parents, teachers, and healthcare providers. The link between diet and behavior in children with ADHD is uncertain and remains a matter of considerable disagreement. A substantial body of literature concludes that the link exists in some children and raises questions about the origins of a heightened sensitivity to these dietary exposures. Genetic and early-life environmental factors must be considered as these questions are explored.

Toxicants and their Health Effects

Toxicant	Health Effects/ Characteristics
Metals	
Cadmium – H, A	Learning disabilities Decreased IQ Motor dysfunction Hyperactivity Hypoactivity
Lead – H, A	Learning disabilities IQ deficit Attention deficit Impulsivity Violence Hyperactivity Aggression
Manganese – H, A	Brain damage Motor dysfunction Compulsive behavior Memory impairment Hyperactivity Learning disabilities Attention deficit
Mercury – H, A	Visual impairment Learning disabilities Attention deficit Motor dysfunction Memory impairment (minimal) *At higher levels:* Smaller brain size, cellular distortions in brain Mental retardation
Solvents	
Ethanol (Alcohol) – H, A	Learning disabilities Attention deficits Memory impairment Behavioral disorders Eating and sleeping disorders Lower brain weight Craniofacial, limb and cardiovascular abnormalities associated with various growth and developmental delays Mental retardation
Styrene - A	Decreased activity Decreased avoidance behavior *In conjunction with dietary protein deficiency:* Lower brain weight, Hyperactivity

Toxicant	Health Effects/ Characteristics
Solvents	
Toluene – H, A	Learning disabilities Speech deficits Motor dysfunction Craniofacial abnormalities
Trichloroethylene - A	Increased exploratory behavior Hyperactivity
Xylene - A	Motor dysfunction Learning disabilities Memory impairment Decreased brain weight
Pesticides	
Organochlorines DDT - A Mixture – H	Hyperactivity Decreased stamina Decreased coordination Decreased memory Decreased ability to draw familiar objects
Organophosphates (including DFP, chlorpyrifos (Dursban), diazinon) - A	Developmental delays Hyperactivity Behavioral disorders Motor dysfunction
Pyrethroids (including bioallethrin, deltamethrin, cypermethrin) - A	Hyperactivity
Other	
Nicotine – H, A	Hyperactivity Learning disabilities Developmental delays in cognitive functions
Dioxins – H, A	Learning disabilities
PCBs – H, A	Learning disabilities Attention deficit Memory impairment Hyperactivity Psychomotor dysfunction
Fluoride – A H	 Hyperactivity Decreased IQ (ecologic studies)

H= Human studies,
A= Animal studies

Notes:

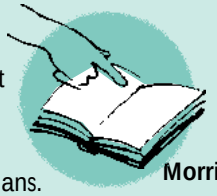
1. Learning disabilities include dysfunctions in listening, speaking, reading, writing, spelling or calculations.

2. Only neurodevelopmental, learning or behavioral effects of toxicants, or physical impairments that lead to them, are listed.

3. Chart information is synthesized from Chapter 6. Please see this chapter for references to studies on these chemicals.

GLOSSARY OF TESTS OF NEUROLOGICAL DEVELOPMENT IN RODENT STUDIES

Many different tests are used to assess the neurological development of experimental animals. It is important that these tests are validated and that they do, in fact, serve as useful indicators of normal or abnormal neurological function. Test validation has several components. Investigators must conduct testing in very similar conditions using standardized testing protocols. If those conditions are met, similar results should be observed in multiple laboratories and should be replicable in a given laboratory. Any test that is not replicable or that shows wide and unexplained variability in results has little utility for neurological testing. Finally, predictive power and species variability (species concordance) must be considered. These issues are particularly important when using animal tests to predict effects in humans.



The following descriptions are intended to provide the reader with a skeletal description only of the tests mentioned in this report. Standardized protocols for administering the tests are not included.

EARLY REFLEXES:

Placing response – the animal is held by the nape of the neck and touched on the chin with a stretched wire. Normally the animal grips the wire with its forelimbs. This response develops within a few days of birth

Righting reflex – the animal is placed on its back and observed for speed and ability to turn upright

AVOIDANCE:

Cliff avoidance – the animal is placed on a raised platform; the normal response is to turn away when visual stimulus suggests dangerous depth (height)

STRENGTH:

Grip strength – the strength with which the animal grips a wire with forelimbs against resistance

LOCOMOTOR ACTIVITY:

Open field activity – the animal is placed in the middle of a transparent plastic cage marked off into squares. Numbers of squares entered (total activity), horizontal and vertical movements (rearing), duration of inactivity, description of gait or any abnormal movements, habituation, and response to novel environments may be observed.

Rotorod performance – tests the ability of the animal to maintain its balance on a small horizontal cylinder that has a rubberized surface and is rotated by a motor at different standardized speeds. This tests balancing reactions and motor coordination.

Running wheel – the animal is observed running inside a rotating wheel

LEARNING AND MEMORY:

Morris water maze – the animal capable of swimming is placed in a tank of water with a small platform submerged just below the surface at a specific place in the tank. The animal finds the platform and can stand on it. This can be repeated at various intervals to test learning and memory. The position of the platform can be changed in order to examine the animal's tendency to perseverate or ability to re-learn.

T maze tests – the animal is placed in a T shaped maze and learns to find the reward in one arm of the maze. Maze tests, like other tests that require choices, can be reversed so that the animal must learn to change response strategies in order to be rewarded. Changing response strategies is more complex than learning the correct response initially and may be a more sensitive indicator of impaired learning.

Visual recognition – various tests are designed to test the animal's ability to recognize shapes, colors, or positions, by rewarding a correct response. Discrimination-reversal learning may then be tested by reversing the correct answer so that the previous correct answer is now incorrect.

Footnotes to diagrams

Mercury - Inadequate Margin of Safety

1 Agency for Toxic Substances and Disease Registry. Toxicologic Profile for Mercury. SU Dept. Health and Human Services, 1997.

2 Wheatley B, Paradis S. Northern exposure: further analysis of the results of the Canadian aboriginal methylmercury program. Int J Circumpolar Health, Suppl 1:586-90, 1998.

3 Wheatley B, Paradis S. Balancing human exposure, risk and reality: questions raised by the Canadian aboriginal methylmercury program. Neurotoxicology 17(1):241-9, 1996.

4 Fujita M, Takabatake E. Mercury levels in human maternal and neonatal blood, hair and milk. Bull Environ Contam Toxicol 18(2):205-7,1977.

5 MacIntosh DL, Spengler JD, Ozkaynak H, et al. Dietary Exposures to Selected Metals and Pesticides. Enivorn Health Perspect 104:202-9,1996.

6 Lebel J, Mergler D, Lucotte M et al. Evidence of early nervous system dysfunction in Amazonian populations exposed to low-levels of methylmercury. Neurotoxicology 17(1):157-67, 1996.

7 Hansen JC. Mercury and selenium concentrations in Greenlandic mother-infant blood samples. In: Dillon HK, Ho MJ, eds. Biological monitoring of exposure to chemicals: Metals. New York:John Wiley and Sons, 11-25. In ATSDR 1997, Toxicologic Profile of Mercury, p. 363.

8 Galster WA. Mercury in Alaskan Eskimo mothers and infants. Environ Health Perspect 15:135-40, 1976. In ATSDR p.347.

9 Airey D. Total mercury in human hair from 13 countries in relation to fish consumption and location. Sci Total Env 31:157-180, 1983.

10 Airey D. Total mercury in human hair from 13 countries in relation to fish consumption and location. Sci Total Env 31:157-180, 1983.

11 Airey D. Total mercury in human hair from 13 countries in relation to fish consumption and location. Sci Total Env 31:157-180, 1983.

Dioxin - Current Exposures

1 Patandin S et al. 1999. Ibid.

2 Schecter A, Ryan JJ, Masuda Y et al. Chlorinated and brominated dioxins and dibenzofurans in human tissue following exposure. Environmental Health Perspectives 102, Suppl. 1:135-47, 1994.

3 EPA. Health Assessment Document for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin and Related Compounds, 1994, p.IX-81.

Dioxin - Inadequate Margin of Safety

1 Malby TA, Moore RW, Peterson RE. In utero and lactational exposure of male rats to 2,3,7,8TCDD: 1.Effects on androgenic status. Toxicol Appl Pharmacol 114:97-107, 1992.

2 Bowman RE, Schantz SL, Gross ML et al. Behavioral effects in monkeys exposed to 2,3,7,8 TCDD transmitted maternally during gestation and for four months of nursing. Chemosphere 18:235-242, 1989.

3 Bowman RE, Schantz SL, Weerasinghe NCA, et al. Chronic dietary intake of 2,3,7,8 TCDD at 5 or 25 ppt in the monkey: TCDD kinetics and dose-effect estimate of reproductive toxicity. Chemosphere 18: 243-252, 1989.

4 Schantz, SL, Ferguson SA, Bowman RE. Effects of 2,3,7,8 TCDD on behavior of monkey in peer groups. Neurotoxicology Teratol 14:433-446, 1992.

Factory to Fetus

1 USEPA. Estimating Exposure to Dioxin-Like Compounds, Volume II: Properties, Sources, Occurrence and Backgroupd Exposures, USEPA, Office of Research and Development, EPA/600/6-88/005Cb, external review draft, June.

2 Cohen M, Commoner B, et al. Quantitative Estimation of the Entry of Dioxins, Furans and Hexachlorobenzene into the Great Lakes from Airborne and Waterborne Sources. Center for the Biology of Natural Systems, Queens College, CUNY, Flushing, NY, 1995.

3 Ahlborg UG, Brouwer A, Fingerhut MA et al. Impact of polycholorinated dibenzp-p-dioxins, dibenzofurans, and biphenyls on human and environmental health, with special emphasis on application of the toxic equivalency factor conctept. Eur J Pharmacol 1992;228(4):179-99.

4 De Voogt P, Brinkman UAT. Pruduction, properties and usage of polychlorinated biphenyls. In:Kimbrough RD, Jensen A editors. Halogenated Biphenyls, Terphenyls, Naphtalenes, Dibenzodioxins and Related Products. 2 ed. Amsterday:Elsevier, 1989:3-46.

5 De Voogt P, Brinkman UAT. Ibid.

6 Ahlborg UG, Brouwer A, Fingerhut MA et al. Ibid.

7 Agency for Toxic Substances and Disease Registry. Toxicological Profile for Polychlorinated Biphenyls. Atlanta: ATSDR. 1997.

8 Eitzer BD, Hites RA. Atmospheric transport and deposition of PCDDs and PCDFs. Environ Sci Toxicol 1989:23:1396-1401.

9 Abramowicz DA. 1995. Aerobic and anaerobic PCB diodegradation in the environment. Environmental Health Perspectives 103(S5):97-99.

10 Paustenbach DJ, Wenning RJ, Lau V et al. Recent developments on the hazards posed by 2,3,7,8 tcdd in soil: Implications for setting risk-based cleanup levels at residential and industrial sites. J Toxicol Environ Health 37(2):103-150, 1991. Cited in ATSDR Tox. Profile for Dioxin, 1997.

11 Wester, RC et al. Percutaneous absorption of PCBs from soil: In vivo rhesus monkey, in vitro human skin, and binding to powdered human stratum corneum. J Toxicol Environ Health 39(3):375-382.

12 Poiger H, Schlatter C, 1980. Influence of solvents and adsorbents on dermal and intestinal absorption of TCDD. Food Cosmet Toxicol 18:477-481.

13 Kimbrough RD, Falk H, Stehr P et al. Health implications of 2,3,7,8 TCDD contamination of residential soil. J Toxicol Environ Health 77-85.

14 Furst P, Beck H, Theelen R. Assessment of human intake of PCDDs and PCDFs from different environmental sources. Toxic Substances Journal 1992:12; 133-150.

15 Patandin S, Dagnelie PC, Mulder PG et al. Dietary exposure to PCBs and dioxins from infancy until adulthood: acomparison between breast-feeding, toddler, and long-term exposure. Environmental Health Perspectives 107(1) 1999.

PCBs: Inadequate Margins of Safety (Serum Levels)

1 Rice DC. Neurotoxicity produced by developmental exposure to PCBs. Mental Retardation and Developmental Disabilities Research Reviews 3:223-229, 1997.

2 Hovinga ME, Sowers M, Humphrey HE. Environmental exposure and lifestyle predictors of lead, cadmium, PCB, and DDT levels in Great Lake fish eaters. Arch Environ Health, 48(2):98-104, 1993.

3 Hovinga ME, Ibid.

4 Laden F, Neas LM, Spiegelman D et al. Predictors of plasma concentrations of DDE and PCBs in a group of US women. EHP 107(1):75-81, 1999.

5 Schwartz PM, Jacobson SW, Fein G et al. Lake Michigan fish consumption as a source of PCBs in human cord serum, maternal serum, and milk. Am J Public Health 73(3):293-6,1983.

6 Jacobson SW, Fein GG, Schwartz PM et al. Perinatal exposure to an environmental toxin: A test of multiple effects model. Devel Psych 20:523-532, 1984.

7 Jacobson SW, Fein GG, Jacobson JS et al. The effect of intrauterine PCB exposure on visual recognition memory. Child Dev 56:853-860, 1985.

8 Jacobson JS, Jacobson SW, Humphrey HEB. Effects of exposure to PCBs and related compounds on growth and activity I children. Neurotoxicol Teratol 12:319-326, 1990.

9 Jacobson JL, Jacobson SW, Humphrey HEB. Effects of in utero exposure to PCBs and related contaminants on cognitive functioning in young children. J Pediatr 116:38-45,1990.

10 Jacobson JL, Jacobson SW. Intellectual impairment in children exposed to PCBs in utero. New England J Med 335:783-789, 1996.

11 Rogan WJ, Gladen BC, McKinney JD et al. PCBs and DDE in human milk: effects of maternal factors and previous lactation. Am J Public Health 1986 76(2):172-7,1986.

12 Jensen AA. PCBs, PCDDs and PCDFs in human milk, blood and adipose tissue. Sci Total Environ 64(3):259-93,1987.

13 Rogan WJ, Gladen BC, McKinney JD et al. Neonatal effects of transplacental exposures to PCBs and DDE. J Pediatr 109:335-341, 1986.

14 Gladen BC, Rogan WJ. Effect of perinatal PCBs and dichlorodiphenyl dichloroethene transplacentally and through human milk. J Pediatr 113:991-995,1988.

15 Rogan WJ, Gladen BC. PCBs, DDE and childrens development at 18 and 24 months. Ann Epidemiol 1:407-413, 1991.

16 Gladen BC, Rogan WJ. Effect of perinatal PCBs and DDE on later development. J Pediatr 119:58-63,1991.

17 Dar E, Kanarek MS, Anderson HA, Sonzogni WC. Fish consumption and reproductive outcomes in Green Bay, Wisconsin. Environ Research 59(1):189-201, 1992.

18 Huisman M, Koopman-Esseboom C, Lanting CI et al. Neurological condition in 18-month children perinatally exposed to PCBs and dioxins. Early Human Dev 43(2):165-76, 1995.

19 Huisman M et al. 1995. Ibid.

20 Koopman-Esseboom C, Weisglas-Kuperus N, de Ridder MAJ et al. Effects of PCB/dioxin exposure and feeding type on infants' mental and psychomotor development. Pediatrics 96:700-706.

21 Koopman-Esseboom C et al. Ibid.

22 Huisman M, Koop-Esseboom C, Lanting CI et al, 1995, Ibid.

Footnotes to text

1 Lin-Fu JS. Vulnerability of children to lead exposure and toxicity. N Engl J Med 289:1289-1293, 1973.

2 Pihl RO, Parkes M. Hair element content in learning disabled children. Science 198:204-206, 1977.

3 Needleman ID, Sewell E, Shapiro I. Subclinical lead exposure in Philadelphia school children: identification by dentine lead analysis. N Engl J Med 290:245-250, 1979.

4 Byers RK, Lord EE. Late effects of lead poisoning on mental development. Amer J Dis Child 66:471-494, 1943.

5 Finkelstein Y, Markowitz M, Rosen J. Low-level lead-induced neurotoxicity in children: an update on central nervous system effects. Brain Res Brain Res Rev 27(2):168-176.

6 Needleman HL, Geiger SK, Frank R. Lead and IQ scores: a reanalysis. Science 227:701-704, 1985.

7 Bellinger D, Leviton A, Waternaux C, et al. Longitudinal analysis of prenatal and postnatal lead exposure and early cognitive development. N Engl J Med 316:1037-1043, 1987.

8 Bellinger D, Leviton A, Allred E, Rabinowitz M. Pre- and postnatal lead exposure and behavior problems in school-age children. Environ Res 66:12-30, 1994.

9 Dietrich KN, Berger OG, Succop PA, et al. The developmental consequences of low to moderate prenatal and postnatal lead exposure: intellectual attainment in the Cincinnati lead study cohort following school entry. Neurotoxicol Teratol 15:37-44, 1993.

10 Tuthill RW. Hair lead levels related to children's classroom attention-deficit disorder. Arch Environ Health 51:214-220, 1996.

11Needleman HL, Schell A, Bellinger D, et al. The long-term effects of exposure to low doses of lead in childhood. An 11-year follow-up report. N Engl J Med 322(2):83-8, 1990.

12 Needleman HL, Reiss JA, Tobin MJ, et al. Bone lead levels and delinquent behavior. JAMA 275:363-369, 1996.

13 Wasserman GA, Staghezza-Jaramillo B, Shrout P, et al. The effect of lead exposure on behavior problems in preschool children. Am J Public Health 88:481-486, 1998.

14 Rice D. Lead-induced changes in learning. Neurotoxicol 14:167-178, 1993.

15Rice DC. Developmental lead exposure: neurobehavioral consequences. In Slikker W, Chang LW, Eds. Handbook of Developmental Neurotoxicology, Academic Press, 1998.

16 Silbergeld EK. Mechanisms of lead neurotoxicity, or looking beyond the lamppost.
FASEB J. 6(13):3201-6, 1992.

17 Lucchi L, Govoni S, Memo M, et al. Chronic lead exposure alters dopaminergic mechanisms in rat pituitary Toxicol Lett 32:255-260, 1986.

18 Rossouw, Toxicol Appl Pharmacol 91:132-139, 1987.

19 US EPA. Mercury study report to Congress. EPA-452/R-97-003.

20 Bornhausen M, Musch MR, Greim H. Operant behavior performance changes in rats after prenatal methylmercury exposure. Toxicol Appl Pharmacol 56:305-316, 1980.

21 Gunderson VM, Grant-Webster KS, Burbacher TM, et al. Visual recognition memory deficits in methylmercury-exposed Macaca fascicularis infants. Neurotoxicol Teratol 10(4):373-379, 1988.

22 Harada H. Congenital Minamata disease: intrauterine methylmercury poisoning. Teratology 18:285-288, 1978.

23 Amin-Zaki L, Ehassani S, Majeed MA, et al. Perinatal methylmercury poisoning in Iraq. Am J Dis Child 130, 1070-1076, 1976.

24 Cox C, Clarkson TW, Marsh DO, et al. Dose-response analysis of infants prenatally exposed to methyl mercury: an application of single compartment model to single-strand hair analysis. Environ Res 49:318-332, 1989.

25 Davidson PW, Myers GJ, Cox C, et al. Longitudinal neurodevelopmental study of Seychellois children following in utero exposure to methylmercury from maternal fish ingestion: outcomes at 19 and 29 months. Neurotoxicol 116(4):677-688, 1995.

26 Davidson PW, Myers GJ, Cox C, et al. Effects of prenatal and postnatal methylmercury exposure from fish consumption on neurodevelopment: outcomes at 66 months of age in the Seychelles Child Development Study. JAMA 280(8):701-707, 1998.

27 Grandjean P, Weihe P, White R, et al. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. Neurotoxicol Teratol 19(6):417-428, 1997.

28 Budtz-Jorgensen E, Keiding N, Grandjean P, White R, Weihe P. Methylmercury neurotoxicity independent of PCB exposure. Environ Health Perspect 107(5):A236-237, 1999.

29 Rice DC, Gilbert SG. Exposure to methylmercury from birth to adulthood impairs high-frequency hearing in monkeys. Toxicol Appl Pharmacol 115(1):6-10, 1992.

30 Rice DC, Gilbert SG. Effects of developmental exposure to methylmercury on spatial and temporal visual function in monkeys. Toxicol Appl Pharmacol 102(1):151-163, 1990.

31 Crump KS, Kjellstrom T, Shipp AM, et al. Influence of prenatal mercury exposure upon scholastic and psychological test performance: benchmark analysis of a New Zealand cohort. Risk Anal 18(6):701-713, 1998.

32 US EPA. Mercury study report to congress. EPA-452/R-97-003, 1997.

33 44 Fed. Reg. 3,990, 3,992. 1979.

34 U.S. General Accounting Office. Reproductive and developmental toxicants: regulatory actions provide uncertain protections. GAO/PEMD-92-3, GAO/PEMD-92-3, p.58, 1991.

35 Institute of Medicine, Committee on Evaluation of the Safety of Fishery Products, Food and Nutrition Board. Seafood safety. Washington: National Academy of Sciences; 1991

36 Atchison WD, Hare MF. Mechanisms of methylmercury-induced neurotoxicity. FASEB J 8(9):622-629, 1994.

37 Sager PR. Selectivity of methylmercury effects on cytoskeleton and mitotic progression in cultured cells. Toxicol Appl Pharm 94(3):473-486, 1988.

38 Sager PR, Matheson DW. Mechanisms of neurotoxicity related to selective disruption of microtubules and intermediate filaments. Toxicology 49(2-3):479-492, 1988.

39 Bemis JC, Seegal RF. Polychlorinated biphenyls and methylmercury act synergistically to reduce rat brain dopamine content in vitro. Environ Health Perspect 107(11):879-885, 1999.

40 Stewert P. PCBs/methylmercury: The Oswego study. Reported at: Children's Health and the Environment: Mechanisms and Consequences of Developmental Neurotoxicology. Little Rock, AR, Oct 1999.

41 Greger JL, Davis CD, Suttie JW, Lyle BJ. Intake, serum concentrations, and urinary excretion of manganese by adult males. Amer J Clin Nutrition 51:457-461, 1990.

42 Dorner K, Dziadzka S, Hohn A, et al. Longitudinal manganese and copper balances in young infants and preterm infants fed on breast milok and adapted cow's milk formula. Br J Nutrition 61(3):559-572, 1989.

43 Lonnerdal B. Nutritional aspects of soy formula. Acta Pediatr Suppl 402:105-108, 1994.

44 Tjalve H, Henriksson J, Tallkvist J, et al. Uptake of manganese and cadmium from the nasal mucosa into the central nervous system via olfactory pathways in rats. Pharmacol Toxicol 79:347-356, 1996.

45 Cotzias GC, Horiuchi K, Fuenzalida S, Mena I. Chronic manganese poisoning: clearance of tissue manganese concentrations with persistence of the neurological picture. Neurology 18:376-382, 1968.

46 Mena I. The role of manganese in human disease. Ann Clin Lab Sci 4(6):487-491, 1974.

47 Dorner K, Dziadzka S, Hohn A, et al.

48 Laskey JW, Rehnberg GL, Hein JF, Carter SD. Effects of chronic manganese (Mn_3O_4) exposure on selected reproductive parameters in rats. J Toxicol Environ Health 8:677-687, 1982.

49 Boyes WK, Miller DB. A review of rodent models of manganese meurotoxicity. Neurotoxicol 19(3):468, 1998.

50 Mergler D, Huel G, Bowler R, et al. Nervous system dysfunction among workers with long-term exposure to manganese. Environ Res 64:151-180, 1994.

51 Iregren A. Using psychological tests for the early detection of neurotoxic effects of low level manganese exposure. Neurotoxicol 15(3):671-678, 1994.

52 Collipp PJ, Chen SY, Maitinsky S. Manganese in infant formulas and learning disability. Ann Nutri Metab 27:488-494, 1983.

53 Pihl RO, Parkes M. Hair element content in learning disabled children. Science 198:204-206, 1977.

54 Crinella FM, Cordova EJ, Ericson JE. Manganese, aggression, and attention-deficit hyperactivity disorder. Neurotoxicol 19(3):468-469, 1998.

55 Singh J, Husain R, Tandon SK, et al. Biochemical and histopathological alterations in early manganese toxicity in rats. Renviron Physiol Biochem 4:16-23, 1974.

56 Tagliaferro P, Ramos AJ, Lopez EM, et al. Comparative neurotoxic effects of serotonin depletion in adult and neonatal rat brain. Neurotoxicol 19(3):473, 1998.

57 Pahren HR, Lucas JB, Ryan JA, et al. Health risks associated with land application of municpal sludge. J Water Pollut Control Fed 51:1588-1598, 1979.

58 Babish JG, Stoewsand GS, Scarlett Krantz JM, et al. Toxicologic studies associated with the agricultural use of municipal sewage sludge and health effects among sewage treatment plant workers. Reg Toxicol Pharmacol 4:305-321, 1984.

59 Agency for Toxic Substances and Disease Registry. Case Studies in Environmental Medicine: Cadmium Toxicity, Atlanta, GA: U.S. Department of Health and Human Services, ATSDR, June, 1990.

60 Hastings L, Miller ML. Developmental neurotoxicity of cadmium. In: Slikker W, Chang LW, Eds. Handbook of Developmental Neurotoxicology, Academic Press, 1998.

61 Baranski B, Stetkiewicz I, Sitarek K, Szymczak W. Effects of oral, subchronic cadmium exposure on fertility, prenatal and postnatal progeny development in rats. Arch Toxicol 54:297-302, 1983.

62 Baranski B. Effect of maternal cadmium exposure on postnatal development and tissue cadmium, copper, and zinc concentrations in rats. Arch Toxicol 58:255-260, 1986.

63 Lehotzky K, Ungvary G, Polinak D, Kiss A. Behavioral deficits due to prenatal exposure to cadmium chloride in CFY rat pups. Neurotoxicol Teratol 12:169-172, 1990.

64 Pelletier M, Satinder K. Low-level cadmium exposure increases one-way avoidance in juvenile rats. Neurotoxicol Teratol 13:657-662, 1991.

65 Pihl RO, Parkes M. Hair element content in learning disabled children. Science 198:204-206, 1977.

66 Thatcher RW, Lester ML, McAlaster, Horst R. Effects of low levels of cadmium and lead on cognitive functioning in children. Arch Environ Health 37(3):159-166, 1982.

67 Bonithon-Kopp C, Huel G, Moreau T, Wendling R. Prenatal exposure to lead and cadmium and psychomotor development of the child at 6 years. Neurobehav Toxicol Teratol 8:307-310, 1986.

68 Hastings L, Miller ML. Developmental neurotoxicity of cadmium. In: Slikker W, Chang LW, Eds. Handbook of Developmental Neurotoxicology, Academic Press, 1998.

69 Butler NR, Goldstein H. Smoking in pregnancy and subsequent child development. Br Med J 4:573-575, 1973.

70 Fung YK. Postnatal behavioural effects of maternal nicotine exposure in rats. J Pharm Pharmacol 40:870-872, 1988.

71 Levin ED, Briggs SJ, Christopher NC, Rose JE. Prenatal nicotine exposure and cognitive performance in rats Neurotoxicol Teratol 15:251-260, 1993.

72 Levin ED, Wilkerson A, Jones JP, et al. Prenatal nicotine effects on memory in rats: pharmacological and behavioral challenges. Dev Brain Res 97:207-215, 1996.

73 Hardy JB, Mellits ED. Does maternal smoking during pregnancy have a long-term effect on the child? Lancet 2:1332-1336, 1972.

74 Butler NR, Goldstein H. Smoking in pregnancy and subsequent child development. Br Med J 4:573-575, 1973.

75 Naeye RL, Peters NC. Mental development of children whose mothers smoked during pregnancy. Obstet Gynecol 64:601-607, 1984.

76 Sexton M, Fox NL, Hebel JR. Prenatal exposure to tobacco. II: Effects on cognitive functioning at age three. Int J Epidemiol 19:72-77, 1990.

77 Picone TA, Allen LH, Olsen PN, Ferris ME. Pregnancy outcome in North American women. II. Effects of diet, cigarette smoking, stress, and weight gain on placentas, and on neonatal physical and behavioral characteristics. Am J Clin Nutr 36(6):1214-1224, 1982.

78 Butler NR, Goldstein H. Smoking in pregnancy and subsequent child development. Br Med J 4(892):573-575, 1973.

79 Fogelman KR, Manor O. Smoking in pregnancy and development into early adulthood. Brit Med J 297(6658):1233-1236, 1988.

80 Eskenazi B, Castorina R. Association of prenatal maternal or postnatal child environmental tobacco smoke exposure and neurodevelopmental and behavioral problems in children. Environ Health Perspect 107:991-1000, 1999.

81 Makin J, Fried PA, Watkinson B. A comparison of active and passive smoking during pregnancy: long-term effects. Neurotoxicol Teratol 13(1):5-12, 1991.

82 Gospe SM, Zhou SS, Pinkerton KE. Effects of environmental tobacco smoke exposure in utero and/or postnatally on brain development. Pediatr Res 39:494-498, 1996.

83 Slotkin TA, Orband-Miller L, Queen KL. Development of [3H]nicotine binding sites in brain regions of rats exposed to nicotine prenatally via maternal injections or infusions. J Pharmacol Exp Ther 242:232-237, 1987.

84 Navarro HA, Seidler FJ, Whitmore WL, Slotkin TA. Prenatal exposure to nicotine via maternal infusions: effects on development of catecholamine system. J Pharmacol Exp Ther 244:940-944, 1988.

85 McFarland BJ, Seidler FJ, Slotkin TA. Inhibition of DNA synthesis in neonatal rat brain regions caused by acute nicotine administration. Brain Res Dev Brain Res 58(2):223-229, 1991.

86 Schantz SL, Bowman RE. Learning in monkeys exposed perinatally to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Neurotoxicol Teratol 11(1):13-19, 1989.

87 Rice DC, Hayward S. Effects of postnatal exposure to a PCB mixture in monkeys on nonspatial discrimination reversal and delayed alternation performance. Neurotoxicol 18(2):479-494, 1997.

88 Rice DC. Behavioral impairment produced by low-level postnatal PCB exposure in monkeys. Environ Res Sect A 80:S113-121, 1999.

89 Bowman RE, Heironimus MP, Barsotti DA. Locomotor hyperactivity in PCB-exposed rhesus monkeys. Neurotoxicol 2:251-268, 1981.

90 Levin ED, Schantz SL, Bowman RE. Delayed spatial alteration deficits resulting from perinatal PCB exposure of monkeys Arch Toxicol 62:267-273, 1988.

91 Holene E, Nafstad I, Skaare JU, et al. Behavioral effects of pre- and postnatal exposure to individual polychlorinated biphenyl congeners in rats. Environ Toxicol Chem 14(6):967-976, 1995.

92 Lilienthal H, Winneke G. Sensitive periods for behavioral toxicity of polychlorinated biphenyls: Determination by cross-fostering in rats. Fundament Appl Toxicol 17:368-375, 1991.

93 Rogan WJ, Gladen BC, Hung KL, et al. Congenital poisoning by polychlorinated biphenyls ands their contaminants in Taiwan. Science 241:334-338, 1988.

94 Chen YC, Guo YL, Hsu CC, Rogan WJ. Cognitive development of Yu-Cheng ("oil disease") children prenatally exposed to heat-degraded PCBs. JAMA 268(22):3213-3218, 1992.

95 Jacobson JL, Jacobson SW. Effects of in utero exposure to PCBs and related contaminants on cognitive functioning in young children. J Pediatr 116(1):38-45, 1990.

96 Jacobson JL, Jacobson SW. Intellectual impairment in children exposed to polychlorinated biphenyls in utero. N Engl J Med 335:783-789, 1996.

97 Gladen BC, Rogan WJ. Effects of perinatal polychlorinated biphenyls and dichlorodiphenyl dichloroethene on later development. J Pediatr 119:58-63, 1991.

98 Lonky E, Reihman J, Darvill T, et al. Neonatal behavioral assessment scale performance in humans influenced by maternal consumption of environmentally contaminated Lake Ontario fish. J Great Lakes Res 22(2):198-212, 1996.

99 Stewart P. PCB's/methylmercury: the Oswego study. Abstract: Children's Health and the Environment: Mechanisms and Consequences of Developmental Neurotoxicology. Little Rock AR, Oct 1999.

100 Patandin S, Lanting CI, Mulder PG, et al. Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age. J Pediatr 134(1):33-41, 1999.

101 Koopman-Esseboom C, Morse DC, Weisglas-Kuperus N, et al. Effects of dioxins and polychlorinated biphenyls on thyroid status of pregnant women and their infants. Pediatr Res 36(4):468-473, 1994.

102 Sewall CH, Flagler N, Vanden Heuvel JP, et al. Alterations in thyroid function in female Sprague-Dawley rats following chronic treatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin. Toxicol Appl Pharmacol 132(2):237-244, 1995.

103 Zoeller RT. Effects of developmental exposure to PCBs on thyroid hormone action in the developing brain are not consistent with effects on circulating thyroid hormone. Abstract: Children's Health and the Environment: Mechanisms and Consequences of Developmental Neurotoxicology. Little Rock AR, Oct 1999.

104 Zoeller RT, Dowling A, Vas A. Developmental exposure to polychlorinated biphenyls exerts thyroid hormone-like effects on the expression of RC3/neurogranin and myelin basic protein messenger ribonucleic acids in the developing rat brain. Endocrinol 141:181-189, 2000.

105 Tilson HA. Neurochemical effects of PCBs – an overview. Neurotoxicol 18(3):727-744, 1997.

106 Seegal RF, Brosch KO, Okoniewski RJ. Effects of in utero and lactational exposure of the laboratory rat to 2,4,2',4' – and 3,4,3',4'-tetrachlorobiphenyl on dopamine function. Toxicol Appl Pharmacol 146(1):95-103, 1997.

107 Ahlbom J, Fredriksson A, Eriksson P. Exposure to an organophosphate (DFP) during a defined period in neonatal life indusces permanent changes in brain muscarinic receptors and behaviour in adult mice. Brain Res 677:13-19, 1995.

108 Chanda SM, Pope CN. Neurochemical and neurobehavioral effects of repeated gestational exposure to chlorpyrifos in maternal and developing rats. Pharmacol Biochem Behav 53(4):771-776, 1996.

109 US EPA. A retrospective analysis of twelve developmental neurotoxicity studies submitted to the US EPA OPPTS. Nov 1998.

110 Spyker JM, Avery DL. Neurobehavioral effects of prenatal exposure to the organophosphate diazinon in mice. J Toxicol Environ Health 3(5-6):989-1002, 1977.

111 Eriksson P, Ahlbom J, Fredriksson A. Exposure to DDT during a defined period in neonatal life induces permanent changes in brain muscarinic receptors and behaviour in adult mice. Brain Res 582(2):277-281, 1992.

112 Guillette EA, Meza MM, Aquilar MG, Soto AD, Enedina I. An anthropological approach to the evaluation of preschool children exposed to pesticides in Mexico. Environ Health Perspect 106:347-353, 1998.

113 Eriksson P, Fredriksson A. Neurotoxic effects of two different pyrethroids, bioallethrin and deltamethrin, on immature and adult mice: changes in behavioural and muscarinic receptor variables. Toxicol Appl Pharmacol 108:78-85, 1991.

114 Malaviya M, Husain R, Seth PK, Husain R. Perinatal effects of two pyrethroid insecticides on brain neurotransmitter function in the neonatal rat. Vet Hum Toxicol 35(2):199-122, 1993.

115 Bigbee J, Sharma K, Gupta J, Dupree J. Morphogenic role for acetylcholinesterase in axonal outgrowth during neural development. Environ Health Perspect 107(suppl 1):81-87, 1999.

116 Slotkin TA. Developmental cholinotoxicants: nicotine and chlorpyrifos. Environ Health Perspect 107(suppl 1):71-80, 1999.

117 Campbell CG, Seidler FJ, Slotkin TA. Chlorpyrifos interferes with cell development in rat brain regions. Brain Res Bull 43:179-189, 1998.

118 Whitney KD, Seidler FJ, Slotkin TA. Developmental neurotoxicity of chlorpyrifos: cellular mechanisms. Toxicol Appl Pharmacol 13:53-62, 1995.

119 Gurunathan S, Robson M, Freeman N, Buckley B, et al. Accumulation of chlorpyrifos on residential surfaces and toys accessible to children. Environ Health Perspect 106:9-16, 1998.

120 Jones KL, Smith DW, Ulleland CN, Streissgut AP. Pattern of malformation in offspring of chronic alcoholic women. Lancet I:1267-1271, 1973

121 Institute of Medicine of the National Academy of Sciences Committee to Study Fetal Alcohol Syndrome. Diagnosis and Clinical Evaluation of Fetal Alcohol Syndrome. In Stratton D, Howe C, Battaglia F, Eds. Fetal Alcohol Syndrome, National Academy Press, 1996.

122 Sulik KK, Johnston MC, Webb MA. Fetal alcohol syndrome: embryogenesis in a mouse model. Science 214:936-938, 1981.

123 West JR, Hamre KM. Effects of alcohol exposure during different periods of development: changes in hippocampal mossy fibers. Dev Brain Res 17:280-284, 1985.

124 Nulman I, O'Haydon B, Gladstone J, Koren G. The effects of alcohol in the fetal brain. In Slikker W, Chang LW, Eds. Handbook of Developmental Neurotoxicology, Academic Press, 1998.

125 Jacobson JL, Jacobson SW, Sokol RJ, Ager JW. Relation of maternal age and pattern of pregnancy drinking to functionally significant cognitive deficit in infancy. Alcohol Clin Exp Res 22(2):345-351, 1998.

126 Nulman I, O'Haydon B, Gladstone J, Koren G. The effects of alcohol in the fetal brain. In Slikker W, Chang LW, Eds. Handbook of Developmental Neurotoxicology, Academic Press, 1998.

127 Streissguth AP, Aase IM, Clarren SK, et al. Fetal alcohol syndrome in adolescents and adults. JAMA 265:1961-1967, 1991.

128 Streissguth AP, Dehaene P. Fetal alcohol syndrome in twins of alcoholic mothers: concordance of diagnosis and IQ. Am J Med Geneet 47(6):857-861, 1993.

129 Rutledge JC. Genetic factors in clinical developmental toxicology. In: Developmental Toxicology, second edition. Eds: Kimmel C, Buelke-Sam J. Raven Press, New York, 1994.

130 Volk B, Maletz M, Tiedemann M, et al. Impaired maturation of Purkinje cells in the fetal alcohol syndrome of the rat. Acta Neuropathol 54:19-29, 1981.

131 Diaz J, Samson HH. Impaired brain growth in neonatal rats exposed to ethanol. Science 208:751-753, 1980.

132 Ramanthan R, Wilkemeyer MF, Mittal B, et al. Alcohol inhibits cell-cell adhesion mediated by human L1. J Cell Biol 133AY:381-390, 1996.

133 Yang HY, Shum AYC, Ng HT, et al. Effect of ethanol on human umbilical artery and vein in vitro. Gyn Obstet Invest 21:131-135, 1986.

134 Broun S. New experiments underscore warnings on maternal drinking. Science 273:738-739, 1996.

135 Snyder R, Andrews LS. Toxic effects of solvents and vapors. In: Casarett and Doull's Toxicology: The basic science of poisons. 5th edition. Ed: Klaassen CD. McGraw-Hill, New York, 1996.

136 Schettler T, Solomon G, Valenti M, Huddle A. Organic solvents. In:Generations at risk: Reproductive health and the environment. Cambridge, MA, MIT Press, 1999.

137 Eskenazi B, Gaylord L, Bracken MB, Brown D. In utero exposure to organic solvents and human neurodevelopment. Devel Med Child Neurol 30:492-501, 1988.

138 Jones HE, Balster RL. Inhalant abuse in pregnancy. Obstet Gynecol Clin North Am 25(1):153-167, 1998.

139 Pearson M, Hoyme H, Seaver L, Rimsza M. Toluene embryopathy: delineation of the phenotype and comparison with fetal alcohol syndrome. Pediatrics 93(2):211-215, 1994.

140 Jones HE, Balster RL. Neurobehavioral consequences of intermittant prenatal exposure to high concentrations of toluene. Neurotoxicol Teratol 19(4):305-313, 1997.

141 Hougaard KS, Hass U, Lund SP, Simonsen L. Effects of prenatal exposure to toluene on postnatal development and behavior in rats. Neurotoxicol Teratol 21(3):241-250, 1999.

142 Kostas J, Hotchkin J. Behavioral effects of low-level perinatal exposure to toluene in mice. Neurobehav Toxicol Teratol 3(4):467-469, 1981.

143 Taylor DH, Lagory KE, Zaccaro DJ, et al. Effect of trichloroethylene on the exploratory and locomotor activity of rats exposed during development. Sci Total Environ 47:415-420, 1985.

144 Dorfmueller MA, Henne S, York R, et al. Evaluation of teratogenicity and behavioral toxicity with inhalation exposure of maternal rats to trichloroethylene. Toxicology 14(2):153-166, 1979.

145 Hass U, Lund SP, Simonsen L, Fries AS. Effects of prenatal exposure to xylene on postnatal development and behavior in rats. Neurotoxicol Teratol 17(3):341-349, 1995.

146 Mirkova E, Zaikov C, Mikhailova A, et al. Prenatal toxicity of xylene. J Hyg Epidemiol Immunol 27(3):337-343, 1983.

147 Shigeta S, Miyake K, Aikawa H, Misawa T. Effects of postnatal low-levels of exposure to styrene on behavior and development in rats. J Toxicol Sci 14(4):279-286, 1989.

148 Khanna VK, Husain R, Hanig JP, et al. Increased neurobehavioral toxicity of styrene in protein malnourished rats. Neurotoxicol Teratol 13:153-159, 1991.

149 Hileman B. Fluoridation of water. Chem Eng News 66:26-42, 1988.

150 Connett P. Fluoride: a statement of concern. Waste Not #459. Canton NY.

151 CDC. Fluoridation of drinking water to prevent dental caries. MMWR 48:986-993, 1999.

152 Mullenix PJ, Denbesten PK, Schunior A, Kernan W. Neurotoxicity of sodium fluoride in rats. Neurotoxicol Teratol 17(2):169-177, 1995.

153 Ross J, Daston G. Letter to the editor. Neurotoxicol Teratol 17(6):685-686, 1995.

154 Mullenix P, Denbesten P, Schunior A, Kernan W. Reply. Neurotoxicol Teratol 17(6):687-688, 1995.

155 Zhao XL, Wu JH. Actions of sodium fluoride on acetylcholinesterase activities in rats. Biomed Environ Sci 11(1):1-6, 1998.

156 Zhao LB Liang GH, Zhang DN, et al. Effect of a high fluoride water supply on children's intelligence. Fluoride 29(4):190-192, 1996.

157 Li XS, Zhi JL, Gao RO, Effect of fluoride exposure on intelligence in children. Fluoride 28(4):189-192, 1995.

158 Olney JW. Excitotoxic food additives: functional teratologic aspects. Prog Brain Res 73:283-294, 1988.

159 Olney JW. Excitotoxins in food. Neurotoxicol 15(3):535-544, 1994.

160 Kimmel CA, Buelke-Sam J (eds). Developmental Toxicology. 2nd ed. New York: Raven Press, 1994.

161 Nemeroff CB, Lamartiniere CA, Mason GA, et al. Marked reduction in gonadal steroid hormone levels in rats treated neonatally with monosodium L-glutamate: further evidence for disruption of hypothalamic-pituitary-gonadal axis regulation. Neuroendocrin 33(5):265-267, 1981.

162 Fernstrom JD. Dietary amino acids and brain function. J Am Diet Assoc 94(1):71-77, 1994.

163 Walker R. The significance of excursions above the ADI. Case study: monosodium glutamate. Regul Toxicol Pharmacol 30(2 pt 2):S119-121, 1999.

164 Fernstrom JD. Dietary amino acids and brain function. J Am Diet Assoc 94(1):71-77, 1994.

165 Olney JW. Excitotoxins in food. Neurotoxicol 15(3):535-544, 1994.

166 Brunner R, Vorhees C, Kinney L, Butcher R. Aspartame: assessment of developmental psychotoxicity of a new artificial sweetener. Neurobehav Toxicol 1(1):79-86, 1979.

167 Feingold BF. Why your child is hyperactive. New York: Random House, 1975.

168 Jacobson MF, Schardt D. Diet, ADHS, behavior: A quarter century review. Center for Science in the Public Interest. Washington DC, 2000. http://www.cspinet.org/new/adhd_resch_bk02.pdf

Chapter 7

Chemicals, Regulations & the Environment

Scope of the Chemical Problem

Scarce information about the health effects of the approximately 80,000 chemicals in commercial use, pervasive human exposures to many toxic chemicals, and seriously inadequate regulatory oversight combine to create a global environmental threat to our children.

"Children today live in a very different environment from years ago," said pediatrician Philip Landrigan, MD, MSc, Chair of the Department of Community and Preventative Medicine at the Mt. Sinai Medical Center. "There are new patterns of illness emerging, and many more chemicals to which children are exposed. More than 10 million products contain chemicals. Toxicity testing has not even begun to keep pace with disease. We are conducting a vast toxicological experiment on our children which will affect generations to come," said Landrigan.[1]

Toxics Release Inventory Reveals Over a Billion Pounds of Neurotoxicants Released Into Environment

The Toxics Release Inventory (TRI) reporting for the year 1997 reveals that a total of 2.58 billion pounds of toxic chemicals were released nationwide in the United States by the large, industrial facilities required to report under TRI.[2] Of the 20 TRI chemicals on the list with the largest total releases, nearly three-quarters are known or suspected neurotoxicants.[3] Nearly a billion pounds of these neurotoxicants were emitted by facilities on-site directly into just the air and surface water, with the potential to be inhaled, absorbed or otherwise ingested through our food and water supplies. Additional amounts were released on and off-site into underground wells, landfills and other disposal facilities, bringing the total releases to over 1.2 billion pounds.

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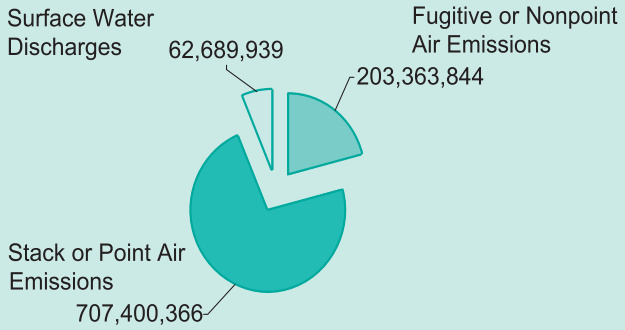
In order of total releases, the top chemicals that are known or suspected neurotoxicants include methanol, ammonia, manganese compounds, toluene, phosphoric acid, xylene, n-hexane, chlorine, methyl ethyl ketone, carbon disulfide, dichloromethane, styrene, lead compounds, and glycol ethers. The 1997 TRI also reports metals released to the environment. Again, over half of those listed are known or

Toxics Release Inventory (TRI)
1997 Top 20 Chemicals Released
On-Site Releases to Air and Surface Water of Known or Suspected Neurotoxic Chemicals

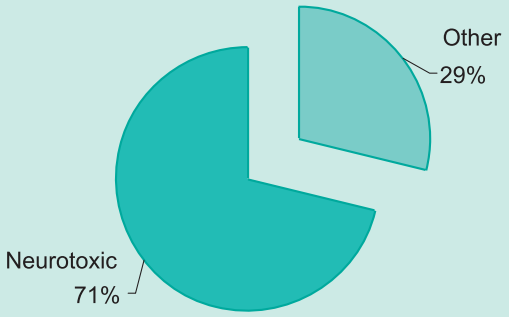


suspected to be toxic to the central nervous system.[4] These include antimony, arsenic, barium, cadmium, lead, manganese, nickel, selenium, thallium, cobalt and mercury.[5]

Known or suspected neurotoxicants represent 81 percent of the total top 20 chemicals released to just air and surface water. They comprise 71 percent of total on-site releases to air, water and land of the top 20 chemicals.

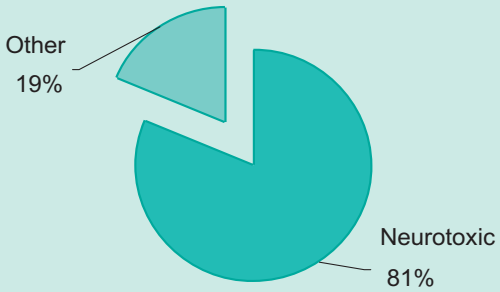
The 1997 TRI release data include information on only about 650 chemicals, or less than 1% of the 80,000 chemicals in commercial use.[6] They also do not provide chemical release information on all industries, including small-quantity generators

Toxics Release Inventory (TRI)
1997 Top 20 Chemicals Released
On-Site Releases to Air, Water and Land
Percentage of Known or Suspected Neurotoxic Chemicals

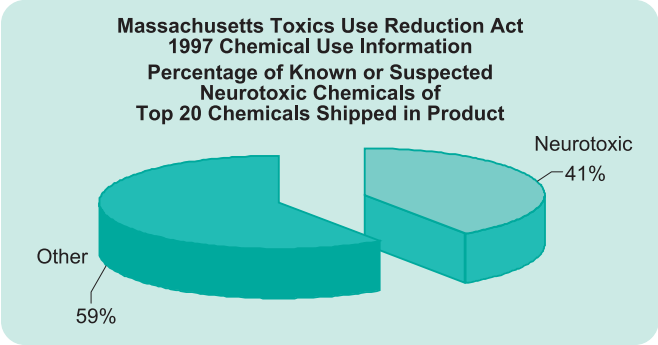


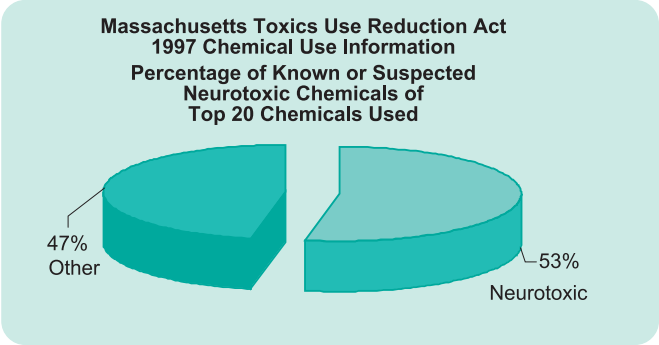
and certain industry sectors. For example, the major sources of mercury, including coal-fired power plants and incinerators, were not required to report to TRI in 1997. Electric utilities and six other industry sectors will be required to report emissions beginning with 1998 data, but incinerators and other facilities will still escape right-to-know reporting requirements. Other exemptions include sources that use less than 25,000 pounds

Toxics Release Inventory (TRI)
1997 Top 20 Chemicals Released
On-Site Releases to Air and Surface Water
Percentage of Known or Suspected Neurotoxic Chemicals



of chemicals. This has important implications for chemicals shown in this report to exert adverse effects at extremely low levels. Due to concern about these low-level effects, EPA recently lowered the reporting thresholds for a number of persistent, bioaccumulative toxic chemicals (PBTs) including mercury, dioxins, PCBs and some pesticides.[7] Unfortunately, lead was not included in this list. A separate rule to ensure the reporting of lead emissions has been opposed by the lead industry and delayed by Congress.[8]





Use of Neurotoxicants High

TRI does not account for toxic chemicals incorporated into products, which may be a source of significant fetal or childhood exposures. However, toxics use information, which is only available in a few states, provides important additional information regarding potential human exposures to neurotoxicants.

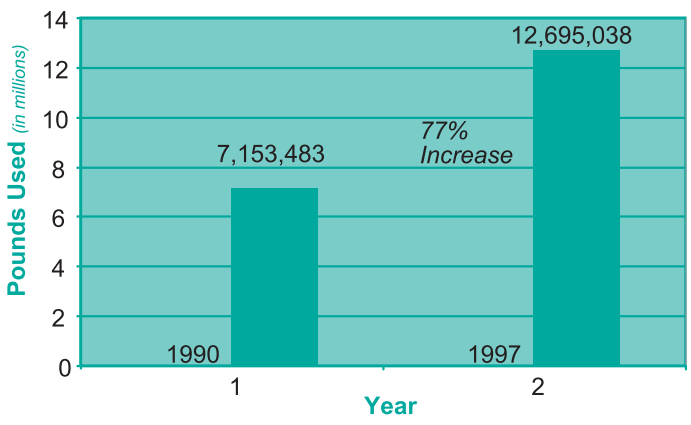
An analysis of 1997 data stemming from the Massachusetts Toxics Use Reduction Act (TURA) reveals that over half of the top 20 chemicals "shipped in product," and half of the top 20 chemicals used by industrial facilities required to report in Massachusetts, are known or suspected neurotoxicants.[9] ("Shipped in product" includes chemicals that are incorporated into final products, such as styrene monomer into polystyrene, and also distribution of chemicals that are themselves the end product, such as solvents.) These neurotoxicants used by industrial facilities total over 500 million pounds and represent over 50 percent by weight of the top 20 chemicals used, and over 40 percent of the top 20 shipped in product in Massachusetts for the latest reporting year.[10] Chemicals bound up in products may not represent a toxic threat during use, but may be a very real threat during shipping or handling, or when they are released during disposal, including incineration. Chemicals used in facilities provide opportunities for occupational exposures, sometimes at high levels, and pose additional risks to people in surrounding communities.

One of the most disturbing observations in the 1997 TURA data is that the use of lead and lead compounds has risen a dramatic 77 percent from 1990-1997 (lead use alone rose 83 percent, lead compounds 75 percent.) [11] Lead compounds appear in the top 20 TURA list for both chemicals shipped in product and used.[12] Products that account for some of the increase include use of lead in polyvinyl chloride (PVC) and coated wire products.

Exposures to Pesticides Pervasive

Although some pesticides were added to TRI in 1995, requiring manufacturers to report releases of listed chemicals, agricultural and other commercial users of pesticides are not required to report releases under TRI. The U.S. used approximately 1.23 billion

Massachusetts Toxics Use Reduction Act, 1997 Data
Lead Use in Massachusetts 1990-1997



Thirty-seven pesticides registered for use on foods are neurotoxic organophosphates.

pounds of "conventional" pesticides in 1997 and a total of about 4.5 billion pounds when all types of pesticides are included, such as wood preservatives and chlorine/hypochlorites. Home pesticide use accounted for about 76 million pounds in 1997. [13] The EPA estimates that about 23 percent of the total U.S. use of pesticides occurs in nonagricultural areas.[14]

The failure to include these intentional environmental pesticide releases in TRI reporting requirements impedes exposure assessment and prevention efforts. This is troublesome since children are among the most vulnerable to adverse health effects from pesticides. The 1993 National Academy of Sciences report, *Pesticides in the Diets of Infants and Children*, emphasized that children are not little adults and that, pound for pound, their chemical exposures are often greater than adults. Children are also frequently less able to detoxify substances such as pesticides, and their developing organs, including the brain, are more vulnerable. Enhanced susceptibility to adverse effects combines with relatively larger exposures to create substantially increased risks.

Children eat more fruits and vegetables than adults, on a weight-adjusted basis. Twenty million American children five and under eat an average of eight pesticides every day through food consumption.[15] Thirty-seven pesticides registered for use on foods are neurotoxic organophosphate insecticides, chemically related to more toxic nerve warfare agents developed earlier this century. One such pesticide, chlorpyrifos (commonly sold as Dursban), is among the most widely-used insecticides in homes. A national health exposure study detected chlorpyrifos residues (as the metabolite TCP) in the urine of 82% of a representative sample of American adults. A more recent study in Minnesota revealed that an even higher 92% of children had detectable levels of this metabolite in their urine.[16] TCP is also a metabolite of chlorpyrifos methyl, used extensively in grain storage, so it is not possible to fully determine the source of exposure.

Seventeen organophosphates (including chlorpyrifos) are registered by EPA for "residential" uses, including in homes, on lawns, in schools, and on playgrounds. Children play in the grass where pesticides have been used and on carpets, which are toxic reservoirs for garden pesticides, lead dust, and other toxic substances.[17] In a 1999 study on the distribution of pesticides and polycyclic aromatic hydrocarbons (PAHs—found in cigarette smoke and the products of fuel combustion) in house dust, 14 pesticides and 10 PAHs were detected in residential house dust collected from a typical North Carolina suburb.[18] Chemicals that might biodegrade quickly outside when exposed to sunlight, water, and microorganisms remain for much longer periods of time in carpets.

Schools are another source of pesticide exposure for children. Surveys in Massachusetts and Connecticut have shown that more than 80% of schools

routinely spray pesticides. A New York study found that at least 50 active pesticide ingredients are regularly applied in the buildings and on the grounds of schools in that state. These applications expose our children to hundreds of active pesticide ingredients as well as an array of solvents and other chemicals misleadingly labeled "inert" ingredients.[19] [20] The trend is toward increasingly common exposures to organophosphates. For example, chlorpyrifos detections in urine increased more than tenfold from 1980 to 1990.[21]

Regulatory Requirements

Limited Toxicity Data

Lack of even the most basic information about the health effects of thousands of chemicals being made, sold, and emitted has serious implications for our most vulnerable population.

Information that might be used to regulate exposure to chemicals comes largely from results of toxicity testing in whole animals, cell cultures, or epidemiological studies of exposed people. However, even for those chemicals that have undergone some degree of examination, studies in both animals and humans have deficiencies.

Because of obvious ethical concerns associated with toxicity testing in humans, our regulatory system for chemicals has historically been based on toxicity testing in animals, with extrapolation of these results to estimate risks for average adult humans. (However, animal studies commonly fail to predict the particular sensitivity of the developing human brain.) Implicit in this approach is the assumption that animal studies are relevant to humans. This assumption is widely accepted because, with some notable exceptions, test animals and humans absorb, metabolize, respond to, and excrete chemicals in substantially similar ways.

Animal studies commonly fail to predict the particular sensitivity of the developing human brain.

Despite validated and standardized testing protocols, toxicity testing data for individual chemicals from animal studies are woefully inadequate. For example, nearly 3,000 "high production volume" (HPV) chemicals are produced at greater than one million pounds per year. Yet, for 75 percent of these top-volume chemicals, even the most basic toxicity testing data are lacking.[22] For about three-quarters of these commercial chemicals, the public record holds no data reporting the results of toxicity testing in developing animals.[23]

Among the approximately 890 registered pesticidal active ingredients, EPA considers about 140 to be neurotoxic.[24] Between 3 and 5% of non-pesticidal chemicals have been estimated to be toxic to the nervous system.[25] Yet the Environmental Protection Agency (EPA) asserts that an overwhelming majority of the materials in commercial use have not been tested specifically for neurotoxic potential, making this estimate highly speculative.[26] Since 1991, for example, EPA has had a validated, accepted guideline for assessing a chemical's toxicity to the nervous system in immature or developing animals. By December 1998, however, manufacturers had submitted results from this

developmental neurotoxicity (DNT) testing for only 12 chemicals — nine pesticides and just three non-pesticide commercial chemicals.[27]

Why Data are Lacking

Laboratory animal tests of single chemicals do not reflect the real world of mixed exposures, and commonly fail to predict the sensitivity of the developing human brain.

Animal toxicity testing data are inadequate for a number of reasons. First, the "core" or basic toxicity testing requirements necessary for registering chemicals are often inadequate. Second, "triggered" or conditional testing requirements may be incompletely or ineffectually enforced. Third, when additional tests are triggered, the testing guidelines or protocols themselves may be deficient. Finally, laboratory animal tests of single chemicals do not reflect the real world of mixed exposures, and commonly fail to predict the sensitivity of the developing human brain.

1. Inadequate "Core" or Basic Testing Requirements

The lack of toxicity data for chemicals currently on the market stems directly from the lack of requirements for testing prior to registration or manufacture of these chemicals. For most non-pesticidal and non-pharmaceutical chemicals that are regulated under the Toxic Substances Control Act (TSCA), manufacturers are required to notify the EPA of their intent to manufacture a new chemical or use an existing chemical in substantially new ways. Yet, there are no requirements for performing developmental neurotoxicity (DNT) testing of the proposed chemical. In fact, *no* pre-manufacturing toxicity testing of any type is required under TSCA.[28] Instead, toxicity testing of these chemicals has largely occurred at the manufacturer's discretion, or after manufacture and use of the chemical has already raised questions about its impact on the health of exposed persons. Though Section 6 of TSCA authorizes the EPA Administrator to take action to control risks from toxic chemicals, in its 20-year history EPA has taken Section 6 regulatory actions against only five chemicals or chemical classes.[29]

In contrast, pesticides must undergo a battery of required toxicity tests prior to their registration, manufacture and use. Of more than 890 pesticide "active ingredients" registered with EPA, 523 are registered for use on food or feeds.[30] Regulation of food-use pesticides takes place under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), the Federal Food, Drug and Cosmetic Act (FFDCA), and since 1996, the Food Quality Protection Act (FQPA). The battery of required toxicology tests for registering or re-registering a pesticide used in or on food are found in the Code of Federal Regulations, last revised in 1984. Even the core requirements are alarming in their omissions. They fail to include, for example, specific tests of a chemical's toxicity to the function of the nervous system, the immune system, or the endocrine system. EPA has repeatedly acknowledged the deficiency of these testing requirements for pesticides, particularly in terms of testing their potential effects on the nervous system, and the agency has signaled its intent to revise them. *See sidebar page 110.*

2. Inadequate "Triggered" or Conditional Testing

Registration of a new pesticide does not require pre-market testing for effects on the developing or adult brain or nervous system. EPA only recommends this kind of testing after certain conditions have been met—in other words, they are "conditionally required." For example, EPA's recommendation for DNT testing is contingent upon the fulfillment of certain criteria, or "triggers," that were decided upon at a decade-old workshop sponsored by both EPA and the National Institute for Drug Abuse. From highest to lowest priority, these triggers include chemicals that are: CNS/behavioral teratogens (and structural analogues), adult neuropathic agents, adult neuroactive agents, hormonally–active compounds, and developmental toxicants that do not necessarily produce CNS effects.[40] [41] After nearly a decade, EPA's tiered or triggered system for making recommendations for developmental neurotoxicity testing has prompted manufacturers to submit just nine complete DNT tests out of 890 registered pesticides. The explanation for this record is multifaceted.

It is not that there is a lack of accepted methods for testing developmental neurotoxicity. EPA has had validated, "accepted" guidelines for performing DNT tests since 1991. Moreover, tests using these validated DNT guidelines appear to be somewhat sensitive at detecting neurotoxicity in developing animals. Of the small number of pesticides tested with it, seventy-eight percent (7 of 9) were found to have an effect on the developing nervous system.[42] Rather, the triggers themselves are inadequate or not enforced. It would not be unreasonable to expect more than nine complete DNT studies over the last decade inasmuch as EPA has already identified 140 or more of existing pesticides to be neurotoxic.

In 1998 a working group of EPA scientists looked at the agency's track record on DNT testing and concluded:

> "In the past, developmental neurotoxicity study was based on criteria or triggers from both adult and developmental toxicity data and a weight-of-the-evidence review of all available data for each chemical. Such triggers were probably a reasonable place to start; however, they were based on experience with a limited number of agents. More recent information suggests that these triggers may not be inclusive enough to signal all chemicals that have the potential to produce developmental neurotoxicity. Based on the data currently available, it is impossible to predict how many neurotoxic agents will show developmental neurotoxicity, nor do we currently have sufficient information to predict how many agents that are not neurotoxic or that do not show CNS malformations will cause developmental neurotoxicity."[43]

It is impossible to predict how many neurotoxic agents will show developmental neurotoxicity.

More generally, the concept of tiered or "triggered" toxicity testing itself is probably flawed, at least with respect to the nervous system. Under existing EPA regulations the trigger for a "conditional" requirement that a chemical undergo

The data call-in fails to answer the need for neurotoxicity testing for new pesticides being registered.

DEVELOPMENTAL NEUROTOXICITY AS A CORE TESTING REQUIREMENT

As early as 1994, EPA recognized that its toxicology testing requirements for registering new pesticides were inadequate, particularly with respect to testing for toxicity to the nervous system. In that year, EPA finished, and asked its FIFRA Scientific Advisory Panel (SAP) to review proposed revisions to these requirements, found in part 158, subpart F, of section 40 of the Code of Federal Regulations. EPA's 1994 proposed revisions would have made it a core requirement for newly registered pesticides to be screened for neurotoxicity, including acute and subchronic testing in adult animals.[31] The SAP generally endorsed the proposal.[32] But EPA has failed repeatedly to issue a proposed rule and finalize these revisions, even after repeated public announcements of its intention to do so.[33,34]

In the intervening years, however, EPA's proposed revisions have expanded. In March 1998, for example, the entire FIFRA SAP recommended to EPA that it consider requiring developmental neurotoxicity (DNT) testing for *all* neurotoxic insecticides, with a portion of the panel urging a developmental neurotoxicity testing requirement for *all* pesticides, period.[35] An internal EPA working group then reexamined the agency's core testing requirements for pesticides, and concluded "40 CFR Part 158.340 (Subpart F) should be updated as soon as possible to include the adult and developmental neurotoxicity guidelines and to refer to the newly revised two-generation reproduction and prenatal developmental toxicity testing guidelines."[36] This recommendation differs from EPA's 1994 proposed revisions with the addition of DNT as a basic core requirement. An October 1998 memorandum—jointly signed by the heads of EPA's Office of Prevention, Pesticides and Toxic Substances (OPPTS), the Office of Research and Development, and the Office of Children's Health Protection—affirmed the agency's intention to accept this recommendation and expand the core requirements for all new pesticides to include DNT testing.[37] The memo referred to the long-delayed revisions which "are expected to go to OMB (Office of Management and Budget) in November (1998), and which are scheduled for public notice and comment in Spring 1999."[38] Neither step occurred.

One thing that did happen in August 1999 is that EPA announced an imminent "data call-in," or DCI, for about 140 already registered pesticides considered to be neurotoxic. The DCI's first phase—initiated September 10, 1999—focuses on just 34 cholinesterase-inhibiting organophosphate insecticides. It requires manufacturers of these chemicals to conduct and submit tests of acute, subchronic and developmental neurotoxicity to EPA within two years.[39] EPA has not estimated how long it will take to complete the entire DCI for all 140 pesticides.

Although this DCI begins the process of collecting neurotoxicity data, it is limited to pesticides already identified as neurotoxic. More importantly, the DCI only applies to chemicals already on the market; it fails to answer the need for neurotoxicity testing for new pesticides being registered. Until this need is met, most new pesticides and other chemicals will continue to enter the market before any testing is done to predict toxicity to the brain and nervous system.

basic screening for nervous system toxicity hinges on results from other, less specific, toxicological testing that generally does not involve the nervous system. Yet, as has been pointed out by Dr. Deborah Rice, an EPA neurotoxicologist, the triggers for recommending a DNT study in some cases depend on information best obtained from the DNT study itself.[44]

Finally, it is critical to note that even when prior testing triggers a recommendation for DNT testing, a chemical manufacturer is under no obligation to perform such testing.[45] Thus, while 12 complete DNT studies had been submitted to EPA by December 1998, various agency scientific review committees had recommended DNT testing of an additional 26 chemicals. Though some of these recommendations date back more than six years, none of the recommended testing has ever been completed. A complete DNT study can be planned and completed in less than 2 years.

3. Deficient Guidelines for Performing Toxicity Testing

Another problem with some of EPA's current guidelines for performing toxicity testing in animals is that they omit key measures of toxicity. For example, manufacturers of organophosphate and carbamate insecticides, specifically designed to inhibit acetylcholinesterase, a key enzyme for the development and function of the nervous system, are not currently required to submit studies that will quantify the level of cholinesterase inhibition stemming from exposure to their product.

Similarly, the current DNT guideline eventually must be revised to better assess

the risks of chemical exposure to the nervous systems in children. For example, a March, 1998 panel of the EPA's Scientific Advisory Panel (SAP) reviewed the DNT guideline. It unanimously agreed that this guideline "must be further refined to develop more sensitive endpoints which are relevant to significant outcomes in humans such as learning disabilities and behavioral issues."[46] In addition, Tilson and others have identified the exposure period in the current DNT guideline as being far too short to reflect the entire vulnerable period of brain development in children.[47] The current DNT guideline requires that test animals be dosed with a chemical through the 10th postnatal day. Yet the critical period of rapid growth in the human brain, extending from the 3rd trimester through the second year of life, corresponds to the first 21-28 days of life in rats or mice—not ten days.[48]

Omissions like these led the National Academy of Science to conclude in 1993 that EPA's "current testing protocols do not, for the most part, adequately address the toxicity and metabolism of pesticides

A complete DNT study can be planned and completed in less than 2 years.

in neonates and adolescent animals or the effects of exposure during early developmental stages and their sequelae in later life".[49] In the first phase of its data call in for 34 registered organophosphate insecticides, EPA has taken steps to ensure that more useful neurotoxicity information is collected. For example, the agency's recent DCI specifically requires that a comparative evaluation of cholinesterase inhibition in both adult and young animals be included. It further requires that animals in the DNT study be dosed from day 6 of gestation through postnatal day 21, significantly beyond the 10th postnatal day required under the current guideline.[50] However, the DCI thus far applies to relatively few pesticides, many of which have already been on the market for two or three decades or more. As noted above, however, there is as yet no requirement that new pesticides be routinely tested for any neurotoxicity, including developmental neurotoxicity.

There is as yet no requirement that new pesticides be routinely tested for any neurotoxicity, including developmental neurotoxicity.

The flaws in the current DNT guideline do not make it worthless. On the contrary, the 1998 EPA review of 12 DNT studies revealed that "The developmental neurotoxicity study protocol (OPPTS 870.6300) includes unique endpoints which are not examined in any other standard toxicity testing protocol, enabling the detection of effects on nervous system development of the offspring following pre- and/or postnatal exposure."[51] And a March 1998 Scientific Advisory Panel concluded that "any pesticide that works by poisoning the nervous system" should be considered for developmental neurotoxicity testing "by the most sensitive validated methods available."[52] The current DNT guideline *is* EPA's most sensitive validated means of doing so.

4. Laboratory Conditions Do Not Reflect the Real World, Animal Studies May Underestimate Sensitivity of Human Brain

Animal testing typically assesses the toxic effects from exposure to only one chemical at a time. This fails to provide information about the cumulative and interactive effects from exposure to multiple chemicals that often occur in real life settings.[53] For example, a five-year study led by Dr. Warren Porter at the University of Wisconsin, identified significant shortcomings in toxicological testing requirements currently used to register pesticides in the United States. The study suggests that combinations of commonly used agricultural chemicals, in levels typically found in groundwater, can significantly influence immune and endocrine systems as well as neurological health. Tests in laboratory animals showed that combinations of the pesticides aldicarb and atrazine, along with nitrates, each widespread contaminants of groundwater in the U.S., resulted in altered immune, endocrine, and nervous system function.[54] The study identified additional deficiencies in EPA's core requirements for registering pesticides, including the lack of testing for low dose exposures, no testing for endocrine and

Spotlight

Autism Cluster Sparks Study of Environment

At the National Institutes of Health state of the science meeting on autism held in 1995, the phrase "environmental cause" was never mentioned.[1] Yet only three years later the Centers for Disease Control (CDC) and the Agency for Toxic Substances and Disease Registry began compiling information on potential environmental pollution contributors to a purported autism cluster in Brick Township, New Jersey. According to the New Jersey Bergen Record, this is "uncharted territory" for the CDC.[2] At the same time the CDC began studying autism and its potential environmental connections in a region around Atlanta. Why the dramatic turnaround?

One catalyst was surely Bobbie Gallagher, Brick Township resident and mother of two autistic children. Frustrated by a lack of information about the cause of her children's disabilities, she began to look for causes in the environment. What she found were plasticizers in the water supply and a nearby Superfund site at the local landfill oozing a toxic soup of chemicals. She also discovered about 30 other children in the area who had been diagnosed with autism. It was small comfort to know that she was not alone.[3] (At least 42 children have subsequently been identified with autism in Brick Township, population 76,000.)

Gallagher teamed up with the National Alliance for Autism Research (NAAR) in Princeton, New Jersey, which proposed to the CDC that five new Centers for Research in Autism Epidemiology be established. As a result of this proposal, studies in Brick Township looking at drinking water and also the Metedeconk River are now underway, as is a study in five counties around Atlanta, Georgia.

According to Dr. Eric London, medical director of NAAR, epidemiologic studies from around the world have shown a steady increase in the prevalence of autism, from around 4/10,000 in the early Eighties to about 12/10,000 in the Nineties. (The CDC fact sheet on autism spectrum disorders estimates prevalence may be as high as 20/10,000 children). Other evidence suggesting that autism may be increasing dramatically includes a recent study done by the California Department of Developmental Services released in March 1999. The study looked at pervasive developmental disorders (PDDs) from 1987 through 1998 and showed a 210 percent increase in cases entered into the autism registry during those years.[4] [5] If the incidence of autism is increasing, and or clusters of autism are being discovered, an environmental influence is likely.[6]

Evidence indicating the environment as a contributing factor to autism is mounting. Studies suggest there are both genetic and environmental components to the disorder.[7] However, definitive causes of autism remain elusive. Brick Township, New Jersey may provide some important missing pieces to the puzzle.

[1] London E. Looking at Hard Topics in Autism. Environmental Influences on Children conference, NY Academy of Medicine, May 24-25 1999.

[2] McEnery R. CDC Studying link between environment and autism. Bergen Country Record, November 8 1999.

[3] Gallagher B. Looking at Hard Topics in Autism. Environmental Influences on Children conference, NY Academy of Medicine, May 24-25 1999.

[4] Boyle C. Epidemiologic Perspective on Autism. Environmental Influences on Children conference, NY Academy of Medicine, May 24-25 1999.

[5] California Department of Developmental Services. Changes in the Population of Persons with Autism and Pervasive Developmental Disorders in California's Developmental Services System: 1987 through 1998. A Report to the legislature, Mar 1999.

[6] London E. Looking at Hard Topics in Autism. Environmental Influences on Children conference, NY Academy of Medicine, May 24-25 1999.

[7] Hollander E. Environmental Factors in the Development of Autism. Environmental Influences on Children conference, NY Academy of Medicine, May 24-25 1999.

immune functions, and no tests of commonly found mixtures of substances that represent real-world exposures.

Neurotoxicity studies submitted to EPA, typically in adult rodents, often vastly underestimate the sensitivity of the developing human brain. For example, based on comparisons of animal and human data, animal studies of lead, mercury and PCBs predict a "safe" exposure level in humans that is 2-4 orders of magnitude (100-10,000 fold) higher than levels that actually cause effects in humans.[55] These limitations must be kept in mind as we use the results of animal testing to estimate "safe" human exposure levels.

Costs incurred by industry, as a result of proposed regulation, must be factored into decision-making.

Additional Regulatory Authority and Weaknesses

Besides TSCA and FIFRA, other major federal laws with regulatory authority over chemicals include the Clean Air Act (CAA), the Clean Water Act (CWA), and the Safe Drinking Water Act (SDWA). Each has weaknesses that allow neurotoxic and other toxic substances to be emitted into air, drinking water, food, and onto land. For example, although the SDWA requires the EPA to set Maximum Contaminant Levels (MCLs) for certain listed chemicals, the level that is actually set to protect health is based on considerations that include costs of water treatment and also best available water treatment technology. Some standards are obsolete due to a decline in the toxic threshold for a previously recognized effect. Others are obsolete because recent evidence has revealed altogether new effects such as endocrine disruption that occur at lower levels of exposure than previously noted.[56]

Except for food-use pesticides, FIFRA and TSCA require cost-benefit analyses of the impact of proposed standards, in addition to health evaluations. This means that costs incurred by industry, as a result of proposed regulation, must be factored into decision-making.[57]

1 Dr. Philip Landrigan quoting Dr. Herbert Needleman. Toxics Release Inventory and Right-to-Know Conference, Washington, DC. September 9, 1997.

2 U.S.EPA,1997 Toxics Release Inventory Public Data Release. May 13, 1999.

3 Environmental Defense Fund "Scorecard" (www.scorecard.org) health effects of chemicals - neurotoxicity-compiled from 21 databases or references including EPA, National Institute for Occupational Safety and Health's Registry of Toxic Effects of Chemical Substances, NJ Dept. of Health Services TRI Fact Sheets and Casarett and Doull's Toxicology, the Basic Science of Poisons, edited by C. Klaassen, M. Amdur and J. Doull, 5th Ed. Pergamon Press, NY 1996.

4 Ibid.

5 U.S. EPA. 1997 Toxics Release Inventory Public Data Release. May 13, 1999.

6 U.S. EPA, Office of Prevention, Pesticides and Toxic Substances. Endocrine Disruptor Screening and Testing Advisory Committee. Final report. Washington DC, 1998.

7 Federal Register October 29, 1999, Vol 64:209, Rules and Regulations, Page 58665-58753.

8 Personal communication with Paul Orum, Right-to-Know Network. January 31, 2000.

9 Environmental Defense Fund "Scorecard" (www.scorecard. org) health effects of chemicals - Ibid.

10 Massachusetts Department of Environmental Protection, Bureau of Waste Prevention, in conjunction with the Office of Technical Assistance for Toxics Use Reduction, Toxics Use Reduction Institute, Massachusetts Executive Office of Environmental Affairs. 1997 Toxics Use Reduction Information Release, March 23, 1999.

11 Personal communication with Liz Harriman, Massachusetts Toxics Use Reduction Institute. 12/29/99.

12 Massachusetts Department of Environmental Protection, Bureau of Waste Prevention, in conjunction with the Office of Technical Assistance for Toxics Use Reduction, Toxics Use Reduction Institute, Massachusetts Executive Office of Environmental Affairs. 1997 Toxics Use Reduction Information Release, March 23, 1999.

13 U.S. EPA. OPPTS. Pesticides Industry Sales and Usage, 1996 and 1997 Estimates. 733-R-99-001, November 1999.

14 U.S. EPA, OPPTS, Pesticides and National Strategies for Health Providers, Workshop Proceedings, April 23-24 1998. EPA 735-R-98-001, July 1998

15 Environmental Working Group. How Bout Them Apples? Pesticides in Children's Food 10 Years After Alar., Washington DC. 2/25/99.

16 U.S.EPA, Chlorpyrifos:HED Preliminary Risk Assessment for the Reregistration Eligibility Decision Document. 10/18/99.

17 Raloff J. Home carpets: Shoeing in toxic pollution. Science News, 138:86, 1990.

18 Lewis R, Fortune C et al. Distribution of pesticides and polycyclic aromatic hydrocarbons in house dust as a function of particle size. Enviro Health Perspect, 107:9, 1999.

19 Johnston L. Primary Exposure: Pesticides in MA Schools. MASSPIRG Education Fund, 1996.

20 Dr. John Wargo. New Directions for Children's Environmental Health Law and Policy. Environmental Influences on Children, Brain, Development & Behavior Conference, New York Academy of Medicine, NY, May 1999.

21 Schettler T, Solomon G. et al. Generations at Risk: Reproductive Health and the Environment. MIT Press, Cambridge, MA. July 1999. Pg. 225.

22 Roe D, Pease W., Florini K, Silbergeld E. Toxic Ignorance: The Continuing Absence of Basic Health Testing for Top-Selling Chemicals in the United States, Environmental Defense Fund, 1997.

23 Ibid.

24 Federal Register. 64(151):2945-42947, 1999.

25 Office of Technology Assessment, Neurotoxicity: Identifying and Controlling Poisons of the Nervous System, OTA-BA-436, Washington, DC: U.S. Government Printing Office, April 1990, p.3.

26 U.S. EPA, Guidelines for Neurotoxocity Risk Assessment, April 30 1998, EPA/630/R-95/001Fa.

27 Makris S, Raffaele K, Sette W, Seed J. A retrospective analysis of twelve developmental neurotoxicity studies submitted to the U.S. EPA Office of Prevention, Pesticides, and Toxic Substances (OPPTS), draft, 11/12/98.

28 Schettler T. et al. Generations at Risk: Reproductive Health and the Environment. MIT Press, Cambridge, MA. July 1999. Pg. 240.

29 Roe D, Pease W., Florini K, Silbergeld E. Toxic Ignorance: The Continuing Absence of Basic Health Testing for Top-Selling Chemicals in the United States, Environmental Defense Fund, 1997. Pg. 28.

30 U.S. EPA. OPPTS. Pesticides Industry Sales and Usage, 1996 and 1997 Estimates. 733-R-99-001, November 1999.

31 U.S. EPA, Changes to 40 CFR. Part 158, September 14, 1994, Presented to the FIFRA Scientific Advisory Panel (SAP), November 29-30, 1994.

32 U.S. EPA, Final Report from the FIFRA Scientific Advisory Panel, A Set of Scientific Issues Being Considered by the Agency in Connection with the 40 CFR Part 158 Proposed Rule: Pesticide Registration Data Requirements, December 19, 1994.

33 U.S. EPA, Office of Pesticide Programs Annual Report for 1994, EPA 735-R-95-001, http://www.epa.gov/oppfead1/annual/1994, January 1995.

34 U.S. EPA, Memorandum to the Administrator from Lynn Goldman, Henry Longest II, and Ramona Trovato, Update and Implementation Plans for the Child Safety Factor of the Food Quality Protection Act, October 14, 1998.

35 U.S. EPA, Office of Science Coordination and Policy, Final Report: Scientific Advisory Panel (SAP) March 1998 Meeting, at http://www.epa. gov/scipoly/sap/1998/march/fqpa_10x.htm/, page 5.

36 U.S. EPA, Toxicology Data Requirements for Assessing Risks of Pesticide Exposure to Children's Health, Draft Report of the Toxicology Workgroup of the EPA 10X Task Force, November 30, 1998, p. 29.

37 U.S. EPA, Memorandum to the Administrator from Lynn Goldman, Henry Longest II, and Ramona Trovato, Update and Implementation Plans for the Child Safety Factor of the Food Quality Protection Act, October 14, 1998.

38 Ibid., p. 2.

39 Federal Register. 64(151):42945-42947, 1999.

40 Claudio L, Kwa WC, Russell AL, Wallinga D. Testing methods for developmental neurotoxicity of environmental chemicals, Toxicol. Appl. Pharmacol., 164. (*accepted January 4, 2000*).

41 Francis, EZ, Kimmel, CA, Rees, DC, Workshop on the qualitative and quantitative comparability of human and animal developmental neurotoxicity: Summary and Implications. Neurotoxicol and Teratol. 12:285-292 (1990).

42 U.S. EPA, Dr. Hugh Tilson, Environmental Influences on Children, Brain Development & Behavior Conference, NY Academy of Medicine, May 1999.

43 U.S. EPA, Draft Report of the Toxicology Workgroup of the EPA 10X Task Force, Toxicology Data Requirements for Assessing Risks of Pesticide Exposure to Children's Health, April 28, 1998, p. 12.

44 Statement by Dr. Deborah Rice, Seventeenth International Neurotoxicology Conference: Roundtable Discussion — Do the EPA Developmental Neurotoxicity Guidelines Detect Human Developmental Neurotoxicity?, Little Rock, AK, October 20, 1999.

45 Ibid., presentation by David Wallinga, M.D.

46 U.S. EPA Report of the FIFRA Scientific Advisory Panel Meeting, December 8, 1998, held at the Sheraton Crystal Hotel, Arlington, VA, SAP Report No. 99-01B, January 22, 1999, p. 18.

47 Tilson, HA, The concern for developmental neurotoxicology: Is it justified and what is being done about it? Environ. Health Perspect. 103(6):147-151.

48 Claudio L, Kwa WC, Russell AL, Wallinga D. Testing methods for developmental neurotoxicity of environmental chemicals, Toxicol. Appl. Pharmacol., 164. (*accepted January 4, 2000*).

49 National Research Council, Pesticides in the Diets of Infants and Children, National Academy Press: Washington, D.C., 1993.

50 U.S. EPA, Letter to Registrants from Lois Rossi, Director, Special Review and Reregistration Division with multiple attachments, OPPTS, September 10, 1999.

51 Makris S, Raffaele K, Sette W, Seed J. A retrospective analysis of twelve developmental neurotoxicity studies submitted to the U.S. EPA Office of Prevention, Pesticides, and Toxic Substances (OPPTS), draft, 11/12/98.

52 U.S. EPA, Office of Science Coordination and Policy, Final Report: Scientific Advisory Panel (SAP) March 1998 Meeting, at http://www.epa.gov/scipoly/sap/1998/march/fqpa_10x.htm/.

53 Schettler T, Solomon G et al. Generations at Risk:Reproductive Health and the Environment. MIT Press, Cambridge, MA. 1999. Pgs. 21-48.

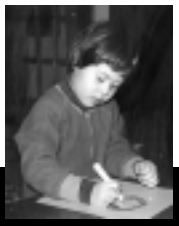
54 Porter WP, Jaeger JW, Carlson IH. Endocrine, immune and behavioral effects of aldicarb (carbamate), atrazine (triazine) and nitrate (fertilizer) mixtures at groundwater concentrations. Journal of Toxicology and Industrial Health 15:133-150, 1999.

55 Rice D, Evangelista de Duffard A, Duffard R et al. Lessons for neurotoxicology from selected model compounds: SGOMSEC joint report. Environ Health Perspect 104(suppl 2):205-215, 1996.

56 Olsen E. Think Before You Drink:The Failure of the Nation's Drinking Water System to Protect Public Health. NRDC, 1993. pg. V.

57 Schettler T, Solomon G et al. Generations at Risk:Reproductive Health and the Environment. MIT Press, Cambridge, MA. 1999. Pg. 236.

Chapter 8



Conclusion

Several important themes emerge from the research reviewed in this report.

1. Neurodevelopmental disabilities are widespread, and chemical exposures are important and preventable contributors to these conditions. Reductionist analyses that separately address environmental and genetic factors may illuminate important details but fail to acknowledge the complexities of multiple, interacting factors that ultimately influence neurological development. Both genetic factors and environmental factors must be simultaneously considered to properly understand these disabilities.

2. Our initial understanding of the impacts of neurotoxic substances regularly underestimates the potential for harm. So called "safe" exposure thresholds regularly become obsolete as research methods improve.

3. Carefully conducted, long-term epidemiological studies have proven to be much more sensitive measures of developmental neurotoxicity than animal studies. Thus, animal models may greatly underestimate true human risks. Indeed, it would be surprising if this were not the case, considering the unique capacities and complexities of the human nervous system.

4. Regulatory policy has repeatedly failed to protect children from widespread harm due to exposures to developmental neurotoxins. Due to the extremely slow rate at which proof of safety or harm materializes, generations of children are at risk, and often harmed, before an adequate regulatory response can occur. Timely action can be ensured only by regulatory processes that are capable of responding during the extended period between the earliest evidence and more complete scientific understanding of the danger.

Generations of children are at risk, and often harmed, before an adequate regulatory response can occur.

5. The failure of the regulatory system to protect public health can often be traced to the influence of vested economic interests upon the regulatory process. Special interests commonly use a variety of tactics to delay or diminish the regulatory response to public health threats. One obstacle to timely action is the frequent presumption that chemical exposures are harmless until a complex, expensive, and rigid process for identifying toxicity and health threats is completed.

6. Neurodevelopmental disabilities impose social and economic costs upon impacted families and the economy as a whole. Preventing these disabilities has the potential to provide major economic benefits.

7. Special interests are not merely tolerated but are actually an integral part of the regulatory process. If we are to successfully respond to the threats posed by the use and environmental releases of neurotoxic chemicals, we must find a way to insulate public health decision-making from conflicts of interest that can corrupt it.

Simplistic Analysis Fails To Address The Complex Causes Of Developmental Disabilities

Genetic and environmental factors interact in complex ways to cause the learning disabilities and cognitive disorders discussed in this report. Yet, in keeping with current toxicological, genetic, and epidemiological research strategies, most research continues to focus on one domain at a time, as if comprehensive understanding would emerge by simply adding up the contributions of each.

This reductionist approach to complex problems characterizes biomedical research in the 20th century. Though dissecting problems into component parts helps to illuminate important details, a broader integration must be accomplished before we can truly understand the infinitely more complex real world, where genetic, environmental, and social factors combine. For the purposes of comprehensive understanding, prevention, and public health protection, these isolated factors must be conceptually reassembled and considered as an integrated whole.

Neurodevelopmental Disabilities Are Expensive Not Only For Families, But For Society As A Whole

Learning and behavioral disabilities are associated with early drop out from high school, substance abuse, unemployment, teen-parenting, welfare dependence, and incarceration. The enormous financial costs of these problems are borne by families, schools, local and national governments, and by businesses faced with workforce disabilities and rising health insurance premiums. Regulatory decisions that affect the neurodevelopment of children impact not only health, but all aspects of society, including the economy as a whole. Indeed, healthy families and a healthy workforce are essential pillars of a vibrant economy.

Regulatory Policy Has Repeatedly Failed To Protect Children's Health

An historical review of our understanding of the risks of neurotoxic chemicals reveals a disturbing pattern. As a rule, these chemicals are recognized as harmful long after their use has become routine and exposures have become widespread. Because the fetus and developing child are most sensitive to the effects of these insidious exposures, children bear the burden of regulatory

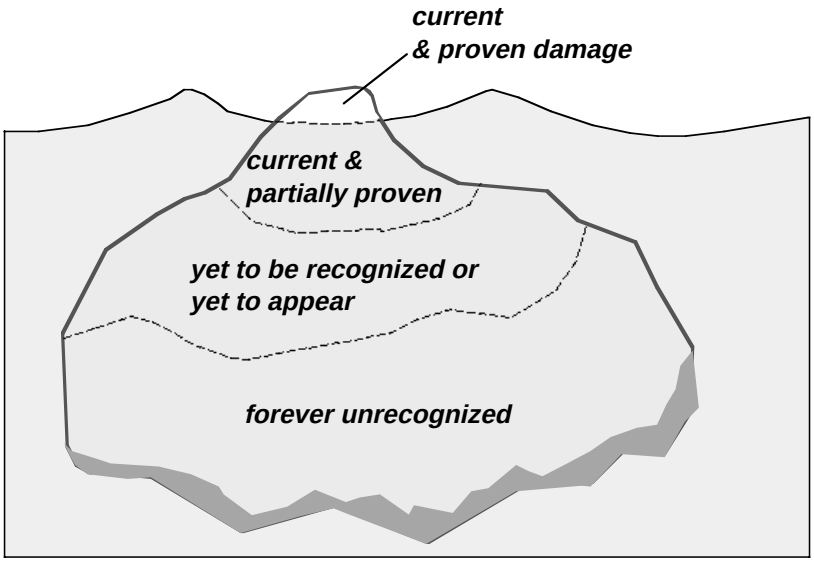
policies that largely consider chemicals safe until proven harmful. After a century of intensive study, the harm from perhaps the single most-studied neurotoxicant can be characterized with fair certainty. Since childhood lead exposure has been ongoing since lead paint was first introduced in the 1890s, five generations of children have been injured while science slowly advanced to where it is now capable of appreciating the magnitude of the problem. This same pattern of "after-the-fact" recognition of harm has been repeated for mercury, PCBs, pesticides, alcohol, and nicotine. In each instance, what we initially believed to be a "safe" exposure level steadily dropped as understanding improved.

With thousands of potentially neurotoxic chemicals in widespread use, our snail's pace approach to regulation clearly sets children in a minefield of uncertainty and potential harm, where the full extent of current hazards will be unknown for the foreseeable future. Meanwhile, thousands of new chemicals come into production and use, creating new exposure hazards. Even when there is substantial evidence of hazard, chemicals continue to be inflicted on the unsuspecting public for decades, as painstaking scientific study slowly clarifies precise magnitudes of risk and cellular mechanisms of harm. Without such information, the regulatory system does not easily respond. Rigid adherence to an inflexible standard for justifying action prevents timely regulatory response to public health threats. As a result, the regulatory system often serves special economic interests at the cost of children's health.

Individual chemicals or classes of chemicals, for which there is plausible evidence of toxicity, should not be considered innocent until fully proven guilty. Rather, such chemicals ought to be regulated in a precautionary manner, much as we regulate pharmaceutical chemicals - shifting the "burden of proof " so that some basic evidence of safety is required before public exposures are permitted. Pharmaceuticals are bioactive chemicals, which people take by choice and which have favorable risk/benefit profiles. Environmental chemicals, on the other hand, are bioactive substances that people usually do not take by choice, but are often exposed to, in varying amounts, without their knowledge or consent. In addition, environmental chemicals that carry risks do not, as a rule, provide countervening health benefits. Clearly, the public deserves the same measure of protection from involuntary environmental exposures, which may be hazardous, as from voluntary pharmaceutical exposures that have therapeutic benefit.

With thousands of potentially neurotoxic chemicals in widespread use, our snail's pace approach to regulation clearly sets children in a minefield of uncertainty and potential harm

Tip of the Iceberg



The regulatory process addresses those few chemicals for which there is rigorous proof of harm, but such harm is likely to be the tip of the iceberg. There is a deeper level at which emerging harm can be identified but is not fully proven, despite clear warning signs. Below this, there are damages that occur with long latency periods, in which harmful exposure has occurred but the manifestation of the damage has yet to appear. And below this there are exposures that are harmful but which will never be recognized due to the difficulties of detection.

There are approximately 80,000 chemicals in the U.S. inventory, with one-to-two thousand new chemicals introduced each year. Since chemical exposures proliferate much faster than their neurodevelopmental toxicities can be understood, the true dimensions of the toxic threat will always be underestimated by "currently available knowledge".

Finally, risks and benefits often accrue to very different groups and are typically not equitably distributed. While manufacturers and particular groups of consumers may benefit from an industrial product or process that utilizes or releases neurotoxic substances, the risks of toxic exposures are often borne by others, such as cultural minorities or economically disadvantaged or socially marginalized groups. For example, children of urban inner cities or children of migrant farm workers are disproportionately exposed to pesticides or other neurotoxic substances. Subsistence fishing among less affluent ethnic communities, due both to economic necessity and cultural tradition, results in increased exposure to fish-borne neurotoxicants, including mercury, dioxin, and PCBs.

Conflicts Of Interest Are An Accepted Part Of The Regulatory Process

In environmental public health decision making, the strong influence of vested economic interests is currently an expected part of the regulatory process. Advocates for public health and representatives of special, corporate interests routinely lock horns in the course of scientific deliberations, in which the parties are considered "stakeholders" of equal importance. This process allows voices into public health decision making that are obviously financially conflicted and often willing to expend considerable sums of money to ensure that a particular financially advantageous action is taken. The failure of the regulatory process to guard against these influences contributes to the lack of children's health protection. Allowing financially conflicted interests a central role in the regulatory arena creates a steeply tilted playing field favoring corporations with enormous political and economic influence.

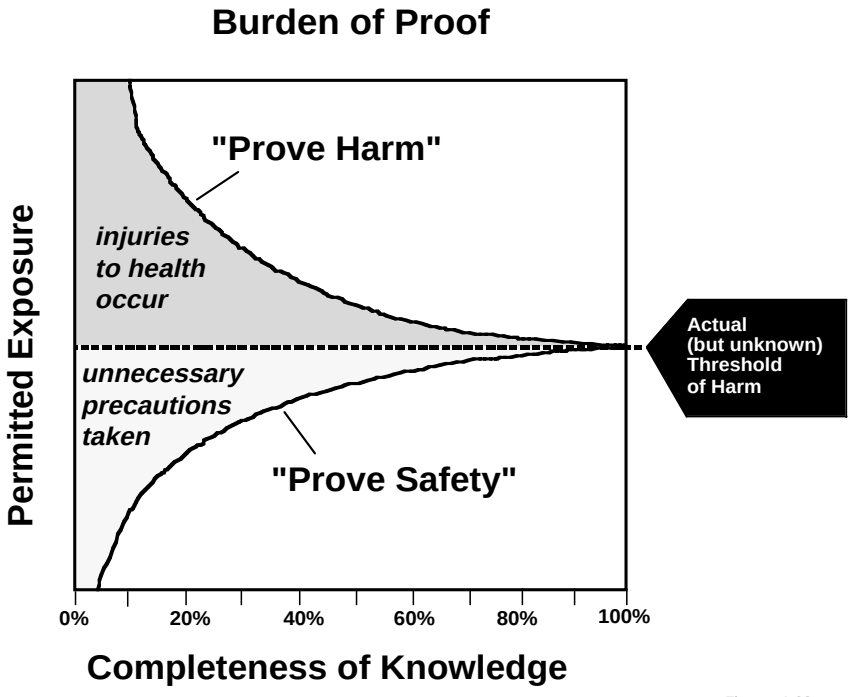
Corporate influence on the regulatory process may include a range of pervasive political and financial pressures, including political lobbying, campaign contributions, well-financed public relations

campaigns, biased interpretation of scientific evidence, and selectively funded research. Unfortunately, public agencies widely perceived as the defenders of public health are often compelled by political pressures to assume the role of mediator between public and corporate interests, rather than advocating on behalf of a safe, healthy environment. It is no surprise that these agencies, thus compromised, are incapable of fully protecting the health of our children.

In the absence of public understanding and involvement, critical decisions regarding public health are likely to be dictated by narrow special interests that have as a core concern neither public health nor the welfare of the economy as a whole. These decisions should not be dictated by the special interests that profit by undermining or resisting safeguards. The role of special interests in the regulation of environmental chemicals is an important matter for public debate, as it has direct relevance to the neurological development of children now and in the future.

Taking Our Children Back Out Of Harm's Way

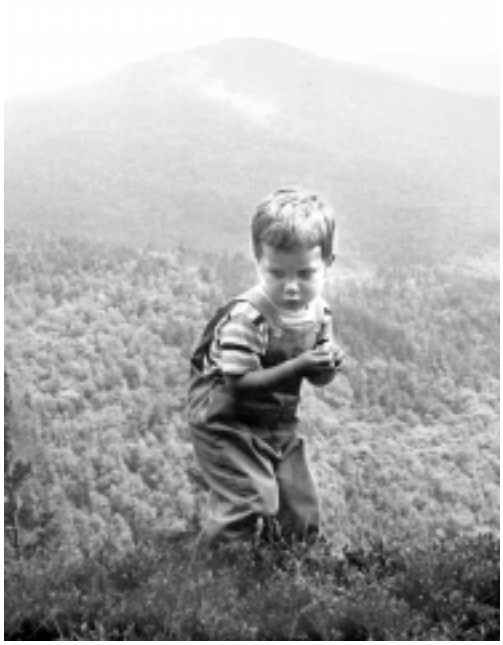
We should not need to identify with certainty exactly how much and through what mechanism a neurotoxic pesticide impairs brain development before coming to the conclusion that public health is not protected when the urine of virtually every child in this country contains residues of these chemicals. We can become more discriminate in home use of pesticides and modify agricultural systems so that we rely less on pesticides that are toxic



Consider a substance for which there is some unknown threshold at which harm occurs. At any given state of knowledge, there is an exposure that has been proven to be harmful. This is the upper curve in the figure.

There is also an exposure level for which evidence of safety exists. This is the lower curve in the figure.

If we decide to allow the regulatory process to follow the upper curve, we will allow exposure until proof of harm accumulates. Then the exposure level will be lowered to reflect the new evidence of harm. This approach guarantees that health will be harmed as knowledge is accumulated. If we decide that the regulatory process should follow the lower curve, human health will be protected. As knowledge of toxicity is gained, it may be found that the standards can be relaxed.



Protecting children from harmful exposures to environmental chemicals is well within our grasp.

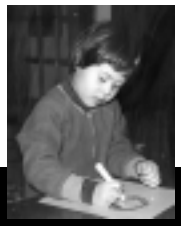
and ubiquitous in the environment. We do not need to exhaustively understand the mechanism by which methylmercury interferes with normal fetal brain development before concluding that it is not acceptable for freshwater and many ocean fish to be sufficiently contaminated with mercury to threaten developing brains. We know how to reduce the environmental releases of mercury so that fish are once again safe to eat regularly. We can modify manufacturing practices so that lead use in products goes steadily down instead of up. We can eliminate or modify outmoded technologies that produce the dioxin that contaminates fetuses and breast milk. We know how to do these things. What is often lacking is the political will to do them.

Though we can do little about genetic contributions to many of these disorders, we have enormous opportunities to mitigate environmental factors. Fifty years into the post war chemical revolution, sufficient evidence has accumulated to permit better understanding of the hazards of chemical exposure and the costs to human health.

Protecting children from harmful exposures to environmental chemicals is well within our grasp. Residual uncertainties can not be an excuse for inaction when the weight of evidence establishes the likelihood of harm.

Many different disciplines bring their own special expertise to bear on understanding the origins of the developmental disabilities we have discussed. Toxicologists, epidemiologists, behavioral geneticists, psychologists, social workers, teachers, parents, and health care providers each have important roles and responsibilities. We hope this report will help empower them and everyone else who cares about our young and vulnerable to better understand the insidious risks to children's health that result from widespread, repetitive chemical exposures. An informed and motivated public is critical to freeing our public agencies from the influence of financial conflicts of interest. This will permit these agencies to exercise their intended role as guardians of public health and strengthen democratic, participatory decision-making. In so doing, we can restore a margin of safety for our current and future children, and take them back, out of harm's way.

Appendix



Clinical Spectrum of Learning, Development and Behavior Disorders: Selected Definitions

The following learning, developmental and behavioral disorders represent a broad spectrum of cognitive, motor, perceptual and behavioral disorders. They describe a set of complex and divergent disorders whose descriptions have evolved/changed over time. The definitions used in this appendix will largely reflect the current criteria as stated in the Diagnostic and Statistical Manual of Mental Disorders IV (1994) published by the American Psychiatric Association.

Learning Disorders (formerly Academic Skills Disorders)

The term "learning disability" covers a variety of disorders in the areas of listening, speaking, reading, math and reasoning. These disabilities interfere with a person's ability to store, process, or produce information. These difficulties are unexpected, given the person's general level of ability.[1] As well as primary difficulties with academics, a learning disability can also result in secondary problems in social and emotional areas.[2] Studies have reported that children with learning disabilities have been found to have lower self-concept, more anxiety and lower peer acceptance than normally-achieving children.[3] It has also been suggested that learning disabilities may be an under-recognized risk factor in adolescent suicide.[4] Learning disabilities are often referred to as hidden handicaps because they frequently go undetected by teachers, physicians and parents.

There are three definitions of learning disabilities worth noting. The first definition was incorporated by the National Advisory Committee on Handicapped Children in 1968 and is used in the Education for All Handicapped Children Act of 1975 (PL-142). Another definition was used by the Joint Committee on Learning Disabilities (NJCLD, 1981) and modified by the Interagency Committee on Learning Disabilities (ICLD) in 1987. The last definition is described in the Diagnostic and Statistical Manual of Mental Disorders IV published by the American Psychiatric Association. The three definitions are listed below:

a.) The Education for All Handicapped Children Act of 1975 (PL - 142) states that "the term specific learning disability means a disorder in one or more of the basic psychological processes involved in understanding or using language, spoken or written, which may manifest itself in an imperfect ability to listen, speak, read,

HISTORICAL DEFINITIONS OF LEARNING DISORDERS (*)

1861

Early studies of aphasia by Broca (difficulty in producing or comprehending speech caused by brain damage rather than produced by deafness or simple motor deficit). Stemmed from observations of adults with acquired brain damage.

1877

Kussmaul proposed word blindness (loss of ability to read).

1895-1917

Congenital word blindness is described as a congenital defect occurring in children with an otherwise normal or undamaged brain, characterized by a disability in learning to read.

1922-1925

Post-Influenzal Behavior Syndrome: children were observed to have a disorder characterized by anti-social behavior, irritability, impulsiveness, emotional lability, hyperactivity and learning problems. First time that structural deficits involving certain parts of the central nervous system were related to behavioral problems. A diagnosis of structural brain damage was given to children who displayed behavioral and learning symptoms similar to those found in post-influenzal encephalitis.

*Hagw. RA, Silver AA. *Disorders of Learning in Childhood*. John Wiley and Sons, New York, 1990.

HISTORICAL DEFINITIONS

continued

1928
Strephosymbolia: five major symptom complexes: developmental alexia, writing disability, developmental word deafness, motor speech delay and developmental apraxia. These syndromes represented a delay or difficulty in establishing cerebral dominance for language function. The term for reading disability is labeled strephosymbolia.

1929
Congenital Auditory Imperception

1934
Organic Driveness: a hyperkinetic behavior disorder related to brain stem pathology.

1941
Developmental Lag

1943-1947
Brain-Injured or Damaged Child: described perceptual differences between retarded children whose history suggested pre-, peri- or postnatal brain injury and those retarded children who did not have such histories. Studies stressed the importance of perceptual functioning (auditory and visual) in the diagnosis of brain-injured children. Diagnosis of brain damage could be given based on the presence of neuro-psychological disturbance in perceptual or conceptual thinking.

1947
Minimally Brain-Damaged Child

1960
Psychoneurological Learning Disorders

1962
Term "Learning Disability" first defined by Kirk as a substitute for labels such as brain injured, perceptually handicapped or minimal brain dysfunction.

write, spell, or do mathematical calculations. The term includes such conditions as perceptual handicaps, brain injury, minimal brain function, dyslexia, and developmental aphasia. Such terms do not include children who have learning difficulties which are primarily the result of visual, hearing, or motor handicaps, of mental retardation, of emotional disturbance, or of environmental, cultural, or economic disadvantage".[5]

b.) The National Joint Committee of Learning Disabilities states that learning disabilities is a generic term that refers to a heterogeneous group of disorders manifested by significant difficulties in the acquisition and use of listening, speaking, reading, writing, reasoning, or mathematical abilities, or of social skills. These disorders are intrinsic to the individual, presumed to be due to central nervous system dysfunction, and may occur across the life span. Problems in self-regulatory behavior, social perception and social interaction may exist with learning disabilities but do not in themselves constitute a learning disability. Learning disabilities may occur concomitantly with other handicapping conditions such as sensory impairment, mental retardation, social and emotional disturbances, or with socio-environmental influences such as cultural differences, insufficient or inappropriate instruction, and psychogenic factors. A learning disability may occur concomitantly with an attention deficit disorder. Although all of these handicapping conditions may cause learning problems, a learning disability is not the direct result of these conditions.[6]

c.) The Diagnostic and Statistical Manual of Mental Disorders (DSM IV, 1994) is a manual for psychiatric diagnoses and classification of mental disorders. The DSM IV provides a definition of a disorder and describes the parameters within which a certain diagnosis is made. Each disorder is conceptualized as a clinically significant behavioral or psychological syndrome or pattern that occurs in an individual. Each disorder is associated with distress (painful symptom) or disability (impairment in one or more important areas of functioning), or with a significantly increased risk of suffering death, pain, disability or an important loss of freedom.[7] In addition, the syndrome or pattern must be more than an expected or culturally-sanctioned response to an event.

The DSM IV states that "learning disorders are diagnosed when the individual achievement on individually administered, standardized tests in reading, mathematics, or written expression is substantially below that expected for age, schooling, and level of intelligence. The learning problems significantly interfere with academic achievement or activities of daily living that require reading, mathematical, or writing skills... Substantially below is usually defined as a discrepancy of more than two standard deviations between achievement and I.Q. (p.46)."[8] However, a smaller discrepancy (between one and two standard deviations) is sometimes used when another disorder or a general medical compromises the I.Q test.

The specific learning disorders listed in the DSM IV are expressive language

disorder, mixed receptive-expressive language disorder, phonological disorder, reading disorder, mathematics disorder, disorder of written expression, and learning disorder not otherwise specified.

Developmental Delays

Mental Retardation (MR)

The essential feature of mental retardation (MR), which affects nearly 1% of the population, is a significantly sub-average general intellectual functioning that is accompanied by a significant limitation in daily adaptive functioning.[9] Both of these factors must be present for a diagnosis of mental retardation. General intellectual functioning is usually defined by I.Q. and is obtained by administering one or more standardized, individually administered intelligence tests such as the Weschler Intelligence Scale (children and adults), Stanford-Binet, etc. In order to be diagnosed as mentally retarded an individual must have an I.Q. of 70 or below, which is two standard deviations below the mean (average I.Q. is from 90-110). There are four different ranges of mental retardation that reflect the level of intellectual impairment. The classifications are mild mental retardation (I.Q. 50 to 70 and the largest segment of MR - 85%), moderate mental retardation (I.Q. 35 to 50), severe mental retardation (I.Q. 20 to 35), and profound mental retardation (I.Q. below 20). The onset of mental retardation must occur before an individual is 18 years old. In addition, according to the DSM IV, individuals with MR are three to four times more likely than the general population to have another mental disorder.

"Mental retardation has many different etiologies and may be seen as a final common pathway of various pathological processes that effect the functioning of the central nervous system (p.39)."[10] Mental retardation may be associated with a general medical condition (e.g., Down's syndrome). According to the DSM IV, etiological factors may be primarily biological, psychosocial, a combination of both, or unknown. DSM IV current estimates are that for approximately 30% - 40% of mental retardation the cause is unknown, approximately 5% is from heredity (inborn errors of metabolism such as Tay-Sachs, single-gene abnormalities such as tuberous sclerosis, and chromosomal aberrations such as fragile x syndrome), approximately 30% results from alterations of embryonic development including chromosomal changes or prenatal damage due to toxins (maternal alcohol consumption, infections), approximately 10% is due to pregnancy and prenatal problems (fetal malnutrition, prematurity, hypoxia, trauma, viral and other infections), approximately 5% is due to general medical conditions acquired in infancy or childhood (infections, poisoning {lead}, and trauma, and approximately 15% to 20% is due to environmental influences and other mental disorders (deprivation of nurturance and of social, linguistic, and other stimulation and severe mental disorders such as autism).

HISTORICAL DEFINITIONS

continued

1962-1963
Minimal Brain Dysfunction (MBD): represented a syndrome of childhood and/or behavioral problems stemming from some form of common but unknown brain dysfunction. Included in the MBD diagnosis were children whose basic symptoms were neuropsychological even though no other evidence of damage to the brain was reported by history of clinical observation.

1964
Developmental Dyslexia

1967-1968
Specific Learning Disabilities defined

1969
First citation of specific "Learning Disabilities" (Public Law 91-230).

1971
Psycholinguistic Learning Disabilities

1977
Learning Disabilities (Public Law 94-142).

1980
Specific Developmental Disorders (Diagnostic and Statistical Manual of Mental Disorders -DSM-, Third Edition). Describes disorders that are characterized by inadequate development of specific academic, language, speech, and motor skills not due to physical or neurologic disorders, a pervasive developmental delay, mental retardation, or educational deficits.

It is usually problems in adaptive functioning (communication, self-care, health, safety) and/or personal independence, rather than low I.Q., that identify an individual as mentally retarded. Examples of such difficulties may include problems handling personal finances, obtaining and keeping employment, managing issues related to hygiene, health, and safety, and/or living independently (shopping, cleaning, etc.). Of course, as with any other disorder, the severity of difficulties and different personality and behavioral features associated with mental retardation are on a continuum. For example, some individuals with mental retardation are passive and/or dependent, while others may be aggressive and/or impulsive. Also an individual with mental retardation may be capable of limited employment, but have difficulties living independently, while another individual with mental retardation may be able to live independently with outside supports but not be capable of employment without supervision.

Pervasive Developmental Disorders (PDDs)

PDDs are characterized by severe and pervasive impairments in several areas of development including reciprocal social interactions, communication skills, and/or the presence of stereotyped behavior. The impairments are deviant from the individual's developmental level or mental age. These disorders may present differently for each individual and they are on a continuum of severity. The disorders, according to the DSM IV, are Autistic Disorder, Asperger's Disorder, Rett's Disorder, Childhood Disintegrative Disorder, and Pervasive Developmental Disorder not Otherwise Specified (used when the criteria are not met for a specific PDD). These disorders are described briefly below:

Autism

Autism prevalence rates are estimated to be 2 per 1,000 individuals, with males four to five times more likely to be autistic.[11] [12] Autism is a disorder of socialization, as it involves severe impairments in an individual's ability to relate to others in a reciprocal manner.[13] In addition to problems in social and emotional reciprocity, individuals with autism also have deficits in communication skills and often exhibit repetitive and purposeless behaviors such as motor mannerisms (rocking back and forth). In most cases Autism is apparent from very early childhood and is often accompanied by mental retardation (75%).[14] Leo Kanner first described autism in 1943. It probably is the most researched disorder of early childhood. Autism is sometimes referred to as early infantile autism, childhood autism, or Kanner's autism.[15]

According to the DSM IV, individuals with autism have markedly abnormal or impaired development in three areas: social interactions, communications skills, and a restricted repertoire of activity and interests with stereotyped patterns of behaviors, interests, and activities. In order to be diagnosed with autism an individual must have a total of six problems in the above-mentioned areas, with at least two problems in social interactions, at least one problem in communication skills, and one problem with repetitive and stereotyped behaviors.

The impairments in social interactions are gross and sustained. According to the DSM IV, they are evidenced by marked impairment in the use of multiple nonverbal gestures (eye-to-eye gaze, facial expression, body postures, and ability to regulate social interactions), failure to develop peer relationships appropriate to developmental age, lack of spontaneous seeking to share enjoyment, interests, or achievements, and lack of social and emotional reciprocity. The impairments in communication are evidenced by delay in, or lack of, the development of spoken language (not accompanied by attempts to compensate through other ways of communication like gestures or mime), impairment in the ability to initiate speech if an individual does speak, stereotyped and repetitive use of language, and a lack of varied and spontaneous make believe play or social imitative play appropriate to developmental level. The repetitive and stereotyped behavior is evidenced by preoccupation with one or more stereotyped and restricted patterns of interest that are abnormal either in intensity or focus, inflexible adherence to specific, nonfunctional routines or rituals, stereotyped and repetitive motor mannerisms (hand or finger flapping or twisting, complex body movements).[16]

According to the DSM IV, rates of the disorder are 4 to 5 times higher in males but females are more likely to have more severe mental retardation. The onset of autism is prior to three years of age typically with no periods of normal development. Also, there may be

abnormalities in the development of cognitive skills. However, usually the development of cognitive skills is uneven, regardless of the general level of intelligence.

Manifestations of the disorder vary greatly depending on the developmental level and chronological age of the individual, and they may change over time. For example, infants may exhibit a failure to cuddle or failure to respond to their parents' voices, whereas a young child may cling to an adult or essentially treat the adult as if they were not there. An autistic person does have the capacity for insight, and although impaired in one area, he or she may have the cognitive and communicative ability to hold a responsible job.[17]

According to the DSM IV, those with autism may exhibit a range of behavioral symptoms including hyperactivity, short attention span, impassivity, aggressiveness, self-injurious behaviors and temper tantrums. Also, additional symptoms may include odd responses to sensory stimulation (high threshold for pain, oversensitivity to

sound or being touched). Those with autism may have eating disorders (limiting food intake to particular foods), sleep disorders, abnormalities in mood or affect (giggling or weeping for no reason), and/or lack a sense of danger or fear. Finally, autism is sometimes observed in association with neurological or other general medical conditions (encephalitis, phenylkentouria, tuberous sclerosis, fragile X syndrome, anoxia during birth, maternal rubella).

Asperger's Syndrome

Prevalence rates of Asperger's syndrome are estimated to be from 1 to 3 per 1000 school-age children, with boys appearing to out number girls by 5:1 to 15:1.[18] Hans Asperger first described Asperger's syndrome in 1944. It received its status as a syndrome in 1981.[19] In contrast to autism, Asperger described a condition he was observing as more of a personality style that gave individuals the appearance of being eccentric or loners.[20] He described a cluster of individuals, labeled as autistic, who had normal I.Q.s, less delayed speech problems, more motor deficits and later onset. All his initial cases were male. Asperger's syndrome is currently a separate mental health disorder at the higher functioning end of the autistic continuum.

According to the DSM IV, to be diagnosed with Asperger's syndrome an individual must present with severe and sustained impairment in social interaction and the development of restricted, repetitive patterns of behavior, interest and activities. Those diagnosed with Asperger's syndrome may have problems with empathy and modulation of social interactions. Difficulties in social interactions (not age-appropriate) may become more apparent at school age, along with the development of a fascination with unusual topics and learning vast amounts of factual information about them.[21] Also, motor delays or motor clumsiness may be observed in the preschool period. According to the DSM IV, the condition must cause clinically significant impairment in social, occupational or other areas of functioning. In addition, those diagnosed with Asperger's syndrome show no clinically significant delays in language, cognitive development, or age-appropriate self-help skills, adaptive behaviors and curiosity about the environment. Asperger's syndrome strictly represents problems in social interactions.

The DSM IV reports that there appears to be an increased frequency of Asperger's syndrome among family members of individuals who have the disorder. Research has suggested a rather significant genetic component, with at least 50% of affected cases having a close relative with Asperger's.[22]

Asperger's syndrome is sometimes referred to as a social learning disability.[23] An adult or child with Asperger's syndrome would commonly exhibit the following essential symptoms: a) poor social interactions as evidenced by: a paucity of empathy; naive, inappropriate, one-sided social interaction; little ability to form friendships; lack of appreciation of social cues, and consequent social

isolation; b) poor nonverbal communication (limited use of gesture, clumsy/gauche body language; limited facial expression; inappropriate expression; peculiar, stiff gaze); c) absorption/preoccupation limited/narrow topics or with interests such as weather, facts about TV, etc., which are learned in a rote fashion and reflect poor understanding, conveying the impression of eccentricity. Associated features include a) some language issues such as delayed development; superficially perfect expressive language; formal, pedantic language; odd prosody; peculiar voice characterizations; impairment of comprehension including misinterpretations of literal/implied meanings and b) clumsy ill-coordinated movements and postures.[24]

Until this decade adults and children with Asperger's syndrome did not come to the attention of mental health professionals, since they were regarded as odd and even aloof, not perceived as having a diagnosable mental disorder, or given some other diagnosis such as obsessive-compulsive, learning disabled, etc. It is easy to understand how proficient verbal skills, adequate I.Q., and a solitary life could easily mask the marked social problems of an adult with Asperger's syndrome. Children were even less likely to be diagnosed with Asperger's syndrome as the nature of the social and emotional problems (delayed developmental milestones such as marriage and family) associated with Asperger's syndrome made it more likely that they would not be identified until adulthood. With the advancements in the understanding of Asperger's syndrome, more individuals are now not only being appropriately diagnosed, but are also being identified earlier.

Rett's Disorder

According to the DSM IV, this disorder is much less common than autism and has been reported only in females. The essential feature of Rett's Disorder is the development of multiple specific deficits following a period of normal functioning after birth. Those with Rett's have an apparently normal prenatal and perinatal development with normal psychomotor development through the first 5 months after birth. However, in the first or second year of life, and after a period of normal development, there is regression in development, which is distinctive and significant. The disorder is usually diagnosed prior to age 4. The developmental regression is evidenced by a deceleration of head growth between five and 48 months, loss of previously acquired purposeful hand movements between five and 30 months with the development of stereotyped hand movements (hand-wringing or hand washing), loss of social engagement rather early (although often social interaction develops later), appearance of poorly coordinated gait or trunk movements, and severely impaired expressive and receptive language development with severe psychomotor retardation.

The DSM IV reports the duration of the disorder is lifelong and the loss of skills is usually persistent and progressive. Recovery is very limited,

although some individuals may make modest developmental gains. Rett's Disorder is usually associated with severe or profound mental retardation.

Childhood Disintegrative Disorder (CDD)

According to the DSM IV, cases of CDD appear to be very rare, more common in males, and are usually associated with severe mental retardation. The essential feature of childhood disintegrative disorder is a regression in multiple areas of functioning after at least two years of apparently normal development as evidenced by the presence of age-appropriate verbal and non-verbal communication, social relationships, play and adaptive behavior. After the first two years (but before age ten) there is a clinically significant loss of previously acquired skills in at least two of these areas: expressive or receptive language, social skills or adaptive behavior, bowel or bladder control, play, or motor skills. Individuals with this disorder demonstrate social problems (failure to develop peer relationships and lack of social or emotional reciprocity), communication problems (delay or lack of spoken language, inability to initiate or sustain a conversation, stereotyped and repetitive use of language, lack of varied make believe play), and behavioral problems (restricted, repetitive, and stereotyped patterns of behavior, interests, and activities, including motor stereotypes and mannerisms) usually observed in autism.

The DSM IV reports that in most cases, the onset of this disorder is between ages three and four. Onset may be insidious or abrupt. Signs can include increased activity levels, irritability, and anxiety followed by a loss of speech and other skills. The disorder is lifelong. Limited improvement is unlikely, but may occur. Although it appears likely that the condition is the result of an insult to developing nervous system, no precise mechanism has been identified.

Behavioral Disorders

The DSM IV classifies two childhood behavioral disorders, Conduct Disorder and Oppositional Defiant Disorder. Attention Deficit Hyperactivity Disorder (formerly called Attention Deficit Disorder), whose symptoms may include both behavioral and cognitive problems, is also described below.

Attention Deficit Hyperactivity Disorder (ADHD)

Attention Deficit Hyperactivity Disorder (ADHD) is the most commonly diagnosed childhood psychiatric disorder in the United States.[25] Prevalence rates vary from less than 1% to as much as 14% of the school-age population depending on the study.[26] Subsequent studies using more sophisticated methods report prevalence rates of 6.7% to 9.5%.[27] The DSM IV reports that prevalence rates are from 3%-5% of school age children with prevalence data on adolescence and adults more limited. The disorder is more frequently diagnosed in males than

in females, with male-to-female ratios ranging from 4:1 to 9:1, depending on the setting (general population or clinics). It is very difficult to diagnosis ADHD in children younger than four or five years old because children that young are not often in situations that require sustained attention. Also, it is a little more difficult to distinguish age-inappropriate play from that of a normal overactive toddler. Therefore, ADHD is usually diagnosed in school-aged children between the ages of six and nine. In addition, more than 70% of children diagnosed with ADHD symptoms will continue to have difficulties throughout adolescence and adulthood.[28]

There are three subtypes of ADHD. The first is Attention Deficit Hyperactivity Disorder, Combined Type, which includes six or more symptoms of inattention and six or more symptoms of hyperactivity-impulsiveness. Second is Attention Deficit Hyperactivity Disorder, Predominantly Inattentive Type, which includes six or more symptoms of inattention but fewer than six symptoms of hyperactivity-impulsiveness. Finally, there is Attention Deficit Hyperactivity Disorder, Predominantly Hyperactive-Impulsive Type, which includes six or more symptoms of hyperactivity-impulsiveness but less than six of inattention.

According to the DSM IV, the essential feature of Attention Deficit Hyperactivity Disorder is a persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequent and severe than is typically observed in individuals at a comparable level of development. The current diagnostic criteria requires the demonstration of at least 6 symptoms of either inattention or hyperactivity - impulsivity that were present before the age of seven years (although many individuals are diagnosed after the symptoms have been present for a number of years). In addition, symptoms must have persisted for more than six months, manifested in two or more settings (school, home, work), and impair developmentally appropriate academic, social, or occupational functioning.[29] The symptoms usually get worse in situations that require sustained attention (class, homework) and may be absent or minimal when the person is in a one-to-one situation, under strict control, or in a novel or especially interesting situation.

The DSM IV states that inattention is demonstrated by failing to give close attention to details or making careless mistakes in school work or other activities. Inattention is also demonstrated by having difficulty sustaining attention in tasks, play or activity (homework or paperwork) and/or finding it difficult to follow through on instructions or persist with tasks until they are completed. Other examples of inattention include not listening, difficulty with organization, being easily distracted by extraneous stimuli (car honking, background conversation), and/or being frequently forgetful in daily activities (missing appointments, forgetting to bring lunch). In social situations, changing the flow or content of the conversation, not keeping focused

on the conversation, and/or not following the rules of games or activities may evidence inattention.

The DSM IV states that hyperactivity is evidenced by fidgeting (squirming in one's seat or leaving one's seat when one is expected to remain seated), excessive running or climbing in situations where it is inappropriate, and/or difficulty playing or engaging in leisure activities. Hyperactivity may also be demonstrated by talking excessively and/or always appearing to be in motion. As expected, the symptoms of hyperactivity vary with an individual's age and developmental level. For example, a toddler or preschooler with ADHD may be constantly on the go as demonstrated by "getting into everything", darting back and forth, running through the house, or jumping on furniture. School-aged children with ADHD, however, may have difficulty staying in their seat or sitting still.

Impulsivity may look like impatience as evidenced by difficulty delaying responses, blurting out answers before the questions have been completed, difficulty awaiting one's turn, commenting out of turn, failing to listen to directions, grabbing objects or touching things they are not supposed to, or clowning around. Impulsivity may result in accidents (knocking over objects, running into people, grabbing something hot) or in more potentially dangerous situations (running into traffic).

The concept of Attention Deficit Hyperactivity Disorder (ADHD) came from studies of brain damage where the sequelae of an insult to the brain might include inattention, hyperactivity and impulsivity.[30] However, by the 1960s it became clear that in the large majority of cases ADHD revealed no evidence of any brain damage, but rather of the brain not functioning the way it should. Over time, the concept of ADHD has undergone many changes. The DSM - II published in 1968 first described the disorder as a "hyperkinetic reaction to childhood" and focused on excessive motor activity.[31] The DSM - III published in 1980 focused on attention and concentration and the distinction between inattention without hyperactivity (ADD/noH) and ADD with hyperactivity (ADD/H). It also described symptoms in three areas (inattention, impulsivity, and motor hyperactivity). The DSM - III - R eliminated the distinction between inattention, impulsivity, and motor hyperactivity, and required the presence of 8 out of 14 symptoms.

During the past decade, there has been an increase in the diagnosis and treatment of ADHD.[32] Stimulants have been used to treat hyperactivity and inattention since the 1930s even though prior to the 1960s hyperactivity and attention deficits were rarely noticed or treated as a medical condition. [33] [34] Stimulants work by increasing the production of dopamine and norepinephrine, two of the brain's neurotransmitters (messengers). The medications increase nervous system alertness, thereby improving attention and reducing restlessness.[35]

The use of stimulants to treat hyperactivity and attention deficits began to increase dramatically after the

Food and Drug Administration (FDA) approved Ritalin for use in children with behavioral problems in 1961. Since 1971 the use of Ritalin has doubled every 4 to 7 years.[36] It has been estimated that in 1975, 150,000 children in the United States were being prescribed drugs to reduce their hyperactivity.[37] By the late 1980s Ritalin was regularly used by about 1 million children in the United States.[38] It is estimated that the use of Ritalin has increased from 2.5 times to 5 times between 1990 and 1995.[39] The production of Ritalin has increased seven fold in the past eight years, with 90% of it consumed in the United States. [40] Although other medications, such as Cylert and Dexedrine, are used to treat ADHD, currently Ritalin is prescribed as a treatment for ADHD in about 90% of all cases.[41] The U.S. Drug Enforcement Administration estimates that by the year 2000, 15% of school age children or an estimated 8 million children will use Ritalin.[42]

Conduct Disorder

According to the DSM IV, the essential feature of a conduct disorder is a repetitive and persistent pattern of behavior in which the basic rights of others or major age-appropriate social norms or rules are violated. These behaviors must have been present during the past 12 months, with at least one present in the past six months. In addition, the behaviors must demonstrate clinically significant impairment in social, academic, or occupational functioning in a variety of settings (home, school, work). The onset of this disorder may occur as early as five or six years, but it usually diagnosed in late childhood or early adolescence. The earlier the onset, the worse the prognosis. Onset is rare after the age of sixteen. The disorder is not diagnosed in individuals over eighteen, as those over eighteen usually meet the criteria for an antisocial personality disorder.

According to the DSM IV, the prevalence of the disorder appears to have increased over the last decades and may be higher in urban than in rural settings. Prevalence rates for males under eighteen range from 6% to 16% and for females from 2% to 9%. There are two subtypes of this disorder, each of which can occur at a different level of severity (mild, moderate, or severe). In addition, the nature, developmental course, and prognosis of the conduct problem differ for the two subtypes. The first subtype, Childhood-Onset Type**,** occurs before the age of ten and the individual must exhibit one of the conduct problems presented below. Individuals diagnosed with this type frequently display physical aggression towards others, have disturbed

peer relationships, and are usually male. The second sub-type, Adolescent-Onset Type, is characterized by the absence of any symptoms before the age of ten years. These individuals are less likely to exhibit aggressive behaviors, tend to have more normal peer relationships, and are less likely to have these problems continue in adulthood. The ratio of males to females is lower for this subtype.

The DSM IV reports that the problematic behaviors of this disorder fall into four main categories: aggression toward people or animals, destruction of property, deceitfulness or theft, and/or serious violations of rules. The aggressiveness must cause or threaten to cause physical harm to other people or animals. Examples of aggression include bullying, threatening or intimidating others, initiating physical fights, and/or using a weapon that can cause serious physical harm to others (bat, knife, gun, etc.). Additional examples of aggression include being physically cruel to people or animals, stealing while confronting a victim (mugging, extortion, robbery, armed robbery), and/or forcing someone into sexual activity. The physical violence may take the form of rape, assault, or in rare cases homicide.

According to the DSM IV, examples of destruction of property include deliberately setting fires with the intention of causing serious damage or deliberately destroying other's property (not including fire-setting). Deceitfulness or theft includes breaking into someone else's house, building, or car, lying to get goods or favors to avoid obligations ("conning" others), and/or stealing items without confronting the victims (shoplifting, forgery). Examples of serious violations of rules include staying out at night despite parental prohibitions (before age 13), running away from home at least twice, and being truant at school (before age 13).

Children with a conduct disorder seem to have little empathy (little guilt or remorse) for others and may frequently misperceive the intentions of others as hostile or threatening. In addition, those with a conduct disorder may have a lower than average I.Q. and may be more likely to use illegal drugs, have an earlier onset of sexual activity, have difficulty with academics (i.e. a learning disorder, ADHD), and may have lower self-esteem (higher suicide rates and attempts).

Oppositional Defiant Disorder

According to the DSM IV, prevalence rates of ODD are estimated to be from 2% to 16%, with males diagnosed more often before puberty and males and females diagnosed at the same rate after puberty. According the DSM IV, the essential feature of oppositional defiant disorder is a recurrent pattern of negativistic, defiant, disobedient, and hostile behavior toward authority figures that persists for at least 6 months. Negative and defiant behaviors include persistent stubbornness, resistance to directions, and unwillingness to compromise or negotiate with adults or other children. Defiance may include deliberate or persistent testing of limits, usually by

ignoring, arguing, or blaming others for misdeeds. Hostility is evidenced by deliberately trying to annoy others or by verbal aggression. Onset of this disorder is usually before eight and no later than early adolescence. Onset is usually gradual, occurring over months and years. Also, symptoms tend to first emerge in the home, with individuals the child knows well, and the number of symptoms seems to increase with age.

The DSM IV states that in order to be diagnosed with oppositional defiant disorder a child must exhibit at least four of the following behaviors: losing temper, arguing with adults, actively defying or refusing to comply with the requests or rules of adults, deliberately doing things that will annoy others, blaming others for their own mistakes or misbehaviors, being easily annoyed by others, being angry and resentful, or being spiteful or vindictive. Behaviors must occur more frequently than is typical in those of comparable age or developmental level and must lead to significant impairment in social, academic, or occupational functioning. Children with this disorder often have low self-esteem, mood lability, low frustration tolerance, inappropriate language (swearing), and use of alcohol and drugs. ADHD and learning disorders also tend to be associated with this disorder.

1 Cramer SC, Ellis E. Learning disabilities: Lifelong issues. Paul H. Brookes Publishing Company, Inc., Baltimore, 1996.

2 Cramer SC, Ellis E. Learning disabilities: Lifelong issues. Paul H. Brookes Publishing Company, Inc., Baltimore, 1996.

3 Dyson LL. The experiences of families of children with learning disabilities: Parental stress, family functioning, and sibling concept. Journal of Learning Disabilities 29(3):280-286, 1996.

4 McBride HEA, Siegel LS. Learning disabilities and adolescent suicide. Journal of Learning Disabilities 30(6):652-659, 1997)

5 U.S. Office of Special Education. 42 Fed. Reg. 65,083 Definition and Criteria for defining Students as Learning Disabled. Washington D.C. U.S. Government Printing Office,1977.

6 Lyon GR. The state of research. In Cramer SC, Ellis E (eds). Learning disabilities: Lifelong issues. Paul H. Brookes Publishing Company, Inc., Baltimore; 1996.

7 American Psychiatric Association. Diagnostic and Statistical Manual, Fourth Edition. Washington, DC. 1994.

8 American Psychiatric Association. Diagnostic and Statistical Manual, Fourth Edition. Washington, DC. 1994.

9 American Psychiatric Association. Diagnostic and Statistical Manual, Fourth Edition. Washington, DC. 1994.

10 American Psychiatric Association. Diagnostic and Statistical Manual, Fourth Edition. Washington, DC. 1994.

11 Centers for Disease Control and Prevention, National Center for Environmental Health, Division of Birth Defects and Disability and Health, Developmental Disabilities Branch. http://www.cdc.gov/nech/programs/CDDH/dd/ddautism.htm.

12 American Psychiatric Association. Diagnostic and Statistical Manual, Fourth Edition. Washington, DC. 1994.

13 Klin A, Volkmar FR. Autism and Asperger's syndrome. Yale University Child Study Center. July/August 8-9, 1994.

14 American Psychiatric Association. Diagnostic and Statistical Manual, Fourth Edition. Washington, DC. 1994.

15 Klin A, Volkmar FR. Autism and Asperger's Syndrome. Yale University Child Study Center.July/August 8-9, 1994.

16 American Psychiatric Association. Diagnostic and Statistical Manual, Fourth Edition. Washington, DC. 1994.

17 American Psychiatric Association. Diagnostic and Statistical Manual, Fourth Edition. Washington, DC. 1994.

18 Gillberg C, Gillberg IC. Asberger's syndrome: Some epidemiological Considerations. Journal of Child Psychiatry, 30:631-638. 1989.

19 Klin A, Volkmar FR. Autism and Asperger's syndrome. Yale University Child Study Center. July/August 8-9, 1994.

20 Klin A, Volkmar FR. Autism and Asperger's syndrome. Yale University Child Study Center. July/August 8-9, 1994.

21 Klin A, Volkmar FR. Autism and Asperger's syndrome. Yale University Child Study Center. July/August 8-9, 1994.

22 Wing (1981) in Gillberg C, Gillberg IC. Asberger's syndrome: Some epidemiological considerations. Journal of Child Psychiatry, 30:631-638. 1989.

23 Klin A, Volkmar FR. Autism and Asperger's syndrome. Yale University Child Study Center. July/August 8-9, 1994.

24 Klin A, Volkmar FR. Autism and Asperger's syndrome. Yale University Child Study Center. July/August 8-9, 1994.

25 DeGrandpre R. Ritalin Nation. Norton: New York, 1999

26 Fletcher JM, Shaywitz BA. Attention-deficit/ Hyperactivity disorder. In Cramer SC, Ellis E (eds). Learning disabilities: Lifelong issues. Paul H. Brookes Publishing Company, Inc. 1996. Pgs. 265-276.

27 Shaywitz SE, Shaywitz BA. Unlocking learning disabilities: The neurological basis. In Cramer SC, Ellis E (eds.) Learning disabilities: Lifelong issues. Paul H. Brookes Publising Company, Inc. 1996. Pgs. 255-260.

28 Inteli-Health, Inc. Attention deficit hyperactivity disorder. Johns Hopkins Health, 1998. http:// www.intelhealth.com

29 American Psychiatric Association. Diagnostic and Statistical Manual, Fourth Edition. Washington, DC. 1994.

30 Kavale KA, Forness SR. Covariance in learning disability and behavior disorders: An examination of classification and placement issues. Advances in Learning and Behavioral Disabilities. 12 (1-42) 1998.

31 Kavale KA, Forness SR. Covariance in learning disability and behavior disorders: An examination of classification and placement issues. Advances in Learning and Behavioral Disabilities. 12 (1-42) 1998.

32 Gibbs N. The age of Ritalin. Time Magazine 152(22), November, 1998. http://cgi.pathfinder.com/time/ magazine/1998/dom/981130/cove1.html.

33 DeGrandpre R. Ritalin Nation. Norton: New York, 1999.

34 Inteli-Health, Inc. Attention deficit hyperactivity disorder. Johns Hopkins Health, 1998. http:// www.intelhealth.com

35 Inteli-Health, Inc. Attention deficit hyperactivity disorder. Johns Hopkins Health, 1998. http:// www.intelhealth.com

36 Inteli-Health, Inc. Attention deficit hyperactivity disorder. Johns Hopkins Health, 1998. http:// www.intelhealth.com

37 DeGrandpre R. Ritalin Nation. Norton: New York, 1999.

38 DeGrandpre R. Ritalin Nation. Norton: New York, 1999.

39 Inteli-Health, Inc. Attention deficit hyperactivity disorder. Johns Hopkins Health, 1998. http:// www.intelhealth.com

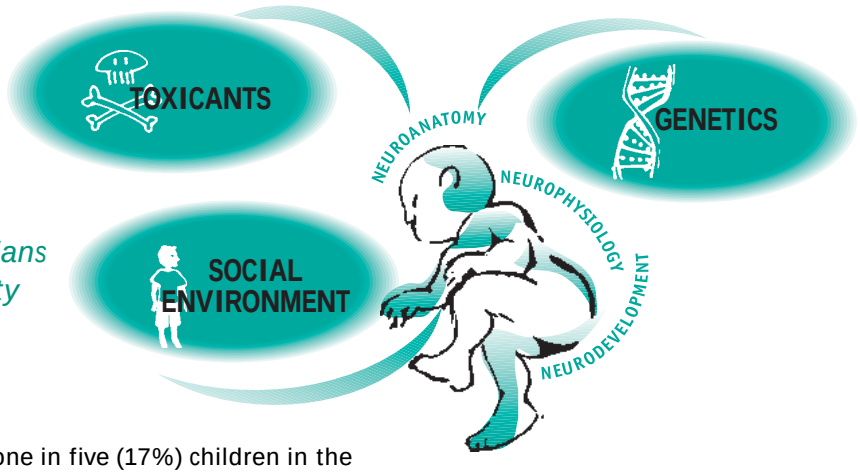
40 Gibbs N. The age of Ritalin. Time Magazine 152(22), November, 1998. http://cgi.pathfinder.com/time/ magazine/1998/dom/981130/cove1.html.

41 DeGrandpre R. Ritalin Nation. Norton: New York, 1999.

42 DeGrandpre R. Ritalin Nation. Norton: New York, 1999.

In Harm's Way:

Toxic Threats to Child Development



A REPORT BY

Greater Boston Physicians for Social Responsibility

Prepared for a Joint Project with Clean Water Fund

Release date: May 2000

Nearly one in five (17%) children in the United States has been diagnosed with one or more developmental, learning or behavioral disability. There is a growing consensus that disorders including Attention Deficit Hyperactivity Disorder (ADHD) and autism are increasing in frequency. These disorders have widespread societal impacts, from health and education costs to the repercussions of criminal behavior. Research demonstrates that pervasive substances such as mercury, lead, PCBs, dioxins, pesticides, and others, are toxic to the developing child's brain (neurotoxic.)

Human development takes place within complex physical, genetic, social and cultural environments.

*The role of toxic chemicals deserves special scrutiny because it is a **preventable** cause of harm.*

Human exposure to neurotoxic substances is global. Tests on humans show that these chemicals now reside in our bones and other organs, blood, breast milk, sperm, fatty tissue and urine. As our knowledge about the toxicity of these chemicals has increased, the "safe" threshold of exposure has been continuously revised downward.

Human development takes place within complex physical, genetic, social and cultural environments. This report examines the contribution of toxic chemicals to developmental, learning and behavioral disabilities.

Included in the report are:

- A "primer" on normal brain development, and how toxic chemicals can alter that development
- The spectrum of developmental disabilities and their multiple causes, including genetics and gene-environment interactions
- Profiles of known and suspected developmental neurotoxicants
- The scope of the chemical problem
- And much more including charts, graphs, illustrations and "spotlight" features on such things as community activism around autism and others

Don't miss this groundbreaking new report with a wealth of information for parents, educators, scientists, advocates, public health and public policy professionals.

This report has been prepared as part of a joint education project with Clean Water Fund. Funding has been provided by the John Merck Fund, the Jessie B. Cox Charitable Trust, the W. Alton Jones Foundation, the Mitchell Kapor Foundation and the Alida R. Messinger Charitable Lead Trust.

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