Children are our most important national resource. Children’s brain, development, and behavior are important to their health, to their ability to contribute to society throughout life, and to the well-being of future generations. Children cannot make choices about their environment; it is up to adults to make the right decisions to ensure that they are protected. Scientists have a significant role to play in assuring that these protections are provided to our children by identifying preventable causes of developmental disabilities and impairment. Federally funded research has played a critical role in identification of long-term effects on the developing brain of exposures to lead, methyl mercury, and polychlorinated biphenyls (PCBs). It is critical that such research be clearly translated into policy.

We know that infants and children may be more susceptible than adults to some chemicals (1), and their exposures to chemicals in foods and in the environment are different, and often greater, than those for adults. Proportionate to body weight, children eat more of certain types of foods, drink more fluids, and breathe more air than adults (2). Toddlers crawl on the floor and grass outside; the older children spend a lot of time outdoors. Thus, children are often more exposed to potentially harmful pollutants.

A research agenda for public health is driven by a number of factors that operate simultaneously including scientific advances, public policy concerns, and public health value. As we come to the end of the National Institutes of Health-declared “decade of the brain,” it is clear that the science of brain development is developing rapidly. There is good reason to expect that the research community is poised to make breakthroughs in our understanding of neurological development and its disruption by exposures to environmental agents. This article addresses some of the policy and public health issues that are relevant to an agenda for research in this area. Specifically, it describes relevant developments in pesticide and chemical regulation and assessment and the public health impact of developmental disabilities in the United States. This article does not attempt to delineate all of the public policy controversies and views of all the players in this arena. Nor does it attempt to develop a detailed agenda for a research strategy.

Public Policy Considerations

Pesticides and the Food Quality Protection Act

Pesticides constitute a variety of chemical, biologic, and other agents that are used to kill or inhibit the growth of pests of economic importance. They include insecticides, fungicides, herbicides, rodenticides, wood preservatives, and disinfectants. In addition to these toxic chemicals, many pesticides may have the potential to cause developmental toxicity. In the United States in 1995, there were 876 pesticides on the market, of which 489 were registered for use on food products. In 1997, there were about 4 billion pounds used in the United States. Of these, some 1.2 billion pounds of conventional pesticides were applied in the United States, mostly for agricultural purposes but also in the home and for other uses (3). From the mid-1960s to 1980, pesticide use sharply increased from 400 million pounds to more than 800 million pounds per year—an increase largely driven by the development and use of chemical herbicides in agriculture. In contrast, nonagricultural use declined from 300 million to 200 million pounds between 1970 and the 1990s (3). It is not known to what extent use reflects risk, since toxicity and exposure potential can differ, pound for pound, for different pesticides.

The Food Quality Protection Act of 1996 (FQPA) is defined by its explicit protection of children; it was passed unanimously and signed into law in August 1996 (4). FQPA requires the U.S. Environmental Protection Agency (U.S. EPA) to make more realistic assessments of the risks posed by exposures to pesticides by assessing aggregate and cumulative risks, as described below. Because of this law, over time some of the current—and least safe—pesticide uses will be replaced by safer ones or by nonchemical alternatives, such as alternative agricultural practices and biological pesticides.

The concepts for the children’s health components of the law came from the 1993 National Research Council (NRC) report, Pesticides in the Diets of Infants and Children (2). The committee concluded that the toxicity of, and exposures to, pesticides are frequently

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different for children and adults. Despite a wealth of scientific information to warrant addressing risks to children, the U.S. EPA did not adequately address those risks (2).

The committee advised the U.S. EPA to incorporate information about dietary exposures to children in risk assessments and augment pesticide testing with new or improved guidelines for neurotoxicity, developmental toxicity, endocrine effects, immunotoxicity, and developmental neurotoxicity. It recommended that the U.S. EPA include cumulative risks from pesticides that act via a common mechanism of action and aggregate risks from nonfood exposures when developing a tolerance for a pesticide (2). The Clinton Administration—the U.S. EPA, the U.S. Department of Agriculture, and the Food and Drug Administration (FDA)—immediately announced an initiative to address the NRC recommendations, including asking Congress for new legislative authorities. Scientists in the U.S. EPA Office of Pesticide Programs were already laying the groundwork for improvements in the U.S. EPA risk assessment processes, including incorporation of children’s dietary intake levels into risk assessments and improvements in the assessment processes for developmental toxicity.

The 1996 law gives the agency one uniform standard to use in registering all pesticides and setting tolerances, which are the limits of allowable pesticide residues on a food. Previously there were three separate standards for pesticides on food: risk/benefit balancing for fresh fruits and vegetables, the zero risk or Delaney clause standard for carcinogens on processed foods, and a public health standard for processed foods generally. The latter standard of a “reasonable certainty of no harm” was adopted as a single standard; this means negligible risk for a carcinogen. In making pesticide registration decisions and in setting tolerances, the agency now must consider available information on aggregate exposure from all nonoccupational exposures, including drinking water and exposures from lawn and household uses. Previously, the U.S. EPA generally took into account only the pesticide exposure from food. The law also requires the U.S. EPA to consider available information on cumulative effects of pesticide residues and other substances that have a common mechanism of toxicity. Previously, the U.S. EPA regulated each pesticide individually.

On top of these new considerations, Congress directed the U.S. EPA to use an additional 10-fold (10x) factor during the decision-making process to account for pre- and postnatal toxicity. This factor is to be applied in addition to the inter- and intraspecies factors and was recommended by the NRC (2). In fact, the committee believed that the U.S. EPA already applied that additional factor when it found significant prenatal developmental toxicity and urged the agency to also apply the factor when postnatal effects are found (2). The agency can eliminate or reduce this additional 10x FQPA factor for children only if it makes a finding that reliable and complete data indicate a different factor will be safe for infants and children. Specifically, the FQPA instructed the U.S. EPA:

In the case of threshold effects . . . an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and postnatal toxicity and completeness of the data with respect to exposure and toxicity to infants and children. Notwithstanding such requirement for an additional margin of safety, the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such a margin will be safe for infants and children. (4)

This provision has been especially controversial, first, because industry opposed its enactment in the first place, second, because of disagreements among scientists about whether it should be required, and third, because of difficulties in implementation, as discussed below.

Risk is a function of hazard and exposure. The basis of most pesticide health decisions is hazard information from animal tests. The most fundamental assumption in hazard identification is that if a chemical is hazardous to animals, it is assumed hazardous to humans. A related assumption is that animal testing predicts relative potency for humans. When the U.S. EPA developed the concept of the reference dose (RfD), it recognized that both interspecies differences and intraspecies variability need to be taken into account when using animal studies in assessing risks to humans (5). For decades, the FDA had used this approach (called an Acceptable Daily Intake or ADI by FDA) in the regulation of food additives under the Federal Food, Drug, and Cosmetic Act (6).

Generally, for noncancer effects, risk is characterized as a percent of the RfD. The chronic RfD is an estimate of a daily exposure to a population, which, over a 70-year life span, is likely to have no significant deleterious effects (5). The acute RfD is its equivalent for short-term exposure. To calculate an RfD, the risk assessor first chooses the most appropriate—usually the most sensitive—effect from a chronic or acute study. Next, the no-observable adverse effect level (NOAEL) is identified for this effect. Finally, the assessor identifies uncertainties in the data and applies uncertainty factors to the NOAEL—generally a 10x factor to account for uncertainty in extrapolating from animals to humans and a 10x factor to account for the variation within the human population. At the U.S. EPA, modifying factors between 3- and 10-fold are applied when critical studies are missing.

Although application of these factors is fundamental to risk assessment as we know it today, few are aware of their origins. These factors were not directly derived solely from scientific experiments. Rather the FDA based them on evaluation of a modest database, along with a large portion of scientific judgment that supported the view that initially one factor of 100 would cover all sources of variability. Over time, this 100-fold factor was split into two factors of 10 (6).

Applying the additional FQPA 10x factor to protect children has become one of law’s most challenging policy issues. While the U.S. EPA applied modifying factors when prenatal developmental studies were incomplete, there was not a routine application of an additional 10x factor when significant prenatal effects were observed. Further, Congress directed the U.S. EPA to account for uncertainties in exposure as well as hazard. This was a new procedure with no precedent for the U.S. EPA to use for its application. Since enactment of the FQPA, the U.S. EPA has issued successive draft policies describing criteria for removal of this uncertainty factor.

An important policy question that has emerged from the debate about the FQPA 10x factor is whether current toxicity testing requirements and exposure information are adequate to assure the safety of infants and children, or whether the U.S. EPA should routinely require additional information. One question that has emerged that needed to be answered quickly is whether the developmental neurotoxicity test (7), previously conducted only if triggered by results of earlier testing, should be required by the U.S. EPA for every food-use pesticide to fully assess the potential for hazard to children. The U.S. EPA has proposed that developmental toxicity be assessed for all pesticides that are neurotoxic, such as the organophosphate and carbamate pesticides (8). Completely lacking in the testing battery used by the U.S. EPA is a test to evaluate the potential for developmental immunotoxicity. Is the absence of this end point in current testing relevant to the debate on application of the FQPA 10x factor? A U.S. EPA advisory committee on endocrine disruptor screening and testing recently recommended development and validation of several additional tests and end points to
While to some environments total amounts in inhibition less than one-tenth carbamates, this allowable cholinesterase inhibition within the times mined FQPA, each pesticide could have been given separate approvals to be present in the food supply, in drinking water, and in residential environments for a total exposure of 120 times the RfD for cholinesterase inhibition. This means that the U.S. EPA could have allowed total exposure to a level for cholinesterase inhibition less than one-tenth of the NOAEL for animals. This is well within an unacceptable range even without taking into consideration the statute’s FQPA 10× Factor. Assuming that the U.S. EPA may ultimately apply the 10× factor for none or all of the OPs, the total allowable amount of cholinesterase inhibition that could ever be allowed by the U.S. EPA for organophosphates alone has been reduced by 120- to 1,200-fold. After including another class of insecticides, the cholinesterase-inhibiting carbamates, this allowable amount is likely to be reduced even further. In reality, the allowable amounts of risk were not used for each pesticide prior to the enactment of the FQPA. Further, generous “default” assumptions are being replaced with real-world data that are lowering assessments of risk for many OPs on the market. However, some individual OPs, such as azinphos methyl (guthion), have been found at levels above the allowable levels even without accounting for cumulative exposures from other products (10). Therefore, it is clear that there will be major changes for pesticide use and marketing in the United States.

The FQPA has created challenges that call for further research in this area. A fundamental question that needs to be examined that applies very broadly is, What is the variation—genetic, gender, age-related, and nutritional—within the human population’s response to exogenous agents? We do not really know. Government needs to work with the research community not only to develop more exposure and biological data and better models for infants and for children but also to understand genetic, aging, gender-related, and other sources of variability. This in turn will help strengthen the scientific underpinning for a rational and systematic alternative to uncertainty and safety factors.

### Toxic Chemicals

There are approximately 85,000 chemicals that have been produced in the United States. Each year an additional 2,000–3,000 new chemicals are brought to the U.S. EPA for review prior to manufacture. The U.S. EPA estimates that about 15,000 of these compounds are produced in quantities of at least 10,000 pounds or greater per year. There has been no systematic gathering of either hazard or exposure information for these chemicals. The U.S. EPA has initiated a major chemical-testing program—the first chemical testing Congress has authorized in 20 years—for industrial chemicals and pesticides. By August 1999, the U.S. EPA was to begin implementing a program to screen and test pesticides and other chemicals for their potential to disrupt endocrine systems of wildlife and humans. Some chemicals, such as dioxins, PCBs, and certain pesticides, have been linked to sexual and reproductive developmental problems in both wildlife and laboratory animals, and there is a strong evidence for human effects as well. The U.S. EPA convened a scientific panel, the Endocrine Disruptor Screening and Testing Advisory Committee, that has proposed protocols for the screening and testing of more than 15,000 chemicals (9). Required by both the FQPA and the Safe Drinking Water Act of 1996, this is a huge undertaking. It involves validating a number of existing in vitro and in vivo tests and creating new tests to detect the abilities of chemicals to interact with the estrogens, androgens, and thyroid hormone systems.

In 1998, there were 2,863 high-production-volume (HPV) chemicals that the United States imported or produced at more than 1 million pounds per year. In 1997 and 1998 Environmental Defense, the U.S. EPA, and the Chemical Manufacturer’s Association concluded that insufficient information was available to determine whether basic screening-level data were available for HPV chemicals. The U.S. EPA found that 43% have no testing data on basic toxicity, and only 7% have a full set of basic test data. According to the information that the U.S. EPA collected, for 78.2%, or 2,240 HPV, there was no screening information for developmental toxicity. For 716 HPVs that are present in consumer products, nearly half (45.8%) were lacking screening developmental toxicity information. One-fourth (23.8%) of the 239 HPVs for which the Occupational Health and Safety Administration had established permissible exposure levels and one-fourth (23.6%) of the 251 HPVs listed in the Toxics Release Inventory lacked information about developmental toxicity. Therefore, we often lack basic screening-level information for developmental toxicity even for chemicals commonly present in commerce and in the workplace. For non-HPVs, information is even more scarce (11).

This lack of toxicity data compromises the public’s right to know about chemicals in their homes, their workplaces, and the products they buy. In April 1998, Vice President Gore issued a challenge to industry to come forward with complete basic test data for these HPV chemicals. In September 1998, the Chemical Manufacturers Association, Environmental Defense, and the U.S. EPA announced a voluntary initiative to fill these information gaps (12).

The vice president also directed the U.S. EPA to establish testing requirements for chemicals to which children may be exposed. This effort will examine several dozen chemicals to which children are likely to be exposed and ensure that they receive testing for potential hazards to children. The required testing will be extensive—comparable to that required for pesticides. At the time of the writing of this article, it was uncertain whether this program would be implemented via rule making by the U.S. EPA or as a voluntary effort by the chemical industry.

### Federal Initiatives

**Executive order**. In 1997, President Clinton signed an historic executive order requiring for the first time that all federal agencies ensure that their policies and rules address disproportionate environmental health and safety risks to infants and children (13). The U.S. Department of Health and Human Services and the U.S. EPA recently moved to establish the first federal research centers dedicated solely to studying children’s environmental health hazards. Grants of between $1.2 and $1.6 million were awarded to establish eight federal research centers. Five of the centers are studying the links between the rise in asthma rates in children and environmental factors, such as second-hand smoke, smog, and other pollutants. The other three centers are conducting research on children’s special vulnerability to pesticides (14). At the U.S. EPA, there is an Office of Children’s Health Protection that is working in a number of areas to strengthen the U.S. EPA’s approach to protecting children. Through the executive order, there are efforts underway across the government to better coordinate activities to prevent asthma, birth defects, childhood lead poisoning, childhood cancer, and childhood injuries.

**National expenditures for research on children**. Many of the most important environmental hazards to humans involve risks to neurological development in children. Lead, methyl mercury, and PCBs are examples of neurotoxic chemicals to which children can be very sensitive. Overall, the
research investment for children has been modest. In 1995, the United States spent $405 billion on education, two-thirds of which were devoted to K–16 education. Another $150 billion were spent on criminal justice, health, and social welfare programs for children for a total of $555 billion. Yet the total amount of money spent on research related to children in 1995, in all categories of effort, was only $2 billion (15). Thus, there is in the United States a mismatch between expenditures and research on interventions to enhance the well-being and development of children.

**Public Health Considerations**

Consider the magnitude of the public health burden of major developmental disabilities. Developmental disabilities are a group of physical, cognitive, psychological, sensory, and speech impairments arising during development and up to 18 years of age. According to the U.S. Centers for Disease Control and Prevention (CDC), some 17% of all U.S. children less than 18 years of age have one or more developmental disabilities. In the great majority of cases, the cause is unknown. Serious developmental disabilities, such as autism, cerebral palsy, and mental retardation, account for much of the total cost to society.

**Autism**

Autism, once believed to be a rare disorder, is a complex developmental disorder with onset and diagnosis during the first three years of life. Autism is part of a collection of disorders referred to as pervasive development disorder or autism spectrum disorder. These disorders involve deficits in social interaction, communication, behavior, and imagination (16). Some people with autism may function below normal intellectual levels, while others may do well in school but have severe social impairments. Some never speak. Success in some cases seems to be best with early education and intervention. Autism may be associated with specific structural brain abnormalities. An estimated 135,000 United States children ages 3–21 have been diagnosed with autism and autism spectrum disorders. The prevalence is estimated at 1–2 per 1,000 children under age 15 (17–20). The rate of autism is believed to be increasing both nationwide and worldwide. Older research estimated the prevalence of autism to be only 0.4–0.5 per 1,000 children. Data from Europe are more extensive, but in the United States, the only effort to monitor prevalence of and trends in autism is the CDC system in metropolitan Atlanta, Georgia. Although research indicates that autism may involve interactions between genetic susceptibility and environmental exposures, there have been few efforts to link autism cases with environmental exposure levels.

Because we have so little information about autism, it is difficult to assess the costs to society. However, the CDC estimated that, in 1995 alone, the total costs for special education for autistic children in the United States were more than $160 million (16). In addition, 1 child with autism can require residential care costing between $70,000 and $100,000 per year (21). Families bear a tremendous burden of the costs; they must adjust in numerous ways, sometimes at the cost of a parent’s career, to care for the autistic child. In addition to these costs there is an unknown but certainly significant burden and cost to society for those children who are not given adequate education when they are young, and those with forms of autism that have long-term impacts on their functioning in society.

In California, the number of children with autism enrolled in statewide Department of Developmental Services programs rose from 3,864 in 1987 to 11,995 in 1998, an increase of more than 210% during those 11 years. By comparison, enrollment of children with other disorders such as cerebral palsy and epilepsy increased by only 30–45% for the same period (22). The rising number of children diagnosed with autism may reflect an actual increase or be due in part to changes in diagnosis and reporting, specifically greater recognition of a broader and subler sub set of symptoms associated with the disorder. For instance, autism spectrum disorders include not only autism but also Asperger’s syndrome, childhood disintegrative disorder, Rett’s syndrome, and pervasive developmental disorders. The changes in criteria for diagnosis of autism complicate efforts to understand trends of prevalence over time.

The cause or causes of autism are not yet known. A strong hereditary component was discovered through early studies of twins (23). There is evidence for interaction with environmental factors such as pre- or postnatal exposure to infectious diseases and exposure to the drugs valproic acid and thalidomide (24). Autism is known to be associated with birth defects. Thalidomide when taken by a pregnant woman between days 20 and 24 of gestation not only causes a high rate of missing or shortened limbs (phocomelia) but also has been associated with a high rate of autism (25). This is the time of closure of the neural tube in fetal development, suggesting that there could be an embryological origin to autism. Further, a large percentage of children with autism have minor malformations of the ear, which would occur in the same time period, compared with children with and without other developmental disorders (26).

Autopsy studies of humans and animal models suggest that there is a very specific set of brain anomalies associated with autism (absence of the facial nucleus and superior olive along with shortening of one region of the brain stem). These studies indicate that these changes can be caused by either a genetic abnormality (lack of the Foxa1 gene in mice) or exposure to an agent such as thalidomide or valproic acid just after neural tube closure during fetal development (27). A recent link between autism and the measles/mumps/rubella vaccine drew a great deal of attention but has not been validated by research. A study in Great Britain found no association between the vaccine and autism (28).

**Cerebral Palsy**

Cerebral palsy (CP) is the most common chronic motor (muscle) disorder in childhood. It is a group of nonprogressive, but often changing, motor impairment syndromes secondary to lesions or anomalies of the brain arising at any time during brain development (29). People with CP have abnormal control of body movement and posture. About 20% of children with CP also have major birth defects. About half of children with CP also have global mental retardation (30). The risk of cerebral palsy is strongly associated with birthweight and preterm birth—the smaller the infant and the younger the gestational age, the greater the risk. Approximately one in every 20 very low birth weight babies who survive infancy will develop disabling CP, compared to 1 in 1,000 of all normal birth weight infants.

CP is one of the most costly developmental disorders affecting children, adding an estimated $500,000 in lifetime medical costs for each affected child (31). One in every 500 children in the United States lives with some form of CP today (32–36). The prevalence of cerebral palsy is believed to be remaining constant or increasing slightly, possibly because more very low birth weight infants are surviving as treatment improves; many of these infants will suffer subsequent developmental disabilities. Although very low birth weight infants (<1,500 g) are 100 times more likely to develop disabling CP than infants of the most common weight groups (37), the higher number of normal birth weight babies results in their contributing to more than half of all CP cases (38). Besides low birth weight and preterm birth, other risk factors include being born feet first, maternal bleeding, and certain other adverse clinical signs in the newborn period (39).

**Mental Retardation**

Mental retardation (MR) is a varied group of conditions characterized by cognitive...
limitations due to organic brain dysfunction, with onset no later than 18–22 years of age (40). The definition of MR also is based on functional limitations in areas that include daily living skills, social skills, and communication. About 50% of children with MR also have structural birth defects. In the 1995–1996 school year, approximately 600,000 U.S. school children age 6–21 with MR were served in special education programs as required by law. Costs were $3.3 billion to the federal government and much more for state and local governments (41). The average cost of caring for children with more serious MR is difficult to estimate, but it may be as high as 10 times the cost of providing for a child without a disability.

The cause of most cases of MR among children is unknown. Some environmental factors include fetal alcohol syndrome, heavy metals poisoning such as lead and methyl mercury, and infections such as meningitis. Environmental exposure to lead can cause a general reduction in IQ and, at high enough doses, mental retardation. MR also occurs in association with a number of major birth defects, CP, preterm birth, and very low birth weight. Therefore, as with CP, identifying causes of MR is critical. Since 1991, the CDC has tracked MR in metropolitan Atlanta. According to the CDC, the prevalence of MR in 3- to 10-year-old children between 1991 and 1994 was 9.7 per 1,000 children, or about 1%.

We know very little about fundamental issues related to the health and neurological development of children, including prevalence and trends for some of the most serious developmental disabilities, autism, CP, and MR. We know even less about which environmental factors may be detrimental. We have little information about developmental toxicity and exposure of children to pesticides and even less information about industrial chemicals. The result is that we do not know how to prevent most childhood developmental and behavioral disorders.

Conclusions

What kind of research will be appropriate? A research agenda for children’s neurodevelopment needs to be backed up by a strong national public health information and assessment function to understand the rates and patterns of developmental disabilities in our children. We do not have much information on exposures to children, yet opportunities exist. New findings in genetics and in mechanism-based toxicology research provide further opportunities to advance the field. A stronger linkage between public health surveillance and basic research efforts could help identify relationships between environmental exposures, as well as genetic components and gene–environment interactions, and major developmental disabilities.

Much of the recent early development research has focused on socioeconomic status as a measure of early childhood deprivation. Lower socioeconomic status communities and minority communities have disproportionately shares of many environmental exposures as well as nutritional and other disparities (42). Collaboration between developmental and environmental researchers is needed to elucidate the role of environment as a component of early childhood deprivation. We need research that not only addresses the most severe impacts but also examines the relationship between population exposures to neurotoxins and the full continuum of intellectual, performance, and behavioral measures. The cases of lead, PCBs, and methyl mercury hold lessons that small individual impacts, over an entire population, can exact enormous costs to society.

An environmental prospective study may be the best avenue to fully address several of these concerns. Prospective studies were necessary for the identification of the subtle long-term neurodevelopmental impacts of lead and PCBs to be identified. Prospective data collection, beginning prenatally, could include a broad range of environmental exposures. Tools are available for assessing many important risk factors, including genetic susceptibility, biomarkers of environmental exposures, and hormonal status. Long-range follow-up of children would be used to assess neurodevelopmental outcomes over time.

With the large number of poorly assessed chemicals used in commerce known to be or possibly harmful to development, such research will be vital to ensure adequate protection for children. If the 1990s was the decade of the brain, perhaps the next decade can be dedicated to using our newfound knowledge on how the brain develops and functions to identify and prevent causes of developmental disabilities.

References and Notes

33. Boyle CA, Decoufle P, Holmgren P. Contribution of develop-