

Vulnerability of Children and the Developing Brain to Neurotoxic Hazards

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For much of the history of toxicology, the sensitivity of the developing organism to chemical perturbation attracted limited attention. Several tragic episodes and new insights finally taught us that the course of early brain development incurs unique risks. Although the process is exquisitely controlled, its lability renders it highly susceptible to damage from environmental chemicals. Such disturbances, as recognized by current testing protocols and legislation such as the Food Quality Protection Act, can result in outcomes ranging from death to malformations to functional impairment. The latter are the most difficult to determine. First, they require a variety of measures to assay their extent. Second, adult responses may prove an inadequate guide to the response of the developing brain, which is part of the reason for proposing additional safety factors for children. Third, neuropsychological tests are deployed in complex circumstances in which many factors, including economic status, combine to produce a particular effect such as lowered intelligence quotient score. Fourth, the magnitude of the effect, for most environmental exposure levels, may be relatively small but extremely significant for public health. Fifth, changes in brain function occur throughout life, and some consequences of early damage may not even emerge until advanced age. Such factors need to be addressed in estimating the influence of a particular agent or group of agents on brain development and its functional expression. It is especially important to consider ways of dealing with multiple risks and their combinations in addition to the prevailing practice of estimating risks in isolation. *Key words:* behavioral teratology, developmental toxicity, earnings, Food Quality Protection Act, IQ, multiple risks, Parkinson's disease, pesticides, social environment. — *Environ Health Perspect* 108(suppl 3):375–381 (2000).

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Near the beginning of our just-expired century, the toxicology of that time was goaded by pioneers like Harvey Wiley, whose persistence and stubbornness helped create the U.S. Food and Drug Administration (FDA). Wiley became the first FDA Commissioner in 1907, but he had earlier become gravely troubled by the adulteration of foods by unscrupulous or ignorant producers. While chief chemist of the U.S. Department of Agriculture, he recruited what became known as the "Poison Squad," a group of young men who consumed food treated with various chemicals to determine if they might experience adverse reactions including depression, headaches, and even more severe symptoms. Photographs taken around 1905 show them seated at dining tables, wearing coats and ties, as they valiantly consumed their tainted diets. Informed consent was not an issue at the time but probably would not have dissuaded Wiley's acolytes. They considered themselves public servants, an intriguing distinction with the current practice and ethical quandaries of paying volunteers to consume pesticides so as to change acceptable exposure standards.

Healthy young men would have been a judicious choice for poison squad subjects because, if they proved sensitive, Wiley could argue that less robust individuals might more easily succumb. There are no reports to indicate that he did so. In fact, the question of children as special targets of food additives, environmental poisons, and even drugs

apparently arose much later. A distinctive label for prenatal ethanol toxicity, Fetal Alcohol Syndrome, did not appear until the 1970s (1) despite centuries of anecdotal observations. The contemporary discipline of teratology is largely a product of the shoddy behavior of the company that concealed the horrors of thalidomide, which had been marketed as a safe effective sedative during pregnancy. A worldwide epidemic of birth defects began to emerge during the 1950s and early 1960s in the babies of women who had been prescribed thalidomide. The German firm, Chemie Grünenthal that had manufactured and marketed thalidomide kept such reports secret until the evidence became overwhelming, but, by that time, the drug had claimed thousands of victims.

The United States was spared this tragedy because of the stubbornness of Frances Kelsey, who received the President's Award for Distinguished Federal Civilian Service in 1962 for denying FDA approval of thalidomide. The Kefauver-Harris amendments that same year to the Food, Drug and Cosmetic Act (2), which had last been amended in 1938, were enacted in response to the thalidomide crisis. The amendments added a requirement for proof of effectiveness for drugs, and also required manufacturers to send reports of adverse drug reactions to the FDA.

Even after the thalidomide incident, the full dimensions of developmental toxicity remained unappreciated. The ancient metals,

mercury and lead, exemplify how little recognition, until quite recently, was accorded the special vulnerabilities of children. Needleman (3) has related the lead story on many occasions, noting the recognition of lead poisoning in workers at the same time that the effects on child development escaped notice. The mercury story is equally baffling in its exclusion of children. Mercury was recognized as a poison even in antiquity. Its neurotoxic properties, in the form of mercury vapor, received labels such as "hatter's shakes," which described its propensity to induce excessive tremor, and "erethism," a collection of psychological disorders manifesting features such as being hyperirritable; blushing easily; having a labile temperament; avoiding friends and/or public places; being timid and/or shy; being depressed and/or despondent; suffering from insomnia; and suffering from fatigue.

Mercury as a potential developmental toxicant received no attention. The childhood affliction of Pink Disease, or acrodynia, which had been discussed in the medical literature earlier in the century, was typically ascribed to infectious disease. Its symptoms did not coincide at all with those expressed by adults who had been poisoned by mercury. Pink disease symptoms included: apathy and irritability; rashes and sloughing of skin; reddening of cheeks and nose; cold blue fingertips and toes; profuse sweating and hypertension; itching and/or burning sensation; photophobia and anorexia; hypotonicity and tremor; pain in extremities and paresthesias; and muscle twitches.

Not until 1947 was Pink Disease linked to mercury. Mercury appeared mostly in the form of calomel (mercurous chloride), which

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was widely used in teething powders (4). Once calomel was removed from teething powders, the incidence of Pink Disease plummeted. Now, Pink Disease is largely a product of exposure to mercury vapor, which is still pervasive in the environment. Older latex paints, which contained a phenylmercury as a fungicide, emitted mercury vapor after application; jewelry factories used elemental mercury to produce gold amalgams and literally left pools of it behind in sites they abandoned; fluorescent bulbs contain mercury in the ballast assemblies; some religious groups use elemental mercury in their ceremonies; and certain ethnic groups use mercury compounds in cosmetics such as skin lighteners.

The Current Scene

Testing for developmental toxicity has become a fundamental component of safety assessment for environmental chemicals. It encompasses the end points of fetal death, malformations, altered growth, and the much broader question of functional abnormalities. This last criterion is the most difficult to determine. It embraces a vast array of possibilities, most of which are themselves comprised of multiple indices; learning deficits, for example, describe a class of problems rather than a single problem. They may emerge clearly long beyond gestation and only in specific settings such as the classroom. Functional measures are typically affected by lower exposure levels than other end points relied on as indices of developmental neurotoxicity.

Fetal Alcohol Syndrome offers an example of the progression from an emphasis on structure to an emphasis on function (1). In its original formulation, it featured craniofacial dysmorphologies. With further investigation focused on the effects of lower levels of maternal alcohol intake than those evoking structural defects, a new syndrome, labeled Fetal Alcohol Effects, emerged. Now known as Alcohol-Related Neurodevelopmental Disorder, it is applied to patients who display behavioral or cognitive abnormalities such as learning difficulties.

The special status of functional disorders inspired the term and discipline of behavioral teratology. Behavioral teratology describes functional abnormalities induced by prenatal exposures rather than the structural deficits assayed by teratologists. That identification has taken on a quasi-official status. Regulatory bodies around the world have come to recognize the importance of testing for functional abnormalities produced by pharmaceuticals, spurred by data that indicate the remarkable scope of drugs capable of leaving a residue of behavioral problems (5). These types of drugs include: vitamin analogs, cytostatics, gastrointestinal, hyperlipemics, bronchiolytics, spasmolytics, analgesics, antiallergens,

antibiotics, cardiovasculars, anticoagulants, and anticonvulsants.

The FDA lags behind its counterparts in Great Britain, France, and Japan in recognizing neurobehavioral assays as an essential aspect of drug testing. One example of how the FDA sometimes discounts neurobehavioral toxicity in children is seen in its requirements for the safety testing of food additives. Despite a string of publications since the late 1970s showing that some children respond adversely to additives, especially food dyes, at levels prevailing in the diet, the agency persists in its claim that "... well-controlled studies ... have produced no evidence that food color additives cause hyperactivity or learning disabilities in children" (6). Such a statement disregards reports based on controlled clinical trials (7-9) and lacks familiarity with the kind of careful statistical analysis required to identify susceptible subpopulations (10).

For most potentially toxic chemicals, we possess only animal, typically rodent, data. To provide an adequate margin of safety for humans, current practice first examines the dose-response function to select a dose statistically indistinguishable from the control preparation [the no-observed-effect level (NOEL)]. If the NOEL is derived from a chronic exposure study, it then divides this dose by a safety or uncertainty factor of 100 to calculate a reference dose or allowable daily intake: a factor of 10 to account for species differences and a factor of 10 to account for variations in sensitivity among individuals. Currently, for food additive toxicity testing, the FDA requires manufacturers to fulfill an extensive set of protocols, including teratological evaluations, in rodents. It then applies the 100-fold safety factor. Neurobehavioral testing is not required. The difference between what the literature shows in children and allowable daily intakes based on traditional protocols is highlighted in Table 1. The levels of food colors eliciting behavioral responses in children are 50-60 times less than the conventional exposure standard.

Table 1. Comparison of food dye doses (in milligrams).

Color	Weiss et al. ^a	Nutrition Foundation ^b	ADI ^c
Blue 1	0.80	0.85	300
Blue 2	0.15	0.46	37
Red 3	0.57	1.66	150
Green 3	0.11	0.04	150
Red 40	13.80	10.45	420
Yellow 5	9.07	7.34	300
Yellow 6	10.70	6.20	300

ADI, allowable daily intake.

^aIn a challenge experiment in which they elicited acute behavioral responses in young children (7). ^bEstimated intakes in children calculated by the Nutrition Foundation and used in several challenge studies (11). ^cADI derived from animal testing and based on NOELs divided by a safety factor of 100 (12). The doses eliciting behavioral responses in children are many times lower than the ADI, which is not based on neurobehavioral testing.

Pesticides and the Food Quality Protection Act

One major outcome of our recognition that developing organisms may be uniquely vulnerable to chemical challenge is the Food Quality Protection Act (FQPA) of 1996 (13). It may be viewed as the second stage of the National Academy of Sciences report (14) that noted the enhanced health risks arising from the combination of developmental susceptibility and the higher relative intakes of pesticides by children. The FQPA embodied the following risk assessment issues: inclusion of an extra 10-fold safety factor for children, *in utero* exposures, cumulative effects of pesticides and substances with a common mode of action, aggregate exposure (e.g., food and water), and endocrine disruption.

The most controversial feature of the FQPA specifies, at the discretion of the U.S. Environmental Protection Agency (EPA), an additional 10-fold safety factor for calculating acceptable intakes for children. This attribute of the FQPA has prompted objections among many elements of the pesticide industry because it can sharply restrict sales of many products whose residues appear in foods.

The other entries in the list arise from the same apprehensions that prompted the added safety factor. *In utero* exposures are required because, for so many agents, as recognized by current pesticide regulations, fetal development is an exceedingly sensitive stage of the life cycle, offering the prospect of latent damage whose consequences will surface later in life. The reference to cumulative effects acknowledges that different products may act in similar ways, especially if they come from the same chemical class; individual chemical exposure levels may fall within regulatory limits but prove toxic in the aggregate. Moreover, even chemicals from different classes may still share the same mechanisms of toxicity or be measured by equivalent end points; for example, both lead and polychlorinated biphenyls (PCBs) can reduce intelligence quotient (IQ) scores. Similarly, exposure may come from different sources such as produce residues, pesticide deposits in areas such as schoolyards where children play, contaminated drinking water, and residential surfaces. It makes little sense to treat standards for each source separately.

The FQPA (13) also included language directed at the question of endocrine disruption. We have come to recognize that many chemicals in the environment, including those found in nature, can exert powerful effects on hormone action, particularly on the role hormones play in early development. In response to FQPA concerns, the EPA created the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) to design a

screening and testing strategy to determine how to select chemicals for screening, how to choose the assays included in a screening battery, and the circumstances under which chemicals should be subjected to further testing. EDSTAC's targets are primarily estrogenic chemicals, however. A number of pesticides act as androgen antagonists and, in rats exposed *in utero*, induce signs of feminization, such as prominent nipples, in males (15). Testing for antithyroid properties is also not projected, although such agents may pose an even greater developmental hazard than estrogenic chemicals because of the high prevalence of iodine deficiency.

Safety Factors for Children

Two opposing viewpoints have clashed over the added 10-fold safety factor. Industry groups contend that current testing guidelines already include provisions aimed at developmental exposures such as two-generation studies. Their challengers argue that the provisions are insufficient to protect children. These latter groups base their argument partly on the lack of information about variations in dietary practices, inadequate monitoring of residues, and other gaps in knowledge. But the strongest argument for the additional protection is what might be called the ecology, particularly the spatial ecology, of childhood. These include such factors as activity altitude (young children spend much time on floors; they stir up and breathe dust and residues; and exposure to dust may be 10 times greater than adults); proportionality (children consume relatively more juice, fruit, and water than adults); exploratory behavior (young children literally lead a hand-to-mouth existence); and breast milk (lipid-soluble agents can be transmitted in quantity).

Children occupy a distinctive ecological niche in a world tuned to adults. Size is important because of what might be termed the altitude factor. Children's activities take place close to ground level. Dense vapors such as mercury collect at much higher concentrations near the floor than at adult waist level. The same would be true for any volatile materials that are denser than air. With their activities, children also stir up floor dust that they then inhale. One reason that farm families and agricultural communities typically experience greater pesticide exposures than the bulk of urban dwellers (16–18) is inadvertent deposition in the home through air currents, foot traffic, and contaminated clothing. In some cities, as in the upper west side of Manhattan, New York, pesticide use also can be heavy because of attempts to eliminate vermin (19). Lead in household dust is an example of a previously neglected exposure source that is significantly correlated with blood levels in the children (20). One frequent concomitant of

child exploration, hand-to-mouth sampling, is another exposure source that is poorly quantified. A recent survey and analysis (21) indicates that a small percentage of children may ingest much greater quantities of soil than the EPA standard of 200 mg/day.

Finally, breast milk, despite its great advantages, is also an efficient medium for transferring lipid-soluble chemicals from mothers to infants. All of these exposure sources demonstrate the futility of trying to characterize risk by reliance on a deductive sequence stretching from NOELs, to reference doses, to residue levels. The stipulations of the FQPA represent only the prelude to the more global, comprehensive analysis of exposure required for a detailed accurate assessment of risk.

Even an additional safety factor for children fails to take account of exposure spikes that may be experienced by many children. Developmental data from humans consist almost entirely of poisoning cases, probably a result of the fact that most calls to poison control centers about pesticides involve children. In Minnesota in 1988, pesticide poisonings accounted for 1,428 case files (22). The mean case age was 5 years, and 50% of all cases were younger than 3 years of age. Insecticides in residences were identified as the source in most of the case files. In Toronto, Ontario, Canada, the Hospital for Sick Children saw 1,026 cases of pesticide poisoning in a single year, 597 of which occurred in children younger than 6 years of age. These rates are typical of poison control centers (23). Follow-up observations are rare, unfortunately, even for those cases that require medical intervention. Children treated for poisoning by pesticides such as lindane and diazinon were observed by Angle et al. (24) to suffer apparently persistent neurobehavioral problems. Angle et al. (24) noted that "... there are no long-term studies of the effects of poisonings on children," and "... a provocative association ... with later intellectual deficit ..." but the intervening 30 years have seen no systematic attempts to explore these questions (25). One exception to the dearth of developmental data is the novel report (26) comparing two agricultural communities in Mexico. Residents came from the same ethnic stock, but one community had adopted chemical-based agriculture, whereas the other had rejected it. Various indices of neuropsychological development suggested that children from the traditional community proved superior on several measures.

One other factor not explicitly acknowledged by the FQPA is what we have learned from agricultural workers. Evidence of subtle neurobehavioral toxicity in adults, even at clinically silent exposure levels (27–29) has been accumulating steadily. Data verifying lingering neurobehavioral deficits in adult

farmworkers after a clinically toxic exposure (30–33) have also been accruing. Given the pronounced vulnerability of the developing brain to most neurotoxicants, we should anticipate that children will display even more pronounced responsiveness to the neurotoxic properties of pesticides than adults. The question might be framed in the form of a pyramid, as depicted in Figure 1. Clinical poisoning severe enough to necessitate medical treatment occurs in a relatively small number of children. Subclinical poisoning detectable with neuropsychological testing would reveal an even larger affected population. Latent toxicity, also conceived of as silent toxicity (34), may not become apparent until additional challenges to function, such as the demands of the classroom, supervene. Another is aging.

Many investigators have suggested that the roots of some neurodegenerative diseases may be found in events that occurred during early development (35). These authors proposed that

... Alzheimer's disease, Parkinson's disease (PD), and motoneuron disease are due to environmental damage to specific regions of the central nervous system and that the damage remains subclinical for several decades but makes those affected especially prone to the consequences of age-related neuronal attrition.

One source of support for such suggestions is the relationship between a history of pesticide exposure and PD. In some parts of the brain, cell numbers dwindle with age. The change is especially noticeable in the substantia nigra (SN), an area in the subcortical collection of nuclei known as the basal ganglia. The cells in one region of SN secrete the neurotransmitter dopamine. Clinical signs of PD emerge when most of these nerve cells die and can no longer synthesize adequate supplies of dopamine. Latent toxicity is one way of viewing the

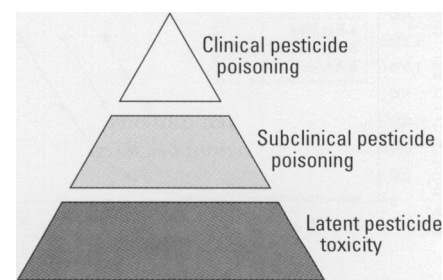


Figure 1. The toxicity pyramid for pesticides is designed to show that, although only a small proportion of children will manifest clear signs of excessive exposure, many more will show effects detectable by neurobehavioral testing, and even more will endure latent or silent toxicity that only emerges with additional challenges such as other pesticides, other environmental chemicals, or other health problems.

association between a history of pesticide exposure and an elevated risk of PD (36). The possibility of such an environmental source for PD is buttressed by the evidence (37) showing no difference in concordance rates for PD in monozygotic and dizygotic twins 60 years of age and older.

One possible explanation of the association is an acceleration of natural cell loss in SN induced by pesticide exposure, as shown in Figure 2. It compares the rate modeled on published data (38) with rates calculated on the basis of additional accelerations of 0.1 and 0.3% annually. Even a rather small acceleration of 0.1% per year means that the 40% reduction in cell density that would have occurred by the early 1970s is advanced by about 10 years. It is hardly a negligible shift and entails significant health and medical consequences.

These consequences are depicted in Figure 3. The rate of onset of PD rises steeply with age. The baseline curve plots representative data from a U.S. urban community (39). The other two curves show equivalent rates of rise but are displaced by 5 and 10 years, respectively. At age 70 and above, the empirical

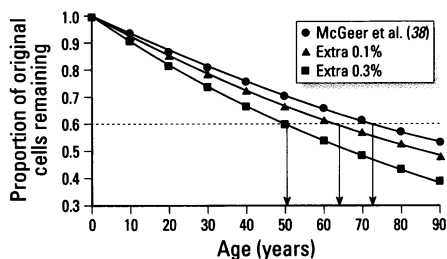


Figure 2. Cell numbers decline with age in several areas of the human brain. In the SN, the decline seems to progress throughout life (38). Slight accelerations of the process (0.1 and 0.3% per year) can foster the earlier clinical emergence of PD. The arrows correspond to a 40% loss, which some data suggest is a precursor of clinical PD.

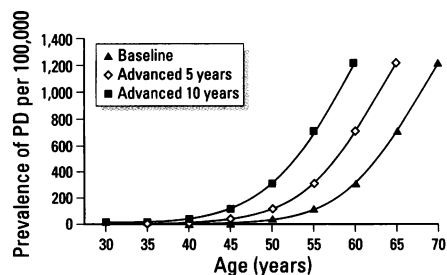


Figure 3. Incidence of PD with age. Baseline data (39) are compared to earlier hypothetical displacements of 5 and 10 years. Assume a baseline prevalence of about 0.012 at age 70 and above (39). In the year 2000, the number of PD patients older than 70 years of age would come to 309,672. Assuming the same prevalence at age 60, that is, displaced by 10 years, would bring the total to 555,696. If the prevalence function were to be shifted 5 years earlier, that number would be 424,728.

curve shows a prevalence of about 0.012. Demographic projections based on that prevalence figure indicate that, in the year 2000, the number of PD patients above 70 years of age would become 309,672. If the prevalence function were to be shifted by 10 years, the total would come to 555,696.

The Social Environment as a Dimension of Risk

Exposures to environmental chemicals represent only one class of risks during child development. Investigators have learned to be highly sensitive to this problem, and when they undertake to study risk factors in human populations, neurotoxicologists typically obey the conventions of traditional epidemiology. If an investigation targets a particular agent, it attempts to strip away those influences that might confound the effects of that agent in isolation. This practice is essential to the analysis of dose-response relationships, to the formulation of experimental hypotheses, to the planning of laboratory research, and to the pursuit of biological mechanisms. The virtues of such a focused approach begin to dissolve, however, when they have to be translated into risk characterizations and policy implications. Neurotoxicant exposure and its consequences for development are molded into a larger environment from which they cannot easily be extricated. The literature on lead offers one illuminating example.

Lead research during the past 30 years has mostly converged on behavioral development in children. The predominant measure, adopted because it is the one most easily communicated, because it is the beneficiary of an immense research effort extending over a century, and because it summarizes a variety of functions, is IQ score. Often confused by the public, and even by some scientists, with an abstract quality termed "intelligence," it remains useful because of its correlations with academic success, earnings, and even broader criteria such as welfare dependency.

What is now a vast literature documents an inverse relationship between indices of lead exposure in children, such as blood level, and IQ score. The relationship itself, as a simple statistical measure, arouses relatively muted debate. What does excite vigorous argument is interpretation. The basis for argument in neurobehavioral toxicology is the contribution of other variables. The contenders agree that lead is only one component of a multitude of factors acting on IQ score. Maternal intelligence, family income, parental intellectual stimulation and care, maternal and paternal education, race, marital status, maternal age, extent of prenatal care, maternal drug use (alcohol, tobacco, and illicit drugs), maternal psychopathology, and other aspects of the child's history and environment also influence

IQ score. The strategy universally adopted by serious investigators is to compensate statistically for these other influences, typically by multiple regression procedures. Disagreements arise over which confounders or control variables to include, and how to do so.

The practice of isolating the contribution of a selected neurotoxicant is scientifically logical but possibly misleading for public policy. Stripping away potential confounders may distort that contribution in a larger context, partly because it can be carried to a point at which it effectively eliminates lead exposure as a variable (40). Given all we know about lead, might it be time to proceed to larger questions? Should the old debates be put to rest? Should we frame another kind of question and adopt another perspective? Should neurotoxicity be viewed as one element in a combination of factors acting jointly as a form of risk vector? These questions are not novel. They have been posed by others and in other forms, as in the dilemma described by Bellinger and Stiles (41). They discussed the utility of different study populations in the context of their own investigations as follows:

Other investigators chose to recruit their samples from inner-city populations at far higher risk of developmental handicap due to a variety of poverty-related risk factors, of which lead is only one. The trade-offs involved in this decision are that, on the one hand, it may be difficult to reject the possibility that any apparent lead-related decrement in performance is not the result of residual confounding (a potential Type I error). On the other hand, it may be difficult to estimate, with adequate accuracy and precision, any true lead-related decrement amidst the "statistical noise" contributed by correlated risk factors (a potential Type II error) ...

Community attributes, beyond the form of covariates, are one of the ways in which customary measures of neurobehavioral function may distort the total effect of toxic exposure. How the influence of lead on IQ scores is evaluated provides one example. In his meta-analysis of lead and IQ, Schwartz (42) calculated that a 10- $\mu\text{g}/\text{dL}$ rise in blood lead would produce a mean estimated loss of 1.85 IQ points in a socially disadvantaged population and a mean loss of 2.89 IQ points in a socially advantaged population. Such a discrepancy might be used to argue that reductions in lead exposure might not be as cost-effective in disadvantaged populations.

IQ Loss in Advantaged and Disadvantaged Communities

If the two populations were to be compared by broader criteria, the message might be different. Figure 4 compares the effects of shifts in mean IQ in two different communities, one

that would be ranked as advantaged and one as disadvantaged. In many surveys, the differences in mean IQ scores of such populations approximate about 15 points (43). Assume, then, for modeling purposes, initial IQ distributions with respective means of 100 and 85, both with standard deviations of 15. As an impact index, calculate the number of scores below 70. Conventional education standards tend to assume (despite the rise in scores over several decades known as the Flynn effect) that a score below 70 indicates the need for remedial measures, and for some school systems, signifies a classification of retarded.

With population sizes of 100,000 each, as shown in Figure 4, a loss of 1 IQ point in the advantaged population increases the number of individuals below 70 from 2,280 to 2,660. In the disadvantaged population, the loss assigns 17,530 rather than 15,870 individuals to the below-70 category. Although the proportional shift is greater in the advantaged population (16.7%) than in the disadvantaged population (10.5%), the number of individuals added to the developmentally disabled category is much larger in the disadvantaged population (1,660) than in the advantaged population (380). The discrepancies enlarge with greater IQ losses, which could result from higher neurotoxic exposures. One result is that expenditures arising from increased demands for remedial education in the disadvantaged community would also greatly exceed those in the advantaged community.

Figure 5 shows one perspective on the multitude of stressors acting on disadvantaged communities. It depicts how an array of challenges to optimal development, none of which by itself exerts a large effect, might combine to create a pronounced depression of functional potential as measured by IQ score. For this conceptual model, the sizes of the entries and their overlaps do not represent actual data. The chart is designed only to underscore the point that individual risk factors, none of which alone might exert conspicuous influence, can jointly effect marked changes in developmental potential. Joint actions might take many forms; additivity is one possibility, synergism is another.

Degraded intellectual potential is only one facet of how environmental stressors can interfere with neurobehavioral development. The Rochester Longitudinal Study (43) followed a cohort of children, beginning at birth, to ascertain the influence of maternal psychopathology, primarily schizophrenia, on developmental outcome. They included other potential risk factors, as well, in their analyses (Figure 6). The unexpected message from their data led the authors to conclude that the number of risk factors, rather than any specific factor, determined outcomes such as IQ and social competence. Figure 6 depicts effects on

measures of IQ and social-emotional competence at 4 years of age. Individually, each risk factor contributes a small amount of the total variance averaging about 4%, about equivalent to a 10-µg/dL increment on blood lead level. Their cumulative effect, as shown in Figure 6, can be dramatic.

Sameroff et al. (43) did not include neurotoxic exposure as a risk factor, although some portion of their study population inhabited housing with high levels of lead in paint and dust (20). The trends depicted in Figure 6 indicate that neurotoxic exposure might well exert a greater effect in combination with other risk factors of the type listed in Figures 5 and 6 than in isolation. Figure 4 shows that the home and community environment exert an enormous influence on the outcomes of neurotoxic exposures.

A second method to illustrate the way in which different stressors, including toxic exposures, might influence development is shown in Figure 7. The uppermost curve depicts the normal trajectory of development. Add exposure to a neurotoxic substance and development proceeds at a lowered rate and

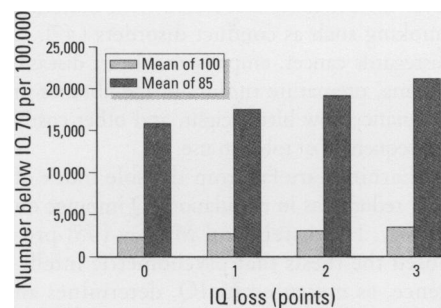


Figure 4. Advantaged communities typically show about a 15-point or 15% higher mean IQ score as compared to disadvantaged communities. If both populations, as a result of neurotoxic exposure, suffer an equivalent decrease in mean IQ, the effect will be greater in the disadvantaged community, as gauged by the number of IQ scores below 70. A score below 70 is taken as evidence of retardation and, in many school districts, requires remedial education.

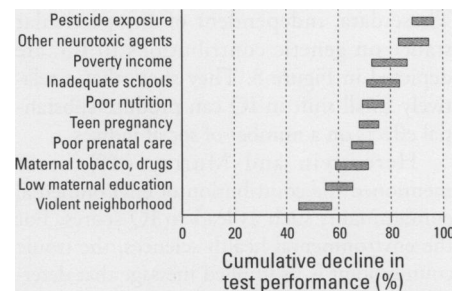


Figure 5. Schematic model to show how individual components of a stressful environment might cumulate to reduce performance on IQ and other tests. The individual stressors are shown as overlapping to suggest a lack of independence, and their length is meant to indicate that no single component is overwhelming in isolation.

reaches a lower asymptote. Add a second stressor, low income (which, in practice, would embody a collection of stresses), and rate and asymptote may fall even further.

Economic Implications of Developmental Neurotoxicity

Impaired child development imposes economic burdens on the entire society, not solely on the individual. Behavioral difficulties expressed in higher rates of crime and delinquency comprise one set of outcomes (44) but are difficult to quantify in economic terms.

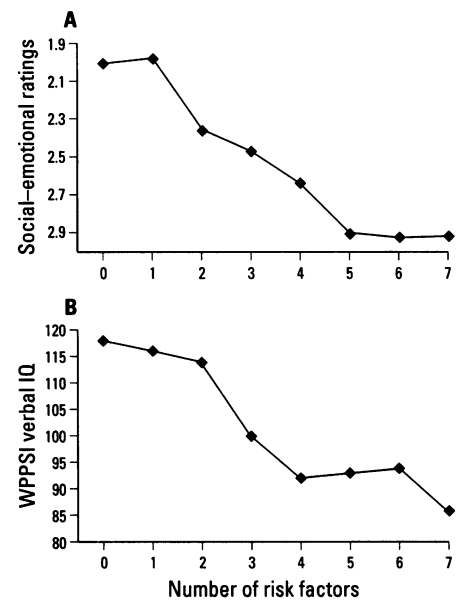


Figure 6. Charts modified from a report on the Rochester Longitudinal Study (43). Two end points are shown for children tested at 4 years of age: (A) a rating of social-emotional competence and (B) verbal IQ on the Wechsler Preschool and Primary Scale of Intelligence (WPPSI). Each individual risk factor accounted for about 4% (4 IQ points). The difference between the lowest and highest risk children was approximately 30 IQ points or 2 SDs. Risk factors are maternal mental illness, high maternal anxiety, rigid parental perspectives, few interactions with infant, minimal maternal education, unskilled occupation, disadvantaged minority, single parenthood, stressful life events, and large family size.

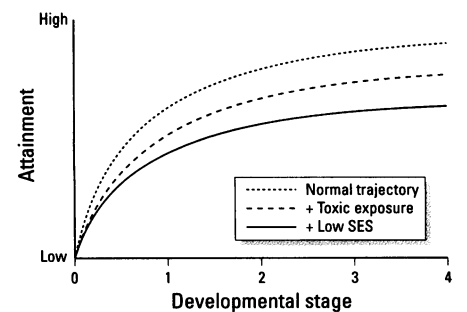


Figure 7. Schematic to show how the normal course of development (intellectual attainment) might be slowed by the addition of toxic exposures, poverty, and other risk factors. SES, socioeconomic status.

Lowered IQ, as measured by standardized tests, provides the best documented relationship with economic criteria such as earnings.

Much of the public, and even some scientists, are confused about what IQ scores measure. IQ tests are not used to gauge some abstract quality called intelligence, but, instead, constitute a sample of performance with established predictive power. For example, IQ scores are correlated with social class, educational attainment, and income. The latter relationship facilitates one form of economic analysis of the costs arising from environmental neurotoxicants. Such an analysis should not be interpreted as a claim that IQ determines earnings rather than as a description of an empirical relationship.

The relationship of IQ to income provides a gauge by which to determine how much society loses by neglecting environmental contamination. Salkever (45) has assembled the most convincing calculations. They include relationships among IQ and years of schooling and also take account of the cost of lost income while in school and the discounted value of future earnings. By Salkever's calculations, in terms of 1995 dollars, each IQ point is worth \$8,346 in lifetime earnings. Although this sum is equivalent to only \$200/year over a working lifetime, it has to be viewed from a population perspective. If environmental contamination diminishes IQ in the U.S. population by an average of 1%, the annual cost would come to \$50 billion and the lifetime costs to trillions. This sum is an underestimate because a shift of the population mean to a lower IQ means more individuals thrust into a score category below 70, which typically mandates remedial education at a cost of approximately \$6,000 annually. Salkever's calculation, if it were to include this expenditure, might raise the loss to the community of one IQ point to as high as \$10,000. Restrictions on environmental pollution cost far less. In its report to Congress on the Costs and Benefits of the Clean Air Act (46), EPA investigators estimated the direct costs of implementing the act at \$523 billion in 1990 dollars. Its estimate of benefits during the same period, mostly from the avoidance of adverse health effects, ranged from \$5.6 to \$49.4 trillion, with a mean of \$22.2 trillion. Based on these calculations, the ratio of benefits to costs ranges from 10.7 to 42. Those who oppose restrictions on the environmental discharge of chemical contaminants typically cite only the estimated costs.

The tobacco settlement offers a compelling example of how ignoring IQ losses seriously underestimated the ultimate health costs of smoking. The economic implications of developmental impairment due to maternal smoking are based on a comprehensive review of the relationship between IQ and

earnings (45) and the effects on IQ of maternal smoking during pregnancy (47). The implications are as follows:

- four million children born in 1994
- 20% of their mothers smoked during pregnancy (800,000 children)
- offspring of smoking mothers average a 3% (3-point) drop in IQ
- assume 1 IQ point = \$10,000 over a working lifetime (\$250/year)
- multiplying 800,000 children by 3 = 2,400,000 lost IQ points
- for the 1994 cohort, total loss = \$24 million
- look back over 30 years (1964–1994) with the same smoking rates
- for 30 years, total earnings loss would be \$720 million (for a 30-year period, the cumulative loss of earnings greatly exceeds the \$200 billion proposed tobacco settlement negotiated in November 1998 by 28 of the State Attorneys General.

These calculations are based only on projected income. Distributed across the offspring of smoking mothers, their sum is more than twice the size of the tobacco settlement. It does not include the costs of other behavioral disturbances associated with maternal smoking such as conduct disorders (47). It disregards cancer, emphysema, heart disease, asthma, premature rupture of membranes in pregnancy, low birthweight, and other costly consequences of tobacco use.

Earnings are far from the sole index of how reductions in population IQ impinge on society. Herrnstein and Murray (48) proposed the thesis that psychometric intelligence, as measured by IQ, determines an individual's position and success in society. It further stoked a fierce debate that continues unabated about the heritability of IQ and the role of race. The empirical data upon which the Herrnstein and Murray (48) analyses rely come from the National Longitudinal Survey of Youth (49), a federal program operated by the Department of Labor to gather information at multiple points in time on the labor market experiences of five selected groups. These data, independent of any particular stance on genetic contributions to IQ, are depicted in Figure 8. They show that a relatively small shift in IQ can produce substantial effects on a number of social indices.

Herrnstein and Murray (48) never mentioned the contribution of environmental contaminants such as lead to IQ scores. For the environmental health sciences, the ironic counterpoint is its implied message that determined efforts to reduce exposures to lead, PCBs, and other developmental neurotoxicants have inadvertently promoted social benefits beyond our original expectations based on improved health. We can also inspect the mirror image of those data to calculate the

massive costs of failure to act on behalf of environmental protection for children.

We have only begun to grasp the breadth of challenges that chemical contamination of the environment poses to the developing brain. Although we finally grasped the extent of hazards arising from lead exposure, we became complacent about modern chemicals, such as pesticides, because their contributions to our lives were striking and transparent. Their shortcomings proved elusive because they were subtle enough not to be immediately apparent; moreover, we simply did not understand how to ask the proper questions about their toxicity. Recall the struggle to document the dangers of smoking. Or the astonishment provoked by Carson's *Silent Spring* (50) and the attacks on hypotheses advanced in *Our Stolen Future* (51). We certainly will discover new threats unforeseen by our current knowledge that likely will take the form of an unraveling puzzle.

A provocative statement about lead from the report by the Centers for Disease Control (52) could serve as a guide. If the references to lead are left blank, the paragraph below can be viewed as a terse description of how our understanding of threats to neurobehavioral development tends to materialize.

[...] is ubiquitous in the human environment as a result of industrialization. It has no known physiologic value. Children are particularly susceptible to [...] toxic effects. [...] poisoning, for the most part, is silent: most poisoned children have no symptoms. The vast majority of cases, therefore, go undiagnosed and untreated. [...] poisoning is widespread. No socioeconomic group, geographic area, or racial or ethnic population is spared.

Neurobehavioral toxicology is one of those disciplines inextricably entangled with larger issues and public policy. A superficially direct index of developmental neurotoxicity such as IQ score evokes broader questions such as how it positions an individual in society, for instance, and in the career and educational

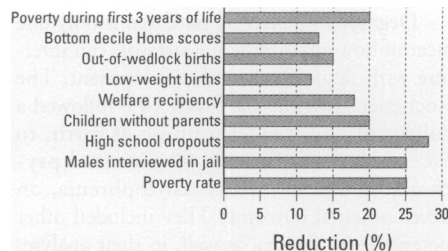


Figure 8. Societal benefits (i.e., reduction in certain undesirable social factors) (48) of a 3% rise in IQ, based on National Longitudinal Survey of Youth data (49). The Home score was based on the Home Observation for Measurement of the Environment Inventory (53).

opportunities it affords and in how it determines social class. Even more broadly, it awakens questions about the structure of society, about its economic potential, and even about the processes of aging. The title of this paper encompasses only the first step in our exploration of children's health and its implications.

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