Editorial

An Unhealthy Start in Life—What Matters Most?

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Life isn't fair. The following monograph describes how neurotoxic metals, micronutrient deficiencies, and social environments can combine to give a child an unhealthy start in life. Visualize a preschool child from a low-income family in the United States, growing up in a poorly maintained older apartment with peeling paint and windowsills laden with lead dust. Perhaps this child also attends a day-care center with a high child-to-caretaker ratio that prevents the caretakers from spending much time interacting with the children, and where the children often squabble over the toys that are present. Because of the high child-to-caretaker ratio, the caretakers are relatively harsh in their discipline. The child's parents both work, but at low-wage part-time jobs without health insurance or sick leave. The family's food stamps run out each month, and only one visit to the food pantry per month is allowed. The child has no picture books and few age-appropriate toys because the family has changed residence three times in the past 2 years. Unable to pay the rent, they lived in a homeless shelter once while between residences, with no place to store their personal belongings.

The scenario I have described above is real life for too many American children. We know that a child growing up with poor nutrition, lead or other toxic exposures, low-quality day care, and little stimulation in the home is getting an unfair start in life. But which of the factors in this child's life are the most influential? Perhaps that question is too simple: The problem is that risk factors often occur in an intercorrelated complex that cannot be untangled easily by statistical control. This monograph, by the interdisciplinary team of Hubbs-Tait, Nations, Krebs, and Bellinger, invites us to think more deeply about how the effects of metallic neurotoxicants, deficiency in micronutrients, and aspects of the social environment can, separately and together, influence children's behavioral health. The effects of combinations of risk factors on children's development have long been a puzzle to developmental researchers. One solution is to say, "Risk factors add up, so more risks are worse—regardless of the type of risk." Certainly there is truth in that answer, but this monograph sets the stage for new inquiries, with the potential to identify both protective factors as well as combinations of events that potentiate each other's negative effects. For example, does iron deficiency make lead exposure more deleterious to a child's cognitive functioning? Alternatively, does treatment of iron or zinc deficiency imply that lead will have weaker effects on a child's cognition or behavior?

The authors make the case that the effects of all three categories of influence may be subject to "effect modifiers," or interactions that exacerbate (or ameliorate) their influence. If we are to identify and establish preventative programs for children who are most susceptible to toxic exposures, micronutrient deficiency, and poor social environments, then we need to consider interactions. The authors also point out that unless all three sources of influence are considered, we could incorrectly attribute stronger or weaker influence to any one individual factor. For example, in epidemiological studies of the effects of neurotoxicants such as lead and mercury, investigators partial out the effects of social variables such as income, social quality of the home, parental education, and racial or ethnic identity of the parents or child. But it is rather unusual for studies of the impact of social influences such as parental sensitivity, parental education, or socioeconomic status to statistically control for either neurotoxic exposures or nutritional status in the child. Because of these standard research practices, estimates of the effects of social factors are likely overestimated, as are the effects of micronutrients.

The report is also cutting edge in the way it combines animal research on the mechanisms by which toxic metals, micronutrients, and environmental stimulation affect neural function and development with epidemiological research on children's cognitive and behavioral outcomes. Some of the latest work on neurotransmitter systems and their complex interactions is reflected here. For example, manganese is both a micronutrient and, at higher exposures, a neurotoxicant. Manganese affects glutamate uptake in certain areas of the brain, but it also affects dopaminergic systems. Lead can also alter glutamate neurotransmitter systems that are known to be involved in learning. These kinds of findings help us understand why lead and manganese are neurotoxic and what behavioral effects to look for. But such findings also raise the issues of coexposure to toxic substances and how micronutrients combine with neurotoxicants. The report calls for research that will address exposure to manganese and cadmium because these neurotoxicants are

understudied while environmental releases of them are increasing. The current situation with respect to cadmium and manganese is reminiscent of how lead and mercury were regarded 40 or so years ago. Before the methylmercury poisoning disaster at Minamata, Japan, and before follow-up studies of children who were lead-poisoned were conducted, there was little societal concern about environmental releases of either lead or mercury. If we don't attack the research tasks set out by Hubbs-Tait and her colleagues in this monograph, we won't know until it is too late.

Neurotoxicants, Micronutrients, and Social Environments

Individual and Combined Effects on Children's Development

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SUMMARY—*Systematic research evaluating the separate and interacting impacts of neurotoxicants, micronutrients, and social environments on children's cognition and behavior has only recently been initiated. Years of extensive human epidemiologic and animal experimental research document the deleterious impact of lead and other metals on the nervous system. However, discrepancies among human studies and between animal and human studies underscore the importance of variations in child nutrition as well as social and behavioral aspects of children's environments that mitigate or exacerbate the effects of neurotoxicants.*

In this monograph, we review existing research on the impact of neurotoxic metals, nutrients, and social environments and interactions across the three domains. We examine the literature on lead, mercury, manganese, and cadmium in terms of dispersal, epidemiology, experimental animal studies, effects of social environments, and effects of nutrition.

Research documenting the negative impact of lead on cognition and behavior influenced reductions by the Center for Disease Control in child lead-screening guidelines from 30 micrograms per deciliter (μg/dL) in 1975 to 25 μg/dL in 1985 and to 10 μg/dL in 1991. A further reduction is currently being considered. Experimental animal research documents lead's alteration of glutamate-neurotransmitter (particularly N-methyl-D-aspartate) activity vital to learning and memory. In addition, lead induces changes in cholinergic and dopaminergic activity. Elevated lead concentrations in the blood are more common among children living in poverty and there is some evidence that socioeconomic status influences associations between lead and child outcomes. Micronutrients that influence the effects of lead include iron and zinc.

Research documenting the negative impact of mercury on children (as well as adults) has resulted in a reference dose (RfD) of 0.1 microgram per kilogram of body weight per day (μg/kg/day). In animal studies, mercury interferes with glutamatergic, cholinergic, and dopaminergic activity. Although evidence for interactions of mercury with children's social contexts is minimal, researchers are examining interactions of mercury with several nutrients.

Research on the effects of cadmium and manganese on child cognition and behavior is just beginning. Experimental animal research links cadmium to learning deficits, manganese to behaviors characteristic of Parkinson's disease, and both to altered dopaminergic functioning.

We close our review with a discussion of policy implications, and we recommend interdisciplinary research that will enable us to bridge gaps within and across domains.

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INTRODUCTION

The primary goal of this monograph is to inform professionals and policymakers in order to protect children who are most susceptible to the effects of neurotoxicants. To attain that goal requires identifying micronutrient deficiencies and social-environment risks linked to maternal and child neurotoxicant

exposure and adverse child outcomes, so that (a) researchers can refine study designs to examine crucial interactions, (b) practitioners can intervene in time to increase cognitive functioning and diminish behavior problems, and (c) policymakers can implement needed changes to the assessment of risks. The current federal risk-assessment process mandates protecting subgroups most vulnerable to neurotoxic effects. Because empirical data on susceptible subgroups are incomplete, uncertainty and modifying factors are applied to specify exposure limits such as reference doses (RfDs; e.g., United States Environmental Protection Agency [U.S. EPA], 2002b). Fetuses, infants, and children are recognized susceptible groups. Even more vulnerable are fetuses, infants, and children experiencing micronutrient deficiencies and/or risks in their social environments. Currently, micronutrient deficiencies and social risks are not recognized risk factors in the federal risk-assessment process. By identifying the diverse micronutrient deficiencies and social risks linked to different neurotoxicants, this monograph will reduce the need, when assessing the risks of those neurotoxicants, to rely on uncertainty factors (i.e., values applied to account for incomplete information, in order to increase the likelihood that exposure standards provide a sufficient margin of safety).

A second goal of this monograph is to provide an interdisciplinary multilevel model of development. This general model is depicted in Figure 1 and will be discussed in more depth later. The model and this monograph are the result of a collaboration of researchers from multiple disciplines. Such an interdisciplinary endeavor is essential to integrating the separate literatures on the impact of neurotoxicants, nutrients, and social environments on child cognition and behavior. Research evaluating the joint impact of these three domains has not yet been conducted. Sufficient research does exist on the impact of each domain singly and on the impact of pairs of domains to infer additive and interactive effects, however. Some effects are independent, whereas others are correlated, due in part to coexposures across and within domains (see Fig. 1). In this monograph we review existing research on the impact of each domain, interactions across domains, and potential mediating pathways, and we recommend crucial interdisciplinary research to bridge gaps within and across domains.

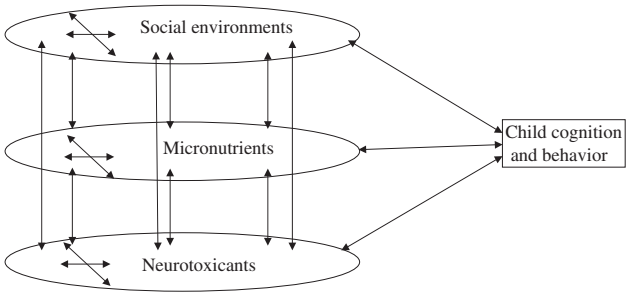

Fig. 1. Model of interrelationships across domains and child outcomes.

Neurotoxicants

Neurotoxicants are trace elements, pesticides, chemicals, and biological agents that have toxic effects on the human nervous system (U.S. EPA, 1998). Such toxic effects are manifested as deleterious changes in behavior and/or the nervous system. Although as many as 80,000 chemicals are used in industrial processes (Stein, Schettler, Wallinga, & Valenti, 2002) data on their toxicities are limited. As of August 31, 2004, the EPA listed only 544 substances in the Integrated Risk Information System for which neurotoxic or other adverse health effects have been characterized (U.S. EPA, 2004b). The likelihood that children are exposed to at least some of these chemicals is high. As of August 31, 2004, there were 1,242 sites on the National Priorities List (NPL) of worst hazardous-waste sites under the Comprehensive Environmental Response Compensation and Liability Act (CERCLA, known as Superfund sites; U.S. EPA, 2004a). The Agency for Toxic Substances and Disease Registry (ATSDR) estimates that 3 to 4 million children live within one mile of at least one hazardous-waste site (U.S. ATSDR, 2003). The CERCLA Priority List ranks hazardous substances based on a combination of frequency, toxicity, and potential for human exposure at NPL sites. The most recent (2003) list identifies arsenic, lead, and mercury as the three hazardous substances of greatest concern in U.S. NPL sites (U.S. EPA, 2004a).

Due to the large number of chemicals with known or potential neurotoxic effects and the larger number of possible interactions of such agents, the world's population at the beginning of the third millenium is faced with combinations of substances about which they have minimal knowledge and over which they currently exercise only negligible control. To begin the process of increasing understanding and control, we review neurotoxic metals with the best-documented impact on human cognition or behavior: lead and mercury. We then extend our analysis to two neurotoxicants whose ill effects are rapidly claiming research and public attention: cadmium and manganese.

Micronutrients

The trace elements are essential micronutrients found in the human body in small amounts, accounting for less than 1% of total body weight. The trace minerals for which a mammalian requirement has been established include iron, zinc, iodine, selenium, copper, manganese, fluoride, chromium, and molybdenum. Although each of these trace minerals is toxic in excess, deficiencies in each are associated with mild to radical changes across a wide range of functions including gene expression, physiology, health, and behavior (e.g., Keen et al., 2003). Because insufficient intake of all micronutrients is linked to poor child health (R.E. Black, 2003; Oppenheimer, 2001; Walter, Olivares, Pizarro, & Munoz, 1997), and poorer health is related to child cognition and behavior (Fernando, Wickremasinghe, Mendis, & Wickremasinghe, 2003; C.G. Neumann, McDonald, Sigman, & Bwibo, 1992), some of the effects of micronutrients on

child cognition and behavior are likely to be indirect effects, mediated by health. For example, micronutrient supplementation causes decreases in respiratory infections, diarrhea, and other infections (Juyal et al., 2004). Maternal nutrient insufficiency is related to breast-fed infants' drowsiness and lethargy (Rahmanifar et al., 1993). In turn, illness and lethargy interfere with normal exploration and cognitive development (Fernando et al., 2003; C.G. Neumann et al., 1992).

Iron and zinc are the two micronutrients most consistently found to be related to children's cognition (M.M. Black, 2003a, 2003b; Bruner, Joffe, Duggan, Casella, & Brandt, 1996; Grantham-McGregor & Ani, 1999, 2001; Halterman, Kaczorowski, Aligne, Auinger, & Szilagyi, 2001; Lozoff, Jimenez, & Wolf, 1991; Penland et al., 1997; Pollitt, 2001; Sandstead et al., 1998). Both play essential roles in neural development and/or chemistry (Beard, Erikson, & Jones, 2003; Sandstead, 2000; deUngria et al. 2000; Zawia, Crumpton, Brydie, Reddy, & Razmiafshari, 2000) and are among the micronutrients proposed to interact with toxic metals and confer protection against their effects or, in deficiency, exacerbate their toxicity (Chapman & Chan, 2000; Clarkson & Strain, 2003; Peraza, Ayala-Fierro, Barber, Casarez, & Rael, 1998).

Extensive data on micronutrient absorption and metabolism are available from human adult or experimental animal research. However, due to limited research on changing nutrient needs as a function of the changing physiology of infants and children, many of the recommendations for child nutrient intakes are based on extrapolations from a few studies of children and studies of human adults and experimental studies of animals (Institute of Medicine [IOM], 2000, 2001; Krebs, 2001). Throughout this monograph, we refer to human nutritional data and data on infants and children wherever possible. However, by necessity much of the information comes from research on laboratory animals.

Social Environments

Social environments include family resources and relationships, child-care and school quality and relationships, and neighborhood and community resources and relationships (Shonkoff & Phillips, 2000). Although each of these components of social environments may exert a unique impact, they tend to be correlated. For example, children with fewer family resources tend also to experience lower-quality public schools (V.E. Lee & Loeb, 1995), more frequent exposure to violence (Osofsky, 1995; Richters & Martinez, 1993), and poorer neighborhoods (Duncan, Brooks-Gunn, & Klebanov, 1994).

Each of the components of social environments has been reliably linked to child cognition and behavior. Lower family resources are associated with lower cognitive and linguistic functioning, greater behavior problems, lower social adjustment, and poorer performance in school (e.g., Conger et al., 2002; Duncan et al., 1994; Hart & Risley, 1995). Parenting behaviors are associated with the same outcomes (e.g., Hubbs-Tait, Culp, Culp, & Miller, 2002; Landry, Smith, Swank, & Miller-Loncar, 2000; McLoyd, Jayaratne, Ceballo, & Borquez, 1994), with recent investigators emphasizing the mediating role of parenting behaviors in the relation between family resources and child outcomes (e.g., Hoff, 2003; Mistry, Vandewater, Huston, & McLoyd, 2002). The idea that individual risk factors are far less important than the total number of risk factors present in a child's family or environment has been discussed for decades (e.g., Rutter, 1979). Sameroff, Seifer, Barocas, Zax, & Greenspan (1987) emphasized the additive nature of risk, because they found no single risk factor to be more important than any other. Measures of cumulative risk consist for each family of the total number of risk factors present (e.g., low income, maternal depression), with children coming from higher-risk families having lower cognitive scores, more behavior problems, and lower social competence.

Child-care and school quality influence both cognitive and behavioral outcomes (Loeb, Fuller, Kagan, & Carroll, 2004; National Institute of Child Health and Human Development Early Child Care Research Network, 2003). Because homes, schools, and child-care centers may be located in areas that provide opportunities for exposure to a variety of neurotoxicants (e.g., Sargent et al., 1995; Viverette et al., 1996) or are associated with micronutrient deficiencies (Alaimo, Olson, Frongillo, & Briefel, 2001), identifying protective or exacerbating impacts of social environments is essential.

Model

The model depicted in Figure 1 indicates that each of the three domains—social environment, neurotoxicant exposure, and micronutrient intake—influences each of the other domains and that these influences are multidirectional. Research confirms coexposures within domains (indicated by the intersecting arrows) and across domains as well. Examples of coexposures within the neurotoxicant domain include exposure to PCBs and methylmercury through fish and sea-mammal consumption (e.g., Grandjean, Weihe et al., 2001; Stewart, Reihman, Lonky, Darvill, & Pagano, 2003) and lead and cadmium through cigarette smoking (Mortada, Sobh, & El-Defrawy, 2004) or pollution (Osman, Zejda, et al., 1998). Examples of coexposures within the micronutrient domain include iron and zinc deficiencies due to low intake of animal sources of protein (C.G. Neumann & Harrison, 1994; Villalpando et al., 2003). Examples of coexposures within social environments include lower family income and lower quality of schools attended by children from impoverished families (V.E. Lee & Loeb, 1995), fewer verbalizations to children (Hart & Risley, 1995), greater parental distress (Duncan et al., 1994; Mistry et al., 2002), more frequent authoritarian parenting practices (Linver, Brooks-Gunn, & Kohen, 2002), and lower parental affection (Mistry et al., 2002). Cross-domain coexposures to some neurotoxicants (e.g., Brody et al., 1994)

and to poorer nutrition (e.g., Looker, Dallman, Carroll, Gunter, & Johnson, 1997; Rose, Habicht, & Devaney, 1998) co-occur with lower family resources. Throughout this report, we will discuss the interrelating influences of domains and their joint impact on child cognition and behavior.

The proposed model and the supporting research reported herein advance the fields of developmental neurotoxicology, experimental psychology, nutrition, and developmental psychology and child development. Much of the research on neurotoxicants has focused on effects of individual chemicals, failing to address the fact that children are exposed to chemical mixtures and that the effects of a particular neurotoxicant might differ depending on the other components of the mixture. Most research on neurotoxicants also fails to acknowledge the possibility that a neurotoxicant's effects might differ as a function of the nonchemical aspects of the environment in which it is found. Such differences are referred to as effect modification (or moderator effects) and are confirmed by statistical interactions. For example, developmental abilities of infants in families with fewer socioeconomic resources are negatively affected by lower levels of lead than are developmental abilities of infants in families with more socioeconomic resources (Bellinger, Leviton, Waternaux, Needleman, & Rabinowitz, 1988). To be sure, neurotoxicant researchers recognize the importance of addressing confounding bias, but this involves ensuring only that a developmental effect attributable to some other factor is not falsely attributed to the neurotoxicant of interest or that effects of neurotoxicants are not misattributed to confounders. Identification of effect modifiers that exacerbate neurotoxic effects is rare, reducing the ability of researchers and practitioners to accurately identify those children who are most susceptible. The difficult task of building complex models that integrate risks within and across domains has rarely been tackled.

Research in child development, developmental psychology, and nutrition has failed to include neurotoxicants as predictors or confounders of effects on child cognition or behavior. In developmental psychology and child development this omission means that estimates of effect sizes, for example, of the relation of socioeconomic status (SES) or parent–child interaction to child outcomes, may be inflated by confounding with neurotoxicant exposure. In nutrition, comparable overestimates of effects of micronutrients on child outcomes can be attributed to the omission of neurotoxicant measurement from research designs.

The general model depicted in Figure 1 is a multilevel model. We have left the nesting (hierarchical ordering) of the three levels unspecified as nesting varies as a function of the particular neurotoxicant, micronutrient, and aspect of the social environment. For example, social environments and micronutrient intake are nested within ubiquitous neurotoxicants, such as was the case for lead in the United States prior to the 1980s. However, neurotoxicant exposures and micronutrient intakes may be nested within family resources or other broad demographic measures of social environments. As is the case with all models, decisions on nesting are theoretically driven. When micronutrient deficiency, neurotoxicants, and aspects of the social environment all overlap, our three-tier model collapses to one tier and each domain can be considered to contribute to children's cumulative risk.

Unifying Themes

Experimental Animal Models and Child Development

Throughout this monograph we present results of experimental laboratory investigations of animal behavior and nerve-cell structure and function. The studies we have selected report results congruent with epidemiological and observational studies of child cognition and behavior. Research studies with children frequently do not allow the inference of causality because of the presence of so many uncontrolled confounding variables. To understand the causal effects of neurotoxicants, deprived social environments, or micronutrient deficiencies on the brain requires conducting experimental animal research. Random assignment to treatment versus control and holding other variables constant allows researchers to make causal inferences. Where researchers in child epidemiology or development discuss cognitive functioning, animal researchers refer to learning and associative processes. Animal models allow researchers to observe changes in neurotransmitters (signaling mechanisms by which the nervous system communicates) that are linked to key animal behaviors indicative of learning.

Neurotransmitters Related to Cognition and Behavior

Neurotransmitters discussed repeatedly in the pages that follow are glutamate, dopamine, and acetylcholine. Glutamate is the most common excitatory neurotransmitter, active throughout the central nervous system, and is closely associated with learning and cognition. Glutamatergic neurons regulate a variety of other neurotransmitters in the brain, for example acetylcholine and dopamine. Acetylcholine is released by neurons throughout the central nervous system, can have either excitatory or inhibitory functions, and is also associated with learning and cognition. Dopamine is a neurotransmitter in the monoamine family; it has both excitatory and inhibitory functions and is linked to motor behavior and reward. It is released by dopamine neurons that originate in lower brain centers, specifically in the ventral tegmental area, and travel to the nucleus accumbens (also known as the ventral striatum), which is one of the most dopamine-rich regions of the brain. In these regions dopamine tends to be an excitatory transmitter (Guyton, 1991). Destruction of dopamine-secreting neurons is thought to be the cause of Parkinson's disease. Neurotransmitters are associated with receptors that are uniquely activated by the specific transmitter, and receptor activity is associated with gene expression. Changes in gene expression reflect changes in receptor activity (such as synthesis of different proteins) that may be linked to

neurotoxicant exposures, micronutrient deficiencies, or social-environmental deprivations.

Interpretive Issues

Effect Sizes

In discussing effect sizes (estimates of the strength of a relationship or the magnitude of the impact of a treatment), we will follow the conventions proposed by Cohen (1988) for small, medium, and large effect sizes.[1] We mention effect sizes sparingly, because of our interdisciplinary and multilevel approach. First, as we noted previously, the field of developmental neurotoxicology has been more attentive to controlling for variables from other disciplines than the other disciplines have been to controlling for neurotoxicants. Second, as we point out in the pages that follow, variables identified as confounders, such as micronutrient deficiencies or low maternal stimulation in the home, may themselves be indicators of neurotoxicant exposure—due to depletion by the neurotoxicant and effects of lead on mothers' behavior, respectively. Statistical adjustment of those confounders actually adjusts for the independent variable, the neurotoxicant under investigation. Finally, although policymakers might be persuaded to ignore small effect sizes in developing child and family policy, the practical consequences of doing so would be profound. Consider, for example, the effect on the population of a drop in IQ of only 5 points—less than the 7.4-point drop as lead in children's blood increases from 0 to 10 micrograms per deciliter (μg/dL; Canfield, Henderson et al., 2003), which we discuss below. Assuming that the standard deviation remained the same and the number of children in the population was 100 million, the number of children with IQs below 70 would increase from 2.2 million to 4.75 million (Bellinger & Matthews, 1998; see Fig. 2).

Similar evidence can be advanced for large population increases in obesity related to very small increases in average population weight (Bellinger, 2004c). Thus, ignoring such effect sizes is ill advised. More importantly, failure to reduce or eliminate small effect sizes in the lives of children exposed to multiple risks across the three domains of our model may well result in a cascade of negative outcomes due to the cumulative impact of risks. To date, no research has examined the impact of all three domains of our model on child cognition and behavior.

Effect Modifiers

Appropriate consideration of effect modifiers (also called moderators) as well as confounders is necessary for understanding which populations are likely to be most affected by neurotoxicants and thus for developing RfDs that will be adequately protective of the most vulnerable children. It should be noted that a given factor may be both a confounder and a moderator. Controlling for the confounder only eliminates the confounder's main effect, which obscures, either by concealing or exaggerating, the relation between the neurotoxicant and the outcome. For example, increases in methylmercury via maternal fish consumption, which negatively impact infant neurodevelopment, are concealed by neurodevelopment-promoting omega-3 fatty acids in the same fish. However, if the factor also interacts with the neurotoxicant—for example, increasing the effects of the neurotoxicant when the nutrient is deficient—such effects will be unknown without testing for moderating effects. Accurate identification of moderating effects in epidemiologic studies requires approximately 20 times as many human participants as animals required for the same level of statistical power in laboratory experiments (see discussion in McClelland & Judd, 1993). Thus, in the pages that follow, we discuss animal research that suggests potential moderating effects that still need to be researched with large-sample epidemiologic studies but that may be helpful for practitioners to consider.

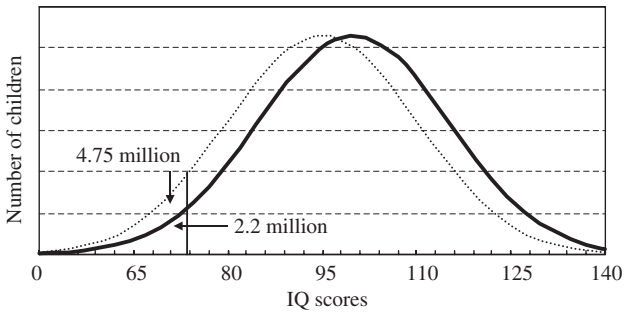

Fig. 2. Effect of 5-point drop in IQ on the number of children with IQs below 70 (an increase from 2.2 million children to 4.75 million children).

LEAD

Lead Epidemiology

Introduction

Lead is a natural constituent of the earth's crust. Because it is a stable element, the amount of lead on earth will remain essentially the same. About 6,000 years ago, humans began to mine it, altering its geologically determined distribution and dispersing it into the wider environment. Approximately half of the 300 million metric tons of lead produced over the course of human history persists in the form of environmental contamination (National Research Council [NRC], 1993). By measuring the amounts of lead in isolated undisturbed media, such as Arctic ice cores, tree rings, and marine sediments, geochemists can look back in time and quantify the time course of lead's long-term transport and deposition. Even in remote areas, present-day lead concentrations exceed preindustrial (or "natural") background levels by two orders of magnitude (Nriagu & Pacyna, 1988). Sharp increases in deposition occurred in the 18th

[1]For *r* and *partial r*, small, medium, and large effect sizes are .10, .30, and .50; for R^2, .02, .13, and .26; for *d* (the difference between means divided by the standard deviation), .20, .50, and .80.

century and in the early 20th century. The first corresponded to the Industrial Revolution, when the malleability and low melting point of lead made it useful in many new production processes. The second corresponded to the introduction of an organic form of lead, tetraethyl, as a gasoline additive. Other major lead-containing products included paint pigments and piping. (The Latin word for lead, *plumbum*, provides the root for "plumbing.") If one set out to maximize population exposures to a known neurotoxicant, it would be difficult to improve on the strategy of lining the walls of residences with it and insuring that it is emitted, submicron-sized and highly breathable, by a mobile source (the automobile) with a virtually unlimited reach.

It is not surprising that, as a result of the dispersal of so much lead into the environment, the levels of lead in present-day humans greatly exceed the levels measured in human bones dating from the premetallurgical era (C.C. Patterson, 1980). Flegal and Smith (1992) estimated that the natural blood-lead level of humans was 0.016 μg/dL. In light of this, it is noteworthy that the Second National Health and Nutrition Examination Survey (NHANES II), a nationally representative survey, revealed that the mean blood-lead level of U.S. preschool children from 1976 to 1980 was 15 μg/dL, approximately 1,000 times higher than the estimated natural blood-lead level. Among poor minority children living in large central cities, the mean level during this period was 23 μg/dL and for 19% of these poor, urban, minority children it exceeded 30 (Mahaffey, Annest, Roberts, & Murphy, 1982). To place these levels in perspective, 100 to 150 μg/dL is a potentially fatal dose for a child. Brain hemorrhage and edema can appear in children with levels of 80 to 100 μg/dL. Thus, in the 1970s, the average child had about one tenth the potentially fatal level and one sixth the level associated with clinically apparent neurological disease. The average level was much closer to the levels at which gross neurotoxicity is apparent than it was to the natural level, and provided a disturbingly small margin of safety.

Fortunately, population exposures to lead have declined dramatically in recent decades, a result that should be regarded as one of the great public health triumphs of the late 20th century. In the NHANES 1999–2002 survey, the mean blood-lead level of U.S. preschool children was 1.9 μg/dL (Centers for Disease Control and Prevention [CDC], 2005), with only 1.6% of children having a level above 10 μg/dL, compared with 88% in NHANES II (P.A. Meyer et al., 2003). Despite this reduction, 310,000 children still have a blood-lead level greater than 10 μg/dL, and ethnic and socioeconomic disparities in the prevalence persist. It is important to note, too, that these levels are still markedly elevated from an evolutionary perspective, as 10 μg/dL is 600 times the natural level, and the current mean level for U.S. preschool children is 100 times the natural level. Therefore, even with the tremendous progress made in recent decades in reducing children's exposures to lead, "average" cannot be interpreted as "physiologically normal," and the margin of safety remains relatively small.

The reasons for this 90% decline in mean level over the past three decades are multifactorial, but among the most important are the federal limit placed in 1977 on the allowable lead content of paint (0.06% by weight) and the phase-down and eventual elimination of lead from gasoline, which was begun in the early 1970s and completed in the mid 1990s. Nevertheless, significant ethnic and socioeconomic disparities remain in the exposure of children to lead. Among high-income non-Hispanic white children in NHANES III, Phase 1 (1988–1991), the percentage with blood-lead levels over 10 was 4%. Among non-Hispanic black children living in large central cities, it was 37%. Among all low-income children, it was 16% (Brody et al., 1994). Children adopted from other countries are another group at risk in the United States. In one survey, 18% of children from China had a blood-lead level greater than 10 μg/dL when tested within a month of arrival (CDC, 2000).

How Much Lead Is Too Much?

The answer to this question, "How much lead is too much?" for children has changed dramatically over the past 40 years. Pediatric textbooks from the 1960s identify a blood-lead level of 60 μg/dL as a "bright line," separating the normal range from the level at which a child is, from a medical standpoint, "poisoned." Consistent with a medical model, lead poisoning was conceptualized dichotomously, with little consideration given to the possibility of a continuum of adverse effects extending downward from the cut-off used to define clinical poisoning (Lin-Fu, 1972). Lead poisoning is a potentially fatal disease, with the risk of mortality increasing when blood-lead level exceeds 100 μg/dL. The early signs of lead poisoning can include hyperirritability, anorexia, behavioral changes, vomiting, abdominal pain, and constipation (Mellins & Jenkins, 1955). In more severe cases, lead poisoning may result in brain pathology (called encephalopathy), characterized by massive cerebral edema (accumulation of fluid) and vasculopathy (disorders of blood vessels) and increased intra-cranial pressure (Pentschew, 1965). Clinical signs can include the sudden onset of persistent vomiting, ataxia (loss of coordination), impaired consciousness, coma, and seizures. Before the introduction of chelating agents—drugs that promote lead diuresis (clearance of lead by the kidneys and excretion in the urine)—65% of children with severe lead poisoning died (Chisolm & Barltrop, 1979). Children who survived were frequently left with mental retardation, seizure disorders, hyperactivity, cerebral palsy, and optic atrophy (degeneration of optic nerve fibers; Chisolm & Harrison, 1956). In their case series of 425 lead-poisoned children, Perlstein and Attala (1966) reported that 39% suffered neurologic consequences, although in children whose disease progressed to an encephalopathy, the figure was 82%.

It was widely thought that the incidence of enduring neurological effects was relatively low among lead-exposed children who did not develop an encephalopathy. With the publication of a clinical case series by Byers and Lord (1943), a landmark in

the field, this view began to change. The children in this series presented with symptomatic lead poisoning, which, in many cases, did not progress to an encephalopathy; yet 19 of the 20 children were unable to make adequate progress in school due to behavioral problems such as poor attention and impulse control, aggression, and explosive temper. This was the first major clue that lead poisoning might better be described as a continuum rather than as a dichotomy. In a harbinger of the acrimonious debate this issue was to incite, the Lead Industries Association threatened Byers with a million-dollar lawsuit (Needleman, 1992).

In this era, in which debate focuses on the neurotoxicity of blood-lead levels in the single digits, it might seem surprising that the controversies about lead in the 1960s and 1970s focused on children with such high blood-lead levels, levels approaching half of the potentially fatal dose. This is, in part, a reflection of the extremely high prevalence of elevated blood-lead levels in U.S. children during this era. It was only in the 1960s that the first lead-screening programs were organized in large cities such as Chicago, Baltimore, Philadelphia, New York, and Boston, and it was not unusual to find that the mean blood-lead level of at-risk children approached 40 μg/dL (Lin-Fu, 1972). For example, among low-income 7- to 60-month-olds in Baltimore attending well-child clinics and outpatient departments in the 1950s, 90% had blood-lead levels above 30 μg/dL and 26% had levels above 60 μg/dL (J.E. Bradley, Powell, Niermann, McGrady, & Kaplan, 1956). Such "normal" levels were apparently not thought to pose a risk to children's well-being.

In the 1970s, however, some prescient clinicians did begin to question whether lead exposures that were not sufficient to produce signs of clinical poisoning might, nevertheless, impair children's neurological functioning, albeit with manifestations that were less severe than mental retardation or seizure disorders. This idea seems reasonable in retrospect but it was quite controversial at the time. Case-control studies were undertaken in which the lead-exposure histories of control children were compared to the lead-exposure histories of children who had been diagnosed with conditions such as mental retardation, learning disability, and hyperactivity (e.g., Beattie et al., 1975; David, Clark, & Voeller, 1972; David, Hoffman, Sverd, & Clark, 1977; David, McGann, Hoffman, Sverd, & Clark, 1976; Moore, Meredith, & Goldberg, 1977; Pihl & Parkes, 1977; Youroukos, Lyberatos, Philippidou, Gardikas, & Tsomi, 1978). Many of these studies did, in fact, find increased risks of elevated lead levels among children carrying such diagnoses, particularly when no event or condition in a child's medical record seemed to be a plausible explanation for the disorder. These studies suffered from a variety of methodological deficiencies common to case-control studies, however. For instance, with such a design, one cannot exclude the possibility that the elevated blood lead of a child with a diagnosis is the result of behaviors, such as increased motor activity or abnormal hand-to-mouth activity, that are associated with the disorder—thus reversing the direction of the causal relationship. The inferences permitted by such studies are also limited by the difficulty of ascertaining the lead-exposure history of school-aged children. The half-life of lead in blood (the time required for half of the lead in blood to be eliminated) is only approximately 30 days (Rabinowitz, Wetherill, & Kopple, 1976), so a blood-lead level measured at school age provides little information about the child's body-lead burden in the early postnatal years—which, from a toxicological perspective, might be the critical exposure window.

Many cross-sectional studies, in which children were identified and classified based on their current blood-lead levels rather than on diagnoses, were also initiated in the 1970s. These studies sought to determine whether children with higher blood-lead levels performed worse on neuropsychological tests than did children with lower blood-lead levels (e.g., de la Burde & Choate, 1972, 1975; Hebel, Kinch, & Armstrong, 1976; Kirkconnell & Hicks, 1980; Kotok, 1972; Kotok, Kotok, & Heriot, 1977; Landrigan, Baker et al., 1976; Landrigan, Baloh et al., 1975; Lansdown et al., 1974; McNeil, Ptasnik, & Croft, 1975; Perino & Ernhart, 1974; Pueschel, Kopito, & Schwachman, 1972; Ratcliffe, 1977; Rummo, Routh, Rummo, & Brown, 1979). These studies, too, were limited by the challenges of reconstructing exposure history based on a blood-lead level determined at school or even preschool age as well as by residual (uncontrolled) confounders such as parent intelligence, social class, quality of the home environment, and nutrition. In addition, in some studies the blood-lead levels of the controls were greatly elevated by today's standards. In one study, for instance, the mean of the controls was 38 μg/dL (Kotok, 1972), permitting estimates of only relative rather than absolute neurotoxicities. Despite the limitations of these studies and the resulting constraints on the inferences they permitted, the U.S. Center for Disease Control (CDC; later, Centers for Disease Control and Prevention) revised the lead-screening guideline in 1975, citing 30 μg/dL as the blood-lead level in a young child (under 6 years of age) that would trigger additional investigation and possible treatment (CDC, 1975).

Another landmark paper in this literature was published in the late 1970s by Needleman et al. (1979). A major innovation of this study was the use of shed deciduous teeth (baby teeth) to estimate a child's chronic exposure to lead. Like calcium, lead is a bone-seeking divalent cation (an ion carrying two positive electrical charges). More than 90% of an adult's and about 65% of a child's total body-lead burden is stored in bone, where it is incorporated into the hydroxyapatite crystal structure (the crystal lattice structure of bones), with a half-life as long as 30 years. A tooth is the most readily accessible mineralized tissue, so investigators have relied on the lead level in a child's shed tooth as an integrated index of a child's exposure to lead from the time the tooth bud began to develop. This index therefore averages a child's exposure over a much longer period than does a current blood-lead level.

Needleman and colleagues (Needleman et al., 1979) measured the lead concentration in the specific region of the tooth,

the circumpulpal layer of the dentine, that is in closest contact with the tooth's blood supply. They collected shed teeth from more than 2,000 first and second graders in two working-class suburbs of Boston. Children who had been identified as having been treated for lead poisoning were excluded. As a result, none of the children in the study sample had come to medical attention because of an elevated lead level. Teachers rated the classroom behaviors of the children. In addition, 158 of the children, selected from those with the highest and those with the lowest dentine-lead levels, underwent neuropsychological examinations. Controlling for potential confounding factors, children in the high-exposure group achieved significantly worse scores on several tests, including IQ, auditory processing, and reaction time. In the larger group of more than 2,000 children, in which children were classified into 6 groups based on dentine-lead level, increases across lead levels were noted in the frequencies of several undesirable behaviors, including distractibility, impulsivity, disorganization, and inability to follow directions. The analyses of the teacher ratings on this larger group of children could not be adjusted for potential confounding. This study provided the best evidence, prior to 1980, for the existence of "silent" or asymptomatic lead poisoning among children whose lead levels did not reach the level considered to be of clinical concern. Additional follow-up evaluations of portions of this cohort showed that these deficits did not disappear over time and were associated with impairments of substantial importance for children's quality of life. In particular, as adolescents, children with higher tooth-lead levels had significantly higher rates of reading disability, significantly higher rates of failure to complete high school with their agemates, and a variety of deficits in attention and executive functions (Bellinger, Hu, Titlebaum, & Needleman, 1994; Bellinger, Needleman, Bromfield, & Mintz, 1984; Needleman, Schell, Bellinger, Leviton, & Allred, 1990).

With the publication of the Needleman et al. (1979) study, controversy erupted about the validity of the concept of "low-level lead poisoning." The findings suggested that many children in the general population were being harmed by lead exposure at levels that did not produce classical medical signs of lead poisoning. This put the spotlight on an important difference between the clinical and the public health perspectives (Bellinger, 2004c). On the one hand, clinicians could offer little in the way of medical intervention to the child who presented without signs or symptoms of physical illness related to lead, and tended to ask questions such as, "How sick could a child be in the absence of such signs and symptoms?" On the other hand, the findings identified a potentially serious health problem at the population level. Not surprisingly, legislators did not rush to expend large amounts of money on a "silent" disease, the solution to which would require expensive remedial and preventive measures. It was therefore important to determine whether the findings of Needleman et al. (1979) were credible, and a large number of studies were begun in an effort to determine this. Because the implications were not specific to the United States, many of these efforts were undertaken in other developed countries, although over time they have been extended to developing countries as well. Like Byers before him, Needleman became the target of the lead industry, eventually being accused of falsifying his data by two scientists serving as expert witnesses for the defense in a lawsuit brought by the Department of Justice. He was exonerated (Palca, 1992). For the perspectives of the scientists who brought these charges, the interested reader is referred to Ernhart, Scarr, and Geneson (1993).

Many cross-sectional or retrospective cohort studies were undertaken in the 1980s by researchers in Great Britain (Harvey, Hamlin, Kumar, & Delves, 1984; M. Smith, Delves, Lansdown, Clayton, & Graham, 1983; Yule, Lansdown, Millar, & Urbanowicz, 1981), Germany (Winneke, Hrdina, & Brockhaus, 1982; Winneke et al., 1983), Denmark (Hansen, Trillingsgaard, Beese, Lyngbye, & Grandjean, 1989), Italy (Bergomi et al., 1989), New Zealand (Fergusson, Horwood, & Lynskey, 1997; Silva, Hughes, Williams, & Faed, 1988), Scotland (Fulton et al., 1987), Greece (Hatzakis et al., 1989), a group of eight European countries (Winneke, Brockhaus, Ewers, Krämer, & Neuf, 1990), and the United States (Hawk et al., 1986). While the findings, from study to study, were mixed to some extent, meta-analyses of the major studies demonstrated that, overall, the evidence was consistent with an adverse effect of blood- or tooth-lead levels in the so-called subclinical range—that is, levels generally less than 30 μg/dL (International Programme on Chemical Safety, 1995; Needleman & Gatsonis, 1990; Pocock, Smith, & Baghurst, 1994; Schwartz, 1994). These meta-analyses all reached more or less similar conclusions, namely that children's IQ scores declined by 1 to 3 points with an increase in blood-lead level from 10 to 20 μg/dL. Based largely on the data of such studies, the U.S. CDC reduced the lead-screening guideline to 25 μg/dL in 1985 (CDC, 1985).

Like the earlier generation of studies, the cross-sectional and retrospective cohort studies conducted in response to the study of Needleman et al. (1979) also had serious limitations. Because relatively few children included in these studies had blood-lead levels below 10 μg/dL, it was difficult to ascertain the shape and quantitative characteristics of the dose–effect relationship in this range and, in particular, to determine whether or not a threshold existed. Even more importantly, these studies, like those that preceded them, could not establish, with certainty, the direction of the underlying causal relationship. When a child's blood-lead level and neurodevelopment are measured at the same age, as in a cross-sectional study, and an inverse association is observed (i.e., higher blood lead, lower performance), one cannot be certain which came first, higher lead exposure or poorer neurodevelopment. It could be that a low-performing child engages in behaviors, such as increased hand-to-mouth activity, that bring him or her into closer contact with potential lead sources. In this scenario, the higher blood-lead level would be the result of the neurodevelopmental impairment rather than

the cause of it. Using tooth-lead level as the exposure biomarker addresses this problem to some extent but not completely, as a higher tooth-lead level might still be the result of the past behaviors of a child who is already developmentally delayed.

Even if one assumes that the inverse association reflects a true effect of lead on neurodevelopment, the data cannot support strong inferences about the blood-lead level at which the damage underlying the reduced performance occurred. The primary reason is that, as mentioned previously, a school-age blood-lead level, under most circumstances, conveys relatively little information about a child's lead-exposure history. Among children living in deteriorated inner-city settings (K.N. Dietrich, Ris, Succop, Berger, & Bornschein, 2001) or near a point source of lead, such as a smelter (Baghurst, Tong, Sawyer, Burns, & McMichael, 1999), blood-lead level begins to rise in the second half of the first year of life. As children become ambulatory, they come into close contact with important pathways of lead exposure, such as house dust and soil. Blood-lead level often peaks around age 2 to 3, perhaps corresponding to the period of greatest oral exploration of the environment. Blood lead then slowly declines over succeeding years. Thus if, in a hypothetical cross-sectional study of 8-year-olds, one were to find that children with blood-lead levels of about 10 μg/dL perform significantly worse than children with levels less than 5 μg/dL, one cannot conclude that a level of 10 produced the damage. The children's levels might have been considerably higher at age 2. Concluding, based on this hypothetical example, that children's levels should be maintained below 10 throughout childhood would therefore result in an excessively conservative exposure standard. With respect to the usefulness of studies that relied on tooth-lead level as the exposure biomarker, it is not possible to translate a tooth-lead level into a blood-lead level. Therefore, while studies using tooth lead as the exposure biomarker were useful in providing data on whether an inverse association holds between exposure and performance, they could not provide the type of information needed in order to set exposure standards. Because the techniques for performing tooth-lead analysis are expensive and not widely available, tooth-lead level will never be the basis for lead screening or, thus, for exposure standards.

To address these and other limitations of cross-sectional and retrospective cohort designs, investigators initiated prospective cohort studies in seven cities in four countries: Boston, Cincinnati, Cleveland, Kosovo (Yugoslavia), Mexico City, Port Pirie (South Australia), and Sydney. In these studies, children were enrolled at or prior to birth, providing the opportunity to compile lead-exposure histories that began prior to birth and thus prior to any assessments of neurodevelopment. By conducting serial assessments of lead exposure and neurodevelopment as children grew, investigators could better assess the temporal relationships between exposure and outcome, and thus answer the question, "Does increased exposure precede or result from neurodevelopmental deficits?" Some cohorts were followed into late adolescence (Ris, Dietrich, Succop, Berger, & Bornschein, 2004) and others to early-to-mid adolescence (Bellinger, Stiles, & Needleman, 1992; Tong, Baghurst, McMichael, Sawyer, & Mudge, 1996). An unusual degree of coordination of the different studies developed as a result of several early meetings in which common issues of concern such as ages at assessment, specific assessment instruments, covariate measurement, exposure-biomarker collection and analysis, and statistical modeling were discussed. Strictly speaking, none of the studies can be viewed as a direct replication of any other, but such coordination did facilitate meta-analyses (Pocock et al., 1994) and pooled analyses (Lanphear et al., 2005) of these data. The study settings, cohort demographic characteristics, and primary lead-exposure pathways differed, in some cases, substantially across studies. Some cohorts consisted largely of disadvantaged inner-city minority children, others of middle- and upper-middle-class suburban children, and others of children living in proximity to a lead smelter. An important benefit of applying reasonably similar assessment methods in a diversity of study settings is that the nature and severity of confounding of lead exposure by other risk factors for lower neurodevelopment likely differed across studies as well. Therefore, if a consistent pattern of association between increased lead exposure and poorer neurodevelopment were observed across studies, one could feel more confident drawing the inference that residual confounding is not likely to account for the entirety of the association.

As in all areas of epidemiological research, the findings of this set of prospective studies were not entirely consistent with one another. Nevertheless, studies in several cities consistently observed, after adjustment for potential confounding factors, inverse relationships between children's blood-lead levels and their scores on IQ and other standardized cognitive tests: Boston (Bellinger et al., 1984, 1991, 1992; Bellinger, Leviton, Needleman, Waternaux, & Rabinowitz, 1986; Bellinger, Leviton, Waternaux, Needleman, & Rabinowitz, 1987), Port Pirie (Baghurst et al., 1992; McMichael et al., 1988; Tong et al., 1996), Kosovo (Wasserman et al., 1994, 1997; Wasserman, Liu et al., 2000; Wasserman, Musabegovic et al., 2000), Cincinnati (K.N. Dietrich et al., 1987; K.N. Dietrich, Berger, Succop, Hammond, & Bornschein 1993; K.N. Dietrich, Succop, Berger, Hammond, & Bornschein, 1991; Ris et al., 2004), and Mexico City (Rothenberg et al., 1989). The Cleveland (Ernhart, Morrow-Tlucak, Marler, & Wolf, 1987) and Sydney (Cooney, Bell, McBride, & Carter, 1989a, 1989b) studies were generally interpreted as failing to observe consistent associations between children's lead exposures and their outcomes.

Although it is known that adverse outcomes of pregnancy, such as low birth weight, mental retardation, and seizure disorders, can result from high maternal exposures to lead during pregnancy (Bellinger, 1994), these prospective cohort studies provided mixed findings with regard to the neurodevelopmental correlates of prenatal exposures that were in the upper range of community levels (i.e., under 30 μg/dL). In some studies, such exposures were associated with developmental delays from

which children generally appeared to recover by preschool age (Bellinger et al., 1987, 1991; K.N. Dietrich et al., 1987, 1991). In the Cincinnati and Kosovo studies, however, some associations were found in outcomes measured as late as 16 years of age (K.N. Dietrich et al., 2001). In the Port Pirie and Sydney studies, prenatal lead levels were, for the most part, not associated with neurodevelopment. The most consistent finding of this set of studies was that children's neurodevelopment was most closely associated with postnatal blood-lead levels (Pocock et al., 1994). The specific age of greatest vulnerability has eluded identification, however. Some studies suggested that it was blood-lead levels measured in the period of 1 to 3 years that were most predictive of long-term outcomes (Bellinger et al., 1992); other studies suggested that recent or concurrent blood-lead levels were most predictive (K.N. Dietrich, Berger, Succop, Hammond et al., 1993; Tong et al., 1996); yet others found little evidence for age-dependent variation in susceptibility (Wasserman, Liu et al., 2000).

Although most of the reports on these studies have focused on IQ as the neurodevelopmental outcome of interest, other outcomes were assessed. Variations in susceptibility across outcome domains have been noted, although the specific pattern has differed somewhat. The most consistent aspect of the pattern is a relative weakness in visual–motor skills among more highly exposed children (e.g., Baghurst et al., 1995; Bellinger et al., 1991; K.N. Dietrich, Berger, & Succop, 1993; Wasserman, Musabegovic et al., 2000), although in other cohorts deficits were also observed in the verbal skills of more highly exposed children (Bellinger et al., 1992; Tong et al., 1996). Several studies also suggested that children's executive functions are vulnerable to lead (Bellinger, Hu et al., 1994; Canfield, Kreher, Cornwell, & Henderson, 2003; Stiles & Bellinger, 1993). One possible explanation for the inconsistencies in the data on this issue is that the domain of function most affected is likely to depend on features of the exposure profile, such as timing, dose, and how chronic or acute the exposure is (Bellinger, 1995). Unfortunately, the exposure data available in most studies is not sufficiently detailed to enable investigators to establish linkages between aspects of the profile and the specific functional deficits. Perhaps it is because an IQ score averages performance across multiple domains that the findings across studies are most consistent for this endpoint.

The cognitive deficits associated with increased lead exposure are, at least, persistent and, perhaps, permanent. It appears, moreover, that the use of drugs that enhance lead excretion (chelation) does not improve the long-term outcomes of lead-poisoned children. The strongest evidence is provided by the Treatment of Lead-Poisoned Children trial, in which 780 children with pretreatment blood-lead levels of 20 to 44 μg/dL were randomly assigned to receive either a placebo or the lead-chelating drug, succimer. At neither 36 months posttreatment nor at 7 years of age were significant differences in cognition or behavior seen between the succimer and placebo groups (K.N. Dietrich et al., 2004; Rogan et al., 2001). Current blood-lead level was significantly associated with cognitive performance at baseline, at 36 months after treatment, and at 7 years of age, however. Moreover, regression coefficients were similar to those estimated in observational studies (i.e., a roughly 3-point IQ decline per 10 μg/dL increase in blood lead).

Although most studies of lead neurotoxicity have focused on cognitive function as the critical health endpoint, concern over possible behavioral pathologies associated with lead exposure have persisted since the early observations of Byers and Lord (1943) and Needleman et al. (1979). Several studies replicated the latter study's findings that higher blood-lead levels are associated with distractibility, overactivity, poor organizational skills, and other behavior problems (Bellinger, Leviton, Allred, & Rabinowitz, 1994; Burns, Baghurst, Sawyer, McMichael, & Tong, 1999; Hatzakis et al., 1989; Wasserman, Staghezza-Jaramillo, Shrout, Popovac, & Graziano, 1998; Yule, Urbanowicz, Lansdown, & Millar, 1984). Case-control studies have not tended to provide strong evidence that lead contributes to attention-deficit disorder (e.g., Milar, Schroeder, Mushak, & Boone, 1981; Gittelman & Eskenazi, 1983), although the retrospective characterization of exposure has been weak in such studies.

Recently, attention has been given to the possible contributions of lead exposure to antisocial behavior. In the Philadelphia cohort of the Collaborative Perinatal Study, a history of childhood lead poisoning was one of the strongest predictors, in males, of adult criminality (Denno, 1990). Needleman, Reiss, Tobin, Biesecker, and Greenhouse (1996) found that among male adolescents, higher bone-lead levels were associated with more self-reported delinquent acts. Moreover, both parents and teachers more frequently assigned scores in the clinical range on the attention, aggression, and delinquent-behavior scales of the Child Behavior Checklist to children with higher bone-lead levels. In the Cincinnati prospective study cohort, the frequencies of self-reported delinquent and antisocial behaviors were significantly associated with both prenatal and early postnatal blood-lead levels (K.N. Dietrich et al., 2001). Needleman, MacFarland, Ness, Feinberg, and Tobin (2002) found that adjudicated delinquents had significantly higher bone-lead levels than did controls. Two other studies provide evidence consistent with this hypothesis, although the inferences that can be drawn are, in both cases, limited by the ecologic designs employed (Nevin, 2000; Stretesky & Lynch, 2001).

Based largely on the findings of the prospective cohort studies, in 1991 the U.S. CDC reduced its screening guideline to 10 μg/dL (CDC, 1991). It emphasized, however, that this figure should not be viewed as a threshold, such that levels below 10 μg/dL are "safe" while levels above 10 are not. It was proposed simply as a risk-guidance and management number. Because so few of the children recruited into the prospective studies had blood-lead levels that were sufficiently low that they could serve as a suitable reference group, it was difficult to address the

question of whether levels near 10 μg/dL pose a neurodevelopmental risk. There were some clues, however. In the Boston prospective study, in which children's blood-lead levels at age 2 years were significantly associated with their IQ and academic achievement scores at age 10 years (e.g., Bellinger et al., 1992), the mean blood-lead level was 7 μg/dL at that time and 90% of the children had blood-lead levels below 13. Furthermore, many did not have a measured blood-lead level greater than 10 μg/dL over the course of their participation in the study. Statistical analyses of the relationship utilizing nonparametric smoothing techniques did not identify any clear point of inflection.

As population exposures to lead have continued to decline, it has become possible to address the threshold issue more rigorously. In the Canfield, Henderson et al. (2003) study, the blood-lead levels of 101 of the 172 children never exceeded 10 μg/dL on any of the 7 occasions on which it was measured between 6 and 60 months of age. In this subgroup of children, Canfield, Henderson et al. still found significant covariate-adjusted associations between blood-lead levels and IQ scores at both 3 and 5 years of age. Surprisingly, the slope of the inverse relationship appeared to be steeper in this group, whose levels remained below 10 μg/dL, than it was in the complete study sample. Reanalysis of the Boston prospective study identified the same pattern (Bellinger & Needleman, 2003). This same pattern was evident, as well, when the data from six prospective studies (Boston, Cincinnati, Cleveland, Kosovo, Mexico City, Rochester) were pooled (Lanphear et al, 2005). It is not clear, however, whether the same functional form describes the dose–effect relationship for lead's apparent effects on noncognitive outcomes, such as behavior disorders. Moreover, no compelling mechanism has been identified to explain why the slope of the dose–effect relationship might be steeper at lower than at higher levels. Even if this turns out not to be the case, and the association is best described as linear, these data suggest, at least, that 10 μg/dL has no special biological significance. Whether these data warrant another reduction in the CDC screening guideline is currently being debated (S.M. Bernard, 2003).

Although the overall thrust of the literature on lead and child neurodevelopment is sufficiently consistent and persuasive to motivate numerous regulatory reforms, many gaps and uncertainties remain in our understanding of lead neurotoxicology. Several of these have been mentioned in passing above. With regard to the dose–effect relationships, the concentration of lead at the critical target organ, the brain, cannot be measured directly, forcing investigators to rely on imperfect biomarkers such as blood- or bone-lead levels. These biomarkers are separated from brain lead by several toxicokinetic steps, creating the possibility of exposure misclassification (e.g., assuming that the child with the higher blood-lead level has higher levels of brain-lead). It is known that, in animal models, brain-lead level tends to decline less rapidly than blood-lead level following chelation or cessation of exposure (Cremin, Luck, Laughlin, & Smith, 1999; Strangle, Strawderman, Smith, Kuypers, & Strupp, 2004).

Our understanding of the critical windows of vulnerability is limited by the types of exposure scenarios experienced by children. Children are typically not exposed to lead only during a specific, limited period, before and after which exposure is essentially absent. Because children's blood-lead levels tend to show some degree of stability over time, the ability to identify the effects associated with exposure at specific ages is limited. In any event, the critical age of exposure is likely to differ for different neurodevelopmental endpoints, as studies with nonhuman primates suggest (Rice, 1996).

An inspection of plots of a lead biomarker and a neurodevelopmental outcome—even partial residual plots (plots of outcomes onto exposures that are adjusted for covariates)—invariably reveals a tremendous degree of scatter about the best-fit line describing the dose–effect relationship. One possible interpretation of this is that children's responses to a given lead dose are highly variable and depend on host characteristics and other features of the larger context in which exposure occurs (Bellinger, 2000). This is certainly the case at high lead doses insofar as some children remain asymptomatic at blood-lead levels measured in children who suffer fatal lead poisoning. The bases of individual differences in susceptibility remain largely unknown, however (Bellinger, 2004b). They could involve toxicokinetic factors (relating to the amount of toxicant that is absorbed and reaches the target organs) and toxicodynamic factors (relating to the impact of the toxicant once it reaches the target organ). The many steps between external dose and the biologically effective dose in the brain provide opportunities for the expression of individual differences in sensitivity. Several genetic polymorphisms (natural variants of a gene) have been shown, or are suspected, to affect susceptibility to lead (including polymorphisms pertaining to apolipoprotein E, amino levulinic acid dehydratase, the vitamin-D receptor, and the HFE protein; Onalaja & Claudio, 2000). Coexposure to other neurotoxicants might modulate susceptibility to lead toxicity, as has been shown in animal studies (Nation, Grover, Bratton, & Salinas, 1990; Newman, Yang, & Magnusson, 2002). Aspects of a child's rearing environment and micronutrient status might also modify vulnerability, as will be discussed later in this monograph.

Finally, the most serious uncertainty with respect to epidemiologic studies of lead neurotoxicity pertains to the inferences drawn regarding causality. All of the studies are, by necessity, observational in design, capitalizing on natural variation in children's exposures to lead. The question must always be asked, "With what degree of confidence can the deficits observed among more highly exposed children be attributed to lead rather than to any of the other risks for poor neurodevelopment with which lead exposure often co-occurs?" Thus, the most contentious issue has often been whether, in a particular study, adequate adjustments have been made for possible confounding. This question can never be settled, as one can always hypothesize unmeasured or poorly measured factors that might explain an association observed between lead and neurodevel-

opmental deficit. As in all areas of epidemiology, it is consistency in findings across studies, and across study samples in which the nature and perhaps even the direction of confounding differ, that provides the strongest basis, albeit still indirect, for the inference that the data are consistent with a causal relationship (Bellinger, 2004a).

Discussions about causality might not be able to advance beyond the stage of argument were it not for the availability of a very large literature on lead neurotoxicity in animal models. In such models, many of the uncertainties identified above can be addressed. Exposure of animals to known amounts of lead can be under the investigator's control. Brain-lead levels, rather than biomarkers that are toxicokinetically distant, can be measured. Life histories can be "programmed" to investigate, in a rigorous manner, the influence on lead neurotoxicity of coexposures to other neurotoxicants, different rearing conditions, and genetic polymorphisms. Perhaps most importantly, animals can be randomly assigned to exposure conditions, eliminating the concern about residual confounding by factors such as social class. At the same time, it is important to acknowledge that because of the relatively small sample sizes used in animal studies, the doses used are often considerably higher than those of interest in epidemiological studies of community exposures. Moreover, species-specificity in biologically effective lead doses, behaviors affected, and behaviors that can even be tested (e.g., tests of learning in primates can use procedures closer to those used with humans than can tests of learning in rats) impose important limitations on the inferences about human neurotoxicity that can be drawn from animal studies. The following section identifies the ways in which this animal literature enriches and extends our understanding of lead neurotoxicity.

Lead Neurotoxicity

Information relating to possible adverse effects associated with lead contamination is available from whole-animal (in vivo) experimental studies as well as from molecular (in vitro) examination of the various processes that contribute to the overall risk profile. Scientific appreciation of the potential health threats imposed by toxicant exposure during early development or adulthood benefits from systematic, well-controlled in vivo and in vitro investigations of neurobiological determinants of lead-induced dysfunction.

Cognition and Associative (Learning) Processes

As noted in the preceding section, arguments favoring strict governmental standards and the enforcement of progressive-abatement programs gain strength from studies showing that lead induces a broad range of cognitive disturbance in humans. Animal studies that confirm lead-associated learning and memory deficits accent concerns over the deleterious impact of developmental lead exposure on behavioral plasticity (change). Learning and memory deficits may take several forms, such as reduced capacity to respond to changing or novel environments and selective failure to make necessary adjustments to shifting reward or punishment conditions. Regardless of the form, when learning is impaired, survival is endangered.

The bulk of information relating to the effects of lead exposure on associative conditioning processes (learning) has come from operant studies employing a variety of reward or punishment schedules. Many of the early studies included fixed-interval training schedules in which an animal receives a reward for the first criterion response that occurs after a set amount of time has passed. The general pattern for rodents and nonhuman primates with respect to the distribution of lever presses for food reward in investigations of neonatal or postweaning lead exposure has been one of increased overall response rate at relatively low levels of lead exposure and reduced overall rate at higher lead levels (Cory-Slechta & Pokora, 1991; Cory-Slechta, Weiss, & Cox, 1985; Rice, 1988). Parallel findings have been reported when lead exposure occurs via drinking water in adult male rats (Nation, Bourgeois, & Clark, 1983). Elsewhere, it has been determined that reduced response rates after high-level lead exposure are the result of learning deficits rather than motoric impairment, because the opposite pattern, increased response rates, are observed on differential-reinforcement-of-low-rates (DRL) schedules of reinforcement (Rice, 1992a). DRL schedules require that the animal not respond for a period of time and then execute a response within a limited time period. Accordingly, disturbances in learning are reflected by the inability to withhold responding—that is, inappropriately high response rates.

More recent work on the behavioral toxicity of lead has attempted to provide direct comparisons to clinical studies that have observed lead-based deficiencies in human cognitive function. To this end, Brockel and Cory-Slechta (1998) designed experiments with rats that measured lead-related changes in impulsivity that were similar to the attentional deficits among adolescents who had been observed earlier by Bellinger, Hu et al. (1994). In the Brockel and Cory-Slechta (1998) study, postweaning lead exposure shortened mean waiting times by 50% on a schedule in which reward was made available only when animals waited to commence responding following a prior reinforcer delivery. It was argued that the inability to exercise impulse control in this operant context was due to attentional deficits analogous to those reported in human studies.

Brockel and Cory-Slechta (1999) completed further systematic inquiry into possible connections between lead contamination and disruption of attention. In this examination of the effects of lead on sustained attention, rats exposed to either 0, 50, or 150 parts per million (ppm) of lead acetate in drinking water from weaning throughout testing as adults were required to respond to a pulsing light (target) and to refrain from responding to a nonpulsing light (distracter). With only a single stimulus being presented at a time, errors of omission (failure to respond

to the target) as well as errors of commission (responding in the presence of the distracter) were recorded. On this task, lead exposure resulted in increased errors of commission when the interstimulus interval between target stimulus presentations was lengthened. These data agree with the findings reported decades before by Needleman et al. (1979), in which lead-exposed children were found to be less able to sustain attention under delay conditions.

Other experimental investigations of lead–learning interactions in rodents and nonhuman primates have explored toxicant-induced impairments in maze learning, spatial discrimination and reversal, delayed alternation, and stimulus control (memory). Although the differential impact of lead-exposure period (prenatal, postnatal, perinatal, adult) has not been adequately characterized in the animal literature, the available evidence supports conclusions from human research (see Cory-Slechta, 2003, for a summary), and therein affirm that the cognitive-intellectual apparatus is a target of lead at virtually any age. Recent advances in neurochemistry and structural biology offer a more complete understanding of precisely how lead burdens may constrain associational processes.

Neurochemical Mechanisms in Lead–Learning Interactions

Toxicology research has profited from selective analyses of lead effects on individual cellular mechanisms and on related morphological changes (Banks, Ferretti, & Shucard, 1997). Of particular interest in this regard is the rapidly expanding literature on the impact of lead exposure on neural-membrane properties and the resulting alterations in neuronal responsiveness.

Glutamate and Long-Term Potentiation (LTP). Glutamate and aspartate are excitatory neurotransmitters in the vertebrate brain. They are released from the presynaptic neuron (the neuron located before the synapse) and diffuse across the synapse to the postsynaptic neuron. The primary effect of these amino acids results from binding to postsynaptic receptor sites known as ionotropic receptors (receptors whose activation results in changes in the neuron's permeability to ions such as sodium, calcium, potassium, and chloride). There are three subtypes of ionotropic glutamate receptors (cf. Guilarte, 1997): (a) N-methyl-D-aspartate (NMDA), (b) quisqualate or AMPA (alpha-amino-3-hydroxy-5-methyl-4-ioxazolepropionic acid), and (c) kainate receptors. Of the three, the NMDA receptor complex is the most directly relevant to issues pertaining to lead and learning impairment.

Activation of the NMDA receptor subtype is believed to be vital to the induction of a phenomenon known as long-term potentiation, or LTP. LTP refers to long-lasting modifications to the synapse that enhance synaptic communication (e.g., necessitating lower levels of stimulation subsequently). LTP is widely studied and is believed to be a complex, cellular model of learning and memory (Malenka & Bear, 2004; Malenka & Nicoll, 1999). It is characterized by an enduring increase in synaptic efficacy following repeated delivery of brief high-frequency stimulation (M.E. Gilbert, Mack, & Lasley, 1996; Lasley, Polan-Curtain, & Armstrong, 1993). Minimal requirements for LTP include elevated release of presynaptic glutamate, selective postsynaptic activation of NMDA receptors, and increased permeability for calcium. Electrophysiological recordings and behavioral studies both reveal that repeated experience (stimulation) results in relatively permanent, and perhaps nonreversible, changes in synaptic plasticity and associative processes (e.g., Clayton, Mesches, Alvarez, Bickford, & Browning, 2002; Collingridge, 1992; Korz & Frey, 2003; Shaw, Commins, & O'Mara, 2003).

The established link between NMDA-receptor activation and learning is important to understanding lead effects on cognition, because lead is a potent inhibitor of NMDA function (Alkondon, Costa, Radhakrishnan, Aronstam, & Albuquerque, 1990; Guilarte & Miceli, 1992; Hashemzadeh-Gargari & Guilarte, 1999; S.J. He, Xiao, Wu, & Ruan, 2004). Much of the work investigating the effects of lead exposure on NMDA-receptor activity has focused on LTP in the hippocampus, partly because this brain region is associated with learning and memory but also because it is considered to be a major site of the action of lead on the central nervous system (Petit, Alfano, & LeBoutillier, 1983). In an early in vitro study, Altmann, Lohmann, and Wiegand (1988) demonstrated that forcing lead (i.e., perfusion) into hippocampal tissue slices briefly diminished the magnitude of excitatory postsynaptic potentials in direct proportion to the amount of lead. In a follow-up in vivo study of their initial investigation, this team of investigators found that lead perfusion impaired LTP in the hippocampus of adult animals (Altmann et al., 1993).

More recent studies of lead effects on NMDA-mediated changes in LTP and learning have concentrated on specific periods of vulnerability that are unique to the formation of new synapses, gene and protein expression, and other molecular changes that may impose limits on the ability of the organism to acquire useful information from the environment (see Nihei & Guilarte, 2001, for a review). It is established that activation of the NMDA receptor subtype mediates the action of glutamate, and thereby learning and memory, because of the permissive role NMDA plays with respect to calcium influx (cf. Loikkanen, Naarala, Vahakangas, & Savolainen, 2003). Fundamental to this process, which is the basis for neuronal communication, distinct genes encode NMDA-receptor properties essential to calcium-channel activity (movement of calcium inside the neuron resulting in neurotransmitter release), and it is now clear that both gene and protein expression of specific NMDA subunits in the hippocampus are reduced by exposure to lead and, as a general rule, the earlier in development that lead exposure occurs the greater the pattern of disruption (Guilarte, 1998; Guilarte & McGlothan, 2003; Nihei, McGlothan, Toscano, & Guilarte, 2001; X. Zhang, Ping, Ruan, & Liu, 2002). Such compromises are persuasive indicators of the neurotoxic effects of lead at a

molecular level and further implicate lead as causal agent in cognitive dysfunction.

Some intriguing recent data point to the reversibility of the molecular deficits induced by developmental lead exposure. Early work demonstrated the link between lead and deficits in spatial learning (Jett, Kuhlmann, & Guilarte, 1997). The possibility that an enriched living environment might ameliorate lead-induced decreases in NMDA subunit gene expression and deficits in spatial learning was investigated by Guilarte, Toscano, McGlothan, and Weaver (2003). Female rats were maintained on food containing added lead throughout gestation and lactation. Male littermates exposed to lead perinatally (before and after birth) via this regimen were randomly assigned to an isolation group (one housed per cage) or an environmental-enrichment condition in which eight animals were housed in a cage containing a variety of toys and other objects such as hanging hammocks, platforms, tunnels, and a running wheel. As adults, isolated and enriched animals were tested on a spatial-learning task (water maze). Analysis of their brains showed that the enrichment manipulation reversed the spatial-learning deficits otherwise produced by lead exposure, and moreover the enriched environment reversed deficits in NMDA-receptor-gene expression and induced a proliferation of brain-derived-neurotrophic-factor (BDNF) mRNA in the hippocampus. The significance of such findings is that they suggest environmental enrichment as a new intervention strategy for treating cognitive deficits in lead-exposed children.

Overall, our understanding of the mechanism of action of lead-induced deficits in learning and cognition is enhanced by the systematic literature on lead–glutamate interactions. At a minimum, some consideration must be given for involvement of lead-based disturbances in glutamatergic activities and attendant declines in intellectual function.

Cholinergic Events. Another type of ionotropic receptor that is important in learning and memory is the nicotinic cholinergic receptor (Jett, Beckles, Navoa, & McLemore, 2002; Jones, Sudweeks, & Yakel, 1999). This type of receptor is found throughout the central and peripheral nervous system in vertebrates and also modulates LTP and cognitive function. A large body of literature shows that activation of the cholinergic neurotransmitter system ameliorates memory impairments in humans suffering from various neurological disorders, as well as in animals with lesions to cholinergic fibers in the hippocampus and/or basal forebrain region (Levin & Simon, 1998; Yamazaki, Hamaue, & Sumikawa, 2002).

Several laboratories have demonstrated that nicotinic acetylcholine receptors are particularly sensitive to the toxic effects associated with inorganic lead exposure (e.g., Ishihara, Alkondon, Montes, & Albuquerque, 1995; Oortgiesen, Leinders, van Kleef, & Vijverberg, 1993), and this is especially the case for the developing brain (Basha, Wei, Brydie, Razmiafshari, & Zawia, 2003; Zawia, Sharon, Brydie, Uyama, & Crumpton, 1998). Animal studies have shown that impairment of LTP in the hippocampus is exacerbated by the loss of septo-hippocampal cholinergic neurons (e.g., Bielarczyk, Tomzig, & Suszkiw, 1994) and direct inhibition of acetylcholine receptor function (Mike, Pereira, & Albuquerque, 2000; Zwart, van Kleef, Van Hooft, Oortgiesen, & Vijverberg, 1997). Additional support for cholinergic involvement in lead-induced deficits in long-term-memory processes comes from the observation that transplanting new cholinergic neurons ameliorates these deficits (Adhani, Husain, Agarwal, & Seth, 2000).

More recent investigations have focused on the effects of cholinergic stimulation on spatial learning and short-term-memory performance in lead-exposed animals. Evidence supporting the mediational role of cholinergic activity in lead-induced associative and cognitive deficits is available from a study by Zhou and Suszkiw (2004). In this study, female rats were exposed to lead via drinking water from the 16th day of gestation through weaning on postnatal day 21; a week later, offspring were tested in a Morris water maze for spatial-reference-memory acquisition and working-memory performance. The findings showed that perinatal lead exposure resulted in a 30% increase in time taken (latency) to find a submerged platform and a 70% increase in the latency to find it again. More directly relevant to the rationale that formed the basis of the investigation, these deficits were reversed by nicotine-based facilitation of the cholinergic system.

Other assays of disruption of cholinergic processes and related performance impairment have noted lead-induced changes in acetylcholinesterase (the enzyme that breaks down and stops the action of acetylcholine) activity (Gietzen and Wooley, 1984; Reddy et al., 2003), acetylcholine receptor gene expression (Sun, Tian, & Suszkiw, 1997), and acetylcholine-receptor-binding affinity (refer to Jett et al., 2002). Coupled with the glutamate–NMDA data, molecular and neurobehavioral assays of cholinergic linkages to learning or memory dysfunction offer clues to neurochemical mechanisms underlying the connection between lead and neurodevelopmental deficiencies.

Targeting Lead–Learning Impairments

Examination of transmitter-activity changes in discrete regions other than the hippocampus yields useful information as well. It is widely accepted that fixed-interval performance falls under the influence of modifications to dopamine systems in the mesolimbic region, most notably in the nucleus accumbens (ventral striatum). As discussed, disruption of fixed-interval schedule-controlled operant behavior has been a key endpoint for studies of the effects of lead on animal learning. In part, the significance of these findings derives from parallels to studies of human infants and children in which protracted increases in response rates have been reported (Darcheville, Riviere, & Wearden, 1992, 1993). That is, the inefficient and unnecessary fixed-interval responding observed in animals and in children ranging from 3 months to 9 years of age is related to "impulsivity" and

"lack of self-control." Because the nucleus accumbens dopamine system might exhibit preferential vulnerability to lead (Cory-Slechta, 1995), it is understandable why this structure has been a focal point for research on the effects of lead on learning. And, although the collective findings do not rule out contributions of anatomically separate circuits in the interplay of lead and fixed-interval performance changes, recent inspection of other potential mediational sites (such as the dorsomedial striatum) reveals that changes in nucleus accumbens dopamine systems alone appear to be sufficient to cause lead-induced increases in overall fixed-interval rates (Cory-Slechta, Brockel, & O'Mara, 2002). It follows that a comparable case may be made for neural substrates for lead-related disturbances in clinical symptomatology (i.e., attentional deficits) and intellectual function (learning).

Consideration has been given to the differential involvement of NMDA (a glutamate receptor) or dopamine changes in subregions of the nucleus accumbens of rats that have been exposed continuously to lead from postweaning through completion of behavioral testing during the adult cycle. Bauter et al. (2003) exposed animals to control or lead-adulterated drinking solutions and tested for learning impairments in an operant setting. Specifically, dopamine and/or MK-801 (a drug that inhibits, or "antagonizes," the action of NMDA) were infused into the core or shell of the nucleus accumbens of control or treated subjects (the core is believed to be of greater importance in learning; Cohn, Cox, & Cory-Slechta, 1993). Subsequent to the dopamine or MK-801 infusions, tests were conducted to determine if there were group differences in learning (correct completion of repeated sequences of a multiple schedule) or performance (simple fixed-ratio-2). In the core, MK-801 administration produced effects identical to lead, i.e., learning but not performance was disrupted (recall that lead also is an NMDA antagonist). In contrast, dopamine infusions were nonselective, negatively impacting learning and performance, and similar nonspecific effects were found with MK-801 in the shell. Thus, lead, like MK-801, has specific effects on learning, in contrast to dopamine, which has global effects on learning and performance.

Such careful, relevant, and systematic evaluations of the relative contributions made by diverse transmitter systems, in different brain regions, to patterns of lead-related behavioral disturbance are exceedingly important to our understanding of the deleterious effects of lead on cognition. As we move ahead in areas of neurotechnology, appreciable gains in our understanding of the mechanisms of lead-induced learning and cognitive dysfunctions will be achieved.

Lead Exposure and Social Behaviors

Because of public health concerns over the effects of early lead exposure on neurodevelopment and intellectual function in humans, it is understandable that animal studies would concentrate on lead-induced perturbations in associative processes and the underlying mechanisms contributing to such disturbances. However, ties between basic research in lead toxicity and other behavioral endpoints can be made, and much of this work has centered on behavioral processes related to human pathology.

Aggression. As summarized in the previous section on epidemiology, increased lead exposure is a risk factor for antisocial behavior. The findings from numerous studies are in agreement with this hypothesis. In a resident–intruder study, it was shown that rodents exposed to neonatal lead displayed heightened aggression relative to their nonexposed counterparts (Delville, 1999). Specifically, male rats exposed to lead during gestation and lactation were faster and more likely to attack and bite intruder rats. Similar results have been observed in tests of predatory attack in which lead-exposed rats (Hahn, Burright, & Donovick, 1991) as well as cats (Li et al., 2003) exhibited heightened aggression. In the Li et al. study, aggressive behavior was selectively elicited by electrical stimulation of the lateral perifornical hypothalamus, a preferential site for lead accumulation (Altmann et al., 1988; Petit et al., 1983). Because the type of feline aggressive-predatory-response pattern studied by Li et al. is believed to be homologous in its neural organization to pathological forms of human aggression (Siegel & Shaikh, 1997), the data from this investigation support the results of human aggression studies and suggest that lead exposure causes increased frequency of antisocial behavior.

Similar effects have been observed with nonhuman primates: It has been shown that social play during infancy is less likely among lead-treated rhesus monkeys (Laughlin, Bushnell, & Bowman, 1991). Thus, it would seem that a variety of inappropriate social behaviors are increased by lead. Interestingly, many factors that are believed to contribute to conditions of social unrest at the human level (e.g., poverty, hyperactivity) also are associated with lead, either as risks for lead exposure or as consequences of lead poisoning.

Lead and Emotional Behavior. Several avenues of research implicate lead in the development and persistence of emotional disorders. Of particular relevance are possible associations between lead exposure and mood disturbance. The seriousness of this issue is evident from prospective studies of mental disorders; even the most conservative estimates indicate that over 7% of the population in North America between 18 and 54 years of age will suffer a bout of major depression or generalized anxiety in a given year (cf. Regier et al., 1993).

Regarding depression, the past decade has witnessed steady growth in our understanding of molecular elements that contribute to this multifaceted disorder. Some of the more compelling evidence along these lines has come from investigations of the supporting role excitatory amino acids such as glutamate play in depression and antidepressant activity (Paul & Skolnick, 2003). It is currently accepted that NMDA and AMPA (glutamate) receptor activity are fundamental to defining the

effectiveness of antidepressant medications. Further, there is evidence implicating disturbance in glutamate metabolism in depression and suicide (e.g., Caldecott-Hazard, Morgan, DeLeon-Jones, Overstreet, & Janowsky, 1991; Manji, Drevets, & Charney, 2001). As discussed in earlier sections of this paper, lead is known to perturb glutamatergic transmission (Alkondon et al., 1990; Guilarte, 1998; Guilarte & McGlothan, 2003; Nihei et al., 2001). In this context, then, it is not surprising that suggestions have been made that lead may be a contributor to emotional difficulties, even as early as childhood (Mendelsohn et al., 1998; Wasserman et al., 1998).

The case for associations between lead and anxiety is perhaps even more clear-cut. In humans, lead contamination increases the risk of anxiety and other forms of mood change, even at modest levels of exposure (Lundberg, 1996; Rhodes, Spiro, Aro, & Hu, 2003). And numerous studies that document the anxiogenic impact of either developmental or adult lead exposure are available (e.g., Moreira, Vassilieff, & Vassilieff, 2001; Vassilieff, Almeida, Luz, & Vassilieff, 1995). Such findings are especially significant because they demonstrate that increases in anxiety are produced at lead concentrations comparable to those of children exposed chronically to low levels of lead. In some instances the effects are observed even when lead concentrations have returned to control levels. In any event, the current position on lead-induced elevation of anxiety states is strengthened by the existing literature on interactions between lead and the neurotransmitter γ-amino-butyric acid (GABA), showing that lead reliably antagonizes GABA and that GABA regulates stress reactivity (Lasley & Gilbert, 2002; Waskiewicz, 1996). The antagonism of GABA mechanisms and the resulting enhanced stress response in lead-exposed animals are of particular interest because recent findings show that stress in rats caused by social defeat actually increases hippocampal LTP (Buwalda et al., 2005). Given the aforementioned lead-induced impairment of LTP in nonstressed animals, it would be of interest to know if, paradoxically, stress might reverse the learning (i.e., LTP) deficits otherwise produced by lead exposure.

Developmental Lead Exposure and Psychoactive Drugs. Recent studies suggest that early lead exposure may promote pathological change in drug selection and use. Using an intravenous self-administration model, Nation, Cardon, Heard, Valles, and Bratton (2003) found that adult rats born to mothers exposed to lead throughout pregnancy and nursing (perinatal lead exposure) exhibited a greater inclination to return to drug seeking at lower doses of a cocaine priming injection. That is, after an extinction period in which saline replaced cocaine as the reinforcement outcome for lever responding, lead-exposed animals were more likely than nonexposed controls to return to cocaine-administering behavior (by lever responding) following intraperitoneal injections of very low doses of cocaine. This increase in relapse behavior among lead-treated animals is consistent with other findings that show accelerated acquisition of cocaine self-administration responding in rats exposed to lead during pregnancy and nursing (Rocha, Valles, Cardon, Bratton, & Nation, 2005), and it has been found that animals perinatally exposed to lead self-administer cocaine at doses that are too low to sustain responding in controls (Nation, Smith, & Bratton, 2004).

Similar metal-related changes in drug sensitivity have been observed with opiates (Miller, Nation, Jost, Schell, & Bratton, 2000; Rocha, Valles, Cardon, Bratton, & Nation, 2004). Because environmental lead exposure continues to be a major problem, especially for inner-city populations where drug use and abuse are more common (Ensminger, Anthony, & McCord, 1997; Mielke, 1999; Pirkle et al., 1998), these findings from behavioral studies have important public health implications. Perhaps by way of the aforementioned lead–glutamate interactions, the potency of psychoactive drugs is altered (Kalivas et al., 2003; McFarland, Lapish, & Kalivas, 2003). Of course, validation from human investigations is required before confident assertions can be made about possible associations between lead toxicity and enhanced drug vulnerability.

Lead and Social Environments

Experimental studies of the impact of lead on animals provide the data necessary to isolate lead as a cause of damage to brain and behavior. The rich experimental animal data on the negative impact of lead are paralleled by equally rich experimental data on the positive impact of environmental enrichment and negative impact of environmental deprivation on brain and behavior (Comery, Stamoudis, Irwin, & Greenough, 1996; Greenough, Black, & Wallace, 1987). Animals randomly assigned to group rearing in enriched environments have not only more enriched social interactions than animals reared in isolation (i.e., in "normal" laboratory environments) but also more opportunities for such nonsocial stimulation as object manipulation and exploration (Rosenzweig & Bennett, 1969, 1996). Social and nonsocial environmental enrichment have unequivocal effects on brain and behavior, particularly learning and memory (Chapillon, Patin, Roy, Vincent, & Caston, 2002). As indicated in the previous section, studies have reported that environmental enrichment enhances LTP and NMDA-receptor expression. Analogous results come from research on differences in behavior and NMDA expression between pups reared by mothers providing high versus low tactile stimulation (i.e., by licking and grooming and arched-back nursing; Bredy, Humpartzoomian, Cain, & Meaney, 2003; D. Liu, Diorio, Day, Francis, & Meaney, 2000). Similarly, maternal deprivation reduces NMDA-receptor expression and levels of BDNF, a neurotrophin (protein secreted by the nervous system) essential to neuronal differentiation and survival as well as to spatial learning and memory (Roceri, Hendriks, Racagni, Ellenbroek, & Riva, 2002).

Such findings suggest environmental enrichment could counteract, and environmental deprivation exacerbate, the

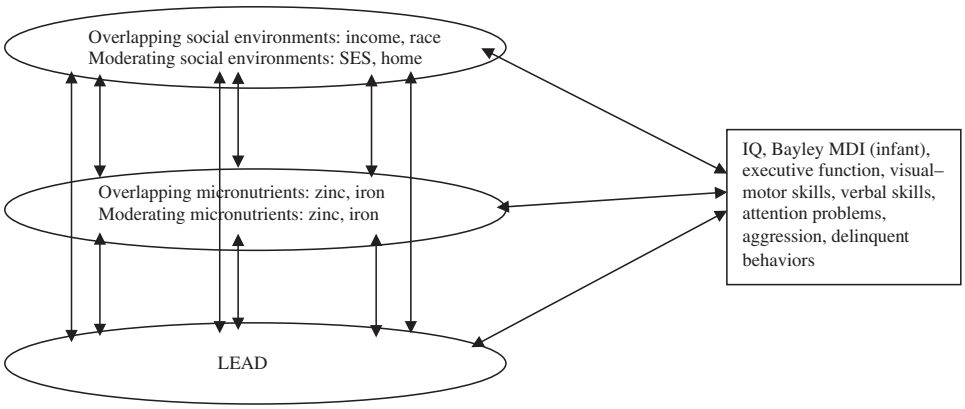

Fig. 3. Model of interrelationships among lead, social environments, micronutrients, and child outcomes. (SES refers to socioeconomic status; MDI refers to Mental Development Index.)

negative impact of lead on LTP and NMDA activity. To date, only the offsetting effects of enrichment have been examined. As noted above, Guilarte et al. (2003) reported that effects of lead exposure on behavior and brain chemistry in young rats are reversed by enrichment (see also Schneider, Lee, Anderson, Zuck, & Lidsky, 2001). These studies supply additional experimental evidence for the causal negative impact of lead and the causal positive impact of enrichment, as well as the interaction of the two. Further, they build a bridge between the animal and human literatures on the impact of lead on development, underscoring the importance of examining how features of children's environments might offset or exacerbate the effects of lead (see Fig. 3).

Poverty, Parenting, and Schools

Lower family income has long been associated with poorer cognitive functioning (Brooks-Gunn & Duncan, 1997; Duncan et al., 1994; Jencks et al., 1972; Klebanov, Brooks-Gunn, McCarton, & McCormick, 1998; K.E. Smith, Landry, & Swank, 2000; Stipek & Ryan, 1997) and, to a lesser extent, poorer socioemotional functioning (Ackerman, Brown, & Izard, 2004; Duncan et al., 1994; Elder, 1974; Evans & English, 2002; McLoyd, 1998) in children. Nonetheless, researchers have appropriately questioned whether the operating variable in the family-income–child-outcomes association is reduced income or the panoply of circumstances associated with it. Among those circumstances are lower parental education, poorer parental mental health, more crowded housing, lower-quality parent–child interactions, lower-quality schools and childcare, poorer nutrition, absent or lower-quality health care, greater exposure to pesticides, higher noise levels, fewer open spaces in which to play, and greater exposure to lead or other neurotoxicants (see reviews in R.H. Bradley & Corwyn, 2002; Brooks-Gunn & Duncan, 1997; Evans, 2004; Shonkoff & Phillips, 2000; see also Simpson et al., 2005).

Poverty and Lead Exposure. Even though average child blood-lead levels dropped precipitously in the years between NHANES II and III (Brody et al., 1994; CDC, 1997; Pirkle et al., 1998), the incidence of blood-lead levels at or higher than 10 μg/dL (recall that this is the current CDC level of concern) was four times greater for young children from lower-income families than it was for young children from higher-income families (see Fig. 4).

Children living in impoverished neighborhoods in urban communities are more likely to live in older housing than are children living in more affluent suburban communities (Brown et al., 2001; Sargent et al., 1995; Sargent, Dalton, Demidenko, Simon, & Klein, 1999). Most houses built before 1978 contained dangerous levels of lead in paint, with housing built prior to 1946 posing an even higher risk for children (see Fig. 4; CDC, 1997). Poor urban children are exposed not only to greater lead in dust and soil due to deteriorating paint but also to lead deposited in soil during earlier decades of high traffic density (Lanphear et al., 1996, 1998; Mielke, Dugas, Mielke, Smith, & Gonzales, 1997; Mielke, Gonzales, Smith, & Mielke, 1999;

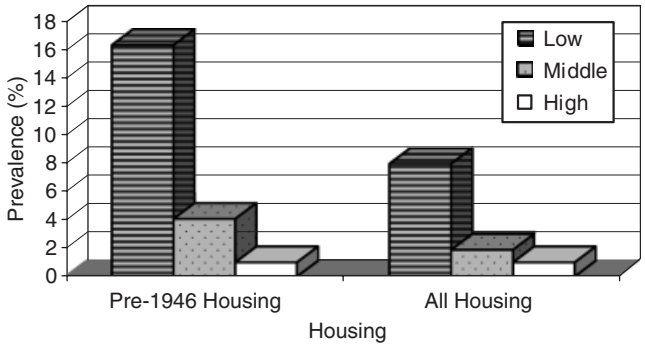

Fig. 4. Prevalence of blood-lead levels of 10 μg/dL or higher in 1991–1994, for low-, middle-, and high-income groups living in pre-1946 housing or all housing. Data are from Centers for Disease Control and Prevention (1997). Income categories are defined by the ratio of family income to the poverty threshold for that year (low: under 1.3; middle: 1.3 to 3.5; high: over 3.5).

Rabinowitz, Leviton, Needleman, Bellinger, & Waternaux, 1985; Weitzman et al., 1993).

Like children living in poverty, children from ethnic or racial minority groups are at greater risk of having blood-lead levels above the current CDC level of concern. As can be seen in Figure 5, it is non-Hispanic black children who are at highest risk. The two data sources for Figure 5, NHANES and CDC surveillance, use very different sampling strategies. NHANES uses a random sampling strategy with oversampling (selecting a greater number of cases than the proportion in the population) for specific minority/ethnic groups (e.g., Pirkle et al., 1998). CDC surveillance data are based on reports from states with wide variations in quality of data. P.A. Meyer et al. (2003) point out that racial or ethnic identity information was omitted from about 50% of the reports. Nonetheless, it is the state surveillances that are targeted to those families and children most at risk. They corroborate that children of minority status continue to be more likely than other children to have elevated blood-lead levels.

Whether from lead deposited by gasoline or paint in soil or dust, children living in poverty are at greater risk for exposure to lead. Although researchers have been most concerned that socioeconomic status and related factors might confound the relation between lead and child cognition and behavior, some (e.g., Rutter, 1983) also have speculated that the impact of lead on young children would interact with SES, such that children made vulnerable by other risks would experience greater cognitive or behavioral deficits as a function of lead than would children protected by better economic resources, supportive parenting practices, and so on. As noted in the introduction, separating modifiers of the effects of neurotoxicants from confounders is essential to identification of the groups of children most susceptible to neurotoxicant effects.

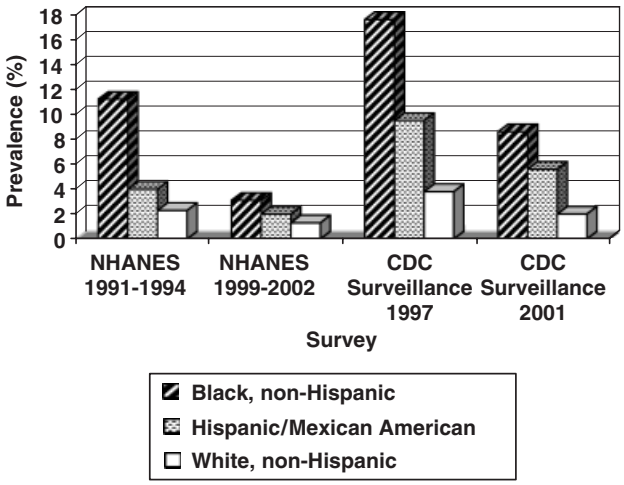

Fig. 5. Percentage of 1- to 5-year-old children with blood lead 10 μg/dL or higher by race/ethnicity. National Health and Nutrition Examination Survey (NHANES) data come from Centers for Disease Control and Prevention (CDC, 2005, Table 1) and CDC data come from P.A. Meyer et al. (2003, Table 4). (Mexican American children were sampled in the two NHANES surveys, whereas the CDC surveillance summary categorized children as Hispanic.)

Interaction of Socioeconomic Risks and Lead. Three early cross-sectional studies reported greater effects of lead on children from lower-SES backgrounds than on those from higher-SES backgrounds (Harvey et al., 1984; Schroeder, Hawk, Otto, Mushak, & Hicks, 1985; Winneke & Krämer, 1984). Three of the prospective studies reported interactions between lead and SES at various stages in the studies: Boston, Cincinnati, and Port Pirie. In the Boston prospective study, SES moderated the impact of lead on infants' Bayley Mental Development Index (MDI). Blood-lead levels of 6 to 7 μg/dL had a negative impact on infants below the median on SES, whereas MDI scores of infants above the median were negatively impacted at blood-lead levels of 10 μg/dL and higher (Bellinger et al., 1988). Similar differences were found between children above and below the median on SES in terms of improvement on cognitive score between 24 and 57 months as well as between children with higher and lower Home Observation for Measurement of the Environment (HOME) scores (Bellinger, Leviton, & Sloman, 1990).

In the Cincinnati prospective study, infants also differed as a function of the interaction of lead and SES (K.N. Dietrich et al., 1987). Evaluation of the participants in this cohort at age 15 identified a marginally significant lead–SES interaction for the Learning/IQ factor of a neuropsychological battery (Ris et al., 2004) with the lower-SES adolescents showing a greater negative impact of lead.

Evaluation of the children between ages 11 and 13 in the Port Pirie prospective study revealed differences in children's full-scale IQ scores as a function of the interaction between parental occupational status and lead in initial analyses. When all other covariates were included in regression models, the interaction effect for full-scale IQ was no longer significant. Analyses of scales and subscales revealed that the interaction effect was significant for the verbal scale and for the arithmetic and vocabulary subscales, with children of parents of lower occupational status scoring lower than children of parents of higher status for equivalent levels of lead (Tong, McMichael, & Baghurst, 2000).

In order to understand the greater impact of lead on children of lower SES, it is necessary to consider what lower SES means for children's developmental outcomes. Which aspects of the social environments of children from lower-SES backgrounds might account for this greater impact of lead?

Poverty and Parenting. Early studies documenting decrements in the IQ or developmental scores of lower-SES children over time (e.g., Golden & Birns, 1976) have been supplemented in recent years by studies examining what parenting behaviors or practices account for relations between family resources such as income and education and child performance. Parenting behaviors and practices that are linked negatively to child cognitive outcomes and positively to behavior problems include

various forms of parental intrusiveness and harsh, punitive parenting. Parenting behaviors and practices that are linked positively to child cognitive outcomes and negatively to behavior problems include various forms of warmth, support, and cognitive stimulation.

Within a low-income sample of Head Start children in Oklahoma, three types of maternal behavior during prekindergarten predicted children's cognitive scores in kindergarten over and above demographic control variables (Hubbs-Tait et al., 2002). Measures of maternal behavior were derived from questionnaires, computer-presented parenting assessments, and behaviors coded from a videotaped teaching task in which mothers assisted their children in folding an origami boat. Maternal emotional support included positive feedback during the teaching task and self-reports of hugging; intrusiveness included physical restraint of the child and preventing the child from completing the teaching task on his or her own; cognitive stimulation included questions or statements during the teaching task that challenged the child to use representational thought. Maternal emotional support explained 7% and intrusiveness 8% of the unique variance in verbal scores (for a total R^2 of .15; partial $r = .39$). The more emotional support mothers demonstrated when their children were in Head Start, the higher were their children's verbal scores at the end of kindergarten. On the negative side, the more mothers physically restrained their children or took over their children's task, the lower were the children's scores the next year. Similar results were found for perceptual scores, but in this case maternal cognitive stimulation also explained significant variance in scores at the end of kindergarten (Hubbs-Tait et al., 2002).

Using data from the national Infant Health and Development Program (IHDP), Klebanov et al. (1998) confirmed that the learning environment provided by parents of 3-year-old children mediated the relation between family income and children's Stanford-Binet Intelligence Scores. Family income-to-needs ratios (total family income divided by the poverty threshold for families of the same size in the same year, with quotients less than 1 indicating families living in poverty) when children were 1 year old predicted children's IQ scores at age 3. Income-to-needs ratios were also significantly related to the environment provided by parents in the home, as measured by the HOME (Caldwell & Bradley, 1984). When both the home environment and income-to-needs ratios were used to predict children's IQ scores at age 3, only the home environment was significant (Klebanov et al., 1998). The HOME consists of a number of subscales that Klebanov et al. combined into three composites: home learning, physical environment, and maternal warmth. Further analyses revealed that the composite that was significant was home learning.

More recent evaluations of mediating effects of parenting in the IHDP have added observations of authoritative parenting practices (i.e., combining warmth and sensitivity or fostering of independence with setting reasonable demands, explaining those demands, and enforcing them consistently) and authoritarian parenting practices (i.e., combining rejection or lack of warmth with high demands for obedience, no explanations of those demands, and coercion; Linver et al., 2002). Structural-equation models confirmed that home learning mediated the relation between family income and child IQ. Home learning and parenting practices both mediated the relation between family income and child behavior problems. Paths were significant even when other key maternal variables such as education and receptive vocabulary (word comprehension) were controlled (Linver et al., 2002).

It is tempting to argue that the positive parenting practices reviewed above (as well as others) would protect children against the negative effects of lead whereas negative parenting practices would exacerbate the negative effects. However, the only measures of parenting included in research on lead to date are scales of the HOME. Effects of lead on children with lower HOME scores were larger than for children with higher HOME scores and reached significance in the Boston prospective study (Bellinger et al., 1990) but not the Port Pirie study (Tong et al., 2000). Thus, there is some evidence that more stimulating home environments might protect children from lead effects, but, because only one study and one measure are involved, more research is needed.

Intergenerational transmission of lead effects may occur directly or indirectly. Research in Mexico (Azcona-Cruz, Rothenberg, Schnaas, Zamora-Muñoz, & Romero-Placeres, 2000; Rothenberg, Schnaas, Perroni, Hernandez, & Ortega, 2000) has identified an association between children's blood-lead levels and maternal practices of cooking in lead-glazed pottery. Such cooking patterns have occurred for generations. Similarly, exposure to lead from gasoline in Mexico, as in the United States, continued over several generations. In Mexico, leaded gasoline only began to be phased out in 1988 (Cortez-Lugo, Téllez-Rojo, Gómez-Dantés, & Hernández-Avila, 2003), so exposure continues still, although to a lesser extent, due to the long half-life of lead deposited by gasoline emissions and paint in urban areas. The intergenerational exposure to lead suggests that maternal lead burden may impact child functioning not only directly through prenatal exposure (Gomaa et al., 2002) but also indirectly through its influence on maternal cognition and parenting behavior. There are several mechanisms that may operate. Maternal health or energy may be affected, and that, in turn, may affect maternal behavior. Alternatively, the effect of excess lead on adult cognition is clear (Barth et al., 2002) and mothers' parenting may be directly affected. In the United States as well as elsewhere, several generations of children were exposed to lead. Recent findings on the continuity of reduced health from childhood through later parenthood and its impact on reduced earnings to support the next generation (Case, Fertig, & Paxson, 2005) underscore the importance of reducing all exposures to lead.

Poverty, Child Care, and Schools. Children living in poverty are more likely to attend lower-income child-care centers than are children from higher-income homes. In turn, lower-income centers are likely to be of lower quality than are centers classified as middle or upper income (Phillips, Voran, Kisker, Howes, & Whitbrook, 1994). Phillips et al. (1994) found that lower-income centers were significantly differentiated from upper- and middle-income centers by lower teacher sensitivity, greater teacher harshness, and greater teacher detachment. In turn, these teacher characteristics have been associated with more negative child outcomes (Peisner-Feinberg & Burchinal, 1997). As children move out of the preschool years into public school, there continues to be inequity in quality of care and education, with children from lower-income family backgrounds receiving lower- or lowest-quality education (V.E. Lee & Loeb, 1995; Pianta, La Paro, Payne, Cox, & Bradley, 2002). Finally, schools and child-care centers in the inner city are probably more likely than those elsewhere to be a source of lead exposure (Viverette et al., 1996).

Recent reports provide estimates of the impact of child-care quality on the cognition and behavior problems of children from less advantaged family backgrounds. First, longitudinal data on 733 child participants in the Cost, Quality, and Child Outcomes in Child Care Centers Study from age 4 through second grade reveal that the effect size of the relation of classroom practices (a composite of four observational measures) to children's cognitive and behavioral outcomes during child care were both small (partial *r*s = .18 and .11) and smaller (one fourth to three fourths of the magnitude) than effect sizes for the relation of maternal education to the same outcomes. However, high-quality classroom practices had a greater effect on children of mothers with lower education, particularly for math scores (Peisner-Feinberg et al., 2001).

Second, for low-income children enrolled in Early Head Start (EHS), not only did random assignment to EHS (as opposed to control) have positive impacts on child outcomes, so also did the quality of child care in which child participants were enrolled (Love et al., 2003). The quality of EHS child-care centers significantly exceeded that of programs in which control children were enrolled. Furthermore, quality of care predicted 36-month receptive-vocabulary and 24-month Bayley scores among those children attending EHS centers (Love et al., 2003), underscoring the importance of high-quality center-based child care for low-income children.

Third, analogous results have been reported for children of 451 low-income mothers enrolled in welfare-to-work programs in San Francisco, San Jose, and Tampa. Adjusted effect sizes (i.e., adjusted for effects of other variables) of the relation of child-care quality to cognitive outcomes were small (.08 to .23 standard deviation, approximately $r = .05$ to $r = .11$) as were those of maternal receptive vocabulary to the same outcomes. One of the effect sizes for the relation of attending child-care centers (as opposed to family-child-care homes or other forms of care) to cognitive outcomes exceeded a small effect (.57 standard deviation), but this was the only exception to the rule of small (or lower) effect sizes (Loeb et al., 2004).

The small effect sizes of child-care quality have generally been interpreted as very important, even when they are exceeded by those of maternal education or receptive vocabulary. One justification is that child-care effects are due only to the environment, whereas maternal effects include both genetic and environmental contributions (e.g., McCartney & Rosenthal, 2000; Peisner-Feinberg et al., 2001). Further, the consensus across investigations is that increased federal subsidies for child care for low-income families have increased access of low-income children to higher-quality care. Whether increased access to higher-quality care and the impact of that care on cognition and behavior have offset some of the negative impact of lead on low-income children has never been investigated.

Lead Effects and Cumulative Risk

As noted previously, several meta-analyses of lead effects have identified average decreases in IQ scores that are associated with specific increases in levels of lead. Needleman and Gatsonis (1990) evaluated the relation between blood-lead levels and children's full-scale IQ scores across seven studies. The effect size of lead adjusted for all other covariates was $r = -.152$. This is a small effect size, equivalent to blood lead's explaining 2% of the variance in full-scale IQ scores net of all other confounders. A recent study of low-income children by Canfield, Henderson et al. (2003) reports drops in IQ for increases in lead net of all confounders. For each increase in lead of 10 μg/dL from approximately 1 to 30 μg/dL, there was a 4.6-point IQ drop, as compared to a 7.4-point drop between 0 and 10 μg/dL (Canfield, Henderson et al., 2003). Although both of these adjusted effect sizes are small, the difference between the two is important, as it suggests that lead effects are more profound at lower levels or, alternatively, that unidentified effect modifiers are accelerating the effects of lead at lower levels or the extent of uncontrolled confounding is greater at lower than at higher levels.

Such small effect sizes are meaningfully consistent with or exceed the effect size for the relation of child-care variables to child outcomes. To put all of these effect sizes into perspective, it is helpful to consider a recent meta-analysis of the impact of parenting on behavior problems of children living in poverty. The effect size of the impact of negative parenting on externalizing behavior problems was $d = .40$ (Grant et al., 2003). This translates (Murphy & Myors, 1998) to $r = .196$, or 3.8% of the variance in externalizing behavior problems of children living in poverty explained by negative parenting over and above other variables. Like effects of lead or child-care quality on child cognition, this is a small effect size.

At the beginning of this monograph, we introduced the concept of cumulative risk. Sameroff et al. (1987) emphasized risk as additive, because they found no single risk factor to be more

important than any other. Their measure of cumulative risk, consisting for each family of the total number of risk factors present (maternal mental health, maternal anxiety, maternal rigidity/flexibility in parenting attitudes, maternal spontaneity in interactive behavior, maternal education, occupational status of head of household, minority-group status, presence of father, family size, and stressful life events), was linearly associated with child verbal IQ.

Recently, a number of research groups have adapted the measurement of cumulative risk to study families living in poverty (Ackerman et al., 2004; Burchinal, Roberts, Hooper, & Zeisel, 2000; Evans & English, 2002). Evans and English (2002) found that children in families living below the poverty threshold experienced more stressors (crowded housing, noise, poor housing quality, family turmoil, violence, and child–family separation) than did children in families above poverty. Further, the relation between poverty and child psychological distress or well-being was mediated by the total number of stressors. In light of such findings, Evans (2004) argues that the impact of poverty on children is a function of the number of stressors associated with poverty rather than the identity of any specific risk factor.

The number and identity of risk factors included in measures of cumulative risk varies widely across research groups. Because no research group to date has included lead in its measurement of cumulative risk, how differing levels of lead contribute to total risk is not known. Research groups studying the impact of lead alone have carefully controlled for other risk factors. For example, Canfield, Henderson et al. (2003) controlled for maternal IQ, race, education, tobacco use during pregnancy, income, and HOME score, as well as child gender, child birth weight, and child iron status. The effect size of lead net of these controls suggests that the impact of lead is at least as great as that of other factors typically included in measures of cumulative risk.

Lead and Micronutrients

Nutrients play a number of important roles in the relation of neurotoxicants to child behavior and cognition. First, deficiencies of many nutrients have independent effects on cognition and behavior, which may add to the effects of neurotoxicants on the same outcomes. Second, nutrients may interact physiologically with neurotoxicants, for example to neutralize or antagonize toxic effects, resulting in protection of the individual's cognitive or behavioral functioning (or in vulnerability to neurotoxic effects in the case of nutrient insufficiencies). These interactions may affect absorption, distribution, metabolism, and excretion of neurotoxicants. Further, they may occur at the level of the system or the cell. Third, nutrient deficiencies are linked to reduced resilience to infection, lower energy levels, and other factors, which, in turn, are linked to lower cognitive and behavioral functioning.

Protective effects of nutrients against lead absorption and retention have been known and discussed for many years. Nutrients with long-documented and well-recognized protection against lead absorption or retention include iron and calcium (Lederer & Franklin, 1940; Mahaffey-Six & Goyer, 1970; Mahaffey-Six & Goyer, 1972; Mahaffey, Gartside, & Glueck, 1986). Research has also suggested the protective function of zinc (Victery, Miller, Zhu, & Goyer, 1987; Victery, Thomas, Shoeps, & Vander, 1982). Thus, any consideration of the impact of lead on child cognition needs to consider the extent to which these effects are exacerbated by dietary inadequacies. In contrast to calcium, for which tight homeostatic processes protect against dietary inadequacies and therefore adverse impact on neural function, deficiencies of the trace minerals zinc (M.M. Black, 2003a, 2003b) and iron (Grantham-McGregor & Ani, 2001; Pollit, 2001) have independent effects on child cognition. Thus, we focus on the main effects of these two micronutrients and on interactions of zinc and iron with lead. Furthermore, nutrient deficiencies both in the United States (e.g., Alaimo et al., 2001) and internationally (e.g., Portillo-Castillo, Solano, & Fajardo, 2004; Watt, Dykes, & Sheiham, 2001) are more likely to be found among children characterized by low income, low parental education, and other indicators of low SES (see also Grantham-McGregor & Ani, 2001; Pollit, 2001), underscoring the importance of considering interactions of social environments, neurotoxicants, and nutrients (see Fig. 3).

Main Effects of Iron

Because both lead and iron have recognized effects on child cognition and behavior, we will first examine the main effects of iron, as they constitute potential confounders of lead effects on child outcomes. Furthermore, because lead and iron interact, as discussed below, deficiencies of iron may exacerbate lead effects. Lead and iron are relatively unique in research on nutrients and/or neurotoxicants in that they affect similar cognitive and behavioral functions, albeit in opposite directions (Kordas et al., 2004; Wasserman et al., 1992).

About 80% of the iron in the human body is contained in hemoglobin, a protein in red blood cells. Additional iron is stored by another protein—ferritin—found in the liver, bone marrow, and spleen. The amount of iron stores available in these organs is reflected in the amount of ferritin in the blood. The progression of iron deficiency corresponds to changes in these iron proteins. Decrements in ferritin occur first. Advanced iron deficiency restricts hemoglobin production (see Beard, Dawson, & Piñero, 1996, for review). *Anemia* refers to hemoglobin concentration or hematocrit (percentage of total blood volume consisting of red blood cells) less than an age-appropriate reference value (e.g., for preschool children, hemoglobin less than 111 grams per liter [g/L] or hematocrit less than 33%; CDC, 1998). *Iron deficiency* refers to reduced serum ferritin (15 nanograms per milliliter [ng/mL] or less; CDC, 1998; Hallberg

et al., 1993). Children with *iron deficiency anemia* (IDA) have both depleted stores and lower circulating iron.

On Child Cognition. In the experimental animal literature, both extent and timing of iron deficiency affect brain functioning (e.g., Beard et al., 2003; Piñero, Jones, & Beard, 2001). In children, extent of iron deficiency is determined by evaluating for evidence of iron deficiency and anemia. Recent reviews have documented the relations between lower cognitive functioning and both anemia and iron deficiency (Grantham-McGregor & Ani, 2001; Pollit, 2001), suggesting that iron concentrations do not have to decrease to the point of anemia for children's cognitive functioning to be impaired. Two U.S. investigations illustrate this point. Bruner et al. (1996) found that supplementation with iron versus placebo explained 7% of the variance in postintervention verbal-learning scores among 73 nonanemic iron-deficient girls. Further, change in serum ferritin from baseline to postintervention was significantly related to verbal-learning scores. Also in the United States, Halterman et al. (2001) found that nonanemic, iron-deficient 6- to 16-year-old children were 2.4 times more likely to score below average in math than were iron-replete children. The fact that variations in iron at levels of deficiency above anemia are linked to variations in cognitive functioning suggests that anemia does not constitute a threshold for iron effects on cognition.

With regard to timing, children's iron status measured at any one point in time, like blood-lead concentration, does not necessarily reflect previous status. Unfortunately, no longitudinal studies exist that have evaluated relations of measures of iron and cognitive performance across multiple points in children's development. Such studies are needed in order to determine whether developmental timing of iron deprivation is related to the magnitude or type of effects (Grantham-McGregor & Ani, 2001).

Recent research on infants of diabetic mothers did examine effects of iron deficiency across the first 12 months of life (Siddappa et al., 2004). Such infants who had brain-iron deficiency at birth (inferred from umbilical-cord or neonatal-serum ferritin under 34 μg/L) differed from those with sufficient brain iron on tests of auditory-recognition memory. The brain-iron-deficient group had impaired auditory-recognition memory at birth. That is, they were less able to differentiate their mother's voice from that of a stranger. Furthermore, at 12 months the motor-development scores of the brain-iron-deficient group were lower than those of the brain-iron-sufficient group (Siddappa et al., 2004).

On Child Behavior. Behaviors linked to iron deficiency include anxiety and attention problems. School-age children who had been iron deficient as infants differed significantly from those who had not been deficient on the anxious/depressed and social-problems subscales of the Child Behavior Checklist (Lozoff, Jimenez, Hagen, Mollen, & Wolf, 2000). IDA infants in Guatemala were more likely to stay in proximity to their mothers than were nonanemic infants (Lozoff, Klein, & Prabucki, 1986), and IDA infants in Costa Rica were more wary and hesitant and were less likely to show positive affect (Lozoff et al., 1998).

Lozoff et al. (2000) also found differences in teacher-, parent-, and child-reported attention problems between formerly iron-deficient infants and their school-age peers who had not been deficient in infancy. This finding is consistent with some of the earlier research on children's learning difficulties. For example, Pollitt, Leibel, and Greenfield (1983) reported significant differences between iron-deficient and iron-sufficient 3- to 6-year-olds in the United States on trials assessing attention.

Brain Mechanisms of Iron Effects From Animal Research. Previously we have discussed brain mechanisms of lead effects. In this section we introduce brain mechanisms of iron effects to clarify the interaction between lead and iron at the level of the brain. Brain mechanisms (see review in Beard & Connor, 2003) that might account for relations between iron deficiency and child cognition and behavior include altered dopaminergic (Beard et al., 2003; Kwik-Uribe, Gietzen, German, Golub, & Keen, 2000) and glutamatergic (Erikson, Shihabi, Aschner, & Aschner, 2002) function, changed myelin composition (myelin is the sheath of mostly lipid cells that covers neurons and increases the speed of conduction of messages; Kwik-Uribe et al., 2000), increased divalent-metal-transporter protein (Erikson, Syversen, Steinnes, & Aschner, 2004), and decreased energy production (deUngria et al., 2000). For example, dopamine transporter (a protein in neuron cell membranes that carries dopamine from the synapse back to the presynaptic neuron) and one dopamine receptor in rats are differentially affected as a function of both brain region and timing (early- versus late-neonatal periods) of iron deprivation (Beard et al., 2003). As we noted previously, dopamine functioning is affected by lead in a like manner. Changes in dopamine functioning in the rat striatum are linked to changes in exploration of novel environments (Beard et al., 2003)—a rat analog to human infant exploration, essential to cognitive development. Although 4 weeks of iron supplementation returns rat dopamine transporter and receptor densities to normal in the nucleus accumbens, it does not normalize transporter and receptor densities in the striatum, nor does it normalize exploratory behavior linked to striatal dopaminergic functioning (Beard et al., 2003). These experimental findings lend credence to arguments by researchers on humans that effects of iron deprivation in infancy are long lasting (Algarin, Peirano, Garrido, Pizarro, & Lozoff, 2003). In fact, Beard et al. suggest there is a critical infant developmental period during which iron deficiency results in alterations in dopaminergic functioning and that needs to be investigated in human infants.

Main Effects of Zinc

In contrast to those available for iron, sensitive biomarkers to assess zinc status are lacking. This has substantially impeded

progress in evaluating effects of zinc deficiency. The gold standard for documentation of a pre-existing zinc deficiency is a response to a controlled, double-blinded trial. Plasma-zinc concentrations, while not optimally sensitive and while reduced by infection or inflamation (Droke, Kennedy, and Hubbs-Tait, in press), are the most commonly used alternative. There remains more uncertainty about levels of zinc indicative of insufficiency than about those of iron (e.g., Hotz, Peerson, & Brown, 2003; Johnson, 1996; Lukaski & Penland, 1996).

On Child Cognition. Nonetheless, zinc deficiency, well recognized for its impact on child growth, mortality, and illness (Bahl, Bhandari, Hambidge, & Bhan, 1998; Krebs, 2000; Walravens, Krebs, & Hambidge, 1983) has also been linked to infant cognition and activity and to child cognition. Randomized controlled supplementation trials using physiologic doses (amounts that would typically occur in the diet) have identified consistent significant effects of zinc supplementation on infant activity during play (Bentley et al., 1997; Sazawal et al., 1996) and on infant motor development (Castillo-Duran et al., 2001). Although one study of zinc supplementation during pregnancy reported improved developmental function in the infants of supplemented women (Kirksey et al., 1994), randomized controlled trials of zinc supplementation during pregnancy or in infancy have not consistently supported its impact on measures of infant mental functioning (M.M. Black et al., 2004; Hamadani, Fuchs, Osendarp, Huda, Grantham-McGregor, 2002; Tamura, Goldenberg, Ramey, Nelson, & Chapman, 2003).

Two supplementation studies, one in China (Penland et al., 1997; Sandstead et al., 1998) and the other of Mexican-American children in the United States (Penland et al., 1999), reported effects of zinc supplementation on cognition in childhood. Specifically, first-grade children supplemented with zinc plus a mix of micronutrients (vitamins and other minerals) performed better on a test of attention, a finger tapping task measuring motor speed, and an oddity task (testing concept formation) than did children who received the micronutrient mix without zinc. Interactions between zinc and other nutrients were suggested by the finding that children who received zinc alone performed worse than did children who received zinc plus the micronutrient mix on two tasks assessing attention (Sandstead et al., 1998). In the study of low-income Mexican American children, the zinc-plus-micronutrient mixture resulted in better performance on the oddity task than did two other supplements or a placebo (Penland et al., 1997). The impact of zinc on child cognition is also supported by the findings of the longitudinal, observational studies of the Nutrition Collaborative Research Support Program in Mexico, Egypt, and Kenya in the 1980s. These studies (see review in C.G. Neumann et al., 2003) showed that independent of such covariates as measures of socioeconomic status, consumption of meat (a rich source of zinc and iron) was significantly related to cognitive scores.

A number of explanations could be offered for why randomized controlled trials show zinc supplementation to be effective in childhood but not in infancy. The most plausible explanation may be the difference between types of abilities tested in childhood and those tested in infancy. The children's cognitive functioning was evaluated with measures of domain-specific cognitive or neuropsychological functions, whereas the infants were evaluated with scales of more global abilities. Employment of more specific measures of cognitive functioning in infants may resolve the discrepancy. An alternative explanation for the lack of effects in infancy is the different timing of supplementation interventions. Human milk generally meets zinc needs through approximately the first 6 months of life. After the first 6 months, the adequacy of zinc provided by typical milk intakes of breastfed infants becomes more marginal (Krebs & Westcott, 2002).

On Child Behavior. Zinc deficiency has been linked to fearfulness and anxiety. Zinc supplementation of female adolescent anorexia nervosa patients in a double-blind, randomized, controlled trial resulted in decreased anxiety and depression (Katz et al., 1987). Zinc supplementation of Brazilian infants increased cooperation with the test administrator during the Bayley Scales of Infant Development and decreased fearful behavior (Ashworth, Morris, Lira, & Grantham-McGregor, 1998). The link between zinc deficiency and fearfulness and anxiety is supported by animal research showing higher emotionality with severe zinc deprivation (Golub, Keen, Gershwin, & Hendrickx, 1995).

Interactions of Lead, Iron, Zinc

Lead and Iron. Physiologic interactions between lead and iron have long been noted (Goyer, 1997; Mahaffey, 1995; Peraza et al., 1998). In experimental animal research, iron deficiency has been found to increase absorption of other divalent metals such as lead (Barton, Conrad, Nuby, & Harrison, 1978; Flanagan, Haist, & Valberg, 1980; Mahaffey-Six & Goyer, 1972). Iron-binding protein in the intestine selectively binds not only iron but also lead and appears to be one of the mechanisms by which iron blocks lead absorption in the digestive tract (Conrad, Umbreit, Moore, & Rodning, 1992). A second protein that acts on both lead and iron is divalent metal transporter 1 (DMT1), discovered in 1997 by Gunshin et al. (see also Bressler, Olivi, Cheong, Kim, & Bannon, 2004). DMT1 transports not only iron and lead but also other divalent metals; DMT1 transport has been identified in the brain and intestine (Erikson et al., 2004; Kordas & Stolzfus, 2004).

Increased absorption of lead has been observed in human adults with reduced iron stores as indicated by low serum ferritin (Watson, Hume, & Moore, 1980). Young children with iron deficiency have a higher prevalence of increased blood-lead concentrations than do those who are not iron deficient (Bradman, Eskenazi, Sutton, Athanasoulis, & Goldman, 2001;

Osman, Schütz, Åkesson, Maciag, & Vahter, 1998; Wright, Tsaih, Schwartz, Wright, & Hu, 2003; Yip, Norris, & Anderson, 1981). Although there is insufficient evidence to conclude that iron deficiency causes elevations in lead levels (Wright et al., 2003), increases in blood lead following iron deficiency (Wright et al. 2003; Wolf, Jimenez, & Lozoff, 2003) and decreases in blood lead following iron supplementation (J.W. Choi & Kim, 2003; Wolf et al., 2003) underscore the interaction of iron and lead.

As we note in the introduction, research on nutrition in human infants and children is more limited than is research on nutrition in animals or human adults. Nutrient needs alter with development and calibrating those changes is still inexact due to the number of variables that influence them (Krebs, 2001). Furthermore, although the bioavailability of iron from breast milk and the gradual depletion of iron stored during gestation provide sufficient iron for normal-weight infants until approximately 6 months (Krebs, 2001), shifts in dietary sources of nutrients at weaning often result in iron insufficiency. In one recent study, dietary-iron intake decreased from 96% of the recommended dietary allowance (RDA) at 12 months to 76% at 18 months, with the researchers emphasizing that insufficient attention has been paid to dietary deficiencies during the transition from infancy to early childhood (Picciano et al., 2000). Similar findings come from an analysis of 1989–1991 dietary intake data from the U.S. Department of Agriculture, showing that 1- to 3-year-olds' intakes of iron were below the RDA (Ganji, Hampl, & Betts, 2003). Thus, the development of age-related dietary inadequacies in iron intake parallel the onset of hand-to-mouth behavior that we discussed previously and that is associated with the transfer of lead in soil and dust to the digestive tract of toddlers (Freeman et al., 2001; Stanek et al., 1998). Whether lead ingested via hand-to-mouth behavior leads to iron deficiency or age-related dietary-iron deficiency increases lead absorption has yet to be determined.

The most recent research suggests that DMT1 may help explain the interaction of iron and lead. Experimentally induced dietary iron deficiency produces increases in DMT1 in specific rat brain regions associated with cognitive functioning—the hippocampus, the globus pallidus, and the substantia nigra (Erikson et al., 2004). Further, an increase in DMT1 in rat glial cells (non-neuronal brain cells that assist neurons by supplying nutrients, eliminating destructive metabolites, and providing other cellular support) is associated with increased uptake of lead into those same cells (Cheong, Bannon, Olivi, Kim, & Bressler, 2004). Taken together, these two studies imply that iron deficiency may increase the transport of lead across the blood–brain barrier via DMT1, providing a potential mechanism to explain lead-based cognitive deficits in iron-deficient children.

Lead and Zinc. Lead also interferes with essential zinc-mediated biological processes. For example, it displaces the zinc atom in zinc-finger proteins (which regulate gene expression), thereby changing the shape of the proteins and hindering their ability to bind with DNA. In rats, this has been associated with altered gene expression in the brain (Basha et al., 2003; Zawia et al., 2000). Further, like iron, zinc was significantly inversely related to blood lead in children with high lead exposure (Osman, Schütz et al., 1998). More recently, Noonan, Kathman, Sarasua, and White (2003) discovered that the relation between environmental and blood lead was markedly reduced in children residing in areas with high environmental zinc, highlighting the physiologic interaction of zinc and lead.

Developmental increases in zinc requirements appear to be on a slightly less steep trajectory than those of iron in the first year of life. Nonetheless, zinc needs usually exceed supply in breast milk by 6 months of age (Krebs, 2001). The NHANES III (1988–1994) data suggest preschool children are more at risk for inadequate zinc than infants are (but see Arsenault & Brown, 2003, who concluded that zinc deficiency is not a problem in U.S. 1- to 5-year-old children). Although 96.3% of formula-fed infants between ages 2 and 11 months had adequate zinc intake (Briefel et al., 2000), only 18.9% of 1- to 3-year-old children did. Thus, toddlers may be deficient in both zinc and iron at approximately the same time period—the period when locomotion extends their boundaries and hand-to-mouth behavior increases their ingestion of soil, dust, and other particles.

Zinc is crucial to a number of biological processes. It is contained in neurons, specifically in glutamatergic neurons (Fredrickson, Suh, Silva, Frederickson, & Thompson, 2000). Zinc plays an essential role in DNA binding and transcription (Zawia et al., 2000), as zinc is the essential ion for the structure of the zinc fingers present in such proteins as neuronal receptors (e.g., NMDA receptors) and transcription factors (proteins that assist in the initial phase of copying DNA to messenger RNA; Zawia et al., 2000), emphasizing the role of zinc in gene expression in the brain. Zinc-containing neurons and the release of zinc in the synapse in the cortex underscore the importance of zinc for normal cognitive functioning (Fredrickson et al., 2000), and release of zinc from zinc-containing neurons in the amygdala (Takeda, Sawashita, Takefuta, Ohnuma, & Ojkada, 1999) may help explain the association of zinc to fear and anxiety.

Of particular importance in understanding interactions of zinc and lead is the work of Zawia et al. (2000). In a series of in vivo studies of competition between lead and zinc, Zawia et al. exposed rat pups to lead by administering lead to their mothers. Lead altered DNA binding by zinc-finger proteins and transcription in all areas of the brain. Supplementing the diet of lead-exposed rat pups with zinc prevented some of the alterations in DNA binding, confirming that lead and zinc compete for the same DNA-binding sites (Zawia et al., 2000). The extent to which dietary zinc contributes to zinc in zinc-finger proteins is unknown (IOM, 2001).

Lead, Zinc, and Iron. Interactions among lead, zinc, and iron are possible in theory, although investigations are limited. As noted in our discussion of lead epidemiology, current lead-

chelation treatment uses succimer. Prior to the development of succimer, lead chelators resulted in increased urinary excretion not only of lead but also of specific essential nutrients, iron and zinc among them (Graziano, Lolacono, & Meyer, 1988), suggesting interactions among these metals. Succimer has a more targeted excretory effect, but experimental work with a primate model of childhood exposure suggested some increase in excretion of total but not specific nutrients (D.R. Smith et al., 2000). DMT1 in the brain transports not only iron (Cheong et al., 2004; Erikson et al., 2004) and lead (Cheong et al.), but also zinc (Erikson et al.) and some other divalent cations. Iron deficiency increased zinc accumulation (Erikson et al.). Whether combined zinc and iron deficiencies result in increased uptake of lead is unknown. Although a simple competition between zinc and iron for absorption in the gut is unlikely to explain all observed effects, evidence of iron–zinc interactions has been provided by large-scale supplementation trials (Kordas & Stolzfus, 2004) using inorganic supplements. DMT1-mediated interactions in the brain have not been ruled out.

Interaction Effects of Lead, Zinc, and Iron on Children. Several of the prospective studies did include measures of iron, but only one measured child iron rather than maternal iron during pregnancy. Wasserman et al. (1992) found iron and lead each contributed independently and significantly to the prediction of preschool children's cognitive functioning. Ruff, Markowitz, Bijur, and Rosen (1996) found children's cognitive functioning increased with decreases in blood lead over time in iron-sufficient children but not in iron-deficient children. Kordas et al. (2004) found that lead and iron each contributed independently and significantly to children's cognitive functioning. The results of these studies emphasize the importance of examining the relation to children's cognition of iron and lead together. No published studies to date have examined relations to child cognition or behavior of children's zinc and iron; zinc and lead; or zinc, iron, and lead.

Micronutrients, Social Environments, and Lead

The link between iron and environmental variables is sufficiently recognized that Lozoff (1998) included uncontrolled confounding by poor environments and altered neuromaturation as equally plausible mechanisms explaining the link between iron and behavioral outcomes. Published estimates of iron deficiency among U.S. children (Looker et al., 1997) do not address the higher incidence of IDA or deficiency reported among low-income and minority children (Alaimo et al., 2001; Ganji et al., 2003; Kahn, Binns, Chen, Tanz, & Listernick, 2002). For example, Alaimo et al. reported 12.2% iron deficiency among low-income preschool children in the NHANES III data set. In a study of infants and toddlers participating in the Women Infants and Children Supplemental Nutrition Program (WIC; the nutrition and food program for low-income women and children; Kahn et al., 2002), anemia as defined by WIC criteria was present in up to 17.7% of children at different time points, with many children remaining anemic over time and others developing anemia despite participation in WIC.

Zinc may not be as closely related to social environments as iron is in the United States. Among U.S. preschool children in households with incomes less than 130% of the federal poverty guidelines, those from households with better incomes had significantly more iron but only marginally more zinc (Rose et al., 1998). However, Ganji et al. (2003) reported that 1- to 3-year-old African-American females fell below 67% of the RDA. The inconsistency between these two reports suggests that additional research is needed on the associations between SES and zinc deficiency in the United States.

One important interaction between micronutrients and social environments concerns the relation between nutrition of pregnant mothers and child outcomes. Poorer nutrition of the mother affects not only prenatal and infant development (Merialdi, Caulfield, Zavaleta, Figueroa, & Dipietro, 1999; Rahmanifar et al., 1993) but also maternal behavior (A.J. Patterson, Brown, Powers, & Roberts, 2000; Valenzuela, 1997). Educational interventions targeted toward malnutrition or blood lead support the importance of interactions between parenting and nutrition or parenting and lead. One early publication from Grantham-McGregor's research group identified an interaction between parenting and micronutrients. Previously malnourished children were less likely than appropriately nourished children to play with a toy unless they had participated in an intervention in which their mothers were trained in appropriately stimulating parenting practices (Grantham-McGregor, Schofield, & Haggard, 1989). One recent randomized trial of education to prevent lead burden (Jordan, Yust, Robison, Hannan, & Dienard, 2003) appears to have been more successful than two randomized control trials of calcium supplementation (Markowitz, Sinnet, & Rosen, 2004; Sargent, Dalton, O'Connor, Olmstead, & Klein, 1999) and one study of iron supplementation (Wolf et al., 2003) to remedy the effects of lead. These educational interventions emphasize the importance of protective parental behaviors that reduce children's exposure to lead or increase nutrient content of children's diets. Such behaviors do not occur in isolation, as parents who are more mindful of children's health risks are also more likely to be cognitively stimulating and emotionally supportive of their children. Recognizing that parental behaviors play a vital role in reducing the risks of neurotoxicant exposure, micronutrient deficiency, and poorer cognitive outcomes is essential to effective public health and epidemiological interventions.

Summary and Conclusions on Lead

Table 1 summarizes the main conclusions of research pertinent to lead across the four disciplines represented by the authors. Our conclusions are predicated on the assumption that conflicts and controversies among disciplines over which discipline may explain more of child cognitive difficulties and behavior problems distracts from the urgent task of protecting the most

vulnerable children. Alternative hypotheses to the moderating effects proposed in the table include, among others, the cumulative-risk hypothesis that lead would add to the risks of micronutrient deficiencies and deprived social environments in predicting child cognition and behavior. The research conclusions in Table 1 and knowledge gaps identified in our review suggest the following research agenda to identify those children most vulnerable to lead:

- Interdisciplinary prospective multilevel studies of interactions among lead, micronutrients, and multiple features of social environments including parenting behaviors and practices, as well as child care and school quality
- Additional experimental animal studies of enrichment/deprivation and lead interactions
- Experimental animal studies of interactions among enrichment/deprivation, micronutrients, and lead

MERCURY

Mercury Epidemiology

Introduction

Three forms of mercury are important from a toxicological standpoint: metallic, inorganic, and organic. Dental amalgams, used to fill cavities in teeth, are approximately 50% metallic mercury, and small amounts of mercury vapor are released during chewing and grinding and are inhaled. The magnitude of the health hazard posed by this exposure is controversial. Some studies of dental professionals have reported associations between indices of mercury burden and performance on neurobehavioral tests (Bittner et al., 1998; Echeverria et al., 1998). Similar studies have not been done on children in whom amalgam restorations were placed, although two large randomized trials on this issue, funded by the U.S. National Institute of

TABLE 1
Conclusions on Effects of Lead by Discipline

Type of finding	Discipline	Conclusion
Replicated	Epidemiology/developmental neurotoxicology	(a) Lead is negatively related to child cognition. (b) Lead is positively related to child behavior problems: attention problems, aggression, delinquent behaviors. (c) Reductions in average lead levels in children have not altered these relations, suggesting no safe level of lead. (d) Socioeconomic status (SES) exacerbates lead effects on child outcomes.
	Experimental psychology (animal)	(a) Lead causes learning deficits, disrupted attention, impulsivity, aggression, and elevated cocaine self-administration. (b) Lead damages functioning and gene expression of neurotransmitters essential to learning and memory.
	Child development/social environments	(a) Poverty and minority status (particularly, non-Hispanic black) are linked to greater lead exposure and poorer child functioning. (b) Parenting practices and behavior are correlated with SES and child cognition and behavior. (c) Child care and public school quality are correlated with SES and child cognition and behavior.
	Nutrition	(a) Iron and zinc are independently related to child cognition and behavior. (b) Experimental animal research confirms that iron or zinc causes reductions in lead absorption and retention. (c) Iron deficiencies are correlated with poverty and ethnicity.
Hypothesized	Interdisciplinary	(a) Maternal lead levels affect parenting practices and behaviors. (b) Iron and zinc are effect modifiers of lead on child cognition and behavior. (c) Parenting practices and behaviors are effect modifiers of lead on child cognition and behavior. (d) Child-care and public-school quality are effect modifiers of lead on child cognition and behavior.
Research needs	Interdisciplinary	(a) Additional experimental animal studies of interactions between enrichment or deprivation and lead (b) Experimental animal studies of interactions among lead, micronutrients, and enrichment/deprivation (c) Prospective studies of interactions among lead; micronutrients; and multiple features of social environments including parenting behaviors, child-care quality, and school quality

Dental and Craniofacial Research, are currently underway (DeRouen et al., 2002; Children's Amalgam Trial Study Group, 2003). Metallic mercury is also widely used in switches and in medical devices such as thermometers and sphygmomanometers. Many rituals of the Caribbean-based religion Santeria also involve metallic mercury.

Inorganic (ionic) mercury was formerly used in a variety of medical and cosmetic products (e.g., laxative, dewormer, teething powder, skin-lightening cream). However, these uses are now uncommon.

Of the several forms of organic mercury, methylmercury and ethylmercury are of greatest concern. The latter was widely used in the United States as a preservative (called thimerosal) in multiuse vials of vaccines until 1999, when concerns were raised over the cumulative mercury dose to an infant receiving the recommended vaccines over the first few years of life. The fact that infants receive many vaccinations during the interval when autism is often diagnosed has led some to hypothesize that mercury plays a role in this syndrome's etiology (S. Bernard, Enayati, Redwood, Roger, & Binstock, 2001). Several studies have failed to support this hypothesis, however.

A population-based ecologic study was conducted in Denmark examining the incidence of autism between 1971 and 1992, when thimerosal was used as a vaccine preservative, and between 1992 and 2000, when it was no longer used (Madsen et al., 2003). The incidence was steady at less than 1/10,000 until about 1990, when it began to rise steadily, reaching almost five 2- to 4-year-olds in 10,000 and three 5- to 6-year-olds in 10,000. Thus, it seems unlikely that the rise in autism observed after 1992 was attributable to thimerosal, given that the incidence had remained stable during the previous decades.

In a Danish case-control study of children diagnosed with autism or other autism spectrum disorders (ASDs) from 1990 through 1996 (Hviid, Stellfield, Wohlfahrt, & Melbye, 2003), neither autism nor ASDs were significantly more frequent among children who received vaccines containing thimerosal than they were among children who received thimerosal-free vaccines. (For autism, the incidence rate ratio was 0.85, 95% confidence interval: 0.6, 1.20; for ASDs, it was 1.12, 95% confidence interval: 0.83, 1.43.) Furthermore, coherent dose–response relationships were not found when a child's risk was calculated in relation to the number of thimerosal-containing vaccines received. (The increase in the relative risk of autism per 25 μg of thimerosal was 0.98, 95% confidence interval: 0.90, 1.06; and for ASDs, 1.03, 95% confidence interval: 0.98, 1.09.) Thus, this study provided no evidence of an association between exposure to thimerosal and the risks of either autism or ASDs.

In a case-control study conducted in Hong Kong (Ip, Wong, Ho, Lee, & Wong, 2004), neither the blood-mercury nor the hair-mercury levels differed significantly between a group of 82 children with autism and 55 controls. In a retrospective cohort study involving almost 110,000 children in the United Kingdom (Andrews et al., 2004), the risk of general developmental disorders, language or speech delays, behavior problems, encopresis (involuntary passage of feces), and enuresis (involuntary passage of urine) were evaluated in relation to diptheria-tetanus-pertussis/diptheria-tetanus doses received. A significant increase in the risk of a tic disorder was found, but for several other disorders (general developmental disorders, unspecified developmental delay, attention-deficit disorder), the risk appeared to decrease significantly with increasing dose. In a two-phased retrospective cohort study conducted using HMO databases and involving more than 140,000 children, Verstraeten et al. (2003) did not find consistent evidence of associations between receipt of thimerosal-containing vaccines and neurodevelopmental outcomes, including autism.

Overall, the evidence does not support an association between receipt of thimerosal-containing vaccines and the risk of autism (Parker, Schwartz, Todd, & Pickering, 2004; Rutter, 2005). Much remains unknown, however. The half-life of ethylmercury in infants might be as brief as 7 days (Pichichero, Cernichiari, Lopreiato, & Treanor, 2002), suggesting that it would largely be cleared between vaccinations given on the recommended schedule. Thimerosal has been removed from most vaccines given to children in the United States, although it does continue to be added to influenza vaccine. It is possible that a small percentage of children are especially vulnerable to ethylmercury but that the deficits induced in these children would not produce a significant elevation in the overall risk estimate. In a case-control study, the mean hair-mercury level was significantly lower in a group of 94 children with autism (0.47 ppm) than in a group of 45 matched controls (3.6 ppm), leading the authors to speculate that enhanced mercury retention plays a role in the etiology of autism (Holmes, Blaxill, & Haley, 2003). The mean hair-mercury level in the control children was much higher than would be expected, however, as the geometric mean in 1- to 5-year-old U.S. children is 0.12 ppm (McDowell et al., 2004). This suggests that the control samples in this study might have been contaminated. Based on available evidence, therefore, it does not appear to be the case that the ethylmercury used to preserve vaccines is responsible for the widespread increase in autism.

People are exposed to methylmercury primarily by consuming fish. This is the species of mercury that is of greatest concern in terms of chronic low-dose exposure of the general population and, therefore, is the primary focus of this section.

Major Sources and Pathways of Mercury Exposure

Inorganic forms of mercury (ionic and metallic) are dispersed into the environment by means of both natural processes and human activities. The former include the weathering of mercury-containing ore and volcanic eruptions, while the latter include emissions from coal-fired power plants, dental amalgams, workplace exposures, accidental spills, and the incineration of medical and municipal wastes. The relative importance of natural and human-created sources is difficult to determine

because of the complex biogeochemistry of mercury's fate and transport. The U.S. EPA estimates that human-created sources account for 50 to 70% of the mercury in the environment, while the World Health Organization (WHO) places the estimate at 25% (NRC, 2000). The most important pathway for exposure to methylmercury begins with airborne inorganic mercury being washed to the earth in precipitation and deposited in bodies of water. It settles into sediments, where bacteria transform it into methylmercury. It then ascends the aquatic food chain. As it does so, it accumulates in living tissue and the concentration is biomagnified. This means that methylmercury levels tend to be highest at the top of the food chain—in large, long-lived, predatory fish such as shark, swordfish, and tuna. The levels of methylmercury in such fish can be thousands of times greater than the concentrations of inorganic mercury in the water. The primary route of exposure of the general population to methylmercury is thus fish consumption. The U.S. EPA has established an RfD for methylmercury of 0.1 micrograms per kilogram (μg/kg) of body weight per day, which it defines as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime" (Rice, Schoeny, & Mahaffey, 2003, p. 108).

It was only with the publication of data from NHANES 1999–2000 that nationally representative estimates of mercury burdens in the U.S. population became available (Schober et al., 2003). The median blood-mercury level in women of reproductive age (16–49 years; $N = 1{,}709$) was 1.02 micrograms per liter (μg/L). The 90th percentile was 4.8 and the 95th percentile 7.1. By making a variety of assumptions, one can estimate that the mercury intakes of approximately 8% of women of reproductive age exceed the RfD. As expected, fish consumption was a strong predictor of blood-mercury level. Levels were highest among the "Other" racial/ethnic category (Asians, Native Americans, Pacific Islanders), presumably reflecting the greater relative importance of fish in the diets of these population subgroups. The geometric mean was four times higher among women who reported eating three or more servings of fish in the previous 30 days than it was among women who reported eating no fish during that period, and seven times higher among women who reported eating nine or more fish meals (Mahaffey, Clickner, & Bodurow, 2004).

It is clear that it is possible to accumulate a mercury burden of concern by frequent consumption of large quantities of fish that are available on the U.S. commercial market and that do not exceed 1 ppm mercury in tissue, the FDA limit (Hightower & Moore, 2003). In March, 2003, the U.S. EPA and FDA issued a Joint Consumer Advisory for women who might become pregnant, pregnant women, nursing mothers, and young children. It recommended that (a) four types of fish not be consumed at all: shark, swordfish, king mackerel, and tilefish; (b) consumption of other fish and shellfish that are lower in mercury (e.g., salmon, canned light tuna, shrimp, pollock, catfish) be limited to 12 ounces (two average meals) a week; (c) only one of the two meals should consist of albacore ("white") tuna; and (d) local advisories be checked for guidance regarding fish caught in local lakes, rivers, and coastal areas.

Health Effects of Methylmercury

The devastating effect on the human nervous system of high-dose prenatal exposure to methylmercury was first brought to the world's attention in the 1950s by the epidemic of poisoning that occurred among residents of the Minamata Bay area of the Japanese island of Kyushu. For decades, an acetaldehyde plant in Minamata City had discharged inorganic mercury into the bay, resulting in very high levels of methylmercury in bay fish. Subsistence fishermen and their families were the most affected and, among these, it was children who were in utero, exposed by means of their mothers' consumption of contaminated fish, who suffered the greatest injuries. Individuals who were exposed only as adults developed focal signs of neurologic injury, such as visual field constriction, paresthesias of the glove and stocking type (abnormal spontaneous sensations in the hands and feet resulting from peripheral nerve damage), and motor impairments. Individuals exposed fetally, however, suffered profound diffuse neurologic injury. They developed cerebral palsy at 50 times the expected rate and mental retardation at 10 times the expected rate. Other signs included abnormal speech articulation, primitive reflexes (reflexes that should disappear with maturation), cerebellar ataxia, movement disorders such as athetosis and chorea, and growth disturbances (Harada, 1995). This disease is now referred to as Congenital Minamata Disease (CMD). In some instances, the mothers of affected children manifested no signs or symptoms or only mild paresthesias. The most severely affected children were unable to carry out simple activities of daily living, and a special hospital (Meisui-en) was built in Minamata City to provide life-long medical treatment and care for these patients, now adults.

Because it was some years before methylmercury was identified as the cause of CMD, no contemporaneous measures of dose were available. In 1959, when methylmercury was finally identified as the cause of CMD, the mean concentration in the hair of the mothers of CMD patients ranged from 2 to 191 ppm. Recently, investigators took advantage of the Japanese custom of retaining a child's umbilical cord and measured the methylmercury concentrations in dried cord tissue in order to estimate what the maternal hair-mercury levels would have been at the delivery of patients with CMD (Akagi, Grandjean, Takizawa, & Weihe, 1998). For the 151 patients for whom samples were available, the estimated level was 41 ppm. The range was 4 to 133, however, reflecting the high degree of uncertainty resulting from the number of toxicokinetic assumptions required in order to estimate maternal hair mercury from cord-tissue methylmercury.

A somewhat better estimate of the prenatal dose of methylmercury required to produce CMD was obtained following

several episodes of poisoning that occurred in Iraq during the 1970s. Seed grain that had been treated with an organic mercury-based fungicide was ground and made into bread rather than planted, as intended. Hundreds of deaths and thousands of cases of severe nonfatal poisoning occurred as a result of this acute, high-dose exposure to methylmercury. As in Minamata, fetuses were the most severely affected, and a study cohort of 81 mother–infant pairs in which fetal exposure occurred were identified (Marsh et al., 1987). By parental report, delays in the ages at which the children walked and talked were dose-related, as were the presence of abnormalities in neurological examinations conducted by investigators. Application of a variety of statistical models (e.g., nonparametric smoothing, logit, hockey-stick) indicated that the risks of delayed walking (past 18 months) and delayed talking (past 24 months) began to increase when the maternal hair-mercury level was between 10 and 20 ppm (Cox et al., 1989).

In a review of the literature, the International Programme on Chemical Safety of the WHO concluded: "A prudent interpretation of the Iraqi data is that a 5% risk may be associated with a peak Hg [mercury] level of 10 to 20 μg/g in maternal hair" (WHO, 1990, p. 103). It did note, however, that risk assessments conducted in order to establish exposure standards for chronic fish consumers would be strengthened by the availability of additional epidemiological studies of children exposed in utero to maternal hair levels of 10 to 20 ppm. In part, this recommendation was due to a variety of limitations of the Iraqi data. The studies were conducted as part of the public health response to an acute poisoning episode, which limited the design options available to the investigators. As noted, the exposures in Iraq were acute rather than chronic. Moreover, the hair-mercury levels were much higher than they are in chronic fish consumers. Among the 81 women studied by Marsh et al. (1987), many had hair-mercury levels greater than 100 ppm. The median mercury level among U.S. women of reproductive age is currently .19 ppm and the 95th percentile is 1.73 ppm (McDowell et al., 2004). In addition, the studies conducted on human health effects suffered from a variety of methodological limitations, such as the relatively small sample size, uncertainty about the base population that generated the 81 cases on which the estimate of threshold was based, the high degree of likelihood of both exposure and outcome misclassification, and the potential influence of outlying observations on the estimates of threshold (Crump et al., 1995).

In the past 15 years, several epidemiological studies of low-dose methylmercury exposure have been published, conducted in diverse settings such as Northern Quebec (McKeown-Eyssen, Ruedy, & Neims, 1983), French Guiana (Cordier et al., 2002), Ecuador (Counter, Buchanan, Ortega, & Laurell, 2002), the United States (Stewart et al., 2003), Peru (Marsh, Turner, Smith, Allen, & Richdale, 1995), the Amazon Basin, (Grandjean, Weihe, White, & Debes, 1998), and Madeira (Murata et al., 1999). Our focus, however, will be restricted to three large prospective cohort studies that identified children at birth, measured biomarkers of prenatal methylmercury exposure, and conducted follow-up exposure and neurodevelopmental assessments at school age. These three studies were conducted in New Zealand, the Faroe Islands, and the Seychelles Islands.

In the New Zealand study (Kjellstrom, Kennedy, Wallis, & Mantell, 1986; Kjellstrom et al., 1989), 16,293 women delivered in the study area during the recruitment period and 10,930 were screened to determine their fish consumption. Among these, 935 high fish consumers (more than three fish meals per week) were identified. Hair samples were collected and 73 women with hair levels over 6 ppm were enrolled. In this "high" mercury group, the mean maternal hair-mercury level was 8.3 ppm (range 6–86, but only one observation greater than 20 ppm). Each woman was matched to three control women as follows: The first control was a woman who was a high fish consumer (more than three fish meals per week) but whose hair-mercury level was less than 3 ppm; this was to address the fact that women who frequently consume fish might differ, in respects that are important for child development, from those who do not. The second control was a woman who was an infrequent fish consumer and who had a hair-mercury level less than 3 ppm. The third control was a woman with a hair-mercury level of 3 to 6 ppm. The three controls were also selected to match the woman with the high mercury level on ethnic group, maternal age, maternal smoking, residence time in New Zealand before the child's birth, and sex of child. Matching for ethnic group was necessary because of the diversity of the population (European, Pacific Islander, Asian).

Children of the New Zealand mothers were assessed at ages 4 and 6. A battery of 26 tests, including the McCarthy Scales of Children's Abilities, the Wechsler Intelligence Scale for Children-Revised (WISC-R), The Test of Language Development (TOLD), the Peabody Picture Vocabulary Test (PPVT), and tests of reading and math achievement, was administered. In robust regression analyses adjusting for a variety of potential confounders, maternal hair-mercury was inversely associated with the children's scores on full-scale IQ, the spoken language quotient of the TOLD, and the perceptual-performance and motor scales of the McCarthy Scales. The investigators reported that these associations were largely due to the children whose maternal hair-mercury levels exceeded 10 ppm. The results were heavily influenced by whether the analyses included or excluded the child for whom maternal hair-mercury level was 86 ppm. The associations were much stronger when this observation was excluded.

In the Faroe Islands study, a birth cohort of 1,353 children was established in 1986–1987 (Grandjean et al., 1992). The population of the Faroe Islands, which are located in the North Atlantic near the Arctic Circle, is almost exclusively Nordic in origin. The exposure of Faroese to methylmercury occurs both by consumption of fish, which constitute 44% of dinners (the average daily consumption is 72 grams), and periodic consumption of pilot whale, which constitutes 10% of dinners (av-

erage daily consumption 7 grams). The concentration of methylmercury in whale meat is approximately 2 ppm, several times higher than the typical concentration in most fish species. The Faroese also eat whale blubber, in which the concentration of methylmercury is low but the concentration of organochlorine contaminants, such as PCBs and dioxins, can be quite high. Prenatal methylmercury concentrations were measured in two tissues: maternal hair collected at delivery (mean 4.3 ppm, inter-quartile range 2.6 to 7.7; 15% over 10) and umbilical-cord blood (mean 22.9 μg/L, inter-quartile range 15 to 50). Total PCB level in umbilical-cord tissue was measured for about half of the children. The first follow-up neurodevelopmental evaluation was performed when children were 7 years old (N = 917; Grandjean et al., 1997). The battery consisted of the California Verbal Learning Test-Children (CVLT-C), the Boston Naming Test, the Bender-Gestalt Test, the Tactual Performance Test (TPT), 3 subtests of the WISC-R (digit span, similarities, block design), and three computer-administered tests from the Neurobehavioral Evaluation System-2 (finger tapping, eye-hand coordination, and continuous-performance test).

While both biomarkers of prenatal methylmercury were inversely associated with children's scores on many of the neuropsychological tests, the associations involving cord-blood mercury tended to be stronger. Adjusting for covariates, increased cord-blood-mercury concentration was associated with worse scores on finger tapping, the continuous performance test (false negatives and reaction time), the digit span subtest of the WISC-R, the Boston Naming Test (both cued and noncued), and the CVLT-C (both short- and long-term reproduction). Results were similar when the 15% of the study sample in which maternal hair-mercury level was greater than 10 ppm was excluded, when children with maternal hair-mercury levels of 10 to 20 ppm were compared to those with maternal hair-mercury levels less than 3 ppm (Grandjean et al., 1998), or when children whose exposure to methylmercury was more variable over the course of gestation (and thus presumably from whale consumption rather than fish consumption) were excluded (Grandjean, White, & Jørgensen, 2003). The investigators estimated that a doubling of cord-blood mercury level was associated with deficits that are equivalent to a 1.5- to 2-month delay (based on the regression coefficients for age). The children were assessed again at age 14 years, but results have not yet been published.

The potentially high exposures of the Faroese to organochlorine contaminants prompted the investigators to explore the extent to which these concomitant exposures might be responsible for the apparent associations between prenatal methylmercury and child neurodevelopment. They evaluated how much the effect of methylmercury varied as a function of PCB (i.e., methylmercury by PCB interaction terms) and also conducted analyses stratified by PCB tertile and determined that the strength of the association between methylmercury and neurodevelopment was not stronger, and might have even been somewhat weaker, among the third of the children with the highest PCB exposure. These analyses led the investigators to conclude that confounding by organochlorine exposure is unlikely to account for the methylmercury associations (Budtz-Jørgensen, Keiding, Grandjean, & White, 1999). Additional analyses suggested that increased exposure to methylmercury might augment the neurotoxicity of PCBs but not the converse (Grandjean et al., 2001). The investigators addressed this issue more directly and in greater detail in a second cohort of 182 children, for whom measurements were made not only of mercury in maternal hair, whole cord blood, and cord serum, but also of 18 pesticides or metabolites in maternal serum, 28 types (congeners) of PCBs in maternal serum and breast milk, selenium in cord blood, and several long-chain polyunsaturated fatty acids (arachidonic, eicosapentanoic, docosahexaenoic, total omega-3) in cord serum. The main outcome, Neurologic Optimality Score at 2 weeks of age, declined significantly with an increase in cord-blood-mercury (but not with an increase in maternal hair mercury), and adjustments for total PCBs and fatty acids did not change the results appreciably (Steuerwald et al., 2000).

Electrophysiological assessments were also conducted at ages 7 and 14 years. At age 7, peaks I, III, and V of brainstem auditory evoked potentials (electrical responses of the brain to stimulation) were delayed among children with higher prenatal methylmercury levels, at both 20 and 40 Hz. Visual acuity, contrast sensitivity, auditory thresholds, and visual evoked potentials were not associated with prenatal methylmercury levels. At age 14 years, III–IV interpeak interval (the time it takes for a signal to be transmitted between stations of the auditory processing pathway) was significantly longer among children who currently had higher hair-mercury levels (Murata, Weihe, Budtz-Jørgensen, Jørgensen, & Grandjean, 2004). This means that with higher mercury levels, auditory information was transmitted more slowly in this region of the auditory system. These findings largely replicated those of a cross-sectional study by the same investigators on a sample of 6- and 7-year-olds in Madeira (Murata et al., 1999).

Residents of the Seychelles Islands, like the Faroese, consume fish regularly, approximately 12 fish meals per week. The Seychellois are more ethnically diverse than the Faroese, including for the most part individuals of African, European, and Indian descent. A study sample of 740 was recruited and hair samples collected from women at delivery (Marsh et al., 1995). The mean mercury level in these samples was 5.8 ppm (ranging from 0.5 to 26.7 ppm, with 22% over 10). The children's development was assessed at ages 6.5, 19, and 29 months and at 5.5 and 9 years. Among the tests applied were the Denver Developmental Screening Test, the Fagan Test of Infant Intelligence, the Bayley Scales of Infant Development, the Preschool Language Scale, the McCarthy Scales of Children's Abilities, the Bender-Gestalt Test, and two subtests of the Woodcock-Johnson Tests of Achievement. At age 9, an effort was made to administer the tests that were found in the Faroe Islands study to be associated with prenatal methylmercury level. These in-

cluded the Boston Naming Test, the California Verbal Learning Test-Children, finger tapping, and a CPT (the Connors' Continuous Performance Test). (Among the other tests administered were the WISC-III, the Developmental Test of Visual-Motor Integration, the Bruininks-Oseretsky Test of Motor Proficiency, the Trail-Making Test, the Grooved Pegboard, the WRAML Design Memory subtest, a Haptic Discrimination Test, the Child Behavior Checklist, and the Hyperactivity Index of the Connors' Teacher Rating Scale.) The data from this study have been examined in many different ways but, as the authors conclude in their most recent paper, these data "indicate no detectable adverse effects in a population consuming large quantities of a wide variety of fish" (Myers et al., 2003, p. 1692).

The apparent inconsistencies among the findings from these three large epidemiological studies of chronic low-dose exposure to methylmercury have provided a challenge to risk assessors seeking to set rational exposure standards. Recent assessments applying a benchmark-dose (BMD) approach and hierarchical Bayesian methods suggest, however, that the body of evidence might be more concordant than it would seem to be upon casual perusal. The BMD is identified, based on a statistical model, as the dose at which the prevalence of a defined health abnormality exceeds the background prevalence of the abnormality by a specified amount. Many assumptions must be made. First, a functional form of the dose–response relationship (e.g., linear, sublinear, supralinear) must be chosen. Second, the critical abnormality must be specified. It can be defined distributionally (e.g., scores more than 2 standard deviations below the mean) or clinically (e.g., the presence of a particular abnormal finding in a neurologic examination). Although the U.S. EPA selected fetal neurotoxicity as the critical health endpoint, emerging evidence suggests that adult cardiovascular toxicity might occur at methylmercury levels that are lower than those associated with adverse fetal effects (Stern, 2005). Third, the excess risk of the abnormality to be avoided, called the "benchmark response," must be specified. A doubling of the background prevalence is typically assumed to be the adverse health effect.

It is important to recognize that the choice of the benchmark response does not rest on scientific consideration but on societal values. It essentially represents the amount of methylmercury-associated morbidity that is deemed tolerable by whomever is assessing the risk. Once the critical dose is identified, the lower bound of its 95% confidence interval (the BMDL) is taken as the "point of departure" for calculating the mercury intake that would result in that dose. Thus, the BMDL is the lowest dose that is statistically consistent with the observed excess risk. It does not represent a "threshold" for the occurrence of toxicity.

The U.S. EPA derived the RfD on the basis of BMD modeling. To do so, the BMDL was adjusted for uncertainties (e.g., pharmacokinetic and pharmacodynamic variability, data-base deficiencies), and the intake of methylmercury that would result in an individual achieving a burden equivalent to the uncertainty-adjusted BMDL calculated. This is the RfD. In deriving the RfD, the U.S. EPA selected 12 ppm as the critical BMDL, producing an uncertainty-adjusted target hair-mercury level of 1.2 ppm. A model involving assumptions about factors such as the elimination constant (the fraction of methylmercury body burden that is eliminated per day), blood volume, methylmercury absorption, and fraction of absorbed dose in the blood was used to determine that a methylmercury intake of 0.1 μg/kg/day over a lifetime would not result in a hair-mercury level exceeding 1.2 ppm (U.S. EPA, 2001).

It turns out that the BMDLs for maternal hair-mercury level calculated on the basis of the New Zealand, Faroe Islands, and Seychelles Islands studies range between 6 ppm (the New Zealand study excluding the observation at 86 ppm) and 25 ppm (Seychelles Islands study). This 4-fold difference between BMDLs from the different studies is less than the 10-fold uncertainty factor by which the BMDL was ultimately divided in calculating the RfD. The fact that the between-study variation in results is smaller than the size of the uncertainty factor applied illustrates the substantial influence the size of the uncertainty factor selected by the risk assessor exerts on the RfD.

Many seem to have been led, on the basis of the difference in statistical significance levels reported in the two studies, to conclude that the Faroe Islands "showed" associations between increased methylmercury exposure and neurodevelopmental deficits while the Seychelles Islands study did not. In a set of recent analyses involving Bayesian hierarchical models, however, Ryan (as cited in U.S. EPA, 2005) showed that, at a deeper quantitative level, the results of the two studies are very similar. In fact, the slopes of the inverse association between prenatal methylmercury exposure and IQ were almost identical: a −0.13 point decline for each ppm increase in maternal hair in the Seychelles Islands study and a −0.12 point decline in the Faroe Islands study. (In the Faroe Islands study, IQ was estimated on the basis of 3 subtest scores using a structural equation model.) The slopes associated with other endpoints assessed in the two studies were also quite similar to one another and to those in the New Zealand study. Thus, much of the recent debate seeking reasons for the discrepancies in the findings of these studies appears to be premature and to divert attention from the actual convergence of results.

In 2000, a committee assembled by the National Research Council of the National Academies to review the U.S. EPA's process in deriving the RfD concluded that the decisions and assumptions made by the EPA were sound (NRC, 2000). It also, however, identified three classes of data gaps that contribute to uncertainty in the calculation. The first class pertains to the possibility of variation in susceptibility to methylmercury. Factors that might affect susceptibility include age, sex, genetics, health status, nutritional status, and toxicokinetic and toxicodynamic processes. The second class of data gaps pertains to the lack of information about the possibility of late-emerging neurodevelopmental effects as children age. The third class of

data gaps pertains to exposure measurement. Factors that contribute to problems in measuring exposure are a lack of dietary-intake data; the necessity of extrapolating from a biomarker such as maternal hair mercury to methylmercury intake; confounding by coexposures to other neurotoxic contaminants (e.g., PCBs); and the impracticality of characterizing short-term temporal variations in exposure using currently available biomarkers, particularly during potentially critical windows of brain vulnerability. Another critical aspect of this class of data gaps is uncertainty about nutritional factors as potential confounders or effect modifiers of methylmercury neurotoxicity (Chapman & Chan, 2000), which we consider in our discussion of micronutrients and mercury below.

Mercury Neurotoxicity

As was the case for lead, a vast number of behavioral disturbances are caused by mercury exposure. But, as we observed in the review of lead, it has been the reports on the effects of the metal(s) on memory, cognition, and learning that have received the greatest attention from scientific investigators.

Cognition and Associative (Learning) Processes

Although the aforementioned Japanese and Iraqi cohorts alerted the scientific community to the adverse effects of high levels of mercury on neurobehavioral function, a more intriguing issue has been the potential neurotoxic effects of very low levels of methylmercury exposure. Of central interest in this regard are the effects of mercury exposure on the developing brain, inasmuch as animal research shows that pathological changes in the more mature brain may be localized and thus less likely to result in cognitive impairments (Costa, Aschner, Vitalone, Syversen, & Soldin, 2004; Pan, Sakamoto, Liu, & Futatsuka, 2005). Although both prenatal and postnatal exposures to methylmercury result in behavior problems, prenatal exposure may pose a greater threat to public health. With some toxicants, placental barriers buffer or at least limit the toxic effects of contaminant exposure during gestation, but prenatal exposure to mercury produces profound changes in the central nervous system (CNS) despite such barriers. In animal studies, Baraldi, Zanoli, Blom, & Brunello (2002) presented evidence of learning and memory deficits in adult rats that had been exposed to methylmercury during pregnancy, and the impairment was traced to the effects of metal exposure on the NMDA (glutamate) receptor, which, as discussed above, is believed to be a substrate for learning and conditioning. Parallel findings were reported by Goulet, Dore, and Mirault (2003) in that mice exposed to methylmercury during pregnancy performed more poorly than did nonexposed controls on a reference- and working-memory task. It is noteworthy that the findings from human investigations of the effects of prenatal methylmercury exposure on human behavior are in agreement with the developmental animal literature. Specifically, Ramirez et al. (2003) found that children exposed to methylmercury in utero scored lower on measures of neuropsychological development, and these deficiencies were persistent when the children were tested at 2 years of age. Because CNS development is accelerated during the gestational period, it is not surprising that toxic insult during this time is likely to have lasting consequences. Of course, more prospective human studies are needed, but they are often difficult to undertake and complete and sometimes even more difficult to interpret.

Timing of exposure is an exceedingly important factor for research on developmental toxicity in general, and this is surely true in the case of organomercury exposure (Slikker, 1994). It is essential that the time and duration of metal exposure in animals match periods of vulnerability in humans, and this necessitates an awareness of interspecies differences in development of the nervous system. Whatever the species, brain growth and development occur most rapidly during gestation, so the majority of animal studies on the effects of methylmercury on associative processes have incorporated prenatal administration into the overall exposure regimen.

Both rodent and nonhuman-primate studies have yielded information useful to helping resolve questions about the impact of mercury poisoning on cognitive and associative functioning. For example, Goulet et al. (2003) gave pregnant mice drinking water containing 0, 4, 6, or 8 ppm methylmercury during pregnancy and nursing. Female and male offspring were tested for rotorod performance (motor coordination), open-field activity, and reference as well as working memory. The results showed that exposed females, but not exposed males, exhibited less locomotion and showed impaired working memory as measured in a T-maze apparatus.

The Goulet et al. (2003) locomotor findings are consistent with other reports of motor impairment in animals exposed to methylmercury either early in development (e.g., B.H. Choi, 1991; Markowski et al., 1998; Roegge et al., 2004), or as adults (M.O. Dietrich, Mantese, dos Anjos, Souza, & Farina, 2005). The significance of these data derives from the aforementioned studies of methylmercury poisoning in Minamata Bay and Iraq. In both instances, one of the most obvious toxic insults was impairment of motor development (Bakir et al., 1973; Harada, 1995; Takeuchi, Eto, & Eto, 1979). So, as with lead, points of considerable overlap are evident in the respective human and animal literatures on mercury-induced disturbances in behavior.

With respect to the primate data, one cohort of monkeys was exposed to methylmercury throughout pregnancy. Even though the exposure protocol was identical across all members of the cohort, noticeably different patterns were evident for animals tested in infancy from those tested as adults. That is, when tested as infants, monkeys exhibited deficits in visual-recognition memory and in spatial memory (Gunderson, Grant, Burbacher, Fagan, & Mottet, 1986; Gunderson, Grant-Webster, Burbacher, & Mottet, 1988). Conversely, when tested at 7 to 9 years of age, there was no evidence of residual memory deficiencies in these same monkeys (S.G. Gilbert, Burbacher, & Rice, 1993). In fact,

the older treated animals exhibited fewer errors on a delayed alternation task than did nontreated controls. On the whole, then, these data suggest that if methylmercury exposure in utero produces cognitive deficits, the effects may be short lived and are seemingly reversible.

However, additional primate investigations argue in favor of the position that enduring changes in complex cognitive and learning processes occur due to developmental methylmercury exposure. In a study involving another cohort of monkeys, Rice (1992b) failed to find differences between controls and methylmercury-treated animals when tested on a nonspatial discrimination-reversal task as juveniles. However, perinatal methylmercury exposure was associated with deficiencies in temporal discrimination—characteristic patterns of responding on a fixed-interval schedule were not as evident among metal-exposed monkeys as they were among controls. This finding is supported by rodent studies of discrimination performance showing that rats exposed to methylmercury during gestation are, as adults, less likely to initiate responding on a visual-discrimination task than are untreated controls (Schreiner, Ulbrich, & Bass, 1986).

Much of the primate literature on the effects of organomercury on learning and associative events is based on changes in schedule-controlled operant responding (Newland & Paletz, 2000). In this procedure, the animal is required to meet detailed, specified conditions in order to receive a response outcome. Because an understanding of the nuances of operant behavior has been gained over many decades, schedule-controlled contexts are ideally suited to test for neurotoxicant-induced disturbances in learning and conditioning.

Reports of learning disruptions in operant-conditioning studies have examined the effects of developmental methylmercury exposure on fixed-interval performance, or on responding under a differential-reinforcement-of-low-rates (DRL) schedule. As indicated in the earlier section on lead neurotoxicity, for the fixed-interval schedule a reinforcer is made available after a specified time period passes, while in the DRL schedule the animal must withhold responding for a set time and then execute the behavior, typically during a brief window (limited hold period). Regarding methylmercury effects on fixed-interval responding, metal exposure is associated with deficits in temporal discrimination, but local response rates through the interval are unaffected by the toxicant (Rice, 1992b). Further, investigators have been unable to show that early methylmercury exposure in rats affects DRL behavioral profiles (Eccles & Annau, 1982). These data contrast sharply from the pattern characteristically produced by lead, for which pronounced increases in fixed-interval and DRL rates are observed in rodents and monkeys (Cory-Slechta, Pokora, & Preston, 1996; Mele, Bowman, & Levin, 1986; Michaelis, Holloway, Bird, & Huerta, 1987; Rice & Gilbert, 1985). Operant methodologies, accordingly, have proven to be sensitive indices of the selective effects of different neurotoxicants on learning and conditioning.

In summary, there is general agreement that the developing brain is more vulnerable to mercury poisoning than the adult brain is and that this is especially true for cases of prenatal exposure. It is noteworthy that considerable parallels exist in the results from investigations involving children and the findings from the developmental animal literature. Finally, it is critical that the time and duration of mercury exposure in animals parallel comparable periods of development in children. For example, because metal exposure does not lead to metal accumulation in the human fetus until later in gestation (Bhattacharyya, 1983), animal studies should follow a similar timetable.

Neurochemical Mechanisms in Effects of Mercury on Learning and Memory

Contributing to our understanding of the complex relation between mercury contamination and challenges to learning and behavioral systems, neurobiological studies have provided needed information at the molecular level. Methylmercury exposure has a negative impact on protein synthesis, mitochondrial function, adenosine triphosphate (ATP) activity, and normal cellular regulatory mechanisms that maintain cell life (Yasui, Strong, Ota, & Verity, 1997).

But of the many neurological processes that have been studied by metal toxicologists, perhaps none has come under closer scrutiny than cellular injury associated with oxidative stress. Oxidative stress involves excessive oxygen intake by the cell that damages the cell and threatens protein function (S.-H. Choi, Lee, Kim, & Jin, 2005), with the ultimate result being cell death due to the formation of free radicals (unpaired electrons that, in excess, damage cell membranes and DNA; Saratian & Verity, 1991). Although there are many pathways for methylmercury to exert its influence on oxidative stress, the aforementioned corruption of mitochondrial function is one of the chief contributors to the process. The methylmercury situation appears to be especially alarming in cases of prenatal exposure in which disturbances in mitochondria activity, perhaps due to elevated glucocorticoid levels, render prenatal organisms more sensitive to oxidative stress (Ahlborn, Gogvadze, Chen, Celsi, & Ceccatelli, 2000). Moreover, the activity of antioxidant enzymes, believed to confer protection against oxidative stress, is significantly decreased in animals exposed prenatally to methylmercury.

Other animal studies have shown that methylmercury-induced enhancement of oxidative stress occurs at very low levels of exposure (Castoldi, Coccini, Ceccatelli, & Manzo, 2001; Sanfeliu, Sebesta, Christofol, & Rodriguez-Farre, 2003). Pathological injury starts at the brain stem, becomes more widespread with continued exposure (Berntssen, Aatland, & Handy, 2003), and has a deleterious effect on the cerebellum in a dose-dependent manner (Yasui et al., 1997). However, even with the broad range of behavioral anomalies associated with acute or chronic exposure to methylmercury, interventions are

possible. For instance, Gasso et al. (2001) have demonstrated that various antioxidant compounds and calcium-channel blockers greatly reduce the neurotoxic effects of methylmercury, particularly oxidative stress, and that these effects appear to be long lasting. As we progress in our understanding of the molecular interactions between methylmercury and threats to cellular function, more treatment options will become available.

Although methylmercury-related events that increase vulnerability to brain damage present significant health problems, the selective nature of the disturbances may ultimately increase our understanding of mercury dynamics. Of particular interest are findings linked to the effects of methylmercury on disturbances in transmitter function. As discussed previously, disruption of these cellular/molecular transmitter features is tied directly to changes in behavioral and cognitive function, and in the next section we address some of the specific effects of methylmercury on neuronal signaling systems that may impact learning and memory.

Effects of Methylmercury on Glutamate Function. In our discussion of physiological substrates for learning impairments associated with lead exposure, we documented the relevance of LTP to learning and memory (M.E. Gilbert et al., 1996; Lasley et al., 1993; Malenka & Nicoll, 1999) and identified glutamatergic transmission as essential to the development and expression of the phenomenon. Like lead, methylmercury disturbs glutamate function and thus may affect learning and memory-process regulation.

Whereas lead affects glutamate transmission by attenuating calcium-mediated neuronal signaling (Nihei & Guilarte, 2001) and inhibits glutamate bioavailability (Guilarte & Miceli, 1992; Hashemzadeh-Gargari & Guilarte, 1999), methylmercury produces a directionally opposite result that ultimately leads to identical behavioral consequences. Specifically, there is evidence that methylmercury results in overstimulation of the glutamatergic system (Farina et al., 2003), most likely via preferential accumulation of the metal in astrocytes (cells that serve to protect neurons from chemical and physical trauma), where glutamate uptake is inhibited (Aschner, Yao, Allen, & Tan, 2000). At high extracellular concentrations, glutamate can act as an excitotoxin (a substance that overexcites neurons; J.M. Lee, Zipfel, & Choi, 1999), inducing neuronal injury and death (excitotoxicity). The resulting lesions, then, may become manifest as impaired LTP performance and learning deficits (Ozawa, Kamiya, & Tsuzuki, 1998).

Further evidence of methylmercury-induced abnormalities in glutamatergic function is available from a report by Baraldi et al. (2002). In this study using rats, it was found that a single dose of methylmercury (8 mg/kg) administered at an advanced stage of pregnancy (15 days) caused impairments in passive avoidance learning and spatial memory when offspring were tested as adults. In addition, this in utero exposure regimen produced pronounced changes in gene expression of NMDA receptor subtypes in the hippocampus. Because NMDA is believed to be the chief glutamate-receptor subtype involved in learning and memory function (Korz & Frey, 2003; Shaw et al., 2003; Xu, 2005), these findings suggest a causal link between methylmercury-based changes in glutamate systems and cognitive or learning deficiencies.

Cholinergic Receptor Activity. Another transmitter system that may contribute to the pattern of learning impairment in mercury-exposed humans and animals is the cholinergic system. As noted previously, this system is considered to play a modulatory role in LTP and cognitive function (Levin & Simon, 1998; Yamazaki et al., 2002), and recent evidence indicates that methylmercury impacts acetylcholine-receptor activity. Methylmercury inhibits the binding affinity of acetylcholine at the postsynaptic receptor site (cf. Coccini et al., 2000).

Such disruptions in cholinergic processes are often slow to develop but tend to endure. This may partially explain how prenatal exposure to mercury can cause cognitive deficits in children even when assessments are made 7 years later (Grandjean et al., 1997). In any event, a convincing case can be made that inorganic or organic mercury compounds are potent neurotoxic agents that produce parallel changes in cholinergic function and learning and memory dysfunction.

Other Neural Mechanisms. In addition to affecting transmitter systems directly tied to associative conditioning and cognition, methylmercury retards dopamine transmission in the striatum by reducing dopamine concentrations in presynaptic neurons (Rice, 2004). Supporting data are presented by Dare et al. (2003), who show that prenatal methylmercury exposure significantly reduces postsynaptic binding of one of several types of dopamine receptors, the D_2 receptor. As indicated, mesolimbic dopamine levels are integral to the rewarding effects of numerous psychoactive drugs, and although there is a meager literature relating to the topic (but see Rasmussen & Newland, 2001), the potential for mercury-related changes in drug selection and use must be acknowledged.

With respect to structural damage to the CNS, numerous developmental studies in rodents show methylmercury-induced lesions in the precentral cortex and cerebellum (Costa et al., 2004). In adult rats, methylmercury exposure results in the retractions of neuronal growth cones and extensions that are instrumental in the formation of dendrites and axons (Miura, Himeno, Koide, & Imura, 2000). These and abundant other challenges to morphologic development surely contribute to the overall pattern of mercury-based deficits in learning, memory, and motor output.

Mercury and Social Environments

Socioeconomic Status, Ethnicity, and Cumulative Risk

As noted in the introduction and in the section on mercury epidemiology, eating fish, particularly by pregnant women, is the

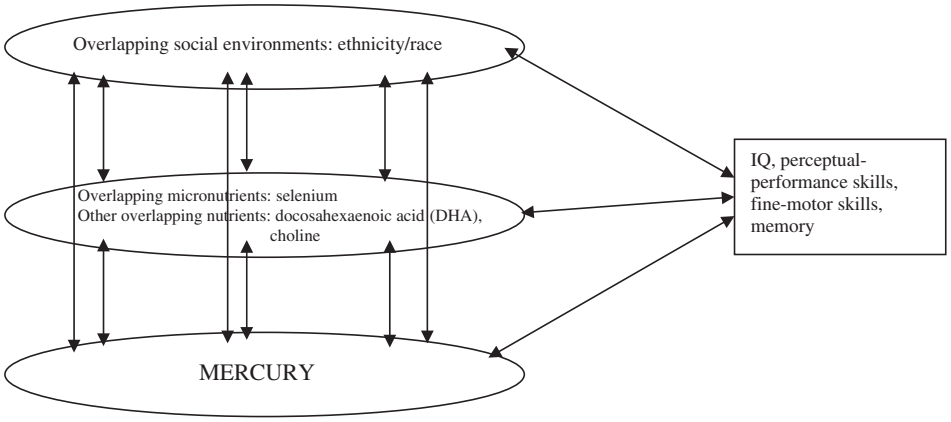

Fig. 6. Model of interrelationships among mercury, social environments, micronutrients, and child outcomes.

most common pathway of children's exposure to mercury. Fish consumption varies by SES, ethnicity, and geographical region. However, in contrast to lead, the children most at risk for effects of mercury exposure are not low-income non-Hispanic black children in urban areas, but low-income children from a variety of ethnic minority groups in both rural and urban regions—particulary Native American,[2] Hispanic, and black children (see Fig. 6).

SES and Fish Consumption. Lower-SES families do consume more fish than middle-SES families do, but so also do high-SES families, particularly in certain geographical regions. Most at risk are low-SES families who are unaware of fish advisories and health risks associated with pollutants in fish. Although we focus on fish consumption because it is related to methylmercury levels, we caution readers that many of the field sites for the research reported below are polluted by other contaminants. The Newark Bay Complex is polluted with PCBs and dioxins (Burger, 2002). The Savannah River is contaminated with both mercury and radionuclides (Burger, Gaines, & Gochfeld, 2001).

In an interview study of adults fishing along the Savannah River in South Carolina, Burger, Stephens et al. (1999) found that the number of fish meals per month and the total grams of fish consumed per year were significantly curvilinearly related to education. Fish consumption was highest among adult fishers who had less than a high-school education and lowest among adult fishers who were high-school graduates. Adult fishers with highest education (some college) were between the other two groups in fish consumption. Burger, Stephens, et al. found that adults with annual incomes $20,000 or under ate self-caught fish more frequently per month than did adults with annual incomes over $20,000. Burger (2002) found that among the fishers in the polluted New York-New Jersey Harbor area, income was highly negatively correlated with fish and crab consumption. Illustrating the link between fish consumption and higher SES in some geographic regions, Hightower and Moore (2003) found extremely elevated mercury burden in upper-middle-class patients in the San Francisco Bay area.

In other geographic regions of the United States and Canada a linear relation between fish consumption and SES has been reported. Among pregnant Inuit women in Quebec, consumption of fish and consumption of seal (but not whale) were significantly inversely related to measures of SES and positively related to measures of maternal mercury in hair (Muckle, Ayotte, Dewailly, Jacobson, & Jacobson, 2001a). Among pregnant women in New Jersey, fish consumption was significantly related to blood-methylmercury and blood-methylmercury was marginally significantly related to education (Stern, Gochfeld, Weisel, & Burger, 2001).

Lack of awareness about safety concerns related to fish consumption is more common among lower-SES families. In March 2004, the EPA and FDA warned U.S. fish consumers not only to avoid specific saltwater fish species with high levels of mercury but also to pay attention to local advisories about fish species with high levels of mercury. In a Mississippi study of 763 female heads of households with Head Start children, women who were high-school graduates were significantly more aware of key environmental and health-safety issues than women without a high-school degree were (Preston, Warren, & Stewart, 2000). In a Florida study of adults fishing in the Everglades (Fleming et al., 1995), adults with lower income or education were less likely to be aware of official advisories reporting the dangers of eating Everglades fish species. In a study of adults fishing and crabbing in the New York-New Jersey Harbor, very-low-income adults were significantly less aware than were adults of other income groups of the risks that eating fish posed to unborn children (Burger, Pflugh, Lurig, Von Hagen, & Von Hagen, 1999). Low-income fishers from minority ethnic groups were least aware of health advisories regarding fish consumption (Burger, Pflugh et al. 1999).

[2]In discussing the original inhabitants of the United States and Canada we use the terms American Indians (or Native Americans) and First Nations, respectively.

Ethnicity and Fish Consumption. Fish, shellfish, or sea mammals are traditional foods of some American Indian nations and tribes in the United States (e.g., Dellinger, 2004; Judd, Griffith, & Faustman, 2004) and First Nations and Inuit people of Canada (Muckle et al., 2001a; Muckle, Ayotte, Dewailly, Jacobson, & Jacobson, 2001b; B. Wheatley & M.A. Wheatley, 2000). In fact, treaties with some American Indian nations and tribes guarantee fishing rights (Roe, 2003). Not only does fishing yield the primary source of protein, but fishing-related tourism and commercial fisheries are also an economic mainstay of many indigenous residents (M.A. Wheatley, 1997). Furthermore, many traditional Native American community activities involve fishing (M.A. Wheatley, 1996).

The importance of fishing and the presence of methylmercury, as well as other pollutants, in local fish species poses both an economic and a health hazard for Native Americans. Spatial analysis of the risk of exposure of Native Americans on reservations (35.4% of the Native American population) to methylmercury based on mean mercury levels in local watersheds revealed 148 reservations at moderate to severe risk for mercury contamination—a clear health hazard (Roe, 2003). Among American Indian nations at particular risk are the Chippewa (Ojibwa) of Wisconsin and Minnesota, whose culture depends on both fishing and fish consumption and whose watersheds are heavily polluted (Roe, 2003). Among high-risk First Nations and Inuit communities in Canada in which fishing was curtailed, traumatic economic and social change resulted (B. Wheatley & M.A. Wheatley, 2000). Among the Inuit, mercury levels in cord blood are similar to those in the Faroe Islands and higher than population averages for the United States and Canada (Muckle et al., 2001b). In the United States, Native Americans are less aware of fish advisories than other ethnic groups are (Burger, 2004), and several American Indian tribes in the Northwest may be at particular risk for elevated methylmercury because of the specific species consumed (Mariën & Patrick, 2001).

Because methylmercury levels are significantly inversely related to SES in American Indian and First Nations populations (Muckle et al., 2001a), there is reason to be seriously concerned about the possibility of additive effects of mercury and SES on the future cognitive functioning of children in these groups, who are already at risk educationally (Hubbs-Tait, Tait, Hare, & Huey, 2005). It is important to note that not all studies of fish-consuming American Indian tribes and nations find high exposures of methylmercury, but in those tribes and nations, careful public health education programs have been implemented and may be responsible for the safe levels (e.g., Dellinger, 2004).

Consumption of self-caught fish is also frequent among minority groups other than American Indian. Burger, Stephens et al. (1999) found that African American adults fishing in the Savannah River in South Carolina consumed more fish than did European American adults. Furthermore, African American adults were more likely to consume species and/or amounts of fish that would place them in excess of the RfD of 0.1 μg/kg/day of mercury (Burger et al., 2001). Among fishers in the polluted New York-New Jersey Harbor, compared to European-American adults, Hispanic adults were more likely to eat self-caught blue crab and African American adults were more likely to eat self-caught bluefish and bass, all species that were the subject of health advisories in New York and New Jersey (Burger, Pflugh et al., 1999).

Cumulative Risk and Potential Moderating Effects. Findings linking greater fish consumption, lack of awareness of fish advisories, and/or elevated mercury levels in humans to SES and ethnicity raise questions about effect modifiers and cumulative risk. Both SES and minority status are linked to children's risk for lower cognitive performance and more behavior problems (e.g., R.H. Bradley, Corwyn, Burchinal, McAdoo, & Coll, 2001; Sameroff et al., 1987). Whether methylmercury adds to cumulative risk needs to be investigated. Additional research is also needed on SES as a potential moderator of the relation between methylmercury and children's cognition and behavior. The only two studies that have examined SES as a moderator, both in the Seychelles, have identified no consistent picture of interactions (Davidson et al., 1999; Davidson, Myers, Shamlaye, Cox, & Wilding, 2004).

In the developmental literature on social environments, maternal parenting behaviors predict children's cognitive performance over and above measures of cumulative risk (Barocas et al., 1991), emphasizing the importance of examining maternal behaviors in research on neurotoxicant effects. Because methylmercury levels in umbilical-cord blood are highly correlated with methylmercury levels in mothers' blood (e.g., Björnberg et al., 2003), effects of methylmercury on maternal parenting skills and mother–child interaction may contribute to the significant associations between maternal hair methylmercury or infant cord methylmercury and child cognitive performance. The potential for methylmercury to affect maternal functioning is apparent in the inverse relation between maternal scores on Raven's Standard Progressive Matrices and methylmercury in cord blood (Grandjean et al., 1997). Due to the fact that maternal cognitive scores are linked to maternal stimulation and other key parenting practices (e.g., Hubbs-Tait et al., 2002), mothers with higher methylmercury exposure might differ in their parenting practices from mothers with lower methylmercury exposure. Whether differences in maternal stimulation interact with effects of mercury has yet to be studied. However, low maternal verbal functioning does exacerbate the inverse relation between PCB exposure and child cognitive performance (Jacobson & Jacobson, 2002) and between lead and child cognitive performance (Bellinger et al., 1990). Knowing that equivalent exposures to methylmercury constitute different levels of risk for children with differing maternal stimulation or nurturing behaviors would help to target parent education or other public health interventions to parents less likely to be stimulating or emotionally nurturing.

Mercury and Micronutrients

Chapman and Chan (2000) conducted an extensive review of nutritional toxicology pertinent to methylmercury toxicity. At the time of their review, evidence for protective effects against mercury toxicity was greatest for selenium. They also suggested that foods high in dietary fiber prevented retention of mercury. Clarkson and Strain (2003) identified docosahexaenoic acid (DHA), iodine, iron, and choline, all of which may be provided by fish consumption, as potential nutrient confounders of the effects of methylmercury on child outcomes. DHA, iodine, and iron have all been found to affect cognition in human populations. Choline is linked with memory in animal studies (Clarkson & Strain, 2003).

Fiber

In a year-long study of dietary habits of 26 women in an Amazonian fish-eating community, Passos et al. (2003) found that tropical-fruit consumption significantly moderated the relation between fish consumption and mercury in the women's hair. For women who consumed one or more fruits per day, the relation between fish consumption and hair mercury approached 0. In contrast, for women who consumed less than one fruit per day, fish consumption explained 65% of the variance in hair mercury. Because of the small sample size, variations in vitamins across fruits, and the different types and quantities of fiber in different varieties of fruit, these data must be interpreted conservatively. Furthermore, the authors could not determine whether fruit consumption altered absorption, distribution, or excretion of mercury (Passos et al., 2003).

Selenium

Selenium, a nonmetallic mineral, is found in soil and its concentration in plants varies as a function of soil-selenium content. Selenium is an essential nutrient for animals. Major human food sources are seafood and meats (IOM, 2000). Dietary deficiencies are common among vegetarian populations residing in areas with selenium-poor soil and reliant on locally grown food (IOM, 2000). Selenium is required as a component of the glutathione peroxidases, which are essential antioxidant enzymes, and of deiodinase enzyme, which is essential for activation of thyroid hormones. These enzymes defend against oxidative stress, which, as noted above, leads to cell death by destruction of peroxides (e.g., lipid peroxidation) and by scavenging of free radicals (Halliwell, 1994). Furthermore, normal thyroid functioning is also important for normal cognitive development in children (Huda, Grantham-McGregor, Rahman, & Tomkins, 1999).

In their review of the extant literature, Chapman and Chan (2000) suggest that one mechanism for a possible protective effect of selenium on the effects of methylmercury involves the activity of the glutathione peroxidases. However, results of studies were inconsistent, with some showing decreased glutathione peroxidase and others not. Moreover, the organs and/or brain areas evaluated varied across studies, rendering conclusions difficult. Another way in which methylmercury and selenium may interact is by methylmercury-induced changes in selenium metabolism. Metabolism of zinc, iron, manganese, and other metals also appears to be affected by increased methylmercury exposure (Chapman & Chan, 2000).

Two recently published studies shed light on how methylmercury and selenium interact. El-Demerdash (2001) reported that, when rats were administered selenium and methylmercury, the result was reduced lipid peroxidation or increased enzymatic activity in brain, liver, and/or blood. Watanabe, Yin, Kasanuma, and Satoh (1999) reported that prenatal exposure to methylmercury had a negative effect on walking and the righting reflex of offspring of selenium-deficient mice but did not have that effect on mice whose mothers had had adequate selenium. These effects of prenatal exposure levels of selenium deficiency and mercury on the neurobehavior of young mice are consistent with the reports of greater impact of prenatal than postnatal mercury on children (Grandjean et al., 1997). However, selenium alone also had positive impacts on mouse behavior (Watanabe et al., 1999), emphasizing the importance of adequate levels of this mineral in and of itself.

One recent human study is consistent with these experimental animal studies confirming an interaction between selenium and mercury. Hol, Vamnes, Gjerdet, Eide, and Isrenn (2001) studied 40 healthy volunteers (half with mercury amalgams) and 40 patients seeking medical help due to symptoms of amalgam illnesses (half with amalgam fillings removed and half with amalgams present). Blood-mercury concentrations were significantly higher in adults with amalgam fillings present than they were in those whose fillings were absent or removed. Patients with self-reported symptoms of amalgam illness had significantly lower levels of selenium than did healthy volunteers with amalgam fillings still present. Whether the differences in selenium levels were due to mineral metabolism altered by elevated mercury levels could not be determined due to the correlational design of the study. However, the authors did speculate that the differences in symptomatology might be due to mercury-impaired selenium metabolism. Dietary differences in selenium consumption or supplementation were not measured and thus constitute another explanation that could not be ruled out. As we noted earlier in our discussion of mercury epidemiology, randomized trials of children with dental amalgams are ongoing in the United States. Recent work in Canada shows that amalgam fillings increased children's odds of having elevated urinary-mercury levels even after adjusting for high fish consumption (Levy et al., 2004). Thus, the work of Hol et al. on selenium is pertinent to the well-being of children with higher levels of mercury exposure, whether from metallic mercury in amalgam or methylmercury in fish.

Both selenium and methylmercury are increased in diets high in fish (Chapman & Chan, 2000) and have been found to be positively correlated in fish-consuming populations (e.g., Bárány et al., 2003), supporting the hypothesis that selenium might offset methylmercury effects in some fish-consuming

TABLE 2
Conclusions on Effects of Methylmercury by Discipline

Type of finding	Discipline	Conclusion
Replicated	Epidemiology/developmental neurotoxicology	(a) Prospective studies in New Zealand and the Faroe Islands found negative relations between methylmercury and child outcomes. (b) The study in the Seychelles did not replicate this finding. (c) Fish and seafood are the major exposure source. (d) Although adults in both the Iraq and Minamata mercury-contamination incidents died, prenatal exposures are of most concern for child development.
	Experimental psychology (animal)	(a) Methylmercury causes motor impairment and deficits in learning and memory, particularly with prenatal or infant exposure. (b) Methylmercury damages functioning and gene expression of neurotransmitters essential to learning and memory.
	Child development/social environments	(a) There are few consistent relations between demographic variables and mercury burden. (b) Lower income and education are associated with lack of awareness about health advisories and risks of eating fish. (c) American Indian, Hispanic, and non-Hispanic black children are more at risk for eating species of fish placing them at risk.
	Nutrition	(a) Potential confounders of the relation between methylmercury and child outcomes include nutrients in fish (e.g., docosahexaenoic acid [DHA], iron, iodine). (b) Animal research shows selenium modifies the relation between methylmercury and behavioral outcomes.
Hypothesized	Interdisciplinary	(a) Selenium is an effect modifier of methylmercury on child cognition and behavior. (b) Parenting practices and behaviors are effect modifiers of methylmercury on child cognition and behavior.
Research needs	Interdisciplinary	(a) Experimental animal studies of enrichment/deprivation and methylmercury (b) Experimental animal studies of interactions among enrichment/deprivation, selenium (and other nutrients from fish), and methylmercury (c) Prospective studies of geographically diverse fish-consuming populations examining differences in micronutrient deficiencies, social environment risks, and child outcomes among children with differing levels of methylmercury

populations. However, several caveats are warranted. With the exception of the study by Hol et al. (2001), human epidemiologic studies showing inverse relations between selenium and symptoms of mercury toxicity have not been reported. Randomized controlled supplementation trials of selenium have not yet been conducted. To our knowledge, no data examining interaction effects of methylmercury or mercury and selenium on children's cognition have been published, but such a study in the Seychelles is ongoing (Clarkson & Strain, 2003).

Summary and Conclusions on Mercury

Table 2 summarizes the main conclusions of research pertinent to mercury across the four disciplines represented by the authors. Fish consumption is the major source for mercury exposure. The only risk factor consistently linked to fish consumption is minority ethnic status, with particularly Native Americans but also non-Hispanic black and Hispanic families at greatest risk. Thus, the research agenda to identify those children most vulnerable to methylmercury differs from that for lead:

- Interdisciplinary prospective multilevel studies of geographically diverse fish-consuming populations examining differences in micronutrient deficiencies, social-environment risks, and child outcomes among children with differing levels of methylmercury
- Experimental animal studies of interactions between enrichment/deprivation and methylmercury
- Experimental animal studies of interactions among enrichment/deprivation, selenium (and other nutrients from fish), and methylmercury

MANGANESE

Manganese Epidemiology and Neurotoxicity

Introduction

In contrast to the other neurotoxicants we have discussed, manganese is an essential trace element. Major food sources of manganese in order of concentration (ppm) are nuts, tea, legumes, pineapples, and grains (U.S. ATSDR, 2000). The fine line

between manganese as a nutrient and its toxicity in excess is apparent in the proximity of recommended dietary intakes and exposure limits. Whereas the Adequate Intake (AI) for adult women and men is 1.8 and 2.3 mg/day respectively, the Tolerable Upper Intake Level is 11 mg/day for all adults (IOM, 2001), comparable to the oral RfD of 10 mg/day established by the U.S. EPA (2002a). The biological half-life of manganese ranges from 12 to 48 days with estimates varying as a function of amount of dietary manganese, gender, and iron stores. Manganese half-life is longer for males (Finley, Johnson, & Johnson, 1994) and for women with diets lower in manganese (Finley, 1999; Finley, Penland, Pettit, & Davis, 2003), particularly for those with higher ferritin (body-iron status; Finley, 1999). Homeostasis of manganese is maintained by a combination of absorption and excretion via biliary secretions; excretion in urine is minimal. Adults absorb less than 5% of an ingested dose (Finley, 1999). Retention is higher in infants, with preterm infants retaining twice as much of an ingested dose as infants born at term do. Whether this is due to greater absorption or less efficient excretion, such as with immature biliary flow, is unknown.

Other than diet, the major vector of manganese exposure is occupational (Chillrud et al., 2005; Mergler et al., 1994), but other vectors are known. Of particular concern are emissions from vehicles fueled by methylcyclopentadienyl manganese tricarbonyl (MMT)-treated gasoline in Canada (Lynum, Roos, Pfeifer, Fort, & Pullin, 1999), where usage since 1976 has resulted in increasing environmental manganese levels, in some cases exceeding the U.S. EPA reference concentration for manganese in air (Thibault, Kennedy, Gareau, & Zayed, 2002). One potential source of overexposure in children comes from the greater levels of manganese in soy formula for infants than in breast milk or cow-milk-based formula (Lönnerdal, 1994; U.S. EPA, 2002a). Other sources of exposure include residence near a facility engaging in toxic-chemical release (C.M. Neumann, Forman, & Rothlein, 1998) and manganese-containing pesticides and fungicides (Mergler & Baldwin, 1997). Because manganese crosses the placenta, maternal environmental exposures during pregnancy may also affect infants.

Current concerns about manganese arise, in part, from the results of the one published prospective study. Takser, Mergler, Hellier, Sahuquillo, and Huel (2003) measured manganese and dopamine levels in maternal and cord blood of 247 pregnant women. Subsequently, both mother and child were monitored for up to 6 years. Interestingly, although there were no initial significant differences in neurobehavioral function based on elevated manganese levels and decreased dopamine levels in the offspring, at 3 years of age attentional deficits were evident in high-manganese children, and nonverbal memory as well as dexterity were negatively affected. This delayed toxicity effect suggests that early manganese exposure may disturb normal maturational processes. Perhaps linked to these patterns of impairment, maternal dopamine function was adversely affected at the time of delivery.

The contrast between the essential and toxic natures of manganese is apparent in enzymatic activity. Manganese is essential for the action of antioxidant enzymes such as superoxide dismutase (McMillan, 1999); but manganese is also a powerful oxidant, and together with dopamine can accelerate oxidation-reduction reactions in the CNS, producing harmful oxidative molecules such as hydrogen peroxide and superoxide free radicals (Verity, 1999). Manganese can also produce free radicals independent of dopamine (Sloot, van der Sluijs-Gelling, & Gramsbergen, 1994). Excess manganese concentrates in mitochondria, where it inhibits selective enzyme activity in a dose-dependent fashion, particularly in the frontal cortex, striatum, substantia nigra, and hippocampus (Zheng & Graziano, 1998). Disruption of energy metabolism in brain mitochondria might thus underlie the clinical findings of memory loss, aggressive behavior, and motor dysfunction in manganese poisoning.

The nervous system is the primary target organ of manganese (Mergler, 1999; Mergler et al., 1999; Sinczuk-Walczak, Jakubowski, & Matczak, 2001). Adults exposed to manganese-contaminated water show subtle signs of neurotoxicity (Kondakis, Makris, Leotsinidis, Prinou & Papapetropoulos, 1989), with the severity depending on cumulative manganese dose. Although it is suspected that chronic low-level exposure to manganese is also neurotoxic in children (cf. Finley, 2004), the evidence is sparse. In a case-control study, elevated hair-manganese levels were more frequent among learning-disabled children than they were among controls (Pihl & Parkes, 1977). Children identified as hyperactive or learning disabled had higher hair-manganese levels than did controls (Collipp, Chen & Maitinsky, 1983; Crinella, Cordova, & Ericson, 1998). Few cohort studies of childhood manganese neurotoxicity have been reported. In a study of 11- to 13-year-olds, children exposed to elevated manganese levels in drinking water had worse short-term memory, manual dexterity, and visuo-perceptual speed than unexposed children did (P. He, Liv, & Zhang, 1994). Striking deficits in memory and listening skills, but intact IQ, were found in a boy exposed to elevated manganese in water (Woolf, Wright, Amarasiriwardena, & Bellinger, 2002).

Accumulation Sites and Behavioral Consequences

There appear to be three sites of manganese entry into the CNS: the cerebral capillaries, the cerebrospinal fluid, and the olfactory nerve (Brenneman et al., 2000; V.A. Murphy, Wadhwani, Smith, & Rapoport, 1991; Rabin, Hegedus, Bourre, & Smith, 1993). Once manganese has gained entrance into the brain, the concentration levels appear to be greatest in the dorsal striatum (caudate and putamen), globus pallidus, substantia nigra, and subthalamic nuclei, all of which are parts of the limbic system (Wadhwani, Murphy, Smith, & Rapoport, 1992). The dorsal striatum and ventral striatum (nucleus accumbens) have traditionally been associated with the interface between the limbic system, motor output, and drugs of abuse (cf. Nation et al., 2004).

A current focus of manganese-neurotoxicity research is on elevated levels of the excitatory amino acid glutamate in the CNS. With respect to the aforementioned preferential accumulation of manganese in the striatum and substantia nigra (Kobayashi et al., 2003; H.M. Liu, Tsai, Cheng, & Chung, 2000), it appears that glutamate levels rise when manganese enters astrocytes (Chen & Liao, 2002). In any event, manganese overexposure significantly decreases antioxidant enzyme activities and interferes with glutamate uptake in astrocytes, which can cause neural cells in the striatum and substantia nigra to be more prone to excitotoxicity and oxidative stress (Chen & Liao, 2002). As noted, the dorsal striatum and the ventral striatum define the physiologic interface between limbic and motor systems (Berlanga et al., 2003). These areas of the brain receive extensive dopamine input from the ventral tegmental area and the substantia nigra, which subserve primarily limbic and motor function, respectively (Berlanga et al., 2003). Since manganese neurotoxicity in the striatum and substantia nigra is linked to the depletion of dopamine and motor deficits, a substantial literature regarding manganese-induced changes in locomotive behavior and neurotransmitter levels is available. Meanwhile, treatment with MK-801, the NMDA antagonist we introduced in our discussion of neurotoxic effects of lead, has been shown to block the general excitotoxic lesions created by manganese exposure (Brouillet, Shinobu, McGarvey, Hochberg, & Beal, 1993). It therefore has been suggested that manganese exerts its neurotoxic effects in the striatum and substantia nigra by an excitotoxic process, which could be affected by NMDA-receptor activation (Brouillet et al., 1993). Since NMDA receptors have been linked to learning and memory, the potential for manganese to affect learning and memory mechanisms also has been examined in previous investigations (e.g., Woolf et al., 2002).

But even though manganese–glutamate interactions are a current interest in toxicologic research, it is not glutamatergic neurotransmission that is receiving the most attention from scientific investigators interested in manganese effects. Rather, it is dopamine transmission, and this stems from the fact that manganese may offer a model for studying Parkinson's disease.

Manganese as a Model for Parkinson's Disease

The most severe forms of manganese toxicity result in prolonged muscle contractions (known as dystonia), decreased muscle movement (known as hypokinesia), rigidity, and muscle tremors. Each of these physical features is characteristic of the advanced stages of Parkinson's disease (cf. Mergler et al., 1994), a disease that affects at least half a million U.S. adults with approximately 50,000 adults diagnosed each year (National Institute of Neurological Disorders and Stroke, 2005). Although the health community is acutely aware of the debilitation that is inherent in Parkinson's disease, medical research has yet to accurately characterize its causes(s). What is known is that while there are features that can differentiate diagnosis between manganese toxicity and Parkinson's disease, such as clinical symptoms, response to the drug levodopa, and patterns of change in brain activity as revealed by neuroimaging studies (Kim et al., 2002; Olanow, 1998), both manganese toxicity and Parkinson's disease produce increases in dopamine turnover during early stages (Erikson & Aschner, 2003; Sossi et al., 2002) and depletion of dopamine during late stages.

Much of the current work on the relation between manganese toxicity and Parkinson's disease involves animal research. Normandin et al. (2004) examined the distribution of three forms of manganese in the brain and correlated distribution with locomotor activity. Manganese sulfate caused a decrease in locomotion, suggesting a disruption of movement patterns that would parallel Parkinson's. Others have looked at the effects of manganese in the brain on oxidative stress and related cell death (Hinerfeld et al., 2004) and at the selective accrual of manganese in mitochondria in brain regions associated with motor output (S.R. Zhang, Zhou, & Fu, 2003). Mitochondrial proteins are essential to normal cellular operations and manganese-induced disturbances in these processes may be related to the symptoms of Parkinson's disease (see above). Finally, it is noted that manganese interacts with other metals to affect cell death associated with manganese exposure and thereby changes, the pattern of manganese-related alterations in behavior (Roth & Garrick, 2003).

In addition to advancing the fundamental information base associated with manganese toxicity, animal and human studies of the sort discussed here will further our understanding of the mechanisms of Parkinson's disease. Ultimately, improved interventions may result as we gain a better grasp of the factors that contribute to such public health problems.

Manganese and Social Environments

Concerns about manganese exposure are relatively recent. In consequence, there exist only limited data on links between manganese exposure and social environments. In one study in the Canary Islands, there was no relation between serum manganese concentration and SES or educational level (Diaz, Lopez, Henriquez, Rodriguez, & Serra-Majem, 2001). In contrast, in central Mexico, where manganese mining and refining is common, SES is low, housing and sanitation are poor, and years of education are few. Nonetheless, in one of the two rural Mexican manganese-mining communities studied by Santos-Burgoa et al. (2001), symptomatic adults had fewer years of education. Furthermore, reported changes in health were related to lower schooling, greater pesticide exposure, and lack of awareness of the relevance of the source of manganese pollution. Thus, like some of the research on U.S. adults who eat self-caught fish in polluted waters, the research on manganese in Mexico suggests that poorly educated adults who are unaware of the risks they face are most likely to suffer from the ill effects of manganese exposure (Santos-Burgoa et al., 2001). In Quebec, demographic variables associated with raised blood-manganese concentra-

tions in pregnant women were urban or agricultural residence (as opposed to village residence) and pesticide spraying within 1 kilometer of the home (Takser, Lafond, Bouchard, St-Amour, & Mergler, 2004). Finally, in Oregon, manganese was one of five chemicals most frequently reported in the EPA's Toxic Chemical Release Inventory. Facilities engaging in toxic-chemical release were significantly more likely to be located in neighborhoods inhabited by racial minorities than in those with white residents (C.M. Neumann et al., 1998).

Manganese and Other Micronutrients

An association between iron deficiency and higher manganese absorption has been recognized in rats for more than a decade (Davis, Ney, & Greger, 1990; Davis, Wolf, & Greger, 1992). Recent research in rats has also confirmed this relationship in the brain, mediated by DMT1 activity. Iron deficiency resulted in increased concentrations of manganese in two brain regions important to learning, memory, and drug addiction: the globus pallidus and the substantia nigra (Erikson et al., 2004). Finley (1999) examined the effects of high (9 mg/day) and low (.7 mg/day) manganese diets on 15 women with low iron stores (serum ferritin) and 11 women with high iron stores. Women with lower serum ferritin absorbed up to four times more manganese than did women with higher ferritin. For women on the high-manganese diet, average retention in the high- versus low-ferritin groups was 6.3 and 2.7 μg/day. Interestingly, the higher manganese diet resulted in less than twice the retention of the lower-manganese diet, indicating the working of an efficient excretory homeostatic mechanism.

In humans, higher circulating manganese concentrations have been observed in infants and seem to reflect an age-dependent pattern. Concentrations are increased during pregnancy, which results in relatively high levels in the fetus. Manganese concentrations in umbilical-cord blood at birth are more than twice the magnitude of manganese concentrations in mother's blood in the third trimester (Takser et al., 2004), further emphasizing the immaturity of homeostatic mechanisms in the fetus. These findings underscore the importance of iron status during pregnancy, because iron-deficient women may transmit more manganese to their offspring than iron-sufficient women do.

After birth the major source of nutritional concern for infants is manganese supplied by soy formula. The AI for human infants is based on five studies of manganese concentrations of human breast milk in infants exclusively fed human milk. The AI is 3 μg/day (IOM, 2001). Breast milk contains from 1.87 to 6.6 μg of manganese per liter (IOM, 2001). In contrast, soy formulas contain 200 to 300 μg per liter (Tran, Chowanadisai, Crinella, Chicz-DeMet, & Lönnerdal, 2002)—that is, a dietary exposure up to 150 times greater for soy-formula-fed infants than for breastfed infants. For ethical reasons, nutrition studies of the effects of high-dose manganese supplementation on infants require the use of animal models. Tran et al. (2002) demonstrated that rat pups supplemented with 500 μg of manganese per day had significantly higher levels of manganese in the brain on the 14th day postpartum. Futhermore, 24% of the variance in avoidance learning was explained by amount of manganese supplementation (0, 50, 250, or 500 μg). Finally, 53% of the variance in striatal dopamine concentrations was explained by amount of manganese supplementation. These findings emphasize the potential risks associated with higher manganese levels present in soy formula. The fact that dopamine concentrations and behavior were both affected parallels the findings of Takser et al. (2003) on relations of maternal postpartum dopamine and child behavior to mothers' manganese levels during pregnancy.

Summary and Conclusions on Manganese

Table 3 summarizes the main conclusions of research pertinent to manganese across the four disciplines represented by the authors. The one prospective study of children and the experimental studies with animals suggest the following needed studies:

- Replication studies of the relations between manganese and children's cognitive functioning
- Initial studies examining parenting behaviors and other social-environment variables linked to manganese exposure

CADMIUM

Cadmium Epidemiology and Neurotoxicity

Introduction

Understandably, because of its environmental ubiquity, lead contamination has been the primary focus of neurotoxicology researchers and practitioners, almost to the point of exclusion during the 80s and 90s. But more recently, another divalent cation, cadmium, has gained the attention of researchers and the general population (see Nordberg, 2004, for a review of historical issues and future trends associated with cadmium toxicity). In toxicology terms, cadmium is a relatively new metal, discovered in 1818 by the German metallurgist Strohmeyer (Bugden, 1924). It was proposed that the newly defined metal be named cadmium because the primary source for the toxicant was "zinc-flowers" (oxide of zinc deposited on the walls of zinc-refining furnaces) or *cadmia fornacum* (J.S. Lee & White, 1983).

In the paragraphs below, we identify four sources of potential cadmium burden in children: maternal smoking during pregnancy, pre- and postnatal exposure to other environmental tobacco smoke, industrial waste, and diet. For nonsmoking individuals, the major source of exposure is food (U.S. ATSDR, 1999), but we could find no published reports of food exposures that controlled for exposure to environmental tobacco smoke. Major food sources of cadmium are leafy vegetables, mollusks,

TABLE 3
Conclusions on Effects of Cadmium and Manganese by Discipline

Type of finding	Discipline	Conclusion
Replicated	Epidemiology/developmental neurotoxicology	(a) The major source of cadmium exposure is cigarette smoking and pollution. (b) There are no recent large-sample studies of the relation of cadmium to children's cognition and behavior. (c) Major sources of manganese exposure are occupations, industrial toxic chemical release, and vehicle emissions (Canada). (d) One study links manganese exposure during pregnancy to later deficits in attention and nonverbal memory.
	Experimental psychology (animal)	(a) Cadmium causes learning deficits. (b) Cadmium affects the dopamine system and intake of opiate and stimulant drugs. (c) Manganese toxicity causes muscle contractions and other symptoms similar to those of Parkinson's disease. (d) Elevated manganese causes depleted dopamine.
	Child development/social environments	(a) Insufficient research exists to determine the association between cadmium exposure and children's social environments. (b) Insufficent research exists to determine the association between manganese exposure and children's social environments.
	Nutrition	(a) Animal studies verify that adequate intakes of zinc, iron, and calcium diminish effects of cadmium and may interact to protect against cadmium. (b) Animal and human studies verify that lower intakes of iron are associated with higher manganese absorption.
Research needs	Interdisciplinary	(a) Prospective studies to identify whether children's cadmium levels are linked to cognitive functioning (b) Replication studies of the relations between manganese and children's cognitive functioning (c) Prospective studies examining parenting behaviors and other social-environment variables linked to cadmium and manganese exposure

organ meats (particularly liver and kidney), cocoa, and grains (WHO, 2001). In adults, both diet and smoking increase total body burden in terms of cadmium in blood and urine (Olsson et al., 2002), with blood cadmium signaling both current and cumulative exposure (CDC, 2003). The half-life of cadmium in blood was estimated to be 2 to 3 months (Welinder, Skerfving, & Henriksen, 1977), but after absorption, cadmium is accumulated in the kidney where it may be stored for decades (CDC, 2003). Because the most recent CDC estimates of exposure to environmental tobacco smoke (by measurement of cotinine, a nicotine metabolite found in urine and blood) from 1999–2000 data show that children's levels are more than twice those of adults, there is cause for concern (CDC, 2003). Further, the use of wastewater-treatment sludge in agriculture is thought to be leading to increased exposure in foods via food-chain accumulation (U.S. ATSDR, 1999).

Among the earliest reports of the toxic effects of cadmium is one made available by the Belgian physician Sovet, who treated several patients who had been polishing silver with this new "white powder" (Sovet, 1858). Symptoms included vomiting, stomach cramps, abdominal pain, and sore throat. In subsequent years, it became clear that this cadmium powder occasioned a broad range of health-related defects, chief among them "itai-itai disease." The disease was first reported by Dr. Noboru Hagino, who employed the Japanese word *itai*, meaning "ouch" or "painful," to describe the endemic bone pathology among elderly women who lived along the Jinzu River, where the metal existed in high concentrations (cf. Nogawa & Kido, 1996). Subsequent studies would show that the array of health problems produced by acute or chronic cadmium exposure also included neurological effects (Moore, 2004).

Despite the known pathological effects of cadmium, industrial production, particularly in the United States, which historically has supplied and consumed over half the world's cadmium stores, continues to expand (cf. J.S. Lee & White, 1983). For example, consumers are familiar with the increased use of cadmium batteries in electronic equipment. And for many years it was the industrial exposure vector that was the principal concern of investigators of the toxic effects of the metal. Cadmium is used in processes such as electroplating and galvanizing, it is a stabilizer of plastics, it is a component of paint pigments, and it exists in most fertilizing products as well (Mishima, Kimura, & Inoue, 2004). And, although the distribution of cadmium via industrial processing remains an issue, the

current point of concern regarding distribution is the fact that the toxicant selects for and accrues in the leaves of tobacco products (Angelova, Ivanov, & Ivanova, 2004; Bachelet et al., 2002; Tsadilas, Karaivazoglou, Tsotsolis, Stamatiads, & Samaras, 2005; Yue, 1992). Not only is cadmium in high concentration in all tobacco products, the tobacco released as cigarette smoke is absorbed passively at such a rate that the blood-cadmium concentrations of nonsmokers who inhale the smoke of nearby smokers matches that of active smokers (Shaham et al., 1996), and this may be especially true for children (Hossny et al., 2001; Mannino, Albalak, Grosse, & Replace, 2003).

From several reviews it is apparent that cadmium may cross placental barriers in pregnant women (Ananth, Savitz, & Luttther, 1996; Shiverick & Salafia, 1999), and the metal accrues in the fetus during early development (Mokhtar, Hossny, El-Awady, & Zekry, 2002). As noted above, a major source of children's cadmium exposure is tobacco smoke. Because smoking among pregnant women has been reported to be greater than 20% in North America (National Institute on Drug Abuse, 1996), the unique effects of in utero cadmium exposure on the development of later health problems poses a potential serious clinical and public health concern for children of women who smoke. However, maternal smoking presents the growing fetus with multiple risk factors other than cadmium (e.g., reduced oxygen, increased carbon monoxide, and exposure to other chemicals). Thus, studies of maternal smoking include inherent confounds of other variables with cadmium and should be interpreted cautiously.

Cognition and Associative (Learning) Processes

The literature on the effects of cadmium exposure on human and animal behavior does not approximate that available from lead studies. However, there is sufficient information from each line of work to warrant concern.

Cadmium Effects on Human Behavior. Much of the effort with respect to investigating the effects of developmental cadmium exposure on behavior has focused on mental processes that are disturbed by contact with the metal. For decades, it has been suspected that early (prenatal or postnatal) cadmium exposure may be correlated with mental deficiency and lower intelligence. Among the first investigations in this area, Marlowe, Errera, and Jacobs (1983) reported that cadmium burdens were significantly elevated among children suffering from mental retardation, and contaminant exposure was correlated with borderline intelligence. However, because cadmium determinations in this report were based on hair assays, the possibility of confounds stemming from the aforementioned maternal-smoking issue must be considered. Yet, whatever the limitations of such early nonexperimental investigations, they alerted scientists to the possibility that cadmium burdens might significantly compromise intellectual functioning.

Informed by the earlier reports on the relation between developmental cadmium exposure and deficiencies in mental and physical functioning, more recent investigations have shown that children who live near waste sites and who have higher body burdens of cadmium are at increased risk for learning disorders (Agusa et al., 2003). More directly related to the effects of cadmium exposure on neonatal development, Mokhtar et al. (2002) found a negative correlation between umbilical-cord serum-cadmium levels and Apgar test (heart rate, muscle tone, respiration, reflex irritability, and skin color) scores of newborns. A recent prospective study documented that prenatal exposure to environmental tobacco smoke (ETS) from smokers other than the mother had a significant deleterious effect on children's cognitive development at age 2 above and beyond measures of socioeconomic disadvantage (Rauh et al., 2004). Although ETS includes numerous chemicals in addition to cadmium (Rauh et al., 2004), it is noteworthy that prenatal ETS exposure alone accounted for a 4.8-point decrease in Bayley MDI score when children were 2 years old. It is becoming increasingly apparent that developmental cadmium exposure, via ETS or some other vector, presents health risks for infants and children during early maturation periods.

Cadmium Effects on Animal Behavior. As has been the case with other animal models of metal toxicity, much of the animal research relating to cadmium-related changes in behavior has employed operant paradigms. Although the literature is not extensive, the behavioral profile that is available reflects a relatively consistent theme. Newland et al. (1986) exposed rats postnatally to varying concentrations of cadmium. Tested as adults, animals were trained to press a lever for reinforcement. A transitional fixed-ratio design was used wherein animals were systematically shifted from one fixed-ratio schedule to another. The results showed that operant performance was impaired by early cadmium exposure.

Other operant studies have shown that cadmium exposure during the adult cycle results in learning deficiencies in concurrent tests that involve choice. Grover et al. (1991) found that animals fed a diet containing 100 ppm of cadmium performed at levels below that of nonexposed controls on a task that offered sucrose or water as reinforcers. In addition to the operant studies that have been conducted, developmental cadmium exposure has been shown to alter a variety of other learned behaviors, such as conditioned avoidance (Ali, Murthy, & Chandra, 1986; Baranski, 1986; Pelletier & Satinder, 1991). Consistent with the human data indicating that cadmium may be related to learning disorders, lower Apgar scores, and differences in measures of cognitive development, the findings from animal investigations affirm that the toxicant presents a risk with respect to normal cognitive functioning.

Neurochemical Mechanisms and Addiction Issues. Because cadmium competes with calcium that is instrumental in neuro-

transmitter release and neural processing in general, the metal is nonspecific and consequently affects most neurotransmitter systems. Of particular relevance, however, is the effect of cadmium exposure on NMDA, which as noted earlier is believed to play a significant role in behavioral plasticity and learning (cf. Malenka & Nicoll, 1999). Cadmium reduces the time calcium channels located on the membranes of neurons remain open to the influx of calcium ions, thereby restricting calcium-mediated release of neurotransmitters (Legendre & Westbrook, 1990; J.C. Liu et al., 2004; Mayer & Westbrook, 1987). Given the demonstrated relation of NMDA function to learning (Clayton et al., 2002; Collingridge, 1992; Korz & Frey, 2003; Shaw et al., 2003), it is possible that the cadmium-induced learning deficits mentioned previously may derive from disturbances in NMDA activity.

Other neurotransmitter systems are similarly affected by cadmium exposure, including serotonergic systems (Andersson et al., 1997) and mu, delta, and kappa opioid receptor sites (Tejwani & Hanissian, 1990). But it is the interference with the dopamine system that has attracted the greatest attention of toxicologists. In rats, both at the adult level (A.F. Hoffman & Gerhardt, 1999; Olivier, Guibert, & Leviel, 1995) and the neonatal level (Antonio, Benito, Leret, & Corpas, 1998), cadmium diminishes dopamine availability. It has been established that one of the consequences of these cadmium-induced changes in dopamine relates to drug issues (Wise & Bozarth, 1987). Striatal dopamine activity is essential to the reward properties of several psychoactive drugs, including opiates and stimulants such as cocaine and amphetamine; thus, it is not surprising that cadmium exposure has been linked to changes in drug responsiveness. Cadmium exposure at the adult level antagonizes morphine sensitization (K.R. Smith, Nation, & Bratton, 2002) and decreases amphetamine-evoked dopamine release in the rat striatum (Miller, Dopheide, Smith, & Casteel, 2005). Curiously, in the Miller et al. study the presence of cadmium in brain slices per se was insufficient to inhibit amphetamine-evoked dopamine release. These data suggest that, in addition to any direct effects on mechanisms associated with transmitter kinetics (e.g., blockade of stimulated calcium-mediated dopamine release), the toxicant may induce a change in the number and/or function of dopamine neurons in the striatum. In terms of changes in drug responsiveness following developmental cadmium exposure, Cardon, Rocha, Valles, Bratton, and Nation (2004) have shown that cocaine self-administration is reduced in rats tested as adults. Because of the incidence of tobacco use and the attendant cadmium burdens, it must be recognized that cadmium toxicity may contribute to drug-abuse profiles and add to the growing list of health-related problems associated with contaminant exposure.

Cadmium and Social Environments

Recent analysis of a nonrandom subsample of the NHANES III (1988–1994) data set confirms that the best predictor of cadmium levels in adults is smoking status, with cadmium levels being twice as high for U.S. smokers as for nonsmokers (Paschal et al., 2000). German researchers have reported the same link between adult smoking status and cadmium levels in a nationwide environmental survey in their country (K. Hoffman et al., 2000). The NHANES 1999–2000 data on children, which were evaluated by the CDC (2003), suggested that cadmium levels were below the current level of medical concern (based on risk of renal tubule dysfunction—a serious kidney condition—in adults) established by WHO (2001) for cadmium excretion of 2.5 μg/g of urinary creatinine (a chemical excreted in urine—and blood—that reflects health of kidney functioning) and well below the occupational criterion for urinary cadmium of 3 μg/g of creatinine. Among children ages 6 to 11, children with cadmium levels at the 95th percentile had .57 μg/g of creatinine. The absence of clinical evidence does not suggest that these population exposure levels are safe, as the CDC (2003) emphasized strongly. Further, the CDC called for more research in light of the lack of knowledge about what cadmium levels constitute a cause for concern. The experimental animal data suggest learning is compromised at cadmium levels lower than those resulting in frank toxicity (e.g., Grover et al., 1991). Uncertainty remains about the levels of cadmium that are associated with changes in child learning and cognitive functioning.

As we noted earlier, smoking during pregnancy is highly correlated with cadmium levels in the placenta. In fact, number of cigarettes smoked per day during pregnancy explains 24% of the variance in placental cadmium (Falcón, Viñas, Osuna, & Luna, 2002). This association suggests that demographic variables associated with maternal smoking will also be associated with children's cadmium exposure. We discuss social environments linked to smoking, but we caution that additional research is needed, because some studies report that levels of cadmium differ in children as a function of parental smoking (Hossny et al. 2001) whereas others do not (Osman, Zejda, et al., 1998; Willers et al., 1992).

In the United States, a 2000–2001 study of attainment of Healthy People 2010 objectives in eight states included data on mothers' smoking during pregnancy (Phares et al., 2004). Smoking during pregnancy was significantly inversely related to both income and education. Smoking during pregnancy was also higher among white and American Indian women than it was among women from other ethnic groups. Data from Germany and Australia are consistent with the American data on the link between lower SES and smoking (Phung, Bauman, Young, Tran, & Hillman, 2003; Scherer et al., 2004). These data suggest that, like lead and mercury, risk of exposure to cadmium is higher for children from lower socioeconomic backgrounds.

Most importantly, economic hardships accelerate the effect of exposure to ETS on children's cognitive functioning (Rauh et al., 2004). Mothers in Washington Heights, Central Harlem, and the South Bronx in New York City were asked to indicate whether basic needs for housing, food, and clothing were unmet (e.g., inadequate food, doing without food) in the previous year. ETS-

exposed children of mothers with more unmet needs had Bayley MDI scores approximately 7 points lower than ETS-exposed children of mothers with no unmet needs (Rauh et al., 2004). With the moderation effect in the statistical model, ETS alone accounted for a drop of about 3 points in MDI score and material hardship alone, not quite a half point in score. Such findings support the impact of both chemical exposures and deprived social environments and emphasize that, unless researchers include measures of both social deprivation and neurotoxicants, the true impact of both will be unknown.

However, vectors of cadmium exposure other than smoking are not consistently associated with demographic variables. Cadmium exposure via proximity to smelters has been linked to some measures of socioeconomic status in Germany such as older homes (I. Meyer, Heinrich, & Lippold, 1999) but not to measures of SES in other studies in Europe (Leroyer et al., 2001). Dietary exposure to cadmium was linked to poverty-level incomes in one nationwide U.S. study (Moschandreas et al., 2002) but was positively correlated with maternal education in a study in Sweden (Bárány, et al., 2002). Recall that the primary sources of dietary exposure are leafy vegetables, mollusks, organ meats, cocoa, and grains (WHO, 2001). Some inconsistencies in findings about the relation of cadmium to socioeconomic variables may be due to differences in cadmium in soil (Welt et al., 2003) leading to different levels of cadmium accumulation in green leafy vegetables (Jinadasa et al., 1997; Ni, Long, & Yang, 2002); higher-SES individuals consume more vegetables than lower-SES individuals do (Neumark-Sztainer, Wall, Perry, & Story, 2003). Other inconsistencies may be explained by interactions between cadmium and specific nutrients.

Cadmium and Micronutrients

The importance of adequate intake of zinc and iron in diminishing the effects of cadmium has long been recognized (Mahaffey & Vanderveen, 1979; Peraza et al., 1998). Cadmium and zinc, both transition metals, bind to the protein metallothionein, which transports zinc in the cell. In early experimental work, Japanese quail fed control diets were compared to quail whose diets had added cadmium and varying amounts of zinc. The level of zinc in the diet was significantly inversely correlated with the amount of cadmium in all tissues studied except the kidney, suggesting that zinc protected against cadmium absorption and retention (Fox, Jacobs, Jones, & Fry, 1979). When cadmium is in excess, it displaces zinc in metallothionein (Peraza et al., 1998). In vitro studies show that, like lead, cadmium alters DNA binding in zinc-finger proteins in the brain (Zawia et al., 2000). As noted earlier, the extent to which dietary zinc contributes to zinc in zinc-finger proteins is unknown (IOM, 2001).

Experimentally induced iron deficiency in mice increases cadmium absorption (Flanagan et al., 1978). Humans with lower serum ferritin absorb significantly more cadmium than humans with normal serum ferritin do (Flanagan et al., 1978), and lower ferritin is correlated with higher cadmium in children (Osman, Schütz et al., 1998). Rats fed two different forms of dietary cadmium had lower cadmium uptake when their diets were also supplemented with iron (Groten, Luten, & van Bladern, 1992). Recent research on iron transport protein, DMT1, has yielded contradictory findings, with some research groups suggesting that DMT1 does transport cadmium into intestinal cells (e.g., Bannon, Abounader, Lees, & Bressler, 2003; Bressler et al., 2004) but other research groups suggesting that DMT1 is not the major means of transport (M.W. Smith et al., 2002). Competitive transport of iron and cadmium to the intestine by DMT1 would explain the long-established interaction between iron deficiency and cadmium elevations (Flanagan et al., 1978).

Recent research suggests that iron and zinc, as well as calcium, may interact to protect against effects of cadmium. Rats fed cadmium-treated rice containing only marginal amounts of iron, zinc, and calcium had as much as eight times more cadmium than did rats fed cadmium-treated rice with adequate levels of iron, zinc, and calcium. Each essential mineral had an independent effect on cadmium retention, and interactions of pairs of minerals did also (Reeves & Chaney, 2002).

Research showing the large differences in cadmium retention as a function of nutrients in the diet demonstrates that populations of children with insufficient iron and zinc (and calcium) will be much more at risk for effects of exposure to cadmium in their diets or through parental smoking. Understanding the greater risk of cadmium to children with inadequate diets is essential to individualized treatment and focused public policy. In previous sections we have pointed out that it is particularly children living in poverty who are most at risk for iron deficiency and perhaps zinc deficiency as well. Thus, careful consideration of cadmium exposure rates of these children is needed.

Summary and Conclusions on Cadmium

Table 3 summarizes the main conclusions of research pertinent to cadmium across the four disciplines represented by the authors. Basic research on effects of cadmium on children's cognition and behavior is still needed. Experimental animal research and the few studies on children suggest the following research agenda:

- Prospective studies to identify whether children's cadmium levels are linked to cognitive functioning
- Initial studies examining parenting behaviors and other social environment variables linked to cadmium exposure

SUMMARY, CONCLUSIONS, AND POLICY RECOMMENDATIONS

Tables 1 to 3 summarize recognized effects of lead, mercury, and manganese and cadmium; recognized effects of confounders and modifiers; and hypothesized interactions. Regulatory agencies

have specified levels of concern or RfDs for each of the neurotoxicants discussed in this monograph (lead: 10 μg/dL; mercury: .1 μg/kg body weight/day; manganese: 0.14 mg/kg/day for a 70 kg adult; cadmium: 2.5μg cadmium/g creatinine). Children with levels exceeding RfDs or levels of concern have been identified for each neurotoxicant. However, among children with levels in excess of or below levels of concern, cognitive and behavioral effects vary widely. Understanding why some children manifest more problems in the face of the same exposures is essential for effective treatment and precise policy.

Advancing this understanding depends on developing and evaluating models of interacting effects. We have taken the position that the model for those interactions is a multilevel one. Furthermore, we have assembled evidence suggesting that social environments and micronutrients interact with neurotoxicants to affect child cognition and behavior. However, the identity of specific micronutrients and aspects of the social environment that function as modifiers vary by neurotoxicant. This means that multilevel models will vary by neurotoxicant. Such variations are explicit in the differing research agendas we propose for each neurotoxicant.

Developing and evaluating models of interacting effects requires convening multidisciplinary teams of researchers and practitioners. No discipline by itself can explain the variations in children's cognition and behavior that result from the same neurotoxicant dose. The costs of assembling such teams are less than those of failing to do so. Accurately identifying children most vulnerable to neurotoxicants and the complex interactions that make them vulnerable is the only way to reduce the health and education costs initiated or exacerbated by neurotoxicant exposure.

Lead, mercury, manganese, and cadmium all cross the placenta. The lead literature tends to show stronger postnatal than prenatal effects and the mercury literature tends to show stronger prenatal than postnatal effects. However, both literatures clearly emphasize the importance of limiting exposures. Federal policies designed to reduce levels of mercury and lead in the environment are indicated, as are educational programs targeted to families most at risk—families with micronutrient deficiencies, families with low education and income, families of minority ethnic/racial status, and immigrant families. We have noted that parenting behavior is a mediating variable between a number of social-environment factors (such as income) and children's cognition and behavior. Targeting parenting behavior is thus essential. Because research shows that families at risk for methylmercury consumption are not helped by current fish advisories, research is needed to determine what will affect the behavior of families most at risk.

The one prospective study of manganese confirms prenatal effects. The prospective study of children's exposure to ETS did not measure cadmium in blood or urine. More research on both of these neurotoxicants is needed. The CDC has argued strongly for such research in the case of cadmium.

Neurotoxicant–neurotoxicant interactions have only just begun to be investigated. Interactions between lead and cadmium as well as between lead and manganese are of great concern due to coexposures from hazardous waste sites (U.S. ATSDR, 2004a, 2004b). Research to identify such exposures and their effects on children is vital.

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