

## A B S T R A C T

The potential for environmental contaminants to produce neurological, cognitive, or other behaviour deficits as a result of developmental exposure has received increasing attention. The focus has shifted from description of frank neurotoxicity observed in a relatively few individuals to more subtle impairment in a much greater number of children. With this shift has come the recognition that subtle deficits such as a small decrease in IQ can have important societal impact when large numbers of children are affected. For example, the result of a 1 µg/dL decrease in blood lead concentration in children in the United States with blood lead concentrations between 10 and 20 µg/dL would translate into a savings of 5-7.5 billion U.S. dollars a year in increased earning power alone. In addition, behavioural problems such as increased aggression and poor social adjustment identified early in childhood may escalate to serious antisocial behaviour such as delinquency as the child approaches puberty. Exposure to neurotoxic agents during development or over a significant portion of the lifespan may also result in acceleration of age-related neurodegenerative diseases. Such changes in the functional abilities of a significant proportion of a population have potentially serious consequences for society as well as for affected individuals.

# Issues in Developmental Neurotoxicology: Interpretation and Implications of the Data

*Deborah C. Rice, PhD*

The potential for contaminants released into the environment as a result of human activity to produce cognitive and other behavioural deficits in infants and children has received increasing attention in recent years by both scientists and concerned citizens.<sup>1,2</sup> It is clearly established that contaminants such as lead and methylmercury can produce deficits ranging from clinically recognized disease to subtle impairment requiring specialized epidemiological analyses to identify.<sup>3,4</sup> As the focus has shifted from frank toxicity observed in relatively few individuals to more subtle impairment in a much greater number of children, the societal as well as personal consequences of ubiquitous exposure to neurotoxic agents has received increasing scrutiny. In addition, there is a growing body of evidence suggesting that exposure to toxicants early in development may have consequences of escalating importance as the child moves into adolescence, and that delayed neurotoxicity may be manifested decades after cessation of exposure. This paper discusses issues relevant to the interpretation of the effects of developmental exposure to environmental neurotoxicants.

### **Clinical manifestations of neurotoxicity versus subtle impairment of function**

It is unfortunate that it is still not uncommon to be confronted with an argument along the line of "People aren't dropping dead in the streets (or, there aren't millions of retarded kids), so how can you say there's a problem?" This argument

confuses identification of a clinical syndrome that is recognizably the result of toxic injury with deficits that may be within the range of normal function for a population, and that can only be identified by comparing exposed and non-exposed (or less-exposed) groups of individuals. When a clinician evaluates the health status of one individual, the pertinent question is whether the neurological and cognitive functions of that individual fall within the bounds considered to be clinically normal. The clinician may determine whether IQ is above the clinical definition of mental retardation, whether there is indication of cerebral palsy, or whether vision and hearing appear to fall within the range of clinically accepted values. Encephalopathy and frank mental retardation produced by very high body burdens of lead, or cerebral palsy and blindness produced by fetal Minamata disease (methylmercury intoxication), probably would be identified in such an evaluation. However, the concerns of the epidemiological investigator more often revolve around whether exposure to a suspected neurotoxic agent produces decrements in cognitive functioning that nevertheless may be within the range considered clinically normal, or subtle deficits in attentional processes or sensory system function that would make learning more difficult. Such questions can only be addressed by studying a relatively large number of individuals with known histories or body burdens of toxic exposure.

### **A small effect is not necessarily an unimportant effect**

A decrement in function that is still considered to be in the "normal" range (i.e., not a manifestation of defined clinical impairment) may nonetheless have

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Toxicology Research Division, Bureau of Chemical Safety, Food Directorate, Health Protection Branch, Health Canada

Correspondence: 785 Main Road, Islesboro, Maine 04848, USA, Tel: 207-734-0904, E-mail: ricekrwc@midcoast.com

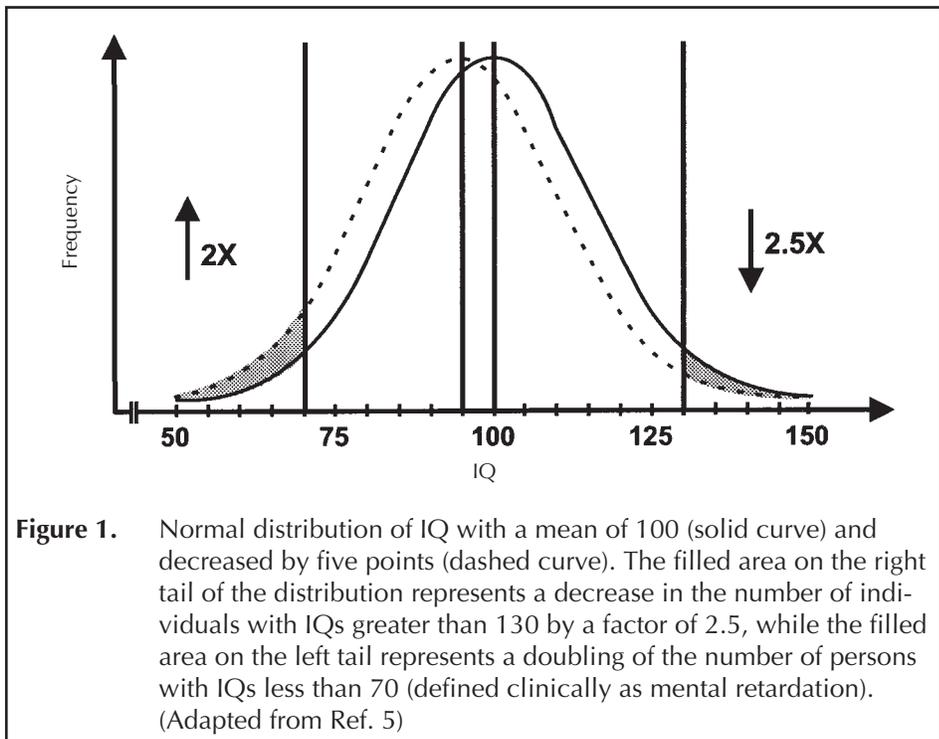
extremely important consequences for a society, particularly if there is widespread exposure of a population to a neurotoxic agent. For example, although a downward shift in the IQ of a population by 5 points would result in most individuals having an IQ above that considered to be in the range of mental retardation (i.e., greater than 70), such a shift would result in an increase of a factor of 2 in persons with IQs of less than 70, and a decrease in the proportion of very gifted people (those with IQs above 130) by a factor of 2.5 (Figure 1).<sup>5</sup> This represents an enormous change in the characteristics of a population, and such consequences of neurotoxic exposure will become increasingly important as the driving force of economies switches from manufacture-based to high-technology-based, requiring an ever-increasing degree of education and specialized skills.

The most studied and therefore the most well-documented example of the economic consequences of ubiquitous exposure of a population to a neurotoxicant is lead. It is clearly established that exposure of fetuses and children to amounts of lead routinely observed as a consequence of environmental contamination produces deficits in IQ.<sup>6</sup> There have been well over a dozen large studies on the effects of developmental exposure of lead on IQ, which have been extensively reviewed.<sup>3,6-8</sup> Studies may be divided into two main categories based on experimental design: cross-sectional and prospective. The cross-sectional design provides a “snap-shot”, comparing performance of children divided into categories based on concurrently measured parameters of lead exposure such as blood or tooth lead. In the stronger prospective design, multiple estimates of lead body burden (usually blood lead concentrations) are obtained from birth onward, and performance at older ages may be analyzed as a function of lead body burden at previous time points or some average of overall exposure. Studies may be combined statistically in a meta-analysis which allows estimation of the effect of lead based on a number of studies. Schwartz<sup>6</sup> reported a 2.6 decrease in IQ associated with an increase in blood lead from 10 to 20 µg/dL in a meta-analysis of eight studies that met inclusion criteria, with no evidence of a

**TABLE I**  
**The Benefits Per Year of a Reduction of 1 µg/dL Mean Blood Lead Concentration in the United States Population, Taking into Account Children Only**

Benefits, Millions of 1994 U.S. Dollars	
Medical care	189
Compensatory education	481
Infant mortality	1140
Neonatal care	67
Decreased earnings	5060
<b>Total</b>	<b>6937</b>

Source: Ref. 33.

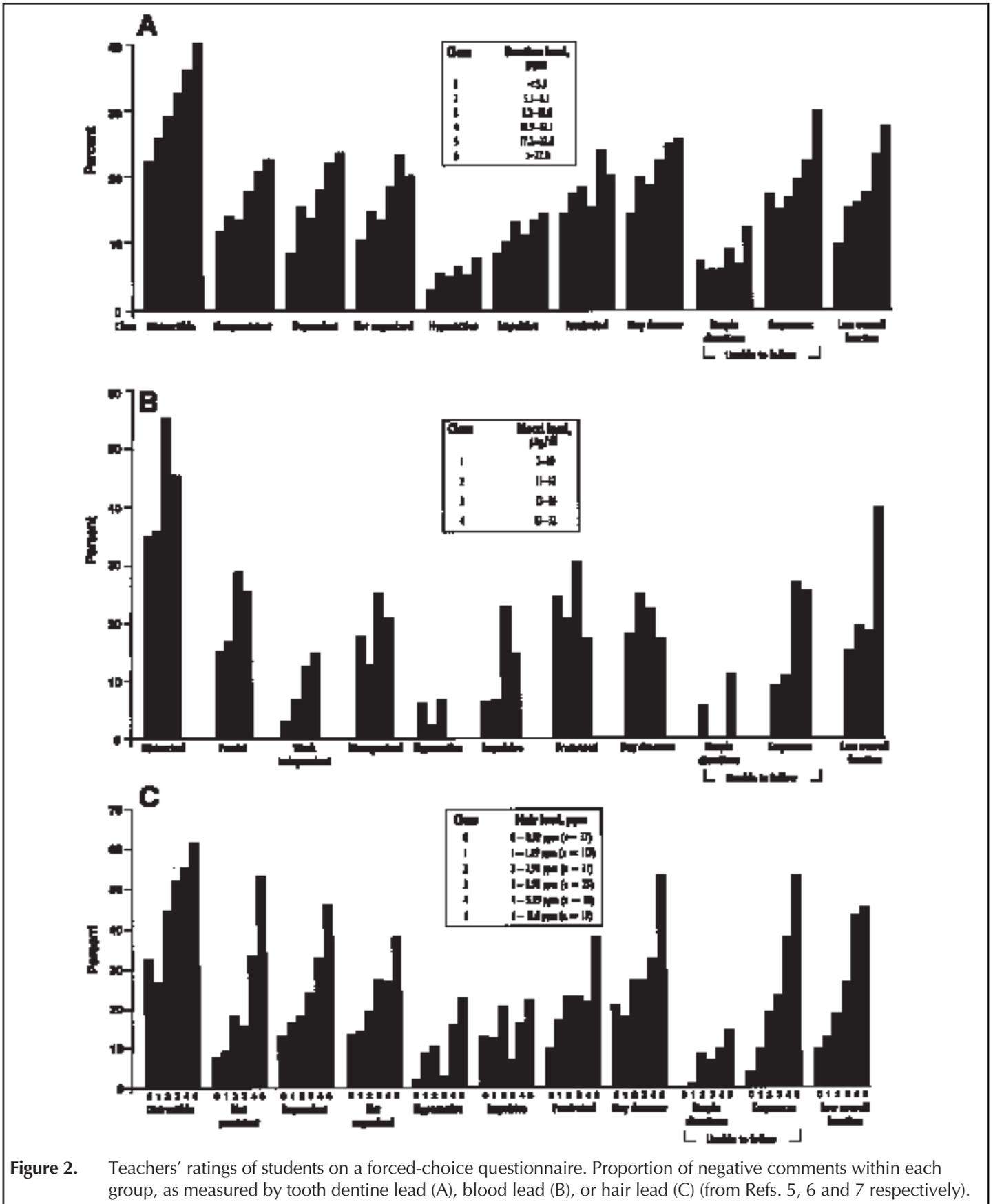


threshold down to a blood lead concentration of 1 µg/dL. Meta-analyses performed by the International Programme on Chemical Safety (IPCS) of the World Health Organization,<sup>3</sup> using full-scale IQ as the outcome measure and performing separate analyses for the available prospective and cross-sectional studies, calculated a decline of about 2-3 IQ points for an increase in blood lead concentration from 10 to 20 µg/dL in each analysis.

Lead affects a number of other behavioural processes in addition to IQ. Assessments by teachers unaware of the lead status of the children have identified attentional problems such as “distractible, not persistent, dependent, immature, easily frustrated, does not follow simple and complex directions.”<sup>9-11</sup> (Figure 2) Other

investigators have also reported attentional problems and poor social abilities in lead-exposed children;<sup>12-17</sup> impaired performance on tasks that specifically assessed vigilance and attention;<sup>18-25</sup> and deficits in school performance in math, reading, spelling and other skills as a consequence of lead exposure.<sup>17,26-30</sup> Consequences of cognitive and attentional deficits produced by lead, perhaps predictably, are an increase in academic failure and the need for special education and increased grade retention.<sup>31,32</sup> It is tempting to speculate that specific deficits in attention processes contribute to the impairment in school performance, and may be more important even than the deficit in IQ.

The monetary cost associated with the ubiquitous exposure of fetuses and children



to lead in industrialized societies has been calculated by Schwartz<sup>33</sup> in an estimation of the benefits of a 1 µg/dL reduction in the population mean blood lead concentration. The analysis was based on the monetary savings of reducing lead levels in children with blood lead concentrations between 10 and 20 µg/dL. (Note that a 1 µg/dL reduction in blood lead concentrations would result in a shift in the population of less than 1 IQ point based on the meta-analyses by Schwartz and the IPCS discussed above.) Schwartz estimated medical costs associated with treatment of children with undue lead exposure, the increase in remedial education, and the costs associated with reduced birthweight and reduced gestational age among other factors (Table I). The largest single cost is lost earnings as a result of decreased intellectual capability. In a later similar analysis using the powerful National Longitudinal Survey of Youth database to monetize the effect of decreased cognitive ability on earning capacity, the estimated gain in earnings would be 7.5 billion U.S. dollars per year for a decrease in blood lead levels of 1 µg/dL in the U.S. population.<sup>34</sup> It is obvious that the “small” effect of lead on IQ is reflected in an enormous cost to society in lost potential and increased need for medical care and special education.

#### Long-term consequences of early behavioural deficits

Again, lead may serve as a model of the potential long-term consequences of behavioural dysfunction early in childhood. An association between lead exposure and antisocial and other problem behaviours has been identified in children as young as 2-5 years of age.<sup>35</sup> In a study in eight-year-old children, tooth dentine levels were associated with total scores of problem behaviour on the Teacher's Report Form of the Child Behaviour Profile.<sup>36</sup> Tooth lead levels were also associated with internalizing (consisting of scores for anxiety or withdrawal) and externalizing (consisting of inattentive, nervous-overactive, and aggressive scores). There was also a weak association between tooth lead levels and prevalence of “extreme” problem behaviour scores.

The consequences in older children of this poor social adjustment were explored

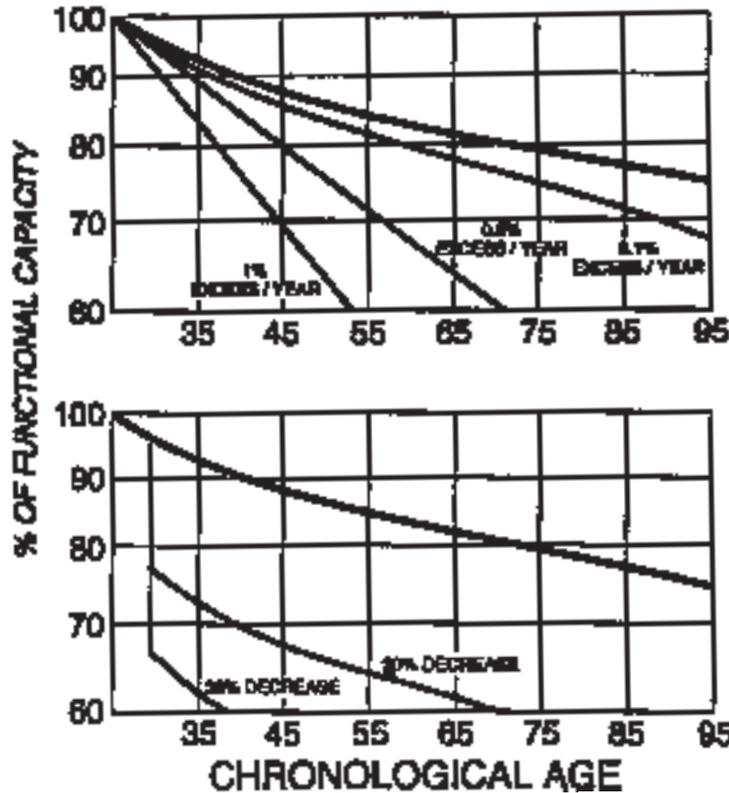
in a retrospective cohort study of the association between bone lead levels and measures of social adjustment in boys at 7 and again at 11 years of age.<sup>37</sup> At 7 years of age, borderline associations after adjusting for covariates were observed between teachers' rating and lead levels for aggression, delinquency, social problems, and externalizing behaviours on the Child Behaviour Checklist (CBCL). When children were 11 years old, parents of higher-lead subjects reported significantly more somatic complaints, more delinquent and aggressive behaviour, and higher internalizing and externalizing scores. Teachers' ratings at 11 years were associated with bone lead for a number of categories, including somatic complaints, anxious/depressed, social and attention problems, delinquent and aggressive behaviours, and internalizing and externalizing. Higher-lead subjects had higher scores in self-reports of delinquency at 11 years. Higher bone lead levels were associated with an increased risk of exceeding the clinical score for attention, aggression, and delinquency, and higher-lead subjects were more likely to obtain worse scores on all items of the CBCL during the four-year period of observation. The long-term consequences of such patterns of behaviour are apt to have very negative consequences for the individual, as well as for society at large.

#### Long-latency delayed neurotoxicity

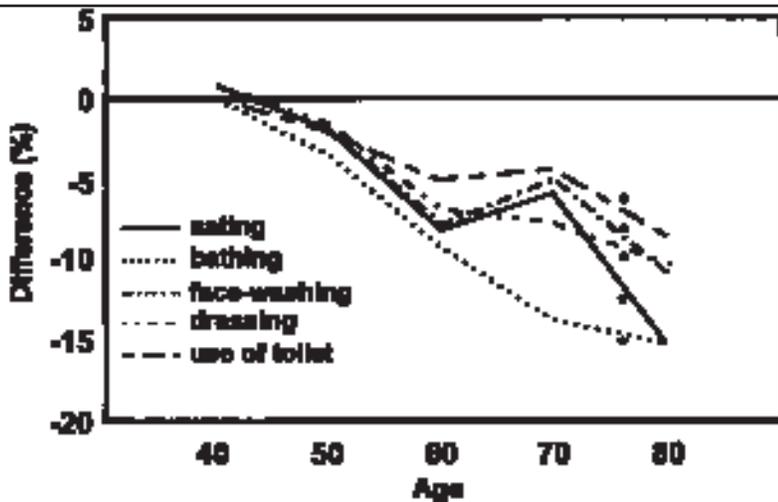
An issue that is of considerable concern to neurotoxicologists is the potential for agents to induce delayed neurotoxicity years after cessation of exposure, or as a result of low-level exposure over a large portion of the lifespan. The possibility of an interaction between aging and exposure to neurotoxic agents is also of critical concern: this possibility was postulated two decades ago<sup>38</sup> and has been raised repeatedly since.<sup>1,2,5</sup> As the normal brain ages, there is a decrease in the number of cells in certain regions, as well as a decline in neurotransmitter levels and repair mechanisms. If this process were accelerated by chronic or historic exposure to a neurotoxicant, the effect as the individual aged would be a decrease in functional capacity (Figure 3). Alternatively, damage that decreased the reserve capacity of the brain at any point in

life might also hasten the appearance of functional deficits. For example, it has become apparent over the last decade that up to 25% of people who contracted polio as children, then apparently recovered and were functioning normally, suffer a recurrence of clinical symptoms as they move into middle age. There is evidence of degeneration in peripheral nerves of these individuals; this may reflect premature senescence of nerves compromised during the acute phase of the disease, or accelerated aging produced by increased metabolic demands on spared normal nerves.

There is both epidemiological and experimental evidence that exposure to the environmental contaminant methylmercury can produce delayed neurotoxicity.<sup>39</sup> It was recognized as early as 1975 that manifestations of Minamata disease (MD) could worsen over time even after cessation of exposure to methylmercury.<sup>40,41</sup> In a study including over 90% of persons diagnosed with MD, 1,144 patients over the age of 40 were compared to an equal number of matched controls to determine the functional ability of people with MD to independently eat, bathe, use the toilet, dress, and wash the face.<sup>42</sup> The relative deficit between controls and people with MD increased with age in a statistically significant manner even though exposure to methylmercury had ceased in all individuals 20-30 years before assessment (Figure 4). Similarly, monkeys exposed to methylmercury from birth to seven years of age exhibited delayed neurotoxicity at 13 years manifested as clumsiness and inability to climb the bars of the exercise cages,<sup>43</sup> which was probably a consequence of somatosensory dysfunction.<sup>44</sup> A group of monkeys exposed to methylmercury *in utero* and continuing after birth until four years of age displayed exacerbation of auditory impairment between 11 and 19 years of age (Rice, submitted). The potential consequences of an interaction of previous or long-term exposure to a neurotoxic agent and acceleration of the aging process are profound. As the large cohort of “baby boomers”, the oldest of whom are now 50, begin aging, the costs of neurological or psychological dysfunction will be significant, and any added increase in dysfunction as a consequence of exposure to neu-



**Figure 3.** Top: The percent of functional capacity vs. chronological age associated with different degrees of acceleration in the decline of the functional capacity of the brain, beginning at 25 years of age. (Adapted from Ref. 38). Bottom: Functional capacity vs. chronological age as affected by a 20 or 30 percent loss of capacity at 30 years of age and normal aging thereafter.



**Figure 4.** Difference between controls and persons diagnosed with Minamata Disease (MD) in their ability to perform tasks independently. Y-axis, the % difference (MD patients minus controls) in the number of people not requiring assistance. \* signifies MD patients statistically significantly worse than controls (from Ref. 42).

rotoxic agents may be expected to place additional burdens on the cost and infrastructure of the health-care system.

**CONCLUSIONS**

While the effects of a few environmental contaminants such as lead and methylmercury that have resulted in episodes of frank neurotoxic poisoning in humans have been extensively characterized, the potential for most of the contaminants in the environment to produce neurotoxicity is unknown.<sup>45</sup> For example, there are virtually no data on the effects of long-term low-level exposure to pesticides, which are designed to be neurotoxic, despite the fact that many are persistent in the environment and are routinely detected in human tissue. For other contaminants, more data are required to fully assess the potential hazard. There is considerable epidemiological and experimental evidence that developmental exposure to PCBs produces impairment in cognitive function and attention that may be similar to that produced by lead,<sup>46,47</sup> but the pattern of behavioural deficits is incompletely characterized. However, it appears that the consequences of developmental exposure to a number of neurotoxic agents including lead, PCBs, cigarettes, alcohol and some other drugs of abuse may be a syndrome characterized by attentional and cognitive deficits. Identification of affected children and implementation of appropriate behavioural and scholastic interventions is of critical importance to affected individuals and to society. The recognition of the far-reaching consequences of “small” changes in function is a critical first step. Similarly, the potential for developmental or long-term neurotoxic insult to accelerate the aging process is of enormous importance given the changing demographics of industrialized populations.

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