Evidence for the Role of Environmental Neurotoxicants in Learning and Behavioral Disabilities

Deborah C. Rice

U.S. Environmental Protection Agency (EPA)

I was asked to talk about the evidence for the role of environmental contaminants in specific behavioral disorders. I am going to talk about effects in humans for a few minutes first, and then present some of the monkey data from my old laboratory at Health Canada.

I am going to be talking about a constellation of effects that really play into, or are part of in a more severe form, various kinds of behavioral disabilities. One, of course, is learning disabilities (SLIDE 2). A classic definition is that it is a group of disorders manifested by significant difficulties in the kinds of things that are required in an industrialized society: reading, writing and mathematical skills.

But I think that a more helpful definition really requires a discontinuity between the performance of the individual or the child and what would have been predicted on the basis of this child's IQ, their age, their background, and so forth (SLIDE 3). So a child with a high IQ who is still having trouble in school is a cue that there may be a learning disability.

I am also going to talk about some aspects of ADHD (SLIDE 4). Kids with attention deficit hyperactivity disorder have problems with organization, they are impulsive, they may or may not be hyperactive. Basically, ADHD is characterized by an inability to organize behavior either in time or in space and to use the information about the consequences of past behavior to make decisions in the future.

Also, there are various conduct disorders, of which the endpoint is frank aggression, but before that is an inability of the child to engage in appropriate social interactions with other children or with authority figures, it is really an inability for the child to put themselves in the place of another person.

Obviously a lot of these children have overlapping syndromes (SLIDE 5). ADHD may be present with mentally retardation or depression, so it becomes very, very difficult to tease these things out, and certainly on the basis of one child it is impossible to attribute any particular behavior to environmental contaminants. That has to obviously be done in terms of a population study.

The apparent prevalence of many of these disabilities has increased dramatically, but it is very unclear to what degree this is due to increased recognition of these disabilities or to an expansion of the inclusion criteria (SLIDE 6). The inclusion criteria for these clinical syndromes are really a moving target. They are much different in the year 2000 than they were in 1990 or in 1980, so it is really not legitimate to say "Oh, there has been a huge increase in prevalence" of any particular disorder because the inclusion criteria in 1980 are not the same as they are now.

Really the question before us today is to what extent and in what way do environmental toxicants contribute to these disabilities?

I am going to talk about, as I said, epidemiological studies relatively briefly (SLIDE 7). They have obvious advantages. Humans are the species of interest. The exposure levels and the timing and the duration is relevant. We can assess endpoints and functions sometimes not possible in animals, and this is certainly true for behavior.

The problem with epidemiological studies, is that when an association is demonstrated, we really do not know whether this association is indicative of causality. One approach, which we have taken with the two contaminants that I am going to talk about, lead and PCBs, is to do five or six multimillion-dollar studies until we can finally say, "Yes, we think it is causative."

Another strategy is to use animal studies, experimental studies, to complement the human studies (SLIDE 8). Obviously, in animal studies, we can control exposure and the other experimental conditions, and we can study mechanisms of action. In the end, we can be sure, particularly when we put the two kinds of literature together, that we can have confidence concerning the causality of effect from a particular toxicant.

I am going to talk about two toxicants, lead and PCBs. Lead does not seem to be included on the list of endocrine disrupters lately. But of course, lead is in fact an endocrine disrupter. Lead has small effects on IQ (SLIDE 9). It produces impulsivity, distractibility, attention problems, poor school performance, increased dropout rate, and antisocial behavior, and even criminality in humans. All of these things tie back to learning disabilities, ADHD, and the conduct disorders that I talked about a couple of minutes ago.

I am going to go through just a very small number of examples of these kinds of effects. The lead literature is huge. There have been four or five really good longitudinal studies, so this discussion is not going to cover the totality of the lead literature by any means.

On the top of SLIDE 10 are data from the original study by Herb Needleman and colleagues in 1979. This is a teacher's rating in a classroom. As a function of dentine level, lead exposed children are more distractible, not persistent, they are dependent, they are not organized, they are hyperactive, they are impulsive, they are frustrated, they are daydreamers, and they have low overall functioning. That sounds a lot like what we are trying to address here.

There were two subsequent studies, one in 1984 and one in 1996, in different parts of the world using different markers for lead. But you can see there is a real consistency on teacher rating scales of the behavior in these children.

Now these same children from Dr. Needleman's 1979 study were assessed for academic failure as 6th-graders (SLIDE 11), and an increased need for academic aid as a function of increased lead, as well as an increase in grade retention were observed as a function of the lead levels at six years of age. In other words these kids were not being passed on to the next grade.

When the investigators looked even later at the percentage of kids not graduating from high school or the percentage of kids at 17 or 18 years old with a reading disability, again there was a nice dose effect function (SLIDE 12). The yellow bar is children who had been diagnosed with frank plumbism, or frank lead poisoning.

Now, remember I talked a few minutes ago about how there needs to be a discontinuity between the IQ of the child and the performance of the child to infer that the child has a learning disability. SLIDE 13 is cumulative IQ for the 1979 Neeldeman cohort at six years of age. The left curve is the lowest 10% of children with respect to lead level and the right curve is the highest 10%. There is, in fact, an IQ decrement, but these kids are not anywhere near being mentally retarded, and I submit that this IQ decrement is not enough to explain the difference in grade retention and failure to graduate from high school. I think there is something else going on.

I would like to describe briefly a test that is used in adults as well as children, called the Wisconsin Card Sort Test (SLIDE 14). I have chosen this test because there is a monkey analog that I am going to be talking about in few minutes.

In this test, the subject sits across a table from the experimenter. The experimenter puts a card down, and then puts three cards down for the subject to choose the one that matches. But the experimenter does not indicate which card is correct.

So what are you supposed to be matching to here? Are you supposed to be matching to the shape, the number, or the color? Well, you take a guess and choose one. By a sequence of trial and error, getting

them wrong and getting them right, maybe eventually you figure out that you are supposed to be matching to the shape.

So you are going along and doing the task. Well, if the diamond is correct on top, then obviously the circle is correct on the bottom because it is the same shape.

So you think you have got this all figured out, and all of the sudden the experimenter says, "No, that is wrong." What the experimenter has done is changed the rule, changed the strategy, and what you, as the subject, have to figure out, again by trial and error, is to come up with the new strategy.

Obviously, the first time you make a mistake, you did not know that the answer was going to be wrong. But if you keep making the same mistake, you keep saying, "I know it is supposed to be the shape! I know it is supposed to be the shape!" when really now it is supposed to be the color, that is called a perseverative error and it is indicative of damage in specific parts of the brain.

SLIDE 15 is the same 1979 cohort from Dr. Needleman's study I already discussed. These are total errors, and perseverative errors on the Wisconsin Card Sort Test as a function of dentine lead level at six years of age in people who are now 19-20 years old. Now they are young adults, their blood lead levels are way down in the range close to the detection level, but they still have deficits. These kinds of deficits are seen with syndromes like ADHD and learning disabilities.

SLIDE 16 represents another lead-exposed cohort and demonstrates another effect of lead. This is the relationship between bone lead concentration and the child-behavior checklist, which is a clinical instrument used to detect various kinds of behavioral abnormalities.

These are teacher scores in 7-11 year old children. There is increased aggression in high-lead versus low-lead children, an increase in delinquent behavior as reported by the teachers but also by self-reports of the children. The children are saying that they are already engaging at the age of 10 or 11 years in delinquent behavior. Also, the higher lead children have poorer attention compared to the low-lead children. Again, this taps into the kinds of behavioral disabilities that we are talking about.

Now I am going to switch to the effects of lead on monkeys. The effects of lead on monkeys are, not surprisingly, very similar to those in humans (SLIDE 17): increased activity, distractibility, perseverative behavior, and inability to inhibit inappropriate responding. The monkey studies that I am going to be talking about were all postnatal exposure at relatively low levels of lead so that the body burden, the blood leads of these monkeys, was very characteristic of blood leads within the population of U.S. children.

The first test that I want to talk about is called Fixed Interval Performance (SLIDE 18). It is a very simple test. All the monkey has to do is to respond one time at the end of a specific interval, in this case eight minutes, in order to receive an apple juice reward. But in fact what the monkey does, and what you or I would do as well, is pause at the beginning of the interval and then start to respond slowly. The rate of response then accelerates gradually until the monkey gets his reward at the end of the interval.

The top schematic represents a higher rate of responding on the fixed interval, and the lower one on a lower rate, so there are fewer total number of responses on the bottom compared to the top.

Fixed Interval Performance really measures some kind of activity, an activity that is specified by the investigator, but nonetheless it is activity (SLIDE 19). We can measure the acquisition of performance, which is learning, and we can measure the efficiency of response, or response inhibition; does the animal eventually learn that he does not have to put out a million responses in order to be able to receive his apple juice?

This task requires timing using internal cues, and remember I said that one of the characteristics of ADHD is an inability to do that.

Fixed Interval Performance is similar in humans and other animals (SLIDE 20). Performance on FI actually predicts performance on tests of impulsivity. In other words, choosing a shorter term gain versus a

larger, long term payoff, which is something we all have to learn how to do if we are going to go through school and be successful. It is something that everybody in this room was good at or we would not be here.

FI performance also discriminates children with ADHD. They exhibit a specific pattern of response that was also shown by my monkeys but which I am not going to talk about in any detail.

SLIDE 21 is session number (days of testing) versus responses per second, or response rate. There are three different groups of monkeys, monkeys that were exposed over their lifetime, during infancy only, and beginning after infancy was over. This study was designed to see whether there were sensitive periods, which there obviously were not on this task, but that is not really the point here.

The lower curve in all three panels is the response rate of the control animals. All three groups of treated monkeys responded at a higher rate than controls. This test was done when these monkeys were several years old, so for the group in the middle panel, it was long after lead exposure had been discontinued.

The next task that I want to talk about is really the analogue of the Wisconsin Card Sort Test, which I talked about earlier, Discrimination Reversal (SLIDE 22). All of our testing was controlled by a computer with a monkey sitting in a chamber looking at a panel. A panel would have had just these two buttons on it.

The monkey learns, for example, that he has to always respond on the square instead of the triangle. So again, he is going along and he is responding on the square and he gets his apple juice, and then the next trial he responds on the square and he gets his apple juice, and life is nice and he knows what he is doing. And all of the sudden, when he responds on the square, it is wrong.

And it is wrong because I, as the investigator, have programmed the computer to now say that the triangle is correct. This is called a reversal, and we can have a number of such reversals. Eventually, a normal animal or a normal human will learn to change strategies more and more quickly with each reversal because it will say, “Oh yes, it is a reversal” and so the first time they make an error they will switch right away.

Again, we can look at acquisition of performance or we can look at the ability to change response strategy (SLIDE 23). This kind of a task is more sensitive than simply the initial learning of the task per se, and as I said, we can look at the learning curve over several reversals.

SLIDE 24 is the same group of monkeys that was in the previous slide. This depicts reversal number versus the number of errors for each reversal. The lowest line is the control group, and then the three treated groups. You can see that the errors for the first reversal, even in the control group, are greater than for the initial acquisition because they have to unlearn the old strategy and learn the new one.

For the animals that were exposed to lead over their lifetime, for example, there is a huge first reversal deficit. These animals all do learn, but they stay at a higher error rate than controls for the most part across 15 reversals, which would be several weeks of testing.

Another test that we did with these same monkeys is called Delayed Alternation (SLIDE 25). Again, this is on the surface a very, very easy task. The monkey faced a panel with two buttons on it; they would both be yellow.

The monkey, on the first trial, gets to choose whichever button he wants, but after that he has to alternate responses between buttons, just back and forth, and every time he makes a correct alternation, he gets an apple juice reward. Between opportunities to respond Left-Right, Left-Right, there can be a delay interposed so that the monkey has to remember for as long as a couple of minutes which button he responded on last.

This is a test of spatial or working memory (SLIDE 26). The monkey has to rely on internal cues and we can assess perseveration very well in this task, in other words, whether the monkey just keeps responding repeatedly on the same wrong button without switching buttons.

SLIDE 27 is a different group of lead monkeys than I just discussed. This indicates low and high lead here, but in fact they were both low levels of lead. If we look at the number of errors across days, across sessions, you can see that the two treated groups have more errors in a dose dependent fashion.

The requirement to finish the session was 100 correct responses. You can see that whereas the control monkeys are finishing in about half an hour, 40 minutes, the higher dose treated animals are taking three hours or more to complete the session. The reason for that was that some of these lead treated monkeys would make the first response correct, and then they would just respond on the incorrect lever again and again and again, dozens, and sometimes hundred of trials before they would switch and get one correct (SLIDE 28).

This is really comparable to the kinds of deficits that one sees with very severe brain lesions. So it was terribly unexpected for us to see this with a low dose of lead.

I am going to switch now to PCBs (SLIDE 29). PCBs produce a lot of the same kinds of effects as lead: decreased IQ, impulsivity, attention problems, poor school performance, and problems with language processing (which again is one of the characteristics of learning disabilities), deficient social behavior, and blurring of gender specific behaviors.

I am going to talk first for a few minutes about the Michigan PCB study (SLIDE 30). I am sure many of you are probably familiar with that study. This is a longitudinal perspective study in which the mothers were recruited during pregnancy. It was begun in the 1980s when PCB levels were high in the environment, higher than they are now. It consisted of mothers who did or did not eat Lake Michigan fish.

The investigators found impaired neurological function during infancy, poor cognitive performance at four years of age, and a variety of deficits at 11 years, which is really what I am going to talk about because they are really where you begin to be able to look at specific syndromes (SLIDE 31).

At eleven years they found a decrease in full scale and verbal IQ, problems in word and reading comprehension, and problems with memory and attention, which is part of the syndrome of ADHD in a more severe form.

SLIDE 32 is the association between full scale IQ and prenatal exposure. The exposure measure is a composite index of maternal body burden in blood and milk, which is designed to be representative of prenatal exposure to the fetus. At the highest body burden there is a decrease in full scale IQ. But if you look at word comprehension (SLIDE 33), there is a deficit in word comprehension at the highest two body burdens, which again suggests that there is something going on that IQ alone is not capturing.

The Dutch PCB study is an ongoing study that is not as far along as the older Michigan study (SLIDE 34). It is a longitudinal perspective study in two centers in the Netherlands. It was designed specifically to look at the potential for breastfeeding to contribute to impairment. Women were recruited by whether or not they planned to breastfeed or formula feed their infants. Exposure was through the general food supply; this was not a fish eating population.

They did a lot of testing during infancy; for example, infant neurological status, but I am going to talk about the 42-month data. The investigators observed a deficit in IQ (SLIDE 35). This is the Kaufman-ABC, which is a young child IQ test, associated with PCBs in maternal plasma.

There were also deficits in verbal comprehension (SLIDE 36) as well as on a vigilance task. On the vigilance task the child faced a computer screen and symbols appeared on the computer screen randomly. It could be a puppy, or a kitten, or a butterfly. The instruction to the child was to respond to the puppy, but do not respond to anything else.

The main dependent variable on this is reaction time, or how long it takes the child to respond when the puppy appears because reaction time is a measure of attention. Children with higher PCB levels had a longer reaction time. They also had more false positive responses. In other words, in addition to

responding to the puppy, they were responding to the butterfly and they were responding to whatever was going on, so this speaks to the idea that they are having problems with impulse inhibition.

(SLIDE 37) These kids also had decreased high-level play and increased non-play in a very controlled environment in a room with their mother. These kids tended to just look around and do nothing. On various rating scales and clinical instruments, they also demonstrated increased activity, increased aggression, and increase on a scale of withdrawal and depression.

Now, some of these were associated with prenatal exposure to PCBs, but some of them were also or only associated with postnatal exposure, with the concurrent blood PCB level of the child at 42 months of age, which presumably is reflective of exposure through breast milk.

(SLIDE 38) There is a study in press from this same group in school age kids demonstrating prenatal PCB exposure to be associated with less masculinized play behavior in boys and more masculinized play behavior in girls. There was also an independent dioxin effect. This is not directly relevant to behavioral disabilities, but it certainly speaks to the fact that PCBs are endocrine disrupting chemicals. As you may remember, these kinds of effects were seen in the poisoning episode in Taiwan, which followed 0children to later ages.

(SLIDE 39) There are newer PCB studies which I am not talking about: one in Oswego, New York, and one in Germany, because they really are not as far along, and they are not to the point where the kids are in school and we can document reading or other kinds of learning disabilities. These studies are replicating at lower body burdens studies that were performed in the 1980s on infant neurological status and early IQ. Even though the early studies were done at higher PCB levels, the same kinds of things are being found at lower PCB levels.

(SLIDE 40) Again, I am going to switch to monkey data. This is Fixed Interval Performance. This is the task where all the monkey has to do is to respond one time at the end of the interval in order to be reinforced. This graphs the responses per second on a log scale versus session number. The lower graph is the control group. You can see that the treated animals are responding at a higher rate, over 50 days of testing.

The Fixed Interval Schedule, though, does not require any specific rate of response. It does not require a high or a low rate of response, and it certainly does not punish a high rate of response. So what we wanted to do was to see whether these PCB treated monkeys could inhibit responding if we asked them to do so. You have already heard about DRL performance the first talk this morning. I might also say that I am one of Bernard Weiss's students, so there are three of us this morning who are students of Bernard Weiss.

(SLIDE 41) The DRL schedule requires the animal to inhibit responding, in this case, for at least 30 seconds, in order to be reinforced with apple juice. So if the monkey waits 30 seconds and then responds, he gets his reward. If he does not wait, then the clock resets and he has to wait another 30 seconds.

So this differential reinforcement of low rate schedule obviously requires very specific internal timing cues and it requires response inhibition (SLIDE 42). Remember, the animal has to wait 30 seconds, so if the average time between responses is above 30 seconds, then the monkey is mostly getting rewards for his responses. SLIDE 43 demonstrates that the control animals, by about session 20 or so have figured this out, and their average time between responses is a little more than 30 seconds. This is efficient and really accurate performance. I often wonder whether I could do as well. But the treated animals even over the course of 51 sessions, really have not gotten it. Their performance is getting better, but they are still below the 30 seconds. So the answer to whether they can inhibit their responding is No.

Another way to look at performance is the ratio of the non-reinforced responses over the reinforced responses (SLIDE 44). This ratio decreases fairly rapidly for the control animals so that it is well below 1

(1:1) by about session 20. Most of their responses are being reinforced, whereas you can see how much higher the ratio is for the treated animals. It is really a very inefficient response strategy.

I think I am going to skip these last two slides and just tell you that PCB treated monkeys were also deficient on delayed alternation. Similar to lead treated monkeys they made more perseverative errors (SLIDE 45, SLIDE 46).

I have talked about lead and PCBs. I chose lead and PCBs because we know a lot more about the effects of these toxicants in children than we do about any other environmental contaminant, or maybe all the other environmental contaminants put together.

(SLIDE 47) We do know that maternal alcohol consumption, maternal smoking, and marijuana consumption all produce pretty much the same constellation of effects as lead and PCBs: decreased IQ, distractibility, impulsivity, all the things that we have been talking about, which really are components of learning disabilities, conduct disorders and ADHD.

I have not said here that we know that these contaminants are producing these kinds of syndromes. But I think it is a reasonable hypothesis that if you are taking a whole population and shifting it in one direction or another, more kids will be in the box of a clinically defined syndrome than had these children or had everybody in society not been exposed to these contaminants.

These are only two contaminants. There are dozens of pesticides out there that were designed to be neurotoxic that we have really almost no information about, as well as all of the other solvents and plasticizers and endocrine disrupting chemicals. So the effects of lead and PCBs are not even the tip of the iceberg. Tip is too big a word to use with regard to how little we know about the contribution of these kinds of chemicals to these clinically defined behavioral disabilities. Thank you.

Q&A

Koibuchi: Thank you very much. The paper is open for discussion. Any questions? Actually for Japanese… yes, please.

Q: Thank you for the very interesting presentation. To tell the truth, I once applied lead to cultured neurons several years ago, but I could not get remarkable results. But hearing from your interesting lecture I would like to try again.
My question is: are there some interactions between other factors, for example, between nutrition factors and lead or PCBs, which are neurotoxic?

For example, the relationship between lead and iron deficiency, or thyroid deficiency, or whether iron deficiency can influence the effect of lead or if some such alterations will occur? Do you have any idea?

Rice: Let me just make sure I understand what you are asking. You were asking about lead and iron deficiency?

Certainly iron deficiency can cause some of the same things that lead can cause. Even in epidemiological studies you can tease those two effects out, but one thing that is really interesting is that in an iron deficient child the effects of lead are much more profound. So yes, there is an interaction, not only in the molecular and biochemical level, but also it is manifested in the functional behavior of the child as well.

Q: Is there any specific site of action of lead in the biochemical pathway?

Rice: Lead does everything. Lead does everything all over the brain. We have been looking for the mechanism for lead toxicity for at least 30 years. It interferes with calcium homeostasis, so given that, it affects everything: second messenger systems, gene expression. It really affects everything, and it affects pretty much all areas of the brain to one degree or another.

But this constellation of symptoms really suggests that one of the areas of the brain or the circuits in the brain that might be particularly vulnerable to toxic insult by lead, but also other things, is the prefrontal cortical area.

Because the prefrontal cortex is responsible for impulse control, it is responsible for organization, organization of behavior in time and place, it is really kind of the master of how you organize your memories what gets stored and what does not. It is also very important for social behavior in primates including humans. So if I had to bet what perhaps the most important area for these kinds of decrements was, prefrontal cortex would be my first choice.

Q: Is there any evidence of lead accumulation in the prefrontal cortex?

Rice: Yes, there is. I do not know if you remember the very old studies that were done in rodents many years ago where the report was that lead preferentially accumulated in hippocampus. If you give low levels of lead, and if you do it with chronic exposure rather than acute exposure, there is not preferential accumulation in hippocampus.

But there is accumulation in various parts of cortex — and this has not been done very well with monkeys and most of the data are in rats — it is layer dependent. I cannot remember which layers it is, but if you look at where calcium goes, you could probably take some pretty good guesses.

Q: I am Keiichi Tanno from Kobe City College of Nursing. I have two questions. Could you take the translation phones?

Rice: All I am getting is a lot of feedback. Maybe if I just step away. OK, go ahead.

Q: That was an extremely interesting presentation. This is a difficult problem, and I believe it would be more accurate for me to ask in Japanese, so please allow me to ask in Japanese.

I have two questions. Did you use the conventional animals or use some specific strain of monkey?

Rice: I used cynomolgus monkeys, *Macaca fascicularis*, Japanese macaques. Was that the question?

Q: Are they genetically controlled like rats?

Rice: No, they are colony born monkeys. They are actually very heterogeneous because they are from different parts of the world and you could actually tell by looking at them that they were from different areas.

Q: I see. I am in the fifth year since beginning education. As for the learning effect of education in your experiment, I think genetic factors and environmental factors are extremely interacted on each other. I have another question. Are there some groups of the world other than the EPA, which is your research group, such as groups studying this problem, the correlation among chemical substances, genetic factors, learning effect and intelligence? Or is there this sort of data?

I would also like to know what you think about genetic factors.

Rice: There are groups at EPA down in North Carolina who are looking at that very thing, they are looking at various strains, they are looking at various knockout mice, and looking at the effects of chemicals including endocrine disrupters. But that work to my knowledge is really just getting started, relatively speaking.

Q: I have a short question. I understand there is extremely clear data that suggests a correlation between intelligence quotient and lead, but have you measured lead for the parents. Also I would like to know about the rate test of the parents for people.

Rice : Are you talking about monkeys or people?

Q: People. I got it. Thank you very much.

Rice: What they do — and those are not my epidemiological studies — they look at the child really for lead, most of the emphasis has been on postnatal exposure. Prenatal exposure also contributes to performance very early in life, but because lead levels in the child peak at about two years of age and then decrease, by the time the child is several years old, the child own postnatal body burden of lead is a better predictor than the prenatal was.

In the longitudinal studies both things where looked at, and what they do in terms of controlling for the intelligence of the parents and so forth, they look at maternal IQ and control for that, they look at a measure of how good the home environment is — it is called the HOME, Home Environment. It is how many books are in the home and how much time does the mother spend interacting with the child and all of those kinds of things.

All of those things are controlled for to try to tease out the effects of lead. In some of the epidemiological studies, the children who were more disadvantaged had higher levels of lead, and so that was a potential confounder.

But there was an epidemiological study done in Boston, in which very upper-middle class professional people were moving back into Boston and renovating old housing stock that had lead based paint in it, so that it was actually the more advantaged children that had the higher lead body burden. When those other factors were controlled for, the effect of lead actually became stronger.

Q: Thank you very much.

Koibuchi: Thank you. Yes, please

.

Q: Thank you very much for the presentation of your dedicated research.

My work is not directly related to the topic of your presentation, but when such research is started, children with ADHD are discovered here and there throughout the community, but I

think this may be the start of research. I am concerned about this problem among the people of Japan, and I was wondering if your research may be able to provide some insight into this.

For example there is the way young Japanese people pronounce their words. Certain pronunciations are extremely different than they used to be a while back. This applies especially for the way they pronounce the syllables “sa, shi, su, se, so”. This goes not only for the general population, but also for specially trained professionals such as radio and television announcers. I don’t know if this is a brain or physical function problem, but I am extremely concerned by it. Have you conducted any research of pronunciation and vocalization in your country?

Rice: That is interesting. I think we usually attribute it to just spoiled kids. I think that one of the things that these contaminants are producing, and methylmercury would be another one of these, is deficits in higher order sensory processing, which is why eventually it shows up as deficits in verbal ability, verbal comprehension, and reading.

It is usually not attributed to a motor deficit, but to a sensory deficit, instead. If that is true, then some of the deficits that are being attributed to lack of intelligence, to IQ decrements, really may be sensory in nature, instead.

I am unaware of what you are describing being observed or being worrisome with respect to young children in the United States. A specific language deficit or pronunciation deficit, I think, is what you are saying.

Q: I am concerned about the pronunciation of not only young Japanese from the general population but of young Japanese who are professional announcers as well. Very few people worry about this when talking with friends and I think it is a problem that involves a very fine line. Thank you very much.

Koibuchi: Thank you very much. Yes, please.

Q: Please allow me to ask in Japanese. I think your friend Dr. Susan Chance has published a paper, which basically concerns impairment of memory due to exposure in older adults, i.e., exposure may cause memory impairment. Do you have any comment on her paper?

Rice: I am sorry, could you repeat the question?

Q: Dr. Susan Chance has published a paper recently which describes memory impairment due to adulthood exposure to PCBs. Do you have any comments on the possibility that exposure to PCBs in adults/older people may cause memory impairment or cognitive dysfunction?

Rice: Oh, you are talking about her older adults, so-called older adults, over 50. Yes, we all really like the fact that she considers over-50 older adults.

I think it is a really interesting observation because we put so much emphasis on children, and rightly so, but what happens at the other end of the lifespan is that some of the ways in which we have been able to compensate we may not be able to compensate quite so well any more. We lose synapses, we lose the ability to make new synapses, we lose neurons, and I think the fact that she is demonstrating these kinds of impairments as people age I think is really important.

As I am sure many in the audience know, the same kinds of effects are being found in people with Minamata disease, who have been functional for many, many years, but then as they become elderly really are not able to even perform normal functions of life, to eat and dress themselves and so forth and so on.

At EPA we are now starting to pay a lot more attention to at least thinking about the importance of looking at not only the consequences of developmental exposure to behavior during adulthood, but the consequences either of very early exposure far out in the lifespan at the end of the lifespan that was not apparent all through the adult life of the person, or exposure during later adulthood being more deleterious than it would be for a younger person.

We are really grappling with that, how we are going to address that, either in terms of research or in terms of regulation. Because the way our testing regulations are written right now, we really pay no attention to that whatsoever, and we are going to have to do a much better job than we have done in the past.

Q: Thank you very much. Can I make one more question, if you do not mind.

Koibuchi: Sorry, but we'd like to get a question from the floor.

Thank you very much, Dr. Rice. I appreciate everyone who attended this session and I thank you for your active discussion. I have to say sorry for the delay, but this is based on the active discussion, so I am happy for that. Thank you very much. This is my closing remark.