

# Workshop on Perinatal Exposure to Dioxin-like Compounds. IV. Neurobehavioral Effects

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Nine participants outlined findings in the area of neurobehavioral effects of dioxin-like compounds and presented plans for new studies. Neurobehavioral effects are among the most sensitive and well studied toxicity end points for this class of compounds. A focus of the workshop was presentation of designs for major new studies in human populations outside the United States that are intended to extend and clarify the results of two previous large-scale studies in populations in Michigan and North Carolina. Improved methods for exposure assessment and more focused approaches to understanding specific neurobehavioral deficits were highlighted. Animal studies and *in vitro* mechanistic studies are emphasizing the importance of alterations in neurotransmitter systems and thyroid function that may underlie behavioral dysfunction. There is continuing improvement in analytical and study design methods to identify the most active congeners of PCB mixtures in the environment. These diverse studies will contribute to effective response of public health and regulatory groups to this continuing problem. — Environ Health Perspect 103(Suppl 2):151–155 (1995)

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## Introduction

The workshop began with reports of two laboratory studies that are helping to define specific neurobehavioral effects resulting from developmental polychlorinated biphenyl (PCB) exposures and the biochemical changes in the brain that underlie them.

Dr. Richard Seegal reported on a series of experiments examining changes in brain biogenic amines by PCBs. Three themes have been the localization, specificity, and duration of these changes. Studies with oral administration of Aroclor 1016 and 1260 (0, 0.8, 1.6, 3.2 mg/kg/day) in monkeys (*Macaca nemestrina*) over a 20-week period led to reduced regional dopamine concentrations that were not reversible upon discontinuation of dosing (1). Regional

dopamine levels and PCB content were found to be correlated. PCB analysis demonstrated prevalence of three congeners, PCB28, PCB47, and PCB52. Studies with 20- and 66-week exposures demonstrated that effects were duration dependent and not asymptotic. A second theme important to the purpose of the workshop is congener specificity. In a series of *in vitro* and *in vivo* experiments, Dr. Seegal has found *ortho*-substituted congeners are most effective in producing changes in catecholamines (2,3). Experiments using the PC12 cell culture system demonstrated that dopamine could also be reduced *in vitro* by direct exposure to PCB concentrations that did not affect cell viability (4). This system allowed exploration of congener specificity using a panel of 50 different congeners. Coplanar congeners were not active; *ortho*-substituted congeners were most active and the most active agent was PCB4 (5). Congener potency was not related to cellular uptake.

A series of experiments in rats using Aroclor 1016 in the diet produced an unexpected result. In contrast to adults, developing organisms exposed to PCB via dam's diet demonstrate increases in regional brain catecholamines after weaning. These results point up the importance of developmental exposure stages and congener analysis to assessment of biomarkers for neurobehavioral effects. Possible mediating mechanisms such as estrogenic activity, effects on thyroid (6), and altered tyrosine hydroxylase function must be considered in reconciling these results from adult and developing organisms.

Dr. Susan Schantz summarized experiments in both monkeys and rats demonstrating a particular type of deficit in the delayed spatial alternation (DSA) task that may represent a specific impairment attributable to perinatal PCB exposure. The DSA task was used because it is a complex and difficult task, and may be particularly sensitive to low-level effects. Also, prior research has delineated specific brain regions and neurotransmitter systems mediating performance of this task, thus suggesting possible mechanisms that can be tested when deficits are detected.

DSA performance is disrupted in monkeys exposed perinatally to Aroclor 1016 or 1248 and tested as adults (7). This deficit was not seen after perinatal 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) exposure in monkeys (8). The particular type of impairment (deficits seen at shorter as well as longer delay intervals) is similar to that produced by lesions to prefrontal cortex (9). Further, a similar pattern of deficits can be seen when dopamine input to the prefrontal cortex via the mesocortical pathway is disrupted chemically. Lesions to the hippocampus (another brain region that mediates DSA performance) typically produce impairments only at longer delays (> 30 sec).

Three congeners administered perinatally to rats (PCB28, 118, and 153) also led to a delayed spatial alternation deficit. In this species the effect was sex specific (limited to females). PCB28 produced the same pattern (deficits at all delays) that was produced by the PCB mixtures in monkeys; the pattern was not as clear for the other

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The Neurobehavioral Effects Working Group: Joseph Jacobson, Wayne State University, Detroit, MI; Corine Koopman-Esseboom, Sophia Children's Hospital, Rotterdam, Netherlands; Gina Muckle, Laval University Hospital, Quebec, Canada; Larry Needham, Centers for Disease Control, Atlanta, GA; Walter Rogan, National Institute of Environmental Health Sciences, RTP, NC; Susan Schantz, University of Illinois, Urbana, IL; Richard Seegal, NY State Department of Health, Albany, NY; Gerson Smoger, Smoger and Associates, Walnut Creek, CA; Nynke Weisglas-Kuperus, Sophia Children's Hospital, Rotterdam, Netherlands.

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two congeners. Notably, PCB28 was most strongly correlated with brain dopamine in Dr. Seegal's experiments (described above). Future plans include measuring regional brain dopamine concentrations and turnover, tyrosine hydroxylase activity, and dopamine receptor numbers, with special attention to the prefrontal cortex.

Dr Schantz pointed out that these results with the DSA task can be generalized to humans by considering specific functions used in performing the task such as representational (short-term) memory and inhibition of a prepotent response. These same functions are tapped in standardized tests such as Piaget's A-not-B task for infants, and the Wisconsin Card Sorting Test and Stroop Test for adults (see Table 1 for brief descriptions of these and other neurobehavioral tests mentioned in this summary).

In discussing behavioral evaluation of infants and children exposed perinatally to PCBs, Dr. Joseph Jacobson also emphasized the need for more specific identification of impairment. He made the distinction between "apical" and "narrow band" or "specific domain" tests. Apical tests, such as IQ tests and maturational scales, assess global function at the apex of a number of contributing processes, and poor scores can be caused by any of these processes. Apical tests are valuable because they have real-world validity in their identification of dysfunction. However, they

are unlikely to distinguish specific toxicant exposures. Specific domain tests probe discrete functions and may provide links to underlying mechanisms or suggest specific remediation strategies.

Three specific domain tests were used by Jacobson and collaborators (10–13) to study 4-year-old children exposed perinatally to PCBs through their mother's consumption of contaminated fish from Lake Michigan. These tests, which focused on cognitive processing efficiency, sustained attention, and activity level, were adapted or modified from well-developed paradigms in cognitive neuroscience. Two tasks, a visual search and recognition task and a visual discrimination task, were used to assess cognitive processing efficiency. In both cases, processing efficiency was measured as the time to respond excluding time required for sensory input and motor response. For the first task, the measure specifically associated with processing efficiency, the change in response time with increased memory load, was not correlated with PCB exposure indices, although a lower overall accuracy in recognition memory was associated with prenatal exposure. The second task found a relationship between prenatal exposure (as indexed by maternal milk PCB level) and efficiency (as indexed by time required for correct responses). No exposure effects on visual discrimination accuracy were seen. For the vigilance or sustained attention task, no

individual performance index (reaction time, number correct, commission errors) was associated with PCB exposure; however, a correlation between prenatal exposure indices and a composite score of several performance indices suggested the importance of further work in the attention domain. Activity level assessment was based on examiner ratings and parent reports. Postnatal PCB exposure (based on analysis of serum samples obtained at 4 years of age) was associated with lower activity level. In response to questions, Dr. Jacobson stated that all analyses controlled for confounders determined to be correlated with the various exposure indices and that data were not analyzed by gender.

Dr. Walter Rogan summarized results from North Carolina and Taiwan cohorts of PCB-exposed children, all of which have appeared in research reports or abstracts. The North Carolina cohort consisted of over 800 children born between 1978 and 1982 in selected rural, suburban, and urban areas. They were evaluated through 5 years of age using the Brazelton Neonatal Neurobehavioral Assessment Scale (NBAS), the Bayley Scales, and the McCarthy Scales (14–17). Associations with prenatal PCB exposure as indexed by breast milk were found; postnatal PCB exposure was not related to neurobehavioral measures. Children in the top 5 to 10% were more frequently hypotonic and hyporeflexic as neonates and scored 4 to 8 points lower

**Table 1.** Some neurobehavioral assessment tools mentioned in workshop presentations.

Test	Age	What is assessed	Reference
<b>Infant tests</b>			
Neonatal Neurobehavioral Assessment Scale (Brazelton)	Newborn–1 month	Reflexes, responsiveness, state regulation	(24)
Neurological and Adaptive Capacity Score (Amiel-Tison)	Newborn	Reflexes, muscle tone, alertness	(24)
Newborn Neurological Exam (Prechtl)	Newborn	Age-appropriate neurodevelopment	(24)
Bayley Scales	2 months–3 years	Age-appropriate cognitive and motor ability	(25)
Visual Recognition Memory Test (Fagan)	3–12 months <sup>a</sup>	Novelty preference; short-term memory; "infant intelligence"	(26)
"A not B" Test (Piaget)	8–12 months <sup>a</sup>	Object constancy; memory; early cognitive function and flexibility	(27)
<b>Child/Adult Tests</b>			
Bender Gestalt Test	— <sup>a</sup>	Ability to draw pictured objects	(28)
Boston Naming Test	> 6 years	Ability to name pictured objects	(25)
California Verbal Learning Test	5–16 years	Verbal learning and memory	(29)
Child Behavior Checklist	6–11 years	Child behavior problems; hyperactivity; vigilance; response inhibition	(30)
Continuous Performance Test	— <sup>a</sup>	Vigilance; response inhibition	(31)
Groninger Behavior Observation Scale	> 6 years	Child behavior problems; attention and activity	(32)
Kaufman Assessment Battery for Children	2.5–12.5 years	Age-appropriate cognitive and motor ability	(25)
McCarthy Scales	2.5–8 years	Age-appropriate cognitive and motor ability	(33)
Neurological Examination (Touwen)	1.5–4 years	Age-appropriate neurodevelopment	(34)
Reynell Developmental Language Scales	—	Age-appropriate development of language	(35)
Rutter Scales	9–13 years	Child behavior problems; hyperactivity; general intelligence	(36)
Stanford-Binet Intelligence Scales	2–18 years	General intelligence	(25)
Stroop Test	— <sup>a</sup>	Cognitive flexibility; response inhibition	(28)
Tactual Performance Test	> 4 years	Tactile form recognition and memory	(25)
Wechsler Intelligence Scales for Children (WISC)	> 6 years	General intelligence	(25)
Wisconsin Card Sorting Test	> 6 years	Concept formation; attentional flexibility	(25)

<sup>a</sup>Standardized age norms not available.

than controls on the psychomotor scale of the Bayley. In the older children no relationships were detected between PCB exposure and McCarthy scores, school grades or hyperactivity reports. Dr. Rogan concluded that there was a consistent motor delay from prenatal PCB exposure that lasted until 2 years of age.

More recently (1985), evaluations were begun in children born to women who were acutely exposed to high PCB and polychlorinated dibenzofuran (PCDF) intake from contaminated rice oil in Taiwan in 1979. Offspring of these women, born from 1979 to 1983 ( $n=117$ ), were evaluated along with matched neighborhood controls (18,19). Children of PCB/PCDF-exposed mothers had consistent deficits in developmental milestones as obtained from parent report. Intelligence testing with several instruments (depending on the child's age), as determined at yearly intervals, revealed a consistent 4- to 8-point deficit. Also, a larger number of exposed than control children were in the lower centiles. Using the Rutter scale, higher activity levels were noted in exposed than in control children; however, this scale is not well normed for Chinese populations so quantitative deviation from standardized norms cannot be obtained. Notably, children born up to 6 years after the exposure were as affected as children born within a year, and there was little evidence of recovery as the children matured. Ongoing work in this population involves evaluation of a new birth cohort (1982-1987) and studies of puberty and sexual maturation in the older cohort. In response to questions, Dr. Rogan noted that the finding of hyperactivity is not necessarily inconsistent with hypoactivity reported in Lake Michigan children because the congener mixture might differ. Also, in contrast to the Michigan study group, exposure was confined to gestation in the Taiwan population because mothers were advised not to breast feed after the incident.

The next presentations dealt with ongoing or planned studies of neurobehavioral end points in a number of different populations that have not previously been studied.

The first presentation was unique to the session in addressing possible neurodevelopmental effects of dioxin, rather than PCB, exposure. Dr. Gerson Smoger, the presenter, cited the lack of information on neurobehavioral developmental effects of the well known dioxin contamination incident in Times Beach, Missouri. Dr. Smoger has been able to gather data from 15 children born in Times Beach after 1971 when diox-

in contamination first occurred and before 1983 when Times Beach was evacuated. Subsequent to examination with a full neuropsychologic test battery, these children were evaluated with a quantitative EEG method developed by E. Roy John (20,21). Results were compared to population norms developed from 700 New York children and validated cross culturally in several populations. The data have not as yet been fully analyzed and interpreted and Dr. Smoger characterized the information presented as "very preliminary." The main measures evaluated by the quantitative EEG method were interhemispheric symmetry and coherence as derived from power spectra analysis at 21 locations. Deviation from population-based norms was identified primarily in the frontal/prefrontal areas. Discriminant functions developed by the New York group to identify learning disabled youngsters were also applied to the Times Beach study group, leading to some interesting suggestions of abnormality. A few other remarkable aspects of the neuropsychologic testing and medical condition questionnaires were commented on by Dr. Smoger. Questions to Dr. Smoger included topics such as selection of the study population and assessment of dioxin exposure.

The remaining presentations addressed new studies of neurodevelopmental effects of PCB exposure. In each case, populations have been identified whose exposures may be higher than those of populations in North Carolina or Michigan. Each of the three studies draws heavily on previous studies in Michigan and North Carolina without replicating them, uses updated analytical tools, and also adds some unique design and evaluation features.

Drs. Corine Koopman-Esseboom and Nynke Weisglas-Kuperus described the neurobehavioral component of an ongoing study in a Dutch-German cohort of children. Dr. Koopman-Esseboom outlined the original study design, which included evaluations from birth to 1.5 years of age in a cohort of 400 children in Netherlands. Half the population was selected from an urban/industrialized area (Rotterdam) and half from a rural area (Groningen). Both breast-fed and bottle-fed children were included.

A distinctive feature of the study is extensive exposure ascertainment. Cord blood, milk, and maternal blood samples were obtained for detailed PCB congener analysis. Human milk samples were collected in the second and sixth week after delivery for PCB, PCDF and polychlorinated dibenzodioxin (PCDD) measurements.

Additional features of this study were examination of vitamin A status and thyroid function. Preliminary consideration of exposure indices indicates that both populations had similar levels of exposure and that various PCB congener levels were highly intercorrelated across individuals and sample types. This holds promise that a single index can be selected to represent the extent of PCB exposure, perhaps PCB153 in maternal plasma in late pregnancy.

Neurobehavioral measures were based on previous studies in Michigan and North Carolina indicating effects on infant muscle tone and reflexes, motor development, and visual recognition memory. The Bayley Scales and an updated and expanded version of the Fagan test were used as in the prior studies; however, the Precht neurodevelopmental assessment procedure rather than the NBAS was used for assessing the newborn; and an additional neurodevelopmental assessment (Touwen) was scheduled for 18 months of age. The assessments through 18 months were to be completed by the end of 1993, at which time preliminary results were to begin to become available.

Dr. Weisglas-Kuperus continued by explaining that follow up and extension of the study became possible through support of the EEC and collaboration with Dr. Gerhard Winneke at the University of Dusseldorf. A German cohort was formed that will add 200 to 300 children to the original Dutch study group. The German study design involves comparison of groups selected for exposures in the highest and lowest 10% of the population as determined from cord blood samples.

A neurodevelopmental follow-up at 3.5 years of age is an important feature of the Dutch study. It includes a neurodevelopment assessment (Touwen, Hemple), assessment of sequential and simultaneous attention and information processing and achievement (Kaufman Assessment Battery for Children), and an evaluation of language development (Reynell Developmental Language Scales). For identifying behavioral problems, the Child Behavior Checklist will be supplemented by the Groninger Behavioral Observation Scale for detecting attention deficit disorders. In addition, tests of visual discrimination, sustained attention, and memory, as described by Dr. Jacobson earlier in the session, are planned to extend previous findings by the Jacobson group. Assessment at this age is considered particularly valuable because, if deficits are detected, interventions can be planned prior to school years when impaired performance is a serious problem for the child.

Dr. Gina Muckle described the neurobehavioral component of the study of Inuit populations in Northern Canada exposed to PCBs via the traditional diet of fat from marine mammals. A cohort of 250 infants will be studied from birth to 1 year of age. Neurobehavioral assessments are designed to be comparable with previous Michigan and North Carolina studies, with some additions and changes in focus. Neonatal CNS function will be measured with the Neurological and Adaptive Capacity Score of Amiel-Tison and with the Brazelton NBAS. Psychomotor and mental abilities assessment will utilize the first two scales of the Bayley Scales as previously; however, a recently revised version will be used and a more differentiated level of scoring may be employed. In addition, the third scale of the Bayley Scales, the Infant Behavioral Record, will be used to ascertain neurobehavioral characteristics. Information processing ability will be measured with the Fagan visual recognition memory test, as previously, as well as a test of crossmodal recognition.

A particular focus of the study is detailed examination and consideration of life history variables. As in other studies, confounding of results by exposure to heavy metals (primarily mercury and lead) and the modifying influence of dietary omega-3 fatty acid content will be considered. However, perinatal complication, social economic status and psychosocial risk will also be examined. Dr. Muckle pointed out that these factors have an important influence on the later cognitive function of children and can either attenuate or amplify effects of early toxicant

exposure. In addition, specific interactions of toxicants with these factors could be important to identify. Measurements of psychosocial risk, a unique feature of this study, will be obtained through information on the quality of intellectual stimulation provided by caretakers, mothers' IQs, mothers' levels of psychological functioning, and mothers' perceptions of social support and social network characteristics.

The final study plan presented by Dr. Larry L. Needham involves a cohort of about 1000 children in the Faroe Islands where dietary dependence on fish and marine mammals (cod pilot whales) has led to elevated exposure to mercury and PCBs. Importantly, this population has very low alcohol and tobacco use, thus reducing confounding from these factors. Developmental exposure is assessed from umbilical cord, cord blood, and maternal hair samples. Studies in this population have been ongoing since 1986 under the direction of Dr. Phillippe Grandjean of Odense University in Denmark (22), but plans to assess neurobehavioral function as related to PCB exposure are in the initial stages. This study has a strong public health focus and intends to support risk assessment and determination of safe exposure levels by identifying neurobehavioral measures that are the most sensitive indicators of health impairment. As is the case in other populations exposed via seafood consumption, concurrent mercury exposure will be a major issue in interpretation of this work.

An important feature of the study is assessment of school-age children (7 years of age) with an emphasis on cognitive function. This is the latest age for follow-up in

any study conducted to date. The more extensive testing possible in these older children may aid in distinguishing effects of mercury and PCBs. Tests of cognitive function (learning and memory) rather than achievement-oriented tests have been selected, including the Bender Gestalt, California Verbal Learning Test, Boston Naming Test, several scales of the Wechsler Intelligence Scales for Children (WISC), the Tactual Performance Test, and the Continuous Performance Test. In addition, sensory and motor function and neurophysiologic testing is planned including assessment of vision, audition, vibration thresholds, finger tapping, eye-hand coordination, postural balance, heart-rate variability, and visual and auditory evoked potentials. Serum samples for PCB analysis will also be obtained.

The workshop demonstrated that sufficient data have been gathered to determine that PCB exposure represents a risk to neurobehavioral development in children and to establish health protective measures. Estimates of minimally safe exposure levels have been derived from the North Carolina studies on neonatal hypotonicity (Brazelton) and infant psychomotor delay (Bayley Scales) and from the Michigan studies on impaired visual recognition memory (23). Currently there is considerable ongoing interaction and collaboration in planning and interpretation of new studies that are contributing to the understanding of this important public health problem. These studies hold promise that the neurobehavioral findings from the initial study groups in Michigan and North Carolina will be confirmed, extended, and clarified.

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