DELAYED BRAINSTEM AUDITORY EVOKED POTENTIAL LATENCIES IN 14-YEAR-OLD CHILDREN EXPOSED TO METHYLMERCURY

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Objective To determine possible exposure-associated delays in auditory brainstem evoked potential latencies as an objective measure of neurobehavioral toxicity in 14-year-old children with developmental exposure to methylmercury (MeHg) from seafood.

Study design Prospective study of a birth cohort in the Faroe Islands, where 878 of eligible children (87%) were examined at age 14 years. Latencies of brainstem evoked potential peaks I, III, and V at 20 and 40 Hz constituted the outcome variables. Mercury concentrations were determined in cord blood and maternal hair, and in the child's hair at ages 7 and 14.

Results Latencies of peaks III and V increased by about 0.012 ms when the cord blood mercury concentration doubled. As seen at age 7 years, this effect appeared mainly within the I–III interpeak interval. Despite lower postnatal exposures, the child's hair mercury level at age 14 years was associated with prolonged III–V interpeak latencies. All benchmark dose results were similar to those obtained for dose-response relationships at age 7 years.

Conclusions The persistence of prolonged I–III interpeak intervals indicates that some neurotoxic effects from intrauterine MeHg exposure are irreversible. A change in vulnerability to MeHg toxicity is suggested by the apparent sensitivity of the peak III–V component to recent MeHg exposure. *(J Pediatr 2004;144:177-83)*

See related article, p 169.

Methylmercury (MeHg) is a worldwide contaminant of seafood and freshwater fish.[1] MeHg toxicity can produce widespread adverse effects within the nervous system, especially when exposures occur during brain development.[2,3] Early adverse effects have been characterized by administering neurobehavioral tests to children exposed in utero from maternal seafood diets.[4-6] Thus, a National Research Council (NRC) committee[7] concluded that intrauterine MeHg exposure was the most critical and emphasized the findings from a prospective birth cohort study carried out in the Faroe Islands.[5] The damage to the developing nervous system is thought to be potentially irreversible.[7] The possibility also exists that exposure during postnatal development may induce brain lesions; clinical[2,8] and experimental[9] information suggests that such effects would tend to be more focal and would particularly involve the sensory cortex and the granular layer of the cerebellum.

Current advisories on fish consumption issued by national and state authorities differ and mainly aim at pregnant women or women of reproductive age groups.[1] Because the risk to children from dietary MeHg exposure is unclear, some fish advisories in the United States also address "young children,"[10] or children as old as, for example, 8 years[11] or 15 years.[12]

As an indicator of MeHg neurotoxicity, delayed evoked potential latencies have been recorded in poisoning victims[13,14] and in laboratory animals.[15] In contrast with

BAEP	Brainstem auditory evoked potential	MeHg	Methylmercury
BMD	Benchmark dose	NRC	National Research Council
BMDL	Benchmark dose level	PCB	Polychlorinated biphenyl
BMR	Benchmark response		

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neuropsychologic test outcomes, this measure is thought to be independent of socioeconomic covariates.[16] As illustrated by environmental exposure to lead, evoked potential abnormalities constituted important objective evidence on neurotoxic effects in children.[17]

In an extended follow-up of the Faroese birth cohort, we have assessed brainstem auditory evoked potentials (BAEPs) at age 14 years. We previously showed that increased intrauterine MeHg exposures were associated with delayed peak III latencies at age 7 years.[5,18] We hypothesized that these delays would remain at age 14 years and that BAEP latencies would also be sensitive to MeHg from adolescent seafood diets.

METHODS

Study Population and Follow-up

A cohort of 1022 births was assembled in the Faroe Islands during a 21-month period in 1986 to 1987.[19,20] The primary indicator of intrauterine exposure to MeHg was the mercury concentration in cord blood, and concentrations in maternal hair at parturition were also determined.[19] MeHg exposures varied considerably: 15% of the mothers had hair mercury concentrations >10 μg/g, whereas 4% were below 1 μg/g, a level that corresponds with the exposure limit recommended by the NRC committee.[7] Concomitant exposure to polychlorinated biphenyls (PCBs) was determined from the concentration in umbilical cords from 438 cohort members.[5] The first follow-up examination was performed 7 years later and included hair mercury assessment, evoked potentials, and pediatric examination.[5,21]

At age 14 years, a total of 878 of 1010 live cohort members (86.9%) were examined. Most examinations took place at the National Hospital in Tórshavn, the capital of the Faroe Islands, from April to June of 2000 and 2001. For families who had moved, examinations were also offered in Odense, Denmark, in November 2000. Each day, four children were examined during the morning and four during the afternoon. The examinations were conducted by a team of health professionals who had no access to information on individual exposure levels. The 438 boys and 440 girls examined had an average age of 13.83 (SD 0.32) years.

Hair samples were again obtained, and the proximal 2-cm segment was analyzed by flow-injection cold-vapor atomic absorption spectrometry after digestion of the hair sample in a microwave oven.[5] The total analytical imprecision for this analysis was estimated to be 4.3% and 5.5% at mercury concentrations of 4.7 μg/g and 11.1 μg/g, respectively. Accuracy was ensured by participation in the Canadian Hair Mercury Quality Control Program; all our results were within 1 SD of the adjusted mean. The high analytical quality is comparable with previous performance.[5,19] Results in micrograms may be converted to nanomol by multiplying by 5.0.

The study protocol was approved by the ethical review committee for the Faroe Islands and the institutional review board at the US institution, and parental informed consent was obtained.

Neurologic Examination

A thorough pediatric examination included otoscopy and assessment of neurologic optimality. None of the children had current middle ear infection. A total of 18 children examined had neurologic disorders thought to be independent of MeHg exposure and were therefore excluded from the data analysis: congenital hypothyroidism, one; Tourette syndrome, one; dystonia, three; epilepsy, two; polyneuropathy sequelae, one; mental retardation, one; psychomotor retardation, four; meningitis sequelae, one; concussion, three; and deafness, one. None of the subjects examined had diabetes. The MeHg exposure of these subjects did not differ from that of other cohort members.

Brainstem auditory evoked potentials were determined in all participating subjects except one refusal (N = 859). We used a four-channel electromyograph (Medelec Sapphire-4ME, Surrey, United Kingdom) also used previously.[5,21] Click signals at an intensity of 65 dB hearing level (0.1-ms impulses of alternating polarity) were presented to the right ear through shielded ear phones at 20 Hz and 40 Hz (sampling time, 0.01 ms); the other ear was masked with white noise at an intensity of 45 dB HL. A frequency of 50 Hz was also attempted, but peak I was poorly defined at this click rate. Evoked potentials were recorded by using three standard electroencephalogram electrodes placed on the vertex, the right mastoid ipsilateral to stimulation, and the left mastoid (ground). Although 1024 responses were used 7 years before,[5,21] the number was increased to 2048 to improve the definition of peak I. Amplification and filtration were unchanged, and one replication of each condition was again performed for calculation of average peak latencies. The coefficients of variation for duplicate assessments remained higher for peak I (mean, 8.4%) than for peaks III and V (means, 4.3% and 3.7%, respectively). As an additional step for quality assurance, latencies from the first 250 children examined in Tórshavn in 2000 were scored twice by the same examiner (K. M.). The results of this blinded scoring–rescoring showed average coefficients of variation of 8.9%, 4.4%, and 3.7% for peaks I, III, and V, ie, similar to the duplicate assessments. Thus, although highly appropriate for latency measurement, the study circumstances did not allow accurate assessment of peak amplitudes. Peaks I, III, and V are thought to reflect the volume-conducted electric activity from the acoustic nerve, pons (superior olivary nucleus), and midbrain (inferior colliculi), respectively.[16]

Audiometry was performed by a trained nurse using Interacoustics Diagnostic Audiometer AD229 with a Peltor H7A headphone (Assens, Denmark) in a sound-insulated room. The patient-controlled Hughson-Westlake procedure was used in accordance with International Organization for Standardization 8253-1. A threshold was defined as two of three correct responses in a procedure with 5-dB increases and

Table I. Results of developmental methylmercury exposure biomarkers for 859 birth cohort members without neurological disease examined at age 14 years*

Biomarker	n	Geometric average	Interquartile range	Association with cord blood†
Cord blood (μg mercury/L)	835	22.6	13.2–40.8	(1)
Hair (μg mercury/g)				
Maternal, parturition	855	4.22	2.55–7.68	0.77
Child, 7 years	800	0.60	0.34–1.24	0.33
Child, 14 years	839	0.96	0.45–2.29	0.35

*Concentrations in μg may be converted to nmol by multiplying by 5.0.
†Correlation coefficient after logarithmic transformation.

10-dB decreases. Pure-tone air-conduction hearing thresholds were measured at 125, 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 6000, and 8000 Hz. Two children did not complete their audiometry examination.

Data Analysis

Pearson correlation coefficients were used to assess bivariate relationships between exposure variables. Regression analysis was used to determine the association of MeHg exposure with the outcome variables. Age and sex may be important predictors of BAEP latencies[16,21] and were therefore included as independent variables along with the exposure variables. In addition, confounders previously included in the analysis of neuropsychologic test results[5] were screened for possible associations with the outcomes in the current study, but no pattern was found. Further models included as an independent variable the latency result obtained 7 years previously along with the age at that examination. Additional analyses incorporated PCB and postnatal MeHg exposure parameters as explanatory variables. Because of skewed distributions, logarithmic transformation of the contaminant concentrations was used, and the mercury regression coefficients therefore correspond to the change in the dependent variable associated with a 10-fold increase in MeHg exposure. Significant exposure effects were further explored in generalized additive models, which do not require linearity assumptions while providing a smooth, nonparametric dose-response curve.[22]

Calculation of the benchmark dose (BMD) is increasingly used for comparison of dose-response curves at low dose levels and for determining exposure limits.[7,18] The BMD is the dose of a substance that increases the risk of an abnormal response by a benchmark response (BMR), ie, from P_0 (usually 5%) for an unexposed child to P_0 + BMR for a child exposed at the BMD.[23] The NRC committee used a BMR of 5% so that an exposure at the corresponding BMD will double the risk of an abnormal response.[7] To take the statistical uncertainty into account, a lower 95% confidence limit (BMDL) for the BMD is also determined. Using linear dose-response models, BMDLs expressed as the maternal hair mercury concentration were approximately 10 μg/g for the most sensitive neuropsychologic and BAEP outcomes in the Faroese children at age 7 years.[7,18,24] For comparison with these dose-response associations, we used the same default settings when calculating BMDL results for BAEP outcomes at age 14 years.

RESULTS

Prolonged Peak III and Peak V Latencies at Higher Prenatal Methylmercury Exposures Were Caused by Increased I–III Intervals That Were Prolonged Already 7 Years Before

Hair mercury concentrations at age 14 years (Table I) indicated that the children's current MeHg exposure had increased since the previous examination ($P < .001$). Approximately half of the children now exceeded the hair mercury limit of 1 μg/g, but the average corresponded to only one fourth of the concentrations in maternal hair at child birth. Nonetheless, the different sets of exposure biomarkers correlated well.

The BAEP latencies were similar to the results obtained at age 7,[5,18,21] and again differed as expected[16] between boys and girls. Age had no effect within the limited range studied.

Intrauterine MeHg exposure biomarkers showed several statistically significant associations with the BAEP latencies, especially peaks III and V at both frequencies (Table II). The same tendency was seen for the interpeak I–III latency, despite being affected by the greater imprecision of peak I determinations. Because peak I and interpeak III–V latencies were clearly not associated with the intrauterine exposure level, MeHg appeared to affect mainly the I–III interval. Neither sex nor age was associated with MeHg exposure levels, and confounder adjustment therefore did not affect the mercury regression coefficients.

Given the more robust findings for the full peak III latency (Fig 1), its better precision, and the parallel results for this outcome obtained at age 7 years,[5,18] this outcome parameter was selected for more detailed calculations. Inclusion of the postnatal exposure biomarkers as additional predictors did not affect the regression coefficients for the prenatal exposures. However, they were almost completely abolished when peak III latencies at age 7 were incorporated as predictors.

Table II. Mean results and regression coefficients for logarithmic transformations of mercury exposure biomarkers as predictors of latencies of brainstem auditory evoked potentials (ms) in 859 Faroese children at 14 years

		Regression coefficient* (*P* value)			
	Mean (SD)	Cord blood (n = 835)	Maternal hair (n = 855)	Hair at 7 y (n = 800)	Hair at 14 y (n = 839)
20 Hz					
I	1.770 (.129)	0.015 (.213)	0.001 (.942)	−0.005 (.622)	0.006 (.553)
III	3.952 (.161)	0.045 (.002)	0.037 (.014)	0.012 (.335)	0.001 (.907)
V	5.788 (.204)	0.049 (.006)	0.032 (.085)	−0.002 (.901)	0.018 (.159)
I–III	2.183 (.152)	0.027 (.051)	0.036 (.013)	0.017 (.150)	−0.004 (.631)
III–V	1.835 (.132)	0.004 (.722)	−0.005 (.686)	−0.014 (.181)	0.017 (.056)
40 Hz					
I	1.806 (.169)	0.027 (.089)	0.014 (.410)	0.007 (.602)	0.012 (.293)
III	4.054 (.178)	0.032 (.048)	0.023 (.169)	0.008 (.536)	0.002 (.847)
V	5.954 (.214)	0.048 (.009)	0.036 (.066)	0.006 (.686)	0.024 (.070)
I–III	2.248 (.190)	0.004 (.805)	0.009 (.614)	0.001 (.925)	−0.010 (.430)
III–V	1.900 (.148)	0.015 (.226)	0.013 (.383)	−0.002 (.852)	0.022 (.028)

*Adjusted for sex and age; because of the logarithmic transformation of the mercury concentrations, the regression coefficient indicates the change in the dependent variable associated with an increase in MeHg exposure by a factor of 10.

Current Methylmercury Exposures Were Associated With Prolonged III–V Interpeak Latencies

The regression coefficients also suggested an effect of recent MeHg exposure, but only on the III–V interpeak interval (Table II, Fig 2). This association was not affected by inclusion of prenatal exposure biomarkers, and neither did the lower mercury concentrations at age 7 years seem to affect this outcome parameter. At the same time, this interpeak variable was significantly associated with all other peak latencies, except for the peak I latency.

Inclusion of PCB exposure within the subset of the cohort for which this parameter was available did not affect any of the MeHg regression coefficients. In addition, the PCB parameter did not reach statistical significance in any of the analyses.

Audiometry results generally showed normal hearing, and hearing thresholds above 30 dB(A) were recorded for only approximately 2% of the children. Hearing thresholds were not associated with MeHg exposure, except for 4 kHz in the right ear (Table III). The association with the peak III latency (Table III) was caused by a prolonged latency for peak I at increased hearing thresholds, whereas the interpeak I–III interval was unaffected. PCB exposure and postnatal MeHg exposure were not associated with the audiometry results. Inclusion of the hearing threshold at 4 kHz as a predictor of BAEP latencies changed the mercury regression coefficients only marginally.

Benchmark Dose Results Were Similar to Those Seen at Age 7 Years

The relative magnitude of the regression coefficients (Table II) can be judged by comparison with the variability of the outcome variables. Thus, for peak III latencies, an average regression coefficient of approximately 0.04 corresponds to almost 25% of the SD. Because a logarithmic transformation of the mercury concentrations was used, the effect of a doubling of the exposure can be determined by multiplying the regression coefficient by 0.301. Accordingly, a doubling of the prenatal exposure results in a latency prolongation by about 7% of the SD. Similarly, a doubling of the current exposure level is associated with a prolongation of the interpeak III–V interval by about 5% of the SD.

Additional comparisons may be based on BMD calculations. Prenatal BMDL results for peak III at the two frequency conditions corresponded to an average of approximately 10 μg/g hair based on either cord blood or maternal hair. For the III–V interval, postnatal BMDLs averaged approximately 5 μg/g for the child's hair mercury concentration at age 14 years.

DISCUSSION

The developing brain is thought to be the organ most vulnerable to MeHg exposure.[1,7] Emphasis in risk assessment has therefore been placed on neurologic function of children with intrauterine exposure to this neurotoxicant, and previous studies have applied neuropsychologic function as a key measure of adverse effects.[4-6] In parallel, neurophysiologic tests, such as BAEP assessment, have been used in population studies as highly standardized, rapid, painless, and inexpensive procedures.[16,25] Prolonged BAEP latencies have been reported as an effect of exposure to MeHg[13-15] and other neurotoxicants, such as lead.[17,25]

We report that BAEP latency assessments were highly reproducible and that several latencies at age 14 years showed a positive association with MeHg exposure. Intrauterine exposure was mainly associated with delays in peaks III and V,

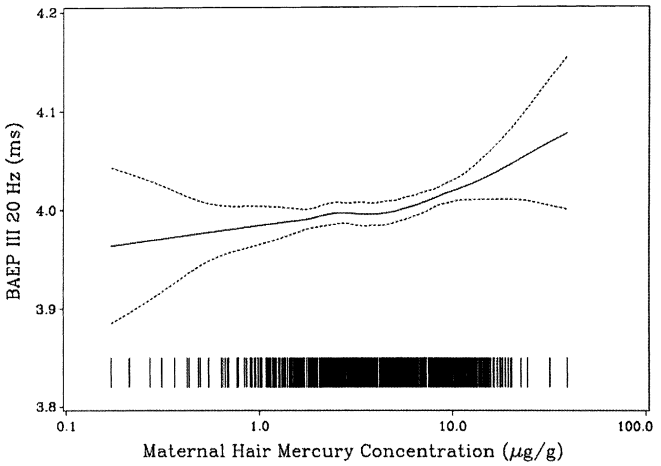

Fig 1. Prenatal dose-effect relationship between maternal hair mercury at birth and the peak III latency of the brainstem auditory evoked potentials in 859 Faroese children at 14 years, adjusted for sex and age. The association is estimated in a generalized additive model analysis in which a smooth nonparametric curve (equivalent degrees of freedom, 3) is fitted to the data while adjusting for confounders. The *broken lines* indicate the point-wise 95% confidence interval for the dose-response relationship. Each *vertical line above the horizontal axis* represents one observation at the exposure level indicated. To convert to nmol/g, multiply mercury concentration in μg/g by 5.0.

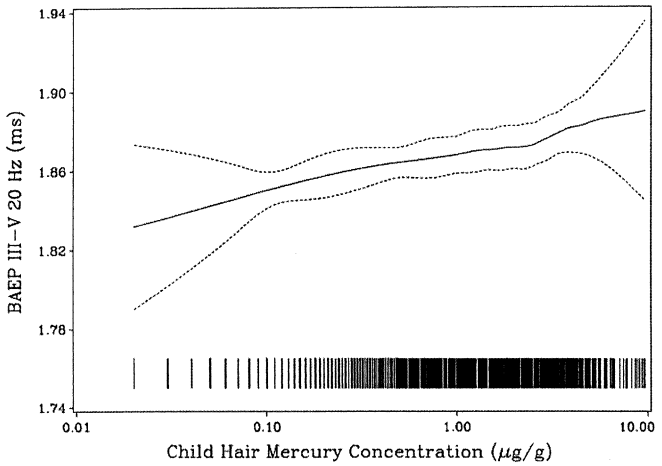

Fig 2. Postnatal dose-effect relationship between the child's current hair mercury and the interpeak III-V latency of the brainstem auditory evoked potentials in 859 Faroese children at 14 years, adjusted for sex and age. The association is estimated in a generalized additive model analysis as in Figure 1, but the horizontal scales differ. The *broken lines* indicate the point-wise 95% confidence interval for the dose-response relationship. Each *vertical line above the horizontal axis* represents one observation at the exposure level indicated. To convert to nmol/g, multiply mercury concentration in μg/g by 5.0.

and the I–III interpeak interval appeared to be most sensitive. This result is in accord with previously reported exposure-associated delays in the same cohort examined at age 7 years and in a cross-sectional study of 7-year-old children from another North Atlantic fishing population.[18,21] However, the regression coefficients at age 7[21] were approximately twice the magnitude observed 7 years later. Furthermore, adjustment of the most recent peak latency for the result obtained 7 years previously virtually abolished the mercury effect. These observations suggest a lasting neurotoxic effect of the intrauterine exposure, although the reduced regression coefficient may perhaps indicate some degree of compensation. The peak III results also suggest that this outcome is not affected by postnatal exposures at the levels occurring in this population.

More recent MeHg exposure, as reflected by the current hair mercury concentrations of the children, was associated with a prolonged interpeak III–V interval. This observation is noteworthy, because the children's current exposures averaged less than one fourth of the maternal levels during pregnancy, and a single hair analysis probably is a very inaccurate marker of the causative postnatal exposure levels. Although paired mother–child exposure data correlated well and thereby suggested relatively stable dietary habits within each household, only the recent exposure level was associated with this outcome. Hair mercury concentrations at age 7 years were the lowest and did not contribute to this association.

Despite the delayed BAEP latencies, the audiometry data suggested only limited, if any, effect of MeHg exposure on hearing thresholds. These results parallel those obtained at age 7 years.[26] All BAEP latencies were recorded with a sound pressure adjusted for audiometry results; no association between hearing thresholds and BAEP latencies was detected, except for peak I at a single sound frequency on one side only. Although deafness has been reported in severe congenital MeHg poisoning cases,[2] hearing loss is not a uniform finding in less serious childhood poisonings or in adult cases.[2,27]

The MeHg-associated prolongation of BAEP latencies in the current study was subtle and comparable with effects associated with lead exposure.[17,25] These changes are much less extensive than clinical findings in patient groups, such as the abnormal BAEP waves with poorly defined or absent peaks III and V in multiple sclerosis, and the markedly prolonged interpeak latencies in patients with acoustic neurinoma or diabetes mellitus.[28] However, the relative change parallels the extent of neuropsychologic deficits determined in the cohort children at age 7 years.[5] Thus, in several functional domains, a doubling of the intrauterine MeHg exposure showed a decrease in performance by 5% to 10% of the SD.[5,29] Subtle neurotoxic effects, sometimes expressed in terms of IQ points, have important societal implications in regard to educational achievement and earning potential.[30]

The BMDL represents a statistically defined point on the dose-response curve that allows comparison between low-range toxicity studies. However, the BMDL should not be interpreted as a threshold indicator. Indeed, significant exposure-related deficits on neuropsychologic tests at age 7 years were documented at maternal hair mercury concentrations below the BMDL.[5] Previous calculations[7,12,24,31] based on the most sensitive neurologic, neuropsychologic, and neurophysiologic endpoints all indicate a BMDL of about 10 μg/g maternal hair, ie, the same level as found for peak III delays at age 14 years. We found that the postnatal BMDL for the prolonged III–V interpeak interval was approximately

Table III. Cord blood mercury concentration (geometric mean) and peak III latency of the brainstem auditory evoked potentials measured at age 14 years (arithmetic means) in 857 Faroese cohort children in relation to the hearing threshold at 4 kHz on the right ear

Hearing threshold (dB[A])	n	Mercury concentration*	Peak III latency (ms) 20 Hz†	Peak III latency (ms) 40 Hz†
<0	158	20.0	3.94	4.03
0	171	20.8	3.92	4.02
5	218	22.8	3.94	4.03
10	161	24.9	3.99	4.09
>10	136	25.4	3.98	4.10

P value for association (Spearman correlation coefficient) with hearing threshold: * < .01, † < .001.

one half of that. However, because of statistical uncertainty, this difference may not necessarily reflect the relative toxic potentials of prenatal and postnatal exposures.

The participation rate at age 14 years was very high, thereby reducing the concern that the results may have been affected by differential follow-up rates. An important strength of this study is that the examinations relied on the same methodology as 7 years before, and were performed by the same examiner, who was blinded to exposure data and previous peak latency results. In addition, the outcome measures were confirmed to be independent of socioeconomic confounders. The known[16] BAEP peak latency difference between boys and girls was replicated, but sex was not associated with MeHg exposure and therefore did not cause confounding. At age 7 years,[21] prolongations of the peak I latency occurred as a result of middle ear infection, but at age 14 years, this trait was absent.

An important limitation is that few postnatal exposure estimates were obtained and that the prenatal and postnatal exposure indicators were highly associated. Although dietary patterns may have been rather stable, the postnatal exposure biomarkers do not necessarily represent the magnitude of the toxic exposure at susceptible time windows. Any exposure misclassification would be mostly random and would tend to dilute the associations with the outcome variables, although this dilution would be limited by the wide exposure interval covered within this cohort. Despite this bias, the size of the cohort allowed separation of latency prolongations associated with intrauterine and recent MeHg exposures. The fact that peaks III and V at both frequencies showed clear associations with two independent indicators of prenatal MeHg exposure, and not with indicators of postnatal exposure, suggests that the findings are robust and credible for human health risk assessment. Likewise, although unanticipated, the association of the prolonged interpeak III–V interval with recent MeHg exposure only was also seen at both frequencies.

As previously reported for the results at age 7 years,[26] concomitant prenatal exposure to PCBs, which occur in whale blubber sometimes eaten in the Faroes, did not influence the BAEP outcomes. Developmental exposure to PCBs is now thought to affect primarily cochlear function and effect on BAEP amplitudes rather than latencies.[32] In addition, lead exposure was comparatively low and not associated with exposure to mercury.[19] The generalizability of this study would therefore not seem to be limited by concomitant exposures to other neurotoxicants.

Although a chance finding in multiple comparisons cannot be ruled out, the possibility that prenatal and postnatal MeHg exposure may affect different targets in the brain is supported by both experimental and clinical evidence. Prenatal exposure of rats to toxic amounts of MeHg results in severe lesions that include the brainstem, whereas effects of postnatal treatment are less diffuse and particularly involve the sensory cortex.[9] Similarly, neuropathologic and imaging evidence reveals a greater degree of focal cortical damage with postnatal MeHg exposure compared with congenital cases.[2,3,8] The results of this study would therefore seem to be plausible, although the specific vulnerability of the interpeak III–V interval to postnatal MeHg exposure was not predicted. Although the significance of postnatal MeHg exposure needs to be documented further in independent studies with more frequent exposure assessments, our results suggest that developmental vulnerability to MeHg neurotoxicity is likely to extend into the teenage period.

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