REFERENCES

1. Carter LJ: Michigan's PBB incident: chemical mix-up leads to disaster. Science 1976; 192:240–243.
2. Kolbye AC: Statement on polybrominated biphenyls (PBBs). Read before the Michigan House of Representatives Committee on Public Health at Lansing, MI, 1977.
3. Anderson HA, Wolff MS, Lilis R, *et al:* Symptoms and clinical abnormalities following ingestion of polybrominated biphenyl-contaminated food products. Ann NY Acad Sci 1979; 320:684–702.
4. Bekesi JG, Holland JF, Anderson HA, *et al:* Lymphocyte function of Michigan dairy farmers exposed to polybrominated biphenyls. Science 1978; 199:1207–1209.
5. Anderson HA, Lilis R, Selikoff IJ, *et al:* Unanticipated prevalence of symptoms among dairy farmers in Michigan and Wisconsin. Environ Health Perspect 1978; 23:217–226.
6. Landrigan PJ, Wilcox KR, Silva J, *et al:* Cohort study of Michigan residents exposed to polybrominated biphenyls:epidemiologic and immunologic findings. Ann NY Acad Sci 1979; 320:284–294.
7. Brown GG, Nixon R: Exposure to polybrominated biphenyls: some effects on personality and cognitive functioning. JAMA 1979; 242:523–527.
8. Dent JG, Nettes KJ, Gibson JE: Effects of chronic administration of polybrominated biphenyls on parameters associated with hepatic drug metabolism. Res Commun Chem Pathol Parmacol 1976; 13:75–82.
9. Kimbrough RD, Burse VW, Liddle JA: Toxicity of polybrominated biphenyls. Lancet 1977; 2:602.
10. Barr M, Keller CA, Rogan WJ, *et al:* Summary of the workshops on perinatal and postnatal defects and neurologic abnormalities from chemical exposures. Ann NY Acad Sci 1979; 320:458–472.
11. Committee on Environmental Hazards: PCBs in breast milk. Pediatr 1978; 62:407.
12. Weil WB, Spencer M, Benjamin D, *et al:* The effect of polybrominated biphenyl on infants and young children. J Pediatr 1981; 98:47–51.
13. McCarthy D: Manual for the McCarthy Scales of Children's Abilities. New York: The Psychological Corporation, 1972.
14. Weschler D: Manual for the Wechsler Preschool and Primary Scale of Intelligence. New York: The Psychological Corporation, 1967.

ACKNOWLEDGMENTS

This study was researched for and supported by the Michigan Department of Public Health. The authors are indebted to George Van Amburg of that Department for the statistical analysis, and to Elizabeth Richards and Margaret Mordarski of the Department of Pediatrics, University of Michigan, for manuscript editing and preparation. An earlier version of this paper was presented at the American Psychological Association meeting in Los Angeles, CA, August 1981.

Developmental Abilities of Children Exposed to Polybrominated Biphenyls (PBB)

ELIZABETH ANN WALKER SEAGULL, PHD

Abstract: To investigate whether ingestion of polybrominated biphenyls has an adverse effect on the neuropsychological development of young children exposed *in utero* and in infancy, five tests of the McCarthy Scales of Children's Abilities were administered to a group of 19 PBB-exposed Michigan children. When the data for the exposed group were analyzed according to body burden of PBB as determined by fat biopsy, correlations ranging from −.5228 to −.3004 were found between the natural logarithms of the children's fat PBB values and their standardized scores on the developmental scales. Four of the five correlations were significant at $p < .05$. Multivariate analysis of covariance confirmed the existence of a significant main effect for fat PBB level, with parental education held constant. Children with higher body burdens of PBB (> .100 ppm) scored significantly lower than exposed children with lower body burdens on the same four tests, and on a composite score representing overall performance. These results suggest the existence of an inverse relationship between body levels of PBB and some developmental abilities in young children. (*Am J Public Health* 1983; 73:281–285.)

Address reprint requests to Elizabeth A. W. Seagull, PhD, Department of Pediatrics and Human Development, B240 Life Sciences, Michigan State University, East Lansing, MI 48824. This paper, submitted to the Journal July 15, 1981, was revised and accepted for publication July 1, 1982.

Editor's Note: See also related articles in Different Views, p 277, and p 286, and in Public Health Then and Now, p 302, this issue.

Introduction

From May 1973 to May 1974, Michigan residents unknowingly ingested polybrominated biphenyls (PBBs) through eggs, meat, and dairy products from animals whose feed had been inadvertently contaminated through the substitution of a fire retardant for a feed supplement in what has been called "one of the most costly agricultural accidents in the history of the United States."[1] The series of errors

through which the PBB was introduced into the food chain has received widespread publicity and has been described in detail elsewhere.[2-4]

Because the nature and source of the contamination was not discovered until May 1974, and identification and quarantine of contaminated farms continued throughout 1975, virtually every resident of the lower peninsula of Michigan during late 1973 to 1975 had some level of exposure to PBB through the ingestion of animal products. On May 10, 1974, the Food and Drug Administration (FDA) set 1 part per million (fat basis) as the "action guideline" for PBB contamination in milk, milk products, and meats. In November 1974, lower guidelines were set at 0.3 ppm (fat basis) for meat, milk, and dairy products and 0.05 ppm (whole basis) for eggs. Consequently, great numbers of cattle, swine, sheep, and chickens were destroyed, as well as thousands of pounds of dairy products, and millions of eggs.[5]

The extent of the PBB contamination in Michigan has been of concern because so little was known about its toxicity in animals and humans. The chemically related polychlorinated biphenyls (PCBs), however, are reported to have caused serious illness in humans in Japan when ingested in contaminated oil.[6] In that incident, children born to exposed mothers were of low birthweight and had hyperpigmented skin.[7] The Michigan incident, therefore, has generated considerable interest in uncovering what, if any, long-term human health effects are associated with ingestion of PBBs.[8]

Animal studies have demonstrated that PBBs concentrate in hepatic and adipose tissue, and are poorly metabolized and very slowly excreted. Thus the potential exists for bioaccumulation and long-term effects of exposure, even in the absence of acute toxic reactions.[9-14] PBBs are readily transferred to offspring in the milk of exposed mothers. The nursing rat pup acquires significantly more PBB via milk than does the fetus via the placenta.[15]

Of particular relevance to the present investigation are animal studies which have demonstrated neurobehavioral effects of exposure to the halogenated aromatic hydrocarbons. Rhesus monkeys exposed to PCBs *in utero* and through ingestion of contaminated mother's milk were hyperactive and were slower in learning reversal tasks than control monkeys. These effects persisted for over two years, even after essentially total clearance of PCBs from the body fat.[16,17]

Rats exposed to PBBs showed more abnormal reflexes at the higher dose, reduced locomotor activity and grip strength, and decreased visual placing responses as compared with controls.[18,19] In another study, PBB-exposed rats demonstrated slower response times and hyperactivity.[20]

Human studies have failed to demonstrate any clear-cut pattern of illness common to PBB-exposed persons. Instead, data are accumulating which suggest that the effects of PBB toxicity are more subtle, for example, exposed persons have increased reporting of skin, neurological, and musculoskeletal symptoms,[21,22] changes in lymphocyte function[23] and liver function tests,[24] alterations in immunologic response,[25] and primary hypothyroidism.[26] A greater number of neuropsychological symptoms were reported by PBB–exposed adults than control adults,[27,28] but since these symptoms (tiredness, headaches, nervousness, etc.) are also known to be associated with depression and anxiety, the interpretation of these self-reported symptoms has been questioned.[29] A study which purported to show that differences in neuropsychological functioning between exposed and control subjects could be accounted for by personality variables, however, failed to control for age, sex, education, or PBB exposure of control subjects.[30]

A study of Michigan farm children found, like the studies of adults, a greater frequency of symptoms reported during the period from 1973 to 1976.[31] A more detailed analysis of the symptoms reported for 1976, however, revealed an inverse relationship between number of symptoms reported and the measured level of serum PBB. In fact, children from the highly contaminated farms had the fewest complaints—fewer even than unexposed Wisconsin farm children.[32] This curious finding has yet to be adequately explained.

The larger study of which the present study was a part found that parents of exposed children reported that their children had a higher number of illnesses than were reported by parents of control children, but no dose-related relationship was present. The exposed and control children did not differ significantly on growth parameters or physical or neurological examination findings.[33]

Because of their sensitivity, behavioral tests can uncover effects on the nervous system of doses of toxins which do not produce grossly observable signs of poisoning.[34] Since the developing nervous system is most likely to show the effects of any neurobehavioral toxicity,[35] the present study was carried out on children exposed to PBBs *in utero* and/or through ingestion of PBB-laden breast milk as well as contaminated food.

Materials and Method

The subjects were 19 PBB-exposed children (eight boys and 11 girls), ranging from the age of 2 years and 5 months to 3 years and 11 months, who were participants in a larger study of possible effects of PBB on child health.[33] This age range was selected to include children who were conceived, born, or nursing during the period of maximal exposure before the contamination had been identified. Families who lived on quarantined farms or who bought their meat and dairy products from quarantined farms had previously been identified by the Michigan Department of Public Health. Those with children in the target age group were invited to participate.

Five tests of the McCarthy Scales of Children's Abilities[36] were administered to the subjects: Block Building, Puzzle Solving, Word Knowledge, Draw-A-Design, and Draw-A-Child. The McCarthy Scales is a well-standardized instrument which can be used for all children in this age range, is intrinsically interesting to children, and is relatively quick and easy to administer. The tests were selected to sample a range of perceptual-motor, attentional, and verbal

abilities not covered in the neurological examination.* The testing was done by three female clinical child psychologists, all experienced in testing young children. To reduce the possible effects of separation on the children's performance, all children were tested in the presence of one or both parents. The examiners did not know which were exposed and which were control children. Subcutaneous fat biopsies were taken after all other testing had been completed.

All protocols were scored using the standard McCarthy scoring criteria, and the raw scores obtained were transformed to standardized scores using McCarthy norms for each age range. The standardized scores are expressed as deviations from the mean, where M = 0; SD = ± 1. The examiners met after all children had been examined to review the scoring of each protocol and resolve any scoring questions.

The scores of the children were analyzed according to body level of PBB, first by correlational analysis, and then by a median split procedure, dividing the group in half according to their level of PBB body burden as measured by PBB concentrations determined by fat biopsy. Ten of the children (six girls and four boys) had PBB fat concentrations of greater than .100 parts per million (ppm); this was labeled the "high" PBB group. Nine of the children (five girls and four boys) had PBB fat concentrations of less than .100 ppm; this was labeled the "low" PBB group. The second group of analyses compared the standardized scores of the high and low PBB groups of children.

Results

The measured fat PBB values ranged from 20.960 ppm to 0.116 ppm for the high (> .100 ppm) group, (M = 4.218; SD = 6.710); and from .074 to .010 ppm (M = .050; SD = .019), for the low (< .100 ppm) group. In order to do a meaningful correlational analysis in the face of such a wide range of values, it was necessary to transform the fat values mathematically to narrow the range and make a linear analysis possible. A natural logarithm transformation of the fat values accomplished this and was used in the correlational analysis.

Pearson product moment correlations between the natural logarithm transformations of the exposed children's fat PBB levels and their standardized scores on each of the five McCarthy Scales tests administered are presented in Table 1. The second through fifth rows in the table show the intercorrelations between the children's performances on the five tests. A high degree of relationship is to be expected between them as each of the tests is part of a larger instrument which yields a cumulative score. These correlations are in the same range as those given for the test standardization sample.[36]

The first row in the correlational matrix shows that performance on all five of the tests has a negative relationship to the natural logarithm of the fat PBB level. As PBB level increases, standardized scores decrease. This relationship is significant ($p < .05$) on four of the five tests** accounting for from 16 per cent to 27 per cent of the variance in the children's scores.

A multivariate analysis of covariance was performed to clarify further the variance being accounted for by the independent variables: level of PBB (greater or less than .100 ppm) and sex. Years of parental education was held constant, to eliminate the effect of this covariate on the children's scores. An additional dependent variable was obtained by summing each child's scaled scores and obtaining a total score, representing overall performance on all five tests. Mean scale scores for each group of children are presented in Table 2. On the Puzzle Solving test, the main effect for high vs low fat PBB level approaches the .01 level of significance [$F(1,14) = 7.690$; $p = .015$]. The main effect for PBB level is significant at $p < .05$ on Block Building [$F(1,14) = 4.648$; $p = .049$], Word Knowledge [$F(1,14) = 5.016$; $p = .042$], and Draw-A-Child, [$F(1,14) = 5.040$; $p = .041$]. The main effect for fat PBB level was not significant on the Draw-A-Design test [$F(1,14) = 2.841$; $p = .114$]. On the total score, the main effect for PBB level approached the .01 level of significance [$F(1,14) = 7.656$; $p = .015$].

A significant main effect for sex was found on one of the five McCarthy tests. Exposed girls scored significantly lower than exposed boys in the Block Building test [$F(1,18) = 9.428$; $p = .008$]. There was no significant main effect for sex on the total score. There were no significant interaction effects between fat PBB level and sex on any of the five McCarthy tests administered, or on the total score.

Since it can be argued that the totaled scores are not meaningful as interval data, since they represent only 5 of the 18 tests on the McCarthy Scales, these data were also

*The McCarthy Scales of Children's Abilities contain 18 separate tests which are grouped into six Scales: Verbal, Perceptual-Performance, Quantitative, Memory, Motor, and General Cognitive. Three of the tests: Leg Coordination, Arm Coordination, and Imitative Action, load only onto the Motor Scale. The other 15 tests all load onto both the General Cognitive Scale and at least one of the other Scales. Four tests load onto two Scales in addition to the General Cognitive Scale: Memory and one other.

The decision-making with regard to which tests to use in the present study was as follows: the abilities examined by the three tests which load only onto the Motor Scale were already being tested by the pediatric neurologist, hence, it was unnecessary to repeat these. This left 15 tests. One test (Right-Left Orientation) is not administered to children under the age of five. Of the 14 remaining tests, two quantitative tests (Number Questions, and Counting and Sorting) were eliminated because, with such young children, we believed knowledge of number concepts was more likely to reflect emphasis on teaching numbers in the home, rather than differences in the child's ability to learn number concepts. Conceptual Grouping and Opposite Analogies were eliminated for similar reasons; a child's ability to group objects by shape and color and to give verbal opposites at this age would probably tell us more about the home environment than about the child. Of the ten remaining tests we chose the five which would be the most interesting to two- and three-year-olds, eliminating the five tests (Pictorial Memory, Verbal Memory, Numerical Memory, Verbal Fluency and Tapping Sequence) which we judged likely to produce outright refusals from some two-year-olds.

**Spearman's Rho correlations were also calculated with similar results. Details available from author.

TABLE 1—Pearson Correlation Coefficients between the Natural Logarithm of Fat PBB Values and Standardized Scores of Exposed Children on Five Tests of the McCarthy Scales of Children's Abilities (N = 19)

		Natural Log of Fat Value	Block Building	Puzzle Solving	Word Knowledge	Draw-A-Design	Draw-A-Child
Natural Log of Fat Value	r	1.000	−.4008	−.4980	−.4836	−.3004	−.5228
	p		.045	.015	.018	.106	.011
Block Building	r		1.000	.6176	.4617	.5218	.5374
	p			.002	.023	.011	.009
Puzzle Solving	r			1.000	.4699	.6166	.4622
	p				.021	.002	.023
Word Knowledge	r				1.000	.8009	.5381
	p					.001	.009
Draw-A-Design	r					1.000	.4511
	p						.026
Draw-A-Child	r						1.000
	p						

tested non-parametrically, treating the data as ordinal, comparing only the ranking of the children within the group. Composite scores of the exposed children were, therefore, compared using the Mann-Whitney U test. The total scores of the high PBB group were significantly lower (p = .0064) than the scores of the low PBB group. There were no significant differences by sex.

Discussion

This is the first report of a dose-related adverse effect of PBB ingestion in humans.

It is only recently that behavioral teratology has begun to be recognized as significant.[37,38] Although it is true that there are multiple variables which impact upon behavioral outcomes, with proper controls these difficulties can be minimized. Parental reactions of anxiety and depression to the PBB contamination incident have been mentioned as possible causes of any behavioral effects seen in the children.[33] This variable, however, does not account for the dose-related effect which was found in the present study, as parents were unaware of their child's PBB level. Parental reactions, if they had been the major determinant of the measured child behaviors, would have served to minimize differences within the exposed group of children. Parental

TABLE 2—Mean Standardized Scores of PBB-Exposed Children on the McCarthy Scales of Children's Abilities (N = 19)

PBB Level	High (>.100ppm)			Low (<.100ppm)			
McCarthy Test	N	M	SD	N	M	SD	P[1]
Block Building							
Boys	4	.180	1.08	4	.833	.740	
Girls	6	−1.25	.855	5	.172	.599	
Both Sexes	10	−.678	1.157	9	.466	.712	.049
Puzzle Solving							
Boys	4	−.505	.261	4	.075	.818	
Girls	6	−.648	.257	5	−.004	.675	
Both Sexes	10	−.591	.254	9	.031	.693	.015
Word Knowledge							
Boys	4	−.503	1.01	4	.543	.601	
Girls	6	−.332	1.15	5	.312	.123	
Both Sexes	10	−.400	1.04	9	.414	.437	.042
Draw-A-Design							
Boys	4	.145	1.05	4	.495	1.36	
Girls	6	−.332	.929	5	.546	.488	
Both Sexes	10	−.141	.952	9	.523	.899	.114
Draw-A-Child							
Boys	4	−.243	.661	4	.35	.971	
Girls	6	−.375	.942	5	.496	.691	
Both Sexes	10	−.322	.802	9	.431	.774	.041
TOTAL							
Boys	4	−.925	3.572	4	2.295	3.528	
Girls	6	−2.937	3.301	5	1.522	1.517	
Both Sexes	10	−2.132	3.201	9	1.866	2.306	.015

[1]MANOVA, with parental education held constant.

socioeconomic status was very similar between the high and low-exposure groups; however, the parents of the high PBB group were slightly better educated than the parents of the low PBB group (mean years of schooling of the two parents combined = 27.4 as compared with 24.66 years). Thus, controlling for parental education actually strengthened the significance of the relationship between test results and PBB level.

Further studies are planned to determine the persistence over time of these effects.

REFERENCES

1. Meester WD, McCoy DJ: Human toxicology of polybrominated biphenyls. *In:* Environmental Toxicology Symposium presented at the joint meeting of the American Academy of Clinical Toxicology, the American Association of Poison Control Centers, and the Canadian Academy of Clinical Toxicology, Seattle, WA, August 4, 1976.
2. Bernstein IA: Perspectives on the polybrominated biphenyl (PBB) contamination incident in the State of Michigan. Testimony presented before the Subcommittee on Science, Technology and Space of the US Senate Commerce Committee at Big Rapids, MI, March 28, 1977.
3. Carter LJ: Michigan's PBB incident: chemical mix-up leads to disaster. Science 1976; 192:240–243.
4. Kay K: Polybrominated biphenyls (PBB) environmental contamination in Michigan, 1973–1976. Environ Res 1977; 13:74–93.
5. Dunckel AE: An updating on the polybrominated biphenyl disaster in Michigan. J Amer Vet Med Assoc 1975; 167:838–841.
6. Goto M, Higuchi K: The symptomatology of Yusho (chlorobiphenyls poisoning) in dermatology. Fukuoka Acta Med 1969; 60:409–431.
7. Yoshimura T: Epidemiological study on Yusho babies born to mothers who had consumed oil contaminated by PCB. Fukuoka Acta Med 1974; 65:74–80.
8. Anon: Health department conducting long and short-term PBB study. Mich Med 1977; 76:564–565.
9. Dent JG, Netter KJ, Gibson JE: Effects of chronic administration of polybrominated biphenyls on parameters associated with hepatic drug metabolism. Res Comm Chem Path Pharm 1976; 13:75–82.
10. Department of Health, Education, and Welfare: Final report on the Subcommittee on the health effect of polychlorinated biphenyls and polybrominated biphenyls, Washington, DC, July 1976.
11. Kimbrough RD, Burse VW, Liddle JA: Toxicity of polybrominated biphenyl. Lancet 1977; 2:602–603.
12. Polybrominated biphenyls, polychlorinated biphenyls, pentachlorophenyl—and all that. Lancet 1977; 2:19–21.
13. Sleight SD, Sanger VL: Pathologic features of polybrominated biphenyl toxicosis in the rat and guinea pig. J Amer Vet Med Assoc 1976; 169:1231–1235.
14. DiCarlo FJ, Seifter J, DiCarlo VJ: Assessment of the hazards of polybrominated biphenyls. Environ Health Perspect 1978; 23:351–365.
15. Rickert DE, Dent JG, Cagen SZ, *et al:* Distribution of polybrominated biphenyls after dietary exposure in pregnant and lactating rats and their offspring. Environ Health Perspect 1978; 23:63–66.
16. Bowman RE, Heironimus MP, Allen JR: Correlation of PCB body burden with behavioral toxicology in monkeys. Pharmacol Biochem Behav 1978; 9:49–56.
17. Allen JR, Barsotti DA, Lambrecht LK, *et al:* Reproductive effects of halogenated aromatic hydrocarbons on nonhuman primates. Annals NY Acad Sci 1979; 320:419–425.
18. Tilson HA, Cabe PA: Studies on the neurobehavioral effects of polybrominated biphenyls in rats. Annals NY Acad Sci 1979; 320:325–336.
19. Tilson HA, Cabe PA, Mitchell CL: Behavioral neurological toxicity of polybrominated biphenyls in rats and mice. Environ Health Perspect 1978; 23:257–263.
20. Geller I, Hartmann RJ, Garcia C, *et al:* Effects of polybrominated biphenyl on a discrimination task in rats. Neurobehav Toxicol 1979; 1:263–267.
21. Selikoff IJ: PBB health survey of Michigan residents, Nov. 4–10, 1976. Initial report of findings presented to Governor Wm. G. Milliken, Jan. 4, 1977.
22. Anderson HA, Lilis R, Selikoff IJ, *et al:* Unanticipated prevalence of symptoms among dairy farmers in Michigan and Wisconsin. Environ Health Perspect 1978; 23:217–226.
23. Bekesi JG, Holland JF, Anderson HA, *et al:* Lymphocyte function of Michigan dairy farmers exposed to polybrominated biphenyls. Science 1978; 199:1207–1209.
24. Anderson HA, Holstein EC, Daum SM, *et al:* Liver function tests among Michigan and Wisconsin dairy farmers. Environ Health Perspect 1978; 23:333–339.
25. Bekesi JG, Anderson HA, Roboz JR, *et al:* Immunologic dysfunction among PBB exposed Michigan dairy farmers. Annals NY Acad Sci 1979; 72:717–726.
26. Bahn AK, Mills JL, Snyder PJ: Hypothyroidism in workers exposed to polybrominated biphenyls. N Engl J Med 1980; 302:31–33.
27. Valciukas JA, Lilis R, Wolff MS, *et al:* Comparative neurobehavioral study of a polybrominated biphenyl-exposed population in Michigan and a nonexposed group in Wisconsin. Environ Health Perspect 1978; 23:199–210.
28. Valciukas JA, Lilis R, Anderson HA, *et al:* The neurotoxicity of polybrominated biphenyls: results of a medical field survey. Annals NY Acad Sci 1979; 320:337–367.
29. Stross JK, Nixon RK, Anderson MD: Neuropsychiatric findings in patients exposed to polybrominated biphenyls. Annals NY Acad Sci 1979; 320:368–372.
30. Brown GG, Nixon R: Exposure to polybrominated biphenyls: some effects on personality and cognitive functioning. JAMA 1979; 242:523–527.
31. Barr M: Pediatric health aspects of PBBs. Environ Health Perspect 1978; 23:291–294.
32. Barr M: Pediatric aspects of the Michigan polybrominated biphenyl contamination. Env Res 1980; 21:255–274.
33. Weil WB, Spencer M, Benjamins D, *et al:* The effect of polybrominated biphenyl (PBB) on infants and young children. J Pediatr 1981; 98:47–51.
34. Woolley DE: Evaluation of behavioral and other neurological endpoints for assessing toxicity. *In:* Proceedings of the Workshop on Behavioral Toxicology. DHEW Pub. No. (NIH) 76-1189. Washington, DC: US DHEW, 1976.
35. Bowman RE: Behavioral and neurological development as parameters in behavioral toxicology. *In:* Proceedings of the Workshop on Behavioral Toxicology. DHEW Pub. No. (NIH) 76-1189. Washington, DC: US DHEW, 1976.
36. McCarthy D: McCarthy Scales of Children's Abilities. New York: The Psychological Corporation, 1972.
37. Barr MJ, Keller CA, Rogan WJ, *et al:* Summary of the workshop in perinatal and postnatal defects and neurological abnormalities from chemical exposures. Annals NY Acad Sci 1979; 320:458–472.
38. Rodier PM: Behavioral teratology. *In:* Handbook of Teratology; Vol. 4. New York: Plenum Press, 1978.

ACKNOWLEDGMENTS

This work was supported in part by the Michigan Department of Public Health. The author would like to thank Margaret Bailey, PhD, and Martha Karson, PhD, for their help in examination of the children. The help of William B. Weil, Jr., MD, in conceptualizing and carrying out this work is also gratefully acknowledged.