IS PCB/PCDF INDUCED LONG-TERM NEUROLOGICAL DYSFUNCTION IN THE CHILD DEPENDENT UPON THE AH RECEPTOR ?

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PCBs, and PCBs/PCDFs can cause a wide range of toxic effects in the human[1]. The toxic mechanism of action of the PCBs, PCB/PCDFs, and dioxin have been reported to occur by these chemicals combining with the Ah cytosolic receptor and thereby altering cellular function[2]. Although this receptor controls many cellular functions, the one Ah dependent function that has been most extensively studied is the induction of cytochrome P450 family 1 activity in the liver of animals and humans. Our preliminary studies of the human ADULT demonstrates that the capacity of dioxins, PBBs, PCBs, PCB/PCDFs, and mirex to induce the activity of P450 family 1 enzyme, hepatic P4501A2, does correlate with the overall observed toxic effects (abstract Dioxin '92[3]) as has been shown in animals[1].

At present, one of the most important toxic effects of these chemicals has been the neurological dysfunctions observed in children exposed to PCBs/PCDFs in utero[1]. The most severe neurologically effected cohort that has been followed since birth is the Yucheng cohort of children exposed in utero to PCBs/PCDFs in 1978[4]. Recent studies by several investigators have suggested that there may be a disassociation between P4501A2 induction and neurotoxicity in animal models.

The purpose of this study was to test the hypothesis that long-term central nervous system dysfunction in the human observed after in utero exposure to PCB/PCDFs are not due to ongoing PCB/PCDF's interactions with the Ah receptor nor due to

ongoing induction of P4501A2 in the child. To test this hypothesis the following study was conducted.

Children from the Yucheng cohort who were exposed in utero to PCB/PCDFs were recruited from the Yucheng registry of 118 children. These children were recently reported[4] to have continued diminished neurological function as compared to control subjects. The caffeine breath test was conducted as a measure of P4501A2 activity and the Wechsler Intelligence Scale for children, Revised Version (WISV-R) was utilized as an assessment of neurological function. The caffeine breath test was performed as previously described[5] and the three WISV-R IQs (Verbal IQ, VIQ; Performance IQ, PIQ; and Full Scale IQ, FIQ) was conducted by trained interviewers using standard techniques[4]. The results of the caffeine breath test were expressed as the per cent dose of administered label exhaled over two hours after the administration of the labeled caffeine (per cent dose exhaled over two hours).

In 1987, the WISV-R and the caffeine breath test were performed in fourteen of these Yucheng children; and in 1991, thirty-four children were assessed by the WISV-R and had the caffeine breath test performed in 1992.

The results showed that the P4501A2 function as determined by the caffeine breath test were not markedly different from the caffeine breath tests we have previously reported in control children[6]. The prepubescent Yucheng children studied in 1987 had caffeine breath test results ranging from 1.5 to 35.7 per cent dose exhaled over two hours with a median value of 5.52 per cent dose exhaled over two hours. The prepubescent and pubescent children studied in 1992 had caffeine breath test results ranging from 2.2 to 14.7 with a median value of 4.6 per cent dose exhaled over two hours. These caffeine breath tests results did not significantly differ from the caffeine breath test results we previously reported in control children[6]. The VIQ, PIQ, and FIQ in the Yucheng children in the 1987 study ranged from 68 to 120 with a median of 87 for the VIQ, 78 to 122 with a median of 101 for PIQ, and 72 to 123 with a median value of 94 for FIQ; and in the 1991 results ranged from 52 to 130 with a median value of 102 for the VIQ, 81 to 147 with a median value of 115 for PIQ, and 49 to 141 with a median of 105 for FIQ.

To test the hypothesis, the correlation between the caffeine breath test and the VIQ, PIQ, and FIQ was examined by regression analysis. There was no correlation between the CBT and the VIQ, PIQ, and FIQ in the children studied in 1987 or 1991 and 1992 ($r^2 < 0.006$ for all comparisons).

The study hypothesis was confirmed by these results. The lack of any correlation between the P4501A2 activity and neurological function in these children indicate that their ongoing neurological deficits are not related to current P4501A2 activity induction nor ah receptor activation.

P4501A2 activity may still be a critical parameter in the formation of PCB/PCDF induced neurological dysfunction. The critical P4501A2 induction (and correlation with neurological dysfunction) may have occurred inutero or the critical P4501A2 induction may not be the offspring's induction but be the induction of the maternal's P450 function. Another possibility is that the body burden where neurological dysfunction begins to occur is lower than that required for P4501A2 induction. Ongoing studies will examine these and other possible relationship between P4501A2 function and neurologic dysfunction. However it must be entertained that there is no direct correlation between P4501A2 induction and neurologic dysfunction, but that PCB/PCDF induction of P4501A2 does correlate with other toxic effects in the human such as anatomical birth defects.[1]

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