CYTOCHROME P4501A2 ACTIVITY IN DIOXIN EXPOSED SEVESO SUBJECTS AS COMPARED TO POLYCHLORINATED BIPHENYL AND POLYCHLORINATED DIBENZO-FURAN EXPOSED YUCHENG SUBJECTS.

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Dioxins, PCBs, and PCDFs (PHBs) are environmental chemicals that have been shown to be some of the most toxic chemicals to animals known to science. In animals cytochrome P4501A2 function has been shown to be a sensitive and useful biomarker of PHBs toxic potential and of an individual's susceptibility to PHB toxicities[1]. The toxic potential of the PHBs correlates to the capacity of the PHBs to induce P4501A2 activity in the animal. In addition, the susceptibility of an animal to PHB induced toxic effects correlates with its genetically controlled capacity to be induced by the PHBs.

Our laboratory has been testing the hypothesis that cytochrome P4501A2 activity is a sensitive biomarker of PHB potential toxicity to humans and a biomarker of the human's susceptibility to specific PHB induced toxicities. We have previously reported the effects of PBBs[2] and the effects of PCBs/PCDFs, PCBs, mirex, and low body burdens of dioxin on P4501A2 activity in accidentally exposed adults[3].

This study reports the comparison of P4501A2 activity in adults from two of the most important cohorts exposed to PHBs. 1] The Seveso cohort exposed to 2,3,7,8 TCDD in 1976 with the exposure resulting in the highest serum levels of dioxin ever measured in the human[4]. 2] The Yucheng cohort exposed to polychlorinated

biphenyls and polychlorinated dibenzofurans in 1978 which resulted in the most severe human health effects reported from exposure to the PHBs[5]. In vivo P4501A2 activity was monitored by the [3-^{13}C-methyl]caffeine breath test which is a measure of cytochrome P4501A2 dependent 3-N demethylation[6].

The studies were carried out in 1992 when 80 Seveso subjects and controls volunteered to participate in the caffeine breath test and have blood drawn for serum dioxin determinations. In addition 10 Yucheng adults with known PCB and PCDF exposure volunteered to participate in the caffeine breath test and have blood drawn for PCB and PCDF serum determinations. Thirty-seven adults who were not exposed to PCB/PCDFs and were neighbors of the Yucheng cohort were the control subjects and they were studied prior to 1992. All cohorts will be compared to the control nonsmokers previously studied in Asia and North America[2,3]. The caffeine breath test was conducted as previously described[2].

All Seveso, Yucheng and control subjects reported in this abstract were healthy, were taking no medications, and did not smoke. All subjects had fasted for at least 8 hours and had refrained from ingesting methyl xanthines for at least 12 hours prior to the study. The dose of labelled caffeine was 3mg/kg up to a maximum dose of 200 mg. The caffeine was ingested by the volunteers in Seveso in either 20ml of unsweetened orange juice or Coke Lite followed by a water wash of the container. The caffeine was dissolved in 20 ml of sterile water for the Yucheng subjects followed by a water wash of the container. Two 15 ml aliquots of end tidal breath samples were collected just before the ingestion of caffeine and at 30, 60, 90, and 120 minutes after the ingestion of the caffeine. All subjects sat quietly for at least 5 minutes before each breath sample. The breath samples were placed in a 15 ml Vacutainer for storage and transport to Chicago where the ratio of $^{13}CO_2$ to $^{12}CO_2$ in the breath as determined by differential mass spectroscopy was measured. The data were normalized for basal metabolic rate and expressed as the per cent of administered label exhaled over two hours after the ingestion of the caffeine. The serum samples are presently being analyzed by isotope dilution HRGC/HRMS.

The differential mass spectroscopy of the breath samples are completed for the Yucheng population. The exposed subjects had caffeine breath tests that ranged from 5.0 to 23.6 per cent dose exhaled over two hours with a median value of 10.2 per cent dose exhaled over two hours. There were 37 control subjects for the Yucheng subjects and their caffeine breath test ranged from 1 to 5.2 with a median value of 3.6 per cent dose exhaled over two hours. The analysis of the caffeine breath tests for 28 Seveso subjects who do not smoke have been completed and ranged from 1.8 to 11.0 with a median value of 4.32 per cent dose exhaled over

two hours. There are only 9 Seveso control subjects who do not smoke and whose data have been analyzed. Their caffeine breath test results from 0.37 to 6.18 with a median value of 4.38 per cent dose exhaled over two hours. The 105 Asian and North American control subjects previously studied had caffeine breath test results that ranged from 0.3 to 9 with a median value of 3.4 per cent dose exhaled over two hours. The serum values for the Yucheng and the Seveso subjects are nearly completed at the present time. The correlations between the caffeine breath test and serum values will examined when all the analysis are completed and reported.

The data, although not at present completely finished, demonstrates the Yucheng subjects currently have higher P4501A2 activities than the Seveso subjects. While the serum data are not available for comparison, the body burdens of PCB/PCDFs in 1992 of the Yucheng cohort were more potent P4501A2 inducers than the 2,3,7,8 TCDD body burdens in the Seveso cohorts. This difference parallels the observations that the Yucheng subjects had more toxic effects than have been reported in the Seveso subjects [5]. This study again confirms that P4501A2 activity as determined by the caffeine breath test may be a good biomarker of PHB toxic potential to the human.

The current P4501A2 activities of the Yucheng subjects was similar to the P4501A2 activities of this cohort in 1987[3]. Therefore despite 5 additional years, the Yucheng adult's body burdens of PCB/PCDFs have not decreased to body burden levels where P4501A2 returns to a normal level of activity.

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Acknowledgement: We thank and appreciate the cooperation of the volunteers and all the professional assistance of the staff of the National Cheng Kung University Hospital and the Hospital of Desio.