THE DOSE RESPONSE RELATIONSHIP BETWEEN THE SERUM LEVELS OF POLYCHLORINATED BIPHENYLS (PCBs) AND POLYCHLORINATED DIBENZOFURANS (PCDFs) AND CYTOCHROME P4501A2 ACTIVITY AS DETERMINED BY THE CAFFEINE BREATH TEST.

Lambert, G.H.[A], Hsu, C.C.[B], Guo,L.[B], Ryan,J.J.[C], Schoeller,D.A.[D].
[A]Dept of Pediatrics & Environ. and Occupational Health Sciences Institute, Robert Wood Johnson Med School, Univ of Med and Dentistry of New Jersey, Piscataway, N J 08855-1179, USA; [B] National Cheng Kung Univ. College of Med, Tainan, Taiwan, ROC, [C]Health and Welfare Canada, Tunney's Pasture, Ottawa, Canada, K1A OL2;[D] Clin Nutrition Unit, Dept of Med, Univ of Chicago, IL. USA 60637.

Objective: To determine the correlation between the serum levels of polychlorinated biphenyls (PCBs) and dibenzofurans (PCDFs) and the induction of cytochrome P4501a2 in the human.

Background: The polyhalogenated biphenyls including PCBs, PCDFs and Dioxin are known to be toxic to animals and the human. One of the mechanisms of toxicity is the capacity of these chemicals to induce cytochrome P4501a2.

The induction of P4501a2 may be a direct pathway of toxicity whereas the higher activity of P450 can increase the metabolism of chemicals to toxic metabolites capable of causing birth defects, cancer, mutations, and a variety of other toxicities. The induction of P4501a2 may also be an indirect monitor of the actual toxic pathway since the binding of the PHBs to the ah receptor which is the first step in the induction of P4501a2 also alters the expression of many other cellular proteins. However, the actual toxic pathway may be through the altered expression of one or more of these other cellular proteins and the induction of the P4501a2 may be an indirect monitor of the toxic pathway.

In animals, the induction of P4501a2 has been used as an excellent biomarker of PHB exposure and toxicity. The induction of P4501a2 appears to be the first or one of the first biological parameters that is altered by the lowest body burden of PHBs. Therefore the induction can be used as an indicator of the PHB body burden which begins to alter the biology of the species and therefore the level below which the PHBs are safe and above which the PHBs may not be safe. The induction also can predict which PHBs or their congeners are the most toxic since the PHBs which are the most toxic are also the most potent inducers of P4501a2. The PHBs induction can also identify the susceptibility of animals to PHB toxicity since the animals that are the most susceptible are the animals who are the most inducible.

We have been examining these relationships between P450

inducibility and PHB toxicity in the **human**. We have demonstrated that PHBs, dioxin, PCBs, and PBBs can induce P4501a2 in the human adult and the degree of induction correlated with the toxic effects of the exposure to the human on a population basis. The current study is designed to determine the dose response relationship between PHB exposure and P4501a2 induction in the Yucheng cohort.

Methods: The serum PCB and PCDF concentration were analyzed by GC-MS[1]. P4501a2 activity was monitored by the caffeine breath test. Subjects came to clinic after fasting for at least 6 hours and absteining from methyl xanthines for at least 8 hours. The subjects had 20 ml of end tidal breath collected just before and at 30,60, 90, and 120 minutes after the ingestion of caffeine. [3 ^{13}C-methyl] caffeine 3 mg/kg up to a maximal dose of 200mg is ingested and the subjects sit through out the 2 hour test. The ratio of $^{13}C/^{12}C$ was determined by differential mass spectroscopy and the excess ^{13}C calculated. P4501a2 activity was expressed as per cent of ^{13}C label administered in the caffeine exhaled over two hours.

Results: Seventeen adults had the CBT conducted and serum analyzed for PCBs and hexylchlorodibenzofurans (HxCDF). There was a good correlation between the CBT and PCB ($r^2 = 0.44$, $p = 0.01$) and the CBT and PCDFs ($r^2 = 0.38$, $p = 0.01$) as shown in figure 1 and 2.

Conclusions: The exposure of the adults to the combination of PCBs and PCDFs caused a marked increase in the P4501a2 activity. This increase was greater than the induction we have reported in subjects exposed to high levels of TCDD, or PCBs, or PBBs, or mirex(2). The higher P4501a2 induction of the Yucheng subjects was observed despite the subjects having at least ten fold less PCB or PBB serum levels than the subjects we have studied who were exposed to PCBs by eating Great Lakes fish or eating PBB contaminated food. The level of P4501a2 induction in this cohort was significantly higher than we have previously reported in subjects with serum levels of TCDD 10 fold lower than the levels of PCDFs we report in this cohort. Due to high range of body burdens, we could not identify a PCB or PCDF serum level where induction of P4501a2 first became evident and below which induction did not occur. The degree of induction seen in the Yucheng cohort may be due to their PCDF level or the combination of specific congeners of PCB and PCDFs. Studies presently underway are designed to identify the dose response association between exposure and induction and the levels of exposure where biologic effect ie induction occurs and if these relationships are gender, age or co-contaminant related.

Bibliography:

1. Ryan JJ, Lau BP-Y, Boyle MJ. Dioxin-like compounds in human blood. In Matsuo T, Seyama Y, Caprioli RM, Gross ML, eds. Biological Mass Spectrometry: Present and Future. Chicester, England: John Wiley, 1993.
2. Lambert GH et al Chemosphere 57, 1992.

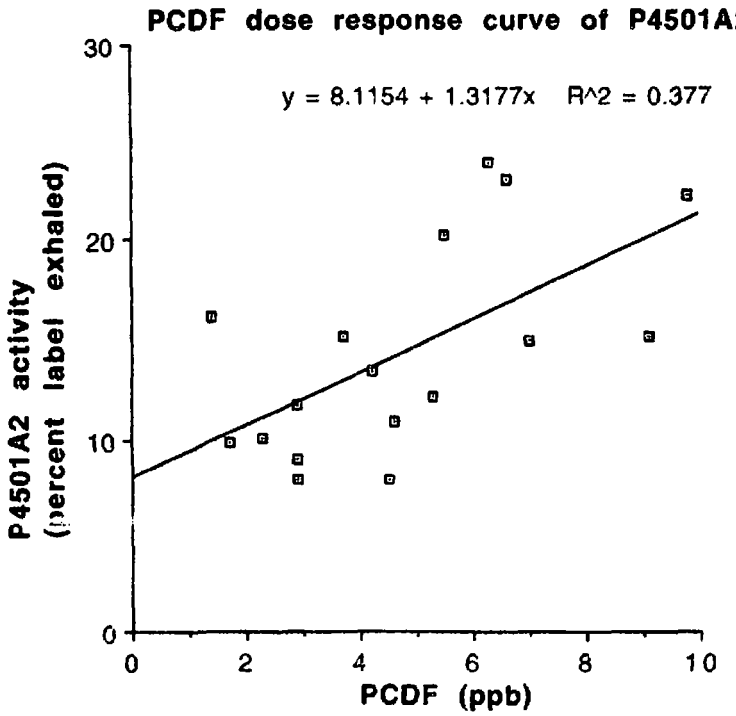
PCDF dose response curve of P4501A2 inductio
y = 8.1154 + 1.3177x R^2 = 0.377
P4501A2 activity
(percent label exhaled)
30
20
10
0
0
2
4
6
8
10
PCDF (ppb)

FIGURE 1

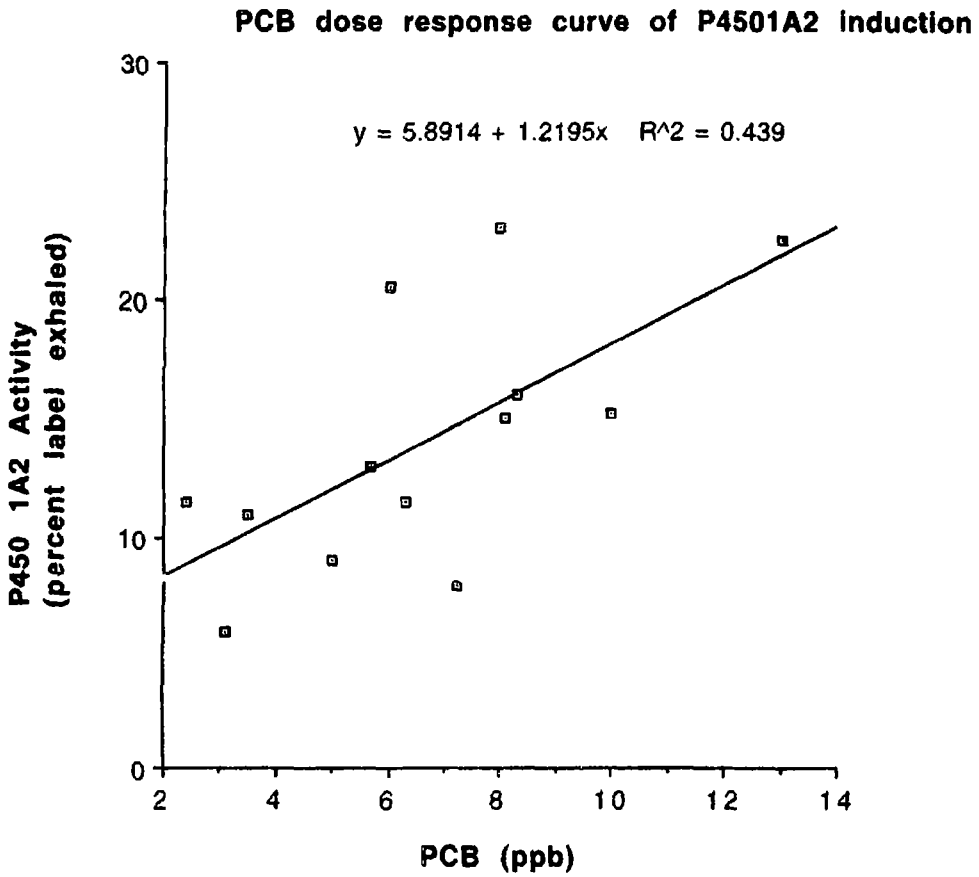
PCB dose response curve of P4501A2 induction
y = 5.8914 + 1.2195x R^2 = 0.439
P450 1A2 Activity
(percent label exhaled)
30
20
10
0
2
4
6
8
10
12
14
PCB (ppb)

FIGURE 2