

## LIVER P450IA2 ACTIVITY IN INDIVIDUALS FROM FISHING COMMUNITIES ALONG THE GULF. OF ST.LAWRENCE (QUÉBEC, CANADA).

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### INTRODUCTION

The population of the Lower-North-Shore of the Gulf of St. Lawrence relies heavily on sea-products for subsistence. Biomagnification of organochlorine compounds (OCs) occurs in the marine aquatic biota, leading to a relatively high body burden of these contaminants in predator species located on top of the food-web and in the local fishermen population.

In 1990, 185 volunteers (fishermen and their spouse) from this remote region participated in a study investigating the possible link between the dietary habits and the OCs body burden. Mean PCBs plasma level (Aroclor 1260) was 35 µg/L, a concentration approximately 10-fold greater than that found in general population living at lower latitudes (3 µg/L)<sup>1</sup>. In 1991, dioxins, furans and non-ortho coplanar PCBs (IUPAC no. 126 and 169) were measured in plasma lipids from 25 individuals from the same population. Mean concentration expressed as 2,3,7,8-TCDD Toxic Equivalent Quantities (TEQs) was 116 ng/kg, whereas the concentration measured in three pooled samples from southern Québec was 20 ng/kg<sup>2</sup>. Sea-bird egg consumption was the only dietary habit strongly associated with the OCs body burden<sup>1</sup>.

Exposure to halogenated polycyclic aromatic compounds, and more specifically those featuring a planar structure (PHPA) (2,3,7,8-chloro-substituted dibenzo-p-dioxins and dibenzofurans, non-ortho coplanar PCBs) can induce

cytochrome P450IA1 and P540IA2. Lambert and co-workers have measured the P450IA2 activity in various PHPA-exposed populations by a non-invasive method, the caffeine breath test (CBT)<sup>3</sup>. They reported a general correlation between toxicity and P450IA2 induction in the human.

The present study was conducted in order to evaluate the health risk due to the relatively high PHPA body burden found in the fishermen by determining cytochrome P450IA2 induction by the caffeine breath test (CBT).

## METHODS

In April 1992, CBT was administered to sixteen caucasian subjects from two settlements. The mean age of the group was 44 years, ranging from 33 to 73 years. Most subjects were selected from the 185 volunteers who participated in the 1990 survey, using the plasma PCB concentration (Aroclor 1260) determined at that time. Efforts were made to recruit subjects covering a PCB concentration range as wide as possible. It was not possible to compare the result of the fishermen group to a non exposed control group from the same region, the population being very homogeneous and the seafood based diet widespread throughout this remote region. Comparisons were effected with two populations previously investigated using the CBT<sup>4</sup>: a "control group" of 99 non exposed individuals (non smokers) of different regions (Toronto, Chicago, Michigan, North Vietnam) and an exposed group of 50 Yucheng subjects.

Each subject was interviewed the day before the CBT to collect information on the smoking status, present medication and history of caffeine intolerance. After signing the consent form, a 80-ml blood sample was drawn from a cubital vein, centrifuged and plasma samples were stored at -20°C until OCs analysis was performed at the Québec Toxicology Center. Subjects were asked to avoid food and beverages containing methyl xanthines such as chocolate or coffee 12 hours before the test and not to eat at all for six hours prior to the CBT on the following morning. They were also asked to provide a sample of the morning urine, which was kept frozen at -20°C. The CBT was performed early in the morning as described previously<sup>3,5</sup>. Determination of chlorinated pesticides and PCBs (congener specific) in plasma samples was performed by dual-column high-resolution gas chromatography coupled to two electron capture detectors. The detection limit was 0.05 µg/L for the various OCs. In order to control for the known effects of smoking on the CBT<sup>3</sup>, urinary cotinine concentration was determined in urine samples by an ELISA method (COTI-TRAQ, Serex Inc., NJ 07670). Statistical analysis were performed using the Statistical Analysis System (SAS Institute, NC, USA).

## RESULTS

The activity of P450IA2 measured by the CBT is expressed as the total cumulative 2-hr CO<sub>2</sub> excretion. Table 1 presents the CBT results for the fishermen group, as well as for a control group and the Yucheng group. Results are presented separately for smokers and non smokers, since smoking is a known inducer of both cytochrome P450IA1 and IA2<sup>3</sup>. Median values for the fishermen group are very close to those obtained in previous studies for non exposed individuals. The median value for the non-smoking fishermen are 4.5 times lower than that measured in Yucheng subjects.

Values for the fishermen group ranged from 1.9 % to 9 %. In an attempt to identify which parameter is related to the P450IA2 induction in the fishermen group, Pearson correlation coefficients were determined. Smoking was the only variable positively correlated to the CBT (urinary cotinine vs CBT:  $r = 0.50$ ;  $p = 0.05$ ). No positive correlation were noted between CBT and the various PCB congeners and chlorinated pesticides measured in the plasma samples. However, statistically significant negative correlations were observed between the CBT and both PCB congener 105 ( $r = -0.52$ ;  $p < 0.05$ ) and congener 118 ( $r = -0.58$ ;  $p < 0.05$ ). A multiple linear regression model was constructed to depict CBT variation according to PCB congener 105 concentration in plasma (log value), the urinary cotinine concentration, the body mass index (weight/height<sup>2</sup>) and the age of the subject. The model explained 67% of the CBT variance ( $p = 0.01$ ), with PCB 105 inversely correlated to the CBT ( $p < 0.0005$ ).

Table 1 : P450IA2 activity as measured by the CBT in fishermen from the Gulf. of St.Lawrence, non exposed historical controls<sup>4</sup> group and a Yucheng group<sup>4</sup>.

GROUP	N	CBT* MEDIAN (RANGE)
Control (non smokers)	99	3.4 (0.3-9.0)
Control (smokers)	80	5.7 (1.1-10)
Fishermen (non smokers)	9	3.6 (1.9-8.0)
Fishermen (smokers)	7	6.1 (4.4-9.6)
Yucheng subjects	50	16 (8.2-23.1)

\* Units are the percentage of the total <sup>13</sup>C administered ([3-<sup>13</sup>C-methyl caffeine) exhaled as <sup>13</sup>CO<sub>2</sub> over a 2-hr period.

## DISCUSSION AND CONCLUSION

Previous studies with the CBT have revealed that this test is generally correlated to the toxicity induced by PHPA. The fishermen group showed a level of P450IA2 activity much lower than that of Yucheng subjects which experienced toxic effects likely induced by polychlorodibenzofuran exposure. This suggests that the fishermen are at low risk with regard to the toxicity induced by dioxin-like compounds, which involves as a first step binding of these substances to the Ah receptor. Dioxins, furans and non-ortho coplanar PCBs are being determined in the plasma samples in order to delineate the influence, if any, of PHPA concentration on P450IA2 activity in this fishermen group. The negative correlations observed with PCB congener 105 and 118 may indicate a more rapid biotransformation of these congeners with increasing P450IA2 activity.

## REFERENCES

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