Study in mice of the transcriptional effects of PCB118 and PCB153 in liver, adipose tissue, muscle and colon: Highlighting of *Glut4* and *Lipin 1* as main target genes for PCB induced metabolic disorders

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PNRPE PROGRAMME NATIONAL DE RECHERCHE SUR LES PERTURBATEURS ENDOCRINIENS

Introduction:

Today there is a worldwide pandemy of diabetes and obesity. The increasing prevalence of these pathologies cannot be only explained by the modification of the way of life (hypercaloric diet and sedentary lifestyle) and genetic susceptibilities. Environmental pollutant exposure seems to be also involved.

PCB are vPvB pollutants which are widespread disseminated, notably in water. Recent epidemiological studies suggested that PCB are potent endocrine disruptors and environmental exposure (notably through fish consumption) is associated to an increase of metabolic diseases such as metabolic syndrome and type 2 diabetes. However, molecular mechanisms involved in the etiology of these diseases are poorly understood.

However, molecular mechanisms involved in PCB-induced metabolic disorders remain poorly understood. The aim of our study performed in mice, was to evaluate in various tissues (liver, visceral adipose tissue, muscle, and colon) the genomic effects of a subchronic exposure to PCB118 (dioxin-like PCB),or to PCB153 (nondioxin-like PCB), or to an equimolar mixture of PCB118 and PCB153.

Methods:

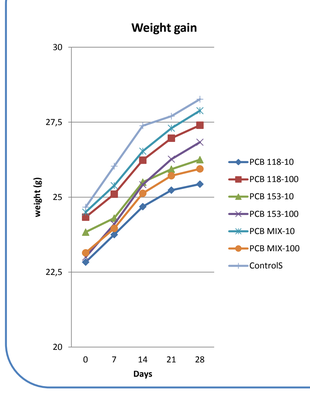
Animals: male C57BL/6 mice were exposed at 10 or 100 µmol/kg bw for 30 days (IP at Day0 and Day15) to a PCB-DL (PCB118), or to PCB-non DL (PCB153), or to a mixture of PCB118 and 153. There were 9 mice per groups.

Blood biochemical parameters: Blood levels of glucose, cholesterol (total and HDL), triglycerides, phospholipids, and hepatic function markers (AST, ALT, ALKT) were evaluated at D30.

Genomic analyses in liver, brown adipose tissue, muscle and colon: Total RNA was extracted using Trizol Reagent®. Genomic analyses were performed using Whole Mouse Genome Microarray Kit (4x44K) from Agilent® (France). Data were analyzed using Genespring® and public data bases. Only changes greater than two fold were considered and further verified by qRT-PCR.

Results

Effect of PCB treatments on body weight gain and liver weight



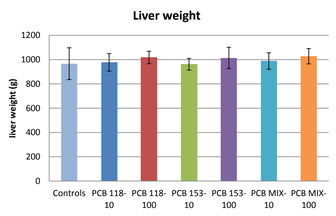
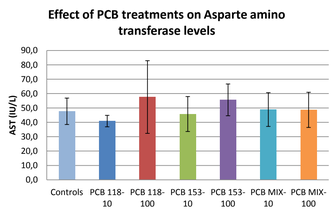
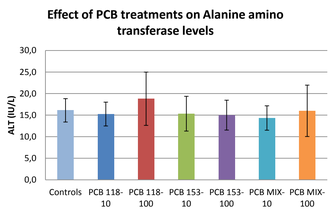


Fig. 1 : Effect of PCB treatments on body weight gain and liver weight
We did not observe any significant modification.

Effect of PCB treatments on hepatic function





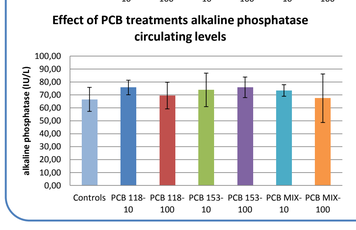
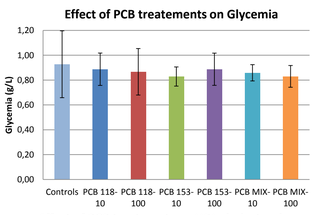
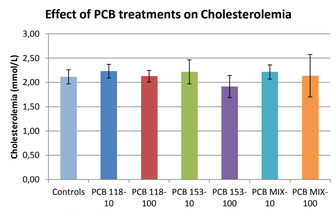
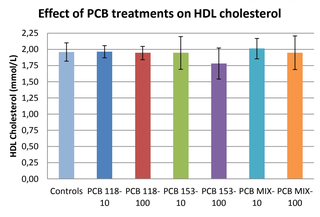


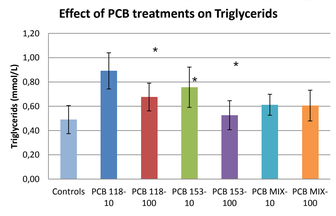
Fig. 2 : Effect of PCB treatments on hepatic function
We did not observe any significant modifications of AST, ALT and ALKP blood circulating levels.

Effect of PCB treatments on biochemical parameters









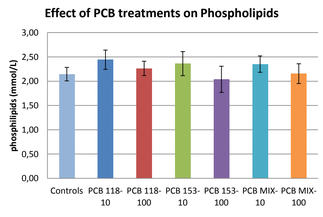


Fig. 3 : Effect of PCB treatments on biochemical parameters
*We did not observe any significant modification of neither glycemia, cholesterolemia (total and HDL) and phospholipidemia, while triglyceridemia was enhanced. Interestingly, the lowest doses of PCB118 and PCB153 are the most effective. * P < 0.05 (one way ANOVA test and Dunnett's multiple comparison test).*

Acknowledgments

This work was supported by the PNRPE (Plan National de Recherche sur les Perturbateurs Endocriniens) from the "Ministère de l'écologie, du développement durable et de l'énergie".

Effect of PCB treatments on xenobiotic metabolizing enzymes

LIVER							
Gene	**C**	**PCB118-10**	**PCB118-100**	**PCB153-10**	**PCB153-100**	**PCB MIX-10**	**PCB MIX-100**
Cyp1a1	1,0 ± 0,2	0,9 ± 0,1	0,7 ± 0,1	**0,6 ± 0,0**	**0,3 ± 0,1**	0,8 ± 0,0	1,1 ± 0,1
Cyp1a2	1,0 ± 0,1	**11,0 ± 3,6**	**5,9 ± 1,6**	**2,6 ± 0,3**	**2,6 ± 0,5**	**3,3 ± 0,6**	0,8 ± 0,5
Cyp2b9	1,0 ± 0,1	**2,7 ± 0,0**	1,1 ± 0,1	**12,3 ± 3,2**	**1,8 ± 0,4**	**11,0 ± 1,3**	1,4 ± 0,4
Cyp2c54	1,0 ± 0,2	**2,0 ± 0,4**	**2,0 ± 0,1**	**2,6 ± 0,3**	1,3 ± 0,1	**1,9 ± 0,3**	1,0 ± 0,5
Cyp2c70	1,0 ± 0,3	**0,3 ± 0,0**	**0,4 ± 0,1**	**0,4 ± 0,0**	**0,4 ± 0,1**	**0,5 ± 0,2**	**0,4 ± 0,1**
Gsta1	1,0 ± 0,1	**0,6 ± 0,0**	**0,5 ± 0,1**	**0,5 ± 0,1**	**0,4 ± 0,0**	**0,6 ± 0,1**	**0,6 ± 0,2**
Gsta2	1,0 ± 0,0	**0,4 ± 0,1**	**0,3 ± 0,0**	**0,4 ± 0,1**	**0,3 ± 0,1**	0,7 ± 0,1	**0,5 ± 0,1**
Gsto1	1,0 ± 0,1	1,0 ± 0,5	**0,5 ± 0,3**	**0,4 ± 0,0**	**0,6 ± 0,2**	**0,4 ± 0,2**	**0,3 ± 0,1**
Sult1e1	1,0 ± 0,3	0,9 ± 0,0	0,8 ± 0,1	**2,8 ± 0,3**	**3,0 ± 1,9**	**2,6 ± 0,5**	1,1 ± 0,3
VISCERAL ADIPOSE TISSUE							
Gene	**C**	**PCB118-10**	**PCB118-100**	**PCB153-10**	**PCB153-100**	**PCB MIX-10**	**PCB MIX-100**
Cyp1a1	1,0 ± 0,5	0,7 ± 0,2	1,0 ± 0,7	0,8 ± 0,1	0,8 ± 0,2	1,4 ± 0,2	0,9 ± 0,2
Gpx3	1,0 ± 0,1	0,8 ± 0,1	2,2 ± 0,6	1,2 ± 0,4	**1,7 ± 0,8**	1,2 ± 0,2	**3,8 ± 1,2**
MUSCLES							
Gene	**C**	**PCB118-10**	**PCB118-100**	**PCB153-10**	**PCB153-100**	**PCB MIX-10**	**PCB MIX-100**
Cyp1a1	1,0 ± 0,1	**1,7 ± 0,3**	**1,7 ± 1,3**	1,4 ± 0,5	1,6 ± 0,8	1,1 ± 0,3	1,2 ± 0,1
Gsta2	1,0 ± 0,1	1,0 ± 0,1	**1,9 ± 0,9**	**3,3 ± 2,2**	**6,4 ± 1,7**	**6,7 ± 2,5**	1,0 ± 0,2
COLON							
Gene	**C**	**PCB118-10**	**PCB118-100**	**PCB153-10**	**PCB153-100**	**PCB MIX-10**	**PCB MIX-100**
Cyp1a1	1,0 ± 0,1	1,4 ± 0,2	**1,7 ± 0,6**	1,4 ± 0,4	2,6 ± 0,6	1,3 ± 0,2	1,5 ± 0,3
Cyp2c70	1,0 ± 0,2	**1,8 ± 0,3**	**0,5 ± 0,0**	**1,9 ± 0,4**	1,2 ± 0,2	1,4 ± 0,9	1,4 ± 0,2

Fig. 4 : Effect of PCB treatments on mRNA level (RT-PCR) of drug metabolizing enzyme
We observed an increase of Cyp1a1 and Cyp1a2 expression in studied tissues of PCB 118 or PCB Mix treated mice, and of Cyp2b9 expression in the liver of PCB118, PCB 153 and PCB Mix treated mice.Cyp1a subfamily is mainly regulated by AhR and PCB118 is a potent ligand of this transcription factor, Cyp2b subfamily is mainly regulated by CAR and PCB153 is a ligand of this nuclear receptor. The induction of Cyp1a subfamily could enhance susceptibility to some environmental procarcinogens such as polycyclic aromatic hydrocarbons and arylamines.
Gst, which are involved in electrophilic compound detoxication, were repressed, notably in liver, suggesting an increased susceptibility to hepatic injury induced by xenobiotic electrophile metabolites.
Interestingly Gpx3 was induced in adipose tissue, and glutathione peroxydases play a major role in the detoxification of hydrogen peroxide that could trigger local inflammation.

Effect of PCB treatments on lipid homeostasis

LIVER							
Gene	**C**	**PCB118-10**	**PCB118-100**	**PCB153-10**	**PCB153-100**	**PCB MIX-10**	**PCB MIX-100**
Alox5	1,0 ± 0,3	**0,5 ± 0,1**	**0,4 ± 0,1**	**0,4 ± 0,1**	**0,3 ± 0,0**	**0,5 ± 0,2**	**0,5 ± 0,1**
Lipc	1,0 ± 0,2	0,8 ± 0,2	1,7 ± 0,4	0,8 ± 0,2	0,9 ± 0,2	0,9 ± 0,1	1,1 ± 0,5
Lpin 1	1,0 ± 0,1	**0,3 ± 0,1**	**0,3 ± 0,0**	**0,3 ± 0,1**	**0,4 ± 0,1**	**0,4 ± 0,1**	**0,6 ± 0,0**
Mgat2	1,0 ± 0,1	0,9 ± 0,2	1,4 ± 0,1	0,8 ± 0,1	1,0 ± 0,2	0,7 ± 0,1	1,1 ± 0,2
Pde8b	1,0 ± 0,1	0,9 ± 0,2	0,9 ± 0,2	1,1 ± 0,2	0,8 ± 0,1	0,9 ± 0,1	0,9 ± 0,2
Pnliprp1	1,0 ± 0,3	**0,5 ± 0,2**	0,9 ± 0,2	0,7 ± 0,0	**0,6 ± 0,2**	1,2 ± 0,5	1,3 ± 0,3
VISCERAL ADIPOSE TISSUE							
Gene	**C**	**PCB118-10**	**PCB118-100**	**PCB153-10**	**PCB153-100**	**PCB MIX-10**	**PCB MIX-100**
Agpat2	1,0 ± 0,1	**0,6 ± 0,0**	**0,4 ± 0,1**	**0,5 ± 0,2**	**0,5 ± 0,0**	**0,5 ± 0,1**	**0,3 ± 0,1**
Fasn	1,0 ± 0,1	**3,7 ± 4,1**	**1,8 ± 1,0**	**0,4 ± 0,1**	**0,4 ± 0,2**	**2,6 ± 0,6**	1,5 ± 0,3
Lpin1	1,0 ± 0,1	0,7 ± 0,1	**0,4 ± 0,0**	1,2 ± 0,5	0,7 ± 0,4	1,3 ± 0,4	0,9 ± 0,2
Pde8b	1,0 ± 0,1	0,9 ± 0,0	0,8 ± 0,1	0,8 ± 0,0	0,7 ± 0,2	1,8 ± 0,4	1,0 ± 0,2
Pla2g1b	1,0 ± 0,3	1,6 ± 0,4	1,1 ± 0,3	1,1 ± 0,4	1,1 ± 0,4	**3,8 ± 1,0**	**1,9 ± 0,3**
MUSCLES							
Gene	**C**	**PCB118-10**	**PCB118-100**	**PCB153-10**	**PCB153-100**	**PCB MIX-10**	**PCB MIX-100**
Lipc	1,0 ± 0,3	1,3 ± 0,3	**2,2 ± 1,1**	**1,8 ± 0,8**	**1,9 ± 1,2**	1,4 ± 0,4	**1,9 ± 0,4**
Lpin2	1,0 ± 0,0	**3,7 ± 1,3**	**4,3 ± 3,0**	**3,3 ± 0,8**	**3,3 ± 0,2**	**2,7 ± 0,4**	**2,5 ± 1,3**
Pfkfb3	1,0 ± 0,1	**3,4 ± 1,4**	**3,5 ± 0,8**	**2,8 ± 0,4**	**3,5 ± 1,2**	**2,1 ± 0,7**	**1,8 ± 0,5**
Pla2g1b	1,0 ± 1,3	**0,0 ± 0,0**	**0,1 ± 0,0**	**0,3 ± 0,4**	0,9 ± 0,8	0,7 ± 0,1	**0,0 ± 0,0**
Pde8b	1,0 ± 0,2	1,4 ± 0,2	1,2 ± 0,3	1,5 ± 0,1	1,5 ± 0,1	**1,9 ± 0,3**	1,2 ± 0,2
Rgs2	1,0 ± 0,1	1,5 ± 0,1	**2,0 ± 0,2**	**3,7 ± 1,2**	**18,4 ± 7,2**	**11,0 ± 5,9**	1,6 ± 0,2

Fig. 6 : Effect of PCB treatments on lipid homeostasis
Concerning lipin 1, our results showed that treatments with PCB118 and/or PCB153 reduce its expression in liver and to a lesser extent in adipose tissue. Studies of lipin 1–deficient mice and cells have shown that lipin 1 is required for adipocyte differentiation. Lipin 1–deficient cells and tissues failed to induce expression of two key transcription factors of adipocyte differentiation, PPARγ and C/EBPα and their downstream target genes. It was described in mice and humans, a strong negative correlation between lipin 1 mRNA levels in adipose tissue and glucose level, insulin level, and insulin resistance. In humans, adipose lipin1 gene expression was strongly associated with both basal and insulin-mediated subcutaneous adipocyte glucose transport, as well as mRNA levels of Glut4.
Treatments with PCB118, and/or PCB153 enhanced lipin-2 expression in muscles. Lipin-2 is prominently expressed in liver and its hepatic expression is induced in mice by fasting and diet-induced obesity. Lipin 2 induction in liver is associated to hepatic insulin resistance. But little is known, concerning the expression of lipin 2 in muscles and its role.
Agpat2 expression was downregulated in adipose tissue after exposure to PCB118, and/or PCB153. Agpat2−/− mice develop severe lipodystrophy affecting both white and brown adipose tissues, severe insulin resistance, diabetes, and hepatic steatosis. Results obtained in 3T3-L1 preadipocytes after knockdown or overexpression of Agpat2 suggested that Agpat2 regulates adipogenesis through the modulation of the lipome, altering normal activation of phosphatidylinositol 3-kinase (PI3K)/Akt and PPARγ pathways in the early stages of adipogenesis.
The expression of Fasn which is the key enzyme required for de novo synthesis of fatty acids, was induced in adipose tissue after treatment with PCB118, alone or in combination with PCB153. In murine adipose tissue, it was demonstrated that large adipocytes are more insulin-resistant than small adipocytes, and in these population the expression of Fasn is higher. In humans, increased FASN gene expression in adipose tissue is linked to visceral fat accumulation, impaired insulin sensitivity, increased circulating fasting insulin, IL-6, leptin and RBP4.

Effect of PCB treatments on glucose homeostasis and insulin signaling

LIVER							
Gene	**C**	**PCB118-10**	**PCB118-100**	**PCB153-10**	**PCB153-100**	**PCB MIX-10**	**PCB MIX-100**
Cnr1	1,0 ± 0,1	**0,4 ± 0,1**	0,8 ± 0,2	0,7 ± 0,1	**0,3 ± 0,0**	1,0 ± 0,0	1,2 ± 0,3
Gck	1,0 ± 0,2	0,8 ± 0,3	0,9 ± 0,2	0,9 ± 0,2	0,7 ± 0,0	**1,9 ± 0,7**	1,1 ± 0,3
Glut 4	1, 0 ± 0,1	0,8 ± 0,1	1,0 ± 0,1	0,8 ± 0,1	**0,6 ± 0,1**	1,6 ± 0,1	1,3 ± 0,1
VISCERAL ADIPOSE TISSUE							
Gene	**C**	**PCB118-10**	**PCB118-100**	**PCB153-10**	**PCB153-100**	**PCB MIX-10**	**PCB MIX-100**
Glut4	1,0 ± 0,3	**0,5 ± 0,0**	**0,6 ± 0,1**	**0,5 ± 0,2**	**0,5 ± 0,2**	1,1 ± 0,1	0,7 ± 0,2
Pygb	1,0 ± 0,1	1,0 ± 0,4	0,8 ± 0,0	0,9 ± 0,1	0,9 ± 0,3	0,7 ± 0,1	0,8 ± 0,4
Foxo3	1,0 ± 0,4	0,8 ± 0,2	0,7 ± 0,0	0,8 ± 0,1	0,7 ± 0,2	0,9 ± 0,2	0,8 ± 0,3
MUSCLES							
Gene	**C**	**PCB118-10**	**PCB118-100**	**PCB153-10**	**PCB153-100**	**PCB MIX-10**	**PCB MIX-100**
Cnr1	1,0 ± 0,2	1,3 ± 0,1	1,5 ± 0,0	**3,8 ± 1,8**	**20,1 ± 13,7**	**13,1 ± 2,1**	1,6 ± 0,2
Glut4	1,0 ± 0,3	1,1 ± 0,3	1,2 ± 0,1	1,3 ± 0,1	1,2 ± 0,4	1,0 ± 0,2	1,2 ± 0,1
Gck	1,0 ± 0,3	1,1 ± 0,0	**3,1 ± 3,3**	**2,1 ± 0,9**	**1,9 ± 1,2**	**2,0 ± 1,2**	1,5 ± 0,1
Gyk	1,0 ± 0,8	0,6 ± 0,0	0,8 ± 0,2	1,0 ± 0,4	1,3 ± 0,6	0,8 ± 0,2	0,9 ± 0,0
Foxo3	1,0 ± 0,4	1,7 ± 0,3	1,4 ± 0,2	1,1 ± 0,1	1,5 ± 0,2	1,3 ± 0,1	1,0 ± 0,2
Pfkfb3	1,0 ± 0,1	**3,4 ± 1,4**	**3,5 ± 0,8**	**2,8 ± 0,4**	**3,5 ± 1,2**	**2,1 ± 0,7**	**1,8 ± 0,5**
COLON							
Gene	**C**	**PCB118-10**	**PCB118-100**	**PCB153-10**	**PCB153-100**	**PCB MIX-10**	**PCB MIX-100**
Glut4	1,0 ± 0,2	0,7 ± 0,1	0,9 ± 0,3	0,8 ± 0,2	0,9 ± 0,2	0,9 ± 0,2	0,9 ± 0,1

Fig. 5 : Effect of PCB treatments on glucose homeostasis and insulin signaling
Recent studies have provided evidence that the endocannabinoid system has significant effects on energy balance and metabolism through the central control of appetite and by affecting peripheral metabolism. PCB treatments slightly modified the hepatic expression of CnR1, but in muscles PCB153 or the mixtures of PCB118 and PCB153 induced a potent increase of its expression. Interestingly, it was shown in human skeletal muscle cells that CnR1 participates in the negative crosstalk between fat and muscle and may play a role in the development of insulin resistance.
We also observed a repression of Glut4 expression in adipose tissue after exposure to PCB118 and/or to PCB153. In other studied tissues, effects are less pronounced. Insulin resistance in type 2 diabetes, obesity, and aging is associated with a marked reduction in the intracellular pool of Glut4 protein in adipose cells, which in turn impairs insulin stimulation of glucose transport.
In muscles, we observed an induction of Foxo3 expression. Foxo family member proteins are highly conserved transcription factors with important roles in cellular homeostasis, notably in skeletal muscle. Foxo1 and Foxo3 are key factors of muscle energy homeostasis through the control of glycolytic and lipolytic flux, and mitochondrial metabolism. Their exacerbated activation that occurs in several diseases, results in atrophy, mitochondrial dysfunction, and a detrimental shift in the muscle phenotype.

Effect of PCB treatments on inflammation and immune system

LIVER							
Gene	**C**	**PCB118-10**	**PCB118-100**	**PCB153-10**	**PCB153-100**	**PCB MIX-10**	**PCB MIX-100**
CD28	1,0 ± 0,2	0,7 ± 0,4	1,0 ± 0,0	0,8 ± 0,1	0,7 ± 0,1	1,2 ± 0,2	**1,8 ± 0,2**
IL-1B	1,0 ± 0,0	1,2 ± 0,1	1,7 ± 0,0	1,0 ± 0,1	0,9 ± 0,0	**2,5 ± 0,9**	1,7 ± 0,1
Infg	1,0 ± 0,5	**0,3 ± 0,1**	0,9 ± 0,1	0,8 ± 0,3	1,1 ± 0,2	1,0 ± 0,3	0,7 ± 0,3
Itgb6	1,0 ± 0,2	0,7 ± 0,0	**0,6 ± 0,0**	**0,5 ± 0,1**	**0,4 ± 0,0**	0,8 ± 0,1	1,0 ± 0,4
Smpd3	1,0 ± 0,1	**0,6 ± 0,1**	**0,6 ± 0,0**	**0,6 ± 0,1**	1,1 ± 0,2	**0,6 ± 0,1**	0,8 ± 0,1
VISCERAL ADIPOSE TISSUE							
Gene	**C**	**PCB118-10**	**PCB118-100**	**PCB153-10**	**PCB153-100**	**PCB MIX-10**	**PCB MIX-100**
CD28	1,0 ± 0,0	0,7 ± 0,4	**0,5 ± 0,1**	**0,4 ± 0,1**	**0,5 ± 0,2**	**2,2 ± 0,3**	1,3 ± 0,1
IL-1B	1,0 ± 0,2	**0,3 ± 0,0**	**0,3 ± 0,1**	**0,2 ± 0,1**	**0,2 ± 0,1**	**1,7 ± 0,8**	0,9 ± 0,1
Itgb6	1,0 ± 0,3	1,0 ± 0,5	**1,9 ± 0,8**	**0,5 ± 0,1**	1,0 ± 0,2	**2,7 ± 0,7**	**1,7 ± 0,2**
Serpine 1	1,0 ± 0,1	0,7 ± 0,1	0,9 ± 0,4	1,4 ± 0,1	0,7 ± 0,3	1,5 ± 0,4	**2,0 ± 1,0**
Slc25a1	1,0 ± 0,2	0,4 ± 0,0	0,5 ± 0,2	0,4 ± 0,1	0,4 ± 0,1	0,7 ± 0,2	**0,5 ± 0,0**
Tank	1,0 ± 0,1	**0,6 ± 0,0**	0,8 ± 0,1	0,9 ± 0,2	0,7 ± 0,2	0,8 ± 0,2	0,7 ± 0,3
MUSCLES							
Gene	**C**	**PCB118-10**	**PCB118-100**	**PCB153-10**	**PCB153-100**	**PCB MIX-10**	**PCB MIX-100**
CD28	1,0 ± 0,9	1,6 ± 2,6	0,9 ± 1,1	**0,2 ± 0,0**	**0,4 ± 0,1**	**0,4 ± 0,1**	**0,0 ± 0,0**
Ifng	1,0 ± 0,2	**2,0 ± 0,5**	**0,5 ± 0,6**	**0,1 ± 0,1**	**0,5 ± 0,7**	**0,3 ± 0,2**	**0,1 ± 0,1**
IL-1beta	1,0 ± 0,2	1,4 ± 0,3	1,5 ± 0,0	**2,4 ± 1,1**	**2,5 ± 1,3**	**3,5 ± 2,4**	1,6 ± 0,2
IL2	1,0 ± 0,2	**2,5 ± 2,2**	0,9 ± 1,1	**0,2 ± 0,1**	1,2 ± 1,4	**0,3 ± 0,2**	ND
IL6	1,0 ± 0,8	**0,1 ± 0,0**	0,9 ± 1,1	**0,1 ± 0,1**	1,0 ± 1,0	**0,5 ± 0,2**	**0,1 ± 0,0**
Itgb6	1,0 ± 0,7	1,0 ± 0,2	1,0 ± 0,0	0,9 ± 0,5	1,0 ± 0,1	1,3 ± 0,5	0,9 ± 0,4
Serpine 1	1,0 ± 1,1	**0,2 ± 0,0**	**0,3 ± 0,2**	**0,2 ± 0,1**	**0,3 ± 0,1**	**0,5 ± 0,1**	**0,3 ± 0,1**
COLON							
Gene	**C**	**PCB118-10**	**PCB118-100**	**PCB153-10**	**PCB153-100**	**PCB MIX-10**	**PCB MIX-100**
IL-1B	1,0 ± 0,2	**0,5 ± 0,1**	**0,5 ± 0,0**	0,8 ± 0,3	0,8 ± 0,1	0,7 ± 0,2	0,9 ± 0,2
Serpine 1	1,0 ± 0,3	1,4 ± 0,0	**0,5 ± 0,2**	1,5 ± 0,3	1,3 ± 0,4	1,6 ± 0,9	1,6 ± 0,7
Tank	1,0 ± 0,1	1,0 ± 0,3	**0,4 ± 0,1**	1,2 ± 0,1	1,4 ± 0,1	1,0 ± 0,2	1,2 ± 0,2

Fig. 7 : Effect of PCB treatments on inflammation and immune system
Pro-inflammatory cytokines and chemokines were slightly modified.
We observed an increase of serpine 1 expression in brown adipose tissue after PCB Mix exposure, and serpine 1, regulated by AhR, was described to be associated with insulin resistance.
In adipose tissue, we also observed after PCB exposure a repression of the expression of Slc25a1. Slc25a1 is a member of the mitochondrial carrier subfamily of solute carrier proteins, and is an essential component of the shuttle system which transports acetyl-CoA from mitochondria to the cytosol where lipogenesis occurs. He plays an important role in glucose-stimulated insulin secretion. Slc25a1 is regulated by SREBP-1,but also by PPARα, and PPARγ in hepatocytes and adipocytes, respectively. Moreover, in C3H10T1/2 cells, the activation of AhR by TCDD, suppresses PPARγ1 expression and subsequent adipocyte differentiation. Therefore, PCB-DL exposure could downregulate PPARγ in adipose tissue, leading to the repression of Slc25a1.

Conclusion:

In summary, our results showed that short term exposure to PCB118, or PCB153, or a mixture of PCB118 and PCB153 enhances triglyceride circulating levels, but glycemia remains unaffected. Interestingly, some observed effects are higher with the lowest studied doses of PCB, as it has already been described for numerous endocrine disruption processes.

Among the studied tissues, we did not observed any modification of the expression of genes involved in inflammation, such as cytokines or chemokines.

The main transcriptional effects were observed in visceral adipose tissue and in liver. We demonstrated a downregulation of lipin1 and glut4 expression in these two target organs. In adipose tissue, we also showed a downregulation of Agpat2, Slc25a1, and Fasn. These genes are involved in lipid metabolism and are associated to insulin resistance. In muscles, we observed an induction of CnR1 and Foxo3 expression which could also be involved at least in part in the reduction of insulin sensitivity. The induction of Foxo3, suggested that PCB could induce mitochondrial dysfunction in muscles. Metabolic side-effects of PCB could also implicated the modulation of CnR1 in the hypothalamus which controls appetite and regulates AMPK activity.

Moreover, we are exposed through our alimentation to various exogenous compounds including procancerogens such as PAH and arylamines. Their bioactivation catalyzed by Cyp1a can induce inflammatory responses, which could enhance metabolic effects of PCB since type 2 diabetes is linked to low grade inflammation of visceral adipose tissue.

Even if our results suggested that adipocytes are the main target in metabolic disorders induced by PCB, further studies are required to fully elucidate the involved mechanisms, notably the link between lipin 1 and Glut4 expression and the redistribution of Glut4 from intracellular storage sites to the plasma membrane. Moreover, it would be of interest to better characterize cocktail effects and evaluate the implication of epigenetic regulations.