Serum Xenohormone activity and DNA integrity of Europeans and Inuits

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Background

The toxicological assessment of the lipophilic persistent organic pollutants (POPs), including PCBs, pesticides and dioxins, is complicated since individuals are exposed to a complex mixture of contaminants [1].
Therefore we developed e*x vivo* cell systems to determine the actual integrated level of xenobiotic activity in the human serum fraction containing the POPs [2, 3, 4].
Sperm DNA integrity is essential for the accurate transmission of genetic information and sperm DNA damage can cause decreased male fertility [5].

The AIM was to determine the integrated serum xenobiotic activity of POPs. The estrogen receptor (ER), androgen receptor (AR) and aryl hydrocarbon receptor (AhR) activity levels were compared among study groups from Greenland (53 adult males) and Europe (247 males from Sweden, Warsaw and Kharkiv) and further evaluated for association to the serum POP proxy markers 2,2',4,4',5,5'-hexachlorobiphenyl (PCB-153) and 1,1-dichloro-2,2-bis (*p*-chlorophenyl)-ethylene (*p,p'*-DDE) and sperm DNA integrity.

Conclusions

No strong consistent correlations between serum xenobiotic activity and the two POP markers were found. However, using the sum of 14 PCBs and/or 10 organoclorine pesticides for analyses of Inuit data clear correlations were found. Thus, our data indicate that the selected POP markers alone can not predict the integrated serum xenobiotic activity.

Significant different serum xenobiotic activities as well as levels of the POP proxy markers and %DFI were observed between Inuits and Europeans. In addition, for Inuits negative correlations between serum xenobiotic activities and %DFI were found, whereas for Europeans positive relations were seen.

We suggest that the variation in serum xenobiotic activity reflects differences in POP exposure mixtures in context with genetic factors and/or life style factors.
We believe that serum xenohormone activity can substantially contribute to the health assessment of chemical body burdens.

Table 1. Serum xenobiotic receptor activities

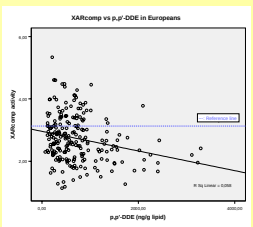
		Greenland	Warsaw	Sweden	Kharkiv
XER	Median (n)	2.9 (72)	3.1 (98)	3.0 (100)	3.2 (88)
	% agonistic	1	21	12	14
	% decreased	35	5	12	17
XER-EEQ	Median (n)	-	103 (21)	75 (10)	139 (11)
XERcomp	Median (n)	2.7 (72)	3.0 (94)	2.9 (94)	2.9 (88)
	% add/syn	1	13	3	1
	% antagonist	71	7	19	30
XAR	Median (n)	3.87 (37)	3.43 (83)	3.73 (59)	3.47 (82)
	% agonist	35	25	34	26
	% decreased	3	5	5	2
XARcomp	Median (n)	3.78 (37)	3.01 (83)	2.89 (59)	2.20 (82)
	% add/syn	22	7	10	0
	% antagonist	3	21	8	50
AhR	Median (n)	24 (75)	34 (99)	33 (78)	26 (86)
	% agonist	92	100	95	100
	% decreased	-	-	-	-
AhR-TEQ	Median (n)	197 (70)	312 (99)	428 (76)	337 (80)
AhRcomp	Median (n)	8.3 (75)	6.4 (99)	6.2 (78)	5.5 (86)
	% add/syn	41	3.0	6.4	18
	% antagonist	2.7	8.0	12	34
PCB153	Median	220	16	210	47
***p,p'*-DDE**	Median	630	570	240	880

XER-EEQ: XER-estradiol equivalents (pg/g lipid).
AhR-TEQ: AhR-TCDD equivalents (pg / g lipid).
XER/XAR/AhRag: % agonistic and % decreased indicates increased or decreased activity, respectively, compared to solvent control (XER/XAR=3.13; AhRag=6.67).
XERcomp/XARcomp/AhRcomp: % additive/synergistic and % antagonistic indicates an increased or decreased activity, respectively, compared to ligand induced solvent control (XER/XAR=3.13; AhRag=6.67).

Results

XER activities: Inuit XER and XERcomp activities differed from the European groups which did not mutually differ (Table 1). XER activity of Inuit samples were negatively correlated to levels of PCB-153 and *p,p'*-DDE. For the Warsaw samples XER was positive correlated to *p,p'*-DDE levels.

XAR activities: XAR activity of the study groups did not differ. XARcomp activity was significant higher for Inuits and lower in Kharkiv compare to the other study Groups (Table 1). For the Europeans a negative correlation between XARcomp and *p,p'*-DDE was found.

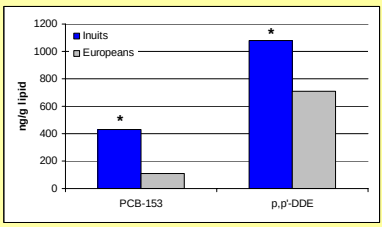


AhR activities: Inuit AhRag were significantly lower than that of European groups while AhRcomp of Inuit was higher than the other groups (Table 1). In Kharkiv group a negative correlation between AhRcomp and PCB-153 was found.

Lifestyle factors: For Inuits no correlations were observed. For the Europeans XER activity was negatively correlated to age whereas XARcomp activity was positively correlated to age and AhR activity was positive correlated to BMI.

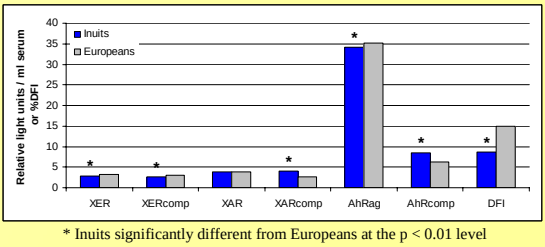
DFI: For the Inuits significant negative correlations were observed between XERcomp, AhRag and AhRcomp activities and %DFI whereas for the Europeans XARcomp was positively correlated to %DFI.

POP proxy marker levels of Inuits and Europeans



* Inuits significantly higher than Europeans at the $p < 0.05$ level

Serum xenobiotic receptor activities and DNA fragmentation index of Inuits and Europeans



* Inuits significantly different from Europeans at the $p < 0.01$ level

Methods

The endogenous-hormone-free serum POP fraction was obtained by solid phase extraction (SPE) followed by High Pressure Liquid Chromatography (HPLC) [6]. The ER activity was determined in human breast cancer cells (MVLN) [2] and the AR activity in the Chinese Hamster Ovary cells (CHO-K1) [3].
Ethanol-hexane extraction followed by cleanup on Florisil + Na2SO4 was used to obtain the lipophilic POPs for determination of AhR activity in mouse hepatoma cells (Hepa1.12cR) [4].

Agonistic serum xenohormone activity was determined as the effect of serum alone (XER, XAR and AhRag). As a mimic of *in vivo* physiological hormone processes antagonistic/synergistic effects (XERcomp, XARcomp and AhRcomp) were determined by co-exposure of serum extracts and receptor ligands.

Human sperm chromatin integrity was assessed as DNA Fragmentation Index (%DFI) using the flow cytometric sperm chromatin structure assay (SCSA) [7].

Oneway-ANOVA and independent samples t-test test was used to compare means between the study groups. Associations between xenobiotic activity and POP markers, DNA integrity or lifestyle factors was evaluated with Spearman's rank correlation.

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