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Physiologically based pharmacokinetic modeling of POPs in Greenlanders

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ABSTRACT

Human exposure to persistent organic pollutants (POPs) and the potential health impact in the Arctic far from the emission sources have been highlighted in numerous studies. As a supplement to human POP biomonitoring studies, a physiologically based pharmacokinetic (PBPK) model was set up to estimate the fate of POPs in Greenlandic Inuit's liver, blood, muscle and adipose tissue following long-term exposure to traditional Greenlandic diet. The PBPK model described metabolism, excretion and POP accumulation on the basis of their physicochemical properties and metabolic rates in the organisms. Basic correlations between chemically analyzed blood POP concentrations and calculated daily POP intake from food questionnaire of 118 middle age (18–35 years) Greenlandic Inuits from four cities in West Greenland (Qaanaaq: n = 40; Qeqertarsuaq: n = 36; Nuuk: n = 20; Narsaq: n = 22) taken during 2003 to 2006 were analyzed. The dietary items included were polar bear, caribou, musk oxen, several marine species such as whales, seals, bird and fish as well as imported food. The contaminant concentrations of the dietary items as well as their chemical properties, uptake, biotransformation and excretion allowed us to estimate the POP concentration in liver, blood, muscle and adipose tissue following long-term exposure to the traditional Greenlandic diet using the PBPK model. Significant correlations were found between chemically analyzed POP blood concentrations and calculated daily intake of POPs for Qeqertarsuaq, Nuuk and Narsaq Inuit but not for the northernmost settlement Qaanaaq, probably because the highest blood POP level was found in this district which might mask the interview-based POP calculations. Despite the large variation in circulating blood POP concentrations, the PBPK model predicted blood concentrations of a factor 2–3 within the actual measured values. Moreover, the PBPK model showed that estimated blood POP concentration increased significantly after consumption of meals. For individuals who had a high internal burden of POPs accumulated over years, the estimated blood levels were less influenced by recent meal intake. The model results also indicated that of the POPs accumulated in the body the concentrations were highest for CB-153 (oxychlordane: 0.6%; DDE and CB-99: 2.9%; HCB: 4.4%; CB-153: 34.5%). Furthermore, the model also estimated a significant internal body POP burden even several years after the mentioned dietetic shift and that contaminant accumulation was 2–6 folds faster than the decay after a shift to a diet low in contaminants. Using the PBPK model approach, we seek to improve the knowledge on contaminant body burden in humans of the Arctic. However, it should be noted that calculations of daily POP intake may be subject to considerable uncertainty due to imprecise information from the dietary interview. Based on these results we suggest that PBPK modeling is implemented as a tool in future human health exposure and effect assessments in Greenland.

1. Introduction

Exposure of humans in the Arctic region to POPs (persistent organic pollutants) has for a long time been recognized as an international health problem (AMAP, 2009; Bonefeld-Jørgensen, 2010; Johansen et al., 2004a, 2004b, 2004c). This exposure mainly originates from traditional diet and it has previously been shown that there is a good agreement between the timing of contaminant concentrations in the blood of Greenlandic Inuits and tissues of ringed seals (*Pusa hispida*), which constitute an important part of the traditional diet (AMAP, 2009; Bonefeld-Jørgensen, 2010; Johansen et al., 2004a, 2004b, 2004c). Based on contaminant concentrations in dietary items such as whale spp., seal spp., bird spp., polar bears (*Ursus maritimus*), fish spp., caribou (*Rangifer tarandus*), musk oxen (*Ovibus moschatus*) and imported foods, the daily contaminant exposure for different Greenlandic Inuit population groups has been estimated from interviews (Deutch et al., 2006). In other studies, the concentration of contaminant concentrations in blood samples was analyzed to assess the impact of different communities in Greenland (Bonefeld-Jørgensen, 2010; Deutch et al., 2006, 2007a, 2007b; Sonne et al., 2013).

For ethical and practical reasons, there are primarily contaminant data available for blood and only few or no data on contaminant concentrations in adipose tissue, liver, kidney and brain among populations in the Arctic areas since these require invasive sampling. However, such data are essential since they could strengthen the assessment of the

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current body burden and possible health effects of contaminants in the Arctic population groups unless these can be reliably modeled from the intake (AMAP, 2009). A physiologically based pharmacokinetic (PBPK) model may therefore complement the use of invasive sampling of different tissues and organs when studying POP exposure and possible health effects in humans of the Arctic, as well as reduce the number of costly chemical analyses. The PBPK modeling links contaminant dietary exposure with contaminant concentrations in the blood and tissues of Arctic populations (Cahill et al., 2003; Redding et al., 2008; Sonne et al., 2009; Verner et al., 2009) and thus improves the knowledge-based risk assessment of exposure of humans in the Arctic region (AMAP, 2009). This inclusion of PBPK modeling could also improve knowledge and assessment criteria when evaluating contaminant exposure of indigenous Arctic humans in the AMAP Human Health Programme (AMAP, 2009).

Based on this we used a generic PBPK model (Cahill et al., 2003) for contaminant exposure in Greenlandic Inuit based on food questionnaires for intake of traditional food and blood POP concentrations including four West Greenland districts around Qaanaaq, Qeqertarsuaq, Nuuk and Narsaq, taken during the years 2003–2006 (Bonefeld-Jørgensen, 2010; Deutch et al., 2006, 2007a, 2007b). To support this formulation of the PBPK model, inter-correlation between groups of POPs and the relationship between calculated dietary POP intake and actual circulating POP concentrations were analyzed by basic statistics.

2. Materials and methods

2.1. Dietary survey and contaminant analyses in Greenlandic Inuit blood

The study included food choice, POP concentrations in traditional diet and contaminant blood concentrations of 118 Inuit within the ages of 18–35 years: 40 people from Qaanaaq taken in 2003 (20 females and 20 males), 36 from Qeqertarsuaq collected in 2006 (20 females and 16 males), 20 from Nuuk collected in 2005 (18 females and two males) and 22 from Narsaq collected in 2006 (16 females and 6 males) (Fig. 1). Briefly, all participants were Greenlandic Inuits defined as having two grandparents born in Greenland. The participants filled out a standard form with questions about demographic and lifestyle parameters and

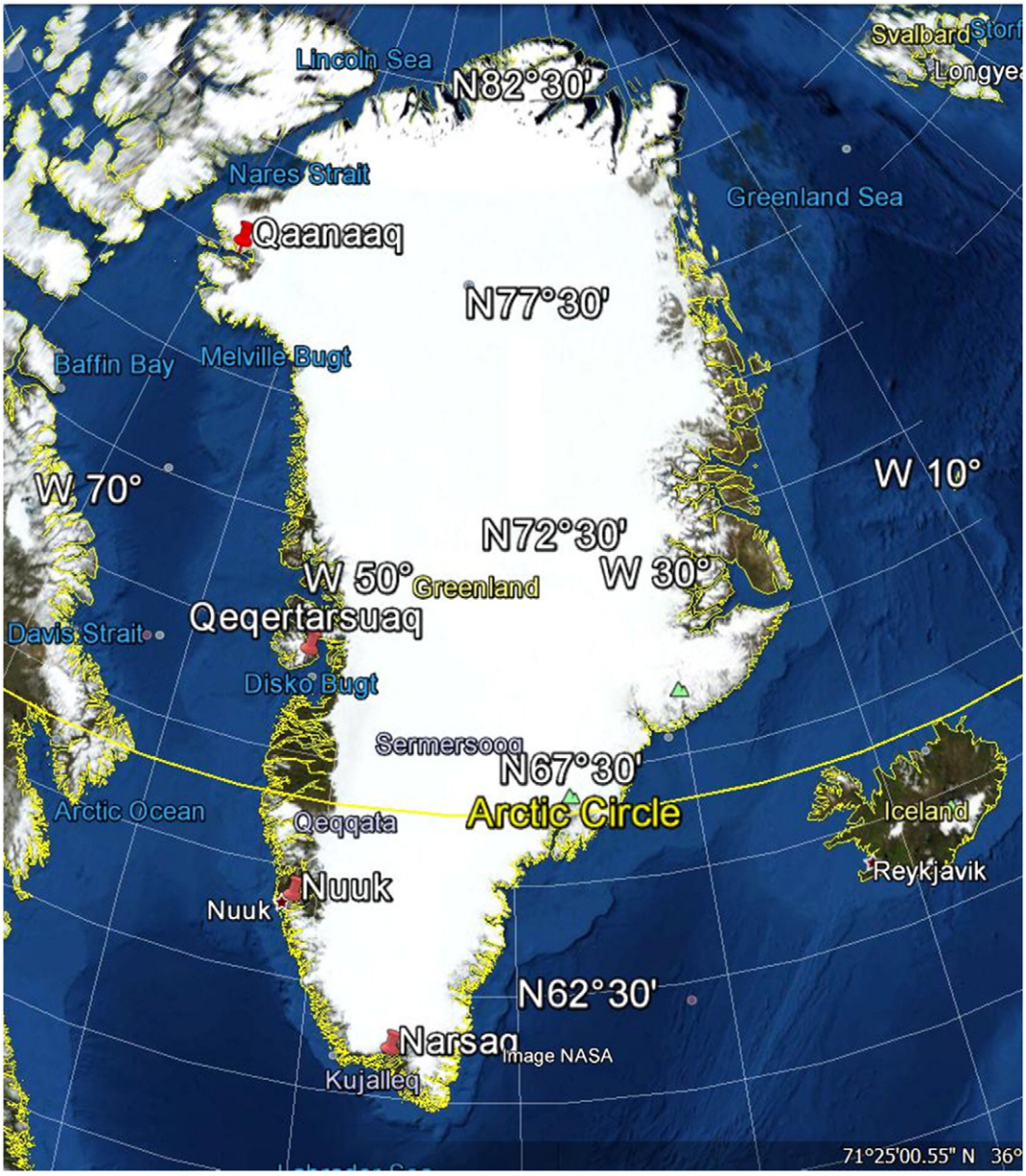

Fig. 1. Map of study locations Qaanaaq, Qeqertarsuaq, Nuuk and Narsaq. Source: Google Earth 2013.

intake of food items including Greenlandic traditional marine food as described by Deutch et al. (2004, 2006, 2007a, 2007b) Deutch and Hansen (2000). Blood samples were collected and stored at −80 °C until measurement of a number of persistent organic pollutants (POPs) at the Centre de Toxicologie, Quebec, Canada by gas chromatography as described by Butler Walker et al. (2003) and Krüger et al. (2012). Of the POPs analyzed we selected CB-99, CB-153, p,p′-DDE, HCB and oxychlordane for the PBPK modeling. The reasons for choosing these congeners and pesticides were that each of these, separately, represents a group of contaminants with different physicochemical properties. All POP values were adjusted to plasma fat content and reported as ng/g lipid weight (lw) in order to facilitate a cross-comparison with tissues analyzed in other studies. The study was conducted on a general license granted by the Ethical Committee for Scientific Research in Greenland under the Greenland Self Government to Director Prof Dr. Bonefeld-Jørgensen, Centre for Arctic Health, Department of Public Health, Aarhus University.

2.2. Measurement of contaminants in traditional diet

During the years 1998–2001, a comprehensive study of contaminant concentrations in the main traditional Greenlandic diet was conducted (Johansen et al., 2004a, 2004b, 2004c). The study included muscle, liver, kidney and blubber samples from fish spp., seabirds, seal spp. and whale spp. as well as terrestrial animals (birds, lamb; *Ovis aries*), musk oxen and reindeer. Samples were collected in central West Greenland from Qaqortoq in the south to Qeqertarsuaq in the mid-west and are the basis for the calculation of daily dietary POP intake by humans in the four areas. The samples were analyzed by the National Laboratory for Environmental Testing, Burlington, Canada that participated in QUASIMEME studies, as well as in various Canadian laboratory inter calibrations as described by Johansen et al. (2004a, 2004b, 2004c). Since polar bear tissues were not included in the study of POP concentrations in traditional food items we used published concentrations averaged over the northern and southern parts of Baffin Island (Verreault et al., 2005). All POP values were adjusted to fat content and reported as ng/g lipid weight (lw) in order to facilitate a cross-comparison with tissues analyzed in other studies.

2.3. Calculation of the daily contaminant intake and dietary survey

The data for dietary daily POP intake is based on the information from Deutch et al. (2004, 2007a, 2007b) and Deutch and Hansen (2000) and for “seal meals” the proportions of species were divided according to Rosing-Asvid (pers. comm.; Greenland Institute of Natural Resources and Piniarneq: http://vintage.nanoq.gl/Emner/Erhverv/Erhvervsomraader/Fangst_og_Jagt/PINIARNEQ.aspx). For Qaanaaq these were 34% ringed seal (*P. hispida*), 33% harp seal (*Phoca groenlandica*) and 33% hooded seal (*Cystophora cristata*), in Qeqertarsuaq it was 100% harp seal, and for Nuuk it was 100% harp seal and for Narsaq 67% ringed seal and 33% harp seal. Regarding “bird meals” these were in all districts composed of 70% thick-billed murre (*Uria lomvia*) and 30% eider (*Somateria molissima*) while “salmon meals” were 100% Arctic char (*Salvelinus alpinus*) in Qaanaaq and Qeqertarsuaq and 70% Arctic char and 30% salmon (*Salmo salar*) in Nuuk and Narsaq, respectively.

2.4. PBPK modeling of concentrations in blood and tissues

Unlike classical pharmacokinetics, PBPK modeling is a powerful tool for many types of extrapolation such as species-to-species, route-to-route, and dose-to-dose. The PBPK modeling in the present study was based on a model developed by the Canadian Environmental Modeling Centre, Trent University (Cahill et al., 2003). Since the variation in dietary intake as well as the relationship between dietary intake and actual measured blood concentrations did not differ between men and women (Krüger et al., 2012), a PBPK model was not build separately for each gender. Briefly, besides simulation time and number of iterations, the model incorporated data for chemical exposure (oral ingestion), biometric data (e.g. mass of body, volume of intestine and organs etc.), rates of metabolism and different physicochemical properties (partition coefficients). The PBPK model described metabolism, excretion, and accumulation of pollutants on the basis of the physicochemical properties of the substances and included distribution coefficients log Kow (partition coefficient octanol/water as an expression of the chemical properties to be bound/accumulated in fat), log Kaw (distribution coefficient of air/water which is an expression of the partition between air and water) and molecular volume (a measure of the diffusion in various media). Constants used for the individual contaminants are shown in Table 1 and further information about the parameterization of variables in the present PBPK model is found in Tables S1 and S2 in the Supplemental Information.

2.5. Validation of the PBPK model

The developed PBPK model was configured for a 70 kg adult person with the corresponding organ-tissue size in order to estimate the POP tissue residues in blood, liver, muscle and adipose tissue following a 30-year exposure period. The model was validated by comparing measured blood POP concentrations and modeled estimated blood POP concentrations for the population in Qaanaaq (Table 2).

2.6. Statistical analyses

The statistical analyses were performed with the statistical package R and the level of significance was set to $p \leq 0.05$ (R Development Core Team, 2011). All data were log-transformed (base e) prior to the analyses in order to meet the assumption of normality and homogeneity of the variance (Zar, 1984). Pearson's correlation coefficient was applied to test for the inter-correlation between groups of POPs and the relationship between estimated dietary POP intake and actual circulating POP concentrations. One-way analyses of variance (ANOVA) including Tukey's post hoc test were used when comparing circulating POP concentrations between districts.

3. Results and discussion

3.1. Chemically analyzed POP concentrations in Greenlandic Inuit blood

The average age and chemically analyzed POP concentrations in the blood from the four districts are shown in Table 3. The variation in POP concentrations was large while the POPs were strongly inter-correlated in all four areas (correlation coefficients were 0.76–0.97, $p < 0.01$) being highest in Qaanaaq and lowest in Nuuk. The average age was similar in the four districts varying from 24.5 years in Narsaq to 30.6 years in Nuuk. Average concentrations of CB-99, CB-153, HCB and oxychlordane were significantly higher in Qaanaaq compared to the other three districts ($p < 0.01$), while no significant difference was found between these remaining three. For DDE a significant higher average concentration was found in Qaanaaq compared to Nuuk and Qeqertarsuaq ($p < 0.01$), whereas no significant difference was found between Qaanaaq and Narsaq ($p = 0.11$) (Table 3). It is well known that the POP concentrations increase with age (Bonefeld-Jørgensen, 2010). Although the mean age was highest in Nuuk and lowest in Narsaq, the highest blood level was found in Qaanaaq and lowest in Nuuk (CB-99, p,p′-DDE, HCB, oxychlordane) and Narsaq (CB-153). Thus the POP blood levels reflect the integrated data for intake of traditional Greenlandic marine food and age.

Table 1
Constants used in the PBPK modeling. The information is from the EPI-Win —US-EPA while the molar volume is calculated from the SMILES notation in web software. (http://www.molinspiration.com/cgi-bin/properties). The metabolic rates are first order rate constant and are estimated by iteration.

Compound	CAS-No.	Mol weight (g/mol)	Mol volume (cm^3/mol)	Log K_{ow} (Unit less)	Log K_{aw} (Unit less)	Metabolic rate (h^{-1})
DDE	72-55-9	318.0	237.0	6.0	−2.8	0.8
HCB	118-74-1	284.8	165.0	5.9	−1.2	0.8
CB-153	35065-27-1	360.8	237.0	7.6	−3.0	0.1
CB-99	38380-01-7	326.0	223.0	7.0	−2.4	1
Oxychlordane	27304-13-8.	423.0	247.0	5.5	−5.5	5

Table 2
Comparison of measured and PBPK modeled blood POP concentrations in the Qaanaaq study group based on mean and max values. The developed PBPK model was validated by comparing measured blood POP concentrations and modeled estimated blood POP concentrations only for the Qaanaaq population. All values in ng/g ww. Data obtained from Deutch et al. (2007a).

	Measured		Modeled	
	Mean	Max	Mean	Max
CB-99	0.03	0.12	0.03	0.2
CB-153	5.4	21	1.4	10
Oxychlordane	0.08	0.3	0.03	0.2
p,p′-DDE	0.25	1.3	0.11	1.1
HCB	0.06	0.22	0.04	0.25

3.2. Calculated daily POP intake

Table 4 shows the average age and the calculated daily POP intake based on the food questionnaire and measured concentrations in traditional food items. The daily intake of the selected POPs was significantly higher in Qaanaaq compared to the other three districts ($p < 0.01$), whereas no significant differences were found among the three other districts and a similar pattern was found for the analyzed POP concentrations in blood (Table 3). As for the POP levels in blood, a wide individual variation was found for the calculated daily POP intake and in general a higher intake of traditional Greenlandic food has been found in smaller towns and settlements like Qaanaaq having a higher frequency of hunting (AMAP, 2009; Deutch et al., 2005, 2006, 2007a, 2007b).

3.3. Circulating POPs in blood vs. questionnaire-based calculated daily intake

For the study population in Qaanaaq there were no significant correlations between chemically analyzed POP concentrations in blood and questionnaire-based calculated POP intake ($-0.12 < r < 0.04$; all $p > 0.48$). The discrepancy may be explained by the relatively high blood variation in POP concentrations and the fact that the highest blood POP levels were found in the Qaanaaq district which could mask the recent POP intake based on the interview-based calculations of POP levels in blood. Similarly to the above-mentioned findings for Qaanaaq, no significant correlation between chemically analyzed POP concentrations in blood and calculated POP intake via traditional food was found for Qeqertarsuaq. This was due to particular 3 individuals who had a very low calculated intake of POPs despite having relatively high POP concentrations in blood. When we handled these three individuals as outliers, possibly due to incorrect information on dietary habits, all correlations were statistically significant (CB-99: $r = 0.45$, $p < 0.01$; CB-153: $r = 0.45$, $p < 0.01$; DDE: $r = 0.41$, $p = 0.02$; HCB: $r = 0.49$, $p < 0.01$; oxychlordane: $r = 0.47$, $p < 0.01$). For the Nuuk study group no significant correlations were found between measured blood POP concentrations and the calculated daily POP intake from traditional food. However, also in Nuuk, 3 individuals were calculated to have a low POP intake from the questionnaires but had relatively high blood POP concentrations. Again assuming incorrect information on dietary habits and removing these 3 observations assumed as outliers, three out of five POPs showed significant correlations (CB-99: $r = 0.50$, $p = 0.04$; CB-153: $r = 0.52$, $p = 0.03$; DDE: $r = 0.53$, $p = 0.03$; HCB: $r = 0.27$, $p = 0.29$; oxychlordane: $r = 0.38$, $p = 0.13$). For the Narsaq study group, significant correlations were found between POP concentrations analyzed in blood and the questionnaire based calculation of CB-99 ($r = 0.49$, $p = 0.02$), DDE ($r = 0.51$, $p = 0.01$) and oxychlordane ($r = 0.45$, $p = 0.03$) intake while no significant relationship was found for CB-153 ($r = 0.27$, $p = 0.23$) and HCB ($r = 0.27$, $p < 0.22$).

We calculated the intake of POPs using the dietary information obtained from questioners and compared this exposure to the chemically analyzed blood POP concentrations in hunted animals. Previous studies by Deutch et al. (2007a, 2007b) and Deutch and Hansen (2000) have reported that the chemically analyzed serum levels of PCB, DDT/DDE and toxaphene within districts increase with age while the calculated intake is relatively independent of age groups. No systematic pattern was

Table 3
Age and actual measured contaminant concentrations (ng/g lw) in blood from Greenlanders in the districts of Qaanaaq, Qeqertarsuaq, Nuuk and Narsaq between 2003 and 2006. Data obtained from Deutch et al. (2007a, 2007b).

	Age	CB-99	CB-153	p,p′-DDE	HCB	Oxychlordane
Qaanaaq ($n = 40$)						
Mean	27.1	77.4	541	749	168	238
SD	5.9	66.1	452	676	133	231
Min–Max	18–35	4–364	30–2070	28–4032	13–656	5–1032
Qeqertarsuaq ($n = 36$)						
Mean	27.6	28.7	176	452	121	70.9
SD	5.0	30.1	160	432	138	95.0
Min–Max	20–35	1–154	22–738	34–2154	12–646	4–446
Nuuk ($n = 20$)						
Mean	30.6	19.5	136	336	55.8	30.1
SD	5.0	14.3	111	295	33.2	27.2
Min–Max	19–35	7–62	51–522	95–1304	25–159	4–112
Narsaq ($n = 22$)						
Mean	24.5	26.5	191	435	64.5	46.0
SD	4.5	18.3	131	363	38.7	37.3
Min–Max	18–34	5–78	31–609	79–1491	19–161	7–172

Table 4
The average age and calculated dietary intake of POPs per day, based on the food questionnaire and measured concentrations in traditional food items in the study groups from Qaanaaq, Qeqertarsuaq, Nuuk and Narsaq between 2003 and 2006. Data obtained from Deutch et al. (2007a, 2007b).

	Age	CB-99	CB-153	p,p′-DDE	HCB	Oxychlordane
Qaanaaq ($n = 40$)						
Mean	27.1	2177	7860	5696	2033	11794
SD	5.9	3681	14866	8377	3011	24087
Min–Max	18–35	38–15645	78–63865	215–44595	63–12723	62–104002
Qeqertarsuaq ($n = 36$)						
Mean	27.6	207	552	1127	408	665
SD	5.0	286	1026	1352	487	1618
Min–Max	20–35	1–1146	1–4522	3–6214	3–2155	1–7176
Nuuk ($n = 20$)						
Mean	30.6	137	282	930	305	256
SD	5.0	135	298	930	272	260
Min–Max	19–35	2–481	2–1189	3–3423	6–868	1–932
Narsaq ($n = 22$)						
Mean	24.5	132	281	1011	200	313
SD	4.5	149	336	1233	186	403
Min–Max	18–34	1–505	12–1091	8–4033	13–726	4–1304

found between calculated food exposure and chemically analyzed blood POP levels which confirms that the calculated food exposure reflects POP exposure through recent dietary habits and not life-long exposure. Moreover it should be kept in mind that several assumptions and calculations were made when calculating POP exposure through food items because the dietary information was very different among districts and not very detailed.

3.4. PBPK modeling and estimation of tissue concentrations

The POPs used in the PBPK modeling were chosen based on their ranges of physicochemical properties (Table 1). Using these different POPs enables us to test the generic value of the PBPK model so that it can be applied to a broad number of lipid-soluble POPs relevant for Arctic human exposure. The results from the PBPK modeling of the Qaanaaq study group are summarized in Table 5. The estimated internal concentrations were significantly highest in adipose tissue and 2–300 folds higher than in blood, while the concentrations in liver and muscle were intermediate, being highest in liver. Modeled concentrations of lipid-corrected CB-99, CB-153 and oxychlordane in adipose tissue and liver are in the ranges of the concentrations found in Greenlanders deceased in the period 1992–1994 as reported by Dewailly et al. (1999).

Table 5
PBPK mean and max estimates for POP tissue concentrations in the people from the Qaanaaq study group in 2003.

	Estimated intake		Estimated concentrations (ng/g ww)			
	μg/day	nmol/day	Blood	Adipose	Liver	Muscle
CB-99						
Mean	2.2	6.7	0.03	5.3	0.3	0.2
Max	16	48	0.2	44	2.4	1.9
CB-153						
Mean	7.8	22	1.4	313	18	13
Max	64	177	10	2350	137	89
p,p′-DDE						
Mean	5.7	18	0.1	25	1.5	1.0
Max	45	140	1.1	199	10	9.3
HCB						
Mean	2.0	7.1	0.04	9.5	0.5	0.4
Max	13	45	0.3	52	3.0	2.1
Oxychlordane						
Mean	12	28	0.03	5.4	0.3	0.2
Max	104	246	0.2	2350	137	1.8

However, the modeled concentrations of p,p′-DDE and HCB are below the ranges found by Dewailly et al. (1999). The model also estimated the relative accumulation and excretion of POPs (Table 6). In general, relatively low accumulation was estimated for the selected POPs with oxychlordane being only 0.6%. However, CB-153 was an exception showing an estimated accumulation of 35% of the intake. The highest excretion of the selected POPs was alveolar followed by urinary pathways and to less extent via feces. Moreover, the majority of the oxychlordane was primarily excreted via the urinary pathways, while higher excretion via feces was estimated for CB-153 (8% of intake). Few other studies have reported human PBPK modeling. For example, Verner et al. (2009) build a model for POP exposure in infants that had a high predicted vs. observed correlation for CB-153 of around 0.9. Similarly, Redding et al. (2008) build a global lactation transfer PBPK model for CB-153 and showed that it was possible to predict 25-year body burdens and the authors also did a small pilot study on Canadian Inuits. The present study complement these very well and show that modeling POP exposure in Greenlandic Inuit using the PBPK approach is possible and can be included in future human health exposure and effect assessments.

3.5. PBPK and the variation in circulating POP concentrations following meals

It is important to have insights on how POP concentrations vary as a function of the last meal dose. Fig. 2 shows the PBPK modeled concentrations of oxychlordane and CB-153 in blood, liver, muscle and adipose tissue over a period of 120 h (app. 5 days) for the Qaanaaq study group. A significant fluctuation for these compounds is seen in blood, liver and muscle, whereas diurnal variation in adipose tissue is relatively small. The PBPK model also predicted that the blood concentrations may increase as much as 40% following a meal. It should be noted that the increase and hence the relative variation in blood will be significantly lower for individuals with a high internal burden of POPs, especially

Table 6
Proportion (%) of the estimated POP intake that is bioaccumulated and excreted by urine and bile as estimated by the PBPK model (Cahill et al., 2003).

	CB-99	CB-153	p,p′-DDE	HCB	Oxychlordane
Bioaccumulated	2.9	35	2.9	4.4	0.6
Alveolar excretion	75	45	75	74	77
Urinary excretion	22	13	22	21	22
Biliary excretion	0.1	7.8	0.1	0.1	0.1

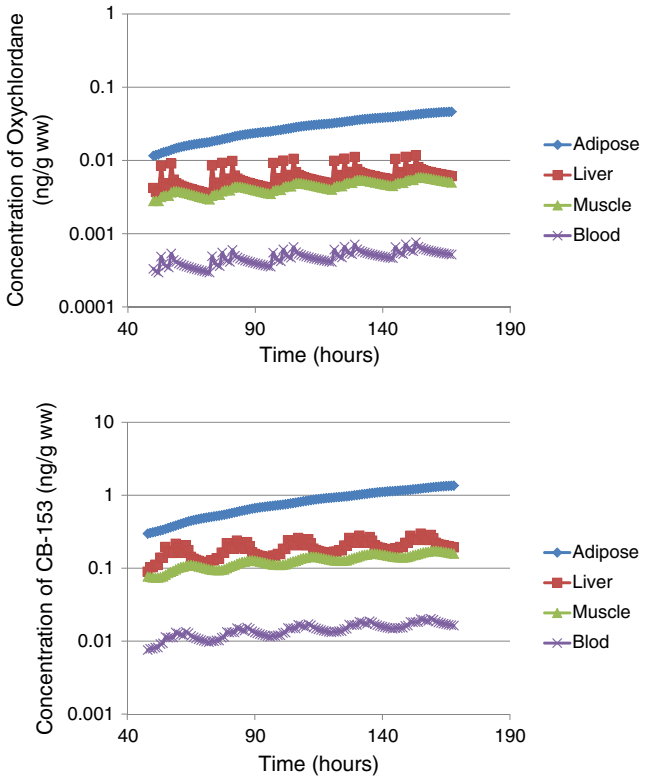

Fig. 2. PBPK modeling showing the variation of oxychlordane (top) and CB-153 (bottom) concentrations in blood, adipose tissue, liver and muscle over a period of 120 h following meals for the communities in Qaanaaq.

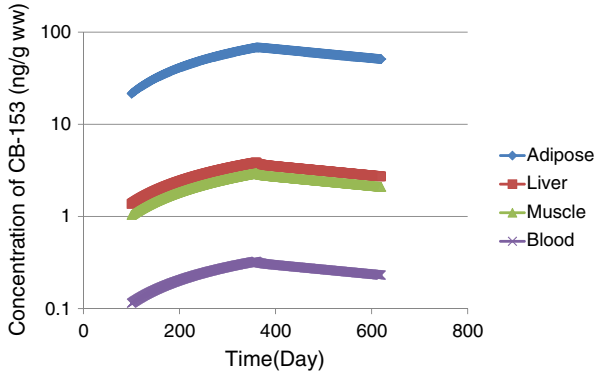

Fig. 3. PBPK modeling showing the increase of CB-153 concentration in tissue and blood following 360 day exposure and decrease in concentration after ended exposure at day 360 for Qaanaaq people.

for CB-153. For oxychlordane with low absorption and low internal burden, the body concentration largely reflects contaminants of the last meal.

3.6. Comparison between PBPK modeling and measured POP blood levels

The present PBPK model is primary modified for POPs. As summarized in Table 2, the PBPK modeled blood concentrations of the five POPs were a factor 2–3 of the analyzed values. Taken the significant variation in measured POP blood concentrations of up to 100-folds in the four study populations into account, this model estimation fits well. The PBPK modeling of contaminants in the Greenlandic Inuit from the four regions is very complex and it is not possible solely from the physicochemical properties in Table 1 to estimate blood and tissue concentrations of the 5 compounds (Cahill et al., 2003). The estimation of blood values is a function of uptake, accumulation, biotransformation and excretion that only a complex model like the PBPK can predict.

3.7. Doubling time and half-life

As given in Fig. 3, the PBPK modeling showed an increase of CB-153 concentrations following 360 days (one year) of exposure and a decrease of CB-153 after ended exposure in the Qaanaaq study group. Upon the end of exposure the concentrations start to decrease in all tissues. The dietary POP contaminants bio-accumulate to a varying degree and blood concentrations reflect what is dietarily consumed as well as internal burdens that accumulated over time. The rate of contaminant increase (doubling time; T_2) and decrease (half-life; $T_{½}$) following dietary exposure is summarized for the Qaanaaq study group in Table 7. The T_2 was significantly shorter than $T_{½}$, which for e.g. CB-153 was almost two years. In other words, there are considerable internal burdens several years after a dietary shift towards food with low contaminant levels. Again; the PBPK modeling is very complex and doubling times and half-lives for the five compounds cannot be predicted from the physicochemical properties alone.

4. Conclusions and recommendations

Given the high variation in chemically measured blood POP concentrations, the estimated intake of contaminants via food was reasonable. However, it should be noted that estimates for daily intake may be subject to considerable uncertainty due to imprecise information about diet. This provides an explanation for the fact that the PBPK modeled estimated blood concentrations were within a factor 2–3 of the actual chemically analyzed circulating concentrations. The PBPK model also showed that POP concentrations in blood can be significantly increased by meals rich in contaminants, while individuals, who already have high body burden bio-accumulated over many years, are not visibly affected by a single meal exposure. However, the model also predicted that only a relatively small proportion of certain dietary contaminants accumulate in the body and that urinary excretion was relatively high and fecal excretion was minor, except for CB-153 for which a significant fecal excretion was found. The model also showed that there may be significant body burdens several years after a conversion to a diet low in POPs. Therefore, the assessment of blood contaminant data should account for size of POP body burdens and intrinsic properties in relation to accumulation, distribution and excretion. Based on the PBPK modeling data it is recommended to implement the modeling in future Greenland human health exposure and effect assessments. With the use of the

Table 7
Doubling time (T_2) and half-life ($T_{½}$) for POPs in blood, adipose tissue, liver and muscle of Qaanaaq people in exposure scenario of Fig. 3. All values are in days.

	Blood		Adipose tissue		Liver		Muscle	
	T_2	$T_{½}$	T_2	$T_{½}$	T_2	$T_{½}$	T_2	$T_{½}$
CB-99	277	315	257	315	277	315	277	315
CB-153	124	693	108	693	122	693	124	693
Oxychlordane	187	347	165	347	187	347	187	347
p,p′-DDE	289	338	267	338	289	338	289	338
HCB	277	315	257	315	277	315	277	315

PBPK modeling it is possible to estimate the contaminant burden of critical organs and thereby potential health effects from human exposure to POPs. Similarly, it is recommended to include other POP contaminants as well as methyl mercury, which is another key focus of human health effects in the Arctic.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.envint.2013.12.006.

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