Environmental Research 142 (2015) 380–386

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Physiologically-based pharmacokinetic modelling of distribution, bioaccumulation and excretion of POPs in Greenland sledge dogs (*Canis familiaris*)

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ARTICLE INFO

Article history:
Received 18 March 2015
Received in revised form
25 June 2015
Accepted 27 June 2015
Available online 25 July 2015

Keywords:
PCBs
Polar bear
Polychlorinated biphenyls
POPs
Persistent Organic Pollutants
Sledge dogs.

ABSTRACT

We used PBPK (physiologically-based pharmacokinetic) modelling to investigate distribution, bioaccumulation and excretion of the seven POPs (persistent organic pollutants) CB-99, CB-153, HCB, oxychlordane, *p,p'*-DDE, BDE-47 and BDE-99 in 4 adult captive Greenland sledge dog (*Canis familiaris*) bitches fed minke whale (*Balaenoptera acuterostrata*) blubber for 500–635 days. The PBPK modelled POP concentrations in adipose tissue, liver, kidney and plasma were mostly within a factor 2 of actual measured tissue levels even for those at the lower concentration end. The excretion route for oxychlordane and CB-153 was modelled to be via faeces while lung alveolar excretion dominated for BDE-47, BDE-99, HCB, *p,p'*-DDE and CB-99. Furthermore the model suggested the retained mass of POPs after 500 and 635 days of exposure, respectively, to be relatively low despite these POPs being highly recalcitrant. The retention increased in the following order (% of total intake); *p,p'*-DDE (1%) < BDE-47 (6%) < CB-99 (14%) < HCB (16%) < CB-153 (18%) < BDE-99 (26%) < oxychlordane (34%). Overall; these results indicate that PBPK modelling may be a strong tool in risk assessment of POPs in arctic mammals.

1. Introduction

Persistent organic pollutants (POPs) undergo long-range transport from lower latitudes via sea currents and atmospheric pathways to the Arctic where top predators such as polar bear bioaccumulate concentrations that affects their general health status (Letcher et al., 2010). Due to the high exposure in top predators and Arctic Inuit people; a substantial effort is allocated to monitor temporal trends in Persistent organic pollutants (POPs) of Arctic wildlife which should be linked to climate change and global transport and regulation of these chemicals (e.g. Dietz et al., 2006, 2009, 2011, 2013a, 2013b; McKinney et al., 2013; Rigét et al., 2013a, 2013b). Persistent organic pollutants in polar bears (*Ursus maritimus*) have been suggested to affect vitamin concentrations (Braathen et al., 2004; Skaare et al., 2001), hormone and neurochemical status (Basu et al., 2009; Braathen et al., 2004; Gustavson et al., 2015; Haave et al., 2003; Oskam et al., 2003, 2004; Pedersen et al., 2015; Skaare et al., 2001), immune systems (Lie et al., 2004, 2005) and sexual organs (Sonne et al., 2006a, 2007a, 2009, 2015) among others. Knowledge about these health effects have often been based on studies using laboratory animal models, although it is generally difficult to extrapolate from laboratory to wild species because of differences in species' metabolism, sensitivity to POPs and reproductive cycles (AMAP, 1998, 2004; Letcher et al., 2010; Sonne, 2010). Laboratory animals are often exposed to short-term toxic concentrations of a single compound while wildlife are long-term exposed to a cocktail of contaminants at lower concentrations (Letcher et al., 2010; Sonne, 2010). In addition to this, cross-sectional investigation of wildlife animals usually gives a "snap-shot" picture of the animals' exposure history except in those cases where capture–recapture is undertaken (Sonne 2010).

A biomonitoring equivalent is the conversion of an external guideline value such as tolerable daily intake (TDI) to an internal dose against which biomonitoring tissue data can be directly compared (Hays et al., 2007, 2008). The use of biomonitoring equivalents for interpreting POP concentrations in Arctic top predators have previously been conducted for polar bears (Dietz et al., 2015; Gustavson et al., 2008; Sonne et al., 2009). These studies have been conducted based on estimates of oral intake of prey issues and risk assessment of reproductive effects of internal doses obtained from physiologically-based pharmacokinetic (PBPK) modelling. Such studies are desirable since information about POP

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http://dx.doi.org/10.1016/j.envres.2015.06.034
0013-9351/

exposure and health effects in Arctic top-predators are difficult, expensive and time consuming to obtain in order to have reasonable sample sizes (Sonne 2010). It is therefore desirable to convert oral POP exposure to internal organ-tissues doses using PBPK modelling that describes absorption, accumulation and excretion from the body.

In the Arctic, PBPK modelling of POPs in polar bears and Inuits has been based on contaminant concentrations in prey and food, respectively (Dietz et al. 2015; Norstrom 2002; Redding et al. 2008; Sonne et al. 2009, 2014a; Verner et al. 2009). In these cases, information about internal tissue concentrations is limited and this therefore warrants the development of PBPK models that convert POP exposure to internal concentrations in susceptible organ-systems. In order to evaluate the already established generic PBPK model described by Cahill et al. (2003) for Arctic ecosystems we decided to investigate distribution, bioaccumulation and excretion of POPs in a controlled setup. For that purpose; four Greenland sledge dog (*Canis familiaris*) bitches were fed POP-contaminated minke whale (*Balaenoptera acuterostrata*) blubber for 500–635 days (Sonne et al. 2006b) from which data on both oral POP exposure and subsequent accumulated concentrations were available.

2. Materials and methods

2.1. Study design

The four sledge dog bitches included in the present PBPK modelling were a subset from a larger cohort study of sixteen West Greenland sledge dogs performed between December 2004 and September 2006 in Aasiaat south of Disco Bay, Central West Greenland. The four bitches were chosen since the most adequate tissue data were available from these specimens. The Aasiaat study focused on relevant dietary POP exposures for Arctic top predators and the subsequent health effects on multiple organ-systems. A detailed description and discussion of concentrations of pollutants, lipids and nutrients in the diet has been published previously by Sonne, (2010), Kirkegaard et al., (2011), Sonne et al., (2006b, 2007b, 2007c, 2008a, 2008b, 2008c, 2010, 2014b, 2014c) and Verreault et al., (2009a, 2009b).

2.2. POP analyses in blood, organs and tissues

Briefly, analysis of CB-99, CB-153, HCB, oxychlordane, *p,p′*-DDE, BDE-47 and BDE-99 was conducted at the National Wildlife Research Centre, Carleton University, Ottawa, Canada. The analyses are described in details elsewhere by Gebbink et al. (2008), Verreault et al. (2008) and Gauthier et al. (2009). Briefly, the selected POPs were a subset of 59 CB-congeners (CB16/32, 17, 18, 22, 31/28, 33/20, 42, 44, 47/48, 52, 56/60, 64/41, 66, 70/76, 74, 85, 87, 92, 95, 97, 99, 101/90, 105, 110, 114, 118, 128, 130, 137, 138, 141, 146, 149, 151, 153, 156, 157, 158, 170/190, 171, 172, 174, 176, 177, 178, 179, 180, 183, 187, 189, 194, 195, 196/203, 199, 200, 202, 206, 207 and 208), three benzene compounds (1,2,4,5-tetrachlorobenzene, pentachlorobenzene and hexachlorobenzene), four chlordane compounds and their two metabolites (*trans*-chlordane, *cis*-chlordane, *trans*-nonachlor, *cis*-nonachlor, heptachlor epoxide and oxychlordane) as well as DDTs (*p,p′*-DDE, *p,p′*-DDD, *p,p′*-DDT). In addition to this, 36 BDE-congeners were analysed (BDE17, 25, 28, 47, 49, 54, 66, 75, 77, 85, 99, 100, 116, 119, 138, 139, 140, 153, 154, 155, 171, 180, 181, 183, 184, 190, 191, 196, 197, 201, 202, 203, 206, 207, 208 and 209). MLOQ was set to 0.01 ng/g ww.

2.3. The PBPK model

The physiologically based pharmacokinetic (PBPK) model used was a structural mathematical model, comprising the tissues and organs of the body of human and animals with each perfused by, and connected via, the blood circulatory system. The model is a computational tool that can refine the assessment of the fate of chemicals in the body by simulation. In PBPK models, the body is subdivided into anatomical compartments representing individual organs or tissue groups. The transport of chemicals in the body is described by mass balance differential equations that incorporate blood flows, partitioning into compartments and tissue volumes. After incorporation of elimination processes like metabolism and excretion, the fate and disposition of the parent chemical and metabolites can be predicted and extrapolated. Numerous specific PBPK models have been used for modelling fate and disposition of a certain drug or cancer risk assessment of industry chemicals. However, only few studies have reported on specific PBPK models for Arctic organisms (Cropp et al., 2014; Hickie et al., 2013). The present generic modelling of the timely fate and accumulation of POPs in sledge dogs is based on the PBPK model described in details by Cahill et al. (2003). A complete model description, including model equations and default parameterization, is presented in the Environmental Toxicology and Chemistry web site (http://onlinelibrary.wiley.com/doi/10.1002/etc.5620220104/suppinfo). Using the generic model by Cahill et al. (2003) requires a minimum of input data including physical–chemical properties of POPs, daily intake, reaction rates and time of exposure.

The model applied to the four Aasiaat sledge dog bitches was a further development of the work presented by Gustavson et al., (2008) and Sonne et al., (2009). First four sledge dog bitches from the cohort study of sixteen West Greenland sledge dogs (e.g. Sonne et al., 2006b) were used independently to calibrate the reaction rate in the model by iterations of different rates compared with actual measured POP adipose tissue concentrations. Briefly, besides simulation time and number of iterations, the model incorporates data for chemical exposure (oral ingestion), biometric data (e.g. mass of body, volume of intestine and organs etc.), reaction rates and different physical–chemical properties of pollutants (partition coefficients). See Supplementary Information for PBPK model input variables and the output from model simulation exemplified by CB-153 (Table S1).

2.4. Estimating concentrations, fate, retention and bioaccumulation

The PBPK model was set up for four Aasiaat sledge dog bitches that were different from those individuals used to calibrate the reaction rate as described above. Weight, exposure time, daily intake of minke whale blubber and calculated daily POP intake are listed in Tables 1 and 2. Physical–chemical properties and metabolic rate used in the modelling are shown in Table 3. The PBPK model simulated POP concentrations in blood, liver, kidney and adipose tissue in the four sledge dogs. This allowed for estimations of tissue concentrations of POPs as well as relative distribution and bioaccumulation (adipose dog: blubber whale).

Table 1
Biological information and daily intake of blubber for the four Greenland sledge dog bitches in the study conducted between December 2004 and September 2006 in Aasiaat, Central West Greenland.

Id No.	Weight	Exposure time	Daily blubber intake
	(kg)	(days)	(g/day)
Dog 31	26	635	123
Dog 41	23	635	104
Dog 61	23	500	118
Dog 71	22	500	105