Toxicology and Applied Pharmacology 315 (2017) 70–79

Contents lists available at ScienceDirect

Toxicology and Applied Pharmacology

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

Physiologically based pharmacokinetic toolkit to evaluate environmental exposures: Applications of the dioxin model to study real life exposures☆

Claude Emond [a,*], Patricia Ruiz [b], Moiz Mumtaz [b]

[a] BioSimulation Consulting Inc, Newark, DE, USA
[b] Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, Atlanta, GA, USA

ARTICLE INFO

Article history:
Received 1 July 2016
Revised 17 November 2016
Accepted 7 December 2016
Available online 10 December 2016

Keywords:
Berkeley-Madonna
Dioxin
PBPK
Risk assessment

ABSTRACT

Chlorinated dibenzo-p-dioxins (CDDs) are a series of mono- to octa-chlorinated homologous chemicals commonly referred to as polychlorinated dioxins. One of the most potent, well-known, and persistent member of this family is 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD).

As part of translational research to make computerized models accessible to health risk assessors, we present a Berkeley Madonna recoded version of the human physiologically based pharmacokinetic (PBPK) model used by the U.S. Environmental Protection Agency (EPA) in the recent dioxin assessment. This model incorporates CYP1A2 induction, which is an important metabolic vector that drives dioxin distribution in the human body, and it uses a variable elimination half-life that is body burden dependent. To evaluate the model accuracy, the recoded model predictions were compared with those of the original published model. The simulations performed with the recoded model matched well with those of the original model. The recoded model was then applied to available data sets of real life exposure studies. The recoded model can describe acute and chronic exposures and can be useful for interpreting human biomonitoring data as part of an overall dioxin and/or dioxin-like compounds risk assessment.

1. Introduction

Chlorinated dibenzo-p-dioxins (CDDs) are a series of mono- to octa-chlorinated homologous chemicals commonly referred to as polychlorinated dioxins. The most potent, well-known, and long-lasting member of this family is 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (ATSDR, 1998, 2012). Dioxins can affect health in many ways including modulation of growth factors and their receptors, immunotoxicity, developmental toxicities and cancer (Devito and Birnbaum, 1994; Emond et al., 2004, 2005). Experimental studies specifically mention TCDD as affecting multiple hormone systems and causing neurotoxicity, reproductive toxicity, immunotoxicity, carcinogenicity, developmental toxicities, ovarian dysfunction, and fetal loss (Birnbaum, 1995; Birnbaum and Tuomisto, 2000; Kogevinas, 2001; WHO, 1998). In addition, dioxin and related dioxin-like (D-DL) chemicals induce several biochemical, physiological, and toxicological responses, including activation of aryl hydrocarbon (Ah) receptors, induction of CYP1A1-2 and 1B isoforms, and modulation of growth factors and their receptors (Birnbaum and Farland, 2003).

Dioxins have been found in at least 126 sites that comprise the National Priorities List that are targeted for long-term federal cleanup (ATSDR, 1998). Dioxins are included in biomonitoring studies worldwide. Numerous programs, recent and ongoing, exist to evaluate environmental exposure of humans to chemicals. Some of these programs are the Expert Team to Support Biomonitoring in Europe [ESBIO], the Consortium to Perform Human Biomonitoring on a European Scale [COPHES], the U.S. CDC National Health and Nutrition Examination Survey (NHANES) (CDC, 2012), and the Canadian Health Measures Survey [CHMS]. The U.S. CDC NHANES is a cross-sectional study of chemical exposures across the United States designed to provide a national representative sample of exposures to adults and children in the general U.S. population (CDC, 2012).

Over the last two decades a number of PBPK and PK models have been published for species such as rodents (mice and rat), trout (fish), and humans (Andersen et al., 1993; Aylward et al., 2005; Carrier et al., 1995; Emond et al., 2004, 2010; Lawrence and Gobas, 1997; Maruyama et al., 2002; Nichols et al., 1998). The distribution of dioxins such as dioxin and dioxin-like (D-DL) is body-burden dependent (Emond et al., 2005). In this process, dioxins PBPK modeling has undergone a constant evolution. The most recent version of the dioxin PBPK model incorporates CYP1A2 induction, an important vector that drives

☆ The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry. Mention of trade names is not an endorsement of any commercial product.

* Corresponding author.
E-mail address: claude.emond@biosmc.com (C. Emond).

http://dx.doi.org/10.1016/j.taap.2016.12.007
0041-008X/

the distribution of dioxins in the human body (Emond et al., 2006). The National Center for Environmental Assessment (NCEA) at the U.S. Environmental Protection Agency (EPA) has used this model to perform a recent dioxin reassessment for human exposure (NCEA-USEPA, 2010). Recently, a new version of the PBPK model built on the same three compartments, but including pregnancy and lactation description was published based on the same basic structure (Emond et al., 2016).

The thrust of our current research work is translational in nature with a goal to make the models easily accessible in a simple simulation language for risk assessors working in field situations. At the outset, we conducted literature review to identify available human PBPK models for the chemicals of interest. Following literature searches of human health-related databases such as Medline, Toxline, and PubMed, we identified several PBPK models. These models varied in their complexity based on the scientific understanding of the chemistry, biological behavior, and insights gained into the mechanism(s) or mode of action of a given chemical's toxicity. Thus, the models contained different numbers of compartments (e.g., liver, kidney, and other organs). Often the compartments were designed for parent chemicals, but some included metabolite(s). The criteria we used for model selection included critical scientific issues such as the number of datasets used to calibrate and evaluate the model, the model's maturity (number of predecessor models from which the model was derived), and the author's experience

The PBPK model described here is based on our previous work of rat TCDD PBPK model for gestational and naïve physiologic conditions extrapolated to the humans (Emond et al., 2003, 2004, 2005). During development of the model, its performance was evaluated using several human datasets (i.e., U.S. Air Force veteran cohort, Viennese women poisoning case, and more recently the Seveso women cohort). It was further modified and improved during the U.S. EPA TCDD reassessment to include gestational exposures (NCEA-USEPA, 2010). Recently, an advanced version of the PBPK model built including pregnancy and lactation has been published based on the same basic structure (Emond et al., 2016). This model has been used by the scientific community and federal agencies such as NIEHS and US EPA and now is being used by European Food Safety Authority.

The aim of this study was to add a dioxin PBPK model to the PBPK tool kit for environmental pollutants, being developed at s the Agency for Toxic Substances and Disease Registry (ATSDR). The following 4-step process was used to achieve this goal: 1) recode the above mentioned dioxin PBPK model into the Berkeley Madonna (BM) platform, 2) assess the performance of the recoded dioxin PBPK model under diverse exposure conditions, 3) compare the accuracy of the recoded model with the original model (Emond et al., 2006), and 4) show the recoded dioxin model's applicability using actual exposure data from case studies.

2. Method

2.1. Model structure and physiological parameters

We reviewed previously published human PBPK dioxin models, and selected the Emond et al. (2006) model for recoding in BM software (version 8.01 for Microsoft Windows, Kagi Shareware, and Berkeley, CA). This model is an extrapolation of the rat model published by Emond et al. (2004). It contains three compartments (i.e., adipose tissue, liver, and the rest of the body) connected by the systemic circulation (Emond et al., 2004, 2005, 2006). (Supplemental material Fig. S1). The compartments corresponding to the organs or tissues in this PBPK model include those that have majors' roles in the pharmacokinetics and developmental toxicity of TCDD. Liver and fat were included in the model because they are involved in the metabolism and storage of TCDD respectively, and account for almost 80% of the body burden of TCDD (Carrier, 1991). A blood compartment was kept to describe the systemic circulation and because this tissue is readily sampled in humans. The rest of the body compartment was included in order to achieve mass balance (Emond et al., 2004).

The three compartments are described as diffusion limited. Each compartment contains two sub-compartments, namely cellular matrix and tissue blood, and each uses a permeability constant to maintain a slow tissue distribution of the chemical, reflecting experimental observations. Human physiological and chemical-specific parameters describing the absorption, distribution, and blood and tissue partitioning of TCDD were taken from the literature (Supplemental material Table 1S).

The role of CYP1A2 is very important in the regulation of TCDD distribution and elimination from the body. The induction of CYP1A2 was demonstrated as a direct confirmation of the hypothesis that CYP1A2 is the hepatic binding protein responsible for the sequestration of TCDD and related compounds in the liver (Diliberto et al., 1997). Also, Santostefano et al., 1996 showed that the induction of CYP1A2 was proportional to the TCDD exposure dose which is related to the body burden. More recently, it has been demonstrated that the induction of CYP1A2 is proportional to the elimination of TCDD which mean the increase of the induction will decrease the half-life or increase the elimination (Emond et al., 2006). Induction of CYP1A2 in the liver starts with the interaction of TCDD and the AhR, which will influence (DEFINE THIS Parameter) the variable parameter (KBILE_LI) changing the rate of elimination.

The recoded model mathematically describes the plausible mode of action of TCDD and dioxin-like compounds: that they bind with the aryl hydrocarbon receptor (AhR) in the liver and form a complex that then activates induction of the CYP1A2 enzyme. In addition, the elimination constant of TCDD varies with the body burden of TCDD. Researchers observed a difference in animals and humans exposed to low or high amounts of TCDD that previously was attributed to the adipose tissue fraction (Michalek et al., 2002; Michalek and Tripathi, 1999). It was observed that higher the body burden of TCDD faster, the TCDD elimination rate. Diliberto et al. (1997) demonstrated that the high body burden of TCDD linked to the CYP1A2 enzyme was concentrated in the liver, and proposed that the proximity of elimination route promoted the disposition of TCDD (Diliberto et al., 1997). They established that the half-life can range from 6 months to >20 years, depending on the body burden of TCDD. Based on this observation, the induction process of the CYP1A2 enzyme was incorporated into the model to account for the elimination of TCDD (Emond et al., 2006).

The recoded model describes the oral exposure route, including diet, soil, and/or drinking water, which are the major exposure sources for dioxins. The model provides an intravenous exposure pathway as an alternate way to study the toxicity of TCDD and to optimize the bioavailability. (Appendix A includes codes for this model in the BM format.)

This PBPK model was designed to predict the absorption, the distribution, and the elimination of TCDD or the dioxin-like compounds expressed as WHO-TEQ. We assume that all the dioxin-like compounds are in fact an equivalent concentration of TCDD. Thus the PBPK model acts as a surrogate of the different dioxin-like exposure scenarios. In some examples we use in this paper exposures measured contained not only the TCDD but also the dioxin-like congeners expressed as a toxic equivalency of TCDD.

2.2. Model evaluation

Development of PBPK is data dependent and the model is as good as the data in-put. Hence, only a high quality data must be used to develop, calibrate and validate PBPK models. So special precaution should be taken while considering such data to ensure best analytical methods and practices currently available have been used including those for sample collection, preparation, and storage. This goal is achieved through establishing standard quality assurance and control procedures and using them. Application of certified standards methods will provide an acceptable evaluation of the quality of data in terms of precision,