Regulatory Toxicology and Pharmacology 70 (2014) 261–269

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

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

An integrative risk assessment approach for persistent chemicals: A case study on dioxins, furans and dioxin-like PCBs in France

Camille Béchaux [a,*], Marco Zeilmaker [b], Mathilde Merlo [a], Bas Bokkers [c], Amélie Crépet [a]

[a] ANSES, French Agency for Food, Environmental and Occupational Health Safety, 27-31 Avenue du Général Leclerc, 94701 Maisons-Alfort, France
[b] RIVM, National Institute for Public Health and the Environment, Centre for Nutrition, Prevention and Health, PO Box 1, 3720 BA Bilthoven, The Netherlands
[c] RIVM, National Institute for Public Health and the Environment, Centre for Safety of Substances and Products, PO Box 1, 3720 BA Bilthoven, The Netherlands

ARTICLE INFO

Article history:
Received 28 October 2013
Available online 16 July 2014

Keywords:
Cumulative risk assessment
Dioxins
PCBs
Biomarker
Pharmacokinetic
Benchmark dose

ABSTRACT

For persistent chemicals slowly eliminated from the body, the accumulated concentration (body burden), rather than the daily exposure, is considered the proper starting point for the risk assessment. This work introduces an integrative approach for persistent chemical risk assessment by means of a dynamic body burden approach. To reach this goal a Kinetic Dietary Exposure Model (KDEM) was extended with the long term time trend in the exposure (historic exposure) and the comparison of bioaccumulation with body burden references for toxicity. The usefulness of the model was illustrated on the dietary exposure to PolyChlorinatedDibenzo-p-Dioxins (PCDDs), PolyChlorinatedDibenzoFurans (PCDFs) and PolyChlorinated Biphenyls (PCBs) in France. Firstly the dietary exposure to these compounds was determined in 2009 and combined with its long term time trend. In order to take differences between the kinetics of PCDD/F and dl-PCBs into account, three groups of congeners were considered i.e. PCDD/Fs, PCB 126 and remaining dl-PCBs. The body burden was compared with reference body burdens corresponding to reproductive, hepatic and thyroid toxicity. In the case of thyroid toxicity this comparison indicated that in 2009 the probability of the body burden to exceed its reference ranged from 2.8% (95% CI: 1.5–4.9%) up to 3.9% (95% CI: 2.7–7.1%) (18–29 vs. 60–79 year olds). Notwithstanding the decreasing long-term time trend of the dietary dioxin exposure in France, this probability still is expected to be 1.5% (95% CI: 0.3–2.5%) in 2030 in 60–79 olds. In the case of reproductive toxicity the probability of the 2009 body burden to exceed its reference ranged from 3.1% (95% CI: 1.4–5.0%) (18–29 year olds) to 3.5% (95% CI: 2.2–5.2%) (30–44 year olds). In 2030 this probability is negligible in 18–29 year olds, however small though significant in 30–44 year olds (0.7%, 95% CI: 0–1.6%). In the case of hepatic toxicity the probability in 2009 even in 60–79 year olds already was negligible. In conclusion this approach indicates that in France dioxin levels in food form a declining, though still present, future health risk with respect to thyroid and reproductive toxicity.

1. Introduction

Chemicals like PolyChlorinatedDibenzo-p-Dioxins (PCDDs), PolyChlorinatedDibenzoFurans, (PCDFs), PolyChlorinated Biphenyls (PCBs), PolyBrominated Diphenyl Ethers (PBDEs), DichloroDiphenyl-Trichloroethane (DDT), cadmium and methyl mercury are known to be slowly eliminated from the body. The successive exposures to these chemicals therefore results in bioaccumulation, i.e. increasing levels in the body. For this reason, the accumulated concentration in the body (body burden), rather than the daily exposure, is considered as the proper starting point for the risk assessment of these chemicals (Van Leeuwen and Younes, 2000; US EPA, 2010).

In comparison with a traditional risk assessment a body burden approach requires various methodological adaptations (NRC, 2006; Gies et al., 2007; Sirot et al., 2012). Firstly, the accumulation in the human body results from the net effect of repeated intakes and elimination. The incorporation of such accumulation in the risk assessment procedure needs the explicit incorporation of chemical kinetics. In this context several kinetic models ranging from single compartment toxico-kinetic (TK) models to complex multi-compartment physiologically-based toxicokinetic (PBTK) models may serve the purpose. Secondly, the exposure to bioaccumulating agents may not be limited to one single chemical, but may consist of the exposure to a mixture of related chemicals. Here PCDD/Fs and dl-PCBs are a typical example (Van den Berg et al., 2006).

* Corresponding author. Fax: +33 (0)1 49 77 38 92.
E-mail address: camille.bechaux@anses.fr (C. Béchaux).

http://dx.doi.org/10.1016/j.yrtph.2014.07.004
0273-2300/

Thirdly, the accumulation kinetics of persistent chemicals may be impeded by their complex historic exposure pattern. For example, it is well highlighted that the exposure to environmental contaminants such as PCDD/Fs have changed significantly over the last decades due to changes in production, in use and successive regulations (Hays and Aylward, 2003; De Mul et al., 2008). Such changes may be different for closely related chemicals such as PCDDs, PCDFs and dl-PCBs (Consonni et al., 2012). In the case of PCDD/Fs previous studies already have addressed the historic exposure pattern of PCDD/Fs (Van der Molen et al., 1996; Pinsky and Lorber, 1998; Aylward and Hays, 2002). To the best of our knowledge, none of these studies performed a full quantitative risk assessment integrating the historic, long term, exposure of PCDD/Fs and dl-PCBs, the resulting bioaccumulation and the corresponding toxic risk. Therefore, the objective of this study is to develop an integrative risk assessment methodology which takes into account the long-term time trend of the exposure to persistent chemicals, their bioaccumulation in the human body and the corresponding toxicity and to apply this methodology on the long-term exposure of PCDD/Fs and dl-PCBs in France.

As dietary intake represents more than 90% of the human exposure to PCDD/Fs and dl-PCBs (WHO, 2002) only this route of exposure was considered. The current dietary exposure in France was assessed by means of a food questionnaires and contamination data in food and scaled over time in concordance with the method of Van der Molen et al. (1996), Van der Molen (1998). The resulting long-term intake was used as input for the Kinetic Dietary Exposure Model (KDEM) as proposed by Verger et al. (2007) for the exposure to methyl mercury, its accumulation in the body and its corresponding toxic risk. In order to take differences between the kinetics of PCDD/F and dl-PCBs into account (Milbrath et al., 2009) and possible differences in historic evolution of exposure, three groups of congeners were considered separately: PCDD/Fs, PCB 126 and remaining dl-PCBs.

This strategy resulted in long-term simulations of the body burden of PCDD/Fs and dl-PCBs in the French population. The toxic risk, i.e. reproductive, hepatic and thyroid toxicity, associated with these body burdens was obtained by comparison with reference body burdens for these types of toxicity. In concordance with current dioxin risk assessment procedures (Van Leeuwen and Younes, 2000; JECFA, 2001), the latter were obtained by means of interspecies extrapolation of animal toxicity. In this work, animal toxicity was analyzed by means of Bench Mark Dose modeling and associated animal body burdens were extrapolated to man. Body burdens estimated from our model were then compared with reference body burdens through a probabilistic approach using distributions for BMDL and population body burdens.

2. Material and methods

2.1. Dietary exposure and blood concentrations of a fishermen French population

Biomonitoring data such as concentrations in blood provides relevant information for the estimation of kinetic parameters such as half-lives and exposure trends of dioxins (Van der Molen et al., 1996; Van der Molen, 1998; Aylward et al., 2005; Hsu et al., 2010; Fromme et al., 2009). Hence blood concentration of PCDD/Fs and dl-PCBs measured in a population of French fishermen families were used to characterize the long-term exposure of the current French population (Anses/InVS, 2011). The blood data were obtained from the French National study on Dioxin blood levels in French consumers of freshwater fish (ICAR study, Anses/InVS, 2011). In 2009, this study recorded the dioxin concentrations in blood (pg per g fat) of 606 adults between 18 and 75 years of age. All individuals were from fishermen families. The concentrations were converted into total body burdens assuming a balance between all lipid compartments in the body and that the fat content of the human body (BF) varies with age, sex, weight and height according to the equation proposed by Deurenberg et al. (1991) i.e. BF% = 1.20 BMI + 0.23 age − 10.8 sex − 5.4. Consumed quantities of 115 food items covering the main diet of each individual taking part in the study, were collected by means of a food frequency questionnaire and a photograph manual of portions size. Dietary exposure of the 606 individuals was assessed by combining these consumed quantities with concentration data from the ICAR study for freshwater fishes, the CALIPSO study (Leblanc, 2006) for marine fishes and other sea foods and the second French Total Diet Study (Sirot et al., 2012) for other foods known to contribute to the exposure to dioxins. Body burdens and levels of dietary exposure for different age classes of the ICAR population are summarized in Table 1.

2.2. Dietary exposure of the general French population

Exposure data of the French population are provided by the Second French Total Diet Study (Sirot et al., 2012). "Total Diet Studies (TDS)" follow a standardized international methodology and aim at assessing the dietary exposure of individuals for many contaminants taking into account residue levels in foods as consumed at home. In a TDS, exposure is assessed by combining individual food consumption data and residue levels data from food sample analysis. The individual food consumption data used in the Second French Total Diet Study (Sirot et al., 2009) were provided by the second "Individual and National Study on Food Consumption", INCA2 survey, carried out by the French Food Safety Agency between late 2005 and April 2007 (Dubuisson et al., 2010; Lioret et al., 2010). Two independent population groups were included in the survey: 2624 adults aged 18–79 years and 1455 children aged 3–17 years. Each participant was asked to complete a 7-day food diary as well as other questionnaires on anthropometric and socio-economic factors. Foods declared were subsequently categorized into 1305 "as consumed" food items. The mean of the quantities of the same food consumed by each individual during the week is used in order to assess chronic exposure. The consumption data were combined with contamination data measured for 212 core foods selected to cover about 90% of the whole diet in terms of quantity consumed through a methodology described in Sirot et al. (2009). Levels of dietary exposure for different age classes of the French population are summarized in Table 2.

2.3. The kinetic model

2.3.1. Model definition

Verger et al. (2007) proposed a Kinetic Dietary Exposure Model (KDEM) which describes the dynamic evolution of the dietary exposure over time. Between intakes, the change of human body burden x is described by a simple one-compartment, first order, pharmacokinetic model. For chemicals with long half-lives, absorption time is insignificant compared to the elimination time. In concordance with Emond et al. (2005); US EPA (2010) and EFSA (2011) the absorption of dioxins, furans and DL-PCBs from food was considered to be complete, i.e. 100%. Given one compartmental kinetics, the elimination rate between two eating occasions is given as:

$$\frac{dx}{dt}(t) = -k \times x(t) \quad (1)$$

The elimination rate k is described by the apparent elimination half-life HL as $k = \ln(2)/HL$.