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Assessing the impact of child/adult differences in hepatic first-pass effect on the human kinetic adjustment factor for ingested toxicants

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ABSTRACT

The objective of this study was to evaluate the impact of interindividual differences in hepatic first-pass effect (FPE) on the magnitude of the human kinetic adjustment factor (HKAF) for ingested toxicants. This factor aims at replacing a default value of 3.2 used in non-cancer risk assessment. Coupled with Monte Carlo simulations, steady-state equations that account for FPE were used to obtain distributions of arterial blood concentrations (CAss) and rates of metabolism in adults, neonates, infants and toddlers continuously exposed to an oral dose of 1 μg/kg/d of theoretical CYP2E1 and CYP1A2 substrates. For such substrates exhibiting a range of blood:air partition coefficients (Pb: 1–10,000) and hepatic extraction ratios in an average adult (E_{ad}: 0.01–0.99), HKAFs were computed as the ratio of the 95th percentile of dose metrics for each subpopulation over the 50th percentile value in adults. The reduced hepatic enzyme content in neonates as compared to adults resulted in correspondingly diminished FPE. Consequently, HKAFs greater than 3.2 could be observed, based on CAss only, in the following cases: for some CYP2E1 substrates with $E_{ad} \leqslant 0.3$, in neonates (max.: 6.3); and for some CYP1A2 substrates with $E_{ad} \leqslant 0.1$ and 0.7, in, respectively, neonates and infants (max.: 28.3). Overall, this study pointed out the importance of accounting for child/adult differences in FPE when determining the HKAF for oral exposure.

1. Introduction

For non-cancer risk assessment, steady-state toxicokinetic analyses have been used to evaluate the impact of interindividual variability on internal dose metrics (Ginsberg et al., 2005; Nong and Krishnan, 2007; Pelekis et al., 2001; Valcke and Krishnan, 2011b). This allows evaluating the magnitude and adequacy of the toxicokinetic component of the 10-fold interindividual variability factor (IVF) that is used to derive chronic reference doses (RfD) or concentrations (RfC) (Dourson et al., 1996; US EPA, 2002). Given that a default value of 3.2 (i.e., $\sqrt{10}$) has been attributed to this component based on pharmaceutical data (Dorne and Renwick, 2005; Renwick and Lazarus, 1998), further evaluation or replacement of this default value can be made by quantifying chemical-specific adjustment factors (CSAFs) described by the International Programme on Chemical Safety (IPCS, 2005). Using this method, the CSAF for interindividual variability in toxicokinetics, also referred to as the human kinetic adjustment factor (HKAF), can be determined based on experimental or modeled upper and median percentile data from population and subpopulation distributions of pharmacokinetic parameters or internal dose metrics (IPCS, 2005; Meek et al., 2002). In this regard, steady-state equations appear particularly useful as they have been shown to significantly simplify the estimation of internal dose metrics as compared to complete physiologically-based toxicokinetic (PBTK) models when simulating continuous chronic exposures to xenobiotics (Andersen, 1981; Aylward et al., 2010; Bogen, 1988; Bogen and Gold, 1997; Bogen and Hall, 1989; Bogen and McKone, 1988; Chiu and White, 2006; Csanady and Filser, 2001; Pelekis et al., 1997, 2001).

Abbreviations: ADH, alcohol dehydrogenase; BSA, body surface area; BH, body height; BW, body weight; Clint, intrinsic clearance; $Clint_{ad}$, intrinsic clearance in average adult; $Clint_{ind}$, intrinsic clearance in any individual; CAss, arterial blood concentration at steady-state; CVss, venous blood concentration at steady-state; CVlss, venous blood concentration leaving the liver at steady-state; Ci, inhaled concentration; CSAF, chemical-specific adjustment factor; CYP, cytochrome P-450; d, days; *E*, hepatic extraction ratio; E_{ad}, hepatic extraction ratio in average adult; E_{ren}, renal extraction ratio; FPE, first-pass effect; GSD, geometric standard deviation; GST, glutathione-*S*-transferase; h, hours; HKAF, human kinetic adjustment factor; ING, ingested dose; IPCS, International Programme on Chemical Safety; IVF, interindividual variability factor; Km, Michaelis–Menten constant; MC, Monte Carlo; mo, months; MSP, microsomal protein; Pb, blood:air partition coefficient; PBTK, physiologicaly-based toxicokinetic; Qc, cardiac output; Qk, kidney blood flow; Ql, liver blood flow; Qp, alveolar ventilation rate; RAM, rate of metabolism; RfC, reference concentration; RfD, reference dose; SD, standard deviation; V_{max}, maximum rate of metabolism; Vl, volume of liver; VOC, volatile organic compound; yr, years.

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For inhalation exposures, steady-state solutions have been shown to generate almost identical results as PBTK models (Pelekis et al., 1997, 2001). For oral exposures, such equations and comparison, requiring the consideration of the first-pass effect (FPE) or pre-systemic clearance, has not yet been performed extensively. Given that the FPE is often relevant to oral exposures (Gibaldi and Perrier, 1982), accounting for it when determining the HKAF for oral guidelines derivation is essential. To date, the interindividual variability of this critically important phenomenon has not been systematically quantified for environmental contaminants. Besides, the approach followed by IPCS (2005) to derive HKAF for oral exposure to several hypothetical chemicals relied on plasma clearance data from oral exposure and therefore did not need to explicitly account for oral bioavailability, which is affected by FPE.

Although experimental studies with some drugs suggest that variability in FPE is not very important (e.g., Edwards and Stoeckel, 1992; Fanta et al., 2007; Hassan et al., 1994), Beck et al. (2002) have considered a sixfold greater oral bioavailability of lead in 2-yr-old children as compared to pregnant women in a modeling exercise. Besides, CYP2E1, CYP1A1/1A2 and other hepatic enzymes involved in the biotransformation of environmental contaminants (Ronis et al., 1996) are less developed in young children compared to adults, particularly during the first year of life (Johnsrud et al., 2003; Sonnier and Cresteil, 1998). This enzyme deficiency affects the metabolic capacity of children, and possibly the resulting steady-state blood concentration for chemical exposure, in this subpopulation as compared to adults and thus the corresponding HKAF (e.g., Ginsberg et al., 2005; Nong et al., 2006; Valcke and Krishnan, 2011a). Recently, Valcke and Krishnan (2011b) computed the HKAF for inhalation and BW-adjusted systemic exposure to chemicals exhibiting various physicochemical and biochemical properties. Thus their results reflect variability in systemic clearance but do not allow accounting for the FPE for ingestion exposures. The objectives of the current study were to: (1) evaluate steady-state equations that account for the FPE of ingested chemicals; and (2) use these equations to compute HKAF for chronic oral exposures based on distributions of internal dose metrics in children and adults.

2. Methods

The methodology followed is similar to the one described previously using a steady-state algorithm for systemic and inhalation exposures (Valcke and Krishnan, 2011b); however, modifications were applied to account for ingestion exposure. Specifically, the approach involved: (1) the derivation and validation of steady-state equations for ingested chemicals with full-blown PBTK models published in the literature; (2) solving these equations with Monte Carlo simulations to generate distributions of internal dose metrics in children and adults for chemicals exhibiting various physicochemical and biochemical characteristics; and (3) computing the HKAF following the IPCS (2005) approach.

2.1. Steady-state equations for ingested chemicals

For chronic, continuous exposure to a given chemical, the amount entering the body is in equilibrium with the amount cleared from it when steady-state is attained. Under this condition, the blood concentration of the chemical (CAss, e.g., in mg/L), is computed as the ratio of the dose rate entering the system (e.g., in mg/h) divided by the systemic clearance (e.g., L/h). For inhaled VOCs, this dose rate has been computed as (Qp × Ci), where Qp is the alveolar ventilation rate and Ci is the inhaled concentration (e.g., Andersen, 1981; Csanady and Filser, 2001; Nong and Krishnan, 2007; Pelekis et al., 1997, 2001). For a systemic exposure, a body-weight adjusted dose rate, expressed in μg/kg/d, has been used in a previous work (Valcke and Krishnan, 2011b). With regard to ingestion exposure, the fraction of a dose of xenobiotics absorbed through the gut that reaches the systemic circulation corresponds to the proportion of the bioaccessible dose that escapes the FPE in the liver (Fig. 1). This fraction, reflecting what becomes "systemically available" following FPE, is computed with knowledge of $(1-E)$, where E is the hepatic extraction ratio (Gibaldi and Perrier, 1982; Gillette, 1980; Rowland and Tozer, 1995). Thus, as derived mathematically in Appendix, the "systemic dose rate" for ingested chemicals is expressed as the ingested dose rate, ING, multiplied by $(1-E)$ (see Fig. 1); it replaces the numerator of the steady-state equation used in Valcke and Krishnan (2011b) to compute CAss for systemic exposure. Precisely, CAss was calculated herein as the "systemic dose rate" for ingestion exposure (i.e., the ingested dose rate ING corrected for the FPE), divided by the systemic clearance. The latter includes the hepatic (Ql × E), pulmonary (Qp/Pb) and renal (Qk × Eren) clearance processes:

$$\mathrm{CAss} = \frac{\mathrm{ING} \times (I - E)}{\mathrm{Ql} \times E + (\mathrm{Qp}/\mathrm{Pb}) + (\mathrm{Qk} \times E_{\mathrm{ren}})} \quad (1)$$

where Qk, Ql, Qp, E_{ren} and Pb are, respectively, the renal blood flow, liver blood flow, alveolar ventilation rate, renal extraction ratio and the blood:air partition coefficient. In accordance with Fig. 1, the calculation of the liver volume (Vl)-adjusted rate of metabolism (RAM) (Valcke and Krishnan, 2011b) was expanded to account for the contribution of FPE, as follows:

$$\mathrm{RAM} = \frac{\mathrm{CAss} \times \mathrm{Q1} \times E + (\mathrm{ING} \times E)}{\mathrm{Vl}} \quad (2)$$

As described previously (Valcke and Krishnan, 2011b), E and E_{ren} above were determined based, respectively, on the intrinsic clearance and the glomerular filtration rate (GFR), whereas other

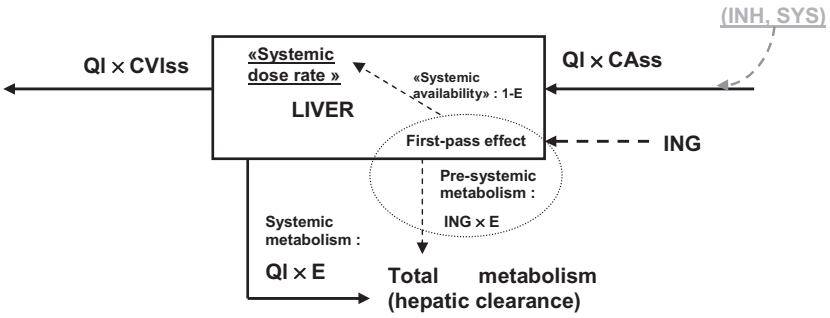

Fig. 1. Illustration of the liver uptake and elimination of chemicals undergoing first-pass effect at steady-state, following oral dosing. For a conceptual comparison, inhaled or systemic dosing are also indicated in grey. CAss, steady-state arterial blood concentration; CVlss, steady-state liver's venous blood concentration; E, hepatic extraction ratio; ING, ingested dose rate; INH, inhaled dose rate; Ql, blood flow to/from the liver; SYS, systemic dose rate.