Supplementary File

Co-PBK: A computational biomonitoring tool for assessing chronic internal exposure to chemicals and metabolites

Xiaoyu Zhang, Zijian Li*

School of Public Health (Shenzhen), Sun Yat-sen University, Shenzhen, Guangdong 518107, China

*Corresponding author: lizijian3@mail.sysu.edu.cn

ORCID: Zijian Li: http://orcid.org/0000-0002-9291-5966

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S1. Complete PBK modeling matrices of the parent compound and its metabolites

The parent compound:

$$\begin{bmatrix}0\\0\\0\\0\\0\\0\end{bmatrix} = BW \times \begin{bmatrix}\gamma_{Oral} \times ADD_{P,Oral}\\ \gamma_{Inha} \times ADD_{P,Inha}\\ \gamma_{Derm} \times ADD_{P,Derm}\\ 0\\ 0\\ 0\end{bmatrix} + k_P \times \begin{bmatrix}m^s_{P,Liver}\\ m^s_{P,Lung}\\ m^s_{P,Blood}\\ m^s_{P,Kidney}\\ m^s_{P,Fat}\\ m^s_{P,Muscle}\end{bmatrix} \tag{s1a}$$

$$k_P = \begin{bmatrix} -(k^P_{BioT,Liver} + k^P_{Liver\to B} + k^P_{Liver\to Bile}) & 0 & k^P_{B\to Liver} & 0 & 0 & 0\\ 0 & -(k^P_{Lung\to A} + k^P_{Lung\to B}) & k^P_{B\to Lung} & 0 & 0 & 0\\ k^P_{Liver\to B} & k^P_{Lung\to B} & -\sum_{j=1}^{5} k^P_{B\to Tissue,j} & k^P_{Kidney\to B} & k^P_{Fat\to B} & k^P_{Muscle\to B}\\ 0 & 0 & k^P_{B\to Kidney} & -(k^P_{Kidney\to U} + k^P_{Kidney\to B}) & 0 & 0\\ 0 & 0 & k^P_{B\to Fat} & 0 & -k^P_{Fat\to B} & 0\\ 0 & 0 & k^P_{B\to Muscle} & 0 & 0 & -k^P_{Muscle\to B} \end{bmatrix} \tag{s1b}$$

Metabolite i (assuming that the metabolite can be only produced from the parent compound):

$$\begin{bmatrix}0\\0\\0\\0\\0\\0\end{bmatrix} = \begin{bmatrix}k^{M,i}_{PR,Liver} m^s_{P,Liver}\\ 0\\ 0\\ 0\\ 0\\ 0\end{bmatrix} + k_{M,i} \times \begin{bmatrix}m^s_{M,i,Liver}\\ m^s_{M,i,Lung}\\ m^s_{M,i,Blood}\\ m^s_{M,i,Kidney}\\ m^s_{M,i,Fat}\\ m^s_{M,i,Muscle}\end{bmatrix} \tag{s2a}$$

$$k_{M,i} = \begin{bmatrix} -(k_{BioT,Liver}^{M,i} + k_{Liver\to B}^{M,i} + k_{Liver\to Bile}^{M,i}) & 0 & k_{B\to Liver}^{M,i} & 0 & 0 & 0 \\ 0 & -(k_{Lung\to A}^{M,i} + k_{Lung\to B}^{M,i}) & k_{B\to Lung}^{M,i} & 0 & 0 & 0 \\ k_{Liver\to B}^{M,i} & k_{Lung\to B}^{M,i} & -\sum_{j=1}^{5} k_{B\to Tissue,j}^{M,i} & k_{Kidney\to B}^{M,i} & k_{Fat\to B}^{M,i} & k_{Muscle\to B}^{M,i} \\ 0 & 0 & k_{B\to Kidney}^{M,i} & -(k_{Kidney\to U}^{M,i} + k_{Kidney\to B}^{M,i}) & 0 & 0 \\ 0 & 0 & k_{B\to Fat}^{M,i} & 0 & -k_{Fat\to B}^{M,i} & 0 \\ 0 & 0 & k_{B\to Muscle}^{M,i} & 0 & 0 & -k_{Muscle\to B}^{M,i} \end{bmatrix} \quad \text{(s2b)}$$

where $m_{P,j}^{s}$ (mg) and $m_{M,i,j}^{s}$ (mg) denote the steady-state masses of the parent compound and its metabolite *i* in tissue *j*. First-order kinetics-based rate constants of the parent compound and its metabolite *i* are defined in the following tables.

Table S1. Summary of first-order kinetics-based rate constants of the parent compound in the human body. The derivation of rate constants was obtained from current modeling studies (Li et al., 2022, 2022).

Compartments	**Rate constants**	**Definitions**	**Equations**
Liver	$k_{BioT,Liver}^{P}$	Biotransformation	Not available. Here, this study used the value of $\frac{V_{max}}{K_M}$ for the Michaelis-Menten kinetic parameter to estimate the metabolic rate constant of naphthalene as 7.776 (d^{-1}) under the low-dosed exposure scenario. The *in vitro* data was obtained from Wang et al. (2020).
	$k_{Liver\to Bile}^{P}$	Liver-to-bile elimination	$k_{Liver\to Bile}^{P} = \frac{Q_{Bile}}{K_{Liver-Bile}^{P} \times M_{Liver}}$ where Q_{Bile} (kg d^{-1}) is the bile excretion rate, $K_{Liver-Bile}^{P}$ (dimensionless) is the liver-bile partition coefficient of the parent compound, and M_{Liver} (kg) is the liver mass.

	$k_{Liver \to B}^{P}$	Liver-to-blood elimination (blood flow out)	$k_{Liver \to B}^{P} = \frac{Q_{Liver \leftrightarrow B}}{K_{Liver-B}^{P} \times M_{Liver}}$ where $Q_{Liver \leftrightarrow B}$ (kg d^{-1}) is the blood flow rate of the liver, and $K_{Liver-B}^{P}$ (dimensionless) is the liver-blood partition coefficient of the parent compound.
	$k_{B \to Liver}^{P}$	Blood-to-liver uptake (blood flow in)	$k_{B \to Liver}^{P} = \frac{Q_{Liver \leftrightarrow B}}{M_{Blood}}$ where M_{Blood} (kg) is the blood mass.
Lung	$k_{Lung \to A}^{P}$	Lung-to-air elimination (exhalation)	$k_{Lung \to A}^{P} = \frac{Q_{Air}}{K_{Lung-A}^{P} \times M_{Lung}}$ where Q_{Air} (kg d^{-1}) is the human inhalation rate, K_{Lung-A}^{P} (dimensionless) is the lung-air partition coefficient of the parent compound, and M_{Lung} (kg) is the lung mass.
	$k_{Lung \to B}^{P}$	Lung-to-blood elimination (blood flow out)	$k_{Lung \to B}^{P} = \frac{Q_{Lung \leftrightarrow B}}{K_{Lung-B}^{P} \times M_{Lung}}$ where $Q_{Lung \leftrightarrow B}$ (kg d^{-1}) is the blood flow rate of the lung, K_{Lung-B}^{P} (dimensionless) is the lung-blood partition coefficient of the parent compound, and M_{Lung} (kg) is the lung mass.
	$k_{B \to Lung}^{P}$	Blood-to-lung uptake (blood flow in)	$k_{B \to Lung}^{P} = \frac{Q_{Lung \leftrightarrow B}}{M_{Blood}}$
Kidney	$k_{Kidney \to U}^{P}$	Kidney-to-urine elimination	$k_{Kidney \to U}^{P} = \frac{Q_{Urine}}{K_{Kidney-U}^{P} \times M_{Kidney}}$ where Q_{Urine} (kg d^{-1}) is the human urinary excretion rate, $K_{Kidney-U}^{P}$ (dimensionless) is the kidney-urine partition coefficient of the parent compound, and M_{Kidney} (kg) is the kidney mass.

	$k^{P}_{Kidney \to B}$	Kidney-to-blood elimination (blood flow out)	$k^{P}_{Kidney \to B} = \frac{Q_{Kidney \leftrightarrow B}}{K^{P}_{Kidney-B} \times M_{Kidney}}$ where $Q_{Kidney \leftrightarrow B}$ (kg d^{-1}) is the blood flow rate of the kidney, and $K^{P}_{Kidney-B}$ (dimensionless) is the kidney-blood partition coefficient of the parent compound.
	$k^{P}_{B \to Kidney}$	Blood-to-kidney uptake (blood flow in)	$k^{P}_{B \to Kidney} = \frac{Q_{Kidney \leftrightarrow B}}{M_{Blood}}$
Fat	$k^{P}_{Fat \to B}$	Fat-to-blood elimination (blood flow out)	$k^{P}_{Fat \to B} = \frac{Q_{Fat \leftrightarrow B}}{K^{P}_{Fat-B} \times M_{Fat}}$ where $Q_{Fat \leftrightarrow B}$ (kg d^{-1}) is the blood flow rate of the fat, K^{P}_{Fat-B} (dimensionless) is the fat-blood partition coefficient of the parent compound, and M_{Fat} (kg) is the fat mass.
	$k^{P}_{B \to Fat}$	Blood-to-fat uptake (blood flow in)	$k^{P}_{B \to Fat} = \frac{Q_{Fat \leftrightarrow B}}{M_{Blood}}$
Muscle	$k^{P}_{Muscle \to B}$	Muscle-to-blood elimination (blood flow out)	$k^{P}_{Muscle \to B} = \frac{Q_{Muscle \leftrightarrow B}}{K^{P}_{Muscle-B} \times M_{Muscle}}$ where $Q_{Muscle \leftrightarrow B}$ (kg d^{-1}) is the blood flow rate of the muscle, $K^{P}_{Muscle-B}$ (dimensionless) is the muscle-blood partition coefficient of the parent compound, and M_{Muscle} (kg) is the fat mass.
	$k^{P}_{B \to Muscle}$	Blood-to-muscle uptake (blood flow in)	$k^{P}_{B \to Muscle} = \frac{Q_{Muscle \leftrightarrow B}}{M_{Blood}}$
Blood	$k^{P}_{Liver \to B}$	Liver-to-blood uptake	$k^{P}_{Liver \to B} = \frac{Q_{Liver \leftrightarrow B}}{K^{P}_{Liver-B} \times M_{Liver}}$ (the same with the liver-to-blood elimination rate constant in the liver)

	$k_{Lung \to B}^{P}$	Lung-to-blood uptake	$k_{Lung \to B}^{P} = \frac{Q_{Lung \leftrightarrow B}}{K_{Lung-B}^{P} \times M_{Lung}}$ (the same with the lung-to-blood elimination rate constant in the lung)
	$k_{Kidney \to B}^{P}$	Kidney-to-blood uptake	$k_{Kidney \to B}^{P} = \frac{Q_{Kidney \leftrightarrow B}}{K_{Kidney-B}^{P} \times M_{Kidney}}$ (the same with the kidney-to-blood elimination rate constant in the kidney)
	$k_{Fat \to B}^{P}$	Fat-to-blood uptake	$k_{Fat \to B}^{P} = \frac{Q_{Fat \leftrightarrow B}}{K_{Fat-B}^{P} \times M_{Fat}}$ (the same with the fat-to-blood elimination rate constant in the fat)
	$k_{Muscle \to B}^{P}$	Muscle-to-blood uptake	$k_{Muscle \to B}^{P} = \frac{Q_{Muscle \leftrightarrow B}}{K_{Muscle-B}^{P} \times M_{Muscle}}$ (the same with the liver-to-blood elimination rate constant in the muscle)
	$\sum_{j=1}^{5} k_{B \to Tissue,j}^{P}$	Blood-to-tissue j elimination	$\sum_{j=1}^{5} k_{B \to Tissue,j}^{P} = \sum_{j=1}^{5} \frac{Q_{Liver \leftrightarrow B}}{M_{Blood}}$ (the same with the blood-to-tissue j update rate constant in tissue j)

Table S2. Summary of first-order kinetics-based rate constants of metabolite *i* in the human body. The derivation of rate constants was obtained from current modeling studies (Li et al., 2022, 2022).

Compartments	Rate constants	Definitions	Equations
Liver	$k_{PR,Liver}^{M,i}$	Production	Not available (using the value of 0.5 for simulating the production of 1-OHN and 2-OHN)
	$k_{BioT,Liver}^{M,i}$	Biotransformation	Not available (using the value of 0 for simulating, here assuming 1-OHN and 2-OHN as the final products through metabolization)
	$k_{Liver\to Bile}^{M,i}$	Liver-to-bile elimination	$k_{Liver\to Bile}^{M,i} = \frac{Q_{Bile}}{K_{Liver-Bile}^{M,i} \times M_{Liver}}$ where Q_{Bile} (kg d^{-1}) is the bile excretion rate, $K_{Liver-Bile}^{M,i}$ (dimensionless) is the liver-bile partition coefficient of metabolite *i*.
	$k_{Liver\to B}^{M,i}$	Liver-to-blood elimination (blood flow out)	$k_{Liver\to B}^{M,i} = \frac{Q_{Liver\leftrightarrow B}}{K_{Liver-B}^{M,i} \times M_{Liver}}$ where $Q_{Liver\leftrightarrow B}$ (kg d^{-1}) is the blood flow rate of the liver, and $K_{Liver\to B}^{M,i}$ (dimensionless) is the liver-blood partition coefficient of metabolite *i*.
	$k_{B\to Liver}^{M,i}$	Blood-to-liver uptake (blood flow in)	$k_{B\to Liver}^{M,i} = \frac{Q_{Liver\leftrightarrow B}}{M_{Blood}}$ where M_{Blood} (kg) is the blood mass.
Lung	$k_{Lung\to A}^{M,i}$	Lung-to-air elimination (exhalation)	$k_{Lung\to A}^{M,i} = \frac{Q_{Air}}{K_{Lung-A}^{M,i} \times M_{Lung}}$ where Q_{Air} (kg d^{-1}) is the human inhalation rate, $K_{Lung-A}^{M,i}$ (dimensionless) is the lung-air partition coefficient of metabolite *i*, and M_{Lung} (kg) is the lung mass.
	$k_{Lung\to B}^{M,i}$	Lung-to-blood elimination (blood flow out)	$k_{Lung\to B}^{M,i} = \frac{Q_{Lung\leftrightarrow B}}{K_{Lung-B}^{M,i} \times M_{Lung}}$ where $Q_{Lung\leftrightarrow B}$ (kg d^{-1}) is the blood flow rate of the lung, $K_{Lung-B}^{M,i}$ (dimensionless) is the lung-blood partition coefficient of metabolite *i*, and M_{Lung} (kg) is the lung mass.

	$k_{B\to Lung}^{M,i}$	Blood-to-lung uptake (blood flow in)	$k_{B\to Lung}^{M,i}=\frac{Q_{Lung\leftrightarrow B}}{M_{Blood}}$
Kidney	$k_{Kidney\to U}^{M,i}$	Kidney-to-urine elimination	$k_{Kidney\to U}^{M,i}=\frac{Q_{Urine}}{K_{Kidney-U}^{M,i}\times M_{Kidney}}$ where Q_{Urine} (kg d^{-1}) is the human urinary excretion rate, $K_{Kidney-U}^{M,i}$ (dimensionless) is the kidney-urine partition coefficient of metabolite *i*, and M_{Kidney} (kg) is the kidney mass.
	$k_{Kidney\to B}^{M,i}$	Kidney-to-blood elimination (blood flow out)	$k_{Kidney\to B}^{M,i}=\frac{Q_{Kidney\leftrightarrow B}}{K_{Kidney-B}^{M,i}\times M_{Kidney}}$ where $Q_{Kidney\leftrightarrow B}$ (kg d^{-1}) is the blood flow rate of the kidney, and $K_{Kidney-B}^{M,i}$ (dimensionless) is the kidney-blood partition coefficient of metabolite *i*.
	$k_{B\to Kidney}^{M,i}$	Blood-to-kidney uptake (blood flow in)	$k_{B\to Kidney}^{M,i}=\frac{Q_{Kidney\leftrightarrow B}}{M_{Blood}}$
Fat	$k_{Fat\to B}^{M,i}$	Fat-to-blood elimination (blood flow out)	$k_{Fat\to B}^{M,i}=\frac{Q_{Fat\leftrightarrow B}}{K_{Fat-B}^{M,i}\times M_{Fat}}$ where $Q_{Fat\leftrightarrow B}$ (kg d^{-1}) is the blood flow rate of the fat, $K_{Fat-B}^{M,i}$ (dimensionless) is the fat-blood partition coefficient of metabolite *i*, and M_{Fat} (kg) is the fat mass.
	$k_{B\to Fat}^{M,i}$	Blood-to-fat uptake (blood flow in)	$k_{B\to Fat}^{M,i}=\frac{Q_{Fat\leftrightarrow B}}{M_{Blood}}$
Muscle	$k_{Muscle\to B}^{M,i}$	Muscle-to-blood elimination (blood flow out)	$k_{Muscle\to B}^{M,i}=\frac{Q_{Muscle\leftrightarrow B}}{K_{Muscle-B}^{M,i}\times M_{Muscle}}$ where $Q_{Muscle\leftrightarrow B}$ (kg d^{-1}) is the blood flow rate of the muscle, $K_{Muscle-B}^{M,i}$ (dimensionless) is the muscle-blood partition coefficient of

			metabolite i, and M_{Muscle} (kg) is the fat mass.
	$k_{B \to Muscle}^{M,i}$	Blood-to-muscle uptake (blood flow in)	$k_{B \to Muscle}^{M,i} = \frac{Q_{Muscle \leftrightarrow B}}{M_{Blood}}$
Blood	$k_{Liver \to B}^{M,i}$	Liver-to-blood uptake	$k_{Liver \to B}^{M,i} = \frac{Q_{Liver \leftrightarrow B}}{K_{Liver-B}^{M,i} \times M_{Liver}}$ (the same with the liver-to-blood elimination rate constant in the liver)
	$k_{Lung \to B}^{M,i}$	Lung-to-blood uptake	$k_{Lung \to B}^{M,i} = \frac{Q_{Lung \leftrightarrow B}}{K_{Lung-B}^{M,i} \times M_{Lung}}$ (the same with the lung-to-blood elimination rate constant in the lung)
	$k_{Kidney \to B}^{M,i}$	Kidney-to-blood uptake	$k_{Kidney \to B}^{M,i} = \frac{Q_{Kidney \leftrightarrow B}}{K_{Kidney-B}^{M,i} \times M_{Kidney}}$ (the same with the kidney-to-blood elimination rate constant in the kidney)
	$k_{Fat \to B}^{M,i}$	Fat-to-blood uptake	$k_{Fat \to B}^{M,i} = \frac{Q_{Fat \leftrightarrow B}}{K_{Fat-B}^{M,i} \times M_{Fat}}$ (the same with the fat-to-blood elimination rate constant in the fat)
	$k_{Muscle \to B}^{M,i}$	Muscle-to-blood uptake	$k_{Muscle \to B}^{M,i} = \frac{Q_{Muscle \leftrightarrow B}}{K_{Muscle-B}^{M,i} \times M_{Muscle}}$ (the same with the liver-to-blood elimination rate constant in the muscle)
	$\sum_{j=1}^{5} k_{B \to Tissue,j}^{M,i}$	Blood-to-tissue j elimination	$\sum_{j=1}^{5} k_{B \to Tissue,j}^{M,i} = \sum_{j=1}^{5} \frac{Q_{Liver \leftrightarrow B}}{M_{Blood}}$ (the same with the blood-to-tissue j update rate constant in tissue j)

S2. Steady-state solutions of PBK modeling matrices of the parent compound and its metabolites

At steady state, the PBK modeling matrices can be solved using analytical solutions. This section contains the steady-state solutions of the parent molecule and its metabolite *i*.

S2.1 Route-specific solutions for the parent compound

For the parent compound, in the blood compartment:

$$m_{P,Blood}^{s} = BW\left(\gamma_{Derm}ADD_{P,Derm} + \frac{\gamma_{Oral}ADD_{P,Oral}k_{Liver\to B}^{P}}{k_{BioT,Liver}^{P} + k_{Liver\to B}^{P} + k_{Liver\to Bile}^{P}} + \frac{\gamma_{Inha}ADD_{P,Inha}k_{Lung\to B}^{P}}{k_{Lung\to A}^{P} + k_{Lung\to B}^{P}}\right)\left(\sum_{j=1}^{5} k_{B\to Ti} \right. \quad \text{(s3)}$$

Due to the linearity of the PBK modeling matrix's first-order kinetics-based equations, the steady-state mass of chemicals in the human body can be computed independently for each exposure route (Li et al., 2022, 2022), namely $m_{P,Blood}^{s,Oral}$, $m_{P,Blood}^{s,Inha}$, and $m_{P,Blood}^{s,Derm}$ for the oral, inhalation, and dermal routes, respectively:

$$m_{P,Blood}^{s,Oral} = BW\left(\frac{\gamma_{Oral}ADD_{P,Oral}k_{Liver\to B}^{P}}{k_{BioT,Liver}^{P} + k_{Liver\to B}^{P} + k_{Liver\to Bile}^{P}}\right)\left(\sum_{j=1}^{5} k_{B\to Tissue,j}^{P} - \frac{k_{Liver\to B}^{P}k_{B\to Liver}^{P}}{k_{BioT,Liver}^{P} + k_{Liver\to B}^{P} + k_{Liver\to Bile}^{P}} - \frac{\ldots}{k_{L}\ldots} \right. \quad \text{(s4a)}$$

$$m_{P,Blood}^{s,Inha} = BW\left(\frac{\gamma_{Inha}ADD_{P,Inha}k_{Lung\to B}^{P}}{k_{Lung\to A}^{P} + k_{Lung\to B}^{P}}\right)\left(\sum_{j=1}^{5} k_{B\to Tissue,j}^{P} - \frac{k_{Liver\to B}^{P}k_{B\to Liver}^{P}}{k_{BioT,Liver}^{P} + k_{Liver\to B}^{P} + k_{Liver\to Bile}^{P}} - \frac{k_{Lung\to B}^{P}k_{B\ldots}}{k_{Lung\to A}^{P} + k_{L}\ldots} \right. \quad \text{(s4b)}$$

$$m_{P,Blood}^{s,Derm} = BW(\gamma_{Derm} ADD_{P,Derm})\left(\sum_{j=1}^{5} k_{B \to Tissue,j}^{P} - \frac{k_{Liver \to B}^{P} k_{B \to Liver}^{P}}{k_{BioT,Liver}^{P} + k_{Liver \to B}^{P} + k_{Liver \to Bile}^{P}} - \frac{k_{Lung \to B}^{P} k_{B \to Lung}^{P}}{k_{Lung \to A}^{P} + k_{Lung \to B}^{P}}\right) \tag{s4c}$$

Then, steady-state masses of the parent compound in other organs can be expressed using $m_{P,Blood}^{s}$ (including route-specific solutions).

In the liver compartment:

$$m_{P,Liver}^{s} = \frac{BW \times \gamma_{Oral} ADD_{P,Oral} + k_{B \to Liver}^{P} m_{P,Blood}^{s}}{k_{BioT,Liver}^{P} + k_{Liver \to Bile}^{P} + k_{Liver \to B}^{P}} \tag{s5}$$

In the lung compartment:

$$m_{P,Lung}^{s} = \frac{BW \times \gamma_{Inha} ADD_{P,Inha} + k_{B \to Lung}^{P} m_{P,Blood}^{s}}{k_{Lung \to A}^{P} + k_{Lung \to B}^{P}} \tag{s6}$$

In the kidney compartment:

$$m_{P,Kidney}^{s} = \frac{k_{B \to Kidney}^{P} m_{P,Blood}^{s}}{k_{Kidney \to U}^{P} + k_{Kidney \to B}^{P}} \tag{s7}$$

In the fat compartment:

$$m_{P,Fat}^{s} = \frac{k_{B \to Fat}^{P} m_{P,Blood}^{s}}{k_{Fat \to B}^{P}} \tag{s8}$$

In the muscle compartment:

$$m_{P,Muscle}^{s} = \frac{k_{B \to Muscle}^{P} m_{P,Blood}^{s}}{k_{Muscle \to B}^{P}} \quad \text{(s9)}$$

Route-specific $m_{P,Tissue,j}^{s}$ values of the parent compound in tissue j can be calculated using $m_{P,Blood}^{s,Oral}$, $m_{P,Blood}^{s,Inha}$, and $m_{P,Blood}^{s,Derm}$.

S2.2 Route-specific solutions for metabolites

For metabolite ***i*** of the parent compound, in the blood compartment:

$$m_{M,i,Blood}^{s} = m_{P,Liver}^{s} \left(\frac{k_{Liver \to B}^{M,i} k_{PR,Liver}^{M,i}}{k_{BioT,Liver}^{M,i} + k_{Liver \to B}^{M,i} + k_{Liver \to Bile}^{M,i}} \right) \left(\sum_{j=1}^{5} k_{B \to Tissue,j}^{M,i} - \frac{k_{Liver \to B}^{M,i} k_{B \to Liver}^{M,i}}{k_{BioT,Liver}^{M,i} + k_{Liver \to B}^{M,i} + k_{Liver \to Bile}^{M,i}} - \frac{k_{Lung-}^{M,i}}{k_{Lung \to A}^{M,i}} \quad \text{(s10)}$$

where $m_{M,i,Blood}^{s}$ links to the steady-state solution of the parent compound, namely $m_{P,Liver}^{s}$. Similar to the parent compound, route-specific $m_{M,i,Blood}^{s}$ values of metabolite *i* can be calculated using respective route-specific $m_{P,Liver}^{s}$ values of the parent compound.

Then, the steady-state masses of metabolite *i* in other tissues can be calculated using $m_{M,i,Blood}^{s}$.

In the liver compartment:

$$m_{M,i,Liver}^{s} = \frac{k_{PR,Liver}^{M,i} m_{P,Liver}^{s} + k_{B \to Liver}^{M,i} m_{M,i,Blood}^{s}}{k_{BioT,Liver}^{M,i} + k_{Liver \to B}^{M,i} + k_{Liver \to Bile}^{M,i}} \quad \text{(s11)}$$

In the lung compartment:

$$m_{M,i,Lung}^{s} = \frac{k_{B\to Lung}^{M,i} m_{M,i,Blood}^{s}}{k_{Lung\to A}^{M,i} + k_{Lung\to B}^{M,i}} \quad \text{(s12)}$$

In the kidney compartment:

$$m_{M,i,Kidney}^{s} = \frac{k_{B\to Kidney}^{M,i} m_{M,i,Blood}^{s}}{k_{Kidney\to U}^{M,i} + k_{Kidney\to B}^{M,i}} \quad \text{(s13)}$$

In the fat compartment:

$$m_{M,i,Fat}^{s} = \frac{k_{B\to Fat}^{M,i} m_{M,i,Blood}^{s}}{k_{Fat\to B}^{M,i}} \quad \text{(s14)}$$

In the muscle compartment:

$$m_{M,i,Muscle}^{s} = \frac{k_{B\to Muscle}^{M,i} m_{M,i,Blood}^{s}}{k_{Muscle\to B}^{M,i}} \quad \text{(s15)}$$

Route-specific $m_{M,i,Tissue,j}^{s}$ values of the parent compound in tissue j can be calculated using $m_{M,i,Blood}^{s,Oral}$, $m_{M,i,Blood}^{s,Inha}$, and $m_{M,i,Blood}^{s,Derm}$.

S3. Partition coefficient

The partition coefficient of the parent compound or its metabolites between human tissues can be approximated using tissue compositions (Chiou et al., 2001; Trapp et al., 2007) as follows:

$$K_{Tissue-B} = \frac{\theta_{Oct,Tissue} + 0.035\theta_{NLO,Tissue} + \frac{\theta_{W,Tissue}}{K_{OW}} \times \frac{\rho_{Oct}}{\rho_W}}{\theta_{Oct,B} + 0.035\theta_{NLO,B} + \frac{\theta_{W,B}}{K_{OW}} \times \frac{\rho_{Oct}}{\rho_W}} \tag{s16}$$

$$K_{Lung-A} = \frac{K_{Lung-W}}{\frac{K_{AW}}{\rho_A}} \tag{s17}$$

where $K_{Tissue-B}$ (dimensionless) represents the partition coefficient of the chemical between the tissue and blood, K_{Lung-W} (L kg^{-1}) represents the partition coefficient of the chemical between the lung and water, K_{AW} (dimensionless) represents the partition coefficient of the chemical between the air and water, and ρ_A (0.0012 kg L^{-1}) represents the air density used for the unit conversion. $\theta_{Oct,Tissue}$ (g g^{-1}), $\theta_{NLO,Tissue}$ (g g^{-1}), and $\theta_{W,Tissue}$ (g g^{-1}) are the contents of the lipid, non-lipid organics (such as protein and carbohydrate), and water of the tissue, respectively. $\theta_{Oct,B}$ (g g^{-1}), $\theta_{NLO,B}$ (g g^{-1}), and $\theta_{W,B}$ (g g^{-1}) are the contents of the lipid, non-lipid organics (such as protein and carbohydrate), and water of the blood, respectively. K_{OW} (L L^{-1}) represents the partition coefficient of the chemical between octanol and water. ρ_{Oct} (0.83 kg L^{-1}) (National Library of Medicine, 2021) and ρ_W (1.0 kg L^{-1}) are the densities of octanol and water, respectively, which are used for the unit conversion.

S4. Biotransformation factor

The BF links the metabolite tissue concentration to the ADD value of the parent compound.

According to Eq. (7) of the main text and Eqs. (s5a)–(s5c), the following relationships can be demonstrated:

$$\frac{m_{P,j}^{s}}{ADD_{P,r}} = constant \tag{s18a}$$

$$\frac{m_{M,i,j}^{s}}{m_{P,j}^{s}} = constant \tag{s18b}$$

Consequently, we have:

$$\frac{m_{M,i,j}^{s}}{ADD_{P,r}} = constant \tag{s18c}$$

Therefore, the $BF_{P\rightarrow M,i,j,r}$ value of the parent compound is equal to the $m_{M,i,j}^{s}$ value when setting the $ADD_{P,r}$ value as 1.0 mg kg^{-1}d^{-1}. To determine the BF value of the parent compound using the metabolite urinary concentration, a thermodynamic partitioning process of the metabolite concentrations between the kidney and urine should be considered as follows:

$$K_{Kidney-U}^{M,i} = \frac{\overbrace{C_{M,i,Kidney}^{s,r}}^{Simulation}}{\underbrace{C_{M,i,Urine}^{s}}_{Measurement}} = \frac{m_{M,i,Kidney}^{s}}{C_{M,i,Urine}^{s}} \times \frac{1}{M_{Kidney}} \tag{s19}$$

where $C_{M,i,Kidney}^{s,r}$ (mg kg^{-1}) and $C_{M,i,Urine}^{s,r}$ (mg kg^{-1}) represent the route-specific steady-state concentrations of metabolite *i* in the kidney and urine, respectively. Therefore, the BF value of the parent compound, according to Eq. (7) of the main text, using the metabolite urinary concentration can be calculated as follows:

$$BF_{P\rightarrow M,i,Urine,r} = \frac{C_{M,i,Urine}^{s,r}}{IR_{P,r}} = \frac{\frac{1}{K_{Kidney-U}^{M,i}} \times \frac{m_{M,i,Kidney}^{s,r}}{M_{Kidney}}}{ADD_{P,r} \times BW} = \frac{m_{M,i,Kidney}^{s,r}}{ADD_{P,r}} \times \frac{1}{K_{Kidney-U}^{M,i} M_{Kidney} BW} \tag{s20}$$

According to Eqs. (s18a)–(s18c), the term "$\frac{m_{M,i,Kidney}^{s,r}}{ADD_{P,r}}$" is a constant value. Thus, the route-specific $BF_{P \to M,i,Urine,r}$ value can be calculated by setting the route-specific ADD value as 1.0 mg kg^{-1}d^{-1} as follows:

$$BF_{P \to M,i,Urine,r} = m_{M,i,Kidney}^{s,r}(ADD_{P,r} = 1) \times \frac{1}{K_{Kidney-U}^{M,i} M_{Kidney} BW} \quad \text{(s21)}$$

Then, the population exposure (external) to the parent compound can be estimated using the measured metabolite urinary concentration as follows:

$$IR_{P,r} = \overbrace{C_{M,i,Urine}^{s}}^{Measurement} \times \underbrace{\frac{K_{Kidney-U}^{M,i} M_{Kidney} BW}{m_{M,i,Kidney}^{s,r}(ADD_{P,r} = 1)}}_{Simulation} = \frac{\overbrace{C_{M,i,Urine}^{s}}^{Measurement}}{\underbrace{BF_{P \to M,i,Urine,r}}_{Simulation}} \quad \text{(s22a)}$$

$$ADD_{P,r} = \overbrace{C_{M,i,Urine}^{s}}^{Measurement} \times \underbrace{\frac{K_{Kidney-U}^{M,i} M_{Kidney}}{m_{M,i,Kidney}^{s,r}(ADD_{P,r} = 1)}}_{Simulation} = \frac{\overbrace{C_{M,i,Urine}^{s}}^{Measurement}}{\underbrace{BF_{P \to M,i,Urine,r}}_{Simulation} BW} \quad \text{(s22b)}$$

where $C_{M,i,Urine}^{s}$ (mg kg^{-1}) denotes the measured urinary concentration of metabolite i.

S5. Model inputs

The model inputs are summarized in the following tables:

Table S3. Summary of the physiological variables of the PBK modeling matrices. The information was gathered by Li et al. (2022b).

Input variable	Symbol	Unit	Value	References
Exhalation rate	Q_{Air}	kg d^{-1}	10.4	(USEPA, 2003)
Urine excretion rate	Q_{Urine}	kg d^{-1}	1.5	(Li et al., 2022)
Bile excretion rate	Q_{Bile}	kg d^{-1}	0.6	(Li et al., 2022)
Tissue mass				
Body	BW	kg	70	Generic (Li et al., 2022)
Blood	M_{Blood}	kg	4.9	(Li et al., 2022)
Liver	M_{Liver}	kg	1.8	Estimated (Dong et al., 2020; Li et al., 2022)

Kidney	M_{Kidney}	kg	0.3	Estimated (Dong et al., 2020; Li et al., 2022)
Lung	M_{Lung}	kg	1.1	Estimated (Dong et al., 2020; Li et al., 2022)
Fat	M_{Fat}	kg	15.0	Estimated (Dong et al., 2020; Li et al., 2022)
Muscle	M_{Muscle}	kg	45.5	Estimated (Dong et al., 2020; Li et al., 2022)
Blood flow rate of tissues				
Liver	$Q_{Liver\leftrightarrow B}$	kg d^{-1}	1634	Estimated (Dong et al., 2020; Li et al., 2022)
Kidney	$Q_{Kidney\leftrightarrow B}$	kg d^{-1}	1318	Estimated (Dong et al., 2020; Li et al., 2022)
Lung	$Q_{Lung\leftrightarrow B}$	kg d^{-1}	216	Estimated using the bronchial circulation given that it supplies nutrients to the lung tissue (Oikonen, 2019)
Fat	$Q_{Fat\leftrightarrow B}$	kg d^{-1}	374	Estimated (Dong et al., 2020; Li et al., 2022)
Muscle	$Q_{Muscle\leftrightarrow B}$	kg d^{-1}	3658	Estimated (Dong et al., 2020; Li et al., 2022)
Uptake efficiencies				
Oral	γ_{Oral}	dimensionless	-	Chemical-specific value (estimated using the lipophilicity) (Li et al., 2022; O'Connor et al., 2013)
Inhalation	γ_{Inha}	dimensionless	1.0	Default value (Li et al., 2022)
Dermal	γ_{Derm}	dimensionless	1.0	Default value(Li et al., 2022)

Table S4. Summary of composition data of tissues and elimination media for the PBK modeling matrices. The data was collected via a modeling study (Li et al., 2022) that analyzed measured, estimated, and modeled data from numerous field and modeling investigations (Li et al., 2021; Mitchell et al., 1945; Sijens et al., 2010; Thomas, 1962; Ueda et al., 1988).

Tissue/elimination media	**Contents (g g^{-1})**		
	Lipid (fat)	**Non-lipid organics**	**Water**
Elimination media			
Urine	0	0	0.95
Bile	0.005	0.002	0.97
Tissues			
Blood	0.002	0.078	0.92
Liver	0.03	0.23	0.73
Kidney	0.007	0.193	0.79
Muscle	0.0	0.20	0.79
Fat	0.8	0.0	0.2
Lung	0.015	0.134	0.837

S6. Case study for naphthalene

In this study, we examined naphthalene and its major metabolites 1-OHN and 2-OHN through a case study. Chemical-specific physicochemical properties, partition coefficients, and rate constants are given in the following tables.

Table S5. Summary of physiochemical properties of naphthalene and its major metabolites 1-OHN and 2-OHN. Information was gathered from current chemical databases (Lewis et al., 2016; National Library of Medicine, 2021).

Chemical	**Log Kow**	**K_{AW} (dimensionless)**
Naphthalene (NAP)	3.3	1.12E-02
1-OHN	2.85	1.47E-09
2-OHN	2.7	6.71E-10

In addition, Li et al. (2021) collected urine levels of 1-OHN and 2-OHN for a general population in Shenzhen and compared the backward-simulated results (i.e., population exposure to naphthalene) with estimated population exposure based on reported naphthalene levels in food (Ding et al., 2013). We used the urine data from Li et al. (2021) and the reported intake rates of naphthalene for the population in Shenzhen to validate the model. The reported urine levels of 1-OHN and 2-OHN (234 data for each) by Li et al. (2021) ranged from 0.31 μg kg^{-1} to 13.48 μg kg^{-1} (with an average and median of 2.14 μg kg^{-1} and 1.344 μg kg^{-1}, respectively) and from 0.294 μg kg^{-1} to 76.6 μg kg^{-1} (with an average and median of 10.65 μg kg^{-1} and 6.02 μg kg^{-1}, respectively), respectively (assuming that the urine density is 1.0 kg L^{-1}). The intake rates of naphthalene for the population in Shenzhen via food consumption by Ding et al. (2013) were estimated as 9.98×10^{-3} mg d^{-1} (males) and 8.48×10^{-3} mg d^{-1} (females).

S7. Results of sensitivity tests

Here, this study supported the results of sensitivity tests on the total steady-state mass of NAP and the total steady-state BFs of 1-OHN and 2-OHN. In detail, the mean value and S.D. are displayed in Table S6 and S7 after the ±10% variation of each related first-order kinetics-based rate constants for the specific sensitivity test.

Table S6. Summary of the sensitivity test on the total steady-state mass of NAP.

Parameter	Variation	Steady-state mass of NAP in body compartments (mg)			
		$m_{P,Blood}^{s}$	$m_{P,Liver}^{s}$	$m_{P,Lung}^{s}$	$m_{P,Kidney}^{s}$
	0	**9.31**	**24.6**	**9.25**	**1.57**
$k_{BioT,Liver}^{P}$	10%	8.56	22.6		
	-10%	10.2	27.2		
	Mean ± S.D.	9.39 ± 0.832	24.9 ± 2.30		
$k_{Liver\rightarrow Bile}^{P}$	10%	9.31	24.6		
	-10%	9.32	24.7		
	Mean ± S.D.	9.31 ± 0.005	24.6 ± 0.014		
$k_{Liver\rightarrow B}^{P}$	10%	10.1	24.5		
	-10%	8.48	24.8		
	Mean ± S.D.	9.31 ± 0.830	24.6 ± 0.168		
$k_{B\rightarrow Liver}^{P}$	10%	8.52	24.8		
	-10%	10.3	24.5		
	Mean ± S.D.	9.39 ± 0.871	24.6 ± 0.176		
$k_{Lung\rightarrow A}^{P}$	10%	9.24		9.16	
	-10%	9.39		9.35	
	Mean ± S.D.	9.31 ± 0.075		9.25 ± 0.096	
$k_{Lung\rightarrow B}^{P}$	10%	9.38		8.49	
	-10%	9.23		10.16	
	Mean ± S.D.	9.30 ± 0.076		9.33 ± 0.835	
$k_{B\rightarrow Lung}^{P}$	10%	9.25		9.98	
	-10%	9.38		8.51	
	Mean ± S.D.	9.31 ± 0.066		9.25 ± 0.734	
$k_{Kidney\rightarrow U}^{P}$	10%	9.31			1.57
	-10%	9.31			1.57
	Mean ± S.D.	9.31 ± 0.001			1.57 ± 0.000
$k_{Kidney\rightarrow B}^{P}$	10%	9.31			1.43
	-10%	9.31			1.74

	Mean ± S.D.	9.31 ± 0.001		1.59 ± 0.158
$k_{B\rightarrow Kidney}^{P}$	10%	9.31		1.73
	-10%	9.31		1.41
	Mean ± S.D.	9.31 ± 0.001		1.57 ± 0.157

Table S7. Summary of the sensitivity test on the total steady-state BFs of 1-OHN and 2-OHN.

Parameter	Variation	Steady-state BFs of NAP's metabolites in biofluids (d/kg)					
		$BF_{P\rightarrow M,i,Blood,r}$		$BF_{P\rightarrow M,i,Urine,r}$		$BF_{P\rightarrow M,i,Bile,r}$	
		1-OHN	2-OHN	1-OHN	2-OHN	1-OHN	2-OHN
	0	**0.190**	**0.173**	**0.036**	**0.043**	**23.9**	**19.2**
$k_{Liver\rightarrow Bile}^{M,i}$	10%	0.177	0.163			20.3	16.4
	-10%	0.204	0.185			28.5	22.7
	Mean ± S.D.	0.190 ± 0.013	0.174 ± 0.011			24.4 ± 4.10	19.5 ± 3.17
$k_{Liver\rightarrow B}^{M,i}$	10%	0.202	0.183			23.2	18.5
	-10%	0.176	0.162			24.6	19.9
	Mean ± S.D.	0.189 ± 0.013	0.173 ± 0.011			23.9 ± 0.740	19.2 ± 0.711
$k_{B\rightarrow Liver}^{M,i}$	10%	0.177	0.163			24.6	19.8
	-10%	0.204	0.185			23.1	18.4
	Mean ± S.D.	0.190 ± 0.013	0.174 ± 0.011			23.8 ± 0.742	19.1 ± 0.713
$k_{Lung\rightarrow A}^{M,i}$	10%	0.190	0.173				
	-10%	0.190	0.173				
	Mean ± S.D.	0.190 ± 0.000	0.173 ± 0.000				
$k_{Lung\rightarrow B}^{M,i}$	10%	0.190	0.173				
	-10%	0.190	0.173				
	Mean ± S.D.	0.190 ± 0.000	0.173 ± 0.000				
$k_{B\rightarrow Lung}^{M,i}$	10%	0.190	0.173				
	-10%	0.190	0.173				
	Mean ± S.D.	0.190 ± 0.000	0.173 ± 0.000				
$k_{Kidney\rightarrow U}^{M,i}$	10%	0.184	0.167	0.035	0.042		
	-10%	0.196	0.180	0.037	0.045		
	Mean ± S.D.	0.190 ± 0.006	0.173 ± 0.006	0.036 ± 0.001	0.044 ± 0.002		
$k_{Kidney\rightarrow B}^{M,i}$	10%	0.195	0.179	0.034	0.041		
	-10%	0.183	0.166	0.039	0.046		
	Mean ± S.D.	0.189 ± 0.006	0.173 ± 0.006	0.037 ± 0.003	0.044 ± 0.003		
$k_{B\rightarrow Kidney}^{M,i}$	10%	0.184	0.167	0.039	0.046		
	-10%	0.196	0.180	0.034	0.041		
	Mean ± S.D.	0.190 ± 0.006	0.173 ± 0.006	0.036 ± 0.003	0.043 ± 0.003		

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