Electronic Supplementary Material (ESI) for Environmental Science: Processes & Impacts.

Supplementary file

Screening of pesticides in foods of animal origin: A matrix-based approach for biotransfer factor modeling of grazing mammals

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S1. Complete pesticide fate and distribution models in animal bodies

In the liver compartment in the steady state:

$$\frac{dm_{Liver}}{dt} = E_{uptake} IR_{Food} C_{Food} + k^{+}_{Blood \rightarrow Liver} m_{Blood} - \left(k^{-}_{Liver \rightarrow Blood} + k_{m,Liver} + k_{e,Blie}\right) m_{Liver} = 0 \quad \text{(A1a)}$$

$$k^{+}_{Blood \rightarrow Liver} = \frac{Q_{Blood \Leftrightarrow Liver}}{M_{Blood}} \quad \text{(A1b)}$$

$$k^{-}_{Liver \rightarrow Blood} = \frac{Q_{Blood \Leftrightarrow Liver}}{M_{Liver} K_{Liver/Blood}} \quad \text{(A1c)}$$

$$k_{e,Blie} = \frac{ER_{Bile}}{M_{Liver} K_{Liver/Bile}} \quad \text{(A1d)}$$

where C_{Food} (mg kg^{-1}) is the pesticide concentration in the food; m_{Liver} (mg) and m_{Blood} (mg) are pesticide masses in liver and blood, respectively; E_{uptake} (unitless) is the gut lumen-to-liver uptake efficiency (considering the first pass effect); IR_{Food} (kg day^{-1}) is the food intake rate; $k^{+}_{Blood \rightarrow Liver}$ (day^{-1}), $k^{-}_{Liver \rightarrow Blood}$ (day^{-1}), $k_{m,Liver}$ (day^{-1}), and $k_{e,Blie}$ (day^{-1}) are the blood-to-liver uptake rate constant, liver-to-blood elimination rate constant, metabolic rate constant, and elimination rate constant via biliary excretion, respectively; M_{Blood} (kg) and M_{Liver} (kg) are blood and liver masses, respectively; $Q_{Blood \Leftrightarrow Liver}$ (kg day^{-1}) is the blood flow of liver; $K_{Liver/Blood}$ and $K_{Liver/Bile}$ are the liver-to-blood and liver-to-bile partition coefficients, respectively; and ER_{Bile} (kg day^{-1}) is the bile excretion rate. The estimation of pesticide E_{uptake} values is provided in S2, and the estimation of pesticide $k_{m,Liver}$ values is provided in S3.

In the kidney compartment in the steady state:

$$\frac{dm_{Kidney}}{dt} = k^{+}_{Blood \rightarrow Kidney} m_{Blood} - \left(k^{-}_{Kidney \rightarrow Blood} + k_{e,Urine}\right) m_{Kidney} = 0 \quad \text{(A2a)}$$

$$k^{+}_{Blood \rightarrow Kidney} = \frac{Q_{Blood \Leftrightarrow Kidney}}{M_{Blood}} \quad \text{(A2b)}$$

$$k^{-}_{Kidney \rightarrow Blood} = \frac{Q_{Blood \Leftrightarrow Kidney}}{M_{Kidney} K_{Kidney/Blood}} \quad \text{(A2c)}$$

$$k_{e,Urine} = \frac{ER_{Urine}}{M_{Kidney}K_{Kidney/Urine}} \quad \text{(A2d)}$$

where m_{Kidney} (mg) is the pesticide mass in the kidney; $Q_{Blood\Leftrightarrow Kidney}$ (kg day^{-1}) is the blood flow of kidney; $k^{+}_{Blood\rightarrow Kidney}$ (day^{-1}), $k^{-}_{Kidney\rightarrow Blood}$ (day^{-1}), and $k_{e,Urine}$ (day^{-1}) are the blood-to-kidney uptake rate constant, kidney-to-blood elimination rate constant, and elimination rate constant via urinary excretion, respectively; M_{Kidney} (kg) is the mass of the kidney; $K_{Kidney/Blood}$ and $K_{Kidney/Urine}$ are the kidney-to-blood and kidney-to-urine partition coefficients, respectively; and ER_{Urine} (kg day^{-1}) is the urine excretion rate.

In the lung compartment in the steady state:

$$\frac{dm_{Lung}}{dt} = k^{+}_{Blood\rightarrow Lung}m_{Blood} - (k^{-}_{Lung\rightarrow Blood} + k_{e,Exhalation})m_{Lung} = 0 \quad \text{(A3a)}$$

$$k^{+}_{Blood\rightarrow Lung} = \frac{Q_{Blood\Leftrightarrow Lung}}{M_{Blood}} \quad \text{(A3b)}$$

$$k^{-}_{Lung\rightarrow Blood} = \frac{Q_{Blood\Leftrightarrow Lung}}{M_{Lung}K_{Lung/Blood}} \quad \text{(A3c)}$$

$$k_{e,Exhalation} = \frac{ER_{Exhalation}}{M_{Lung}K_{Lung/Air}} \quad \text{(A3d)}$$

where m_{Lung} (mg kg^{-1}) is the pesticide mass in the lung; $Q_{Blood\Leftrightarrow Lung}$ (kg day^{-1}) is the blood flow of lung; $k^{+}_{Blood\rightarrow Lung}$ (day^{-1}), $k^{-}_{Lung\rightarrow Blood}$ (day^{-1}), and $k_{e,Exhalation}$ (day^{-1}) are the blood-to-lung uptake rate constant, lung-to-blood elimination rate constant, and elimination rate constant via exhalation, respectively; M_{Lung} (kg) is the mass of the lung; $K_{Lung/Blood}$ and $K_{Lung/Air}$ are the lung-to-blood and lung-to-air partition coefficients, respectively; and $ER_{Exhalation}$ (kg day^{-1}) is the exhalation rate.

In the fat (or adipose tissue) compartment in the steady state:

$$\frac{dm_{Fat}}{dt} = k^{+}_{Blood\rightarrow Fat}m_{Blood} - k^{-}_{Fat\rightarrow Blood}m_{Fat} = 0 \quad \text{(A4a)}$$

$$k^{+}_{Blood\rightarrow Fat} = \frac{Q_{Blood\Leftrightarrow Fat}}{M_{Blood}} \quad \text{(A4b)}$$

$$k^{-}_{Fat\rightarrow Blood} = \frac{Q_{Blood\Leftrightarrow Fat}}{M_{Fat}K_{Fat/Blood}} \quad \text{(A4c)}$$

where m_{Fat} (mg kg^{-1}) is the pesticide mass in fat; $Q_{Blood\Leftrightarrow Fat}$ (kg day^{-1}) is the blood flow of lung; $k^{+}_{Blood\rightarrow Fat}$ (day^{-1}) and $k^{-}_{Fat\rightarrow Blood}$ (day^{-1}) are the blood-to-fat uptake rate constant and fat-to-blood elimination rate constant, respectively; M_{Fat} (kg) is the mass of the fat; $K_{Fat/Blood}$ is the fat-to-blood partition coefficient.

In the muscle compartment in the steady state:

$$\frac{dm_{Muscle}}{dt} = k^{+}_{Blood\rightarrow Muscle}m_{Blood} - k^{-}_{Muscle\rightarrow Blood}m_{Muscle} = 0 \quad \text{(A5a)}$$

$$k^{+}_{Blood\rightarrow Muscle} = \frac{Q_{Blood\Leftrightarrow Muscle}}{M_{Blood}} \quad \text{(A5b)}$$

$$k^{-}_{Muscle\rightarrow Blood} = \frac{Q_{Blood\Leftrightarrow Muscle}}{M_{Muscle}K_{Muscle/Blood}} \quad \text{(A5c)}$$

where m_{Muscle} (mg kg^{-1}) is the pesticide mass in fat; $Q_{Blood\Leftrightarrow Muscle}$ (kg day^{-1}) is the blood flow of lung; $k^{+}_{Blood\rightarrow Muscle}$ (day^{-1}) and $k^{-}_{Muscle\rightarrow Blood}$ (day^{-1}) are the blood-to-muscle uptake rate constant and muscle-to-blood elimination rate constant, respectively; M_{Muscle} (kg) is the mass of the muscle; $K_{Muscle/Blood}$ is the muscle-to-blood partition coefficient.

In the mammary gland compartment in the steady state:

$$\frac{dm_{Mammary\ gland}}{dt} = k^{+}_{Blood\rightarrow Mammary\ gland}m_{Blood} - (k^{-}_{Mammary\ gland\rightarrow Blood} + k_{e,Milk})m_{Mammary\ gland} = 0 \quad \text{(A6a)}$$

$$k^{+}_{Blood\rightarrow Mammary\ gland} = \frac{Q_{Blood\Leftrightarrow Mammary\ gland}}{M_{Blood}} \quad \text{(A6b)}$$

$$k^{-}_{Mammary\ gland\rightarrow Blood} = \frac{Q_{Blood\Leftrightarrow Mammary\ gland}}{M_{Mammary\ gland}K_{Mammary\ gland/Blood}} \quad \text{(A6c)}$$

$$k_{e,Milk} = \frac{ER_{Milk}}{M_{Mammary\ gland}K_{Mammary\ gland/Milk}} \quad \text{(A6d)}$$

$$C_{Milk} = \frac{C_{Mammary\ gland}}{K_{Mammary\ gland/Milk}} \quad \text{(A6e)}$$

where $c_{\text{Mammary gland}}$ (mg kg^{-1}) and c_{Milk} (mg kg^{-1}) are the pesticide concentrations in the mammary gland and milk, respectively; $m_{\text{Mammary gland}}$ (mg) is the pesticide mass in the mammary gland; $Q_{\text{Blood}\Leftrightarrow\text{Mammary gland}}$ (kg day^{-1}) is the blood flow of mammary gland; $k^{+}_{\text{Blood}\rightarrow\text{Mammary gland}}$ (day^{-1}), $k^{-}_{\text{Mammary gland}\rightarrow\text{Blood}}$ (day^{-1}), and $k_{\text{e,Milk}}$ (day^{-1}) are the blood-to-mammary gland uptake rate constant and mammary gland-to-blood elimination rate constant, and elimination rate constant via milk excretion, respectively; $M_{\text{Mammary gland}}$ (kg) is the mass of the mammary gland; $K_{\text{Mammary gland/Blood}}$ and $K_{\text{Mammary gland/Milk}}$ are the mammary gland-to-blood and mammary gland-to-milk partition coefficients, respectively.

In the blood compartment in the steady state:

$$\frac{dm_{\text{Blood}}}{dt} = \sum\left(k^{+}_{\text{Tissue i}\rightarrow\text{Blood}} m_{\text{Tissue i}}\right) - \sum\left(k^{-}_{\text{Blood}\rightarrow\text{Tissue i}} m_{\text{Blood}}\right) = 0 \qquad \text{(A7a)}$$

$$k^{+}_{\text{Tissue i}\rightarrow\text{Blood}} = \frac{Q_{\text{Blood}\Leftrightarrow\text{Tissue i}}}{M_{\text{Tissue i}} K_{\text{Tissue i/Blood}}} \qquad \text{(A7b)}$$

$$k^{-}_{\text{Blood}\rightarrow\text{Tissue i}} = \frac{Q_{\text{Blood}\Leftrightarrow\text{Tissue i}}}{M_{\text{Blood}}} \qquad \text{(A7c)}$$

where $k^{+}_{\text{Tissue i}\rightarrow\text{Blood}}$ (day^{-1}) is the tissue i-to-blood uptake rate constant; $Q_{\text{Blood}\Leftrightarrow\text{Tissue i}}$ (kg day^{-1}) is the blood flow of tissue i; $k^{-}_{\text{Blood}\rightarrow\text{Tissue i}}$ (day^{-1}) is the blood-to-tissue i elimination rate constant; and $M_{\text{Tissue i}}$ (kg) is the mass of tissue i.

S2. Estimation of E_{uptake} values

In the present study, we approximated the E_{uptake} values of pesticides using the octanol–water partition coefficient (K_{OW}) (O’Connor et al., 2013). (O’Connor et al., 2013) and (Hendriks et al., 2001) have proposed a simple model for estimating the uptake efficiency of pesticides via oral ingestion based on a series of resistance rates and fractions of water and lipids in food, which can be expressed as follows:

$$E_{\text{uptake}} \approx \left(\frac{1}{\eta_W + \frac{\eta_M}{K_{OW}} + \frac{1}{\zeta\left(\left(1 - f_{\text{Lip}}^A\right)f_{\text{Lip}}K_{OW} + \left(1 - f_W^A\right)\left(1 - f_{\text{Lip}}\right)\right)}}\right)\left(\frac{1}{\left(1 - f_{\text{Lip}}^A\right)f_{\text{Lip}}K_{OW} + \left(1 - f_W^A\right)\left(1 - f_{\text{Lip}}\right)}\right)\frac{1}{\zeta} \quad \text{(A8a)}$$

$$E_{\text{uptake}} \approx \frac{1}{0.05\left(0.000037 + \frac{0.12}{K_{OW}}\right)(0.006K_{OW} + 0.485) + 1} \quad \text{(A8b)}$$

where η_W (3.7×10^{-5} day kg$^{-0.25}$) and η_M (0.12 day kg$^{-0.25}$) are the water layer and out membrane layer, respectively (O'Connor et al., 2013); ζ (0.05) is the food ingestion coefficient (Hendriks et al., 2001); f_W^A (0.5) (Schroeder, 1981; Steffens, 1996) and f_{Lip}^A (0.8) (Calder and Braun, 1983; Edwards, 1975) are water and lipid assimilation efficiencies, respectively; f_{Lip} (0.03, generic) is the lipid fraction (O'Connor et al., 2013). Figure A1 shows the simulated E_{Uptake} values of 736 pesticides that are plotted against K_{OW} values.

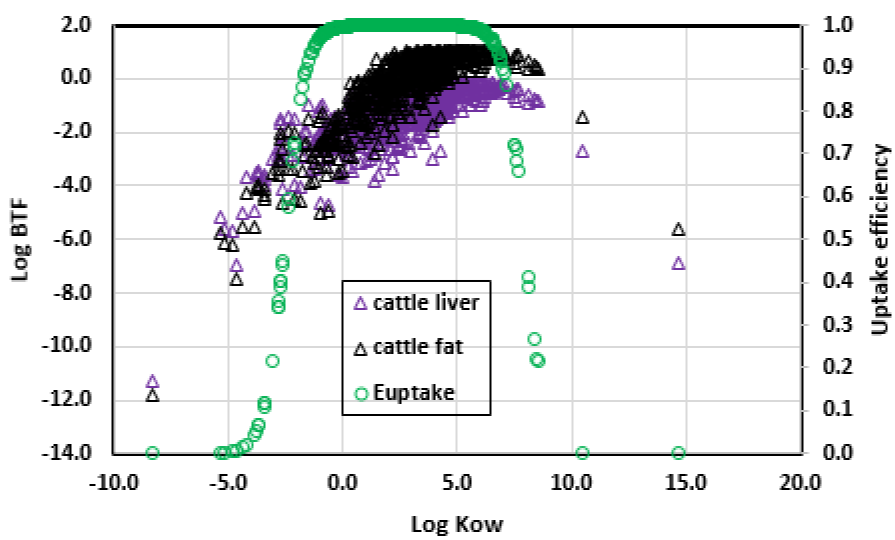


Figure A1. Simulated logarithms of the biotransfer factors (log BTF) and uptake efficiencies of 736 pesticides in cattle liver and fat plotted against log K_{OW} values.

S3. Estimation of $k_{m,Liver}$ values

In the present study, we approximated the pesticide $k_{m,Liver}$ values in the mammalian livers using the biotransformation rate constants in fish, for which an empirical multiplication factor of 5.0 was applied, assuming that the metabolic rates of pesticides in the mammalian livers are 5 times higher than those in fish (Arnot et al., 2009; Ciffroy and Radomyski, 2021). The biotransformation rate constants in fish were converted from biotransformation half-lives obtained from EPI Suite (BCFBAF V3.01, United States) (Arnot et al., 2009; Papa et al., 2014; USEPA, 2012). As EPI Suite provides half-lives at a temperature of 15°C, we adjusted the metabolic rates at the mammalian body temperature of 38.5°C (Aswini et al., 2017; Piccione et al., 2002) using a multiplication factor of $e^{0.01(38.5-15)}$ (Arnot et al., 2009). The data are provided in the supporting database.

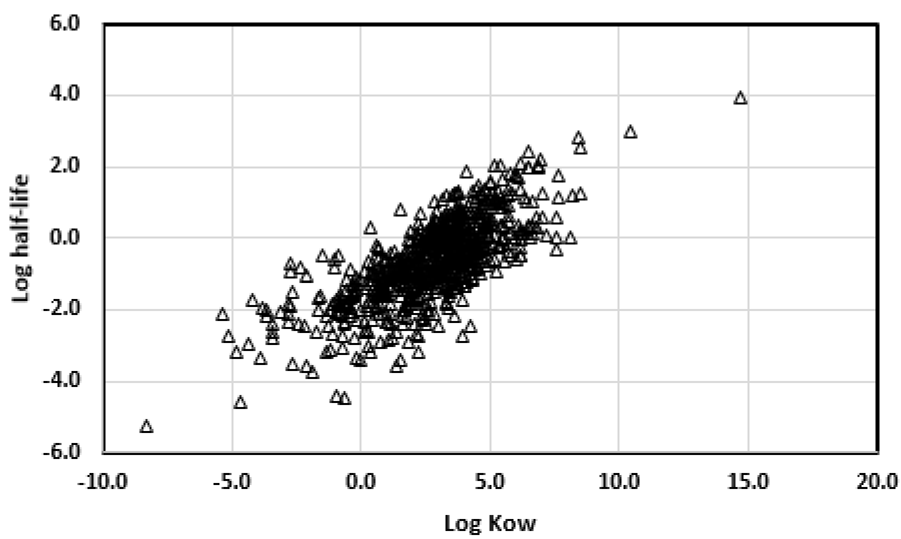


Figure A2. Logarithms of the half-lives of 736 pesticides (biotransformation in fish) (data obtained from EPI Suite) plotted against log K_{OW} values.

S4. Estimation of partition coefficients

In this study, we adopted the content-based method (i.e., three-phase partitioning approach) (Kelly and Gobas, 2003; Li, 2020) for estimating partition coefficients of pesticides as follows:

$$K_{i/i+1} = \frac{\theta_{Oct,i} + 0.035\theta_{NLO,i} + \frac{\theta_{Water,i}}{K_{OW}} \times \frac{\rho_{Octanol}}{\rho_{Water}}}{\theta_{Oct,i+1} + 0.035\theta_{NLO,i+1} + \frac{\theta_{Water,i+1}}{K_{OW}} \times \frac{\rho_{Octanol}}{\rho_{Water}}} \quad \text{(A9a)}$$

$$K_{Lung/Air} = \frac{K_{Lung/Water}}{\frac{K_{Air/Water}}{\rho_{Air}}} \quad \text{(A9b)}$$

where $\theta_{Oct,i}$ (g g^{-1}), $\theta_{NLO,i}$ (g g^{-1}), and $\theta_{Water,i}$ (g g^{-1}) are the lipid, non-lipid organics, and water contents of compartment i (or elimination medium i) of livestock animals, respectively; subscription i + 1 denotes compartment i + 1; $\rho_{Octanol}$ (kg L^{-1}) and ρ_{Water} (kg L^{-1}) are densities of octanol (0.824 kg L^{-1}) and water (1.0 kg L^{-1}), respectively, which are applied to convert the unit of $K_{i/i+1}$ to kg kg^{-1} (or unitless). $K_{Lung/Air}$, $K_{Lung/Water}$, and $K_{Air/Water}$ are the lung-air, lung-water, and air-water partition coefficients, respectively; ρ_{Air} (kg L^{-1}) is the density of the air (0.0012 kg L^{-1}), which is applied to convert the unit of $K_{Lung/Air}$ to kg kg^{-1} (or unitless). Nutrition compositions of animal raw products (or excretion media) for common livestock animals (i.e., cattle and sheep) are provided in Tables S1 and S2.

Table A1. Nutrition compositions of raw products and elimination media for cattle.

Media/Products	Contents (g g^{-1})				References	Notes
	Lipid (fat)	Non-lipid organics	Water	Others		
Blood	0.0023	0.1737	0.809	0.015	(Alencar, 1983; Duarte et al., 1999)	
Urine	0	0	0.95	0.05	(Gulhane et al., 2017)	Lipid and non-lipid organics are negligible.
Bile	0.0056	0.0004	0.894	0.1	(Hertrampf and Piedad-Pascual, 2000)	Lipid content is the sum of lecithin and cholesterol
Milk	0.037	0.084	0.872	0.007	(Guetouache et al., 2014)	Non-lipid organics include proteins and lactose.
Liver	0.036	0.243	0.708	0.013	(NutritionData, 2018)	
Kidney	0.031	0.177	0.779	0.013	(NutritionData, 2018)	
Muscle	0.028	0.232	0.731	0.009	(Williams, 2007)	Estimated by lean tissues.
Fat	0.8	0	0.2	0	(Murphy, 1992)	Generic (adipose tissue).
Lung	0.025	0.162	0.794	0.0098	(USDA, 2021)	
Mammary gland	0.15	0.13	0.72	0	(Calorie-charts, 2018)	No information was found about nutrition composition of mammary gland; we applied the data of beef udder based on a cached webpage.

Table A2. Nutrition compositions of raw products and elimination media for sheep.

Media/Products	Contents (g g^{-1})				References	Notes
	Lipid (fat)	Non-lipid organics	Water	Others		
Blood	0.005	0.165	0.82	0.01		Estimated.
Urine	0	0	0.95	0.05		Estimated; lipid and non-lipid organics are negligible.
Bile	0.0056	0.0004	0.894	0.1		Applying cattle's data.
Milk	0.07	0.114	0.807	0.009	(NutritionData, 2018)	Non-lipid organics include proteins and lactose.
Liver	0.05	0.222	0.714	0.014	(NutritionData, 2018)	
Kidney	0.03	0.165	0.792	0.013	(NutritionData, 2018)	
Muscle	0.047	0.215	0.732	0.006	(Williams, 2007)	Estimated by lean tissues.
Fat	0.8	0	0.2	0	(Murphy, 1992)	Generic (adipose tissue).
Lung	0.026	0.167	0.797	0.011	(USDA, 2021)	
Mammary gland	0.15	0.13	0.72	0		Estimated by beef udder.

S5. Physiological variables

Physiological variables for common livestock animals (cattle and sheep) are provided in Tables A3 and A4. Generic values of 1.0, 1.1, and 0.9 kg L^{-1} were applied as the densities of mammal organs (Ciffroy and Radomyski, 2021), muscle, and fat, respectively. A generic value of 1.0 kg L^{-1} was applied as the density of mammal blood, urine, hepatic bile, and milk (Al-Atabi et al., 2012; Vitello et al., 2015).

Table A3. Summary of the model input variables for cattle.

Variables	Symbol	Unit	Value	Note
Food intake rate	IR_{Food}	kg day^{-1}	20	Estimated (dry mass) based on 3% of the body mass (600 kg)
Exhalation rate	$ER_{Exhalation}$	kg day^{-1}	260	Estimated from the tidal volume and the breath per minute of cattle with the air density of 0.0012 kg L^{-1} (Stevens, 1981).
Urine excretion rate	ER_{Urine}	kg day^{-1}	20	Estimated from the urine volume per body weight per day (Ashara and Shah, 2016).
Bile excretion rate	ER_{Bile}	kg day^{-1}	6.5	(Symonds et al., 1982) and (Sutton, 1985) estimated the combined bile and pancreatic secretion rate of 13 L day^{-1}. It was assumed that the bile secretion rate is half of the pancreatic juice secretion rate.
Milk excretion rate	ER_{Milk}	kg day^{-1}	32.6	Estimated (Løvendahl and Sehested, 2016)
Body mass	---	kg	600	Generic
Blood mass	M_{Blood}	kg	22.8	Estimated (3.8% of the body mass) (Lautz et al., 2020)
Liver mass	M_{Liver}	kg	7.8	Estimated (1.3% of the body mass) (Lautz et al., 2020)
Kidney mass	M_{Kidney}	kg	1.2	Estimated (0.2% of the body mass) (Lautz et al., 2020)
Lung mass	M_{Lung}	kg	4.8	Estimated (0.8% of the body mass) (Lautz et al., 2020)
Fat mass	M_{Fat}	kg	110.4	Estimated (adipose tissue) (18.4% of the body mass) (Lautz et al., 2020)
Muscle mass	M_{Muscle}	kg	240	Estimated (40% of the body mass; averaged from dairy and beef cattle) (Lautz et al., 2020)
Mammary gland mass	$M_{Mammary\ gland}$	kg	13.2	Estimated (2.2% of the body mass) (Lautz et al., 2020)
Blood flow rate of liver	$Q_{Blood \Leftrightarrow Liver}$	kg day^{-1}	56739	Estimated from dairy cattle (sum of hepatic artery and portal vein flows) (Lautz et al., 2020)
Blood flow rate of kidney	$Q_{Blood \Leftrightarrow Kidney}$	kg day^{-1}	1375	Estimated from dairy cattle (Lautz et al., 2020)
Blood flow rate of lung	$Q_{Blood \Leftrightarrow Lung}$	kg day^{-1}	2579	Estimated from sheep (Lautz et al., 2020)
Blood flow rate of fat	$Q_{Blood \Leftrightarrow Fat}$	kg day^{-1}	5846	Estimated from dairy cattle (Lautz et al., 2020)
Blood flow rate of muscle	$Q_{Blood \Leftrightarrow Muscle}$	kg day^{-1}	1633	Estimated from dairy cattle (Lautz et al., 2020)
Blood flow rate of mammary gland	$Q_{Blood \Leftrightarrow Mammary\ gland}$	kg day^{-1}	14185	Estimated from dairy cattle (Lautz et al., 2020)

Table A4. Summary of the model input variables for sheep.

Variables	Symbol	Unit	Value	Note
Food intake rate	IR_{Food}	kg day^{-1}	2.1	Estimated (dry mass) based on 3% of the body mass (70 kg)
Exhalation rate	$ER_{Exhalation}$	kg day^{-1}	25	Estimated from the tidal volume and the breath per minute of sheep (30 bpm) with the air density of 0.0012 kg L^{-1} (Gomes da Silva et al., 2002).
Urine excretion rate	ER_{Urine}	kg day^{-1}	3.0	Estimated (Marsden et al., 2020).
Bile excretion rate	ER_{Bile}	kg day^{-1}	0.5	Estimated (Brown, 1967).
Milk excretion rate	ER_{Milk}	kg day^{-1}	1.5	The milk excretion rate was estimated from Manchega and Lacaune dairy ewes (Castillo et al., 2009).
Body mass	---	kg	70	Generic
Blood mass	M_{Blood}	kg	3.3	Estimated (4.7% of the body mass) (Lautz et al., 2020)
Liver mass	M_{Liver}	kg	1.0	Estimated (1.5% of the body mass) (Lautz et al., 2020)
Kidney mass	M_{Kidney}	kg	0.2	Estimated (0.3% of the body mass) (Lautz et al., 2020)
Lung mass	M_{Lung}	kg	0.8	Estimated (1.1% of the body mass) (Lautz et al., 2020)
Fat mass	M_{Fat}	kg	13.4	Estimated (adipose tissue) (19.2% of the body mass) (Lautz et al., 2020)
Muscle mass	M_{Muscle}	kg	24.7	Estimated (35.3% of the body mass) (Lautz et al., 2020)
Mammary gland mass	$M_{Mammary\ gland}$	kg	1.2	Estimated (1.7% of the body mass) (Lautz et al., 2020)
Blood flow rate of liver	$Q_{Blood \Leftrightarrow Liver}$	kg day^{-1}	3788	Estimated (sum of hepatic artery and portal vein flows) (Lautz et al., 2020)
Blood flow rate of kidney	$Q_{Blood \Leftrightarrow Kidney}$	kg day^{-}	1318	Estimated (Lautz et al., 2020)
Blood flow rate of lung	$Q_{Blood \Leftrightarrow Lung}$	kg day^{-}	276	Estimated (Lautz et al., 2020)
Blood flow rate of fat	$Q_{Blood \Leftrightarrow Fat}$	kg day^{-}	212	Estimated (Lautz et al., 2020)
Blood flow rate of muscle	$Q_{Blood \Leftrightarrow Muscle}$	kg day^{-}	3060	Estimated (Lautz et al., 2020)
Blood flow rate of mammary gland	$Q_{Blood \Leftrightarrow Mammary\ gland}$	kg day^{-1}	682	Estimated (Lautz et al., 2020)

S6. Derivation of BTF values

According to Eq. (7), the $\mathrm{BTF_i}$ is equal to the $\mathrm{C_i}$ value (i.e., $\frac{m_i}{M_i}$) by setting the $\mathrm{C_{Food}}$ value as 1.0 mg kg^{-1}. Then, the analytical solutions of $\mathrm{BTF_i}$ values of the pesticide using the value of 1.0 mg kg^{-1} for $\mathrm{C_{Food}}$ can be expressed as follows:

$$\mathrm{BTF_{Blood}} = \frac{1}{\mathrm{M_{Blood}}}\left(\frac{k^{+}_{\mathrm{Liver\rightarrow Blood}}\mathrm{E_{uptake}IR_{Food}}}{k^{-}_{\mathrm{Liver\rightarrow Blood}} + k_{\mathrm{m,Liver}} + k_{\mathrm{e,Blie}}}\right)\Bigg[\sum k^{-}_{\mathrm{Blood\rightarrow Tissue\ i}} - \left(\frac{k^{+}_{\mathrm{Liver\rightarrow Blood}}k^{+}_{\mathrm{Blood\rightarrow Liver}}}{k^{-}_{\mathrm{Liver\rightarrow Blood}} + k_{\mathrm{m,Liver}} + k_{\mathrm{e,Blie}}} + \frac{k^{+}_{\mathrm{Kidney\rightarrow Blood}}k^{+}_{\mathrm{Blood\rightarrow Kidney}}}{k^{-}_{\mathrm{Kidney\rightarrow Blood}} + k_{\mathrm{e,Urine}}} + \frac{k^{+}_{\mathrm{Lung\rightarrow Blood}}k^{+}_{\mathrm{Blood\rightarrow Lung}}}{k^{-}_{\mathrm{Lung\rightarrow Blood}} + k_{\mathrm{e,Exhalation}}} + \frac{k^{+}_{\mathrm{Mammary\ gland\rightarrow Blood}}k^{+}_{\mathrm{Blood\rightarrow Mammary\ gland}}}{k^{-}_{\mathrm{Mammary\ gland\rightarrow Blood}} + k_{\mathrm{e,Milk}}} + \frac{k^{+}_{\mathrm{Fat\rightarrow Blood}}k^{+}_{\mathrm{Blood\rightarrow Fat}}}{k^{-}_{\mathrm{Fat\rightarrow Blood}}} + \frac{k^{+}_{\mathrm{Muscle\rightarrow Blood}}k^{+}_{\mathrm{Blood\rightarrow Muscle}}}{k^{-}_{\mathrm{Muscle\rightarrow Blood}}}\right)\Bigg]^{-1} \tag{A10a}$$

$$\mathrm{BTF_{Liver}} = \frac{1}{\mathrm{M_{Liver}}}\left(\frac{\mathrm{E_{uptake}IR_{Food}} + k^{+}_{\mathrm{Blood\rightarrow Liver}}\mathrm{BTF_{Blood}M_{Blood}}}{k^{-}_{\mathrm{Liver\rightarrow Blood}} + k_{\mathrm{m,Liver}} + k_{\mathrm{e,Blie}}}\right) \tag{A10b}$$

$$\mathrm{BTF_{Kidney}} = \frac{1}{\mathrm{M_{Kidney}}}\left(\frac{k^{+}_{\mathrm{Blood\rightarrow Kidney}}\mathrm{BTF_{Blood}M_{Blood}}}{k^{-}_{\mathrm{Kidney\rightarrow Blood}} + k_{\mathrm{e,Urine}}}\right) \tag{A10c}$$

$$\mathrm{BTF_{Lung}} = \frac{1}{\mathrm{M_{Lung}}}\left(\frac{k^{+}_{\mathrm{Blood\rightarrow Lung}}\mathrm{BTF_{Blood}M_{Blood}}}{k^{-}_{\mathrm{Lung\rightarrow Blood}} + k_{\mathrm{e,Exhalation}}}\right) \tag{A10d}$$

$$\mathrm{BTF_{Fat}} = \frac{1}{\mathrm{M_{Fat}}}\left(\frac{k^{+}_{\mathrm{Blood\rightarrow Fat}}\mathrm{BTF_{Blood}M_{Blood}}}{k^{-}_{\mathrm{Fat\rightarrow Blood}}}\right) \tag{A10e}$$

$$\mathrm{BTF_{Muscle}} = \frac{1}{\mathrm{M_{Muscle}}}\left(\frac{k^{+}_{\mathrm{Blood\rightarrow Muscle}}\mathrm{BTF_{Blood}M_{Blood}}}{k^{-}_{\mathrm{Muscle\rightarrow Blood}}}\right) \tag{A10f}$$

$$\mathrm{BTF_{Mammary\ gland}} = \frac{1}{\mathrm{M_{ammary\ gland}}}\left(\frac{k^{+}_{\mathrm{Blood\rightarrow Mammary\ gland}}\mathrm{BTF_{Blood}M_{Blood}}}{k^{-}_{\mathrm{Mammary\ gland\rightarrow Blood}} + k_{\mathrm{e,Milk}}}\right) \tag{A10g}$$

$$\mathrm{BTF_{Milk}} = \frac{\mathrm{BTF_{Mammary\ gland}}}{\mathrm{K_{Mammary\ gland/Milk}}} \tag{A10h}$$

S7. Uptake-to-elimination ratios

The uptake-to-elimination ratio ($R_{\frac{U}{B},i}$) of the pesticide in animal tissue i is defined as the constant rate ratio of the uptake to elimination process in tissue i. Then, the uptake-to-elimination ratios in selected animal tissues can be expressed as follows:

$$R_{\frac{U}{B},Liver} = \begin{cases} \dfrac{\dfrac{E_{uptake} IR_{Food}}{M_{Liver}}}{k^{-}_{Liver\rightarrow Blood} + k_{m,Liver} + k_{e,Blie}}; from\ food\ in\ gut\ lumen \\ \dfrac{k^{+}_{Blood\rightarrow Liver}}{k^{-}_{Liver\rightarrow Blood} + k_{m,Liver} + k_{e,Blie}}; from\ blood \end{cases} \quad \text{(A11a)}$$

$$R_{\frac{U}{B},Kidney} = \frac{k^{+}_{Blood\rightarrow Kidney}}{k^{-}_{Kidney\rightarrow Blood} + k_{e,Urine}} \quad \text{(A11b)}$$

$$R_{\frac{U}{B},Lung} = \frac{k^{+}_{Blood\rightarrow Lung}}{k^{-}_{Lung\rightarrow Blood} + k_{e,Exhalation}} \quad \text{(A11c)}$$

$$R_{\frac{U}{B},Fat} = \frac{k^{+}_{Blood\rightarrow Fat}}{k^{-}_{Fat\rightarrow Blood}} \quad \text{(A11d)}$$

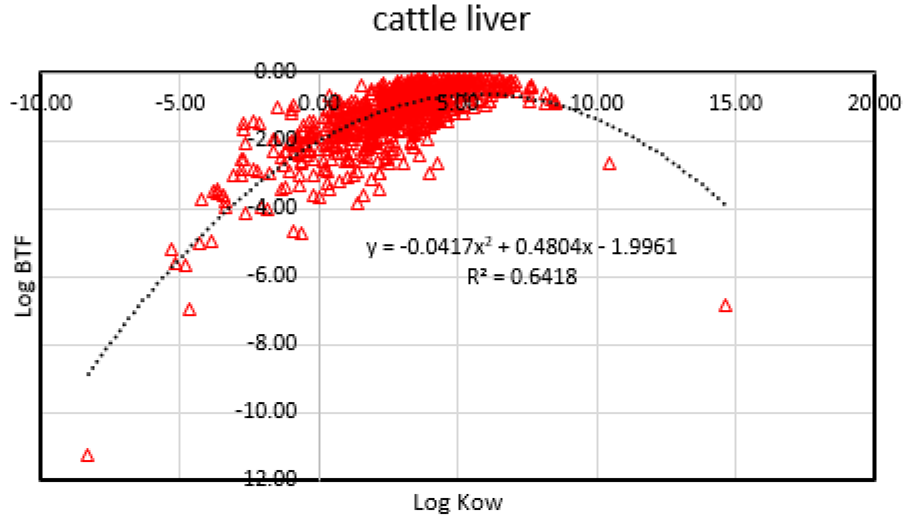
$$R_{\frac{U}{B},Muscle} = \frac{k^{+}_{Blood\rightarrow Muscle}}{k^{-}_{Muscle\rightarrow Blood}} \quad \text{(A11e)}$$

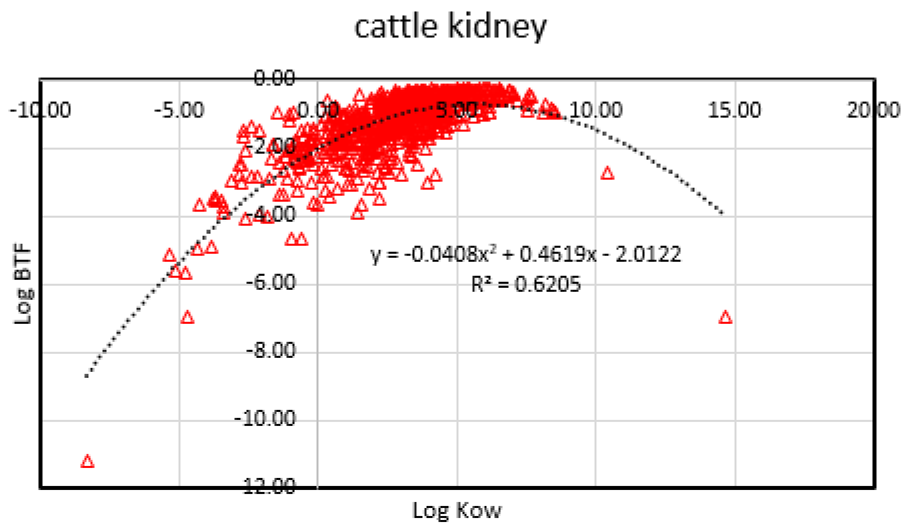
$$R_{\frac{U}{B},Mammary\ gland} = \frac{k^{+}_{Blood\rightarrow Mammary\ gland}}{k^{-}_{Mammary\ gland\rightarrow Blood} + k_{e,Milk}} \quad \text{(A11f)}$$

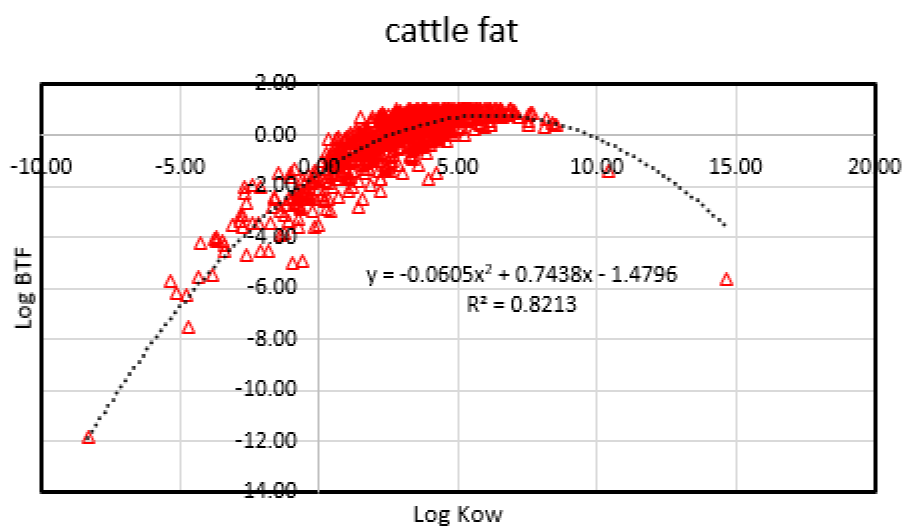
$$R_{\frac{U}{B},Milk} = \frac{R_{\frac{U}{B},Mammary\ gland}}{K_{Mammary\ gland/Milk}} \quad \text{(A11g)}$$

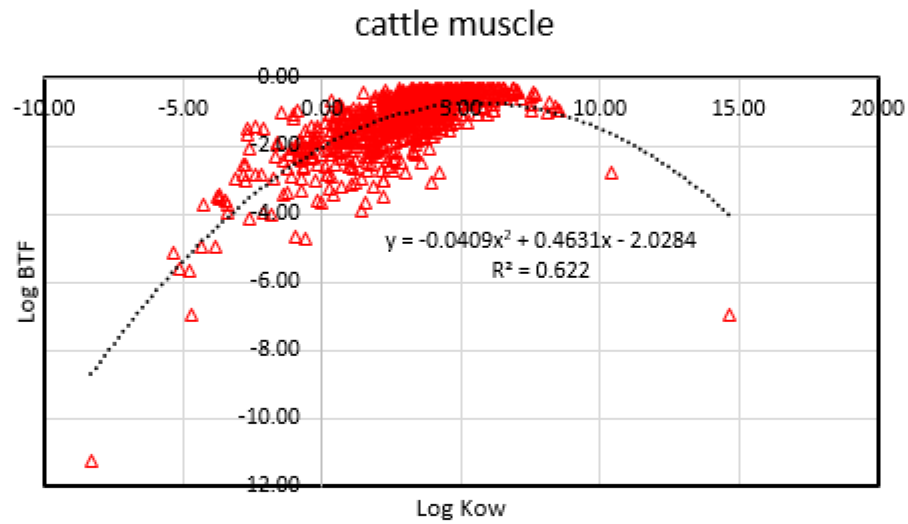
S8. Model parameterization (BTF vs log K_{OW})

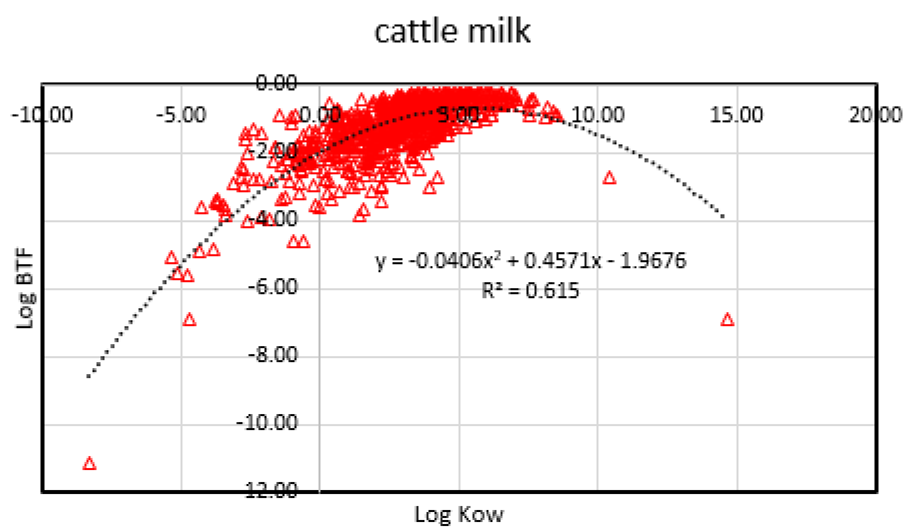
The relationship between the simulated log BTF values of 736 pesticides in foods of animal origin and log K_{OW} values is illustrated in Figure A3.

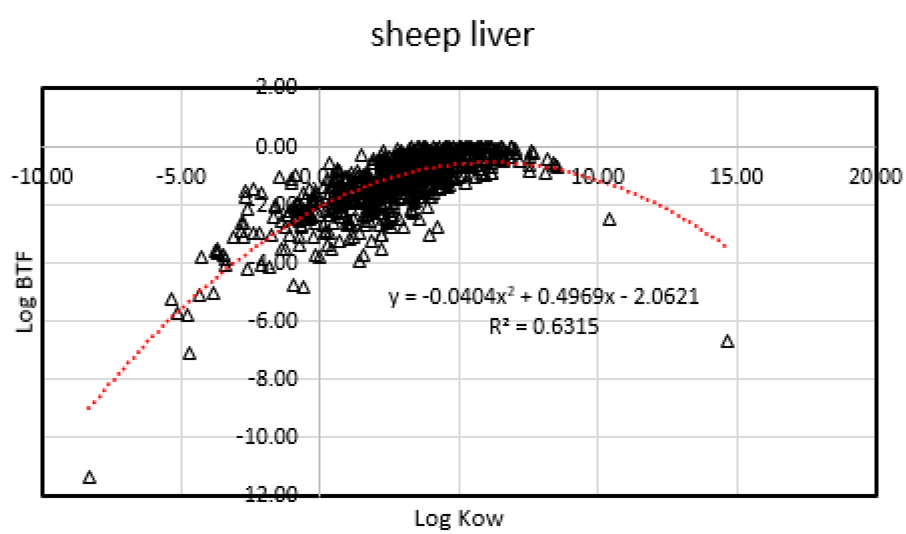

cattle liver
0.00
-2.00
-4.00
-6.00
-8.00
-10.00
-12.00
-10.00
-5.00
0.00
5.00
10.00
15.00
20.00
y = -0.0417x² + 0.4804x - 1.9961
R² = 0.6418
Log BTF
Log Kow


cattle kidney
0.00
-2.00
-4.00
-6.00
-8.00
-10.00
-12.00
-10.00
-5.00
0.00
5.00
10.00
15.00
20.00
y = -0.0408x² + 0.4619x - 2.0122
R² = 0.6205
Log BTF
Log Kow

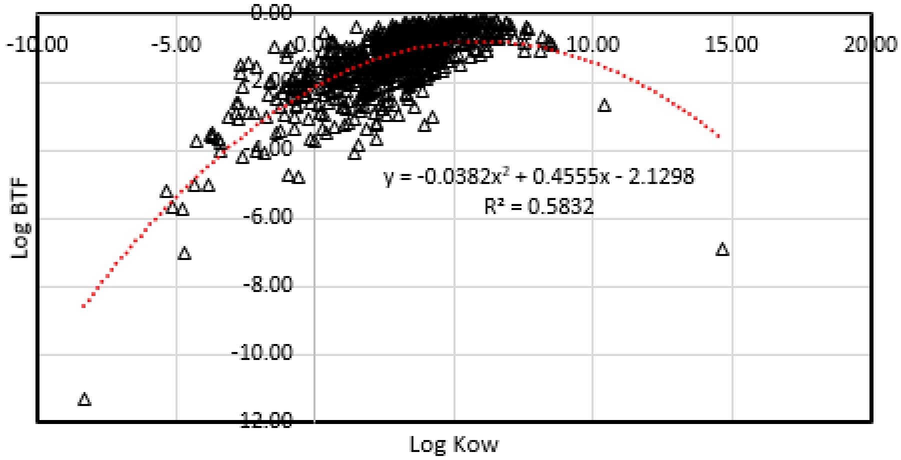

cattle fat
2.00
0.00
-2.00
-4.00
-6.00
-8.00
-10.00
-12.00
-14.00
-10.00
-5.00
0.00
5.00
10.00
15.00
20.00
y = -0.0605x² + 0.7438x - 1.4796
R² = 0.8213
Log BTF
Log Kow


cattle muscle
0.00
-10.00
-5.00
0.00
5.00
10.00
15.00
20.00
-2.00
-4.00
-6.00
-8.00
-10.00
-12.00
Log BTF
Log Kow
y = -0.0409x² + 0.4631x - 2.0284
R² = 0.622

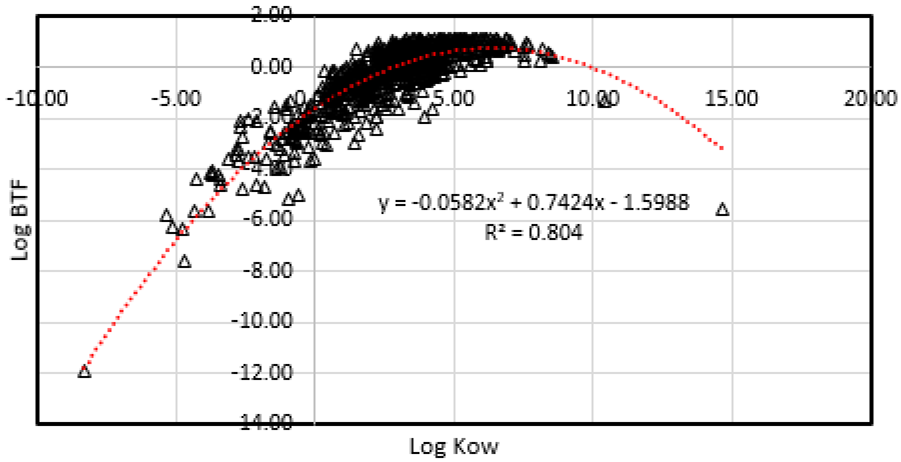

cattle milk
0.00
-10.00
-5.00
0.00
5.00
10.00
15.00
20.00
-2.00
-4.00
-6.00
-8.00
-10.00
-12.00
Log BTF
Log Kow
y = -0.0406x² + 0.4571x - 1.9676
R² = 0.615


sheep liver
2.00
0.00
-10.00
-5.00
0.00
5.00
10.00
15.00
20.00
-2.00
-4.00
-6.00
-8.00
-10.00
-12.00
Log BTF
Log Kow
y = -0.0404x² + 0.4969x - 2.0621
R² = 0.6315

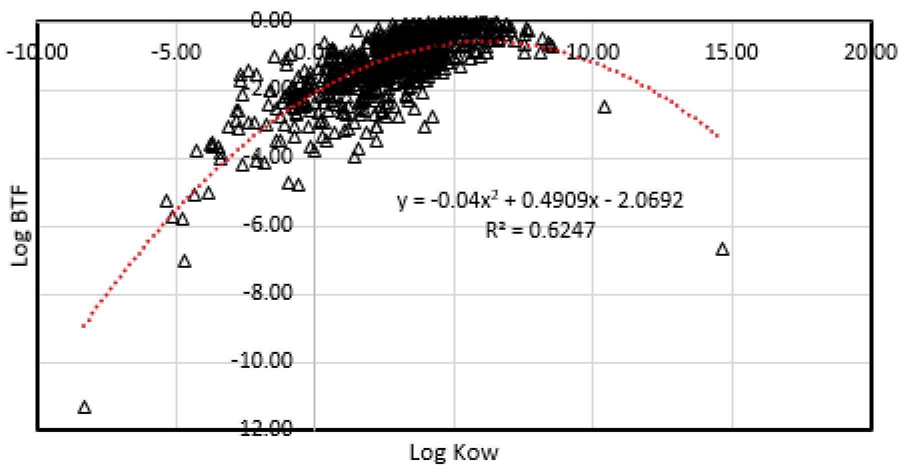
sheep kidney



sheep fat



sheep muscle



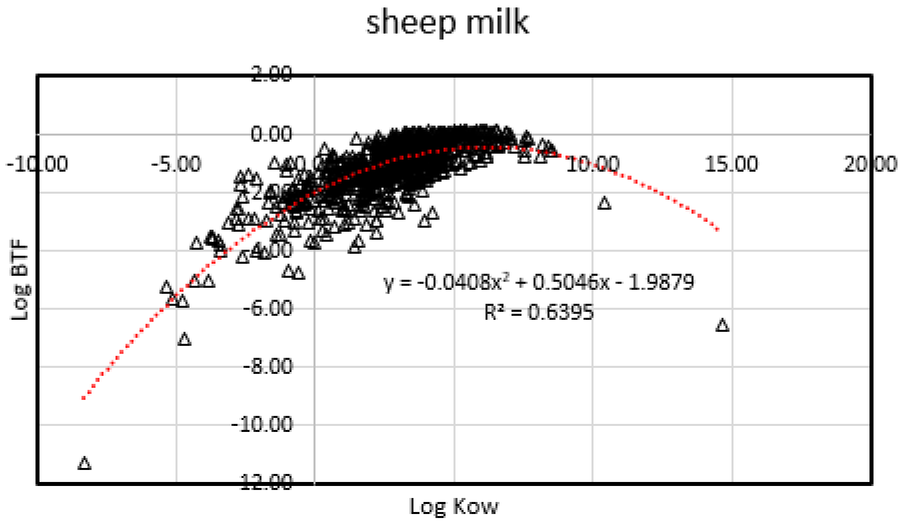


Figure A3. Relationships between the simulated log BTF values of 736 pesticides in foods of animal origin and log K_{OW} values.

S9. Linear relationships of BTFs among cattle and sheep products

The linear relationships of BTFs among cattle and sheep products simulated for 736 pesticides are shown in the following figures. The fitted linear equations are given by the following equations.

Using the BTF of the cattle liver (BTF^{Cattle}_{Liver}) as the surrogate, pesticide BTFs of the other cattle products can be expressed as follows:

$$BTF^{Cattle}_{Kidney} = 0.83 \times BTF^{Cattle}_{Liver} \quad \text{(A12a)}$$

$$BTF^{Cattle}_{Fat} = 18.10 \times BTF^{Cattle}_{Liver} \quad \text{(A12b)}$$

$$BTF^{Cattle}_{Muscle} = 0.81 \times BTF^{Cattle}_{Liver} \quad \text{(A12c)}$$

$$BTF^{Cattle}_{Milk} = 0.88 \times BTF^{Cattle}_{Liver} \quad \text{(A12d)}$$

Using the BTF in sheep liver (BTF_{Liver}^{Sheep}) as the surrogate product, pesticide BTFs in sheep products can be expressed as follows:

$$BTF_{Kidney}^{Sheep} = 0.62 \times BTF_{Liver}^{Sheep} \quad \text{(A13a)}$$

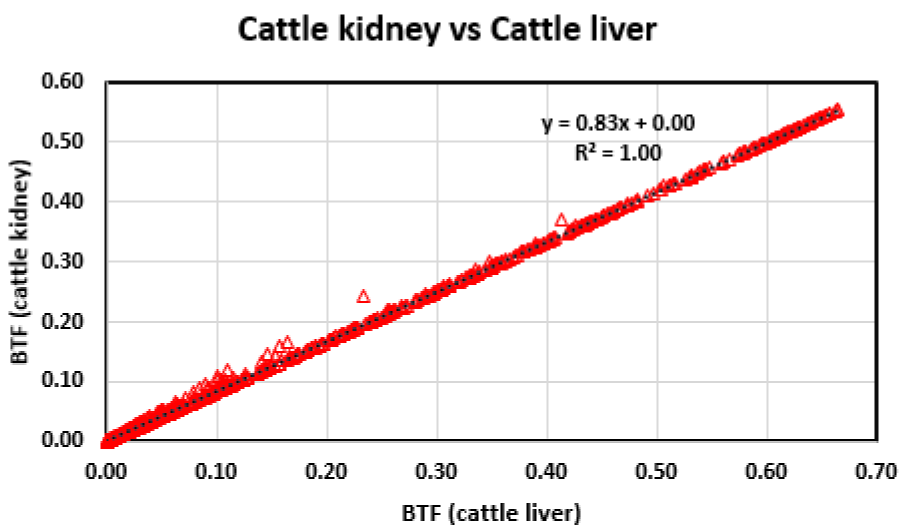
$$BTF_{Fat}^{Sheep} = 13.88 \times BTF_{Liver}^{Sheep} \quad \text{(A13b)}$$

$$BTF_{Muscle}^{Sheep} = 0.94 \times BTF_{Liver}^{Sheep} \quad \text{(A13c)}$$

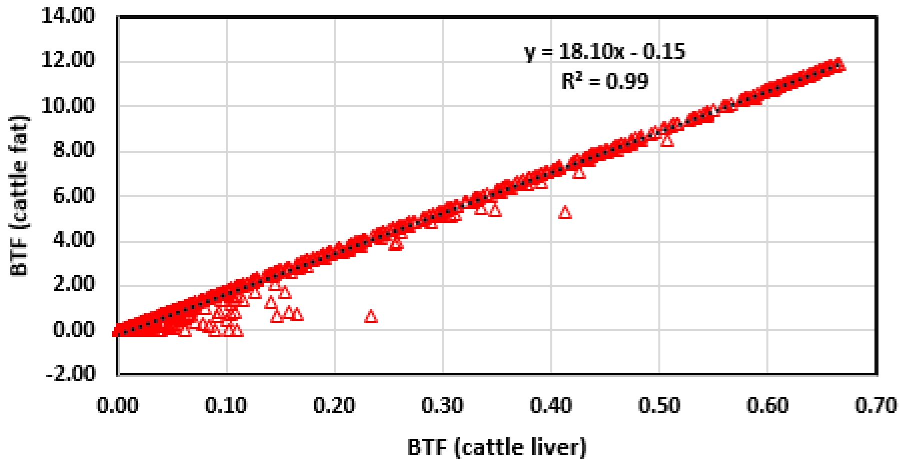
$$BTF_{Milk}^{Sheep} = 1.26 \times BTF_{Liver}^{Sheep} \quad \text{(A13d)}$$

The fitted linear relationship between BTF_{Liver}^{Cattle} and BTF_{Liver}^{Sheep} can be expressed as follows:

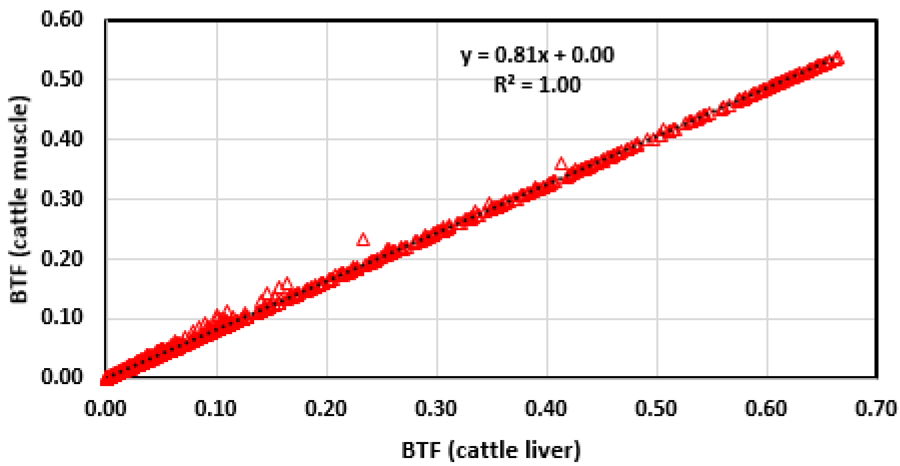
$$BTF_{Liver}^{Sheep} = 1.42 \times BTF_{Liver}^{Cattle} \quad \text{(A14)}$$



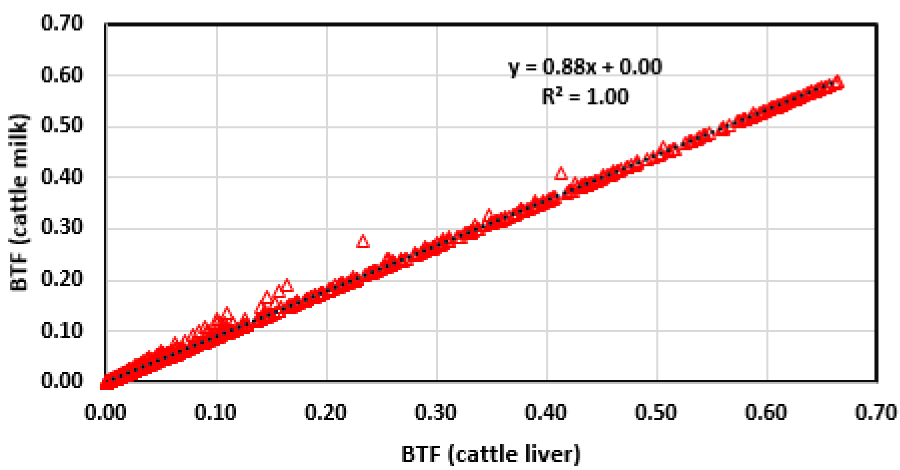
Cattle fat vs Cattle liver

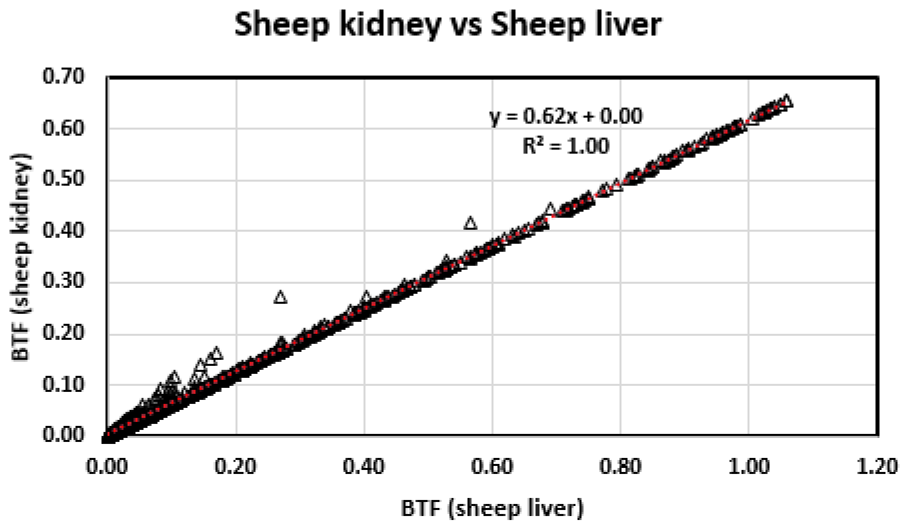


Cattle muscle vs Cattle liver

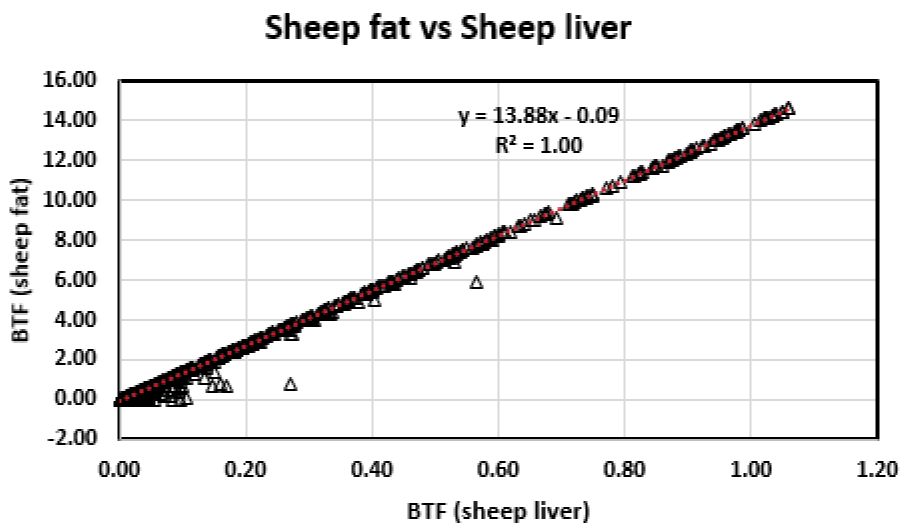


Cattle milk vs Cattle liver

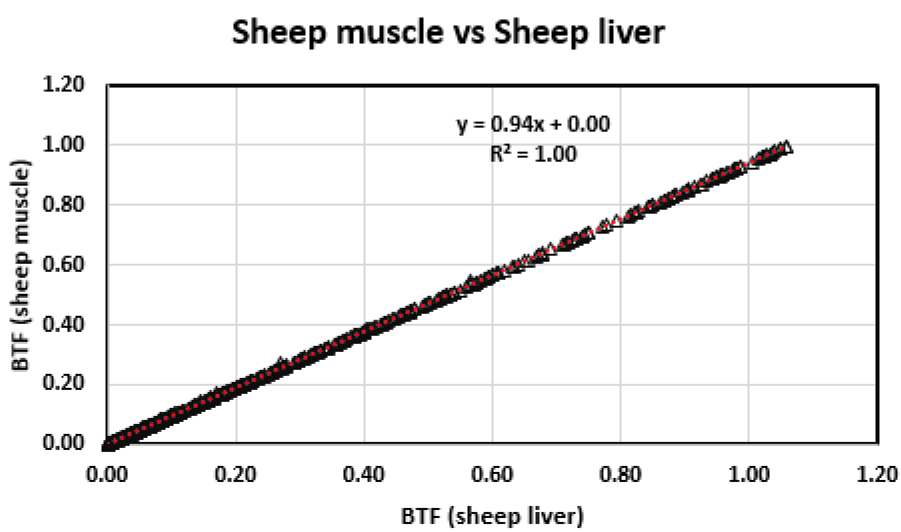




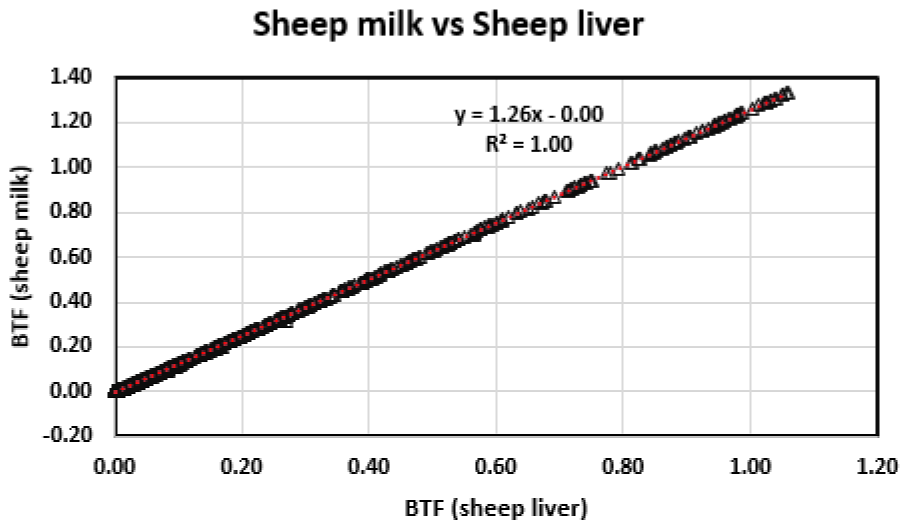
Sheep kidney vs Sheep liver
y = 0.62x + 0.00
R² = 1.00
BTF (sheep kidney)
BTF (sheep liver)



Sheep fat vs Sheep liver
y = 13.88x - 0.09
R² = 1.00
BTF (sheep fat)
BTF (sheep liver)



Sheep muscle vs Sheep liver
y = 0.94x + 0.00
R² = 1.00
BTF (sheep muscle)
BTF (sheep liver)



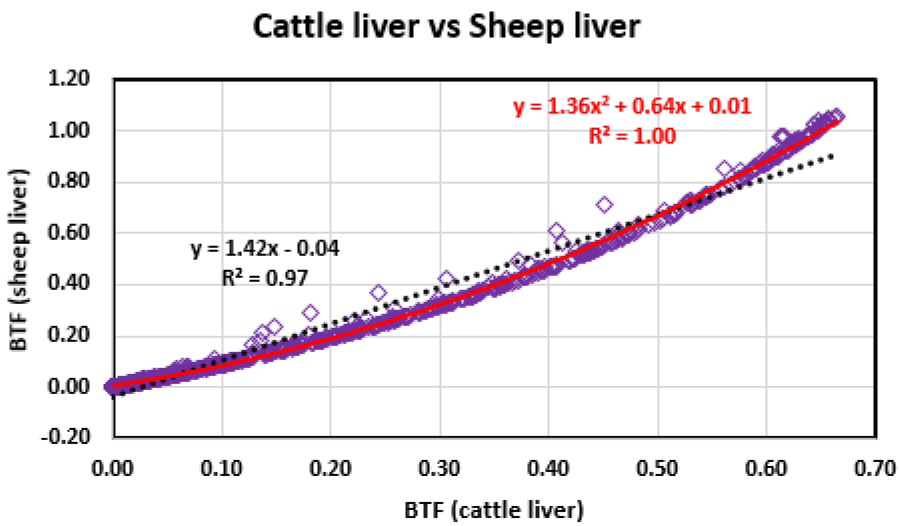


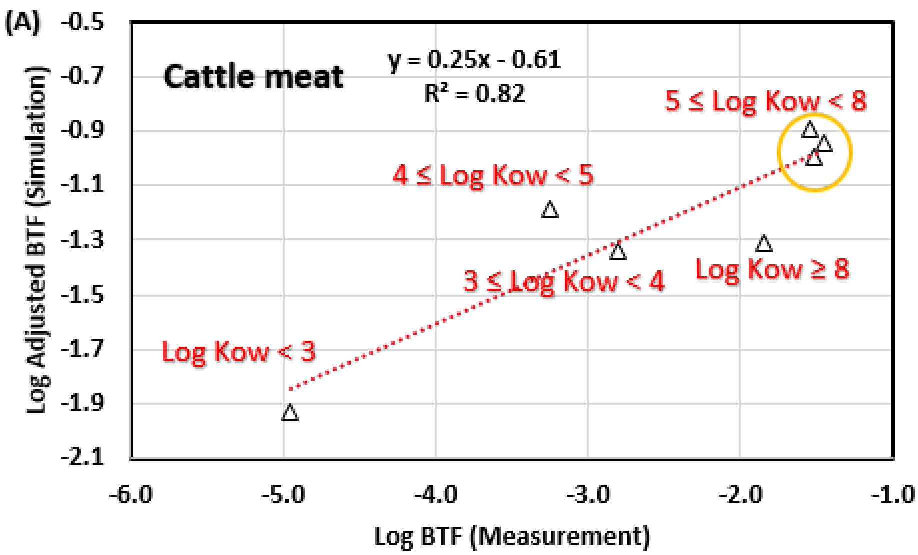
Figure A4. Fitted linear relationships of simulated BTFs of 736 pesticides in cattle and sheep products (liver, kidney, fat, muscle, and milk).

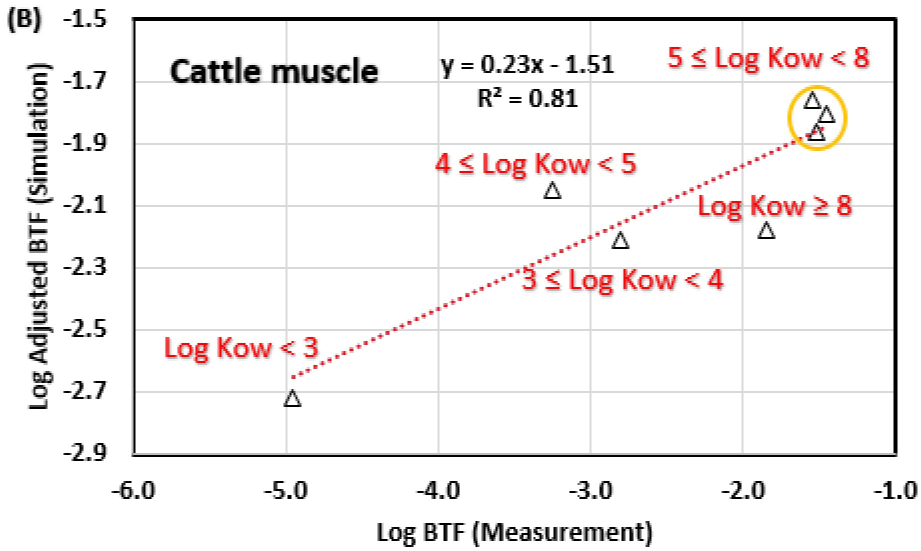
S10. Model evaluation

Table A5. Means of log BTF[A] values of organic compounds in cattle meat, muscle, and milk for each log K_{OW} intervals.

Log Kow	Average log BTF[A]					
	Measurement (meat)	Model (meat)	Measurement (meat)	Model (muscle)	Measurement (milk)	Model (milk)
< 3	-4.95	-1.93	-4.95	-2.72	-5.62	-2.67
3-4	-2.81	-1.34	-2.81	-2.21	-3.29	-2.17
4-5	-3.25	-1.18	-3.25	-2.05	-3.03	-2.01
5-6	-1.46	-0.94	-1.46	-1.81	-2.47	-1.77
6-7	-1.55	-0.89	-1.55	-1.76	-2.35	-1.72
7-8	-1.53	-1.00	-1.53	-1.86	-2.10	-1.82
≥ 8	-1.85	-1.31	-1.85	-2.18	-2.38	-2.14

Note: mean absolute errors between the measurement and simulation for meat, muscle, and milk are 0.96, 0.50, and 0.67, respectively.





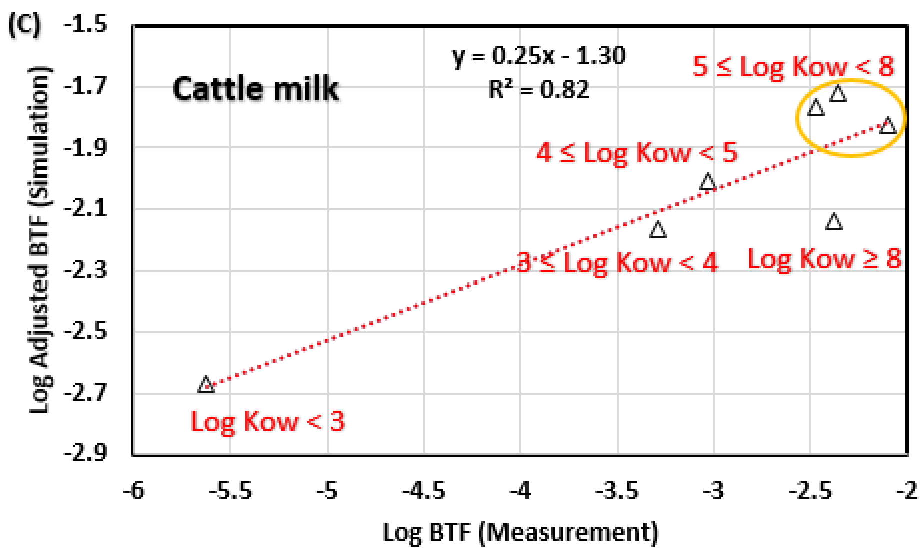


Figure A5. (A) The means of the simulated log BTF^A values of cattle meat for pesticides in each log K_{OW} interval plotted against those of measurement (meat). (B) The means of the simulated log BTF^A values of cattle muscle for pesticides in each log K_{OW} interval plotted against those of measurement (meat). (C) The means of the simulated log BTF values of cattle milk for pesticides in each log K_{OW} interval plotted against those of measurement.

S11. Sensitivity analysis

Sensitivity analysis of the DDT $K_{Milk/Blood}$ was conducted for evaluating the impacts of nutritional compositions of cattle raw products on the output results.

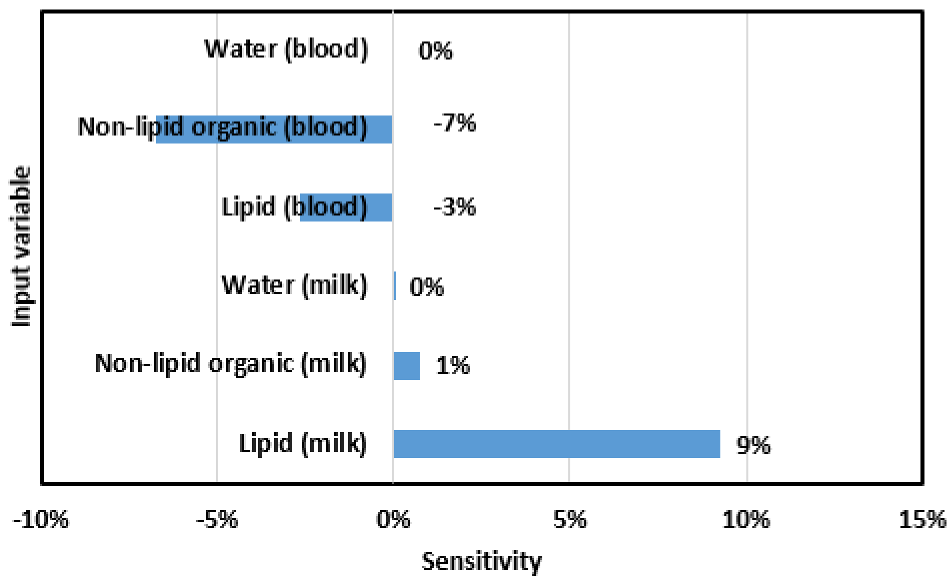


Figure A6. Sensitivity analysis of the DDT $K_{Milk/Blood}$ (cattle) by varying 10% of the input variables (nutritional compositions). Water (blood) – water content of blood, non-lipid organic (blood) – non-lipid organic content of blood, lipid (blood) – lipid content of blood, Water (milk) – water content of milk, non-lipid organic (milk) – non-lipid organic content of milk, and lipid (milk) – lipid content of milk.

S12. Uncertainty analysis

In this section, the spreadsheet-based approach for generating uncertainty intervals and customizing the BTF simulation for specific livestock varieties is illustrated by using the data collected by Rossow et al. (2020) (Table A6). Chlorothalonil, ethephon, and glyphosate was used as examples to show the output results for each type of dairy cows (Table A6), and ratios of BTF_{Milk}

between dairy cows 1 and 2 (control group) were plotted against log K_{OW} for the selected 736 pesticides (Figure A7). Readers can apply the same approach for their chemicals/mammals of interest.

Table A6. Model input variables for control and enzyme-treated dairy cows.

Model input variables	Input positions in the spreadsheet (Supplementary database)	Dairy cow 1		Dairy cow 2		Dairy cow 3	
		Control	Enzyme-treated	Control	Enzyme-treated	Control	Enzyme-treated
Fat content (%)	Sheet 'Cattle' – Table 'Media/Products'	4.56	4.46	3.80	3.86	4.03	4.02
Non-lipid organic content (%)		2.91	2.92	2.94	2.91	2.95	2.92
Cow body mass (kg)	Sheet 'Cattle' – Table 'Physiological variables'	654	656	564	565	635	637
Milk excretion rate (kg d^{-1})		37.6	38.2	37.9	41.5	43.5	43.7
Model output results (BTF_{Milk})							
Chlorothalonil (log K_{OW} = 3.05)		0.31	0.30	0.29	0.27	0.27	0.27
Ethephon (log K_{OW} = -0.22)		0.02	0.02	0.02	0.02	0.02	0.02
Glyphosate (log K_{OW} = -3.40)		2.3×10^{-4}	2.3×10^{-4}	2.3×10^{-4}	2.3×10^{-4}	2.3×10^{-4}	2.3×10^{-4}

Note:

Data were taken from Rossow et al. (2020), and average values were used.

Non-lipid organic contents were approximated using the protein contents provide by Rossow et al. (2020).

Water contents for the BTF simulation in the Spreadsheet were estimated based on the mass balance, with a default value of 0.007 g g^{-1} for 'others' (inorganics).

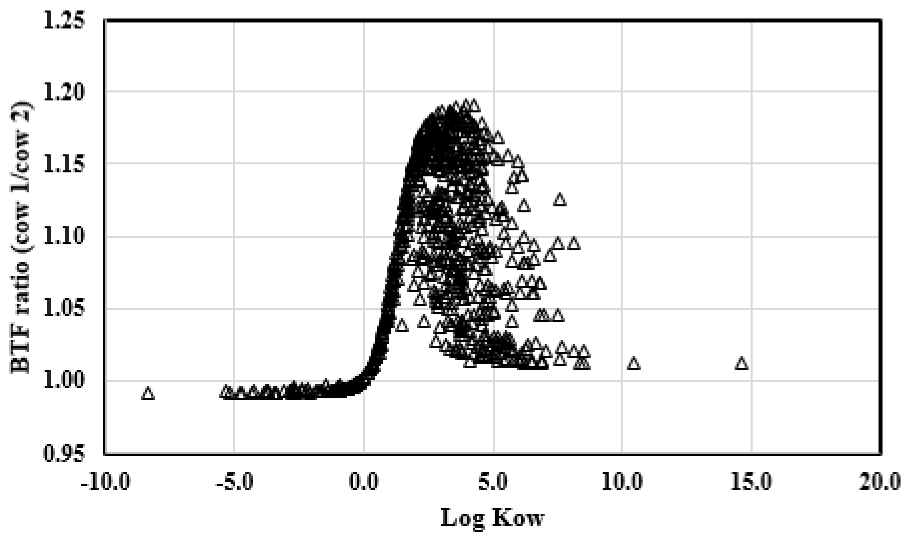


Figure A7. Ratios of biotransfer factors in milk (BTF_{Milk}) between dairy cows 1 and 2 (control group) of the 736 pesticides plotted against log K_{OW}.

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