APPROACHES FOR THE APPLICATION OF PHYSIOLOGICALLY -BASED PHARMACOKINETIC DATA AND MODELS IN RISK ASSESSMENT

APPENDIX 1:
Algorithms for predicting chemical-specific parameters for PBPK models

Prepared by :
Dr. Kannan Krishnan

For

NATIONAL CENTER FOR ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C.

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Table I : *In silico* approaches for estimating the tissue:air partition coefficients (P) of chemicals

Approach[a]	Species[b]	Chemical Class[c]	Reference
QSARs: LFE-type equations			
Electrostatic descriptors			
$\text{Log } P_{adipose:air} = -0.294-0.172R_2+0.729\pi_2^H+1.7474\alpha_2^H+0.219\beta_2^H+0.895\text{Log}P_{he:a}$	H	Inert gases; LMWVOCs	(2)
$\text{Log } P_{brain:air} = -1.074+0.427R_2+0.286\pi_2^H+2.781\alpha_2^H+2.787\beta_2^H+0.609\text{Log}P_{he:a}$	H	Inert gases; LMWVOCs	(2)
$\text{Log } P_{heart:air} = -1.208+0.128R_2+0.987\pi_2^H+0.643\alpha_2^H+1.783\beta_2^H+0.597\text{Log}P_{he:a}$	H	Inert gases; LMWVOCs	(2)
$\text{Log } P_{kidney:air} = -1.084+0.417R_2+0.226\pi_2^H+3.624\alpha_2^H+2.926\beta_2^H+0.534\text{Log}P_{he:a}$	H	Inert gases; LMWVOCs	(2)
$\text{Log } P_{liver:air} = -1.031+0.059R_2+0.774\pi_2^H+0.593\alpha_2^H+1.049\beta_2^H+0.654\text{Log}P_{he:a}$	H	Inert gases; LMWVOCs	(2)
$\text{Log } P_{lung:air} = -1.300+0.667R_2+0.680\pi_2^H+3.539\alpha_2^H+3.35\beta_2^H+0.458\text{Log}P_{he:a}$	H	Inert gases; LMWVOCs	(2)
$\text{Log } P_{muscle:air} = -1.14+0.544R_2+0.216\pi_2^H+3.4714\alpha_2^H+2.924\beta_2^H+0.578\text{Log}P_{he:a}$	H	Inert gases; LMWVOCs	(2)
Steric descriptors			
$\text{Log } P_{adipose:air} = (0.734\,{}^{1}x^{v})-(0.029x^{v}_{s})-(1.57(1/{}^{1}x))-(0.559(1/{}^{1}x^{v}))-0.098\,{}^{3}x^{v}_{c}+2.213$	R	Haloalkanes	(25)
$\text{Log } P_{adipose:air} = 0.734\,{}^{1}X^{v}-0.0291X_s^{v}-1.570/{}^{1}X^{v}-0.559\,{}^{1}X^{v}-0.098\,{}^{4}X_c^{v}+2.213$	R	Haloalkanes	(14)
$\text{Log } P_{adipose:air} = 0.563N_{Cl}+1.028N_{Br}+0.467N_C+0.270Q_H-0.199N_F-0.097$	R	Haloalkanes	(7, 25)
$\text{Log } P_{adipose:air} = 1.037\,{}^{1}x^{v}-(0.007(1/x^{v}_{s}))+0.022Q_H-0.177\,{}^{3}x^{v}_{c}-0.199N_F-0.0036$	R	Haloalkanes	(25)
$\text{Log } P_{liver:air} = (1.072\,{}^{1}x^{v})-(0.021(1/x^{v}_{s}))+(0.647(1/{}^{1}x^{v}))-(0.304\,{}^{4}x^{V}_{C})-1.212$	R	Haloalkanes	(25)
$\text{Log } P_{liver:air} = 0.366N_{Cl}-0.588N_{Br}+0.345Q_H-0.179N_F-0.007$	R	Haloalkanes	(25)
$\text{Log } P_{liver:air} = -0.685\,{}^{1}x^{v}-(0.020(1/x^{v}_{s}))+0.232Q_H+(0.298(1/{}^{1}x^{v}))+0.104N_{Cl}-0.726$	R	Haloalkanes	(25)
$\text{Log } P_{liver:air} = 1.072\,{}^{1}X^{v}-0.021/X_s^{v}+0.647/{}^{1}X^{v}-0.304\,{}^{4}X_c^{v}-1.212$	R	Haloalkanes	(14)
$\text{Log } P_{muscle:air} = 0.379Q_H-0.278N_{Cl}+0.536N_{Br}-0.190N_F+0.169N_{Cl}-0.439$	R	Haloalkanes	(25)
$\text{Log } P_{muscle:air} = 0.399\,{}^{1}x^{v}-(0.007(1/x^{v}_{s}))+0.295Q_H+0.259\,{}^{4}x^{v}_{pc}-0.194N_F-0.217$	R	Haloalkanes	(25)
$\text{Log } P_{muscle:air} = (0.995\,{}^{1}x^{v})-(0.018(1/x^{v}_{s}))-(0.424\,{}^{4}x^{v}_{c})-(0.559(1/{}^{1}x^{v})+(0.602(1/{}^{1}x^{v}))-1.334$	R	Haloalkanes	(25)
Hydrophobic descriptors			
$\text{Log}(P_{adipose:water}-V_{wt})=0.9P_{o:w}+0.31$	F	Chloroethanes; Benzene	(8)
$\text{Log}(P_{kidney:water}-V_{wt})=0.72P_{o:w}-0.56$	F	Chloroethanes; Benzene	(8)
$\text{Log}(P_{liver:water}-V_{wt})=1.06P_{o:w}-1.43$	F	Chloroethanes; Benzene	(8)
$\text{Log}(P_{muscle:water}-V_{wt})=0.63P_{o:w}-0.60$	F	Chloroethanes; Benzene	(8)
$\text{Ln } P_{adipose:air} = 0.032T_b-5.456$	H	Haloalkanes	(14)
$\text{Ln } P_{liver:air} = 0.022T_b-4.638$	H	Haloalkanes	(14)
$\text{Log } P_{adipose:air} = 0.209+0.0628\text{Log}P_{w:a}+0.8868\text{Log}P_{o:a}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{adipose:air} = 0.21\text{Log}P_{o:a}+0.24\text{Log}P_{w:a}$	H	hydrophilic VOCs	(72)

$\text{Log } P_{adipose:air} = 0.782 \text{LogP}_{o:a} + 0.201 \text{LogP}_{w:a} + 0.432$	H	hydrophobic VOCs	(71)
$\text{Log } P_{adipose:air} = 0.901 \text{LogP}_{o:a} + 0.150$	H	LMWVOCs	(21)
$\text{Log } P_{adipose:air} = 0.174 + 0.910 \text{LogP}_{o:a}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{brain:air} = -0.16 \text{LogP}_{o:a} + 0.82 \text{LogP}_{w:a} + 0.47$	H	hydrophilic VOCs	(72)
$\text{Log } P_{brain:air} = 0.274 + 0.537 \text{LogP}_{w:a} + 0.444 \text{LogP}_{o:a}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{brain:air} = 0.394 + 1.096 \text{ LogP}_{w:a}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{brain:air} = 0.471 \text{LogP}_{o:a} + 0.630 \text{Log } P_{w:a} – 0.305$	H	hydrophobic VOCs	(71)
$\text{Log } P_{brain:air} = 0.844 \text{LogP}_{o:a} - 1.124$	H	LMWVOCs	(21)
$\text{Log } P_{brain:air} = -0.850 + 0.773 \text{ LogP}_{o:a}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{brain:air} = -3.692 + 1.253 R_G$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{kidney:air} = -0.18 \text{LogP}_{o:a} + 0.82 \text{LogP}_{w:a} + 0.53$	H	hydrophilic VOCs	(72)
$\text{Log } P_{kidney:air} = 0.277 + 1.111 \text{LogP}_{w:a}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{kidney:air} = 0.466 \text{LogP}_{o:a} + 0.379 \text{LogP}_{w:a} - 0.332$	H	hydrophobic VOCs	(71)
$\text{Log } P_{kidney:air} = 0.700 \text{LogP}_{o:a} - 0.877$	H	LMWVOCs	(21)
$\text{Log } P_{kidney:air} = -0.920 + 0.764 \text{LogP}_{o:a}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{liver:air} = -0.388 + 0.502 \text{LogP}_{w:a} + 0.497 \text{LogP}_{o:a}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{liver:air} = 0.432 + 1.064 \text{LogP}_{w:a}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{liver:air} = 0.746 \text{LogP}_{o:a} + 0.178 \text{LogP}_{w:a} - 0.767$	H	hydrophobic VOCs	(71)
$\text{Log } P_{liver:air} = 0.871 \text{LogP}_{o:a} - 1.044$	H	LMWVOCs	(21)
$\text{Log } P_{liver:air} = -0.875 + 0.773 \text{LogP}_{o:a}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{lung:air} = -0.21 \text{LogP}_{o:a} + 0.91 \text{LogP}_{w:a} + 0.41$	H	hydrophilic VOCs	(72)
$\text{Log } P_{lung:air} = -0.057 + 0.870 \text{LogP}_{w:a} + 0.146 \text{LogP}_{o:a}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{lung:air} = 0.057 + 0.978 \text{LogP}_{w:a}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{lung:air} = 0.373 \text{LogP}_{o:a} + 0.416 \text{LogP}_{w:a} - 0.216$	H	hydrophobic VOCs	(71)
$\text{Log } P_{lung:air} = 0.644 \text{LogP}_{o:a} - 0.815$	H	LMWVOCs	(21)
$\text{Log } P_{lung:air} = -0.833 + 0.911 \text{LogP}_{o:a}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{muscle:air} = -0.19 \text{LogP}_{o:a} + 0.82 \text{LogP}_{w:a} + 0.54$	H	hydrophilic VOCs	(72)
$\text{Log } P_{muscle:air} = 0.49 \text{LogP}_{o:a} + 0.39 \text{LogP}_{w:a} - 0.31$	H	hydrophobic VOCs	(72)
$\text{Log } P_{muscle:air} = -0.263 + 0.575 \text{LogP}_{w:a} + 0.423 \text{LogP}_{o:a}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{muscle:air} = 0.351 + 1.108 \text{LogP}_{w:a}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{muscle:air} = 0.652 \text{LogP}_{o:a} - 0.702$	H	LMWVOCs	(21)
$\text{Log } P_{muscle:air} = -0.852 + 0.768 \text{LogP}_{o:a}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{muscle:air} = -3.247 + 0.965 R_G$	H	Inert gases; LMWVOCs	(1)
$P_{adipose:air} = 0.447 P_{o:a} + 0.075 P_{w:a} + 6.59$	H	LMWVOCs; CFC	(44)
$P_{brain:air} = (0.026 S_o + 0.51 S_w)/S_a$	H	LMWVOCs	(51)

$P_{brain:air}=0.020P_{o:a}+0.380P_{w:a}+0.94$	H	LMWVOCs; CFC	(44)
$P_{kidney:air}=(0.014S_o+0.51S_w)/S_a$	H	LMWVOCs	(51)
$P_{kidney:air}=0.011P_{o:a}+0.400P_{w:a}+0.69$	H	LMWVOCs; CFC	(44)
$P_{kidney:air}=-0.391+0.550LogP_{w:a}+0.440LogP_{o:a}$	H	Inert gases; LMWVOCs	(1)
$P_{liver:air}=(0.028S_o+0.51S_w)/S_a$	H	LMWVOCs	(51)
$P_{liver:air}=0.028P_{o:a}+0.79$	H	LMWVOCs; CFC	(44)
$P_{muscle:air}=0.014P_{o:a}+0.384P_{w:a}+0.94$	H	LMWVOCs; CFC	(44)
$Ln\ P_{adipose:air}=0.032T_b-5.456$	R	LMWVOCs	(14)
$Ln\ P_{liver:air}=0.022T_b-4.638$	R	LMWVOCs	(14)
$Log\ P_{adipose:air}=0.920LogP_{o:a}+0.136$	R	LMWVOCs	(26)
$Log\ P_{adipose:air}=0.927LogP_{o:a}-0.032LogP_{w:a}+0.120$	R	LMWVOCs	(26)
$Log\ P_{adipose:air}=1.027LogP_{o:a}-0.046LogP_{w:a}-0.119$	R	Haloalkanes	(25)
$Log\ P_{liver:air}=0.574LogP_{o:a}+0.302LogP_{w:a}-0.278$	R	Haloalkanes	(25)
$Log\ P_{liver:air}=0.730LogP_{o:a}+0.128LogP_{w:a}-0.550$	R	LMWVOCs	(26)
$Log\ P_{muscle:air}=0.477LogP_{o:a}+0.365LogP_{w:a}-0.374$	R	Haloalkanes	(25)
$Log\ P_{muscle:air}=0.644LogP_{o:a}+0.180LogP_{w:a}-0.725$	R	LMWVOCs	(26)
$P_{adipose:air}=0.594P_{o:a}+0.085P_{w:a}+9.40$	R	LMWVOCs; CFC	(44)
$P_{brain:air}=0.054P_{o:a}+0.832P_{w:a}$	R	LMWVOCs; CFC	(44)
$P_{kidney:air}=0.097P_{o:a}+0.826P_{w:a}$	R	LMWVOCs; CFC	(44)
$P_{liver:air}=0.026P_{o:a}+0.878P_{w:a}+2.36$	R	LMWVOCs; CFC	(44)
$P_{muscle:air}=0.010P_{o:a}+0.772P_{w:a}+0.29$	R	LMWVOCs; CFC	(44)
Mechanistically-based equations			
$P_{tissue:air} = (S_sV_{wt}+S_vV_{nt}+0.7S_sV_{pt}+0.3S_vV_{pt})/S_a$	R, H	LMWVOCs	(55)
$P_{tissue:air} = P_{o:w}P_{w:a}(V_{nt}+0.3V_{pt})+P_{w:a}(V_{wt}+0.7V_{pt})$	R, H	LMWVOCs	(57)

Table II : *In silico* approaches for estimating the blood:air partition coefficients (P) of chemicals

Approach[a]	**Species**[b]	**Chemical Class**[c]	**Reference**
QSARs: LFE-type equations			
Electrostatic descriptors			
$\text{Log } P_{blood:air} = -1.269+0.612R_2+0.916\pi_2^H+3.614\alpha_2^H+3.381\beta_2^H+0.362\text{LogP}_{he:a}$	H	Inert gases; LMWVOCs	(2)
$\text{Log } P_{plasma:air} = -1.48+0.490R_2+2.04\pi_2^H+3.5074\alpha_2^H+3.911\beta_2^H+0.157\text{LogP}_{he:a}$	H	Inert gases; LMWVOCs	(2)
Steric descriptors			
$\text{Log } P_{blood:air} = 0.0072MW+0.197$	H	Trihalomethanes	(7)
$\text{Log } P_{blood:air} = 0.321N_{Br}+1.06$	H	Trihalomethanes	(7)
$P_{blood:air} = 0.07MW+5.59$	H	volatile hydrocarbons	(52)
$\text{Log } P_{blood:air} = 0.443Q_H-0.303N_F+0.225N_{Cl}+0.510N_{BR}+0.155N_C-0.104$	R	Haloalkanes	(25)
Hydrophobic descriptors			
$\text{Log } (P_{blood:water}-V_{wb})=0.7P_{o:w}-0.75$	F	Chloroethanes; Benzene	(8)
$\text{Ln } P_{blood:air} = 0.038T_b-13.3$	H	volatile hydrocarbons	(14)
$\text{Log } P_{blood:air} = 0.0109T_b-2.584$	H	Trihalomethanes	(7)
$\text{Log } P_{blood:air} = -0.14\text{LogP}_{o:a}+0.86\text{LogP}_{w:a}+0.47$	H	Hydrophilic VOCs	(72)
$\text{Log } P_{blood:air} = 0.685\text{logP}_{o:a}-0.6565$	H	Trihalomethanes	(7)
$\text{Log } P_{blood:air} =0.45\text{LogP}_{w:a}+1.21$	H	VOCs	(38)
$\text{Log } P_{blood:air}= -0.003\text{LogP}_{w:a}+1.47$	H	VOCs	(38)
$\text{Log } P_{blood:air}= -0.074+0.802\text{LogP}_{w:a}+0.218\text{LogP}_{o:a}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{blood:air}= -0.07\text{LogS}_w+1.21$	H	VOCs	(38)
$\text{Log } P_{blood:air}= -0.09\text{LogP}_{o:a}+2.45$	H	VOCs	(38)
$\text{Log } P_{blood:air}= -0.102+0.675\text{LogP}_{w:a}+0.315\text{LogP}_{o:a}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{blood:air}= -0.295+0.588\text{LogP}_{w:a}+0.411\text{LogP}_{o:a}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{blood:air}= -0.338\text{LogP}_{o:a}+3.121$	H	Hydrocarbures halogénés	(70)
$\text{Log } P_{blood:air}= -0.6737+0.5319\text{LogP}_{o:a}\text{LogP}_{w:a}$	H	VOCs	(65)
$\text{Log } P_{blood:air}= 0.695\text{LogP}_{o:a}-1.076$	H	LMWVOCs	(21)
$\text{Log } P_{blood:air}= -0.820+0.754\text{LogP}_{o:a}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{blood:air}=0.09\text{LogS}_w+8.25\text{LogV}_o-11.09$	H	VOCs	(38)
$\text{Log } P_{blood:air}=0.11\text{LogS}_w+1.91$	H	VOCs	(38)
$\text{Log } P_{blood:air}=0.180\text{LogP}_{o:a}+0.889\text{LogP}_{w:a}+0.054$	H	Hydrophobic VOCs	(71)
$\text{Log } P_{blood:air}=0.20\text{LogS}_w+1.29$	H	VOCs	(38)

Log $P_{blood:air}$=0.22Log$P_{w:a}$+0.67Log$P_{o:a}$-0.98	H	VOCs	(38)
Log $P_{blood:air}$=0.22LogS_w+10.78LogV_w-40.99	H	VOCs	(38)
Log $P_{blood:air}$=0.262+0.996Log$P_{w:a}$	H	Inert gases; LMWVOCs	(1)
Log $P_{blood:air}$=0.27Log1000/P+5.10LogV_o-6.67	H	VOCs	(38)
Log $P_{blood:air}$=0.31LogS_w+3.90LogV_o-4.53	H	VOCs	(38)
Log $P_{blood:air}$=0.35Log1000/P+1.01	H	VOCs	(38)
Log $P_{blood:air}$=0.35LogS_w+0.79Log1000/P+1.34LogV_o-2.23	H	VOCs	(38)
Log $P_{blood:air}$=0.37LogS_w+10.09LogV_w-38.40	H	VOCs	(38)
Log $P_{blood:air}$=0.38LogS_w+0.91Log1000/P-0.45	H	VOCs	(38)
Log $P_{blood:air}$=0.45LogS_w+0.81Log1000/P-0.40	H	VOCs	(38)
Log $P_{blood:air}$=0.48LogS_w+0.75Log1000/P+1.67LogV_o-2.77	H	VOCs	(38)
Log $P_{blood:air}$=0.51Log1000/P+0.37	H	VOCs	(38)
Log $P_{blood:air}$=0.581Log$P_{o:a}$+0.332Log$P_{w:a}$-0.599	H	LMWVOCs	(26)
Log $P_{blood:air}$=0.63Log1000/P+0.38	H	VOCs	(38)
Log $P_{blood:air}$=0.65Log$P_{o:a}$-0.84	H	VOCs	(38)
Log $P_{blood:air}$=0.851LogS_w+1.78	H	VOCs	(38)
Log $P_{blood:air}$=0.984Log$P_{w:a}$+0.053	H	Ketones; Esters; Gases	(70)
Log $P_{blood:air}$=1.07Log$P_{w:a}$+0.27Log$P_{o:a}$-0.79	H	VOCs	(38)
Log $P_{blood:air}$=1.21LogV_o-0.17	H	VOCs	(38)
Log $P_{blood:air}$=3.05-0.34$P_{o:n}$	H	Ketones	(10)
Log $P_{blood:air}$=-3.922+1.369R_G	H	Inert gases; LMWVOCs	(1)
Log $P_{blood:air}$=5.89LogV_w-21.43	H	VOCs	(38)
Log $P_{blood:air}$=7.86LogV_o-10.40	H	VOCs	(38)
/id Log $P_{blood:air}$=8.90LogV_w-33.40	H	VOCs	(38)
Log $P_{milk:air}$ = 0.900log$P_{o:a}$-1.095	H	Trihalomethanes	(7)
Log $P_{plasma:air}$= -0.079+0.896Log$P_{w:a}$+0.149Log$P_{o:a}$	H	Inert gases; LMWVOCs	(1)
Log $P_{plasma:air}$= -0.082+0.894Log$P_{w:a}$+0.152Log$P_{o:a}$	H	Inert gases; LMWVOCs	(1)
Log $P_{plasma:air}$= -0.848+0.890Log$P_{o:a}$	H	Inert gases; LMWVOCs	(1)
Log $P_{plasma:air}$= -3.696+1.208R_G	H	Inert gases; LMWVOCs	(1)
Log $P_{plasma:air}$=0.038+1.019Log$P_{w:a}$	H	Inert gases; LMWVOCs	(1)
$P_{blood:air}$ = 0.0072$P_{o:a}$+0.898$P_{w:a}$+0.03	H	LMWVOCs; CFC	(44)
$P_{blood:air}$ = 0.08$e^{0.0308Tb}$	H	volatile hydrocarbons	(52)
$P_{blood:air}$=0.00442$P_{o:a}$	H	volatile hydrocarbons	(52)
$P_{blood:air}$=0.88$P_{w:a}$+0.012	H	VOCs	(20)

$P_{blood:air}=0.89P_{w:a}+0.011P_{o:a}$	H	LMWVOCs	(70)
$P_{blood:air}=0.90LogP_{w:a}-461$	H	Esters; Alcohols	(35)
$P_{blood:air}=P_{w:a}+(P_{o:a}/100)$	H	Anaesthesics	(17)
$P_{blood:air}=S_w(1+0.0035P_{o:w})/S_a$	H	LMWVOCs	(51)
$Log\ P_{blood:air}=P_{w:a}*\{V_{lb}P_{o:w}^{0.85}+V_{prb}(86.2/P_{o:w}+3.70)+V_{wb}$	H, R	LMWVOCs	(12)
$Log\ P_{blood:air}=0.426LogP_{o:a}+0.515LogP_{w:a}-0.070$	R	Haloalkanes	(25)
$Log\ P_{blood:air}=0.553LogP_{o:a}+0.351P_{w:a}-0.286$	R	LMWVOCs	(26)
$P_{blood:air}=0.0054P_{o:a}+0.931P_{w:a}+1.16$	R	LMWVOCs; CFC	(44)

QSARs: Free-Wilson-type equations

$P_{blood:water} = BS_{(C-C)}\ (28.4) + nCL_2(-12.9) + nCL_3(12.9)$	F	Chloroethanes	(23)
$P_{blood:air} = BS_{(C-C)}\ (26.2) + nH_3(-34.9) + nCL(-4.51) + nCL_2(29.4) + nCL_3(11.5)$	H	Chloroethanes	(22)
$P_{blood:air} = BS_{(C-C)}\ (45.6) + nH_3(-51.5) + nCL(-8.86) + nCL_2(36.4) + nCL_3(11.1)$	R	Chloroethanes	(22)

Mechanistically-based equations

$P_{blood:air} = P_{o:w}P_{w:a}(V_{nb}+0.3V_{pb})+P_{w:a}(V_{wb}+0.7V_{pb})$	R, H	LMWVOCs	(57)
$P_{blood:air} =[f_e(S_sV_{we}+S_vV_{ne}+0.7S_sV_{pe}+0.3S_vV_{pe})+f_p(S_sV_{wp}+S_vV_{np}+0.7S_sV_{pp}+0.3S_vV_{pp})]/S_a$	R, H	LMWVOCs	(56)

Table III : *In silico* approaches for estimating the tissue:blood partition coefficients (P) of chemicals

Approach[a]	Species[b]	Chemical Class[c]	Reference
QSARs: LFE-type equations			
Steric descriptors			
$\text{Log } P_{adipose:blood} = 0.168+0.198R_2+0.130\pi_2^H -1.211\alpha_2^H-3.267\beta_2^H+2.275V_x$	H	Inert gases; LMWVOCs; CFCs	(2)
$\text{Log } P_{brain:blood} = -0.166+0.239R_2-0.626\pi_2^H -0.368\alpha_2^H-0.615\beta_2^H+1.072V_x$	H	Inert gases; LMWVOCs; CFCs	(2)
$\text{Log } P_{brain:blood} =-0.0148PSA+0.152\text{Log}P_{o:w}+0.139$	H	Inert gases; HMWOCs; LMWVOCs	(11)
$\text{Log } P_{brain:blood}=1.359+0.338\text{Log}P_{cyh}-0.00618V_m$	H	H_2-R antagonists	(34)
$\text{Log } P_{heart:blood} = -0.346+0.204\pi_2^H -2.150\alpha_2^H-0.853\beta_2^H+0.931V_x$	H	Inert gases; LMWVOCs; CFCs	(2)
$\text{Log } P_{kidney:blood} = -0.188+0.226R_2-0.559\pi_2^H -0.433\beta_2^H+0.832V_x$	H	Inert gases; LMWVOCs; CFCs	(2)
$\text{Log } P_{liver:blood} = -0.270+0.233R_2-0.375\pi_2^H -1.004\alpha_2^H-1.118\beta_2^H+0.832V_x$	H	Inert gases; LMWVOCs; CFCs	(2)
$\text{Log } P_{lung:blood} = -0.150-0.195\pi_2^H +0.389V_x$	H	Inert gases; LMWVOCs; CFCs	(2)
$\text{Log } P_{muscle:blood} = -0.222-0.479\pi_2^H -0.517\beta_2^H+0.999V_x$	H	Inert gases; LMWVOCs; CFCs	(2)
$P_{adipose:plasma}=1.9988-0.5004UNS+0.1793NPL+0.05931DIFF^2$	H	PCBs	(48)
$\text{Log } P_{brain:blood} = 0.088+0.264R_2-0.966\pi_2^H-0.705\Sigma\alpha_2^H-0.756\Sigma\beta_2^H+1.189V_x$	R	H_2-R antagonists	(47)
$\text{Log } P_{brain:blood} = -0.088+0.272 \text{ Log } P_{o:w}-0.00116MW$	R	H_2-R antagonists	(34)
$\text{Log } P_{brain:blood}=-0.00116MW+0.272\text{Log}P_{o:w}-0.088$	R	Inert gases; volatile hydrocarbons	(47)
$\text{Log } P_{brain:blood}=-0.01V_m+0.35\text{Log}P_{o:w}+0.99I_3+1.25$	R	Drug-like molecules	(47)
$\text{Log } P_{brain:blood}=-0.021PSA-0.003MV+1.643$	R	Inert gases; HMWOCs; LMWVOCs	(11)
$\text{Log } P_{brain:blood}=-0.0322DPSA+1.33$	R	HMWOCs	(47)
$\text{Log } P_{brain:blood}=-0.038+0.198R_2-0.687\pi_2^H-0.715\Sigma\alpha_2^H-0.698\Sigma\beta_2^H+0.995V_x$	R	H_2-R antagonists; Inert gases; SOMs	(47)
$\text{Log } P_{brain:blood}=-0.218(N_N+N_O)+0.235\log P_{o:w}-0.027$	R	HMWOCs	(47)
$\text{Log } P_{brain:blood}=0.476+0.541\text{Log}P_{o:w}-0.00794MW$	R	H_2-R antagonists	(34)
$\text{Log } P_{brain:blood}=1.296+0.309\text{Log}P_{cyh}-0.00570MW$	R	H_2-R antagonists	(34)
Hydrophobic descriptors			
$\text{Log } P_{brain:blood}=0.39\text{Log}P_{o:w}+0.68$	H	Drugs, Hormones	(66)
$\text{Log } P_{brain:blood}=0.054G^o+0.43$	H	H_2-R antagonists; LMWVOCs	(43)
$P_{adipose:blood}=[(V_{lt}P_{o:w}^{A1}+V_{wt})/(V_{lb}P_{o:w}^{A2}+V_{wb})]+B$	H, R	LMWVOCs	(16)
$P_{brain:blood}=[(V_{lt}P_{o:w}^{A1}+V_{wt})/(V_{lb}P_{o:w}^{A2}+V_{wb})]+B$	H, R	LMWVOCs	(16)
$P_{kidney:blood}=[(V_{lt}P_{o:w}^{A1}+V_{wt})/(V_{lb}P_{o:w}^{A2}+V_{wb})]+B$	H, R	LMWVOCs	(16)
$P_{liver:blood}=[(V_{lt}P_{o:w}^{A1}+V_{wt})/(V_{lb}P_{o:w}^{A2}+V_{wb})]+B$	H, R	LMWVOCs	(16)
$P_{muscle:blood}=[(V_{lt}P_{o:w}^{A1}+V_{wt})/(V_{lb}P_{o:w}^{A2}+V_{wb})]+B$	H, R	LMWVOCs	(16)
$\text{Ln } P_{kidney:blood}=0.0065\sum o$	R	HMWOCs	(75)
$\text{Ln } P_{liver:blood}=0.025\sum i$	R	HMWOCs	(75)

$\ln P_{muscle:blood}=0.0069\sum i$	R	HMWOCs	(75)
$\log P_{brain:blood}=0.035\Delta G_{solv}+0.259$	R	H_2-R antagonists; LMWVOCs	(47)
$\log P_{brain:blood}=0.4275-0.3873n_{acc,solv}+0.1092\log P_{o:w}-0.0017A_{pol}$	R	Drugs; LMWVOCs; Anaesthetics	(19)
$\log P_{brain:blood}=1.979+0.373\log P_{cyh}-0.00275V_{wav}$	R	H_2-R antagonists	(34)
$\log P_{brain:plasma} = -0.48*\Delta\log P_{oct-cyc}+0.89$	R	H_2-R antagonists	(69)
$\ln P_{adipose:blood}=0.05\sum i+0.021$	R	HMWOCs	(75)
$P_{adipose:blood}=0.915P_{o:w}^{0.573}$	Rb	Basic drugs	(76)
$P_{adipose:plasma} = 0.016P_{o:w}^{1.255}$	Rb	Basic drugs	(77)
$P_{bone\ marrow:blood} =1.975P_{o:w}^{0.273}$	Rb	Basic drugs	(76)
$P_{bone:plasma} = 0.036P_{o:w}^{0.947}$	Rb	Basic drugs	(77)
$P_{brain:blood}=3.157P_{o:w}^{0.312}$	Rb	Basic drugs	(76)
$P_{brain:plasma} = 0.062P_{o:w}^{0.984}$	Rb	Basic drugs	(77)
$P_{gut:blood} = 3.002P_{o:w}^{0.346}$	Rb	Basic drugs	(76)
$P_{gut:plasma} = 0.058P_{o:w}^{1.02}$	Rb	Basic drugs	(77)
$P_{heart:blood}=1.678P_{o:w}^{0.422}$	Rb	Basic drugs	(76)
$P_{heart:plasma} = 0.032P_{o:w}^{1.098}$	Rb	Basic drugs	(77)
$P_{kidney:plasma} = 0.075P_{o:w}^{1.037}$	Rb	Basic drugs	(77)
$P_{liver:plasma} = 0.064P_{o:w}^{0.884}$	Rb	Basic drugs	(77)
$P_{lung:blood}=1.158P_{o:w}^{0.565}$	Rb	Basic drugs	(76)
$P_{lung:plasma} = 0.031P_{o:w}^{1.236}$	Rb	Basic drugs	(77)
$P_{muscle:blood}=4.928P_{o:w}^{0.221}$	Rb	Basic drugs	(76)
$P_{muscle:plasma} = 0.099P_{o:w}^{0.889}$	Rb	Basic drugs	(77)
$P_{skin:blood}=2.997P_{o:w}^{0.256}$	Rb	Basic drugs	(76)
$P_{skin:plasma} = 0.058P_{o:w}^{0.927}$	Rb	Basic drugs	(77)
$P_{spleen:blood}=3.002P_{o:w}^{0.346}$	Rb	Basic drugs	(76)
QSARs: Free-Wilson-type equations			
$P_{adipose:blood} = BS_{(C-C)}(94.5) + nCL_2(-29.2) + nCL_3(29.2)$	F	Chloroethanes	(23)
$P_{liver:blood} = BS_{(C-C)}(2.93) + nCL_2(-0.238) + nCL_3(0.238)$	F	Chloroethanes	(23)
$P_{muscle:blood}= BS_{(C-C)}(3.02) + nCL_2(-0.175) + nCL_3(0.175)$	F	Chloroethanes	(23)
$P_{adipose:blood} = BS_{(C-C)}(49.2) + nH_3(-0.440) + nCL(-14.54) + nCL_2(-6.65) + nCL_3(26.5)$	H	Chloroethanes	(22)
$P_{liver:blood} = BS_{(C-C)}(2.64) + nH_3(-0.61) + nCL(-0.66) + nCL_2(-0.18) + nCL_3(1.68)$	H	Chloroethanes	(22)
$P_{muscle:blood} = BS_{(C-C)}(1.11) + nH_3(0.08) + nCL(-0.02) + nCL_2(-0.21) + nCL_3(0.15)$	H	Chloroethanes	(22)
$P_{adipose:blood} = BS_{(C-C)}(30.1) + nH_3(-9.88) + nCL(-6.02) + nCL_2(-3.90) + nCL_3(17.3)$	R	Chloroethanes	(22)
$P_{liver:blood} = BS_{(C-C)}(1.79) + nH_3(-0.9) + nCL(-0.38) + nCL_2(-0.21) + nCL_3(1.27)$	R	Chloroethanes	(22)
$P_{muscle:blood} = BS_{(C-C)}(0.69) + nH_3(-0.12) + nCL(0.04) + nCL_2(-0.12) + nCL_3(0.17)$	R	Chloroethanes	(22)

Mechanistically-based equations

$P_{tissue:blood} = (S_oV_{nt}+S_w*0.7V_{pt}+S_o*0.3V_{pt}+S_wV_{wt})/(S_oV_{nb}+S_w*0.7V_{pb}+S_o*0.3V_{pb}+S_wV_{wb})$	H	LMWVOCs	(53)
$P_{tissue:blood} = (P_{o:w}V_{nt}+V_{wt}+P_{o:w}*0.3V_{pt}+0.7V_{pt})/[f_e(P_{o:w}V_{ne}+V_{we}+P_{o:w}*0.3V_{pe}+0.7V_{pe})$ $+f_p(P_{o:w}V_{np}+V_{wp}+P_{o:w}*0.3V_{pp}+0.7V_{pp})]$	R	Ketones; Alcohols; Esters	(54)
$P_{tissue:blood} = [P_{o:w}(V_{nt}+0.3V_{pt})+(V_{wt}+0.7V_{pt})]/[P_{o:w}(V_{nb}+0.3V_{pb})+(V_{wb}+0.7V_{pe})]$	R, H	LMWVOCs	(56)

[a] π_2^H=dipolarity/polarizability, α_2^H=overall hydrogen-bond acidity, β_2^H=overall hydrogen-bond basicity, ΔG_{solv}=free energy of solvation in hexadecane, Σi=molecular structure Fujita value, Σo=molecular structure Fujita value, A_1,A_2=Collander-type coefficient, A_{pol}=polar surface area, B=correction factor, BS=Basic structure, DIFF=variable dependant on the number of chloride atoms in the aromatic cycle, DPSA=Dynamic polar surface area, f_e=fraction of erythrocytes in blood, f_p=fraction of plasma in blood, I_3=variable dependant on the presence of an amino nitrogen or carboxyl group, MV=molecular volume, MW=Molecular weight, $n_{acc,solv}$=number of solvated hydrogen-bond acceptors, nCL=number of CL fragments, nCL_2=number of CL_2 fragments, nCL_3=number of CL_3 fragments, nH_3=number of H_3 fragments, N_N=number of nitrogens, N_O=number of oxygens, NPL=variable dependant on the number of chloride atoms in the molecule in ortho position, ^oG=Gibbs free energy related to the solvation of the substance in water, P_{cyh}=cyclohexane:water partition coefficient, $P_{o:w}$=n-octanol:water partition coefficient (or vegetable oil:water), $P_{oct\text{-}cyc}$=octanol-cyclohexane, PSA=polar surface area, R_2=Excess molar refraction, S_o=solubility in n-octanol (or vegetable oil), S_w=solubility in water, UNS=variable dependant on the number of atoms in the molecule that are not chlorides, V_{lb}=volume fraction of lipids in blood, V_{lt}=volume fraction of lipids in tissue, V_m=molar volume, V_{nb}=volume fraction of neutral lipids in blood, V_{ne}=volume fraction of neutral lipids in erythrocytes, V_{np}=volume fraction of neutral lipids in plasma, V_{nt}=volume fraction of neutral lipids in tissues, V_{pb}=volume fraction of phospholipids in blood, V_{pe}=volume fraction of phospholipids in erythrocytes, V_{pp}=volume fraction of phospholipids in plasma, V_{pt}=volume fraction of phospholipids in tissues, V_{wav}=volume of water needed in order to solubilize the substance, V_{wb}=volume fraction of water in blood, V_{wb}=volume fraction of water in blood, V_{we}=volume fraction of water in erythrocytes, V_{wp}=volume fraction of water in plasma, V_{wt}=volume fraction of water in tissue, V_{wt}=volume fraction of water in tissues, and V_x=McGowan characteristic volume.

[b] F=fish, H=human, and R=rats.

[c] CFCs = chlorofluorocarbons, HMWOCs = high molecular weight organic chemicals, LMWVOCs=low molecular weight volatile organic chemicals, PCBs=polychlorobiphenyls, and VOCs = volatile organic chemicals.

Table IV: *In silico* approaches for estimating the skin permeability coefficient (K_p) of chemicals

Approach[a]	Species[b]	Chemical Class[c]	Reference
QSARs: LFE-type equations			
Electrostatic descriptors			
$\text{Log } K_p = -0.626\Sigma Ca - 23.8\Sigma(Q+)/\alpha - 0.289SsssCH - 0.0357SsOH - 0.482I_B + 0.405B_R + 0.834$	H	LMWVOCs; HMWOCs	(45)
$\text{Log } K_p = 0.44R_2 - 0.49\pi_2^H - 1.48\Sigma\alpha_2^H - 3.44\Sigma\beta_2^H + 1.94V_x - 5.13$	H	LMWVOCs; HMWOCs	(45)
$\text{Log } K_p = -0.59\pi_2^H - 0.63\Sigma\alpha_2^H - 3.48\Sigma\beta_2^H + 1.79V_x - 5.05$	H	LMWVOCs; HMWOCs	(45)
$\text{Log } K_p = -5.33 - 0.62\pi_2^H - 0.38\Sigma\alpha_2^H - 3.34\Sigma\beta_2^H + 1.85V_x$	H	Alcohols, Steroids	(27)
Steric descriptors			
$K_p = (b_1 + 0.0025/(b_2 + b_3 + P_{o:w}^{b4}))^{-1} MW^{b5}$	H	LMWVOCs; HMWOCs	(45)
$K_p = (b_1 + b_2P_{o:w})e^{(b3MW)}$	H	LMWVOCs; HMWOCs	(45)
$\text{Log } K_p = -5.14 - 0.47\Sigma Ca + 0.23\Sigma Cd + 0.038Pol$	H	Alcohols, Steroids	(60)
$\text{Log } K_p = -6.14 - 0.42\Sigma Ca + 0.23\Sigma Cd + 0.21L - 0.11W$	H	Alcohols, Steroids	(60)
$\text{Log } K_p = -7.29 + 0.15Pol$	H	Alcohols	(60)
$\text{Log } K_p = b_1 + b_2\text{Log}P_{o:w} + b_3MW^{0.5}$	H	LMWVOCs; HMWOCs	(45)
$\text{Log } K_p = -0.428\delta - 4.80\,{}^4X_{PC}^V + 28.06$	H	Hydrocorticone esters	(27)
$\text{Log } K_p = 0.652\text{Log}P_{o:w} - 0.00603MW - 0.623ABSQon - 0.313SsssCH - 2.3$	H	Dermal drugs; LMWVOCs; HMWOCs	(50)
$\text{Log } K_p = 0.77\text{Log}P_{o:w} - 0.0103MW - 2.33$	H	LMWVOCs; HMWOCs	(45)
$\text{Log } K_p = -0.786OT + 0.252\,{}^2\kappa - 1.617q_s^+ - 5.767$	H	Alcohols, Steroids	(27)
$\text{Log } K_p = 0.82\text{Log}P_{o:w} - 0.0093V_m - 0.039MP_t - 2.36$	H	Steroids	(45)
$\text{Log } K_p = 0.84\text{Log}P_{o:w} - 0.07(\log P_{o:w})^2 - 0.27Hb - 1.84\text{Log}MW + 4.39$	H	LMWVOCs; HMWOCs	(45)
$\text{Log } K_p = 28.4q^- + 0.018V_m + 2.824$	H	Barbiturates; Isoquinoline; Salicyclic acid	(27)
$\text{Log } K_p = 3.99\log TA + 4.53q_s^- - 0.762OT - 11.364$	H	Alcohols, Steroids	(27)
Hydrophobic descriptors			
$K_p = 1.17*10^{-7}P_{o:w}^{0.751} + 2.73*10^{-8}$	H	Pharmaceuticals	(45)
$K_p = b_1(P_{o:w}^{b2}/(b_3 + P_{o:w}^{b2}))$	H	HMWOCs	(45)
$\text{Log } K_p = -0.207\text{ Log}P_{o:w}^2 + 1.49\text{ Log}P_{o:w} - 5.42$	H	Steroids	(66)
$\text{Log } K_p = -0.37\text{Log}P_{o:w}^2 + 2.39\text{Log}P_{o:w} - 8.71$	H	Phenols	(69)
$\text{Log } K_p = 0.544\log P_{o:w} - 2.88$	H	Aliphatic alcohols	(66)
$\text{Log } K_p = 0.80\log P_{o:w} - 8.883$	H	Hydrocorticone esters	(27)
$\text{Log } K_p = -1.46\Delta\text{Log}P_{o:w} + 0.29\text{Log}P_{o:w} - 3.75$	H	Alcohols, steroids	(69)
$\text{Log } K_p = -4.36 - 0.38\Sigma Ca + 0.24\Sigma Cd$	H	Steroids	(60)

Mechanistically-based equations

$K_p = (P_{vo:w}*0.028D_l/0.0340)+(P_{p:w}*0.88D_p/0.0018)$	H	Acids; Alcohols; Hydrocarbons	(59)

[a] δ=solubility parameter, π_2^H=dipolarity/polarizability, α_2^H=overall hydrogen-bond acidity, β_2^H=overall hydrogen-bond basicity, ΣCa=Hydrogen bond acceptor free energy in the molecule, ΣCd=Hydrogen bond donor in the molecule, $^2\kappa$=molecular shape index, $^4X_{pc}^v$=connectivity indices, ABSQon=sum of absolute charges on oxygen and nitrogen atoms, b_1,b_2,b_3,b_4,b_5=regression coefficients without any assigned role, B_R=number of rotatable bonds, D_l=coefficient for diffusion into the lipid fraction of stratum corneum, D_p=coefficient for diffusion into the protein fraction of stratum corneum, Hb=number of hydrogen bonds formed by the substance, I_B=Balaban index, L=molecular length, MP_t=melting point, MW=molecular weight, OT=number of hydrogen bonding heteroatoms, $P_{o:w}$=n-octanol:water partition coefficient (or vegetable oil:water), Pol=describes bulk or volume related effects, $P_{p:w}$=Protein:water partition coefficient for stratum corneum, $P_{vo:w}$=vegetable oil:water partition coefficient, q^-=the most negative charge on the hydrogen bond accepting heteroatoms, Q^+/α=positive charge per unit volume, q_s^-=sum of atomic charges on hydrogen bonding heteroatoms, q_s^+=sum of atomic charges on hydrogen bonding hrydrogens, R_2=Excess molar refraction, SsOH=sum of E-state indices for all hydroxy groups, SsssCH=sum of E-state indices for all methyl groups, TA=total solvant accessible surface, V_m=molar volume, V_x=McGowan characteristic volume, and W=molecular width.

[b] F=fish, H=human, and R=rats.

[c] CFCs = chlorofluorocarbons, HMWOCs = high molecular weight organic chemicals, LMWVOCs=low molecular weight volatile organic chemicals, and VOCs = volatile organic chemicals.

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