

**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**

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

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

$P_{\text{brain:air}}=0.020P_{\text{o:a}}+0.380P_{\text{w:a}}+0.94$	H	LMWVOCs; CFC	(44)
$P_{\text{kidney:air}}=(0.014S_{\text{o}}+0.51S_{\text{w}})/S_{\text{a}}$	H	LMWVOCs	(51)
$P_{\text{kidney:air}}=0.011P_{\text{o:a}}+0.400P_{\text{w:a}}+0.69$	H	LMWVOCs; CFC	(44)
$P_{\text{kidney:air}}=-0.391+0.550\text{Log}P_{\text{w:a}}+0.440\text{Log}P_{\text{o:a}}$	H	Inert gases; LMWVOCs	(1)
$P_{\text{liver:air}}=(0.028S_{\text{o}}+0.51S_{\text{w}})/S_{\text{a}}$	H	LMWVOCs	(51)
$P_{\text{liver:air}}=0.028P_{\text{o:a}}+0.79$	H	LMWVOCs; CFC	(44)
$P_{\text{muscle:air}}=0.014P_{\text{o:a}}+0.384P_{\text{w:a}}+0.94$	H	LMWVOCs; CFC	(44)
$\text{Ln } P_{\text{adipose:air}}=0.032T_{\text{b}}-5.456$	R	LMWVOCs	(14)
$\text{Ln } P_{\text{liver:air}}=0.022T_{\text{b}}-4.638$	R	LMWVOCs	(14)
$\text{Log } P_{\text{adipose:air}}=0.920\text{Log}P_{\text{o:a}}+0.136$	R	LMWVOCs	(26)
$\text{Log } P_{\text{adipose:air}}=0.927\text{Log}P_{\text{o:a}}-0.032\text{Log}P_{\text{w:a}}+0.120$	R	LMWVOCs	(26)
$\text{Log } P_{\text{adipose:air}}=1.027\text{Log}P_{\text{o:a}}-0.046\text{Log}P_{\text{w:a}}-0.119$	R	Haloalkanes	(25)
$\text{Log } P_{\text{liver:air}}=0.574\text{Log}P_{\text{o:a}}+0.302\text{Log}P_{\text{w:a}}-0.278$	R	Haloalkanes	(25)
$\text{Log } P_{\text{liver:air}}=0.730\text{Log}P_{\text{o:a}}+0.128\text{Log}P_{\text{w:a}}-0.550$	R	LMWVOCs	(26)
$\text{Log } P_{\text{muscle:air}}=0.477\text{Log}P_{\text{o:a}}+0.365\text{Log}P_{\text{w:a}}-0.374$	R	Haloalkanes	(25)
$\text{Log } P_{\text{muscle:air}}=0.644\text{Log}P_{\text{o:a}}+0.180\text{Log}P_{\text{w:a}}-0.725$	R	LMWVOCs	(26)
$P_{\text{adipose:air}}=0.594P_{\text{o:a}}+0.085P_{\text{w:a}}+9.40$	R	LMWVOCs; CFC	(44)
$P_{\text{brain:air}}=0.054P_{\text{o:a}}+0.832P_{\text{w:a}}$	R	LMWVOCs; CFC	(44)
$P_{\text{kidney:air}}=0.097P_{\text{o:a}}+0.826P_{\text{w:a}}$	R	LMWVOCs; CFC	(44)
$P_{\text{liver:air}}=0.026P_{\text{o:a}}+0.878P_{\text{w:a}}+2.36$	R	LMWVOCs; CFC	(44)
$P_{\text{muscle:air}}=0.010P_{\text{o:a}}+0.772P_{\text{w:a}}+0.29$	R	LMWVOCs; CFC	(44)

Mechanistically-based equations

$P_{\text{tissue:air}} = (S_{\text{s}} V_{\text{wt}} + S_{\text{v}} V_{\text{nt}} + 0.7S_{\text{s}} V_{\text{pt}} + 0.3S_{\text{v}} V_{\text{pt}}) / S_{\text{a}}$	R, H	LMWVOCs	(55)
$P_{\text{tissue:air}} = P_{\text{o:w}} P_{\text{w:a}} (V_{\text{nt}} + 0.3V_{\text{pt}}) + P_{\text{w:a}} (V_{\text{wt}} + 0.7V_{\text{pt}})$	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			
<i>Electrostatic descriptors</i>			
$\text{Log } P_{\text{blood:air}} = -1.269 + 0.612R_2 + 0.916\pi_2^H + 3.614\alpha_2^H + 3.381\beta_2^H + 0.362\text{Log}P_{\text{he:a}}$	H	Inert gases; LMWVOCs	(2)
$\text{Log } P_{\text{plasma:air}} = -1.48 + 0.490R_2 + 2.04\pi_2^H + 3.5074\alpha_2^H + 3.911\beta_2^H + 0.157\text{Log}P_{\text{he:a}}$	H	Inert gases; LMWVOCs	(2)
<i>Steric descriptors</i>			
$\text{Log } P_{\text{blood:air}} = 0.0072\text{MW} + 0.197$	H	Trihalomethanes	(7)
$\text{Log } P_{\text{blood:air}} = 0.321N_{\text{Br}} + 1.06$	H	Trihalomethanes	(7)
$P_{\text{blood:air}} = 0.07\text{MW} + 5.59$	H	volatile hydrocarbons	(52)
$\text{Log } P_{\text{blood:air}} = 0.443Q_{\text{H}} - 0.303N_{\text{F}} + 0.225N_{\text{Cl}} + 0.510N_{\text{BR}} + 0.155N_{\text{C}} - 0.104$	R	Haloalkanes	(25)
<i>Hydrophobic descriptors</i>			
$\text{Log } (P_{\text{blood:water}} - V_{\text{wb}}) = 0.7P_{\text{o:w}} - 0.75$	F	Chloroethanes; Benzene	(8)
$\text{Ln } P_{\text{blood:air}} = 0.038T_{\text{b}} - 13.3$	H	volatile hydrocarbons	(14)
$\text{Log } P_{\text{blood:air}} = 0.0109T_{\text{b}} - 2.584$	H	Trihalomethanes	(7)
$\text{Log } P_{\text{blood:air}} = -0.14\text{Log}P_{\text{o:a}} + 0.86\text{Log}P_{\text{w:a}} + 0.47$	H	Hydrophilic VOCs	(72)
$\text{Log } P_{\text{blood:air}} = 0.685\text{log}P_{\text{o:a}} - 0.6565$	H	Trihalomethanes	(7)
$\text{Log } P_{\text{blood:air}} = 0.45\text{Log}P_{\text{w:a}} + 1.21$	H	VOCs	(38)
$\text{Log } P_{\text{blood:air}} = -0.003\text{Log}P_{\text{w:a}} + 1.47$	H	VOCs	(38)
$\text{Log } P_{\text{blood:air}} = -0.074 + 0.802\text{Log}P_{\text{w:a}} + 0.218\text{Log}P_{\text{o:a}}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{\text{blood:air}} = -0.07\text{Log}S_{\text{w}} + 1.21$	H	VOCs	(38)
$\text{Log } P_{\text{blood:air}} = -0.09\text{Log}P_{\text{o:a}} + 2.45$	H	VOCs	(38)
$\text{Log } P_{\text{blood:air}} = -0.102 + 0.675\text{Log}P_{\text{w:a}} + 0.315\text{Log}P_{\text{o:a}}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{\text{blood:air}} = -0.295 + 0.588\text{Log}P_{\text{w:a}} + 0.411\text{Log}P_{\text{o:a}}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{\text{blood:air}} = -0.338\text{Log}P_{\text{o:a}} + 3.121$	H	Hydrocarbures halogénés	(70)
$\text{Log } P_{\text{blood:air}} = -0.6737 + 0.5319\text{Log}P_{\text{o:a}}\text{Log}P_{\text{w:a}}$	H	VOCs	(65)
$\text{Log } P_{\text{blood:air}} = 0.695\text{Log}P_{\text{o:a}} - 1.076$	H	LMWVOCs	(21)
$\text{Log } P_{\text{blood:air}} = -0.820 + 0.754\text{Log}P_{\text{o:a}}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{\text{blood:air}} = 0.09\text{Log}S_{\text{w}} + 8.25\text{Log}V_{\text{o}} - 11.09$	H	VOCs	(38)
$\text{Log } P_{\text{blood:air}} = 0.11\text{Log}S_{\text{w}} + 1.91$	H	VOCs	(38)
$\text{Log } P_{\text{blood:air}} = 0.180\text{Log}P_{\text{o:a}} + 0.889\text{Log}P_{\text{w:a}} + 0.054$	H	Hydrophobic VOCs	(71)
$\text{Log } P_{\text{blood:air}} = 0.20\text{Log}S_{\text{w}} + 1.29$	H	VOCs	(38)

$\text{Log } P_{\text{blood:air}} = 0.22\text{Log}P_{\text{w:a}} + 0.67\text{Log}P_{\text{o:a}} - 0.98$	H	VOCs	(38)
$\text{Log } P_{\text{blood:air}} = 0.22\text{Log}S_{\text{w}} + 10.78\text{Log}V_{\text{w}} - 40.99$	H	VOCs	(38)
$\text{Log } P_{\text{blood:air}} = 0.262 + 0.996\text{Log}P_{\text{w:a}}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{\text{blood:air}} = 0.27\text{Log}1000/P + 5.10\text{Log}V_{\text{o}} - 6.67$	H	VOCs	(38)
$\text{Log } P_{\text{blood:air}} = 0.31\text{Log}S_{\text{w}} + 3.90\text{Log}V_{\text{o}} - 4.53$	H	VOCs	(38)
$\text{Log } P_{\text{blood:air}} = 0.35\text{Log}1000/P + 1.01$	H	VOCs	(38)
$\text{Log } P_{\text{blood:air}} = 0.35\text{Log}S_{\text{w}} + 0.79\text{Log}1000/P + 1.34\text{Log}V_{\text{o}} - 2.23$	H	VOCs	(38)
$\text{Log } P_{\text{blood:air}} = 0.37\text{Log}S_{\text{w}} + 10.09\text{Log}V_{\text{w}} - 38.40$	H	VOCs	(38)
$\text{Log } P_{\text{blood:air}} = 0.38\text{Log}S_{\text{w}} + 0.91\text{Log}1000/P - 0.45$	H	VOCs	(38)
$\text{Log } P_{\text{blood:air}} = 0.45\text{Log}S_{\text{w}} + 0.81\text{Log}1000/P - 0.40$	H	VOCs	(38)
$\text{Log } P_{\text{blood:air}} = 0.48\text{Log}S_{\text{w}} + 0.75\text{Log}1000/P + 1.67\text{Log}V_{\text{o}} - 2.77$	H	VOCs	(38)
$\text{Log } P_{\text{blood:air}} = 0.51\text{Log}1000/P + 0.37$	H	VOCs	(38)
$\text{Log } P_{\text{blood:air}} = 0.581\text{Log}P_{\text{o:a}} + 0.332\text{Log}P_{\text{w:a}} - 0.599$	H	LMWVOCs	(26)
$\text{Log } P_{\text{blood:air}} = 0.63\text{Log}1000/P + 0.38$	H	VOCs	(38)
$\text{Log } P_{\text{blood:air}} = 0.65\text{Log}P_{\text{o:a}} - 0.84$	H	VOCs	(38)
$\text{Log } P_{\text{blood:air}} = 0.851\text{Log}S_{\text{w}} + 1.78$	H	VOCs	(38)
$\text{Log } P_{\text{blood:air}} = 0.984\text{Log}P_{\text{w:a}} + 0.053$	H	Ketones; Esters; Gases	(70)
$\text{Log } P_{\text{blood:air}} = 1.07\text{Log}P_{\text{w:a}} + 0.27\text{Log}P_{\text{o:a}} - 0.79$	H	VOCs	(38)
$\text{Log } P_{\text{blood:air}} = 1.21\text{Log}V_{\text{o}} - 0.17$	H	VOCs	(38)
$\text{Log } P_{\text{blood:air}} = 3.05 - 0.34P_{\text{o:n}}$	H	Ketones	(10)
$\text{Log } P_{\text{blood:air}} = -3.922 + 1.369R_{\text{G}}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{\text{blood:air}} = 5.89\text{Log}V_{\text{w}} - 21.43$	H	VOCs	(38)
$\text{Log } P_{\text{blood:air}} = 7.86\text{Log}V_{\text{o}} - 10.40$	H	VOCs	(38)
$/\text{id } \text{Log } P_{\text{blood:air}} = 8.90\text{Log}V_{\text{w}} - 33.40$	H	VOCs	(38)
$\text{Log } P_{\text{milk:air}} = 0.900\text{log}P_{\text{o:a}} - 1.095$	H	Trihalomethanes	(7)
$\text{Log } P_{\text{plasma:air}} = -0.079 + 0.896\text{Log}P_{\text{w:a}} + 0.149\text{Log}P_{\text{o:a}}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{\text{plasma:air}} = -0.082 + 0.894\text{Log}P_{\text{w:a}} + 0.152\text{Log}P_{\text{o:a}}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{\text{plasma:air}} = -0.848 + 0.890\text{Log}P_{\text{o:a}}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{\text{plasma:air}} = -3.696 + 1.208R_{\text{G}}$	H	Inert gases; LMWVOCs	(1)
$\text{Log } P_{\text{plasma:air}} = 0.038 + 1.019\text{Log}P_{\text{w:a}}$	H	Inert gases; LMWVOCs	(1)
$P_{\text{blood:air}} = 0.0072P_{\text{o:a}} + 0.898P_{\text{w:a}} + 0.03$	H	LMWVOCs; CFC	(44)
$P_{\text{blood:air}} = 0.08e^{0.0308T_{\text{b}}}$	H	volatile hydrocarbons	(52)
$P_{\text{blood:air}} = 0.00442P_{\text{o:a}}$	H	volatile hydrocarbons	(52)
$P_{\text{blood:air}} = 0.88P_{\text{w:a}} + 0.012$	H	VOCs	(20)

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

QSARs: Free-Wilson-type equations

$P_{\text{blood:water}} = \text{BS}_{(\text{C-C})} (28.4) + n\text{CL}_2(-12.9) + n\text{CL}_3(12.9)$	F	Chloroethanes	(23)
$P_{\text{blood:air}} = \text{BS}_{(\text{C-C})} (26.2) + n\text{H}_3(-34.9) + n\text{CL}(-4.51) + n\text{CL}_2(29.4) + n\text{CL}_3(11.5)$	H	Chloroethanes	(22)
$P_{\text{blood:air}} = \text{BS}_{(\text{C-C})} (45.6) + n\text{H}_3(-51.5) + n\text{CL}(-8.86) + n\text{CL}_2(36.4) + n\text{CL}_3(11.1)$	R	Chloroethanes	(22)

Mechanistically-based equations

$P_{\text{blood:air}} = P_{\text{o:w}}P_{\text{w:a}}(V_{\text{nb}}+0.3V_{\text{pb}})+P_{\text{w:a}}(V_{\text{wb}}+0.7V_{\text{pb}})$	R, H	LMWVOCs	(57)
$P_{\text{blood:air}}=[f_e(S_s V_{\text{we}}+S_v V_{\text{ne}}+0.7S_s V_{\text{pe}}+0.3S_v V_{\text{pe}})+f_p(S_s V_{\text{wp}}+S_v V_{\text{np}}+0.7S_s V_{\text{pp}}+0.3S_v V_{\text{pp}})]/S_a$	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			
<i>Steric descriptors</i>			
$\text{Log } P_{\text{adipose:blood}} = 0.168 + 0.198R_2 + 0.130\pi_2^H - 1.211\alpha_2^H - 3.267\beta_2^H + 2.275V_x$	H	Inert gases; LMWVOCs; CFCs	(2)
$\text{Log } P_{\text{brain:blood}} = -0.166 + 0.239R_2 - 0.626\pi_2^H - 0.368\alpha_2^H - 0.615\beta_2^H + 1.072V_x$	H	Inert gases; LMWVOCs; CFCs	(2)
$\text{Log } P_{\text{brain:blood}} = -0.0148\text{PSA} + 0.152\text{Log}P_{\text{o:w}} + 0.139$	H	Inert gases; HMWOCs; LMWVOCs	(11)
$\text{Log } P_{\text{brain:blood}} = 1.359 + 0.338\text{Log}P_{\text{cyh}} - 0.00618V_m$	H	H ₂ -R antagonists	(34)
$\text{Log } P_{\text{heart:blood}} = -0.346 + 0.204\pi_2^H - 2.150\alpha_2^H - 0.853\beta_2^H + 0.931V_x$	H	Inert gases; LMWVOCs; CFCs	(2)
$\text{Log } P_{\text{kidney:blood}} = -0.188 + 0.226R_2 - 0.559\pi_2^H - 0.433\beta_2^H + 0.832V_x$	H	Inert gases; LMWVOCs; CFCs	(2)
$\text{Log } P_{\text{liver:blood}} = -0.270 + 0.233R_2 - 0.375\pi_2^H - 1.004\alpha_2^H - 1.118\beta_2^H + 0.832V_x$	H	Inert gases; LMWVOCs; CFCs	(2)
$\text{Log } P_{\text{lung:blood}} = -0.150 - 0.195\pi_2^H + 0.389V_x$	H	Inert gases; LMWVOCs; CFCs	(2)
$\text{Log } P_{\text{muscle:blood}} = -0.222 - 0.479\pi_2^H - 0.517\beta_2^H + 0.999V_x$	H	Inert gases; LMWVOCs; CFCs	(2)
$P_{\text{adipose:plasma}} = 1.9988 - 0.5004\text{UNS} + 0.1793\text{NPL} + 0.05931\text{DIFF}^2$	H	PCBs	(48)
$\text{Log } P_{\text{brain:blood}} = 0.088 + 0.264R_2 - 0.966\pi_2^H - 0.705\alpha_2^H - 0.756\beta_2^H + 1.189V_x$	R	H ₂ -R antagonists	(47)
$\text{Log } P_{\text{brain:blood}} = -0.088 + 0.272 \text{Log } P_{\text{o:w}} - 0.00116\text{MW}$	R	H ₂ -R antagonists	(34)
$\text{Log } P_{\text{brain:blood}} = -0.00116\text{MW} + 0.272\text{Log}P_{\text{o:w}} - 0.088$	R	Inert gases; volatile hydrocarbons	(47)
$\text{Log } P_{\text{brain:blood}} = -0.01V_m + 0.35\text{Log}P_{\text{o:w}} + 0.99I_3 + 1.25$	R	Drug-like molecules	(47)
$\text{Log } P_{\text{brain:blood}} = -0.021\text{PSA} - 0.003\text{MV} + 1.643$	R	Inert gases; HMWOCs; LMWVOCs	(11)
$\text{Log } P_{\text{brain:blood}} = -0.0322\text{DPSA} + 1.33$	R	HMWOCs	(47)
$\text{Log } P_{\text{brain:blood}} = -0.038 + 0.198R_2 - 0.687\pi_2^H - 0.715\alpha_2^H - 0.698\beta_2^H + 0.995V_x$	R	H ₂ -R antagonists; Inert gases; SOMs	(47)
$\text{Log } P_{\text{brain:blood}} = -0.218(\text{N}_N + \text{N}_O) + 0.235\text{log}P_{\text{o:w}} - 0.027$	R	HMWOCs	(47)
$\text{Log } P_{\text{brain:blood}} = 0.476 + 0.541\text{Log}P_{\text{o:w}} - 0.00794\text{MW}$	R	H ₂ -R antagonists	(34)
$\text{Log } P_{\text{brain:blood}} = 1.296 + 0.309\text{Log}P_{\text{cyh}} - 0.00570\text{MW}$	R	H ₂ -R antagonists	(34)
<i>Hydrophobic descriptors</i>			
$\text{Log } P_{\text{brain:blood}} = 0.39\text{Log}P_{\text{o:w}} + 0.68$	H	Drugs, Hormones	(66)
$\text{Log } P_{\text{brain:blood}} = 0.054G^o + 0.43$	H	H ₂ -R antagonists; LMWVOCs	(43)
$P_{\text{adipose:blood}} = [(V_{\text{lt}}P_{\text{o:w}}^{A1} + V_{\text{wt}}) / (V_{\text{lb}}P_{\text{o:w}}^{A2} + V_{\text{wb}})] + B$	H, R	LMWVOCs	(16)
$P_{\text{brain:blood}} = [(V_{\text{lt}}P_{\text{o:w}}^{A1} + V_{\text{wt}}) / (V_{\text{lb}}P_{\text{o:w}}^{A2} + V_{\text{wb}})] + B$	H, R	LMWVOCs	(16)
$P_{\text{kidney:blood}} = [(V_{\text{lt}}P_{\text{o:w}}^{A1} + V_{\text{wt}}) / (V_{\text{lb}}P_{\text{o:w}}^{A2} + V_{\text{wb}})] + B$	H, R	LMWVOCs	(16)
$P_{\text{liver:blood}} = [(V_{\text{lt}}P_{\text{o:w}}^{A1} + V_{\text{wt}}) / (V_{\text{lb}}P_{\text{o:w}}^{A2} + V_{\text{wb}})] + B$	H, R	LMWVOCs	(16)
$P_{\text{muscle:blood}} = [(V_{\text{lt}}P_{\text{o:w}}^{A1} + V_{\text{wt}}) / (V_{\text{lb}}P_{\text{o:w}}^{A2} + V_{\text{wb}})] + B$	H, R	LMWVOCs	(16)
$\text{Ln } P_{\text{kidney:blood}} = 0.0065\sum o$	R	HMWOCs	(75)
$\text{Ln } P_{\text{liver:blood}} = 0.025\sum i$	R	HMWOCs	(75)

Mechanistically-based equations

$$P_{\text{tissue:blood}} = (S_o V_{nt} + S_w * 0.7 V_{pt} + S_o * 0.3 V_{pt} + S_w V_{wt}) / (S_o V_{nb} + S_w * 0.7 V_{pb} + S_o * 0.3 V_{pb} + S_w V_{wb}) \quad \text{H} \quad \text{LMWVOCs} \quad (53)$$

$$P_{\text{tissue:blood}} = (P_{o:w} V_{nt} + V_{wt} + P_{o:w} * 0.3 V_{pt} + 0.7 V_{pt}) / [f_e (P_{o:w} V_{ne} + V_{we} + P_{o:w} * 0.3 V_{pe} + 0.7 V_{pe}) + f_p (P_{o:w} V_{np} + V_{wp} + P_{o:w} * 0.3 V_{pp} + 0.7 V_{pp})] \quad \text{R} \quad \text{Ketones; Alcohols; Esters} \quad (54)$$

$$P_{\text{tissue:blood}} = [P_{o:w} (V_{nt} + 0.3 V_{pt}) + (V_{wt} + 0.7 V_{pt})] / [P_{o:w} (V_{nb} + 0.3 V_{pb}) + (V_{wb} + 0.7 V_{pb})] \quad \text{R, H} \quad \text{LMWVOCs} \quad (56)$$

^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, $n_{\text{acc,solv}}$ =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, $^{\circ}G$ =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), $P_{\text{oct-cyc}}$ =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			
<i>Electrostatic descriptors</i>			
$\text{Log } K_p = -0.626\Sigma\text{Ca} - 23.8\Sigma(\text{Q}+)/\alpha - 0.289\text{SsssCH} - 0.0357\text{SsOH} - 0.482\text{I}_B + 0.405\text{B}_R + 0.834$	H	LMWVOCs; HMWOCs	(45)
$\text{Log } K_p = 0.44\text{R}_2 - 0.49\pi_2^H - 1.48\Sigma\alpha_2^H - 3.44\Sigma\beta_2^H + 1.94\text{V}_x - 5.13$	H	LMWVOCs; HMWOCs	(45)
$\text{Log } K_p = -0.59\pi_2^H - 0.63\Sigma\alpha_2^H - 3.48\Sigma\beta_2^H + 1.79\text{V}_x - 5.05$	H	LMWVOCs; HMWOCs	(45)
$\text{Log } K_p = -5.33 - 0.62\pi_2^H - 0.38\Sigma\alpha_2^H - 3.34\Sigma\beta_2^H + 1.85\text{V}_x$	H	Alcohols, Steroids	(27)
<i>Steric descriptors</i>			
$K_p = (b_1 + 0.0025/(b_2 + b_3 + P_{o:w}^{b_4}))^{-1} \text{MW}^{b_5}$	H	LMWVOCs; HMWOCs	(45)
$K_p = (b_1 + b_2 P_{o:w}) e^{(b_3 \text{MW})}$	H	LMWVOCs; HMWOCs	(45)
$\text{Log } K_p = -5.14 - 0.47\Sigma\text{Ca} + 0.23\Sigma\text{Cd} + 0.038\text{Pol}$	H	Alcohols, Steroids	(60)
$\text{Log } K_p = -6.14 - 0.42\Sigma\text{Ca} + 0.23\Sigma\text{Cd} + 0.21\text{L} - 0.11\text{W}$	H	Alcohols, Steroids	(60)
$\text{Log } K_p = -7.29 + 0.15\text{Pol}$	H	Alcohols	(60)
$\text{Log } K_p = b_1 + b_2 \text{Log } P_{o:w} + b_3 \text{MW}^{0.5}$	H	LMWVOCs; HMWOCs	(45)
$\text{Log } K_p = -0.428\delta - 4.80^4 \text{X}_{\text{PC}}^V + 28.06$	H	Hydrocorticone esters	(27)
$\text{Log } K_p = 0.652 \text{Log } P_{o:w} - 0.00603 \text{MW} - 0.623 \text{ABSQon} - 0.313 \text{SsssCH} - 2.3$	H	Dermal drugs; LMWVOCs; HMWOCs	(50)
$\text{Log } K_p = 0.77 \text{Log } P_{o:w} - 0.0103 \text{MW} - 2.33$	H	LMWVOCs; HMWOCs	(45)
$\text{Log } K_p = -0.786 \text{OT} + 0.252^2 \kappa - 1.617 q_s^+ - 5.767$	H	Alcohols, Steroids	(27)
$\text{Log } K_p = 0.82 \text{Log } P_{o:w} - 0.0093 \text{V}_m - 0.039 \text{MP}_t - 2.36$	H	Steroids	(45)
$\text{Log } K_p = 0.84 \text{Log } P_{o:w} - 0.07 (\text{log } P_{o:w})^2 - 0.27 \text{Hb} - 1.84 \text{Log } \text{MW} + 4.39$	H	LMWVOCs; HMWOCs	(45)
$\text{Log } K_p = 28.4 q^- + 0.018 \text{V}_m + 2.824$	H	Barbiturates; Isoquinoline; Salicyclic acid	(27)
$\text{Log } K_p = 3.99 \text{log } \text{TA} + 4.53 q_s^- - 0.762 \text{OT} - 11.364$	H	Alcohols, Steroids	(27)
<i>Hydrophobic descriptors</i>			
$K_p = 1.17 * 10^{-7} P_{o:w}^{0.751} + 2.73 * 10^{-8}$	H	Pharmaceuticals	(45)
$K_p = b_1 (P_{o:w}^{b_2} / (b_3 + P_{o:w}^{b_2}))$	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)
$\text{Log } K_p = 0.544 \text{log } P_{o:w} - 2.88$	H	Aliphatic alcohols	(66)
$\text{Log } K_p = 0.80 \text{log } P_{o:w} - 8.883$	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)
$\text{Log } K_p = -4.36 - 0.38 \Sigma \text{Ca} + 0.24 \Sigma \text{Cd}$	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, $ABSQ_{on}$ =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 hydrogens, 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 solvent 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, LMWOCs=low molecular weight volatile organic chemicals, and VOCs = volatile organic chemicals.

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