# 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.

**RFQ-DC-03-00328**

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*** | | | |
| $\text{Log } P_{adipose:air} = (0.734\,{}^1x^v) - (0.029x^v_s) - (1.57(1/{}^1x)) - (0.559(1/{}^1x^v)) - 0.098\,{}^3x^v_c + 2.213$ | R | Haloalkanes | (25) |
| $\text{Log } P_{adipose:air} = 0.734\,{}^1X^v - 0.0291X_s^v - 1.570/{}^1X^v - 0.559\,{}^1X^v - 0.098\,{}^4X_c^v + 2.213$ | 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) |
| $\text{Log } P_{adipose:air} = 1.037\,{}^1x^v - (0.007(1/x^v_s)) + 0.022Q_H - 0.177\,{}^3x^v_c - 0.199N_F - 0.0036$ | R | Haloalkanes | (25) |
| $\text{Log } P_{liver:air} = (1.072\,{}^1x^v) - (0.021(1/x^v_s)) + (0.647(1/{}^1x^v)) - (0.304\,{}^4x^V_C) - 1.212$ | 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) |
| $\text{Log } P_{liver:air} = -0.685\,{}^1x^v - (0.020(1/x^v_s)) + 0.232Q_H + (0.298(1/{}^1x^v)) + 0.104N_{Cl} - 0.726$ | R | Haloalkanes | (25) |
| $\text{Log } P_{liver:air} = 1.072\,{}^1X^v - 0.021/X_s^v + 0.647/{}^1X^v - 0.304\,{}^4X_c^v - 1.212$ | 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) |
| $\text{Log } P_{muscle:air} = 0.399\,{}^1x^v - (0.007(1/x^v_s)) + 0.295Q_H + 0.259\,{}^4x^v_{pc} - 0.194N_F - 0.217$ | R | Haloalkanes | (25) |
| $\text{Log } P_{muscle:air} = (0.995\,{}^1x^v) - (0.018(1/x^v_s)) - (0.424\,{}^4x^v_c) - (0.559(1/{}^1x^v) + (0.602(1/{}^1x^v)) - 1.334$ | 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) |

| | | | |
|---|---|---|---|
| $\text{Log } P_{adipose:air} = 0.782 \text{Log} P_{o:a} + 0.201 \text{Log} P_{w:a} + 0.432$ | H | hydrophobic VOCs | (71) |
| $\text{Log } P_{adipose:air} = 0.901 \text{Log} P_{o:a} + 0.150$ | H | LMWVOCs | (21) |
| $\text{Log } P_{adipose:air} = 0.174 + 0.910 \text{Log} P_{o:a}$ | H | Inert gases; LMWVOCs | (1) |
| $\text{Log } P_{brain:air} = -0.16 \text{Log} P_{o:a} + 0.82 \text{Log} P_{w:a} + 0.47$ | H | hydrophilic VOCs | (72) |
| $\text{Log } P_{brain:air} = 0.274 + 0.537 \text{Log} P_{w:a} + 0.444 \text{Log} P_{o:a}$ | H | Inert gases; LMWVOCs | (1) |
| $\text{Log } P_{brain:air} = 0.394 + 1.096 \text{ Log} P_{w:a}$ | H | Inert gases; LMWVOCs | (1) |
| $\text{Log } P_{brain:air} = 0.471 \text{Log} P_{o:a} + 0.630 \text{Log } P_{w:a} - 0.305$ | H | hydrophobic VOCs | (71) |
| $\text{Log } P_{brain:air} = 0.844 \text{Log} P_{o:a} - 1.124$ | H | LMWVOCs | (21) |
| $\text{Log } P_{brain:air} = -0.850 + 0.773 \text{ Log} P_{o:a}$ | H | Inert gases; LMWVOCs | (1) |
| $\text{Log } P_{brain:air} = -3.692 + 1.253 R_G$ | H | Inert gases; LMWVOCs | (1) |
| $\text{Log } P_{kidney:air} = -0.18 \text{Log} P_{o:a} + 0.82 \text{Log} P_{w:a} + 0.53$ | H | hydrophilic VOCs | (72) |
| $\text{Log } P_{kidney:air} = 0.277 + 1.111 \text{Log} P_{w:a}$ | H | Inert gases; LMWVOCs | (1) |
| $\text{Log } P_{kidney:air} = 0.466 \text{Log} P_{o:a} + 0.379 \text{Log} P_{w:a} - 0.332$ | H | hydrophobic VOCs | (71) |
| $\text{Log } P_{kidney:air} = 0.700 \text{Log} P_{o:a} - 0.877$ | H | LMWVOCs | (21) |
| $\text{Log } P_{kidney:air} = -0.920 + 0.764 \text{Log} P_{o:a}$ | H | Inert gases; LMWVOCs | (1) |
| $\text{Log } P_{liver:air} = -0.388 + 0.502 \text{Log} P_{w:a} + 0.497 \text{Log} P_{o:a}$ | H | Inert gases; LMWVOCs | (1) |
| $\text{Log } P_{liver:air} = 0.432 + 1.064 \text{Log} P_{w:a}$ | H | Inert gases; LMWVOCs | (1) |
| $\text{Log } P_{liver:air} = 0.746 \text{Log} P_{o:a} + 0.178 \text{Log} P_{w:a} - 0.767$ | H | hydrophobic VOCs | (71) |
| $\text{Log } P_{liver:air} = 0.871 \text{Log} P_{o:a} - 1.044$ | H | LMWVOCs | (21) |
| $\text{Log } P_{liver:air} = -0.875 + 0.773 \text{Log} P_{o:a}$ | H | Inert gases; LMWVOCs | (1) |
| $\text{Log } P_{lung:air} = -0.21 \text{Log} P_{o:a} + 0.91 \text{Log} P_{w:a} + 0.41$ | H | hydrophilic VOCs | (72) |
| $\text{Log } P_{lung:air} = -0.057 + 0.870 \text{Log} P_{w:a} + 0.146 \text{Log} P_{o:a}$ | H | Inert gases; LMWVOCs | (1) |
| $\text{Log } P_{lung:air} = 0.057 + 0.978 \text{Log} P_{w:a}$ | H | Inert gases; LMWVOCs | (1) |
| $\text{Log } P_{lung:air} = 0.373 \text{Log} P_{o:a} + 0.416 \text{Log} P_{w:a} - 0.216$ | H | hydrophobic VOCs | (71) |
| $\text{Log } P_{lung:air} = 0.644 \text{Log} P_{o:a} - 0.815$ | H | LMWVOCs | (21) |
| $\text{Log } P_{lung:air} = -0.833 + 0.911 \text{Log} P_{o:a}$ | H | Inert gases; LMWVOCs | (1) |
| $\text{Log } P_{muscle:air} = -0.19 \text{Log} P_{o:a} + 0.82 \text{Log} P_{w:a} + 0.54$ | H | hydrophilic VOCs | (72) |
| $\text{Log } P_{muscle:air} = 0.49 \text{Log} P_{o:a} + 0.39 \text{Log} P_{w:a} - 0.31$ | H | hydrophobic VOCs | (72) |
| $\text{Log } P_{muscle:air} = -0.263 + 0.575 \text{Log} P_{w:a} + 0.423 \text{Log} P_{o:a}$ | H | Inert gases; LMWVOCs | (1) |
| $\text{Log } P_{muscle:air} = 0.351 + 1.108 \text{Log} P_{w:a}$ | H | Inert gases; LMWVOCs | (1) |
| $\text{Log } P_{muscle:air} = 0.652 \text{Log} P_{o:a} - 0.702$ | H | LMWVOCs | (21) |
| $\text{Log } P_{muscle:air} = -0.852 + 0.768 \text{Log} P_{o:a}$ | 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*** | | | |
| $\text{Log } P_{blood:air} = -1.269+0.612R_2+0.916\pi_2^H+3.614\alpha_2^H+3.381\beta_2^H+0.362\text{Log}P_{he:a}$ | H | Inert gases; LMWVOCs | (2) |
| $\text{Log } P_{plasma:air} = -1.48+0.490R_2+2.04\pi_2^H+3.5074\alpha_2^H+3.911\beta_2^H+0.157\text{Log}P_{he:a}$ | 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) |
| $\text{Log } P_{blood:air} = -0.14\text{Log}P_{o:a}+0.86\text{Log}P_{w:a}+0.47$ | H | Hydrophilic VOCs | (72) |
| $\text{Log } P_{blood:air} = 0.685\text{log}P_{o:a}-0.6565$ | H | Trihalomethanes | (7) |
| $\text{Log } P_{blood:air} =0.45\text{Log}P_{w:a}+1.21$ | H | VOCs | (38) |
| $\text{Log } P_{blood:air}= -0.003\text{Log}P_{w:a}+1.47$ | H | VOCs | (38) |
| $\text{Log } P_{blood:air}= -0.074+0.802\text{Log}P_{w:a}+0.218\text{Log}P_{o:a}$ | H | Inert gases; LMWVOCs | (1) |
| $\text{Log } P_{blood:air}= -0.07\text{Log}S_w+1.21$ | H | VOCs | (38) |
| $\text{Log } P_{blood:air}= -0.09\text{Log}P_{o:a}+2.45$ | H | VOCs | (38) |
| $\text{Log } P_{blood:air}= -0.102+0.675\text{Log}P_{w:a}+0.315\text{Log}P_{o:a}$ | H | Inert gases; LMWVOCs | (1) |
| $\text{Log } P_{blood:air}= -0.295+0.588\text{Log}P_{w:a}+0.411\text{Log}P_{o:a}$ | H | Inert gases; LMWVOCs | (1) |
| $\text{Log } P_{blood:air}= -0.338\text{Log}P_{o:a}+3.121$ | H | Hydrocarbures halogénés | (70) |
| $\text{Log } P_{blood:air}= -0.6737+0.5319\text{Log}P_{o:a}\text{Log}P_{w:a}$ | H | VOCs | (65) |
| $\text{Log } P_{blood:air}= 0.695\text{Log}P_{o:a}-1.076$ | H | LMWVOCs | (21) |
| $\text{Log } P_{blood:air}= -0.820+0.754\text{Log}P_{o:a}$ | H | Inert gases; LMWVOCs | (1) |
| $\text{Log } P_{blood:air}=0.09\text{Log}S_w+8.25\text{Log}V_o-11.09$ | H | VOCs | (38) |
| $\text{Log } P_{blood:air}=0.11\text{Log}S_w+1.91$ | H | VOCs | (38) |
| $\text{Log } P_{blood:air}=0.180\text{Log}P_{o:a}+0.889\text{Log}P_{w:a}+0.054$ | H | Hydrophobic VOCs | (71) |
| $\text{Log } P_{blood:air}=0.20\text{Log}S_w+1.29$ | H | VOCs | (38) |

| | | | |
|---|---|---|---|
| $\text{Log } P_{blood:air}=0.22\text{Log}P_{w:a}+0.67\text{Log}P_{o:a}-0.98$ | H | VOCs | (38) |
| $\text{Log } P_{blood:air}=0.22\text{Log}S_{w}+10.78\text{Log}V_{w}-40.99$ | H | VOCs | (38) |
| $\text{Log } P_{blood:air}=0.262+0.996\text{Log}P_{w:a}$ | H | Inert gases; LMWVOCs | (1) |
| $\text{Log } P_{blood:air}=0.27\text{Log}1000/P+5.10\text{Log}V_{o}-6.67$ | H | VOCs | (38) |
| $\text{Log } P_{blood:air}=0.31\text{Log}S_{w}+3.90\text{Log}V_{o}-4.53$ | H | VOCs | (38) |
| $\text{Log } P_{blood:air}=0.35\text{Log}1000/P+1.01$ | H | VOCs | (38) |
| $\text{Log } P_{blood:air}=0.35\text{Log}S_{w}+0.79\text{Log}1000/P+1.34\text{Log}V_{o}-2.23$ | H | VOCs | (38) |
| $\text{Log } P_{blood:air}=0.37\text{Log}S_{w}+10.09\text{Log}V_{w}-38.40$ | H | VOCs | (38) |
| $\text{Log } P_{blood:air}=0.38\text{Log}S_{w}+0.91\text{Log}1000/P-0.45$ | H | VOCs | (38) |
| $\text{Log } P_{blood:air}=0.45\text{Log}S_{w}+0.81\text{Log}1000/P-0.40$ | H | VOCs | (38) |
| $\text{Log } P_{blood:air}=0.48\text{Log}S_{w}+0.75\text{Log}1000/P+1.67\text{Log}V_{o}-2.77$ | H | VOCs | (38) |
| $\text{Log } P_{blood:air}=0.51\text{Log}1000/P+0.37$ | H | VOCs | (38) |
| $\text{Log } P_{blood:air}=0.581\text{Log}P_{o:a}+0.332\text{Log}P_{w:a}-0.599$ | H | LMWVOCs | (26) |
| $\text{Log } P_{blood:air}=0.63\text{Log}1000/P+0.38$ | H | VOCs | (38) |
| $\text{Log } P_{blood:air}=0.65\text{Log}P_{o:a}-0.84$ | H | VOCs | (38) |
| $\text{Log } P_{blood:air}=0.851\text{Log}S_{w}+1.78$ | H | VOCs | (38) |
| $\text{Log } P_{blood:air}=0.984\text{Log}P_{w:a}+0.053$ | H | Ketones; Esters; Gases | (70) |
| $\text{Log } P_{blood:air}=1.07\text{Log}P_{w:a}+0.27\text{Log}P_{o:a}-0.79$ | H | VOCs | (38) |
| $\text{Log } P_{blood:air}=1.21\text{Log}V_{o}-0.17$ | H | VOCs | (38) |
| $\text{Log } P_{blood:air}=3.05-0.34P_{o:n}$ | H | Ketones | (10) |
| $\text{Log } P_{blood:air}=-3.922+1.369R_{G}$ | H | Inert gases; LMWVOCs | (1) |
| $\text{Log } P_{blood:air}=5.89\text{Log}V_{w}-21.43$ | H | VOCs | (38) |
| $\text{Log } P_{blood:air}=7.86\text{Log}V_{o}-10.40$ | H | VOCs | (38) |
| /id $\text{Log } P_{blood:air}=8.90\text{Log}V_{w}-33.40$ | H | VOCs | (38) |
| $\text{Log } P_{milk:air} = 0.900\text{log}P_{o:a}-1.095$ | H | Trihalomethanes | (7) |
| $\text{Log } P_{plasma:air}= -0.079+0.896\text{Log}P_{w:a}+0.149\text{Log}P_{o:a}$ | H | Inert gases; LMWVOCs | (1) |
| $\text{Log } P_{plasma:air}= -0.082+0.894\text{Log}P_{w:a}+0.152\text{Log}P_{o:a}$ | H | Inert gases; LMWVOCs | (1) |
| $\text{Log } P_{plasma:air}= -0.848+0.890\text{Log}P_{o:a}$ | H | Inert gases; LMWVOCs | (1) |
| $\text{Log } P_{plasma:air}= -3.696+1.208R_{G}$ | H | Inert gases; LMWVOCs | (1) |
| $\text{Log } P_{plasma:air}=0.038+1.019\text{Log}P_{w:a}$ | H | Inert gases; LMWVOCs | (1) |
| $P_{blood:air} = 0.0072P_{o:a}+0.898P_{w:a}+0.03$ | H | LMWVOCs; CFC | (44) |
| $P_{blood:air} = 0.08e^{0.0308Tb}$ | H | volatile hydrocarbons | (52) |
| $P_{blood:air}=0.00442P_{o:a}$ | H | volatile hydrocarbons | (52) |
| $P_{blood:air}=0.88P_{w:a}+0.012$ | 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) |
| $\text{Log } P_{brain:blood} =-0.0148PSA+0.152LogP_{o:w}+0.139$ | H | Inert gases; HMWOCs; LMWVOCs | (11) |
| $\text{Log } P_{brain:blood}=1.359+0.338LogP_{cyh}-0.00618V_m$ | 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) |
| $\text{Log } P_{brain:blood}=-0.00116MW+0.272LogP_{o:w}-0.088$ | R | Inert gases; volatile hydrocarbons | (47) |
| $\text{Log } P_{brain:blood}=-0.01V_m+0.35LogP_{o:w}+0.99I_3+1.25$ | 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) |
| $\text{Log } P_{brain:blood}=-0.218(N_N+N_O)+0.235logP_{o:w}-0.027$ | R | HMWOCs | (47) |
| $\text{Log } P_{brain:blood}=0.476+0.541LogP_{o:w}-0.00794MW$ | R | $H_2$-R antagonists | (34) |
| $\text{Log } P_{brain:blood}=1.296+0.309LogP_{cyh}-0.00570MW$ | R | $H_2$-R antagonists | (34) |
| ***Hydrophobic descriptors*** | | | |
| $\text{Log } P_{brain:blood}=0.39LogP_{o:w}+0.68$ | 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) |

| | | | |
|---|---|---|---|
| $\text{Ln } P_{muscle:blood}=0.0069\sum i$ | R | HMWOCs | (75) |
| $\text{Log } P_{brain:blood}=0.035\Delta G_{solv}+0.259$ | R | $H_2$-R antagonists; LMWVOCs | (47) |
| $\text{Log } P_{brain:blood}=0.4275-0.3873n_{acc,solv}+0.1092\text{Log}P_{o:w}-0.0017A_{pol}$ | R | Drugs; LMWVOCs; Anaesthetics | (19) |
| $\text{Log } P_{brain:blood}=1.979+0.373\text{Log}P_{cyh}-0.00275V_{wav}$ | R | $H_2$-R antagonists | (34) |
| $\text{Log } P_{brain:plasma} = -0.48*\Delta\text{log}P_{oct-cyc}+0.89$ | R | $H_2$-R antagonists | (69) |
| $\text{Ln } P_{adipose:blood}=0.05\sum i+0.021$ | 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] $\pi_2^H$=dipolarity/polarizability, $\alpha_2^H$=overall hydrogen-bond acidity, $\beta_2^H$=overall hydrogen-bond basicity, $\Delta G_{solv}$=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), $P_{oct-cyc}$=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) |
| $K_p = (b_1 + b_2 P_{o:w}) e^{(b3MW)}$ | 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) |
| $\text{Log } K_p = b_1 + b_2 LogP_{o:w} + b_3 MW^{0.5}$ | H | LMWVOCs; HMWOCs | (45) |
| $\text{Log } K_p = -0.428\delta - 4.80^4 X_{PC}^V + 28.06$ | H | Hydrocorticone esters | (27) |
| $\text{Log } K_p = 0.652LogP_{o:w} - 0.00603MW - 0.623ABSQon - 0.313SsssCH - 2.3$ | H | Dermal drugs; LMWVOCs; HMWOCs | (50) |
| $\text{Log } K_p = 0.77LogP_{o:w} - 0.0103MW - 2.33$ | H | LMWVOCs; HMWOCs | (45) |
| $\text{Log } K_p = -0.786OT + 0.252^2\kappa - 1.617q_s^+ - 5.767$ | H | Alcohols, Steroids | (27) |
| $\text{Log } K_p = 0.82LogP_{o:w} - 0.0093V_m - 0.039MP_t - 2.36$ | H | Steroids | (45) |
| $\text{Log } K_p = 0.84LogP_{o:w} - 0.07(logP_{o:w})^2 - 0.27Hb - 1.84LogMW + 4.39$ | H | LMWVOCs; HMWOCs | (45) |
| $\text{Log } K_p = 28.4q^- + 0.018V_m + 2.824$ | H | Barbiturates; Isoquinoline; Salicyclic acid | (27) |
| $\text{Log } K_p = 3.99logTA + 4.53q_s^- - 0.762OT - 11.364$ | 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) |
| $\text{Log } K_p = -0.207\ LogP_{o:w}^2 + 1.49\ LogP_{o:w} - 5.42$ | H | Steroids | (66) |
| $\text{Log } K_p = -0.37LogP_{o:w}^2 + 2.39LogP_{o:w} - 8.71$ | H | Phenols | (69) |
| $\text{Log } K_p = 0.544logP_{o:w} - 2.88$ | H | Aliphatic alcohols | (66) |
| $\text{Log } K_p = 0.80logP_{o:w} - 8.883$ | H | Hydrocorticone esters | (27) |
| $\text{Log } K_p = -1.46\Delta LogP_{o:w} + 0.29LogP_{o:w} - 3.75$ | 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] $\delta$=solubility parameter, $\pi_2^H$=dipolarity/polarizability, $\alpha_2^H$=overall hydrogen-bond acidity, $\beta_2^H$=overall hydrogen-bond basicity, $\Sigma$Ca=Hydrogen bond acceptor free energy in the molecule, $\Sigma$Cd=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, $Q^+/\alpha$=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.

## References


1. Abraham, M. H., Kamlet, M. J., Taft, R. W., Doherty, R. M., and Weathersby, P. K. (1985). Solubility properties in polymers and biological media. 2. The correlation and prediction of the solubilities of nonelectrolytes in biological tissues and fluids. J.Med.Chem. **28**, 865-870.

2. Abraham, M. H. and Weathersby, P. K. (1994). Hydrogen bonding. 30. Solubility of gases and vapors in biological liquids and tissues. J.Pharm.Sci. **83**, 1450-1456.

5. Arms, A. D. and Travis, C. C. Reference Physiological Parameters in Pharmacokinetic Modeling. Office of Health and Environmental Assessment. EPA. EPA/600/6-88/004, 1-1-7.16. 1988. Washington, DC.

6. Balimane, P.V., Chong, S., and Morrison, R.A. (2000). Current methodologies used for the evaluation of intestinal permeability and absorption. J. Pharmacol. Toxicol. Methods. **44**, 301-312.

7. Batterman, S., Zhang, L., Wang, S., and Franzblau, A. (2002). Partition coefficients for the trihalomethanes among blood, urine, water, milk and air. Sci.Total Environ. **284**, 237-247.

8. Bertelsen, S. L., Hoffman, A. D., Gallinat, C. A., Elonen, C. M., and Nichols, J. W. (1998). Evaluation of log Kow and tissue lipid content as predictors of chemical partitioning to fish tissues. Environ.Toxicol.Chem. **17**, 1447-1455.

11. Clark, D. E. (1999). Rapid calculation of polar molecular surface area and its application to the prediction of transport phenomena. 2. Prediction of blood-brain barrier penetration. J.Pharm.Sci. **88**, 815-821.

12. Connell, D. W., Braddock, R. D., and Mani, S. V. (1993). Prediction of the partition coefficient of lipophilic compounds in the air-mammal tissue system. Sci.Total Environ. **Suppl Pt 2**, 1383-1396.

14. Csanady, G. A. and Laib, R. J. (1990). Use of linear free energy relationships in toxicology: prediction of partition coefficients of volatile lipophilic compounds. Arch.Toxicol. **64**, 594-596.

22. Fouchécourt, M.-O. and Krishnan, K. (2000). A QSAR-type PBPK model for inhaled chloroethanes. Toxicol.Sci. **54**, 88.

23. Fouchécourt,M.-O., Walker,J., and Krishnan,K. (2000). An integrated QSAR-PBPK model for conducting rat-fish extrapolation of the biokinetics of chloroethanes. In Handbook on QSARs for Predicting Effects of Chemicals on Environmental-Human Health Interactions (J.Walker, Ed.), SETAC Press, Pensecola, FL.

25. Gargas, M. L., Seybold, P. G., and Andersen, M. E. (1988). Modeling the tissue solubilities and metabolic rate constant (Vmax) of halogenated methanes, ethanes, and ethylenes. Toxicol. Lett. **43**, 235-256.

26. Gargas, M. L., Burgess, R. J., Voisard, D. E., Cason, G. H., and Andersen, M. E. (1989). Partition coefficients of low-molecular-weight volatile chemicals in various liquids and tissues. Toxicol. Appl.Pharmacol. **98**, 87-99.

27. Ghafourian, T. and Fooladi, S. (2001). The effect of structural QSAR parameters on skin penetration. Int.J.Pharm. **217**, 1-11.

34. Kalizan, R. and Markuszewski, M. (1996). Brain/blood distribution described by a combination of partition coefficients and molecular mass. Int. J. Pharmacol. **145**, 9-16.

35. Kaneko, T., Wang, P. Y., and Sato, A. (1994). Partition coefficients of some acetate esters and alcohols in water, blood, olive oil, and rat tissues. Occup.Environ.Med. **51**, 68-72.

38. Laass,W. (1987). Estimation of blood/air partition coefficients of organic solvents. In QSAR in drug design and toxicology (D.Hadzi and B.Jerman-Blazic, Eds.), pp. 131-134. Elsevier Science Publishers, Amsterdam.

43. Lombardo, F., Blake, J. F., and Curatolo, W. J. (1996). Computation of brain-blood partitioning of organic solutes via free energy calculations. J.Med.Chem. **39**, 4750-4755.

44. Meulenberg, C. J. and Vijverberg, H. P. (2000). Empirical relations predicting human and rat tissue:air partition coefficients of volatile organic compounds. Toxicol. Appl. Pharmacol. **165**, 206-216.

45. Moss, G. P., Dearden, J. C., Patel, H., and Cronin, M. T. (2002). Quantitative structure-permeability relationships (QSPRs) for percutaneous absorption. Toxicol. In Vitro **16**, 299-317.

47. Norinder, U. and Haeberlein, M. (2002). Computational approaches to the prediction of the blood-brain distribution. Adv.Drug Deliv.Rev. **54**, 291-313.

48. Parham, F. M., Kohn, M. C., Matthews, H. B., DeRosa, C., and Portier, C. J. (1997). Using structural information to create physiologically based pharmacokinetic models for all polychlorinated biphenyls. Toxicol. Appl.Pharmacol. **144**, 340-347.

51. Paterson, S. and Mackay, D. (1989). Correlation of tissue, blood, and air partition coefficients of volatile organic chemicals. Br.J.Ind.Med. **46**, 321-328.

52. Perbellini, L., Brugnone, F., Caretta, D., and Maranelli, G. (1985). Partition coefficients of some industrial aliphatic hydrocarbons (C5- C7) in blood and human tissues. Br.J.Ind.Med. **42**, 162-167.

53. Poulin, P. and Krishnan, K. (1995a). A biologically-based algorithm for predicting human tissue: blood partition coefficients of organic chemicals. Hum.Exp.Toxicol. **14**, 273-280.

54. Poulin, P. and Krishnan, K. (1995b). An algorithm for predicting tissue: blood partition coefficients of organic chemicals from n-octanol: water partition coefficient data. J.Toxicol. Environ.Health **46**, 117-129.

55. Poulin, P. and Krishnan, K. (1996a). A tissue composition-based algorithm for predicting tissue:air partition coefficients of organic chemicals. Toxicol. Appl.Pharmacol. **136**, 126-130.

56. Poulin, P. and Krishnan, K. (1996b). A mechanistic algorithm for predicting blood:air partition coefficients of organic chemicals with the consideration of reversible binding in hemoglobin. Toxicol. Appl.Pharmacol. **136**, 131-137.

57. Poulin, P. and Krishnan, K. (1996c). Molecular structure-based prediction of the partition coefficients of organic chemicals for physiological pharmacokinetic models. Toxicol. Methods **6**, 117-137.

59. Poulin, P. and Krishnan, K. (2001). Molecular structure-based prediction of human abdominal skin permeability coefficients for several organic compounds. J.Toxicol. Environ.Health **62**, 143-159.

65. Sato, A. and Nakajima, T. (1979). Partition coefficients of some aromatic hydrocarbons and ketones in water, blood and oil. Br.J.Ind.Med. **36**, 231-234.

66. Seydel, J. K. and Schaper, K. J. (1982). Quantitative structure-pharmacokinetic relationships and drug design. Pharmacol.Ther. **15**, 131-182.

69. Testa, B., Crivori, P., Reist, M., and Carrupt, P.-A. (2000). The influence of lipophillicity on the pharmacokinetic behavior of drugs: concepts and examples. Perspect.Drug Discov.Des. **19**, 179-211.

71. Tichy, M. (1991). QSAR approach to estimation of the distribution of xenobiotics and the target organ in the body. Drug Metabol.Drug Interact. **9**, 191-200.

72. Tichy, M. (1991). QSAR approach to target organ estimation. Sci.Total Environ. **109-110**, 407-410.

75. Yamaguchi, T., Yabuki, M., Saito, S., Watanabe, T., Nishimura, H., Isobe, N., Shono, F., and Matsuo, M. (1996). Research to develop a predicting system of mammalian subacute toxicity, (3). Construction of a predictive toxicokinetics model. Chemosphere **33**, 2441-2468.

76. Yokogawa, K., Nakashima, E., Ishizaki, J., Maeda, H., Nagano, T., and Ichimura, F. (1990). Relationships in the structure-tissue distribution of basic drugs in the rabbit. Pharm.Res. **7**, 691-696.

77. Yokogawa, K., Ishizaki, J., Ohkuma, S., and Miyamoto, K. (2002). Influence of lipophilicity and lysosomal accumulation on tissue distribution kinetics of basic drugs: a physiologically based pharmacokinetic model. Methods Find.Exp.Clin.Pharmacol. **24**, 81-93.