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Solubility of inert gases in biological fluids and tissues: a review

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Weathersby PK, Homer LD. Solubility of inert gases in biological fluids and tissues: a review. Undersea Biomed Res 1980; 7(4):277–296.—Data have been tabulated from more than 150 references on the solubility of inert gases in fluids and tissues of biological interest. Thirty-two gases have been studied in blood with measured solubility ranging from 0.005 to 16 ml of gas at 37°C per ml of blood per ATA (Ostwald coefficient). For most gases, solubility in other tissues such as muscle or brain is between 60% and 300% of blood solubility. Measured solubilities in biological tissues do not correspond well to solubility in water and oil. Most gases decrease in solubility by 1%–6% for each °C rise in temperature. The effect of pressure on solubility has not been well studied, and only crude estimates can be obtained by using methods of chemical thermodynamics.

inert gas
solubility
partition coefficient

SCOPE

Central to most questions in hyperbaric physiology is a quantitative appreciation of the equilibrium solubility coefficient of inert gases in biological fluids and tissues. This review contains a summary and bibliography of reported gas solubility measurements and a brief description of applicable theory and measurement technique. Other reviews should be consulted for the physical chemistry of gas solubility (10, 61, 117, 144) or for gases used in clinical anesthesia (34, 37, 81, 129). Reference 129 is particularly extensive, and its organization may be more useful to some readers than the present report. English language reports from 1930 to mid-1980 have been reviewed; a few earlier important studies have also been included. Except for the authoritative water solubilities (144) and data cited as unpublished or private communication in review articles (34, 37), the references used to obtain the tabulated data are the original reports.

Our report focuses on the inert gases. At a molecular level, there is a blurred distinction between inert gases that interact by nonspecific forces and active gases that selectively interact with solvent molecules. In principle, a useful distinction can be made on the basis of whether a saturation is evident; that is, whether a negative deviation from Henry's law appears at a discrete concentration of gas. Henry's law says that the dissolved gas content is

directly proportional to the partial pressure of the gas phase. For most of the biologically important solvents, however, such studies are lacking. For purposes of this report, two major exclusions were made: 1) solubility of oxygen and carbon monoxide in blood, which is dominated by well-studied gas-hemoglobin association: and 2) solubility of the strongly acid gases (SO_2, SO_3, NO_2) in aqueous solution, which is dominated by complex buffer-ion equilibria.

Some 32 gases have been studied. These range in molecular weight from 2 to nearly 200 daltons, and they include the inhalation anesthetics, the noble gases, the diving gases, and a few gases that have only been used in research laboratories. Table 1 lists the values of solubility by increasing gas molecular weight in terms of the Ostwald coefficient, L, at 37°C (310°K). This measure (L) has units of gas volume, measured at ambient temperature and at 1 ATA partial pressure, which dissolves in a unit volume (V) of fluid. Other common units that are used can be related to the Ostwald coefficient by the following formulas (61):

$$\text{Bunsen coefficient } (\alpha) \quad \text{V of gas at STPD/V of fluid} = L\ (273°/310°) \tag{1}$$

$$\text{Kuenen coefficient } (S) \quad \text{V of gas in ml at STPD/g of fluid} = L\ (273°/310°)/\rho \tag{2}$$

where ρ is the fluid density in g/ml. We treated a few reports that used the Kuenen coefficient as if they had used the Bunsen coefficient, because overall variability was greater than the error of assuming a tissue density of 1.0 g/ml and because tissue densities were not measured in those studies.

$$\text{Henry's constant } (H) \quad \text{gas pressure/gas mole fraction in fluid} = 1413/L \text{ (for water)} \tag{3}$$

The common units of H are atmospheres of gas partial pressure per mole fraction of dissolved gas. The numerical constant given in Eq. *3* is only valid for a dilute aqueous solution. A generally lower value will apply for biological solvents that have a higher average molecular weight than water.

$$\text{partition coefficient } (\lambda) \quad \text{ratio of gas concentration in substance 1/substance 2} \tag{4}$$

If substance 2 is a pure gas phase at 1 ATA and if concentration is measured in milliliters of gas at STPD or 1 ATA and 37°C, the partition coefficient is numerically equal to the Bunsen and Ostwald coefficients, respectively. A few studies have directly measured partition coefficients between blood and some other biological substance; these results are summarized in Table 2. Unfortunately, a number of investigators have not reported the unit of solubility they used. In such instances, the tabulated values of solubility may be incorrect.

THEORY OF SOLUBILITY

Henry's constant is the unit most frequently used in thermodynamic calculations involving solubility changes caused by pressure, temperature, or composition (117). Solubility is an equilibrium property, so all the theoretical and semiempirical approaches that have been used in the chemical process industry might be applied when specific data are lacking (117). The equation that describes the equilibrium is the generalized Henry's law:

$$\mathrm{P\ y}\ \gamma = H\ \mathrm{x}\ \phi \tag{5}$$

where P is the total gas pressure, H is Henry's coefficient, y and x are the mole fractions of gas

TABLE 1
OSTWALD SOLUBILITY COEFFICENTS AT 37° C
(ml gas @37° C/ml fluid)

Gas M.W.	Water	Plasma	Oil	Blood	Brain	Muscle	Other
H2 2	0.0189(144)						
Hydrogen	0.0185(87)	0.0174(87)		0.0170(87)		0.0218(18)	Placenta 0.0187(87)
	0.0184(140)	0.0174(140)		0.0170(140)			
	0.0185(112)		0.0495(112)	0.018(86)			RBC Ghost 0.027(112)
	0.0186(97)	0.0166(97)		0.0166(97)		0.0175(97)	
				0.00169(95)			
He 4	0.00977(144)						
Helium				0.0085(33)		0.0117(18)	Lung 0.0105(19)
	0.0097(59)			0.0099(59)			
	0.0099(11)		0.0168(11)	0.010(86)			
	0.0101(21)			0.0104(21)			
	0.0096(62)	0.0086(62)		0.0080(62)			
CH4 16	0.0290(144)						
Methane	0.030(143)		0.309(18)	0.041(143)		0.047(18)	
	0.0291(104)			0.0379(104)	0.0410(104)		
	0.0296(97)	0.0257(97)		0.030(97)		0.031(97)	
				0.044(143)			
				0.036(86)			
Ne 20	0.0109(144)						
Neon	0.0110(112)		0.0274(112)	0.0093(33)			RBC Ghost 0.014(112)
	0.0111(104)			0.0098(104)	0.0155(104)		
C2H2 26	0.849(144)						
Acetylene	0.87(143)		1.75(18)	0.89(143)		1.07(18)	Lung 0.87(19)
				0.99(143)			
				0.84(114)			
	0.85(53)	0.78(53)		0.86(53)			
				0.80(20)			
				0.87(98)			
				0.84(68)			

TABLE 1 (CONTINUED)

Gas M.W.	Water	Plasma	Oil	Blood	Brain	Muscle	Other
CO 28	0.0207(144)						
Carbon	0.0215(113)			0.0215(113)			Lung 0.0203(113)
Monoxide	0.0213(112)		0.0974(112)				Placenta 0.021(113)
							RBC Ghost 0.107(112)
C2H2 28	0.0965(144)						
Ethylene			1.26(121)	0.174(24)			
				0.221(24)			
	0.089(53)			0.149(53)			
N2 28	0.0143(144)						
Nitrogen	0.0145(11)		0.076(11)	0.0112(28)	0.010(17)		Marrow 0.051(17)
	0.0137(104)		0.052(17)	0.0141(104)	0.0159(104)		RBC Ghost 0.109(112)
	0.0144(44)	0.0137(44)		0.0145(44)	0.011(16)		
	0.0143(112)		0.0730(112)	0.0185(114)			
	0.0144(139)	0.0131(139)		0.0149(139)			
	0.0145(21)			0.0158(21)			
C2H6 30	0.0355(144)						
Ethane	0.035(143)			0.101(143)			Lung 0.052(149)
				0.128(143)			
				0.122(149)			
		0.054(150)		0.099(150)			
		0.042(150)		0.124(150)			
				0.078(29)			
				0.101(29)			
O2 32	0.0272(144)						
Oxygen	0.0270(113)			0.0261(113)			Lung 0.0242(113)
	0.0271(112)		0.133(112)				Placenta 0.024(113)
	0.0271(22)	0.243(22)					RBC Ghost 0.13(112)
Ar 40	0.0297(144)						
Argon	0.027(6)		0.16(83)	0.030(33)			
	0.0296(104)			0.0305(104)	0.0327(104)		
	0.030(11)		0.16(11)				
	0.0295(97)	0.0241(97)		0.026(97)		0.023(97)	
	0.0303(62)	0.0281(62)		0.0305(62)			

TABLE 1 (CONTINUED)

Gas M.W.	Water	Plasma	Oil	Blood	Brain	Muscle	Other
C3H6 42	0.227(144)						
Cyclopropane	0.22(143)		11.1(12)	0.58(143)			
	0.204(94)			0.68(94)	0.83(94)	0.51(94)	Heart 0.85(94)
	0.20(105)		7.0(105)	0.46(105)			Liver 0.70(94)
	0.212(100)		11.9(121)	0.74(143)			Kidney 0.64(94)
	0.22(36)	0.242(100)	12.(36)	0.84(149)			Lung 0.31(149)
		0.35(150)		0.61(150)			
		0.27(150)		0.80(150)			
	0.23(85)			0.68(24)		0.43(85)	Liver 0.65(85)
				0.42(110)			
	0.24(88)			0.95(24)			Kidney 0.5(88)
				0.52(88)	0.63(88)	0.55(88)	Liver 0.70(88)
	0.20(118)	0.32(118)		0.57(118)			
		0.245(77)		0.429(77)			
				0.60(52)			
				0.51(29)			
				0.60(29)			Kidney 0.43(89)
	0.24(89)			0.45(89)	1.7(89)	0.35(89)	Liver 0.59(89)
CH3OCH3 42	15.3(14)			14.3(14)			
Dimethyl							
Ether				11.5(68)			
CO2 44	0.642(144)						
Carbon	0.623(112)		1.40(112)				RBC Ghost 1.0(112)
Dioxide	0.627(126)		1.28(148)		0.56(126)		CSF 0.601(126)
N2O 44	0.448(144)						
Nitrous	0.482(9)			0.423(84)		0.54(18)	Lung 0.462(19)
Oxide				0.48(69)	0.50(69)		Rt.Ventricle 0.525(73
	0.492(73)	0.454(73)		0.475(73)			Lt.Ventricle 0.449(73
				0.47(7)	0.50(7)	0.54(7)	Lung 0.37(7)
				0.465(107)			Placenta 0.38(7)
	0.44(121)			0.47(121)			Skin 0.52(7)
	0.462(48)			0.471(26)			Heart 0.56(7)
	0.476(94)			0.46(94)	0.44(94)	0.35(94)	Heart 0.40(94)
	0.478(21)			0.455(21)			Liver 0.42(94)
				0.455(58)			Kidney 0.41(94)
	0.367(133)			0.395(133)			
				0.418(101)			

TABLE 1 (CONTINUED)

Gas M.W.	Water	Plasma	Oil	Blood	Brain	Muscle	Other
CH3COCH3 58 Acetone	280.(143)			340.(143) 360.(143) 300.(149)			Lung 290.(149)
		313.(150) 376.(150)		263.(150) 283.(150) 300.(29) 290.(29)			
H2C=CHOCH=CH2 70 Divinyl Ether	1.6(88)			2.3(88) 2.8(37)	3.5(88)	2.3(88)	Kidney 2.5(88) Liver 3.1(88)
	1.3(89)			2.8(103)	3:3(89)	2.1(89)	Kidney 2.1(89) Liver 3.1(89)
(C2H5)2O 74 Diethyl Ether	16.(55) 13.1(39) 13.1(9) 15.(143)	12.3(9)	65.(39)	15.(55) 12.1(39) 12.0(9) 12.5(143) 12.7(143)			Lung 15.2(19) Lung 12.3(149)
	13.7(88)			11.9(88) 11.7(149)	12.(88)	11.(88)	Kidney 12.(88) Liver 12.8(88)
		11.6(150) 11.8(150)		9.3(150) 10.0(150) 11.2(24) 11.4(24) 14.4(50)			
	16.2(14)			16.4(14) 11.2(58) 12.(116) 11.7(29) 10.7(29)			Liver 10.2(89)
	13.(89)			12.(89)	12.1(89)	9.2(89)	Kidney 9.(89)
CS2 Carbon Disulfide	0.80(92)	0.8(92)		2.0(92)	8.(92)		Liver 6.0(92) Kidney 7.9(92)

TABLE 1 (CONTINUED)

Gas M.W.	Water	Plasma	Oil	Blood	Brain	Muscle	Other
Kr 84	0.0504(144)						
Krypton	0.050(57)	0.051(57)	0.49(83)	0.060(57)			Eye 0.042(74)
	0.048(71)	0.050(71)	0.45(71)	0.061(71)			Choroid 0.030(132)
	0.044(74)		0.459(148)	0.046(147)	0.045(147)	0.044(147)	Sclera 0.028(132)
	0.067(132)	0.059(132)		0.083(132)			Retina 0.062(132)
				0.064(95)			Vitreous 0.059(132)
		0.055(100)		0.085(100)			Kidney 0.043(70)
	0.047(70)			0.057(70)	0.041(70)	0.040(70)	Liver 0.077(70)
							Eye 0.040(70)
							BoneMarrow 0.13(70)
							Heart 0.030(70)
							Liver 0.069(72)
CHClF2 86	0.64(13)		4.4(18)			1.08(18)	
Freon 22	0.57(108)						
CHCl3 119	4.1(9)			8.6(88)	18.(88)	16.4(88)	Liver 13.(88)
Chloroform	3.9(88)			8.4(37)			Kidney 9.(88)
	3.8(89)			9.1(89)	21.(89)	9.8(89)	Kidney 11.(89)
							Liver 17.(89)
CF3CH2OCH=CH2 126	0.84(102)		48.(102)	1.37(102)	2.0(102)	3.1(102)	Liver 3.1(102)
Fluroxene	0.897(143)			1.54(143)			
Fluoromar				1.73(143)			Liver 2.0(88)
	0.94(88)			1.2(88)	1.8(88)	1.5(88)	Kidney 1.5(88)
	0.83(131)			1.35(131)			CSF 0.77(131)
				1.26(40)			Kidney 1.2(89)
	0.95(89)			1.49(89)	1.80(89)	3.7(89)	Liver 2.1(89)
ClCH=CCl2 131	1.51(88)			6.7(88)	21.(88)	13.(88)	Kidney 13.(88)
Trichloroethylene				9.9(37)			Liver 23.(88)
	1.55(111)			9.2(111)			Kidney 11.(89)
	1.58(89)			8.9(89)	21.(89)	8.1(89)	Liver 24.(89)

TABLE 1 (CONTINUED)

Gas M.W.	Water	Plasma	Oil	Blood	Brain	Muscle	Other
Xe 131	0.0834(144)						
Xenon	0.083(71)	0.094(71)	1.88(71)	0.146(71)			Liver 0.181(72)
			1.83(148)	0.141(147)	0.093(147)	0.082(147)	
	0.093(67)	0.103(67)	1.9(83)	0.152(67)	0.183(67)		
	0.091(119)			0.142(119)			
		0.107(100)		0.137(100)			
		0.240(100)		0.177(100)			
		0.116(100)		0.175(100)			
		0.091(100)		0.185(100)			
		0.112(100)		0.221(100)			
		0.112(100)		0.222(100)			
	0.102(37)		1.9(37)	0.20(37)			
	0.090(142)	0.103(142)		0.156(142)	0.161(142)		
	0.0834(78)	0.091(78)	1.79(78)	0.139(78)			Kidney 0.124(41)
	0.0837(41)	0.091(41)		0.142(41)	0.175(41)		Liver 0.120(41)
SF6 146	0.00475(144)						
Sulfur	0.0042(6)		0.293(35)	0.0075(33)		0.0108(18)	Lung 0.0068(149)
Hexafluoride	0.0030(143)			0.0064(143)			Lung 0.0077(19)
	0.0044(87)	0.0073(87)		0.0076(87)			Placenta 0.0089(87)
	0.00376(104)			0.00815(104)		0.0165(104)	
	0.00438(112)	0.0053(150)	0.261(112)	0.0058(150)			RBC Ghost 0.17(112)
	0.00412(97)	0.00446(97)		0.0070(97)		0.0142(97)	
	0.00395(62)	0.0056(62)		0.0068(62)			
		0.0039(150)		0.0085(150)			
				0.0064(86)			
				0.0095(143)			
				0.0098(149)			
				0.0049(29)			
				0.0074(29)			
CH3OCF2CHCl2 165	3.5(88)			8.4(88)	24.(88)	13.(88)	Kidney 16.(88)
Methoxyflurane	4.7(131)			14.1(131)			Liver 25.(88)
				11.1(37)			CSF 4.4(131)
	4.5(38)		825.(38)	13.0(38)	26.(38)	17.4(38)	
				13.9(101)			
				12.9(40)			Kidney 32.(89)
				10.4(89)	24.(89)	20.(89)	Liver 23.(89)
CF3CHFBr 181	0.32(32)		29.(32)	0.60(32)	1.11(32)	2.2(32)	Liver 1.0(32)
Teflurane							

TABLE 1 (CONTINUED)

Gas M.W.	Water	Plasma	Oil	Blood	Brain	Muscle	Other
$CHF_2OCHClCF_3$ 185 Isoflurane Forane	0.61(25)		98.(25)	1.43(25) 1.41(34) 1.4(64) 1.42(101)	3.7(34)	5.6(34)	Liver 3.5(34)
CHF_2OCF_2CHFCl 185 Enflurane Ethrane			98.(34) 98.(35)	1.78(34) 2.00(101) 1.72(29) 2.17(29)	2.6(34)	3.0(34)	Liver 3.7(34)
$CHF_2CF_2CH_2Br$ 195 Halopropane			323.(96)	5.8(96) 5.4(89)			
$CF_3CHClBr$ 197 Halothane Fluothane	0.74(80) 1.16(143) 0.87(36)		224.(80) 220.(36)	2.3(80) 2.5(143) 3.8(143)	5.9(80)	7.5(80)	Kidney 3.6(80) FatTissue 138.(80) Liver 6.0(80)
		2.8(150) 1.7(150)		4.0(149) 2.5(150) 3.7(150)		6.7(88)	Lung 2.0(149) Kidney 4.2(88)
	0.87(88)			2.7(88)	5.3(88)	5.2(88)	Liver 6.8(88)
	0.82(131)		225.(131)	2.46(131) 2.7(24) 3.5(24)			CSF 0.77(131)
	0.75(3)			2.3(146)			
		3.2(56)		2.2(56) 2.36(37)	5.0(56)		Heart 4.2(128) Kidney 5.0(128)
	0.78(76)	2.3(76) 2.44(128)		2.4(76) 3.5(128)	6.0(128)	5.5(128)	Liver 6.6(128) Gut 4.2(128)
	0.76(65)			2.8(65) 3.2(93)	8.3(65) 6.1(93)	3.6(93)	Heart 10.8(93) Liver 9.0(93)
				1.3(120) 2.33(101) 2.64(122) 2.60(40)			Kidney 6.8(93) Kidney 3.0(89)
	0.89(89)			2.24(89)	5.1(89)	2.9(89)	Liver 4.5(89)

Notes:
1. Values are tabulated with the significant digits consistent with the original work.
2. Molecular weights are for naturally occurring isotopes; radioactive atoms used as tracers may be different.
3. Numbers in parentheses are the reference cited below.
4. Values for blood refer to a 50% Hematocrit, where possible.
5. Carbon dioxide solubilities in brain and cerebrospinal fluid(CSF) measured in acidified solution to prevent bicarbonate formation (126).
6. Abbreviations used in Tables: M.W. Molecular weight; RBC red blood cell; CSF cerebrospinal fluid.

TABLE 2

TISSUE-BLOOD PARTITION COEFFICENTS
(ml gas @37°C/ml tissue)/(ml gas @37°C/ml blood)

Gas	Brain	Muscle	Other	
Hydrogen			Kidney 1.0(8)	
Nitrous Oxide			Heart 1.05(31) Heart 1.13(31)	
Diethyl Ether	1.1(54)			
Krypton	1.09(138) 1.06(82) 0.91(51)		Liver 1.06(63) Urine 0.68(136)	
Xenon	0.73(4) 0.92(23)	0.63(4) 0.69(23) 0.62(137) 0.77(141) 0.69(109)	Kidney 0.68(4) Kidney 0.65(23) Fat Tissue 9.4(4) Liver 0.72(4) Cartilage 0.54(109) Synovial Fl. 0.58(109) CSF 0.50(23)	Heart 0.69(4) Heart 0.72(23) Eye 0.72(47) Liver 0.70(27) Tendon 0.36(109) Liver 0.70(23) Fat Tissue 9.8(79)

in the gas and fluid phases, respectively, and γ and ϕ are gas activity coefficients in the gas and liquid phases, respectively. The product on the left side of Eq. *5* is called the "fugacity" in thermodynamics. In an ideal dilute solution of ideal gases both γ and ϕ are unity, and a simplified equation such as Eq. *3* results.

The virtue of Eq. *5* is that specific nonidealities of either the gas or the liquid can be isolated from the equilibrium constant, H. For example, the effect of pressure on solubility is given to a first approximation as

$$H_2 = H_1 \exp [V_g (P_2 - P_1)/RT] \quad (6)$$

where RT is the product of the gas constant and the temperature (25,400 ml · ATA/mol, at body temperature) and V_g is the partial molar volume of the gas in the fluid. For small inert gases in aqueous liquids, V_g is in the range of 25–40 ml/mol (10, 117, 135). Because the Ostwald coefficient is inversely related to Henry's coefficient, the effect of increased pressure is expected to be a slow exponential decrease in the solubility per se. In practice, the pressure effect on either the gas or fluid phases is likely to change solubility more than the effect of Eq. *6*.

The change in solubility with temperature is given by a version of the Clausius-Clapeyron equation.

$$H_2 = H_1 \exp [h (T_2 - T_1)/RT_1T_2] \quad (7)$$

where h is the partial molar enthalpy of solution, and R the gas constant. Enthalpies are tabulated for many gases in water (144) and fats (148) and can be estimated for other systems (117). Equation *7* is usually accurate over a modest temperature range and will probably be satisfactory over physiological temperatures. The data of Table 3 are given in a linear form, i.e., percentage of change per degree. If more than a few degrees of extrapolation must be performed, an exponential extrapolation as suggested by Eq. *7* is to be preferred. Methods for estimating the gas-phase activity coefficient, γ, are given in physical chemistry texts and compilations (117). For the gases of interest in diving (helium, oxygen, nitrogen) sufficient

TABLE 3

TEMPERATURE DEPENDENCE OF SOLUBILITY
(percent change per degree)

Gas	Water	Blood	Other Tissue
Hydrogen	-0.025(144)		
Helium	+0.33(144) +0.3(21)	-0.2(33) +1.6(21)	
Methane	-1.17(144)		
Neon	+0.021(144)	-0.4(33)	
Acetylene	-1.33(144)		
Carbon Monoxide	-0.84(144) -1.5(112)		Oil -3.6(112) RBC Ghost -15.(112)
Ethylene	-1.41(144)		
Nitrogen	-0.72(144) -0.9(21) -0.9(139)	0.0(21)	Oil -0.4(112)
Ethane	-1.89(144)		
Oxygen	-0.95(144) -1.5(22)		Oil -0.2(112) Plasma -1.7(22)
Argon	-1.14(144) -1.1(6)	-1.6(33)	
Cyclopropane	-2.02(144) -2.(36)		Oil -3.1(12) Oil -2.(36)
Carbon Dioxide	-1.97(144)		Oil -1.1(148)
Nitrous Oxide	-2.21(144) -2.3(21) -2.2(48)	-2.4(21)	
Diethyl Ether	-8.9(9) -2.(55)	-7.8(9) -2.(55) -4.9(50)	Plasma -8.0(9)
Krypton	-1.41(144) -3.0(74)		Brain -2.0(147) Eye -3.8(74) Muscle -2.0(147) Oil -0.3(148)
Freon-22	-6.2(108) -3.2(13)		
Fluroxene	-3.3(102)	-4.6(131)	CSF -5.5(131)
Trichloroethylene	-6.9(111)		
Xenon	-1.76(144)		Brain -2.0(147) Muscle -2.1(147) Oil -1.0(148)
Sulfur Hexafluoride	-1.51(144) -1.4(6)	-1.9(33)	
Methoxyflurane		-6.5(131)	CSF -4.2(131)
Halothane	-7.0(76) -3.9(65) -6.(36) 0.(56)	-5.7(76) -5.3(65) -8.7(120) -6.(56) -3.6(131)	Plasma -6.2(76) Brain -2.2(65) Oil -5.(36) Brain 0.(56) CSF -4.2(131)

data exist to predict gas phase behavior to within a few percent. Virtually no data are available on the behavior of the tissue-phase activity coefficient, ϕ. More detailed treatments of Eqs. 5–7 can be found in many physical chemistry texts and especially in reference 117.

EXPERIMENTAL METHODS

The procedure for determining solubility usually includes the following steps: 1) the tissue is allowed to equilibrate with a gas phase; 2) the gas and tissue are separated; 3) the tissue is allowed to equilibrate with a new gas phase ("extraction"); 4) the gas of interest is separated from both gas phases; and 5) the quantities of gas and tissue are measured. The first steps may be performed either in vitro or in vivo, and some of the steps may be omitted. For tissues other than blood, the tissue is generally minced and mixed with several times its own volume of saline before equilibration. Calculation of solubility is performed by using mass balances.

The equilibration time necessary is usually determined empirically as the time beyond which no further change in apparent solubility is measurable. This equilibration usually requires several minutes to a few hours. A few valuable experiments have not produced solubility data because the equilibration clearly was not achieved (30, 46, 91).

The extraction and separation steps have been standardized by specific apparatus and procedures by Van Slyke and associates (139, 140). The need for careful work and application of many temperature and pressure corrections has been emphasized (48, 106, 107). The detection of the gas in these studies has traditionally been indirect; that is, the residual gas after oxygen and carbon dioxide absorption is presumed to be the inert gas under study. For some reactive gases such as halothane (30), cyclopropane (118), and diethyl ether (55) the extraction is followed by a chemical reaction and measurement of the reaction products. More modern separation techniques use gas chromatography (1, 15, 90, 115, 146) or mass spectrometry (58) to separate the gases. In some studies the final gas detection is by specific electrodes (22), flame ionization (90, 146), infrared absorption (84), thermal conductivity (115), or electron capture detectors. The use of radioisotopes has allowed solubility measurements to become very specific with a minimum of sample handling, because the gas can be measured while still in the tissue.

The precision of measurement on individual tissues has varied from 0.5% to 20%. For macroscopic samples, one of the limits on precision is the variability of biological specimens obtained. In general, the reported values may be precise to about 10%. Some careful work has estimated that the variability of solubility among members of the same species may vary from 20% to 35% in the same tissue (128). The table entries have been prepared with the number of significant figures consistent with the precision of the original data; only the final digit is expected to contain the experimental imprecision. As a gauge to accuracy, the individual reports of solubility in water have also been included. Comparison with the value of water solubility accepted in a recent careful review (144) can be used as a gauge to the experimenter's bias.

TISSUE DIFFERENCES

No biological tissue is a pure solvent, and standardization of tissues is limited by the reproducibility of tissue samples. The variability caused by biochemical factors is poorly understood. Originally, gas solubility in tissues was treated as a linear combination of solubility of water and "fat." The measure of fat in the tissue is defined as the fraction of material extracted into midrange hydrocarbon solvents (i.e., petroleum ether). We used olive oil to

assess the intrinsic gas solubility in lipid; most of the "oil" entries in Table 1 use this oil, though other vegetable oils were used on occasion. This "two-solvent" approach to prediction of solubilities has failed. For very simple gases such as krypton (70, 147) addition of a third solvent to account for protein binding has some utility. In most instances, however, the simplification is inadequate either to indicate the range of tissue solubilities (nearly all measurements span only a small fraction of the oil-water range) or to predict the value for a new tissue or a new gas.

In general, added salt decreases gas solubility in aqueous liquids; data are available on this point for ethers (9, 14). Most gases will dissolve in physiological saline to at least 90% of their solubility in pure water. Lipid content does influence solubility: krypton and xenon dissolve more in liver as the triglyceride content increases (27, 72), and some steroids increase the oxygen solubility in serum (49). Blood lipid levels are positively correlated with solubility of halothane (122, 143) and sulfur hexafluoride (143). The correlations are too weak for quantitative prediction, but in some cases a 50%–80% change in gas solubility is associated with the normal range of blood lipid. Solubility of halogenated anesthetics in blood may increase by as much as 10% after eating (101).

More recently, the solvent power of proteins has become appreciated (45). The strong association between hemoglobin and both carbon monoxide and oxygen is well documented. Hemoglobin is also known to associate with xenon (23, 125), cyclopropane (52), nitrogen, hydrogen, argon (99), methoxyflurane (38), and butane and propane (145). Myoglobin binds cyclopropane (123), nitrogen, argon, hydrogen (99), and xenon (23, 124). For both hemoglobin and myoglobin, the gas-bonding site is not the heme group, and the oxygen affinity of the protein is not seriously affected. Albumin binds cyclopropane (100), xenon (23), and propane and butane (145). Lysozyme, however, does not have a significant affinity for propane or butane (145). Xenon also appears to have a sigmoidal binding isotherm with proteinaceous components of tissue (75).

Many gases have a solubility in blood that depends strongly on the concentration of red cells, presumably because of interaction of hemoglobin and gas. The gases that have an increased solubility with increased hematocrit include helium; acetylene (53); nitrogen (44, 139); ethylene (24); nitrous oxide (73); ethane (150); cyclopropane (24, 77, 150); krypton (57, 71); trichlorethylene (88, 111); xenon (5, 71); chloroform (88); and sulfur hexafluoride (150). Dimethyl ether (14, 68, 150), acetone (150), and methoxyflurane (88) have a lower solubility in blood as hematocrit increases. Reports are contradictory on the hematocrit effect for diethyl ether (14, 24, 88) and halothane (24, 56, 76, 88, 122, 128, 150). The magnitude of the changes can be ranked according to the ratio of gas solubility in packed red cells to that in plasma. This ratio is less than 0.9 for dimethyl ether and acetone; 0.9 to 1.3 for acetylene, nitrous oxide, and nitrogen; 1.3 to 2.0 for ethylene, krypton, and chloroform; and more than 2.0 for ethane, xenon, and sulfur hexafluoride. Much of the controversy can probably be resolved by studies using better characterized blood samples. For example, the apparent dependence of halothane solubility on many plasma and cellular components could be well described by a linear dependence on triglycerides alone (122). Wherever possible, the data of Tables 1 and 2 have been selected to refer to a blood of 50% hematocrit or 15 g hemoglobin per 100 ml of blood.

Solubility is also known to differ between similar anatomic structures. For example, many anesthetics are twice as soluble in the white matter of the brain as in the gray matter; these include cyclopropane, fluroxene, diethyl ether, halothane, trichloroethylene, chloroform (88, 89), methoxyflurane (38, 88), and xenon (66). For studies that include separate measurements on the two brain tissues, the entries in Tables 1 and 2 presume a brain of 60% gray and 40% white matter.

Several papers have reported no difference in solubility measurements between completely in vitro studies and those where tissue saturation occurred in a live animal (43, 70, 130). Interspecies differences have also been documented. Blood, again, is the most studied tissue. Discussions of interspecies data are available for kypton (70, 100), xenon (100), and other gases (29, 150). Eel blood has an unusual pH dependence of nitrogen and argon solubilities at low temperatures (127).

EFFECTS OF TEMPERATURE

Over the range of physiological temperatures, all gases but helium show a decreasing solubility in aqueous solvents with increasing temperature. Hydrogen and neon have a minimum water solubility at body temperature (144). The limited experimental data are summarized in Table 3, which gives the temperature effect as percentage change in Ostwald coefficient per °C. In 1973 a similar compilation was published that emphasized water and oil as solvents (2). As actual solubility data are not linear with temperature (cf. Eq. 7), the value given should not be applied to temperatures more than a few degrees from 37°C.

Table 3 also includes values for water. The ratio of tissue solubility to water solubility has been found to be nearly independent of temperature for blood solutions of oxygen (22, 60), and nitrous oxide (21), but not for helium or nitrogen (21). Few data are available for other tissues.

EFFECTS OF PRESSURE

The most important environmental variable for hyperbaric operations is the least studied. The first constraint on gases at pressure is the maximum partial pressure of a gas that can be obtained at body temperature. Gases that can liquify at 37°C have their vapor pressure as a maximum (117): acetylene, 60 ATA; ethane, 50 ATA; cyclopropane, 9.7 ATA; dimethyl ether, 8.7 ATA; nitrous oxide, 73 ATA; acetone, 0.49 ATA; diethyl ether, 1.1 ATA; carbon disulfide, 0.73 ATA; Freon-22, 13.5 ATA; chloroform, 0.42 ATA; trichloroethylene, 0.17 ATA; sulfur hexafluoride, 73 ATA; methoxyflurane, 0.06 ATA; Forane, 0.49 ATA; and halothane, 0.48 ATA. Other of the tabulated gases are above their critical pressures, so that liquifaction is impossible, and any pressure may be obtained: for example—hydrogen, helium, methane, neon, carbon monoxide, ethylene, nitrogen, oxygen, argon, carbon tetrafluoride, krypton, and xenon are far above their critical temperatures. Some gases are near their critical temperatures: acetylene, 35°C; ethane, 32°C; carbon dioxide, 31°C; nitrous oxide, 36°C; and sulfur hexafluoride, 46°C. Phase behavior of these gases is erratic, especially when they are subject to compression near their critical pressures (generally 45 to 75 ATA).

Theory can be usefully invoked for pressure dependence. For water, Eq. 6 is an excellent approximation for several gases through 100 ATA (42, 135). The effect of pressure on the gas phase nonidealities, however, first must be treated by adjusting the activity coefficients, γ, in Eq. 5 (134).

Experimental data on solubility above atmospheric pressure are almost nonexistent. Hawkins and Shilling found that helium solubility in blood follows Henry's law up to 6 ATA (59). Xenon showed evidence of saturating binding sites in subcellular brain components in pressures up to 4 ATA (75).

In the pressure range below 1 ATA, Henry's law has been verified for a few systems: in blood, for xenon (23, 78), nitrous oxide (26), ethylene and acetylene (53), and cyclopropane (77); in plasma, for oxygen (22); but it was found to be violated for others. Diethyl ether (39)

and halothane (88, 121) become more soluble in water with increasing gas partial pressure. The blood solubility of cyclopropane and methoxyflurane decrease with increasing gas partial pressure (88). This deviation is probably due to gas molecules saturating the available protein binding sites. Nonlinear solubility phenomena will undoubtedly become more important under hyperbaric conditions, since the higher driving forces will progressively recruit more types of specific binding molecules.

CONCLUSIONS

Because of the wide disparity in reported results, no single set of values can be recommended. Those wishing to use solubility per se should choose measurements from studies that agree best with well-established values of gas solubility in pure water (144). Those wishing to apply tissue-blood partition coefficients should choose pairs of values from the same study, or directly from Table 2.

This compilation has attempted to summarize the equilibrium property of gas molecules most important to hyperbaric research and operations. How much gas can actually dissolve in the body? Except for the well-studied clinical anesthetics cyclopropane, nitrous oxide, and halothane, and the common radiotracers krypton and xenon, the question remains unanswered. Of the more than 500 measurements tabulated in this report only a single determination was found that pertains directly to the hyperbaric environment (59). The discrepancies among different studies frequently exceeds a factor of 2, far too imprecise for most predictive work. The dearth of data is especially prominent for the peripheral tissues most at risk in hyperbaric exposures—i.e., joints, ears, bones, and spinal cord—and for the gases most likely to be used—i.e., nitrogen, helium, argon, and hydrogen.

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Weathersby PK, Homer LD. La solubilité des gas nobles dans les fluides biologiques et les tissues. Undersea Biomed Res 1980; 7(4):277–296.— Les données de plus de 150 références sur la solubilité des gaz nobles dans les fluides et les tissus d'intêret biologique ont été disposées en forme de tables. Trente-deux des gaz ont été studiés dans le sang avec une solubilité déterminée s'étendant de 0.005 à 16 ml de gaz à 37°C par ml du sang par ATA (coefficient Ostwald). Pour la plupart des gaz, la solubilité dans les autres tissus telles que les tissus des muscles et du cerveau est entre 60% et 300% de la solubilité du sang. Les solubilités déterminées dans les tissus biologiques ne correspondent pas avec la solubilité dans l'eau et dans l'huile. La plupart des gaz diminuent en solubilité par 1%–6% pour chaque ascension °C en température. L'effet de la pression sur la solubilité n'a pas été bien studié, et seulment les calculs par aperçus peuvent être obtenus avec les méthodes de thermo-dynamique chimique.

gaz noble
solubilité
coefficient de partition

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