Interesting molecule of the day

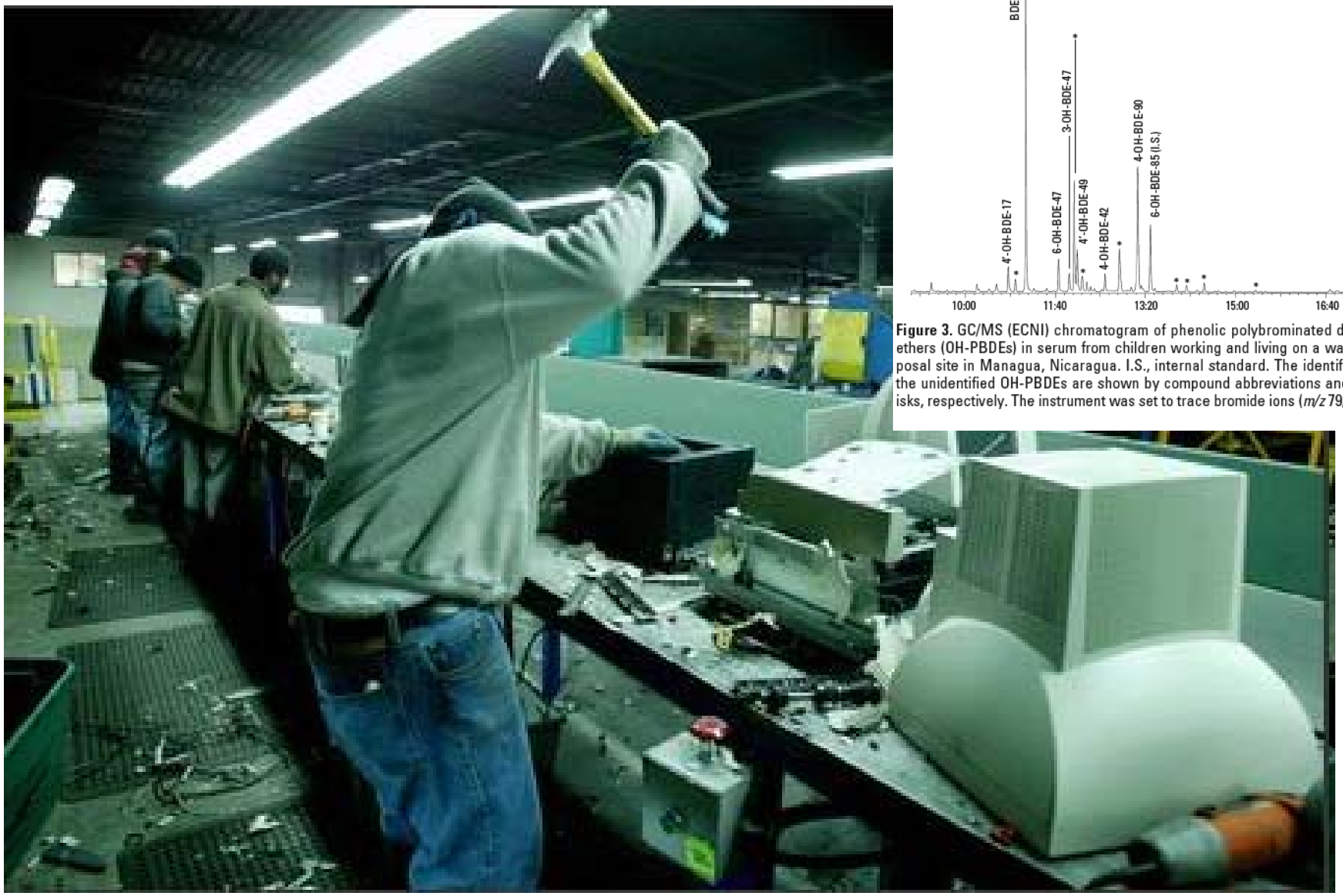
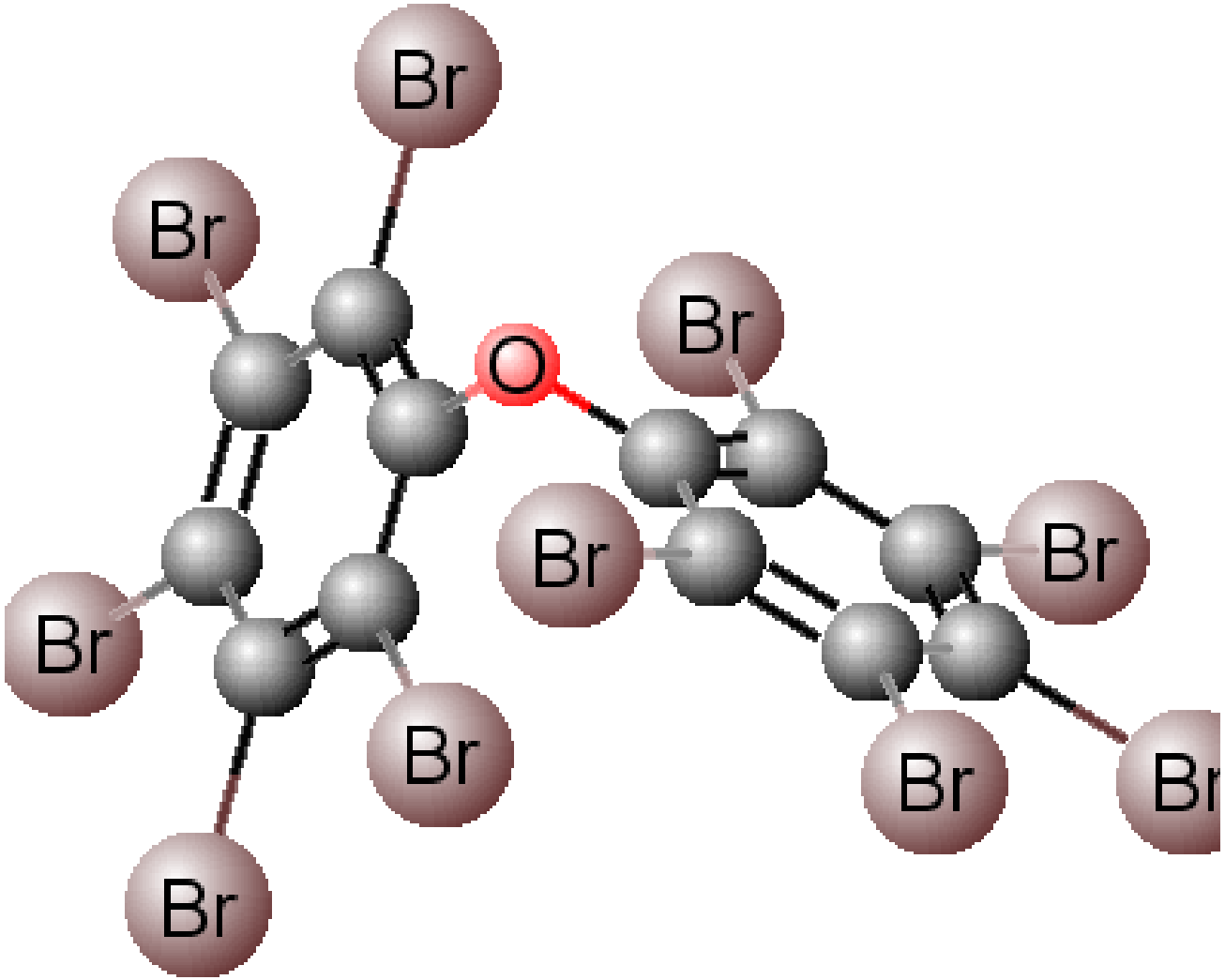


Figure 3. GC/MS (ECNI) chromatogram of phenolic polybrominated diphenyl ethers (OH-PBDEs) in serum from children working and living on a waste disposal site in Managua, Nicaragua. I.S., internal standard. The identified and the unidentified OH-PBDEs are shown by compound abbreviations and asterisks, respectively. The instrument was set to trace bromide ions (*m/z* 79/81).

Interesting molecule of the day

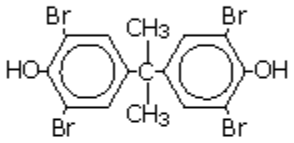
- decabromobiphenylether (“deca”)



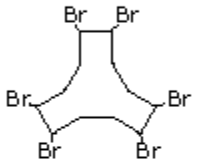
Interesting molecule of the day

Chemical Fire Retardants

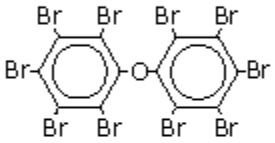
- Nitrogen-based
- Aluminum-hydroxides
- Red phosphorous
- Zinc borate
- Magnesium-hydroxides
- Organophosphorous compounds
- Ammonium polyphosphates
- **Bromine-based compounds**



Hexabromo-cyclododecane (HBCD)



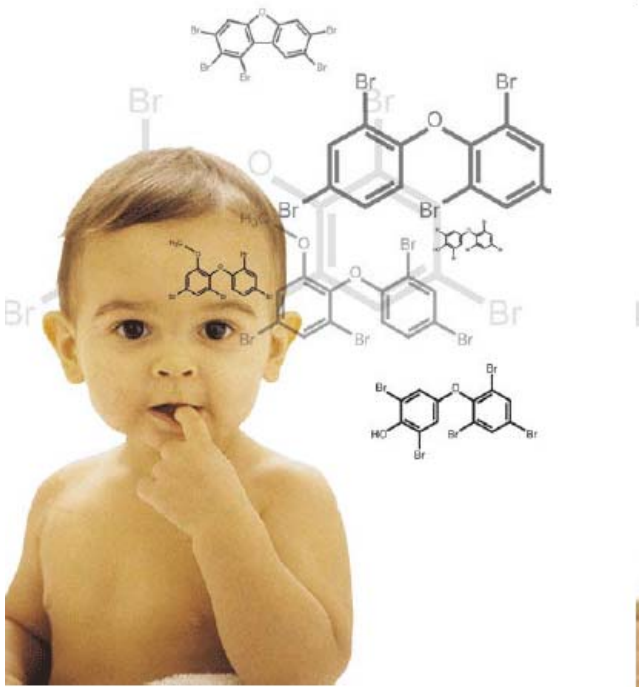
Tetrabromo-bisphenol A (TBBPA)



Polybrominated diphenylethers (PBDEs)

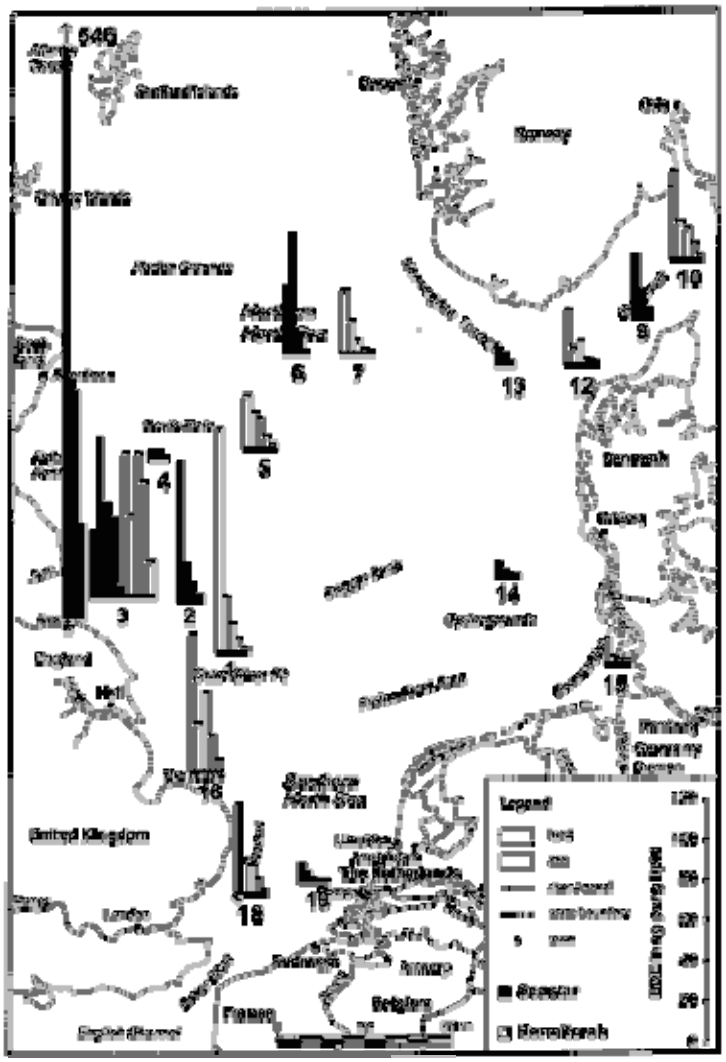
Deca* Mixture			Octa* Mixture			Penta* Mixture		
Component Congeners	Number of Bromines	Percent of Total	Component Congeners	Number of Bromines	Percent of Total	Component Congeners	Number of Bromines	Percent of Total
PBDE-209	10	97%	PBDE-153	6	85%	PBDE-47	4	31%
			PBDE-154	6	14%	PBDE-99	5	48%
						PBDE-100	5	8.8%
						PBDE-153	6	6.6%
						PBDE-154	6	4.4%

*The names of the commercial PBDE mixtures (Deca, Octa, Penta) often do not reflect their actual congener make-up. For example, the "Penta" product actually contains a mixture of tetra-, penta-, and hexa-BDEs with four, five and six bromines, respectively.



Interesting molecule of the day

Figure 1. Representative ECNI mass chromatograms with SIM of the $m/z = 79$ and 81 ions presented for a referent (*A*; an abattoir worker without known occupational PBDE exposure), an electronics dismantler (*B*), and a rubber mixer (*C*). BDE-183 is the dominating peak in the dismantler (*B*), and octa-BDE congeners to BDE-209 dominate in the rubber mixer (*C*). The peak heights of the surrogate standard (SS; BDE-138) are approximately the same in *A*–*C*.

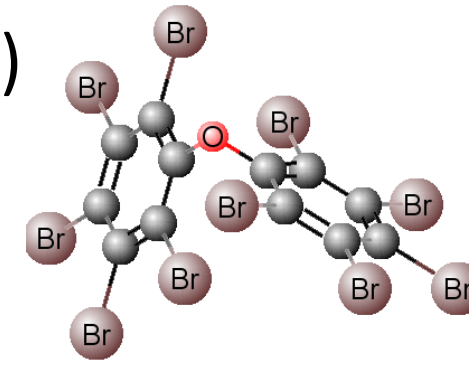


Levels of Polybrominated Diphenyl Ether (PBDE) Flame Retardants in Animals Representing Different Trophic Levels of the North Sea Food Web Environmental Science and Technology 1oct02

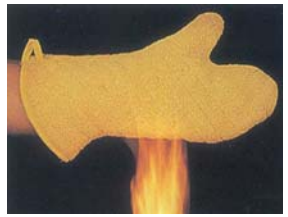
Jan P Boon,*,† Wilma E Lewis, #,† Michael R. Tjoen-A-Choy,† Colin R. Allchin, ‡ Robin J. Law,‡ Jacob de Boer, § Cato C. Tenhallers-Tjabbes, ,† and Bart N. Zegers†

Interesting molecule of the day

- decabromobiphenylether (mw = 959.2 Da)
  - T_m = 295 C, T_b = 530 C
  - $C_w^{sat} = 1.0 \times 10^{-10}$ M
  - $K_H = 1.2 \times 10^{-5}$ bar L mol^{-1}, $K_{ow} = 10^{12.11}$ (!)



- flame retardant additive
  - plastics (e.g., polystyrene in appliances, computers)
  - foams, carpets, upholstery (furniture, vehicles)
  - production: 55,000 tons per year
  - photodegrades to more toxic by-products



- "Everyday Items, Complex Chemistry" (NY Times, Dec 22, 2007)
  - being phased out by Dell Computer

Octanol-Water Partition

- Match these compounds with their K_{ow}

compound		K_{ow}
2,3,7,8-tetrachlorodibenzo-*p*-dioxin	A.	$10^{2.39}$
1,2,3,5-tetrachlorobenzene	B.	$10^{2.88}$
tetrachloroethene	C.	$10^{4.65}$
1,1,2,2-tetrachloroethane	D.	$10^{5.74}$
2,4,5-trichlorobiphenyl	E.	$10^{6.64}$

Octanol-Water Partition

- Match these compounds with their K_{ow}

compound		K_{ow}
2,3,7,8-tetrachlorodibenzo-*p*-dioxin		$10^{6.64}$
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2,4,5-trichlorobiphenyl	$10^{5.74}$

Estimating K_{ow}

- Structural contributions
  - Leo, Hansch (1975)
    - based on LFERs
  - fragments f_i
    - compounds' atomic building blocks
  - factors F_i
    - atomic arrangement
    - intramolecular interactions

$$\log K_{ow} = \sum_i f_i + \sum_j F_j$$

LINEAR FREE ENERGY RELATIONSHIPS

Estimating K_{ow}

- Fragments f_i
  - an atom
  - a string of atoms (multi-atom fragment)
    - exterior bonds to "isolating carbon atom"
      - isolating carbon atom has 4 single bonds, at least 2 to non-heteroatoms
      - multiple bonds to other carbon atoms
- multi-atom fragments can be derived
  - $f(\text{-}CH_3) = 0.89$
  - $f(\text{-C}) + 3\ f(\text{-H}) = 0.20 + 3(0.23) = 0.89$

TABLE 1-5

Fragment Constants[a]

Fragment[b]	f	f^{ϕ}	$f^{\phi\phi}$	Special Types
Without C or H				
–F	–0.38	0.37		$f^{\phi/2} = 0.00$
–Cl	0.06	0.94		$f^{\phi/2} = 0.50$
–Br	0.20	1.09		$f^{1R} = 0.48$, $f^{\phi/2} = 0.64$
–I	0.59	1.35		$f^{\phi/2} = 0.97$
–N<	–2.18	–0.93	–0.50[c]	$f^{1R} = -1.76$
–O–	–1.82[d]	–0.61	0.53	$f^{X1} = -0.22$, $f^{X2} = +0.17$, $f^{\phi/2} = -1.21$
–S–	–0.79	–0.03	0.77	
–NO		0.11		
$-NO_2$	–1.16	–0.03		$f^{X2} = 0.09$
$-ONO_2$	–0.36			
$-IO_2$		–3.23		
$-OP(O)O_2<$	–2.29	–1.71		$f^{X1} = -1.50$
–P(O)<				Triple aromatic = –2.45
$-P(O)O_2<$		–2.33		
$-OP(S)O_2<$		–0.30[c]		
$>NP(S)(N<)_2$	–3.37			
$-SP(S)O_2<$	–2.89			
$-SO_2F$		0.30		
$-SO_2N<$		–2.09		
–S(O)–	–3.01	–2.12	–1.62	
$-SO_2-$	–2.67	–2.17	–1.28	
$-SO_2O-$	–2.11	–2.06	–0.62	$f^{1/\phi} = -1.42$
$-SF_5$		1.45		
$-SO_2O^{-e}$	–5.87	–4.53		
$-OSO_3^{-e}$	–5.23			
–N=N–			0.14	
–NNN–		0.69		
–N=NN<		–0.85		$f^{X1} = -0.67$
>NNO	–2.40	–0.84		
$-O^{-e}$		–3.64		
–Si<	–0.09[c]	0.65[c]		$f^{1R} = -0.38$[c]

(continued)

TABLE 1-5 (Continued)

Fragment[b]	f	f^{ϕ}	$f^{\phi\phi}$	Special Types
Without C,with H				
–H	0.23	0.23		
–NH–	–2.15	–1.03	–0.09	$f^{X1} = -0.37$
$-NH_2$	–1.54	–1.00		$f^{X1} = -0.23$, $f^{1R} = -1.35$
–OH	–1.64	–0.44		$f^{X1} = 0.32$, $f^{1R} = -1.34$
–SH	–0.23	0.62		
$-SO_2NH-$		–1.75[c]	–1.10	$f^{1/\phi} = -1.72$
$-SO_2(NH_2)$		–1.59		$f^{X1} = -1.04$
$-SO_2NH(NH_2)$	–2.04			
$-NHSO_2(NH_2)$		–1.50		
–NH(OH)		–1.11		
–NHNH–			–0.74	$f^{1R} = -2.84$
$-NH(NH_2)$		–0.65		
–SP(O)(O–)NH–	–2.18[c]			
–SP(O)(NH_2)O–	–2.50			
$-As(OH)_2O-$		–1.84		
$-As(O)(OH)_2$		–1.90		
$-B(OH)_2$		–0.32		
With C,without H				
–C(–)–	0.20	0.20		
$-CF_3$		1.11		
–CN	–1.27	–0.34		$f^{1R} = -0.88$
–C(O)N<	–3.04	–2.80	–1.93	$f^{1/\phi} = -2.20$
–SCN	–0.48	0.64		$f^{1R} = -0.45$
–C(O)–	–1.90	–1.09	–0.50	$f^{X1} = -0.83$, $f^{1R} = -1.77$
–C(O)O–	–1.49	–0.56	–0.09	$f^{X1} = -0.36$, $f^{1R} = -1.38$, $f^{1/\phi} = -1.18$
$-C(O)O^{-e}$	–5.19	–4.13		
$-N=CCl_2$		0.64		
–OC(O)N<	–2.54?	–1.84		
–C(O)N–N=N–				$f^{1/\phi} = -0.87$
–C(=S)O–	–1.11			

TABLE 1-5 (Continued)

Fragment[b]	f	f^{ϕ}	$f^{\phi\phi}$	Special Types
With C and H				
$-CH_3$	-0.89	0.89		
$-C_6H_5$ (benzene)	1.90			
–C(O)H	–1.10	–0.42		
–C(O)OH	–1.11	–0.03		$f^{1R} = -1.03$
–C(O)NH–	–2.71	–1.81	–1.06	$f^{1/\phi} = -1.51$
$-C(O)NH_2$	–2.18	–1.26		$f^{X1} = -0.82$, $f^{1R} = -1.99$
–OC(O)NH–	–1.79	–1.46		$f^{1/\phi} = -0.91$
$-OC(O)NH_2$	–1.58	–0.82		$f^{1R} = -1.24$
–CH=N–		–1.03	+0.08[c]	
–CH=NOH	–1.02	–0.15		
–CH=NNH–	–2.75			
–NHC(O)NH–	–2.18	–1.57	–0.82	
$-NHC(O)NH_2$	–2.18	–1.07		
$>NC(O)NH_2$		–2.25	–2.15	
>C=NH			–1.29	
>NC(O)H	–2.67	–1.59		
–OC(O)NH–	–1.79	–1.45		$f^{1/\phi} = -0.91$
–C(=S)NH–	–2.00			$f^{1/\phi} = -0.96$
–NHCN		–0.03		
–CH=NN<		–1.71		
–NHC(O)N<		–2.29		$f^{1/\phi} = -2.42$
–NNO(C(O)NH–)	–1.50			$f^{1/\phi} = -0.76$
–OC(O)H	–1.14	–0.64		
–NHC(O)H		–0.64		
–C=NOH(OH)		–1.64		
$-C(=S)NH_2$		–0.41		
$-N(C(O)NH_2)-$		–2.25	–2.07	
$-SO_2NHN=CH-$				$f^{1/\phi} = -1.47$
–NHC(=S)NH–		–1.79		
$-NNO(C(O)NH_2)$	–0.95			
$-C(O)NHNH_2$		–1.69		
$-NHC(=S)NH_2$	–1.29	–1.17		
$-CNH_2$ (=NH·HCl)		–3.49		
$-NHC=NH(NH_2)$	–5.65			
–C(O)C(O)–	–3.00		–0.30	

(continued)

TABLE 1-5 (Continued)

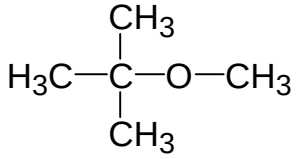
Fragment[b]	f	f^{ϕ}	$f^{\phi\phi}$	Special Types
–C(O)NHC(O)–	–3.31		–3.00[c]	
–C(O)NHC(O)H	–2.84			
–C(O)NHN=CH–			–1.12	
$-C(O)NHC(O)NH_2$	–1.91			$f^{1R} = -1.57$
$-CH(NH_2)C(O)OH$	–3.97			
$-CH=NNHC(O)NH_2$	–0.63	–0.86		
$-CH=NNHC(=S)NH_2$		–0.05		
$-CH=NNHC(O)NHNH_2$		–1.09		
–C(O)NHC(O)NHC(O)–	–2.38			

Fused to Aromatic Ring[f]

Fragments[b] Without C	f^{ϕ}	Fragments[b] With C	f^{ϕ}
–N=	–1.12	C	0.13
–N<	–1.10[c]	C (ring fusion carbon)	0.22[g]
–N<	–0.56	C (ring fusion hetero)[g]	0.44
–N=N–	–2.14	CH	0.35[g]
–N= O	–3.46	–C(O)–	–0.59
–O–	–0.08	–OC(O)–	–1.40
–S–	0.36	–CH=NNH–	–0.47
–S– O	–2.08	–N=CHNH–	–0.79
–Se–	0.45	–NHC(O)–	–2.00
–NH–	–0.65	–N=CH–O–	–0.71
–NHN=N–	–0.86	–N=CH–S–	–0.29
		–CH=N–O–	–0.63
		–N=CHN–	–1.46
		–NHC(O)NH–	–1.18
		–C(O)NHC(O)–	–1.06[c]
		–C(O)NHC(O)NH–	–1.78
		–C(O)NHC(O)NHN=	–1.36

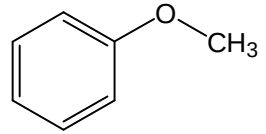
Estimating K_{ow}

f (-O-)



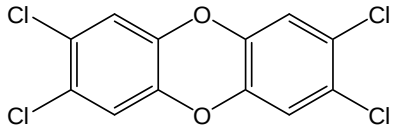
- f – aliphatic

f^{ϕ} (-O-)



- f^{ϕ} – bonded to aromatic carbon
- $f^{\phi\phi}$ – bonded to aromatic carbon on both sides

$f^{\phi\phi}$ (-O-)



- $f^{1/\phi}$ – attached to aromatic ring from right
  - e.g., f^{ϕ}(-CO_2-) for Ar-CO_2-; $f^{1/\phi}$(-CO_2-) for -CO_2-Ar
- f^{Xn} (n = 1, 2) – aromatic attachment for which value is enhanced by second electron-withdrawing substituent
- f^{1R} – benzyl attachment ($C_6H_5CH_2$-)
- $f^{\phi/2}$ – attachment to vinyl carbon (>C=C<)

Estimating K_{ow}

- Factors F_j – corrections accounting for:
  - bonds
    - unsaturation – double and triple bonds
    - geometry – chains, rings, branching
  - multiple halogenation
    - on geminal carbon, on vicinal carbon
  - H-polar proximity
    - along chains, rings (aromatic and aliphatic)
  - intramolecular H-bond
    - for nitrogen and oxygen

TABLE 1-6

Summary of Rules for Calculating Factors

- **Involving BONDS**

Unsaturation

	Double	Triple
Normal: $F_{(=)}$	$= -0.55$	$F_{(\equiv)} = -1.42$
Conjugate to ϕ: $F^{\phi}_{(=)}$	$= -0.42$	$F^{\phi\phi}_{(\equiv)} = 0.00$
Conjugate to 2ϕ: $F^{\phi\phi}_{(=)}$	$= -0.00$	
Conjugate to second = in chain: $F_{(=)}$	$= -0.38$	

Geometric

	Proportional to length: x(n − 1)	Branching in short chains: one-time	
Chain:	$F_b = -0.12$	Alkane chain:	$F_{cBr} = -0.13$
Ring:[a]	$F_b = -0.09$	H-polar fragment:	$F_{gBr} = -0.22$
Branching:	$F_{bYN} = -0.20$ (-amine)	Ring cluster:	$F_{rCl} = -0.45$
	$F_{bYP} = -0.31$ (phosphorus esters)		

- **Involving MULTIPLE HALOGENATION**

On same carbon (geminal) F_{mhGn}: $\begin{cases} (n = 2) = 0.30^b \\ (n = 3) = 0.53^b \\ (n = 4) = 0.72^b \end{cases}$

On adjacent carbon (vicinal) $F_{mhVn} = 0.28\ (n - 1)$

- **Involving H-POLAR PROXIMITY**

Chain: $F_{P1} = -0.42\ (f_1 + f_2)$

$F_{P2} = -0.26\ (f_1 + f_2)$

$F_{P3} = -0.10\ (f_1 + f_2)$

Aromatic ring: $F^{\phi}_{P1} = -0.16\ (f_1 + f_2)$

$F^{\phi}_{P2} = -0.08\ (f_1 + f_2)$

Aliphatic ring: $F_{P1} = -0.32\ (f_1 + f_2)$

$F_{P2}{}^c = -0.20\ (f_1 + f_2)$

- **Involving INTRAMOLECULAR H-BOND**

$F_{HBN} = 0.60$ for nitrogen $\qquad F_{HBO} = 1.0$ for oxygen

a. Aromatic rings excluded.
b. Values per halogen atom, if α or β to H-polar fragment, additional factor required: see Table 1-7.
c. For morpholine and piperazine derivatives, use coef. = −0.10

Source: Hansch and Leo [14]. *(Reprinted with permission from John Wiley & Sons, Inc.)*

double and triple bonds lower K_{ow}

chains, rings, branching all lower K_{ow}

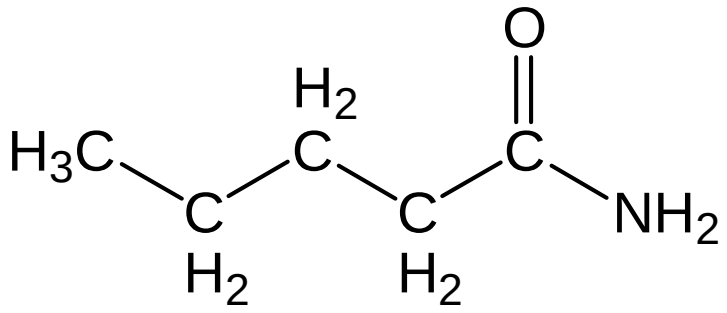
multiple halogens increase K_{ow}

-OH, -O-, $-NH_2$ near each other lowers K_{ow}

H-bond in molecule increases K_{ow}

Estimating K_{ow}

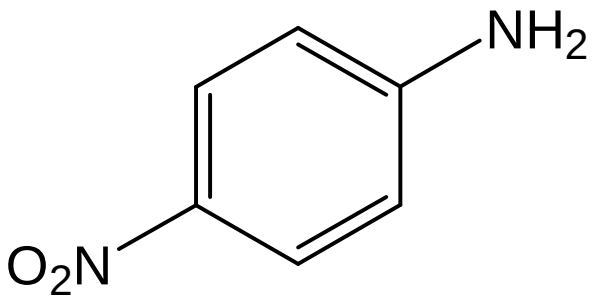
- Example: valeramide



f or *F*	number	contrib	total
f(C)	4	0.20	0.80
f(H)	9	0.23	2.07
f($CONH_2$)	1	-2.18	-2.18
F_b	(4-1) bonds	-0.12	-0.36
		log K_{ow}	0.33
		log K_{ow} (meas.)	0.31

Estimating K_{ow}

- Example: *p*-nitroaniline

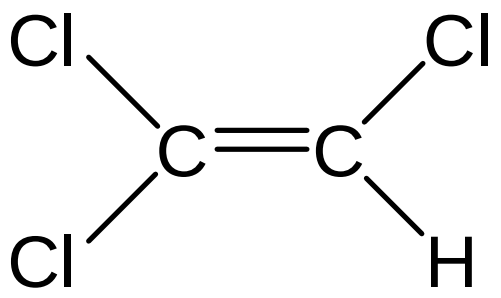


f or *F*	number	contrib	total
$f(C_6H_5)$	1	1.90	1.90
$f^{\phi}(H)$	-1	0.23	-0.23
$f^{X2}(NH_2)$*	1	-0.23	-0.23
$f^{\phi}(NO_2)$	1	-0.03	-0.03
		log K_{ow}	1.41
		log K_{ow} (meas.)	1.39

* f^{X2} for aromatic attachment, value enhanced by the presence of second substituent of electron-withdrawing character with $\sigma_I > 0.75$ (e.g., $-NO_2$)

Estimating K_{ow}

- Example: trichloroethene

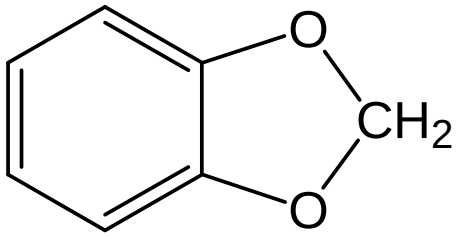


* site of unsaturation should be considered saturated for the purpose of fragment constants and bond factors (F_b) (i.e., >C=C< is >CH-CH<)

f or F	number	contrib	total
f(C)	2	0.20	0.40
f(H)	3*	0.23	0.69
$f^{\phi/2}$(Cl)	3	0.50	1.50
$F_{=}$	1	-0.55	-0.55
F_b	(4-1) bonds H bonds not counted	-0.12	-0.36
F_{mhG2}	2	0.30	0.60
		log K_{ow}	2.28
		log K_{ow} (meas.)	2.29

Estimating K_{ow}

- Example: 1,2-methyldioxybenzene



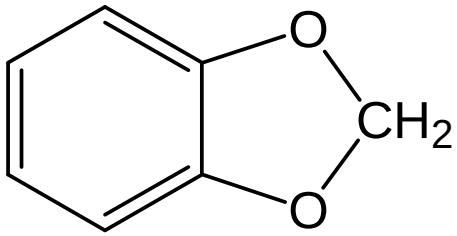
f or F	number	contrib	total
f(CH)	4	0.355	1.42
f^{ϕ}(C•)	2	0.44	0.88
f^{ϕ}(-O-)	2	-0.61	-1.22
f(H)	2	0.23	0.46
f(C)	1	0.20	0.20
F_b	(4-1) ring	-0.09	-0.27
F_{P1}*	1	-0.32[(-0.61)+(-0.61)]	0.39
F^{ϕ}_{P2}*	1	-0.08[(-0.61)+(-0.61)]	0.10
		log K_{ow}	1.96
		log K_{ow} (meas.)	2.08

* F_{P1} for two polar fragments separated by one C in aliphatic ring

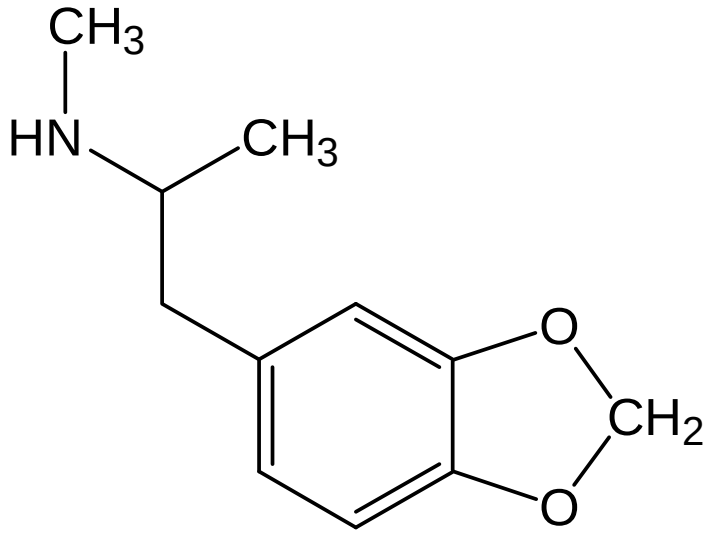
* F^{ϕ}_{P2} for two polar fragments separated by two C's in aromatic ring

Estimating K_{ow}

- Which compound has a higher K_{ow}?



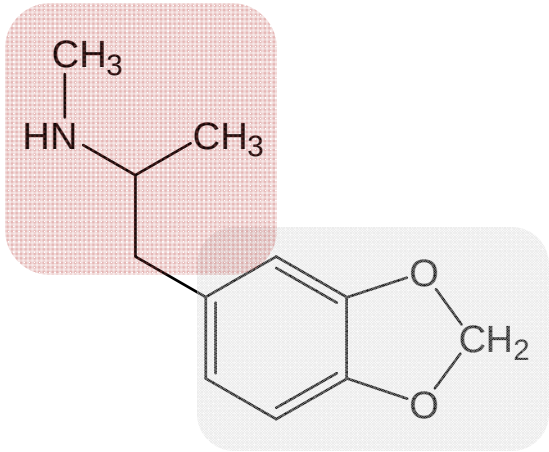
A. 1,2-methylenedioxybenzene (MDB)



B. *N*-methyl-3,4-methylene-dioxymethamphetamine (MDMA)

Estimating K_{ow}

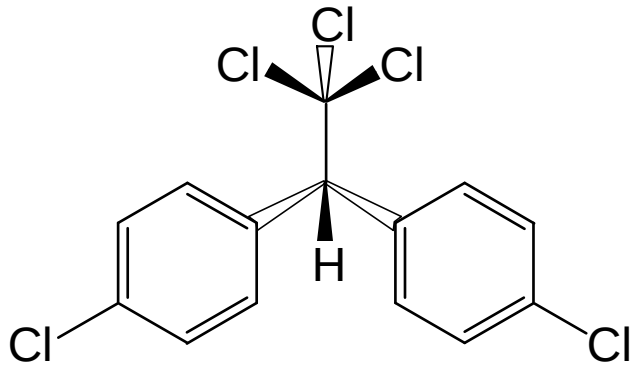
- Example



f or *F*	number	contrib	total
1,2-methylenedioxybenzene			2.08
f^{ϕ}(H)	-1	0.23	-0.23
f^{ϕ} (C)	1	0.20	0.20
f(C)	1	0.20	0.20
f(H)	3	0.23	0.69
f(-NH-)	1	-1.54	-1.54
f(-CH_3)	2	0.89	1.78
F_{bYN}	5-1 bonds	-0.20	-1.00
		log K_{ow}	2.18
		log K_{ow} (est.)	2.25 (±0.54)

Estimating K_{ow}

- Example: DDT



f or F	number	contrib	total
f(Cl)	3	0.06	0.18
f (C)	2	0.20	0.40
f(H)	1	0.23	0.23
$f(C_6H_5)$	2	1.90	3.80
f^{ϕ}(H)	-2	-0.23	-0.46
f^{ϕ}(Cl)	2	0.94	1.88
F_b	(6-1)	-0.12	-0.60
F_{mhG}	3	0.53	1.59
		log K_{ow}	7.02
		log K_{ow} (meas.)	4.89 (6.19) 6.91

Estimating K_{ow}

- General Advice
  - draw the structure!
  - start from a structurally related compound with known K_{ow}
  - assume overall error of $\pm$0.12 log K_{ow}
    - errors from individual fragments, factors can be summed also
  - consult your colleagues and strive for consensus
  - and…

Estimating K_{ow}

- …give up and use a computer program!

"Hand calculations are not for the *faint-hearted* or for those who are poorly versed in chemistry. Even the designers of the methods use the computer version in order to uniformly and correctly apply the rules…

An indication of the difficulty in applying Leo's method uniformly by hand is that some published estimates of log K_{ow} can't be duplicated…"

Baum, E.J., 1998. *Chemical Property Estimation: Theory and Practice*. Lewis Publishers, Boca Raton, Florida.

Estimating K_{ow}

- DDT
  - log K_{ow} measurements range from 4.89 to 6.91 (6.19 best)
  - SMILES: C(C(C1=CC=C(Cl)C=C1)C2=CC=C(Cl)C=C2)(Cl)(Cl)Cl
  - CAS: 50-29-3
- Estimate K_{ow} with web-based programs
  - VCC Labs ALOGPS Program
  - Interactive Analysis logP
  - Biobyte ClogP
  - Syracuse Research logkow
  - XLOGP (not interactive except through VCC)