Vol. 12 No. 1 November 2012

The Octanol/Water Partition Coefficient: What is it for and, how good is it?

Watson's Notes

Innovative Solutions for Difficult Problems

You have recently been in Afghanistan, I perceive"

With these words was born the most famous team in detective fiction; Sherlock Holmes and his trusted comrade and biographer, Dr. John H. Watson.

In the spirit of Watson, who chronicled the exploits of Holmes, we have created this newsletter named "Watson's Notes".

In the pages of "Watson's Notes", modern day scribes document the discoveries, unusual cases and other news of Investigative Science Incorporated, our scientific consulting firm in Burlington, Ontario, Canada.

Please contact us if you have comments, and please read on.

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Octanol/Water Partition Coefficient by HPLC (117) or Flask Method (107)

The octanol/water partition coefficient is simply the extent to which a substance partitions between octanol and water. Octanol floats on the water and if the test material is fat soluble, it will partition preferentially into the upper, or octanol, phase. The partition coefficient (P_{OW}, or K_{ow}) is the ratio of the concentration of the test substance in the octanol phase divided by the concentration in the water phase.

The test was developed many years ago to estimate the extent to which a chemical dissolved in water would partition into a cell membrane, such as the skin of a mammal. Octanol was used because its polarity was thought to be closely similar to that of the inside of a cell membrane. The octanol/water partition coefficient, or its logarithm (log P_{OW}, or log K_{ow}), has gained worldwide acceptance in the environmental regulatory world. It provides an estimate of the tendency of a material to bioaccumulate in animals.

According to the theory, any chemical with a log P_{OW} of 3 or greater will bioaccumulate by building up in animal fat, assuming that the chemical is not already broken down. A value of 3 means essentially that the material is 1000 times more soluble in octanol (and theoretically, fat) than in water. It has been shown experimentally that there is a good correlation between log P_{OW} and bioaccumulation in fish.

There are essentially four ways of estimating the log P_{OW}. OECD method 107 employs a flask containing octanol, water and the test substance. After a suitable equilibration period, the concentration of the test substance in each phase is measured and the log of the ratio calculated. More recently, High Pressure Liquid Chromatography (HPLC) using a C18 reverse phase column (OECD 117) has become the preferred method, according to Health Canada. This approach exploits the correlation between log P_{OW} and HPLC retention time (how long it takes for the unknown compound to elute from the HPLC). The HPLC is calibrated using a series of chemicals with known P_{OW}. A plot of log P_{OW} versus the log of the retention time gives a straight line (see Figure 1). The unknown is run on the same system, and from the retention time, the P_{OW} can be determined.

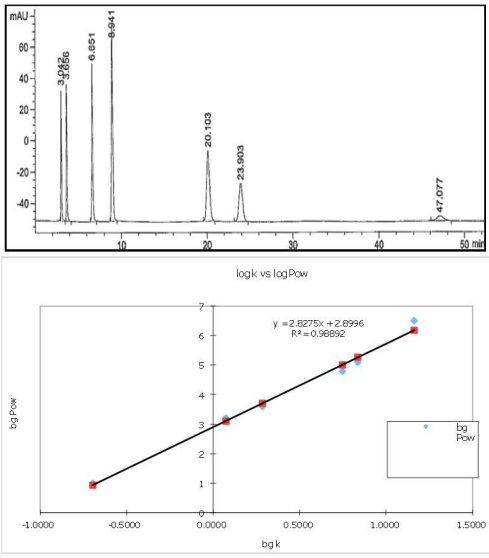

Figure 1: Chromatogram of P_{OW} Standards and Calibration Curve

For test substances that are for any reason incompatible with these tests, the log P_{OW} may be estimated from the solubility in water and octanol. Lastly, the log P_{OW} can be computer modelled. These models rely on a large data base of known compounds and assume that new, unknown compounds will behave according to established patterns.

In practice, these methods all have limitations. For example, many factors such as charge affect the HPLC retention time of a compound. For this reason, the HPLC method is usually restricted to neutral or weakly acidic or weakly basic compounds. As well, with a polymer, one usually sees a series of peaks, so the calculated P_{OW} is the weighted average of the peaks that are detected. Surface active compounds cannot be done by HPLC. The flask method (OCED 107) is subject to the usual measurement errors, which are compounded when the ratio is computed. The calculation based on the individual solubilities assumes that the

ELEMENTARY MY DEAR WATSON

These ideas about science were gleaned from 5th and 6th graders (and from www, ahajokes. com):

! Talc is found on rocks and on babies.

! The law of gravity says no fair jumping up without coming back down.

! Water freezes at 32 degrees and boils at 212. There are 180 degrees between freezing and boiling because there are 180 degrees between north and south.

! Many dead animals in the past changed to fossils while others preferred to be oil.

! Vacuums are nothings.

! Some oxygen molecules help fires burn while others help make water, so sometimes it's brother against brother.

! In looking at water under a microscope, we find that there are twice as many H's as O's.

solubilities in water and octanol reflect the actual partition. This is a dubious assumption. The computer models work well for known compounds or analogues well represented in the model database. For new or unusual compounds, nobody knows how good the estimates are.

In this fact sheet, we compare the various approaches applied to a range of compounds measured in our lab.

The flask method is useful for compounds with a log P_{ow} of between -2 and 4, while the HPLC method is good up to log POW of 6. Outside this range we enter the realm of estimation for which there are several models available. Realistically the key point is whether a molecule has a log P_{ow} of 3 or more, indicating that it may bioaccumulate. It probably doesn't matter whether a molecule has a log P_{ow} value of 6 or 15, in either case it is going to be fat soluble!

So how well do the methods agree? Tables 1 and 2 summarize our work on this issue.

TABLE 1: OECD 117 & 107 Comparison

Compound	Log Pow		
	Literature	1171	107[1]
1	n/a	4.8	3.7
2	n/a	4.9	4.1
3	n/a	4.4	3.2
4[3]	n/a	>5.1[2]	3.8
5	n/a	>5.1[2]	4.8
Bisphenol	2.2-3.6	2.3	2.8
Naphthalene	3.6	3.5	3.5

Note 1: Analysis done at ISI
Note 2: In both cases the test substance eluted after the last standard, therefore only a "greater than" value can be reported.
Note 3: Polymer

The results in Table 1 show that there is reasonable, but not great, agreement between the OECD 117 and 107 methods. It is not surprising that the worst agreement was with a polymer. This is likely because, in addition to the features affecting chromatographic behaviour discussed above, issues such as how big a molecule is or how it folds up in mobile phase can influence the chromatographic behaviour of polymers. As well, the P_{ow} of a polymer is calculated as a weighted average of many peaks appearing in the chromatogram. This introduces another level of error. It is probably safe to say though, that whichever method is used, there is rarely a dispute over whether the test material has a log Pow of less than or greater than 3; the key cut-off for bio-accumulation.

How about Modelled and Literature P_{ow} Values?

We have also reviewed how well our measured values agree with values determined by computer models and reported in the literature. Table 2 summarizes our results.

TABLE 2: Comparison of Literature, Modelled and Measured Values.

Chemical	Log Pow		
	Lit.[1]	Model[2]	117[3]
Acetanilide	1.0	1.2	1.3
Salicylic Acid		2.3	1.9
Ethyl Benzoate	2.6	2.6	2.9
Naphthalene	3.6	3.4	3.5

Note 1: OECD Method 117, Table 1.
Note 2: LOGKOW - Sangster Research Laboratories.
Note 3: Measured using OECD 117 at the ISI lab.

Table 2 shows that there is reasonable agreement between literature, modelled and measured values, at least for pure chemicals. In some cases, such as Bisphenol-A, shown in Table 1, the literature values can vary by more than 10¬ fold (i.e. more than 1 log unit). The modelled values we investigated typically varied by 0.2 log units or less depending on which model was used, but in some cases, we observed a difference of 0.5 log units or more, even for pure chemicals.

Given that the partition coefficient idea is essentially a hypothesis (octanol/water partition mimics cell membranes) wrapped inside a concept (the Pow model can be extrapolated to make decisions about animals) bundled with a bunch of measurement uncertainty, the results of the various approaches agree remarkably well. Whether, these results actually reflect events in the natural environment, well, that's another question!

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