



Whither QSAR?

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To see the future, we must look at the past (German proverb).

A QSAR (quantitative structure-activity relationship) is a mathematical equation that relates a property of interest such as a biological potency with one or more molecular properties (called descriptors), for a series of (usually) related compounds. A good example is the correlation of the anti-inflammatory potency of a series of ring-substituted aspirin derivatives in the rat:¹

$$\log\left(\frac{1}{ED_{50}}\right) = 1.958 + 1.029 \log P - 0.195(\log P)^2$$

Eq.(1)

$$n = 20 \quad r^2 = 0.904 \quad s = 0.118$$

In equation 1, ED_{50} = dose required to reduce paw inflammation by 50%, P = octanol-water partition coefficient, n = number of compounds used to develop the QSAR, r^2 =coefficient of determination, and s = standard error of the model.

The statistics are very good, for $r^2 = 0.904$ means that the QSAR model accounts for 90.4% of the variation of anti-inflammatory potency. The use of $\log P$ as sole descriptor suggests that penetration of each compound to the site of action is the controlling factor. I wonder how many hundreds of aspirin derivatives were made and tested in years gone by in the hope of finding “a better aspirin”, when the above model indicates that the best possible potency (assuming the same mode of action) would be only about 1.75 times that of aspirin.

In line with the sentiment expressed in the German proverb that heads this Editorial, I have recently published two papers dealing with the history of QSAR.^{2,3} I was amazed to discover how much early work had been done. The earliest quantitative property prediction that I could find is that of Döbereiner, who in 1816 accurately predicted the specific weight of strontium sulphate by interpolation (read-across, in modern parlance) from those of calcium and barium sulphates.⁴

Even more amazing, in a way, is the insight shown by the Roman poet and philosopher Titus Lucretius Carus (ca. 99-55 B.C.), who in his *De Rerum Natura*⁵ wrote:

We see how quickly through a colander

The wines will flow; how, on the other hand,

The sluggish olive oil delays: no doubt,
Because 'tis wrought of elements more large,
Or else more crook'd and intertangled.

So over 2000 years ago, Lucretius was proposing that liquid viscosity is a function of molecular size and shape – not QSAR as we now know it, but definitely a precursor.

One of the most important early QSAR works is that of Brown and Fraser,⁶ who postulated that “there can be no reasonable doubt but that a relation exists between the physiologic action of a substance (Φ) and its chemical composition and constitution (C)”. Hence $\Phi = fC$. Although they did not go on to suggest what functions of composition and constitution might be important, their equation is nevertheless a valid generic QSAR.

The outstanding QSAR work by N.V. Lazarev⁷ in the 1940s is still hardly recognised outside Russia.⁸ His QSARs for narcotic effects of chemicals on animals are virtually indistinguishable from those currently being reported.

Of course the work of Corwin Hansch and his co-workers is synonymous with the growth and development of modern QSAR,² and it is not for nothing that Hansch has been called the father of QSAR.⁹ It has even been claimed² that a car was seen on a U.S. highway with a bumper sticker reading: “Corwin Hansch walks on octanol”.

The growth of QSAR publications continues apace,² with over 1500 QSAR publications in both 2015 and 2016. At the same time, the range and complexity of techniques is also steadily increasing –to the concern, it has to be said, of many practitioners, since QSAR requires human expertise as well as computational proficiency.

It is pertinent to mention that several years ago I became so disquieted at the number of submitted QSAR manuscripts and published papers that contained errors that I and two colleagues wrote a paper¹⁰ on “how not to develop a QSAR”; we reported, with examples (including some of our own!), on 21 separate types of error. Sadly, such errors still occur.

A recent much-cited paper¹¹ covers many recent QSAR advances, but also, importantly, looks back; its title includes the phrase “Where have you been?” In our quest for advancement, we should not forget the sound advice given in Occam’s

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Razor: “Pluralitas non est ponenda sine necessitate”; there are numerous English interpretations, of which one of the best in my view is: “The simplest explanation for some phenomenon is more likely to be accurate than are more complicated explanations”.

Two recent publications confirm the continuing and growing importance of QSAR. Doweyko¹² confidently stated in 2008 that: “QSAR lives on, not only as a stand-alone technique, but even more so in disguised forms within the more popular drug design approaches of the modern era”. Cherkasov et al.¹¹ commented in 2014: “QSAR modeling is widely practiced in academy, industry, and government institutions around the world. Recent observations suggest that following years of strong dominance by the structure-based methods, the value of statistically based QSAR approaches in helping to guide lead optimization is starting to be appreciatively reconsidered by leaders of several larger CADD (computer-aided drug design) groups. QSAR models find broad application for assessing potential impacts of chemicals, materials, and nanomaterials on human health and ecological systems. An area of active QSAR expansion is in the use of predictive models for regulatory purposes by government agencies, where a still growing number of specialized regulatory tools and databases are being developed and validated...QSAR continues as a vibrant scientific enterprise and is advancing and contributing to many scientific disciplines along the paths [that Hansch] originally laid forth”.

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