of the approach belies the tremendous complexity of the intermolecular interactions at play in the overall biological response.

Biological systems are a complex mix of heterogeneous phases. Drug molecules usually traverse many of these phases to get from the site of administration to the eventual site of action. Along this random-walk process, they perturb many other cellular components such as organelles, lipids, proteins, and so forth. These interactions are complex and vastly different from organic reactions in test tubes, even though the eventual interaction with a receptor may be chemical or physicochemical in nature. Thus, depending on the biological system involved—isolated receptor, cell, or whole animal—one expects the response to be multifactorial and complex. The overall process, particularly in *vitro* or in *vivo*, studies a mix of equilibrium and rate processes, a situation that defies easy separation and delineation.

Meyer and Overton were the first to attempt to get a grasp on biological responses by noting the relationship between oil/water partition coefficients and their narcotic activity. Ferguson recognized that equitoxic concentrations of small organic molecules was markedly influenced by their phase distribution between the biophase and exobiophase. This concept was generalized in the form of Equation 1.60 and extended by Fujita to Equation 1.61 (182,183).

$$C = kA^m \tag{1.60}$$

$$\text{Log } 1/C = \text{m Log}(1/A) + \text{constant} \tag{1.61}$$

C represents the equipotent concentration, k and m are constants for a particular system, and A is a physicochemical constant representative of phase distribution equilibria such as aqueous solubility, oil/water partition coefficient, and vapor pressure. In examining a large and diverse number of biological systems, Hansch and coworkers defined a relationship (Equation 1.62) that expressed biological activity as a function of physicochemical parameters (e.g., partition coefficients of organic molecules) (19).

$$\text{Log } 1/C = a \log P + b \tag{1.62}$$

Model systems have been devised to elucidate the mode of interactions of chemicals with biological entities. Examples of linear models pertaining to nonspecific toxicity are described. The effects of a series of alcohols (ROH) have been routinely studied in many model and biological systems. See QSAR 1.63–1.67.

4.1.1 Penetration of ROH into Phosphatidylcholine Monolayers (184)

$$\text{Log } 1/C = 0.87(\pm 0.01)\log P + 0.66(\pm 0.01) \tag{1.63}$$

$$n = 4, \quad r^2 = 0.998, \quad s = 0.002$$

4.1.2 Changes in EPR Signal of Labeled Ghost Membranes by ROH (185)

$$\text{Log } 1/C = 0.93(\pm 0.09)\log P - 0.41(\pm 0.16) \tag{1.64}$$

$$n = 6, \quad r^2 = 0.996, \quad s = 0.092$$

4.1.3 Induction of Narcosis in Rabbits by ROH (184)

$$\text{Log } 1/C = 0.72(\pm 0.16)\log P + 1.35(\pm 0.12) \tag{1.65}$$

$$n = 11, \quad r^2 = 0.924, \quad s = 0.142$$

4.1.4 Inhibition of Bacterial Luminescence by ROH (185)

$$\text{Log } 1/C = 1.10(\pm 0.07)\log P + 0.16(\pm 0.12) \tag{1.66}$$

$$n = 8, \quad r^2 = 0.996, \quad s = 0.103$$

4.1.5 Inhibition of Growth of Tetrahymena pyriformis by ROH (76, 186)

$$\text{Log } 1/C = 0.82(\pm 0.04)\text{Clog } P + 0.89(\pm 0.10) \tag{1.67}$$

$$n = 34, \quad r^2 = 0.982, \quad s = 0.173$$

In all cases, there is a strong dependency on