12

Prediction of Toxicity, Sensory Responses and Biological Responses with the Abraham Model

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1. Introduction

Modern drug testing and design includes experimental *in vivo* and *in vitro* measurements, combined with *in silico* computations that enable prediction of the drug candidate's ADMET (adsorption, distribution, metabolism, elimination and toxicity) properties in the initial stages of drug discovery. Recent estimates place the discovery and development cost of a small drug molecule close to US $1.3 billion, from the time of conception to the time when the drug finally reaches the market place. Less than one-fourth of conceived drug candidates proceed to clinical trial stage testing, and of the compounds that enter clinical development less than one-tenth actually receive government approval. Reasons for the low success percentage include poor efficacy, low solubility, unsatisfactory bioavailability, unfavorable pharmacokinetic properties, toxicity concerns and drug-drug interactions, degradation and poor shelf-life stability. Unfavorable pharmacokinetic and ADME properties, toxicity and adverse side effects account for up to two-thirds of drug failures.

Safety evaluation of drug candidates is crucial in the early stages of drug discovery and development. For drug development, safety requires that the potential drug molecule have sufficient selectivity for the desired target receptor so that an adequate dose range can be found where the intended pharmacological action is essentially the only physiological effect exhibited by the drug candidate. Pharmaceutical compounds often exhibit the desired therapeutic action at one concentration range, but may be quite toxic or even lethal at higher dosages and concentrations. Drug induced liver injury (DILI) is the most frequent reason for discontinuation of new drug candidates. Drug-induced liver injuries are classified as predicted/intrinsic or idiosyncratic depending upon whether the injury is dose dependent. Predictable DILIs are dose-dependent, and the injury is largely reversible once the medication is discontinued. Idiosyncratic DILIs, on the other hand, are independent of drug dosage level and believed to be related in part to individual's hypersensitivity or immune system reactions to the medication. Idiosyncratic DILIs depend upon the individual's potential genetic and epigenetic constitution, and immunological responses (Ozer *et al.*, 2010). Examples of drug and/or drug candidates that either failed in late stage clinical testing or were removed from the market because of drug-induced liver injury concerns include: ximelagatran (an anticoagulant that was promoted extensively as a replacement for

warfarin, withdrawn in from US market in 2006); troglitazone (an anti-diabetic and anti-inflammatory drug, withdrawn from the UK market in 1997 and US market in 2000); ebrotidine (an H2-reciptor antagonist, marketed in Spain in 1997, withdrawn from the market in 1998); ticrynafen (a diuretic drug used in treatment of hypertension, withdrawn from US market in 1979); benoxaprofen (a nonsteroidal anti-inflammatory drug, withdrawn from US market in 1982); ibufenac (nonsteroidal anti-inflammatory drug used for the treatment of Rheumatoid arithritis, withdrawn from UK market in 1970) and bromfenac (a nonsteroidal anti-inflammatory drug introduced in 1997 as a short-term analgesic for orthopedic pain, withdrawn from the market in 1998) (Lamment *et al*., 2008; Andrade *et al*., 1999; Goldkind and Laine, 2006). Other drugs, such as valproic acid, ketoconazole, nicotinic acid, rifampin, chlorzoxazone, isoniazid, dantrolene, nefazodone, telethromycin, nevirapine, atomoxetine and inflixmab have received strong heptatoxicity warnings from the U.S. Food and Drug Administration (Lamment *et al*., 2008). Sibutramine and phenylpropanolamine, used in the treatment of obesity, were removed from the U.S. market due to adverse effects associated with cardiovascular disease and hemorrhagic stroke, respectively. (Chaput and Tremblay, 2010). Additional drugs withdrawn from the market for cardiovascular toxicities and concerns include: rotecoxib (used to relieve acute pain and symptoms of chronic inflammation, removed from market in 2005) and valdecoxib (used to relieve acute pain and symptoms of chronic inflammation, removed from market in 2005) (Shi and Klotz, 2008).

Toxicity screening identifies drug candidates that exhibit predictable/intrinsic drug-induced liver injury. Idiosyncratic DILI occurs infrequently and only in treated patients which are highly susceptible to the given pharmaceutical compound. Conventional preclinical safety testing is not the best method to detect idiosyncratic DILI. Fourches and coworkers (2010) examined the possibility of using laboratory test animals as viable means to screen drug candidates for possible drug-induced liver injuries. The authors compiled a data set of 951 compounds reported to induce a wide range of liver effects in humans and in different animal species. Of the 951 compounds considered, 650 had been identified as causing liver effects in humans, 685 had been reported in the literature as causing liver effects in rodents, and only 166 had shown liver effects in nonrodents. The concordance between two species, CONC(species A, species) was defined as

$$CONC(species\,A + species B) = \frac{(Toxic\ for\ both\ A\ and\ B) + (Nontoxic\ for\ both\ A\ and\ B)}{Total\ number\ of\ compounds\ studied} \quad (1)$$

as the number of compounds that exhibited toxicity for both animal species plus the number of compounds that showed notoxicity for both animal species divided by the total number of compounds considered. Equation 1 was applied to the liver effect data gathered from the published literature. The authors found a relatively low concordance of between 39 % to 44 % between different species – for human + rodents the concordance was equal to 44.2 % ((402 + 18)/951); and for human + nonrodents that concordance was equal to 39.9 % ((122+257)/951). Animal testing, while informative, does not necessarily provide an accurate indication of the pharmaceutical compound's likelihood to produce a liver effect in humans. For the concordance calculations it was assumed that the pharmaceutical compound had been tested on all three species groups. The above calculations further underscore the importance of finding suitable testing methods and models for use in drug discovery.

Drug safety considerations also include unwanted side effects, and the impact that the pharmaceutical product will have on environment. A significant fraction of the

pharmaceutically-active compounds sold each year find their way into the environment as the result of human/animal urine and feces excretion (excreted unchanged drugs or as drug metabolites), direct disposal of unused household drugs by flushing into sewage systems, accidental spills and releases from manufacturing production sites, and underground leakage from municipal sewage systems and infrastructures. Dietrich and coworkers (2010) recently examined the environmental impact that four pharmaceutical compounds (carbamazepine, diclofenac, 17α-ethinylestradiol and metoprolol) had on the growth and reproduction of *Daphnia Magna* after exposure to the individual drugs and drug mixtures at environmentally relevant concentrations. The authors found that effects were still detectable even several generations after first exposure to the pharmaceutical compound. The *Daphnia Magna* had not developed complete resistance to the compound. In the case of metoprolol, both the body length of the females at first reproduction and the number of offspring per female were significantly less than the control group. The same body length pattern was observed for females in the third and fourth generations. No difference in female body length was observed in the first, second and fifth generations. The number of offspring per female was also reduced for the fourth generation. Experimental data further revealed that drugs acting in combination can lead to impairments that are not predicted by the response to single substances alone. The authors noted that aquatic organisms may not evolve a total resistance to pharmaceuticals in natural aquatic systems, presumably due to high fitness costs. One cannot exclude the potential long-term harmful effects that pharmaceuticals might have on the environment. The Chapter will focus on the predicting the toxicity, sensory response and biological response of organic and drug molecules using the Abraham solvation parameter model.

2. Abraham solvation parameter model

The Abraham general solvation model is one of the more useful approaches for the analysis and prediction of the adsorption, distribution and toxicological properties of potential drug candidates. The method relies on two linear free energy relationships (lfers), one for transfer processes occurring within condensed phases (Abraham, 1993a,b; Abraham *et al*., 2004):

$$SP = c + e \cdot \mathbf{E} + s \cdot \mathbf{S} + a \cdot \mathbf{A} + b \cdot \mathbf{B} + v \cdot \mathbf{V} \quad (2)$$

and one for processes involving gas-to-condensed phase transfer

$$SP = c + e \cdot \mathbf{E} + s \cdot \mathbf{S} + a \cdot \mathbf{A} + b \cdot \mathbf{B} + l \cdot \mathbf{L} \quad (3)$$

The dependent variable, SP, is some property of a series of solutes in a fixed phase, which in the present study will include the logarithm of drug's water-to-organic solvent (log P) and blood-to-tissue partition coefficients, the logarithm of the drug's molar solubility in an organic solvent divided by its aqueous molar solubility (log $C_{solute,org}/C_{solute,water}$), the logarithm of the drug's plasma-to-milk partition coefficient, percent human intestinal absorption and the logarithm of the kinetic constant for human intestinal absorption, and the logarithm of the human skin permeability coefficient (log k_p). The independent variables, or descriptors, are solute properties as follows: **E** and **S** refer to the excess molar refraction and dipolarity/polarizability descriptors of the solute, respectively, **A** and **B** are measures of the solute hydrogen-bond acidity and basicity, **V** is the McGowan volume of the solute and **L** is the logarithm of the solute gas phase dimensionless Ostwald partition

coefficient into hexadecane at 298 K. For a number of partitions into solvents that contain large amounts of water at saturation, an alternative hydrogen bond basicity parameter, $\mathbf{B^o}$, is used for specific classes of solute: alkylpyridines, alkylanilines, and sulfoxides. Several of the published Abraham model equations for predicting the toxicity of organic compounds to different aquatic organisms use the $\mathbf{B^o}$ solute descriptor, rather than the **B** descriptor.

Equations 1 and 2 contain the following three quantities: (a) measured solute properties; (b) calculated solute descriptors; and (c) calculated equation coefficients. Knowledge of any two quantities permits calculation of the third quantity through the solving of simultaneous equations and regression analysis. Solute descriptors are calculated from measured partition coefficient ($P_{solute,system}$), chromatographic retention factor (k') and molar solubility ($C_{solute,solvent}$) data for the solutes dissolved in partitioning systems and in organic solvents having known equation coefficients. Generally partition coefficient, chromatographic retention factor and molar solubility measurements are fairly accurate, and it is good practice to base the solute descriptor computations on observed values having minimal experimental uncertainty. The computation is depicted graphically in Figure 1 by the unidirectional arrows that indicate the direction of the calculation using the known equation coefficients that connect the measured and solute descriptors. Measured $P_{solute,system}$ and $C_{solute,solvent}$ values yield solute descriptors. The unidirectional red arrows originating from the center solute descriptor circle represent the equation coefficients that have been reported for nasal pungency, aquatic toxicity, upper respiratory irritation and inhalation anesthesia Abraham model correlations. Plasma-to-milk partition ratio predictions are achieved (Abraham *et al*., 2009a) through an artificial neural network with five inputs, 14 nodes in the hidden layer and one node in the output layer. Linear analysis of the plasma-to-milk partition ratios for 179 drugs and hydrophobic environmental pollutants revealed that drug molecules preferentially partition into the aqueous and protein phases of milk. Hydrophobic environmental pollutants, on the other hand, partition into the fat phase.

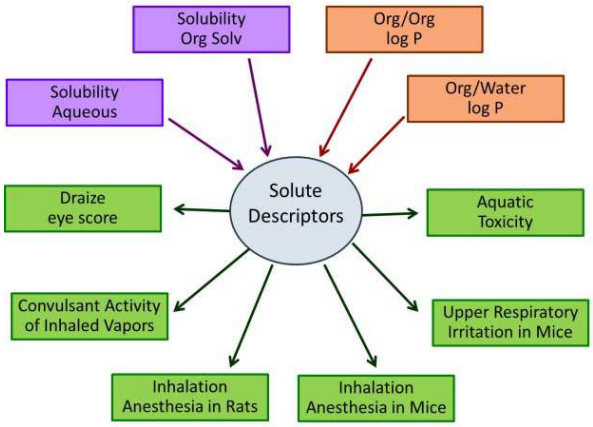

Fig. 1. Outline illustrating the calculation of Abraham solute descriptors from experimental partition coefficient and solubility data, and then using the calculated values to estimate sensory and biological responses, such as toxicity of organic chemicals to aquatic organisms, Draize eye scores, convulsant activity of inhaled vapors, upper respiratory irritation in mice, and inhalation anesthesia in rats and mice.

Prediction of the fore-mentioned toxicities, and sensory and biological responses does require a prior knowledge of the Abraham solute descriptors for the drug candidate of interest. The descriptors **E** and **V** are quite easily obtained. **V** can be calculated from atom and bond contributions as outlined previously (Abraham and McGowan, 1987). The atom contributions are given in Table 1; note that the numerical values are in cm^3 mol^{-1}. A value of 6.56 cm^3 mol^{-1} is subtracted for each bond in the molecule; irrespective of whether the bond is a single, double or triple bond. For complicated molecules it is time consuming to count the number of bonds, Bn, but this can be calculated from the algorithm given by Abraham (1993a)

$$Bn = Nt - 1 + R \tag{4}$$

where Nt is the total number of atoms in the molecule and R is the number of rings.

C	16.35		N	14.39		O	12.43
Si	26.83		P	24.87		S	22.91
Ge	31.02		As	29.42		Se	27.81
Sn	39.35		Sb	37.74		Te	36.14
Pb	43.44		Bi	42.19			
H	8.71		He	6.76		B	18.32
F	10.48		Ne	8.51		Hg	34.00
Cl	20.95		Ar	19.00			
Br	26.21		Kr	24.60			
I	34.53		Xe	32.90			
			Rn	38.40			

Table 1. Atom contributions to the McGowan volume, in cm^3 mol^{-1}

Once **V** is available, **E** can be obtained from the compound refractive index at 20°C. If the compound is not liquid at room temperature or if the refractive index is not known the latter can be calculated using the freeware software of Advanced Chemistry Development (ACD). An Excel spreadsheet for the calculation of V and E from refractive index is available from the authors. Since E is almost an additive property, it can also be obtained by the summation of fragments, either by hand, or through a commercial software program (ADME Boxes, 2010). The remaining four descriptors **S**, **A**, **B**, and **L** can be determined by regression analysis of experimental water-to-organic solvent partition coefficient data, chromatographic retention factor data, and molar solubility data in accordance to Eqns 1 and 2. Solute descriptors are available for more than 4,000 organic, organometallic and inorganic solutes. Large compilations are available in one published review article (Abraham *et al*., 1993a), and in the supporting material that has accompanied several of our published papers (Abraham *et al*., 2006; Abraham *et al*., 2009b; Mintz *et al*., 2007).

Experimental data-based solute descriptors have been obtained for a number of pharmaceutical compounds, for example 230 compounds in an analysis of blood-brain distribution (Abraham et al., 2006). Zissimos *et al*. (2002a) calculated the **S**, **A** and **B** solute descriptors of thirteen pharmaceutical compounds (propranolol, tetracaine, papaverine, trytamine, diclorfenac, chloropromazine, ibuprofen, lidocaine, deprenyl, desipramine,

fluoxetine, procaine, and miconazole) from measured water-to-octanol, water-to-chloroform, water-to-cyclohexane and water-to-toluene partition coefficient data. Equation coefficients for the four water-to-organic solvent partition coefficients were known. Four mathematical methods based on the Microsoft Solver Progam, the Triplex Program, Descfit/SIMPLEX minimization and Reverse Regression were investigated. The authors (Zissimos *et al*., 2002b) later illustrated the calculation methods using experimental data from seven high performance liquid chromatographic systems. Solute descriptors of acetylsalicylic acid (Charlton *et al*., 2003), naproxen (Daniels *et al*., 2004a), ketoprofen (Daniels *et al*., 2004b) and ibuprofen (Stovall *et al*., 2005) have been calculated based on the measured solubilities of the respective drugs in water and in organic solvents.

Abraham model correlations for predicting blood-to-body organ/tissue partition coefficients and the chemical toxicity of organic compounds towards aquatic organisms involve chemical transfer between two condensed phases. Predictive expressions for such solute properties do not contain the Abraham model L solute descriptor. There are however published Abraham model correlations for estimating important sensory and biology responses (such as convulsant activity of inhaled vapors, upper respiratory irritation in mice, inhalation anesthesia in rats and in mice) that do involve solute transfer from the gas phase. To calculate the L solute descriptor one must convert water-to-organic solvent partition coefficient data, P, into gas-to-organic solvent partition coefficients, K,

$$\text{Log } K = \log P + \log K_w \tag{5}$$

and water-to-organic solvent solubility ratios, $C_{solute,organic}/C_{solute,water}$, into gas-to-organic solvent solubility ratios, $C_{solute,organic}/C_{solute,gas}$,

$$C_{solute,organic}/C_{solute,gas} = C_{solute,organic}/C_{solute,water} * C_{solute,water}/C_{solute,gas} \tag{6}$$

where $C_{solute,water}/C_{solute,gas}$ is the gas-to-water partition coefficient, usually denoted as K_w. The water-to-organic solvent and gas-to-organic solvent partition coefficient equations are combined in the solute descriptor computations. If log K_w is not known, it can be used as another parameter to be determined. This increases the number of unknowns from four (**S**, **A**, **B** and **L**) to five (**S**, **A**, **B**, **L**, and K_w), but the number of equations is increased significantly as well. Numerical values of the four solute descriptors and K_w can be easily calculated Microsoft Solver. The computations are described in greater detail elsewhere (Abraham *et al*., 2004; Abraham *et al*., 2010). The calculated value of the L descriptor can be checked against an Abraham model correlation for estimating the L solute descriptor

$$\mathbf{L} = -0.882 + 1.183\,\mathbf{E} + 0.839\,\mathbf{S} + 0.454\,\mathbf{A} + 0.157\,\mathbf{B} + 3.505\,\mathbf{V} \tag{7}$$

$$(N = 4785,\ SD = 0.31,\ R^2 = 0.992,\ F = 115279)$$

from known values of **E, S, A, B** and **V**. Van Noort *et al*. (2010) cited a personnel communication from Dr. Abraham as the source of Eqn. 7. If one is unable to locate sufficient experimental data for performing the fore-mentioned regression analysis, commercial software (ADME Boxes, version*, 2010) is available for estimating the molecular solute descriptors from the structure of the compound. Several correlations (Jover *et al*., 2004; Zissimos *et al*., 2002; Lamarche *et al*., 2001; Platts *et al*., 1999; Platts *et al*., 2000) have been reported for calculating the Abraham solute descriptors from the more structure-

based, topological-based and/or quantum-based descriptors used in other QSAR and LFER treatments.

3. Presence and toxicity of pharmaceutical compounds in the environment

A significant fraction of the pharmaceutically-active compounds sold each year find their way into the environment as the result of human/animal urine and feces excretion (excreted unchanged drugs or as drug metabolites), direct disposal of unused household drugs by flushing into sewage systems, accidental spills and releases from manufacturing production sites, and underground leakage from municipal sewage systems and infrastructures. While most pharmaceutical compounds are designed to target specific metabolic pathways in humans and domestic animals, their action on non-target organisms may become detrimental even at very low concentrations. The occurrence of pharmaceutical residues and metabolites in the environment is a significant public and scientific concern. If not addressed, pharmaceutical pollution will become even a bigger problem as the world's increasing and aging population purchases more prescription and more self-prescribed over-the-counter medicines to improve the quality of life.

There have been very few published studies that have attempted to estimate the quantity of each pharmaceutical compound that will be released each year into the environment. Escher and coworkers (2011) evaluated the ecotoxicological potential of the 100 pharmaceutical compounds expected to occur in highest concentration in the wastewater effluent from both a general hospital and a psychiatric center in Switzerland. The authors based the calculated drug concentrations on the hospital's records of the drugs administered in 2007, the number of patients admitted, the days of hospital care, and the water usage records for the main hospital wing that houses patients and here pharmaceuticals are excreted. Amounts of the active drugs excreted unchanged in urine and feces were based on published excretion rates taken from the pharmaceutical literature. Table 2 gives the usage pattern of 25 pharmaceutical compounds, expressed as predicted effluent concentration in the hospital wastewater. The predicted concentration is compared to compound's estimated baseline toxicity towards green algae (*Pseudokirchneriella subcapitata*), which was calculated from Eqn. 8

$$-\text{Log } EC_{50} \text{ (Molar)} = 0.95 \log D_{lipw(\text{at pH} = 7)} + 1.53 \quad (8)$$

using the drug molecule's water-to-lipid partition coefficient measured at an aqueous phase pH of 7. The "baseline" concentration would be the concentration of the pharmaceutical compound needed for the toxicity endpoint to be observed assuming a nonspecific narcosis mechanism. In the case of the green algae, the toxicity endpoint corresponds to the molar concentration of the tested drug substance at which the cell density, biomass, or O_2 production is 50 % of that of the untreated algae after a 72 to 96 hour exposure to the drug.

The authors also reported predictive equations for estimating the baseline median lethal concentration for fish (*Pimephales promelas*, 96-hr endpoint)

$$-\text{Log } LC_{50} \text{ (Molar)} = 0.81 \log D_{lipw(\text{at pH} = 7)} + 1.65 \quad (9)$$

and the baseline effective concentration for mobility inhibition for water fleas (*Daphnia magna*, 48-hr. endpoint)

$$-\text{Log } EC_{50} \text{ (Molar)} = 0.90 \log D_{lipw(\text{at pH} = 7)} + 1.61 \quad (10)$$

Pharmaceutical Compound	PEC_{HWW} (µg/L)	$PNEC_{HWW}$ (µg/L)	PEC versus PNEC
Amiodarone	0.80	0.009	**PEC Greater**
Clotrimazole	0.90	0.014	**PEC Greater**
Trionavir	1.00	0.028	**PEC Greater**
Progesterone	15.85	1.40	**PEC Greater**
Meclozine	0.77	0.12	**PEC Greater**
Atorvastatin	0.99	0.16	**PEC Greater**
Isoflurane	94	29.8	**PEC Greater**
Tribenoside	0.79	0.26	**PEC Greater**
Ibuprofen	11.40	6.60	**PEC Greater**
Clopidogrel	1.74	1.60	**PEC Greater**
Amoxicillin	499	625	**PEC Smaller**
Diclofenac	2.35	3.30	**PEC Smaller**
Floxacillin	38.9	233	**PEC Smaller**
Salicylic acid	17.2	134	**PEC Smaller**
Paracetamol	64	583	**PEC Smaller**
Thiopental	21	201	**PEC Smaller**
Oxazepam	1.84	32	**PEC Smaller**
Clarithromycin	5.41	122	**PEC Smaller**
Rifampicin	0.59	16	**PEC Smaller**
Tramadol	1.92	57	**PEC Smaller**
Carbazmazepine	0.50	18	**PEC Smaller**
Tetracaine	0.48	18	**PEC Smaller**
Metoclopramide	3.27	136	**PEC Smaller**
Prednisolone	2.10	139	**PEC Smaller**
Erythomycin	1.40	132	**PEC Smaller**

Table 2. Predicted Effluent Concentration of Pharmaceutical Compounds in the Wastewater of a General Hospital, PEC_{HWW} (in µg/L) and the Predicted No Effect Concentration of the Pharmaceutical Compound to Green Algae, $PNEC_{HWW}$ (in µg/L)

Pharmaceutical Compound	PEC_{HWW} (µg/L)	$PNEC_{HWW}$ (µg/L)	PEC versus PNEC
Ritonavir	0.86	0.03	**PEC Greater**
Clotrimazole	0.39	0.01	**PEC Greater**
Diclofenac	73.0	3.31	**PEC Greater**
Mefanamic acid	5.38	0.78	**PEC Greater**
Lopinavir	0.26	0.05	**PEC Greater**
Nefinavir	0.71	0.16	**PEC Greater**
Ibuprofen	26.3	6.62	**PEC Greater**
Clorprothixen	2.53	0.91	**PEC Greater**
Trimipramine	0.63	0.49	**PEC Greater**
Meclozin	0.11	0.12	**PEC Smaller**
Nevirapine	0.98	1.30	**PEC Smaller**
Venlafaxine	24.6	35.5	**PEC Smaller**
Promazine	1.67	2.70	**PEC Smaller**
Olanazpine	8.41	14.9	**PEC Smaller**
Levomepromazine	1.15	2.40	**PEC Smaller**
Clopidogrel	0.72	1.60	**PEC Smaller**
Methadone	3.75	10.5	**PEC Smaller**
Carbamazepine	5.00	17.7	**PEC Smaller**
Oxazepam	7.24	32.5	**PEC Smaller**
Hexitidine	0.21	1.00	**PEC Smaller**
Duloxetine	0.38	2.30	**PEC Smaller**
Valproate	4.05	51	**PEC Smaller**
Fluoxetine	0.54	6.90	**PEC Smaller**
Lamotrigine	0.65	8.70	**PEC Smaller**
Clozapine	0.97	16	**PEC Smaller**
Diazepam	0.48	10	**PEC Smaller**
Tramadol	2.60	57	**PEC Smaller**
Pravastatin	3.39	77	**PEC Smaller**
Amoxacillin	22.8	625	**PEC Smaller**
Doxepin	0.17	4.90	**PEC Smaller**
Citolopram	0.51	17	**PEC Smaller**
Paracetamol	9.61	583	**PEC Smaller**
Clomethiazole	0.28	23	**PEC Smaller**

Table 3. Predicted Effluent Concentration of Pharmaceutical Compounds in the Wastewater of a Psychiatric Hospital, PEC_{HWW} (in µg/L) and the Predicted No Effect Concentration of the Pharmaceutical Compound to Green Algae, $PNEC_{HWW}$ (in µg/L)

Most published baseline toxicity QSAR models were derived for neutral organic molecules and require the water-to-octanol partition coefficient, $K_{o/w}$ as the input parameter. For compounds that can ionize, the water-to-octanol partition coefficient is an unsuitable measure of bioaccumulation and chemical uptake into biomembranes, the target site for baseline toxicants. Of the 10 of 25 pharmaceutical compounds listed in Table 2 have a predicted effluent concentration greater predicted no effect value, PNEC value. These 10 compounds would be expected to exhibit toxicity towards the green algae if the algae where exposed to the hospital wastewater for 72 to 96 hours. The drug concentrations in the hospital wastewater would be significantly reduced once the effluent entered the general sewer system. Table 3 provides the predicted effluent concentration and calculated PNEC values of 33 pharmaceutical expected to be present in the wastewater from a psychiatric hospital. The pharmaceutical concentrations were based on hospital records of the 2,008 patients who received 70,855 days of stationary care treatment. Many of the individuals who received treatment had acute psychiatric disorders that required strong medication. Nine of the 33 drugs listed have predicted effluent concentrations in excess of the PNEC value for green algae. Readers are reminded that the "baseline" concentration assumes a nonspecific narcosis mechanism, and that if the compound exhibits a reactive or other specific mode of toxic mechanism, the concentration would be much less.

Since 1980, the U.S. Food and Drug Administration has required that environmental risk assessments be conducted on pharmaceutical compounds intended for human and veterinary use before the product can be marketed. Similar regulations were introduced by the European Union in 1997. The environmental impact tests are generally short-term studies that focus predominately on mortality as the toxicity endpoint for fish, daphnids, algae, plants, bacteria, earthworms, and select invertebrates (Khetan and Colins, 2007). There have been very few experimental studies directed towards determining the no effect concentration (NEC) of pharmaceutical compounds, and even fewer studies involving mixtures of pharmaceutical compounds. The limited experimental data available shows that the NEC is highly dependent upon animal and/or organism type, and on the specific endpoint being considered. For example, the NEC for ibuprofen for 21 day growth for freshwater gastropod (*Planorbis carinatus*) is 1.02 mg/L; the NEC for 21 day reproduction for *Daphnia magna* is less than 1.23 mg/L; the NEC for 30 day survival of Japanese medaka (*Oryzias latipes*) is 0.1 mg/L; the NEC for 90 day survival of Japanese medaka is 0.1 µg/L. Mortality due to ibuprofen exposure was found to increase as the medaka fish matured (Han *et al*., 2010). More experimental NEC data is needed in order to properly perform environmental risk analyses. Until such data becomes available, one must rely on whatever acute toxicity data that one find and on *in silico* methods that allow one to predict missing experimental values from molecular structure considerations and from easy to measure physical properties.

4. Abraham model: Prediction of environmental toxicity of pharmaceutical compounds

Significant quantities of pharmaceutical drugs and personal healthcare products are discarded each year. The discarded chemicals find their way into the environment, and many end up in the natural waterways where they can have an adverse effect on marine life and other aquatic organisms. Standard test methods and experimental protocols have been established for determining the median mortality lethal concentration, LC_{50}, for evaluating

the chronic toxicity, for determining decreased population growth, and for quantifying developmental toxicity at various life stages for several different aquatic organisms. Experimental determinations are often very expensive and time-consuming as several factors may need to be carefully controlled in order to adhere to the established, recommended experimental protocol.

Aquatic toxicity data are available for relatively few organic, organometallic, and inorganic compounds. To address this concern, researchers have developed predictive methods as a means to estimate toxicities in the absence of experimental data. Derived correlations have shown varying degrees of success in their ability to predict the aquatic toxicity of different chemical compounds. In general, predictive methods are much better at estimating the aquatic toxicities of compounds that act through noncovalent or nonspecific modes of action. Nonpolar narcosis and polar narcosis are two such modes of nonspecific action. Nonpolar narcotic toxicity is often referred to as "baseline" or minimum toxicity. Polar narcotics exhibit effects similar to nonpolar narcotics; however, their observed toxicities are slightly more than "baseline" toxicity. Most industrial organic compounds have either a nonpolar or polar narcotic mode of action, which lacks covalent interactions between toxicant and organism. Predictive methods are generally less successful in predicting the toxicity of compounds whose action mechanism involves electro(nucleo)philic covalent reactivity or receptor-mediated functional toxicity. An example of a reactive toxicity mechanism would be alkane isothiocyanates that act as Michael-type acceptors, and undergo N-hydro-C-mercapto addition to cellular thiol functional groups (Schultz *et al.*, 2008).

The Abraham general solvation parameter model has proofed quite successful in predicting the toxicity of organic compounds to various aquatic organisms. Hoover and coworkers (Hoover *et al.*, 2005) published Abraham model correlations for describing the nonspecific aquatic toxicity of organic compounds to:

Fathead minnow:

$$-\log LC_{50}\ (\text{Molar, 96 hr}) = 0.996 + 0.418\,\mathbf{E} - 0.182\,\mathbf{S} + 0.417\,\mathbf{A} - 3.574\,\mathbf{B} + 3.377\,\mathbf{V} \quad (11)$$
$$(N= 196, SD = 0.276, R^2 = 0.953, F = 779.4)$$

Guppy:

$$-\log LC_{50}\ (\text{Molar, 96 hr}) = 0.811 + 0.782\,\mathbf{E} - 0.230\,\mathbf{S} + 0.341\,\mathbf{A} - 3.050\,\mathbf{B} + 3.250\,\mathbf{V} \quad (12)$$
$$(N= 148, SD = 0.280, R^2 = 0.946, F = 493.1)$$

Bluegill:

$$-\log LC_{50}\ (\text{Molar, 96 hr}) = 0.903 + 0.583\,\mathbf{E} - 0.127\,\mathbf{S} + 1.238\,\mathbf{A} - 3.918\,\mathbf{B} + 3.306\,\mathbf{V} \quad (13)$$
$$(N= 66, SD = 0.272, R^2 = 0.968, F = 359.8)$$

Goldfish:

$$-\log LC_{50}\ (\text{Molar, 96 hr}) = 0.922 - 0.653\,\mathbf{E} + 1.872\,\mathbf{S} + -0.329\,\mathbf{A} - 4.516\,\mathbf{B} + 3.078\,\mathbf{V} \quad (14)$$
$$(N= 51, SD = 0.277, R^2 = 0.966, F = 253.7)$$

Golden orfe:

$$-\log LC_{50}\ (\text{Molar, 96 hr}) = -0.137 + 0.931\,\mathbf{E} + 0.379\,\mathbf{S} + 0.951\,\mathbf{A} - 2.392\,\mathbf{B} + 3.244\,\mathbf{V} \quad (15)$$
$$(N= 49, SD = 0.269, R^2 = 0.935, F = 127.0)$$

and *Medaka high-eyes:*

$$-\log LC_{50} \text{ (Molar, 96 hr)} = -0.176 + 1.046\,\mathbf{E} + 0.272\,\mathbf{S} + 0.931\,\mathbf{A} - 2.178\,\mathbf{B} + 3.155\,\mathbf{V} \quad (16)$$
(N= 44, SD = 0.277, R^2 = 0.960, F = 181.8)

$$-\log LC_{50} \text{ (Molar, 48 hr)} = 0.834 + 1.047\,\mathbf{E} - 0.380\,\mathbf{S} + 0.806\,\mathbf{A} - 2.182\,\mathbf{B} + 2.667\,\mathbf{V} \quad (17)$$
(N= 50, SD = 0.292, R^2 = 0.938, F = 132.8)

The Abraham model described the median lethal toxicity (LC_{50}) to within an average standard deviation of SD = 0.279 log units. The derived correlations pertain to chemicals that exhibit a narcosis mode-of-toxic action, and can be used to estimate the baseline toxicity of reactive compounds and to identify compounds whose mode-of-toxic action is something other than nonpolar and/or polar narcosis. For example, in the case of the fathead minnow database, Hoover *et al*. (2005) noted that 1,3-dinitrobenzene, 1,4-dinitrobenzene, 2-chlorophenol, resorcinol, catechol, 2-methylimidazole, pyridine, 2-chloroaniline, acrolein and caffeine were outliers, suggesting that their mode of action involved some type of chemical specific toxicity. These observations are in accord with the earlier observations of Ramos *et al*. (1998) and Gunatilleka and Poole (1999).
In a follow-up study (Hoover *et al*., 2007) the authors reported Abraham model expressions for correlating the median effective concentration for immobility of organic compounds to three species of water fleas:
Daphnia magna:

$$-\log LC_{50} \text{ (Molar, 24 hr)} = 0.915 + 0.354\,\mathbf{E} + 0.171\,\mathbf{S} + 0.420\,\mathbf{A} - 3.935\,\mathbf{B} + 3.521\,\mathbf{V} \quad (18)$$
(N= 107, SD = 0.274, R^2 = 0.953, F = 410.0)

$$-\log LC_{50} \text{ (Molar, 48 hr)} = 0.841 + 0.528\,\mathbf{E} - 0.025\,\mathbf{S} + 0.219\,\mathbf{A} - 3.703\,\mathbf{B} + 3.591\,\mathbf{V} \quad (19)$$
(N= 97, SD = 0.289, R^2 = 0.964, F = 475.4)

Ceriodaphnia dubia:

$$-\log LC_{50} \text{ (Molar, 24 hr \& 48 hr combined)} = 2.234 + 0.373\,\mathbf{E} - 0.040\,\mathbf{S} - 0.437\,\mathbf{A} - 3.276\,\mathbf{B} + 2.763\,\mathbf{V} \quad (20)$$
(N= 44, SD = 0.253, R^2 = 0.936, F = 111.0)

Daphnia pulex:

$$-\log LC_{50} \text{ (Molar, 24 hr \& 48 hr combined)} = 0.502 + 0.396\,\mathbf{E} + 0.309\,\mathbf{S} + 0.542\,\mathbf{A} - 3.457\,\mathbf{B} + 3.527\,\mathbf{V} \quad (21)$$
(N= 45, SD = 0.311, R^2 = 0.962, F = 233.2)

The data sets used in deriving Eqns. 18 – 21 included experimental log EC_{50} values for water flea immobility and for water flea death. The two toxicity endpoints were taken to be equivalent. Insufficient experimental details were given in many of the referenced papers for Hoover *et al*. to decide whether the water fleas were truly dead, or whether they were severely immobilized but still barely alive. Often, individual authors have reported the numerical value as a median immobilization effective concentration at the time of measurement, and in a later paper, the same authors referred to the same measured value as

the median lethal molar concentration, and vice versa. Von der Ohe *et al*. (2005) made similar observations regarding the published toxicity data for water fleas in their statement "…. some studies use mortality (LC_{50}) and immobilization (EC_{50}, effective concentration 50%) as identical endpoints in the context of daphnid toxicity". Von der Ohe *et al*. made no attempt to distinguish between the two. For notational purposes, we have denoted the experimental toxicity data for water fleas as –log LC_{50} in the chapter. We think that this notation is consistent with how research groups in most countries are interpreting the endpoint.

Organic compounds used in deriving the fore-mentioned water flea correlations were for the most common industrial organic solvents. Hoover *et al*. (2007) did find published toxicity data for six antibiotics to both *Daphnia magna* and *Ceriodaphnia dubia* (Isidori *et al*. 2005). Solute descriptors are available for three of the six compounds. One of the compounds, ofloxacin, has a carboxylic acid functional group, and would not be expected to fall on the toxicity correlation for nonpolar–polar narcotic compounds to daphnids. Solute descriptors for the remaining two compounds, erythromycin (**E** = 1.97, **S** = 3.55, **A** = 1.02, **B** = 4.71, and **V** = 5.77) and clarithromycin (**E** = 2.72, **S** = 3.65, **A** = 1.00, **B** = 4.98, and **V** = 5.914), differ considerably from the the compounds used in deriving Eqns. 18-21. There was no obvious structural reason for the authors to exclude erythromycin and clarithromycin from the database; however, except that they did not want the calculated equation coefficients to be influenced by two compounds so much larger than the other compounds in the database and the calculated solute descriptors for both antibiotics were based on very limited number of experimental observations. Inclusion of erythromycin (–log LC_{50} = 4.51 for *Daphnia magna* and –log LC_{50} = 4.86 for *Ceriodaphnia dubia*) and clarithromycin (–logLC_{50} = 4.60 for *Ceriodaphnia dubia* and –log LC_{50} = 4.46 for *Daphnia magna*) in the regression analyses yielded:

Daphnia magna:

$$\text{–log } LC_{50} \text{ (Molar, 24 hr)} = 0.896 + 0.597\,\mathbf{E} - 0.089\,\mathbf{S} + 0.462\,\mathbf{A} - 3.757\,\mathbf{B} + 3.460\,\mathbf{V} \quad (22)$$

Ceriodaphnia dubia:

$$\text{–log } LC_{50} \text{ (Molar, 24 hr)} = 1.983 + 0.373\,\mathbf{E} + 0.077\,\mathbf{S} - 0.576\,\mathbf{A} - 3.076\,\mathbf{B} + 2.918\,\mathbf{V} \quad (23)$$

Both correlations are quite good. The one additional compound had little effect on the statistics, SD = 0.253 (data set B correlation in Hoover *et al*., 2007) versus SD = 0.253 for *Daphnia magna* and SD = 0.256 versus SD = 0.253 for *Ceriodaphnia dubia*. Abraham model correlations have also been developed for estimating the baseline toxicity of organic compounds to *Tetrahymena pyriformis* (Hoover *et al*., 2007), *Spirostomum ambiguum* (Hoover *et al*., 2007), *Psuedomonas putida* (Hoover *et al*., 2007), *Vibrio fischeri* (Gunatilleka and Poole, 1999) and several tadpole species (Bowen *et al*., 2006).

5. Methods to remove pharmaceutical products from the environment

The fate and effect of pharmaceutical drugs and healthcare products is not easy to predict. Medical compounds may be for human consumption to combat diseases or treat illnesses, or to relive pain and reduce inflammation. Many anti-inflammatory and analgesic drugs are available commercially without prescription as over-the-counter medications, with an

estimated annual consumption of several hundred tons in developed countries. Pharmaceutical products are also used as veterinary medicines to treat illnesses, to promote livestock growth, to increase milk production, to manage reproduction, and to prevent the outbreak of diseases or parasites in densely populated fish farms. Antibiotics and antimicrobials are used to control and prevent diseases caused by microorganisms. Antiparasitic and anthelmintic drugs are approved for the treatment and control of internal and external parasites. The pharmaceutical compounds find their way into the environment by many exposure pathways, human/animal urine and feces excretion, discharge and runoff from fish farms, as shown in Figure 2. Once in the environment, the drugs and their degradation metabolites are adsorbed onto the soil and dissolved into the natural waterways.

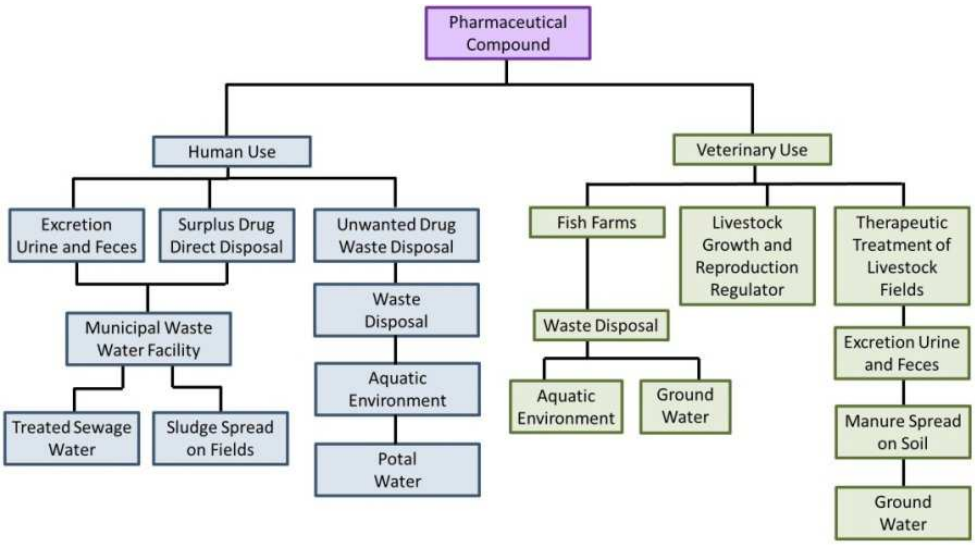

Fig. 2. Environmental occurrence and fate of pharmaceutical compounds used in human treatments and veterinary applications.

Published studies have reported the environmental damage that human and veterinary compounds have on aquatic organisms and microorganisms, on birds and on other forms of wildlife. For example, diclofenac (drug commonly used in ambulatory care) inhibits the microorganisms that comprise lotic river biofilms at a drug concentration level around 100 µg/L (Paje *et al*., 2002), and damages the kidney and liver cell functions of rainbow trout at concentration levels of 1 µg/L (Triebskorn, *et al*., 2004). Diclofenac affects nonaquatic organisms as well. India, Pakisan and Nepal banned the manufacture of veterinary formulations of diclofenac to halt the decline of three vulture species that were being poisoned by the diclofenac residues present in domestic livestock carcasses (Taggart *et al*., 2009). The birds died from kidney failure after eating the diclofenac-tained carcasses. Concerns have also been expressed about the safety of ketoprofen. Naidoo and coworkers (2010a,b) reported vulture mortalities at ketoprofen dosages of 1.5 and 5 mg/kg vulture body weight, which is within the level for cattle treatment. Residues of two fluorquinolone veterinary compounds (enrofloxacin and ciprofloxacin), found in unhatched eggs of giffon

vultures (*Gyps fulvus*) and red kites (*Milvus milvus*), are thought to be responsible for the observed severe alterations of embryo cartilage and bones, that prevented normal embryo development and successful egg hatching (Lemus *et al*., 2009).

Removal of pharmaceutical residues and metabolites in municipal wastewater treatment facilities is a major challenge in reducing the discharge of these chemicals into the environment. Many wastewater facilities use an "activated sludge process" that involves treating the wastewater with air and a biological floc composed of bacteria and protozoans to reduce the organic content. Treatment efficiency for removal of analgesic and anti-inflammatory drugs varies from "very poor" to "complete breakdown" (Kulik *et al*., 2008), and depends on seasonal conditions, pH, hydraulic retention time and sludge age (Tauxe-Wuersch *et al*., 2005; Nikolaou *et al*., 2005).

Advanced treatment processes, in combination with the activated sludge process, results in greater pharmaceutical compound removal from wastewater. Advanced processes that have been applied to the effluent from the activated sludge treatment include sand filtration, ozonation, UV irridation and activated carbon adsorption. Of the fore-mentioned processes, ozonation was found to be the most effective for complete removal for most analgesic and anti-inflammatory drugs. Ozone reactivity depends of the functional groups present in the drug molecule, as well as the reaction conditions. For example, the presence of a carboxylic functional group on an aromatic ring reduces ozone reaction with the aromatic ring carbons. Carboxylic groups are electron withdrawing. Electron-donating substituents, such as –OH groups, facilitate the attack of ozone to aromatic rings. Not all pharmaceutical compounds are reactive with ozone. For such compounds, it may be advantageous to perform the ozonation under alkaline conditions, where hydroxyl radicals are readily abundant. Hydroxyl radicals are highly reactive with a wide range of organic compounds, converting the compound to simplier and less harmful intermediates. With sufficient reaction time and appropriate reaction conditions, hydroxyl radicals can convert organic carbon to CO_2.

Several methods have been successfully employed to generate hydroxyl radicals. Fenton oxidation is an effective treatment for removal of pharmaceutical compounds and other organic contaminants from wastewater samples. The process is based on

$$Fe^{2+} + H_2O_2 \text{ ------> } Fe^{3+} + OH^- + OH^{\cdot} \quad (24)$$

the production of hydroxyl radicals from Fenton's reagent (Fe^{2+}/H_2O_2) under acidic conditions, with Fe^{2+} acting as a homogeneous catalyst. Once formed, hydroxyl radicals can oxidize organic matter (i.e. organic pollutants) with kinetic constants in the 10^7 to 10^{10} M^{-1} s^{-1} at 20 ^oC (Edwards *et al*., 1992; Huang *et al*., 1993). Fenton's technique has been used both as a wastewater pretreatment prior to the activated sludge process and as a post-treatment method after the activated sludge process. A full-scale pharmaceutical wastewater treatment facility using the Fenton process as the primary treatment method, followed by a sequence of activated sludge processes as the secondary treatment method, has been reported to provide an overall chemical oxygen demand removal efficiency of up to 98 % (Tekin *et al*., 2006).

UV/H_2O_2 is an effective treatment for removal of pharmaceutical compounds and other organic contaminants from wastewater samples. The effluent is subjected to UV radiation. Some of the dissolved organic will absorb UV light directly, resulting in the destruction of chemical bonds and subsequent breakdown of the organic compound. Hydrogen peroxide is added to treat those compounds that do not degrade quickly or efficiently by direct UV photolysis. Hydrogen peroxide undergoes photolytic cleavage to $OH^{\bullet}$ radicals

$$H_2O_2 + hv \text{ ------> } 2\ OH^{\cdot} \quad (25)$$

at a stoichiometric ratio of 1:2, provided that the radiation source has sufficient emission at 190 – 200 nm. Disadvantages of the advanced oxidation processes are the high operating costs that are associated with: (a) high electricity demand (ozone and UV/H_2O_2); (b) the relatively large quantities of oxidants and/or catalysts consumed (ozone, hydrogen peroxide, and iron salts); and (c) maintaining the required pH range (Fenton process).

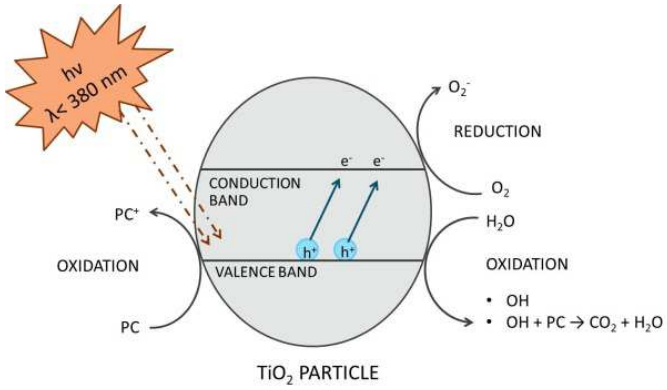

Fig. 3. Basic photocatalyic process involving TiO_2 particle

Photo-catalytic processes involving TiO_2 and/or TiO_2 nanoparticles have also been successful in removing pharmaceutical compounds pharmaceutical compounds (PC) from aqueous solutions. The basic process of photocatalysis consists of ejecting an electron from the valence band (VB) to the conduction band (CB) of the TiO_2 semiconductor

$$TiO_2 + hv \rightarrow e_{cb}^- + h_{vb}^+ \quad (26)$$

creating an h^+ hole in the valence band. This is due to UV irradiation of TiO_2 particles with an energy equal to or greater than the band gap (hv > 3.2 eV). The electron and hole may recombine, or may result in the formation of extremely reactive species (like $^{\bullet}OH$ and O_2^{-*}) at the semi-conductor surface

$$h_{vb}^+ + H_2O \rightarrow \cdot OH + H^+ \quad (27)$$

$$h_{vb}^+ + OH^- \rightarrow \cdot OH_{ads} \quad (28)$$

$$e_{cb}^- + O_2 \rightarrow O_2^{*-} \quad (29)$$

as depicted in Figure 3, and/or a direct oxidation of the dissolved pharmaceutical compound (PC)

$$h_{vb}^+ + PC_{ads} \rightarrow PC^+_{ads} \quad (30)$$

The O_2^{-*} that is produced in reaction scheme 35 undergoes further reactions to form

$$O_2^{-*} + H^+ \rightarrow HO_2^{\cdot} \quad (31)$$

$$H^+ + O_2^{-*} + HO_2^{\cdot} \rightarrow H_2O_2 + O_2 \quad (32)$$

$$H_2O_2 + hv \rightarrow 2 \cdot OH \quad (33)$$

additional hydroxyl radicals that subsequently react with the dissolved pharmaceutical compounds (Gad-Allah *et al*., 2011). Titanium dioxide is used in the photo-catalytic processes because of its commercial availability and low cost, relatively high photo-catalytic activity, chemical stability resistance to photocorrosion, low toxicity and favorable wide band-gap energy.

Published studies have shown that sonochemical degradation of pharmaceutical and pesticide compounds can be effective for environmental remediation. Sonolytic degradation of pollutants occurs as a result of the continuous formation and collapse of cavitation bubbles on a microsecond time scale. Bubble collapse leads to the formation of a hot nucleus, characterized with extremely high temperatures (thousands of degrees) and pressure (hundreds of atmospheres).

6. Abraham model: Prediction of sensory and biological responses

Drug delivery to the target is an important consideration in drug discovery. The drug must reach the target site in order for the desired therapeutic effect to be achieved. Inhaled aerosols offer significant potential for non-invasive systemic administration of therapeutics but also for direct drug delivery into the diseased lung. Drugs for pulmonary inhalation are typically formulated as solutions, suspensions or dry powders. Aqueous solutions of drugs are common for inhalational therapy (Patton and Byron, 2007). Yet, about 40% of new active substances exhibit low solubility in water, and many fail to become marketed products due to formulation problems related to their high lipophilicity (Tang *et al*., 2008; Gursoy and Benita, 2004). Formulations for drug delivery to the respiratory system include a wide variety of excipients to assist aerosolisation, solubilise the drug, support drug stability, prevent bacterial contamination or act as a solvent (Shaw, 1999; Forbes *et al*., 2000). Organic solvents that are used or have been suggested as propellents for inhalation drug delivery systems include semifluorinated alkanes (Tsagogiorgas *et al*., 2010), binary ethanol-hydrofluoroalkane mixtures (Hoye and Myrdal, 2008), fluorotrichloromethane, dichlorodifluoromethane and 1,2-dichloro-1,1,2,2-tetrafluoroethane (Smyth 2003).

Eye irritation thresholds (EIT), nasal irritation (pungency) thresholds (NPT), and odor detection thresholds (ODT) are related in that together they provide a warning system for unpleasant, noxious and dangerous chemicals or mixtures of chemicals. ODT values should not be confused with odor recognition. The latter area of research was revolutionized by the discovery of the role of odor receptors by Buck and Axel (Nobel Prize in physiology and medicine, 2004). It is now known that there are some 400 different active odor receptors in humans, that a given odor receptor can interact with a number of different chemicals, and that a given chemical can interact with several different odor receptors (Veithen *et al*., 2009; Veithen *et al*., 2010). This leads to an almost infinite matrix of interactions, and is a major reason why any connection between molecular structure and odor recognition is limited to rather small groups of chemicals (Sell, 2006). However, the first indication of an odor is given by the detection threshold; only at appreciably higher concentrations of the odorant can it be recognized. Another vital difference between odor detection and odor recognition is that ODT values can be put on a rigorous quantitative scale (Cometto-Muňiz, 2001), whereas odor recognition is qualitative and subject to leaning and memory (Wilson and Stevenson, 2006). As we shall see, it is possible, with some limitations, to obtain equations

that connect ODT values with chemical structure in a way that is impossible for odor recognition.

A 'back-up' warning system is provided through nasal irritation (pungency) thresholds, where NPT values are about 10^3 larger than ODT. Nasal pungency occurs through activation of the trigeminal nerve, and so has a different origin to odor itself. Because chemicals that illicit nasal irritation will generally also provoke a response with regard to odor detection, it is not easy to determine NPT values without interference from odor. Cometto-Muñiz and Cain used subjects with no sense of smell, anosmics, in order to obtain NPT values through a rigorous systematic method; a detailed review is available (Cometto-Muñiz *et al*., 2010). Cometto-Muñiz and Cain also devised a similar rigorous systematic method to obtain eye irritation thresholds (Cometto-Muñiz, 2001). Values of EIT are very close to NPT values. Eye irritation and nasal irritation (or pungency) are together known as sensory irritation. In addition to these human studies, a great deal of work has been carried out on upper respiratory tract irritation in mice. A quantitative scale was devised by Alarie (Alarie, 1966, 1973, 1981, 1988) and developed into a procedure for establishing acceptable exposure limits to airborne chemicals.

Before applying any particular equation to biological activity of VOCs, it is useful to consider various possible models (Abraham, *et al*., 1994). A number of models were examined; the 'two-stage' model shown in Figure 4 gave a good fit to experimental data, whilst still allowing for unusual or 'outlying' effects. In stage 1, the VOC is transferred from the gas phase to a receptor phase. This transfer will resemble the transfer of chemicals from the gas phase to solvents that have similar chemical properties to the receptor phase. In particular there will be 'selectivity' between VOCs in accordance with their chemical properties and the chemical properties of the receptor phase. In stage 2, the VOC activates the receptor. If this is simply an on-off process, so that all VOCs activate the receptor similarly, then the resultant biological activity will correspond to the selectivity of the VOCs in the first stage, and can then be represented by some structure-activity correlation. However, if some of the VOCs activate the receptor through 'specific' effects, they will appear as outliers to any structure-property correlation. Indeed, if the majority of VOCs act through specific effects, then no reasonable structure-activity correlation will be obtained.

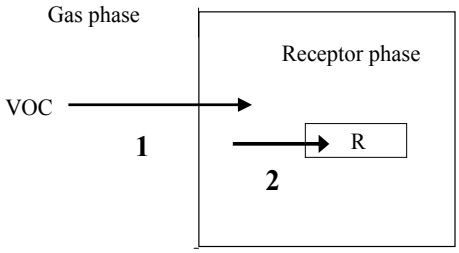

Fig. 4. A two-stage mechanism for the biological activity of gases and vapors; R denotes the receptor.

A stratagem for the analysis of biological activity of VOCs in a given process is therefore to construct some quantitative structure-activity equation that resembles similar equations for the transfer of VOCs from the gas phase to solvents. If the obtained equation is statistically and chemically reasonable, then it may be deduced that stage 1 is the main step. If a

reasonable equation is obtained, but with a number of outliers, then stage 1 is probably the main step for most VOCs, but stage 2 is important for the VOCs that are outliers. If no QSAR can be set up, then stage 2 will be the main step for most VOCs. The linear free energy relationship or LFER, Eqn. 3, has been applied to transfers of compounds from the gas phase to a very large number of solvents (Abraham *et al*., 2010a), and so is well suited as a general equation for the analysis of biological activity of VOCs.

Early work on attempts to correlate ODT values with various VOC properties has been summarized (Abraham, 1996). The first general application of Eqn. 3 to ODT values yielded Eqn. 34 (Abraham *et al*., 2001; 2002). Note that (1/ODT) is used so that as log (1/ODT) becomes larger, the VOC becomes more potent, and that the units of ODT are ppm. There were a considerable number of outliers, including carboxylic acids, aldehydes, propanone, octan-1-ol, methyl acetate and t-butyl alcohol, suggesting that for many of the VOCs studied stage 2 in Figure 4 is important.

$$\text{Log (1/ODT)} = -5.154 + 0.533\,\mathbf{E} + 1.912\,\mathbf{S} + 1.276\,\mathbf{A} + 1.559\,\mathbf{B} + 0.699\,\mathbf{L} \quad (34)$$
$$(N= 50, SD = 0.579, R^2 = 0.773, F = 28.7)$$

Aldehydes and carboxylic acids could be included in the correlation through an indicator variable, **H**, that takes the value **H** = 2.0 for aldehydes and carboxylic acids and **H** = 0 for all other VOCs. The correlation could also be improved slightly by use of a parabolic expression in **L**, leading to Eqn. 35 (Abraham *et al*., 2001; 2002).

$$\text{Log (1/ODT)} = -7.720 - 0.060\,\mathbf{E} + 2.080\,\mathbf{S} + 2.829\,\mathbf{A} + 1.139\,\mathbf{B} + 2.028\,\mathbf{L} - 0.148\,\mathbf{L}^2 + 1.000\,\mathbf{H} \quad (35)$$
$$(N= 60, SD = 0.598, R^2 = 0.850, F = 44.0)$$

Although Eqn 35 is more general than Eqn 34, it suffers in that it cannot be compared to equations for other processes obtained through the standard Eqn 3. Coefficients for equations that correlate the transfer of compounds from the gas phase to solvents as log *K*, the gas-solvent partition coefficient, are given in Table 4 (Abraham *et al*., 2010a). The most important coefficients are the s-coefficient that refers to the solvent dipolarity, the a-coefficient that refers to the solvent hydrogen bond basicity, the b-coefficient that refers to the solvent hydrogen bond basicity, and the l-coefficient that is a measure of the solvent hydrophobicity. For a solvent to be a model for stage 1 in the two-stage mechanism, we expect it to exhibit both hydrogen bond acidity and hydrogen bond basicity, since the peptide components of a receptor will include the –CO-NH- entity. In Table 4 we give details of solvents mainly with significant b- and a-coefficients. There is only a rather poor connection between the coefficients in Eqn. 42 and those for the secondary amide solvents in Table 4, suggesting, once again, that for odor thresholds stage 2 must be quite important.

The importance of stage 2 is illustrated by the observations of a 'cut-off' effect in odor detection thresholds (Cometto-Muñiz and Abraham, 2009a, 2009b, 2010a, 2010b). On ascending a homologous series of chemicals, ODT values decrease regularly with increase in the number of carbon atoms in the compounds. That is, the chemicals become more potent. However, a point is reached at which there is no further decrease in ODT or, even, ODTs begin to rebound and increase with increase in carbon chain length (Cometto-Muñiz and Abraham, 2009a, 2010a). This outcome could possibly be due to a size effect. A point is reached at which the VOC becomes too large and the increase in potency, reflected in decreasing ODTs is halted as just described.

Solvent	c	E	s	a	b	l
Methanol	-0.039	-0.338	1.317	3.826	1.396	0.773
Ethanol	0.017	-0.232	0.867	3.894	1.192	0.846
Propan-1-ol	-0.042	-0.246	0.749	3.888	1.076	0.874
Butan-1-ol	-0.004	-0.285	0.768	3.705	0.879	0.890
Pentan-1-ol	-0.002	-0.161	0.535	3.778	0.960	0.900
Hexan-1-ol	-0.014	-0.205	0.583	3.621	0.891	0.913
Heptan-1-ol	-0.056	-0.216	0.554	3.596	0.803	0.933
Octan-1-ol	-0.147	-0.214	0.561	3.507	0.749	0.943
Octan-1-ol (wet)	-0.198	0.002	0.709	3.519	1.429	0.858
Ethylene glycol	-0.887	0.132	1.657	4.457	2.355	0.565
Water	-1.271	0.822	2.743	3.904	4.814	-0.213
N-Methylformamide	-0.249	-0.142	1.661	4.147	0.817	0.739
N-Ethylformamide	-0.220	-0.302	1.743	4.498	0.480	0.824
N-Methylacetamide	-0.197	-0.175	1.608	4.867	0.375	0.837
N-Ethylacetamide	-0.018	-0.157	1.352	4.588	0.357	0.824
Formamide	-0.800	0.310	2.292	4.130	1.933	0.442
Diethylether	0.288	-0.347	0.775	2.985	0.000	0.973
Ethyl acetate	0.182	-0.352	1.316	2.891	0.000	0.916
Propanone	0.127	-0.387	1.733	3.060	0.000	0.866
Dimethylformamide	-0.391	-0.869	2.107	3.774	0.000	1.011
N-Formylmorpholine	-0.437	0.024	2.631	4.318	0.000	0.712
DMSO	-0.556	-0.223	2.903	5.037	0.000	0.719

Table 4. Coefficients in Eqn. 3 for Partition of Compounds from the Gas Phase to dry Solvents, at 298 K

As regards nasal pungency thresholds, a very detailed review is available on the anatomy and physiology of the human upper respiratory tract, the methods that have been used to assess irritation, and the early work on attempts to devise equations that could correlate nasal pungency thresholds (Doty *et al*., 2004). The first application of Eqn 3 to nasal pungency thresholds used a variety of chemicals including aldehydes and carboxylic acids (Abraham *et al*., 1998c). Later on, NPT values for several terpenes were included (Abraham *et al*., 2001) to yield Eqn. 36 (Abraham *et al*., 2010b) with NPT in ppm; of all the chemicals tested, only acetic acid was an outlier. Note that the term $s \cdot \mathbf{S}$ was statistically not significant and was excluded. Unlike ODT, it seems as though for the compounds studied, stage 1 in

the two-stage mechanism is the only important step. This is reflected in that there are several solvents in Table 4 with coefficients quite close to those in Eqn. 36; N-methylformamide is one such solvent, and would be a reasonable model for solubility in a matrix containing a secondary peptide entity.

$$\text{Log } (1/\text{NPT}) = -7.700 + 1.543 \cdot \mathbf{S} + 3.296 \cdot \mathbf{A} + 0.876 \cdot \mathbf{B} + 0.816 \cdot \mathbf{L} \quad (36)$$
$$(N = 47, SD = 0.312, R^2 = 0.901, F = 45.0)$$

Along a homologous series of VOCs, the only descriptor in Eqn. 36 that changes significantly is **L.** Since **L** increases regularly along a homologous series, then log 1/(1/NPT) will increase regularly – that is the VOC will become more potent. A very important finding (Cometto-Muňiz *et al*., 2005a) is that this regular increase does not continue indefinitely. For example, along the series of alkyl acetates log (1/NPT) increases up to octyl acetate, but decyl acetate cannot be detected. This is not due to decyl acetate having too low a vapor pressure to be detected, but is a biological 'cut-off' effect. One possibility (Cometto-Muňiz *et al*., 2005a) is that for homologous series, the cut-off point is reached when the VOC is too large to activate the receptor. The effect of the cut-off point is shown in Figure 5 where log (1/NPT) is plotted against the number of carbon atoms in the n-alkyl group for n-alkyl acetates. A similar situation is obtained for the series of carboxylic acids, where the irritation potency increases as far as octanoic acid which now exhibits the cut-off effect. However, the compounds phenethyl alcohol, vanillin and coumarin also failed to provoke nasal irritation which suggests that stage 1 in the two-stage process is not always the limiting step. Two other equations for NPT have been reported (Famini *et al*., 2002; Luan *et al*., 2010) but the equations contain fewer compounds than Eqn. 36 and neither of them have improved statistics.

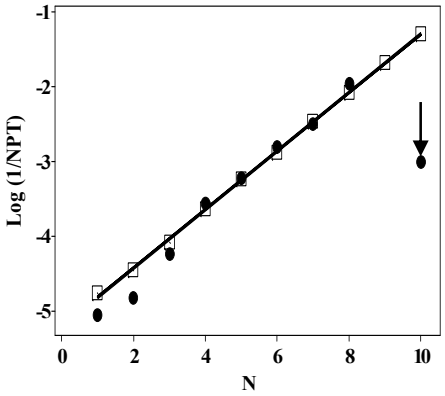

Fig. 5. A plot of log (1/NPT) for n-alkyl acetates against N, the number of carbon atoms in the n-alkyl group; ● observed values, □ calculated values from Eqn 36.

A related property to eye irritation in humans is the Draize rabbit eye irritation test (Draize *et al*., 1944). A given substance is applied to the eye of a living rabbit, and the effects of the substance on various parts of the eye are graded and used to derive an eye irritation score.

All kinds of substances have been applied, including soaps, detergents, aqueous solutions of acids and bases, and various solids. The test is so distressing to the animal that it has largely been phased out, but Draize scores of chemicals as the pure liquid are of value and were used to develop a quantitative structure-activity relationship (Abraham *et al*., 1998a). It was reasoned that if Draize scores of the pure liquids, DES, were mainly due to a transport mechanism, for example step 1 in Figure 4, then they could be converted into an effect for the corresponding vapors through DES / P^o = *K*. Here *K* is a gas to solvent phase equilibrium or partition coefficient, P^o is the saturated vapor pressure of the pure liquid in ppm at 298 K, and DES/ P^o is equivalent to the solubility of a gaseous VOC in the appropriate receptor phase.

Values of DES for 38 liquids were converted into DES/ P^o and the latter regressed against the Abraham descriptors. The point for propylene carbonate was excluded and for the remaining 37 compounds Eqn. 37 was obtained; the term in e · **E** was not significant and was excluded. The coefficients in Eqn. 37 quite resemble those for solubility in N-methylformamide, Table 4, and this suggests that the assumption of a mainly transport mechanism is reasonable.

$$\text{Log (DES / } P^o) = -6.955 + 1.046 \cdot \mathbf{S} + 4.437 \cdot \mathbf{A} + 1.350 \cdot \mathbf{B} + 0.754 \cdot \mathbf{L} \quad (37)$$
$$(N = 37, SD = 0.320, R^2 = 0.951, F = 155.9)$$

At that time, values of EIT for only 17 compounds were available, and so an attempt was made to combine the modified Draize scores with EIT values in order to obtain an equation that could be used to predict EIT values in humans (Abraham *et al*.,1998b). It was found that a small adjustment to DES / P^o values by 0.66 was needed in order to combine the two sets of data as in Eqn. 38; SP is either (DES / P^o - 0.66 or EIT). EIT is in units of ppm.

$$\text{Log (SP)} = -7.943 + 1.017 \cdot \mathbf{S} + 3.685 \cdot \mathbf{A} + 1.713 \cdot \mathbf{B} + 0.838 \cdot \mathbf{L} \quad (38)$$
$$(N = 54, SD = 0.338, R^2 = 0.924, F = 149.69)$$

A slightly different procedure was later used to combine DES / P^o values for 68 compounds and 23 EIT values (the nomenclature MMAS was used instead of DES). For all 91 compounds, Eqn. 39 was obtained. Instead of the adjustment of -0.66 to DES / P^o, an indicator variable, **I**, was used; this takes the value **I** = 0 for the EIT compounds, and **I** = 1 for the Draize compounds (Abraham *et al*., 2003).

$$\text{Log (SP)} = -7.892 - 0.397 \cdot \mathbf{E} + 1.827 \cdot \mathbf{S} + 3.776 \cdot \mathbf{A} + 1.169 \cdot \mathbf{B} + 0.785 \cdot \mathbf{L} + 0.568 \cdot \mathbf{I} \quad (39)$$
$$(N = 91, SD = 0.433, R^2 = 0.936, F = 204.5)$$

The eye irritation thresholds in humans, based on a standardized systematic protocol, were those determined over a number of years (Cometto-Muñiz & Cain, 1991, 1995, 1998; Cometto-Muñiz *et al*., 1997, 1998a, 1998b).

Later work (Cometto-Muñiz *et al*., 2005b, 2006, 2007a, 2007b; Cometto-Muñiz and Abraham, 2008) revealed the existence of a cut-off point in EIT on ascending a number of homologous series. Just as with NPT, these cut-off points are not due to the low vapor pressure of higher members of the homologous series, but appear to relate to a lack of activation of the receptor. If this is due to the size of the VOC, then the overall length may be the determining factor, because on ascending a homologous series, both the width and depth of the homologs remain constant. It is interesting that odorant molecular length has been suggested as one factor in the olfactory code (Johnson and Leon, 2000). Whatever the cause

of the cut-off point, it renders all equations for the correlation and prediction of EIT subject to a size restriction.

The only animal assay concerning VOCs is the very important 'mouse assay' first introduced by Alarie (Alarie, 1966, 1973, 1981, 1998; Alarie *et al*., 1980), and developed into a standard test procedure for the estimation of sensory irritation (ASTM, 1984). In the assay, male Swiss-Webster mice are exposed to various vapor concentrations of a VOC and the concentration at which the respiratory rate is reduced by 50% is taken as the end-point and denoted as RD_{50}. An evaluation of the use RD_{50} to establish acceptable exposure levels of VOCs in humans has recently been published (Kuwabara *et al*., 2007)

There were a number of attempts to relate RD_{50} values for a series of VOCs to physical properties of the VOCs such as the water-octanol partition coefficient, P_{oct}) or the gas-hexadecane partition coefficient, but these relationships were restricted to particular homologous series (Nielsen and Alarie, 1982; Nielsen and Bakbo, 1985; Nielsen and Yamagiwa, 1989; Nielsen *et al*., 1990). A useful connection was between RD_{50} and the VOC saturated vapor pressure at 310 K, viz: RD_{50} / VP^o = constant (Nielsen and Alarie, 1982). This is known as Ferguson's rule (Ferguson, 1939) and although it was claimed to have a rigorous thermodynamic basis (Brink and Posternak, 1948) it is now known to be only an empirical relationship (Abraham *et al*., 1994).

RD_{50} values were also obtained using a different strain of mice, male Swiss OF_1 mice (De Ceaurriz *et al*., 1981) and were used to obtain relationships between log (1/ RD_{50}) and VOC properties such as log P_{oct}, or boiling point for compounds that were classed as nonreactive (Muller and Gref, 1984; Roberts, 1986). The data used previously (Roberts, 1986) were later fitted to Eqn. 3 to yield Eqn 40 for unreactive compounds (Abraham *et al*., 1990)

$$\text{Log } (1/FRD_{50}) = -0.596 + 1.354 \cdot \mathbf{S} + 3.188 \cdot \mathbf{A} + 0.775 \cdot \mathbf{L} \quad (40)$$
$$(N = 39, SD = 0.103, R^2 = 0.980)$$

FRD_{50} is in units of mmol m^{-3}, rather than ppm, but this affects only the constant in Eqn 40. The fine review of Schaper lists RD_{50} values for not only Swiss-Webster mice but also for Swiss OF_1 mice (Schaper, 1993), and an updated equation for Swiss OF_1 mice in terms of RD_{50} was set out (Abraham, 1996).

$$\text{Log } (1/RD_{50}) = -6.71 + 1.30 \cdot \mathbf{S} + 2.88 \cdot \mathbf{A} + 0.76 \cdot \mathbf{L} \quad (41)$$
$$(N = 45, SD = 0.140, R^2 = 0.962, F = 350)$$

The Schaper data base was used to test if log (1/RD_{50}) values for nonreactive VOCs could be correlated with gas to solvent partition coefficients, as log *K*, and reasonable correlations were found for a number of solvents (Abraham *et al*., 1994; Alarie *et al*., 1995, 1996). In order to analyze values for a wide range of VOCs it was thought important to distinguish compounds that illicit an effect through a 'chemical' mechanism or through a 'physical' mechanism, these terms being equivalent to 'reactive' or 'nonreactive' (Alarie *et al*., 1998a). The Ferguson rule was used to discriminate between the two classes; if RD_{50} / VP^o > 0.1 the VOC was deemed to act by a physical mechanism (p), and if RD_{50} / VP^o < 0.1 the VOC was considered to act by a chemical mechanism (c). For 58 VOCs acting by a physical mechanism, Eqn 42 was obtained (Alarie *et al*., 1998b) for Swiss OF_1 mice and Swiss-Webster mice.

$$\text{Log } (1/RD_{50}) = -7.049 + 1.437 \cdot \mathbf{S} + 2.316 \cdot \mathbf{A} + 0.774 \cdot \mathbf{L} \quad (42)$$
$$(N = 58, SD = 0.354, R^2 = 0.840, F = 94.5)$$

A more recent analysis has been carried out (Luan *et al*., 2006), using the previous data and division into physical and chemical mechanisms. For 47 VOCs acting by a physical mechanism, Eqn 43 was obtained.

$$\text{Log } (1/RD_{50}) = -5.550 + 0.043 \cdot \text{Re} + 6.329 \cdot \text{RPCG} + 0.377 \cdot \text{ICave} + 0.049 \cdot \text{CHdonor} - 3.826 \cdot \text{RNSB} + 0.047 \cdot \text{ZX} \quad (43)$$

(N = 47, SD = 0.362, R^2 = 0.844, F = 36.1)

The statistics of Eqn 43 are not as good as those of Eqn 42, and since some of the descriptors in Eqn 43 are chemically almost impossible to interpret (ICave is the average information content and ZX is the ZX shadow) it has no advantage over Eqn 42. What is of more interest is that it was possible to derive an equation for VOCs acting by a chemical mechanism (Luan *et al*., 2006),

$$\text{Log } (1/RD_{50}) = 8.438 + 0.214 \cdot \text{PPSA3} + 0.017 \cdot \text{Hf} - 22.510 \cdot V^{c}\text{max} + 0.229 \cdot \text{BIC} + 44.508 \cdot (\text{HDCA} + 1/\text{TMSA}) + 0.049 \cdot BO^{min}C \quad (44)$$

(N = 67, SD = 0.626, R^2 = 0.737, F = 28.0)

Although, again, Eqn 44 is chemically difficult to interpret, it does show that it is possible to estimate RD_{50} values for VOCs that are reactive and act through a chemical mechanism.

About 20 million patients receive a general anesthetic each year in the USA. In spite of considerable effort the specific site of action of anesthetics is still not well known. However, even if the actual site of action is not known, it is possible that a general mechanism on the lines shown in Figure 4 obtains. In the first stage the anesthetic is transported from the gas phase to a site of action, and in the second stage interaction takes place with a target receptor, a variety of which have been suggested ((Franks, 2006; Zhang *et al*., 2007; Steele *et al*., 2007). Then if stage 1 is a major component, we might expect that a QSAR could be constructed for inhalation anesthesia. It is noteworthy that a QSAR on the lines of Eqn. 2 was constructed for aqueous anesthesia as long ago as 1991 (Abraham *et al*., 1991). Since then, rather little has been achieved in terms of inhalation anesthesia. The usual end point in inhalation anesthesia is the minimum alveolar concentration, MAC, of an inhaled anesthetic agent that prevents movement in 50 % of subjects in response to noxious stimulation. In rats, this is electrical or mechanical stimulation of the tail. MAC values are expressed in atmospheres, and correlations are carried out using log (1/MAC) so that the smaller is MAC the more potent is the anesthetic. It was shown (Sewell and Halsey, 1997) that shape similarity indices gave better fits for log (1/MAC) than did gas to olive oil partition coefficients, but the analysis was restricted to a model for 10 fluoroethanes for which R^2 = 0.939 and a different model for 8 halogenated ethers for which R^2 = 0.984 was found. A completely different model of inhalation anesthesia.has been put forward (Sewell and Sear, 2004, 2006) in which no consideration is taken as to how a gaseous solute is transported to a receptor, but solute-receptor interactions are calculated. However, two different receptor models were needed, one for a particular set of nonhalogenated compounds and one for a particular set of halogenated compounds, so the generality of the model seems quite restricted.

A QSAR for inhalation anesthesia was eventually obtained using the LFER, Eqn. 3, as follows (Abraham *et al*., 2008)

$$\text{Log } (1/\text{MAC}) = -0.752 - 0.034 \cdot \mathbf{E} + 1.559 \cdot \mathbf{S} + 3.594 \cdot \mathbf{A} + 1.411 \cdot \mathbf{B} + 0.687 \cdot \mathbf{L} \quad (45)$$

(N = 148, SD = 0.192, R^2 = 0.985, F = 1856.1)

The only compounds not included in Eqn. 45 were 1,1,2,2,3,3,4,4,5,5,6,6-dodecafluorohexane and 2,2,3,3,4,4,5,5,6,6,7,7-dodecafluoroheptan-1-ol which were known to be subject to cut-off effects, and 1-octanol where the observed MAC value was subject to a greater error than usual. Hence Eqn. 45 is a very general equation, and it can be suggested that stage 1 in Figure 4 does indeed represent the main process.

A related biological end point to inhalation anesthesia is that of convulsant activity. It has been observed that a number of compounds expected to exhibit anesthesia actually provoke convulsions in rats (Eger *et al*., 1999). The end point, as for inhalation anesthesia, is taken as the compound vapor pressure in atm that just induces convulsion, CON. Eqn 3 was applied to the observed data yielding Eqn 46 (Abraham and Acree, 2009)

$$\text{Log}\,(1/\text{CON}) = -0.573 - 0.228\cdot\mathbf{E} + 1.198\cdot\mathbf{S} + 3.232\cdot\mathbf{A} + 3.355\cdot\mathbf{B} + 0.776\cdot\mathbf{L} \quad (46)$$
$$(N = 44,\ SD = 0.167,\ R^2 = 0.978,\ F = 344.2)$$

In terms of structural features it was shown that the anesthetics tended to have large hydrogen bond acidities whereas convulsants tended to have zero or small hydrogen bond acidities. The only other notable structural feature was that convulsants had larger values of **L** and anesthetics tended to have smaller values of **L**. Since **L** is somewhat related to size, the convulsants are generally larger than the inhalation anesthetics.

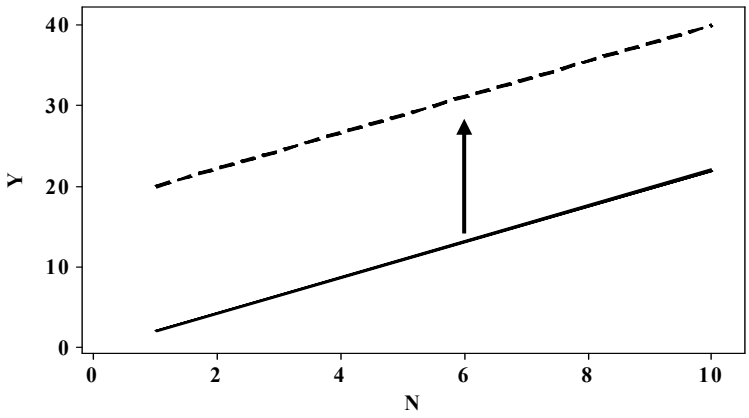

Fig. 6. Plots of VOC activity, **Y**, against VOC carbon number, **N**, illustrating the use of an indicator variable, **I.**

It was pointed out (Abraham *et al*., 2010c) that a large number of equations on the lines of Eqn. 3 for various biological and toxicological effects of VOCs had been constructed, these equations mainly representing stage 1 in Figure 4. Since this stage refers to the transfer of a VOC from the gas phase to some biological phase, it was argued that it might be possible to amalgamate all these equations into one general equation for the biological and toxicological activity of VOCs. Consider plots of toxicological activity, **Y**, against the number of carbon atoms, **N**, in a homologous series of VOCs. If the two lines are parallel, then a simple indicator variable, **I**, could be used to bring then both on the same line, as shown in Figure 6. If the two lines are not parallel, then after use an indicator variable, they will appear as

shown in Figure 7. But even in this situation a general equation (or general line) might be used to correlate both sets of data, albeit with an increase in the regression standard deviation. It remained to be seen exactly how much error was introduced by use of a general equation.

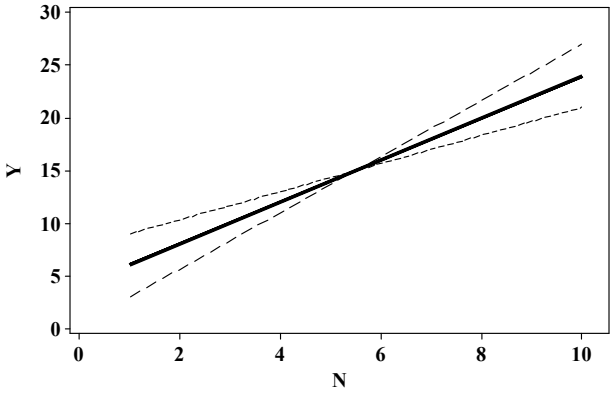

Fig. 7. Plots of VOC activity, **Y**, against VOC carbon number, **N**, showing how a general equation may be used to correlate two sets of data that give rise to lines of different slope.

Various sets of data on toxicological and biological activity, **Y**, for a number of processes were used to construct an equation in which a number of indicator variables, **I**, were used in order to fit all the sets of data into one equation. The result was Eqn. 51 (Abraham *et al*., 2010c).

$$\mathbf{Y} = -7.805 + 0.056 \cdot \mathbf{E} + 1.587 \cdot \mathbf{S} + 3.431 \cdot \mathbf{A} + 1.440 \cdot \mathbf{B} + 0.754 \cdot \mathbf{L} + 0.553 \cdot \mathbf{Idr} + \quad (47)$$
$$+ 2.777 \cdot \mathbf{Iodt} - 0.036 \cdot \mathbf{Inpt} + 6.923 \cdot \mathbf{Imac} + 0.440 \cdot \mathbf{Ird50} + 8.161 \cdot \mathbf{Itad} + 7.437 \cdot \mathbf{Icon} +$$
$$+ 4.959 \cdot \mathbf{Idav}$$
$$(N = 643, SD = 0.357, R^2 = 0.992, F = 6083.0)$$

The 'standard' process was taken as eye irritation thresholds, as log (1/EIT) for which no indicator variable was used. The given processes and the corresponding indicator variables are shown in Table 5.

There are two processes listed in Table 5 that have not been considered here. The data on gaseous anesthesia on tadpoles were derived from aqueous anesthesia together with water to gas partition coefficients, and so are indirect data, and the compounds in the data set for inhalation anesthesia on mice cover a very restricted range of descriptors. Of the 720 data points, 77 were outliers. Nearly all of these were VOCs classed as 'reactive' or 'chemical' in respiratory tract irritation in mice, or VOCs that acted by specific effects in odor detection thresholds. The remaining 643 data points all refer to nonreactive VOCs or to VOCs that act through selective and not specific effects. The SD value of 0.357 in Eqn. 47 is quite good by comparison to the various SD values for individual processes, suggesting that the general equation has incorporated these with little loss in accuracy; the predicted standard deviation in Eqn. 47 is only 0.357 log units. The equation is scaled to eye irritation thresholds, but it is noteworthy that the coefficient for the NPT indicator variable is nearly zero. Thus EIT and NPT can be estimated through Eqn. 48 for any nonreactive VOC for which the relevant descriptors are available.

$$\mathbf{Y} = \log (1/EIT) = \log (1/NPT) = -7.805 + 0.056 \cdot \mathbf{E} + 1.587 \cdot \mathbf{S} + 3.431 \cdot \mathbf{A} + \\ + 1.440 \cdot \mathbf{B} + 0.754 \cdot \mathbf{L} \quad (48)$$

The Abraham general solvation model provides reasonably accurate mathematical correlations and predicitions for a number of important biological responses, including Eye irritation thresholds (EIT), nasal irritation (pungency) thresholds (NPT), odor detection thresholds (ODT) inhalation anesthesia (rats) and convulsant actictivity (mice).

Activity	Units	**Y**	**I**	VOCs	
				Total	Outliers
Eye irritation thresholds	ppm	log(1/EIT)	None	23	0
EIT from Draize scores	ppm	log(D/P^o)	Idr	72	0
Odor detection thresholds	ppm	log(1/ODT)	Iodt	64	20
Nasal pungency thresholds	ppm	log(1/NPT)	Inpt	48	0
Inhalation anesthesia (rats)	atm	log(1/MAC)	Imac	147	0
Respiratory irritation (mice)	ppm	log(1/RD_{50})	Ird50	147	53
Gaseous anesthesia (tadpoles)	mol/L	log(1/C)	Itad	130	4
Convulsant activity (rats)	atm	log(1/CON)	Icon	44	0
Inhalation anesthesia (mice)	vol %	log(1/vol)	Idav	45	0
Total				720	77

Table 5. Toxicological and Biological Data on VOCs used to construct Eqn. 47

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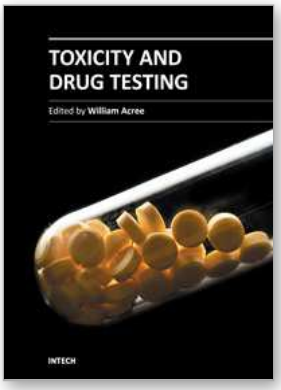

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Modern drug design and testing involves experimental in vivo and in vitro measurement of the drug candidate's ADMET (adsorption, distribution, metabolism, elimination and toxicity) properties in the early stages of drug discovery. Only a small percentage of the proposed drug candidates receive government approval and reach the market place. Unfavorable pharmacokinetic properties, poor bioavailability and efficacy, low solubility, adverse side effects and toxicity concerns account for many of the drug failures encountered in the pharmaceutical industry. Authors from several countries have contributed chapters detailing regulatory policies, pharmaceutical concerns and clinical practices in their respective countries with the expectation that the open exchange of scientific results and ideas presented in this book will lead to improved pharmaceutical products.

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