A Review of Terms Critical to Predictive Toxicology

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Confusion

- often arises in the use of the terms
  - nonspecific toxicity
  - baseline toxicity
  - specific toxicity
  - selective toxicity
- such terminology is important to predicting toxicity
- they imply whether or not toxicity results from a particular chemical substructure or a particular pathway

Toxic Effects

- arise from the interaction of chemical with biological molecules or molecular initiating events
- intensity related to the binding affinity of the toxicant at the molecular sights
- can be subdivided based to toxicant-target interactions

Toxicant-Target Interactions

- can be subdivided into:
  - 1) reversible toxicity that is related to weak binding from hydrophobic and other weak forces
  - 2) irreversible toxicity that is related to covalent binding
  - 3) receptor-based toxicity that is the result of strong binding from multiple hydrogen bonds when steric factors are essential

Nonspecific Toxicity

- reversible toxicity
- manifested by a physical presents of the toxicant in the biophase
- gives an estimate of the minimal toxicity of a substance and referred to as “baseline toxicity’’
- linearly related to water solubility and vapor pressure
- largely independent of molecular structure

Nonspecific Toxicity

- once the protocol is factored in potency does not vary across species
- endpoint-to-endpoint and species-to-species extrapolations are possible with a high degree of confidence
- baseline toxicity can be used as a reference point, even when it can not be empirically measured

Specific Toxicity

- has two sub-cases
  - irreversible toxicity
  - receptor-based toxicity
- result of a chemical having a specific chemical substructure
- effects have definable structural or applicability domains
- potency can be related to toxic pathways or mechanisms

Selective Toxicity

- most confusing of the terms
- reflects the venerability of a species or life-stage to a particular toxic pathway
- often due to the presence or absence of particular enzyme along a pathway

Nonspecific Toxicants

- the classic nonspecific toxicants are the depressants or nonpolar narcotics
- toxic effect is dependent on chemical structure only to the degree necessary to make the substance reach the central nervous system
- xenon, has been used as a general anesthetic; the lack of a dipole moment and spherically symmetrical structure indicates that this physically and chemical non-reactive gas acts in the bulk phase rather than by adsorption to a surface

Nonspecific Toxicants

- as the toxicant physically occupies space in the biophase this type of toxicity is often referred to a "physical" toxicity
- nonspecific narcosis takes place as soon as a constant fraction of the total volume of some non-aqueous phase of the cell is occupied
- since baseline toxicants all act at concentrations that produces a standard thermodynamic activity, the mechanism of action is almost certainly the same xenon

Nonspecific Toxicants

- this constant activity reflects Ferguson's principle
- at equilibrium the thermodynamic potential of baseline chemicals is the same in all phases
- it follows that measuring the thermodynamic activity in the external phase measures the potential in the biophase
- even if one does not know the exact location or chemical nature of the biophase

Nonspecific Toxicants

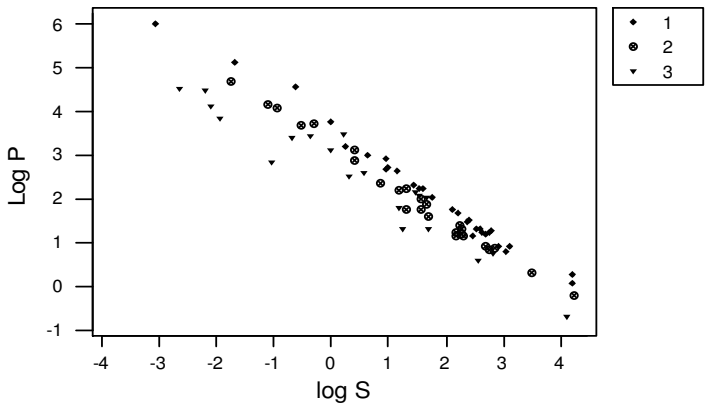
- nonspecific toxicants elicit an effect by physically occupying some vital part of a cell, typically thought to be the membrane, and thus inhibit basic cellular processes
- if the cell can acclimate to the presence of a nonspecific toxicant normal cellular function is resumed
- if the accumulation of the toxicant is larger that the cell can acclimate to the cell due to lose of osmotic regulation swells and ruptures
- to paraphrase Albert (1951) baseline toxicants act as "foreign bodies" that are "accumulated by the cells to some favorable partition-coefficient"

Saturated Aliphatic Alcohols

- unique among the various chemical classes that compose the nonspecific toxicants in that water solubility (log S), 1-octanol/water partitioning (log P), and aquatic toxic potency (log (1/T)) values have been experimentally determine for a large number of derivatives

$$\log P = 3.649 - 0.909 \log S;$$
$$n = 38, \text{R-Sq(adj)} = 0.990$$

Variation in Hydrophobicity vs Solubility



Saturated Aliphatic Alcohols

log (1/T) = 0.861 - 0.716 log S;
n = 30, R-Sq(adj) = 0.979

log (1/T) = -1.979 + 0.776 log P;
n = 26, R-Sq(adj) = 0.989

Models for Nonspecific Toxicants

- changes in molecular structure such as adding a methylene group within a homologous series lower water solubility, increase hydrophobicity, and increase narcotic potency in a step-wise fashion
- between homologous series these changes are not equal
- so log P-and log S-dependent robust models for nonspecific toxicants, while linear, tend to have slopes of 0.8 and coefficients of determination of 0.85

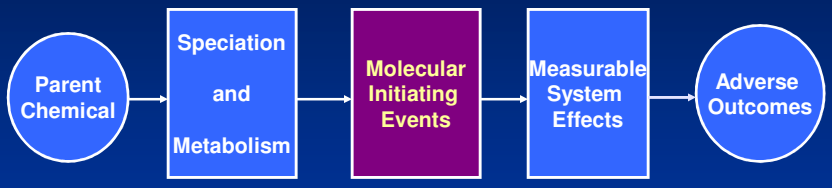
Specific Toxicants

- since receptor-based specific toxicity will be discussed in detail, I will focus on specific toxicants that act via covalent binding
- there is some specificity in terms of structures that can be electrophiles as there there is some specificity of the nucleophiles they attack
- the electro(nucleo)philic interaction itself is fairly nonspecific, especially as compare to receptor interactions

Specific Toxicants

- covalent reactions are fairly specific relative to the structures that can participate in a given interaction mechanism
- soft interacts with soft and hard interacts with hard
- but within the reaction domain, the interactions poorly discriminate between specific nucleophiles

Framework for Predicting Specific Irreversible Toxicity



Rather than developing statistical models of a complex toxic endpoint, molecular initiating events are modeled and used to estimate the probabilities for adverse outcomes

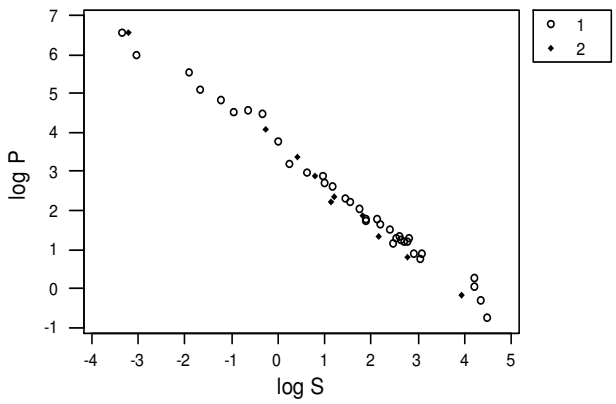
Specific Toxicants-Acrylated

- polarized α,β-unsaturates that act via Michael addition to covalently bond to soft nucleophiles in particular the thiol group of cysteine
- not as extensive studied as aliphatic alcohols, but sufficient water solubility (log S), 1-octanol/water partitioning (log P), and aquatic toxic potency (log (1/T)) values are available for an examination of relationships

Log P = 3.587 - 0.982 log S;

n = 10, R-Sq(adj) = 0.993

Alcohols (circles) and Acrylates (diamonds)



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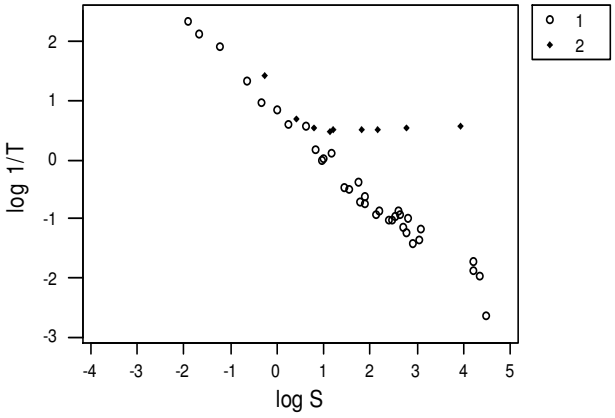

Selective Toxicity- Narcosis of Tricaine

- tricaine or ethyl 3-aminobenzoate methanesulfonate (MS-222) is a selective anesthesia for poikilotherms
- 150 and 250 mg/kg) is the anesthetic doses in all poikilotherms tested
- 250 mg/kg injected i.p. into a variety of mammals produced not apparent response
- biological half-life in frogs is ≈ 70 minutes at 37.5ºC

Selective Toxicity- Narcosis of Tricaine

- in the mouse tricaine is metabolized rapidly; 5 minutes after i.p. administration (250 mg/kg) none of the unchanged compound could be recovered
- biotransformation pathways are the same in mice and frogs
- in vitro studies revealed that mouse liver metabolized tricaine 39X more rapidly than frog liver
- the selective toxicity for frogs is a consequence of them having a slower rate of hepatic biotransformation

Selective Toxicity of Diazinon

- species-specific acute toxicity of organophosphorous pesticides among fish exceeds two orders of magnitude
- highly to guppy and rainbow trout with LC50 values of 2.3 and 4.2 μmol/L, respectively
- lower to zebra fish and carp with LC50 values of 23 and 46 μmol/L, respectively
- differences tentatively traced to the sensitivity of the target enzyme acetylcholine esterase (AChE)

Selective Toxicity of Diazinon

- it is known that diazinon in itself does not inhibit AChE
- diazinon can be metabolized to diazoxon by cytochrome P-450 monooxygenases
- diazoxon (a potent inhibitor of AChE) is usually not detectable in vivo because it is rapid hydrolysis to 2-methyl-4-hydroxy-6-isopropyl-pyrimidine
- P-450 enzymes are present in fish at different levels; thus, it was likely that the rate of formation of the diazoxon also plays a role in diazinon toxicity in fish

Role of Different Factors

Species	LC50 µmol/L	rate of diazoxon formations	AChE	detox sensitivity	enzymes
Guppy	2.3	↑		↑	↔
Trout	4.2	↓		↑	↓
Zebra fish	23	↓		↓	↔
Carp	46	↓		↓	↑

- the selective toxicity to diazinon toxicity among fish can be explained by metabolic differences in the liver and sensitivity of the target enzyme