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GREEN CHEMISTRY

DESIGNING FOR REDUCED HAZARD

Image: Wikimedia Commons, Fume Hood ,
Author: U.S. National Institute for Occupational Safety and Health

DAY 4 SESSION I
4-DAY PRESENTATION

www.greenchemistry-toolkit.org

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GREEN CHEMISTRY

Topics To Be Covered

1. Hazard and Risk – Past and Present
2. Toxicology
3. Assessing Hazards and Exposure
   - What Happens When You're Exposed?
4. Hazard Minimization Through Molecular Design
5. QSAR - Quantitative Structure Activity Relationship
6. Molecular Design Research Network (MoDRN)

THE CHALLENGE OF ENVIRONMENTAL RISK

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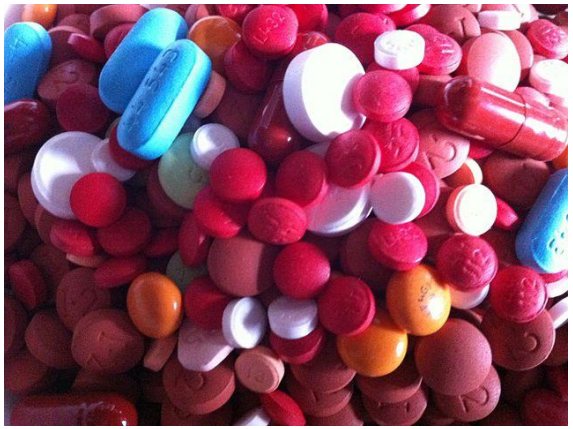
- There are over 100,000 chemicals in global circulation.
- 700+ chemicals are introduced to the US Market each year.
- 85% of these chemicals lack experimental data.
- There has been unintended biological activity which has led to increased hazard as well as toxic endpoints for humans and the environment.



Source: Wikimedia Commons

HAZARD

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- The ability cause adverse consequence.

- What types of chemical hazards are there?
  - Global Hazards (global warming, acid rain, security threat, ozone depletion)
  - Physical Hazards (explosivity, corrosivity, oxidizers/reducers)
  - Toxicological
    - Environmental (aquatic toxicity, avian toxicity, mammalian toxicity)
    - Human (e.g., carcinogenicity, neurotoxicity, hepatotoxicity, dermal toxicity)

RISK EQUATION

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Risk = f(Hazard, Exposure)

Environmental risk is resulting from exposure to a potential environmental hazard

Risk can be reduced by in two ways:
If as hazard ⬆, exposure needs to be reduced to 0
If hazard = 0, exposure can be ⬆

Ultimate goal is to use BENIGN materials

WHY USE BENIGN MATERIALS?

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- Exposure becomes irrelevant
- Less dependence on systems which can fail or be sabotaged
- Competitive advantage – reduces costs associated with toxic materials

MITIGATION OF RISK THROUGH DESIGN

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The traditional approach to hazards focuses on reducing risk by minimizing exposure.

- For example, wearing personal protective equipment or space ventilation if the chemical is volatile.

Green chemistry focuses on reducing risk by reducing hazard.

- If there is no hazard, exposure becomes irrelevant

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How have we dealt with chemicals and the environment in the past?

HISTORICAL APPROACH TO ENVIRONMENTAL PROBLEMS

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- Waste treatment, control, and disposal; pollutant monitoring; hazardous waste site cleanup.
- Development of standards for emissions to air, releases to water, and disposal by land, as well as regulation of these standards.
- "Command and Control"

CHEMICALS IN THE ENVIRONMENT

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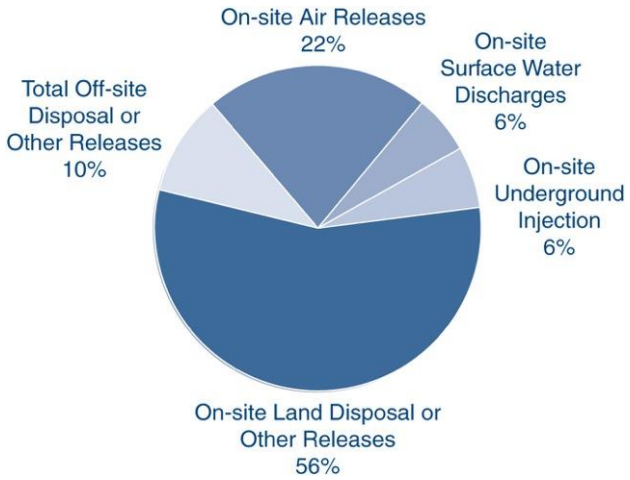
- In U.S., 3.93 billion lbs. of toxic chemicals were released directly to air, water, and land in 2011



- Only 650 of toxic chemicals and toxic chemical categories out of 100,000 in commerce are tracked by Toxic Release Inventory

Mihelcic, J. R.; Zimmerman, J. B., *Environmental engineering: Fundamentals, sustainability, design*. Wiley Global Education: 2014.

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Why should we care?

BODY BURDEN

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- 148 xenobiotics in the body
- Of the chemicals found:
  - 76 cause cancer in humans or animals,
  - 94 are toxic to the brain and nervous system, and
  - 79 cause birth defects or abnormal development.
- The dangers of exposure to these chemicals in combination has never been studied.

One of Green Chemistry's greatest strengths is the ability to design for reduced hazard.

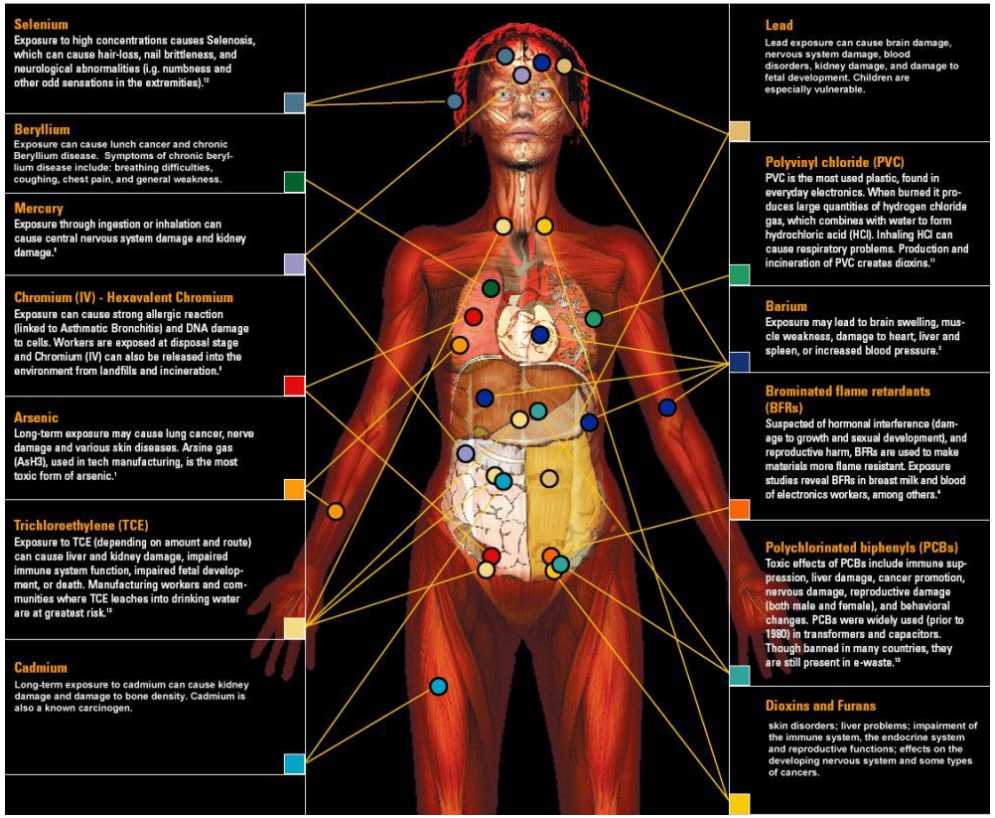

Image Source: http://svtc.org/our-work/e-waste/

WHAT IS TOXICOLOGY

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The traditional definition of toxicology is *"the science of poisons."*

A more descriptive definition of toxicology is

"the study of the adverse effects of chemicals or physical agents on living organisms".

WHAT COUNTS AS TOXIC

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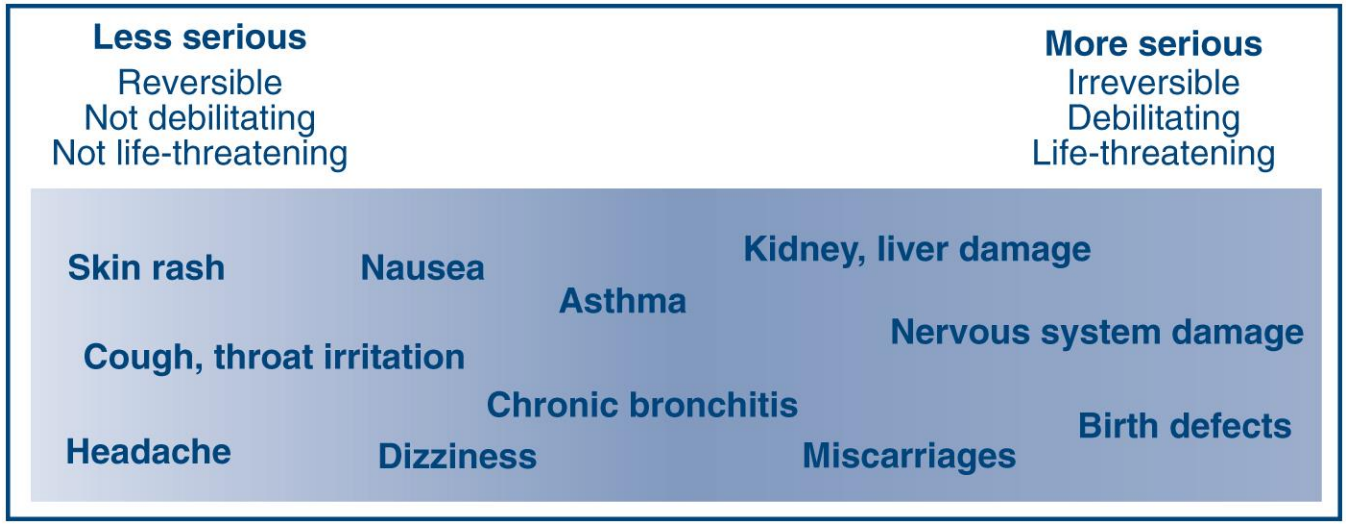

Mihelcic, J. R.; Zimmerman, J. B., *Environmental engineering: Fundamentals, sustainability, design*. Wiley Global Education: 2014.

RELATING TOXIC ENDPOINTS TO MOLECULAR FEATURES & PROPERTIES

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Acute toxicity	Carcinogenicity	Bioconcentration
Subchronic & chronic toxicity	Neurotoxicity	Degradation & transport
Reproductive toxicity	Immunotoxicity	Aquatic toxicity
Developmental toxicity	Genotoxicity	Terrestrial organism toxicity

Molecular weight	Molecular volume	Dipole moment
Hydrophilic surface area	Hydrophobic surface area	Rotatable bonds
Hydrogen bonds	Ionization potential	Electron affinity
Partition coefficients	Acid/base properties	Polarizability

DEFINITIONS

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A **toxic agent** is anything that can produce an adverse biological effect.

It may be chemical, physical, or biological in form.

For example, toxic agents may be

- chemical *(such as cyanide)*,
- physical *(such as radiation),* and
- biological *(such as snake venom)*

What is the most important factor in bringing about the adverse biological impact?

DOSE

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Dose is the amount of a substance administered at given times.

For example:

- 650 mg Tylenol as a single dose
- 500 mg Penicillin every 8 hours for 10 days

DOSE MAKES THE POISON

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An apparently nontoxic chemical can be toxic at high doses. (Too much of a good thing can be bad)

Highly toxic chemicals can be life saving when given in appropriate doses.

Source: Wikimedia Commons

LETHAL DOSES

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Approximate Lethal Doses of Common Chemicals (Calculated for a 160 lb. human from data on rats)	
Chemical	**Lethal Dose**
Sugar (sucrose)	3 quarts
Alcohol (ethyl alcohol)	3 quarts
Salt (sodium chloride)	1 quart
Herbicide (2, 4-D)	one half cup
Arsenic (arsenic acid)	1-2 teaspoons
Nicotine	one half teaspoon
Food poison (botulism)	microscopic

Source: Marczewski, A.E., and Kamrin, M. Toxicology for the citizen, Retrieved August 17, 2000: www.iet.msu.edu/toxconcepts/toxconcepts.htm.

How is toxicity testing done?

DOSE-RESPONSE

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The dose-response relationship is a fundamental and essential concept in toxicology. It correlates exposures and the spectrum of induced effects.

The dose-response relationship is based on observed data from experimental animal, human clinical, or cell studies.

DOSE-RESPONSE

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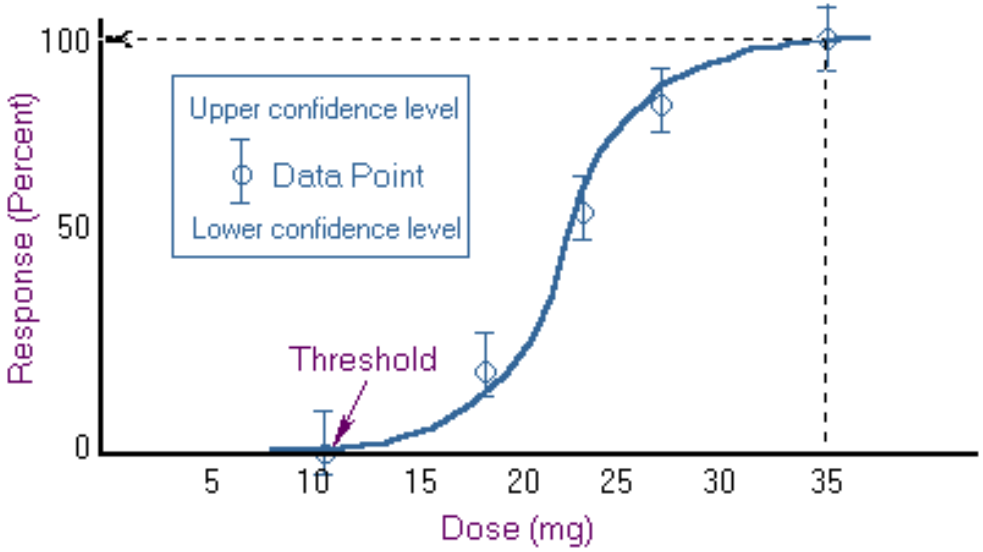
Knowledge of the dose-response relationship:

- establishes causality that the chemical has in fact induced the observed effects
- establishes the lowest dose where an induced effect occurs - the threshold effect
- determines the rate at which injury builds up - the slope for the dose response.



LD50, NOAEL, LOAEL, AND RFD

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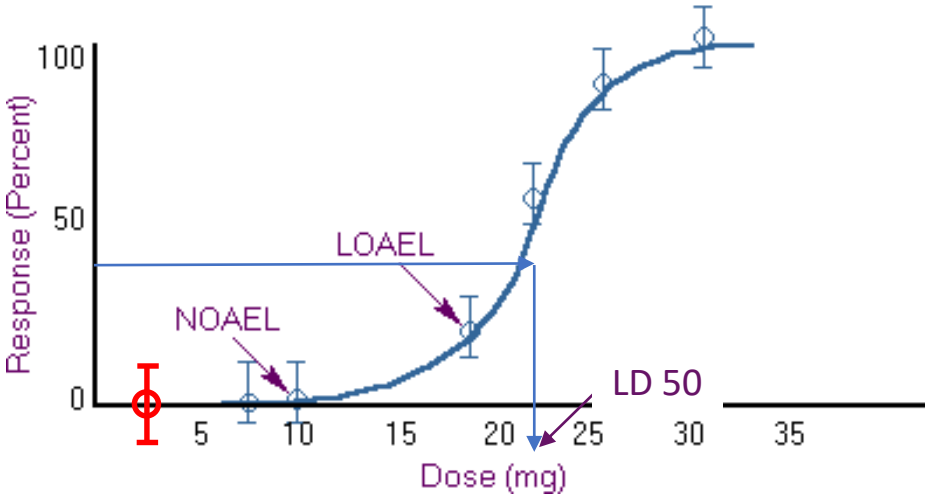

LD 50- A common dose estimate for acute toxicity is the LD50 (Lethal Dose Response 50%).

This is a statistically derived dose at which 50% of the individuals will be expected to die.

NOAEL - No Observed Adverse Effect Level

Highest data point at which there was no adverse effect

LOAEL - Low Observed Adverse Effect Level

Lowest data point at which there was an adverse effect

$$RfD = \frac{NOAEL}{UF}$$

UF = Uncertainty factor (10-1000)

RfD – estimate of a daily oral exposure to the human population, that's likely to be without risk of an effect

IN-CLASS DISCUSSION- WHICH SOLVENT WOULD YOU USE?

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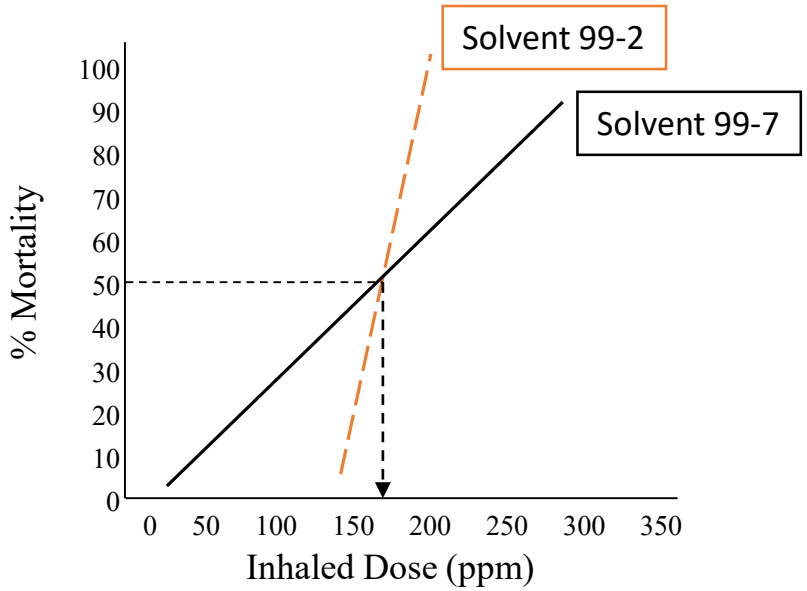

Plotted here are two theoretical curves for the toxicity of solvents used in the cleaning of silicon compounds. Both solvent 99-2 and 99-7 performed equally well against a variety of manufactured silicon compounds. The task at hand for you is to determine which solvent would you pick to be "safer" for use. As you can see from the accompanying data both compounds have an equivalent Lethal dose 50 value (LD50). These are based on average values during a 6 hour exposure period.

IN-CLASS DISCUSSION- WHICH SOLVENT WOULD YOU USE?

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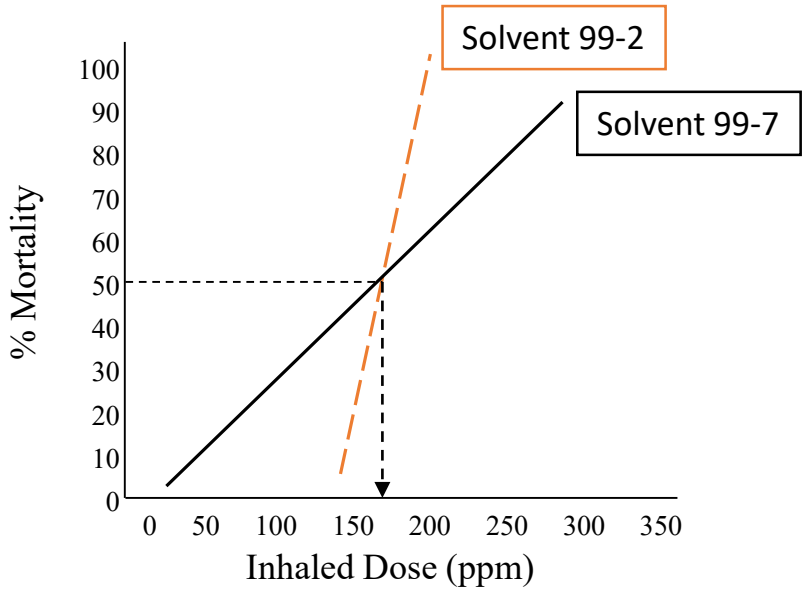

Solvent 99-7 causes lethality at much lower levels than 99-2 (20ppm versus 100ppm respectively), and the response is much more predictable (i.e. less population heterogeneity). Solvent 99-2 because higher levels can be inhaled before any harmful effects should begin.

HAZARD ASSESSMENT

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- Review and analysis of toxicology data and assessing if the substance causes toxic effects
- Sources include animal and human studies and computational data
- These studies have difficulty with showing causation (if a risk factor lead to disease)

Table / 6.10

Difficulties of Epidemiology Studies

Matching control groups is difficult, because factors that lead to exposure to a chemical may be associated with other factors that affect health.
Society has become more mobile, so individuals may no longer live in the same community all of their life.
Death certificates typically measure only the cause of death, so they miss health conditions that individuals had over the course of their life.
Other toxicity end points besides death (e.g., miscarriages, infertility, learning disorders) might not be measured with use of death certificates.
Accurate exposure data can be difficult to obtain for a large group of individuals.
Large populations are required for these studies so that rigorous statistical analysis can be applied to the data.
Many diseases can take years to develop.

Mihelcic, J. R.; Zimmerman, J. B., *Environmental engineering: Fundamentals, sustainability, design*. Wiley Global Education: 2014.

EXPOSURE ASSESSMENT

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- Determines the extent and frequency of human exposure to target chemicals.
- Guidelines for residential, industrial and commercial sites
- For engineers, the knowledge of risk and exposure provides information whether the site needs to be remediated.

Table / 6.15

Amount of Soil Assumed to Adhere to Surface of Skin and Taken in Daily for Specific Populations Based on Land Use and Associated Employment

Target Population	Soil Adherence (mg soil/cm^2 skin)	Mass of Soil Taken in Daily (mg/day)
Adult living in residential area	0.07	50
Child living in residential area	0.2	200 for ages 1–6; 100 for all others
Adult worker at commercial III	0.01	50
Adult worker at commercial IV	0.1	50
Industrial worker	0.2	50

Table / 6.12

Some Questions Answered during the Exposure Assessment

What are the important sources of chemicals (e.g., pesticide application)?
What are the pathways (e.g., water, air, food) and routes of exposure (e.g., ingestion, inhalation, dermal contact)?
What amount of the chemical are people exposed to?
How often are people exposed?
How much uncertainty is associated with the estimates?
What segments of society (or ecosystem) are more at risk?

Mihelcic, J. R.; Zimmerman, J. B., *Environmental engineering: Fundamentals, sustainability, design*. Wiley Global Education: 2014.

RISK CHARACTERIZATION

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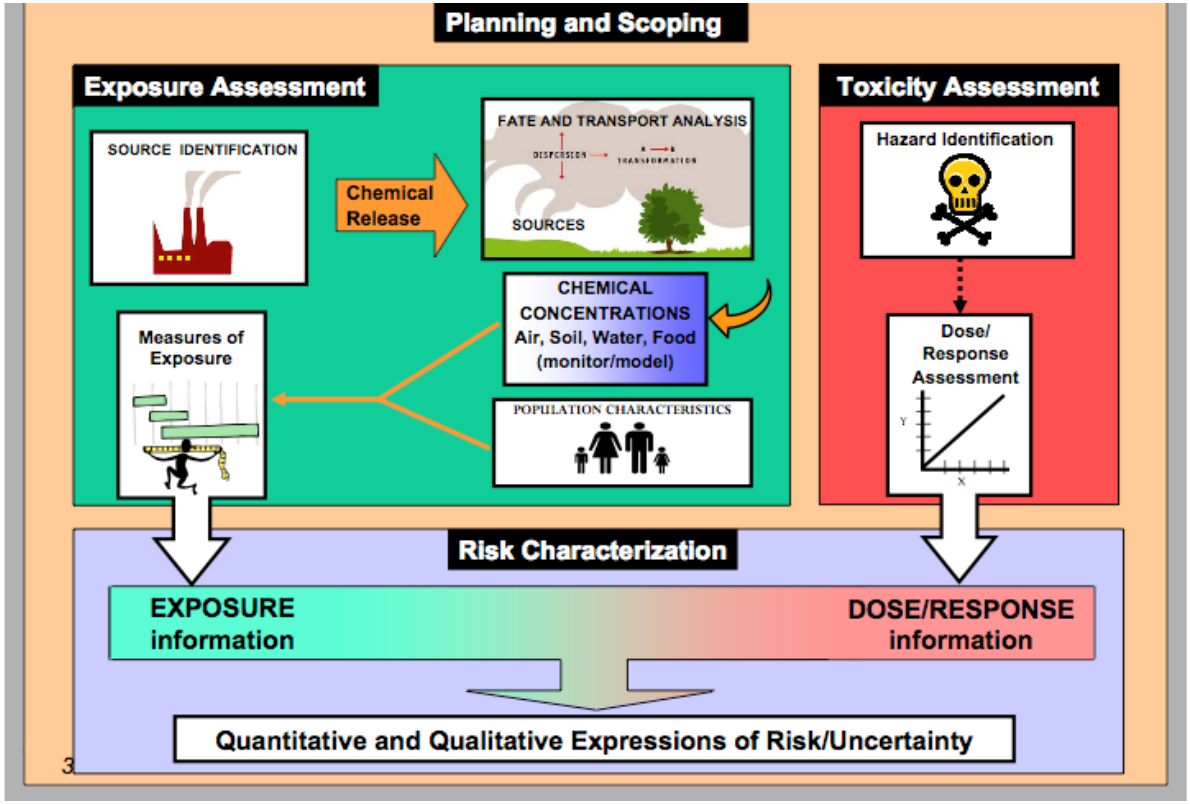

Hazard assessment, dose-response & exposure assessment

TOOLS FOR HAZARD CHARACTERIZATION

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- ChemHAT - easy way to access summarized information on chemical hazards in the workplace
- ChemSpider
- Protox

} toxicity assessment based on experimental or predicted LD 50

- Safer Choice - for consumers, businesses, and purchasers to find products that perform and are safer for human health and the environment.

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What happens once you are exposed to a toxicant?

ADME

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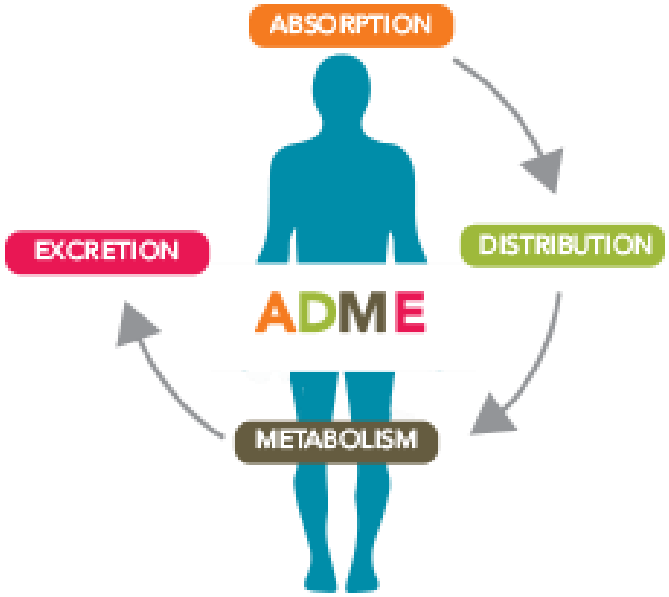
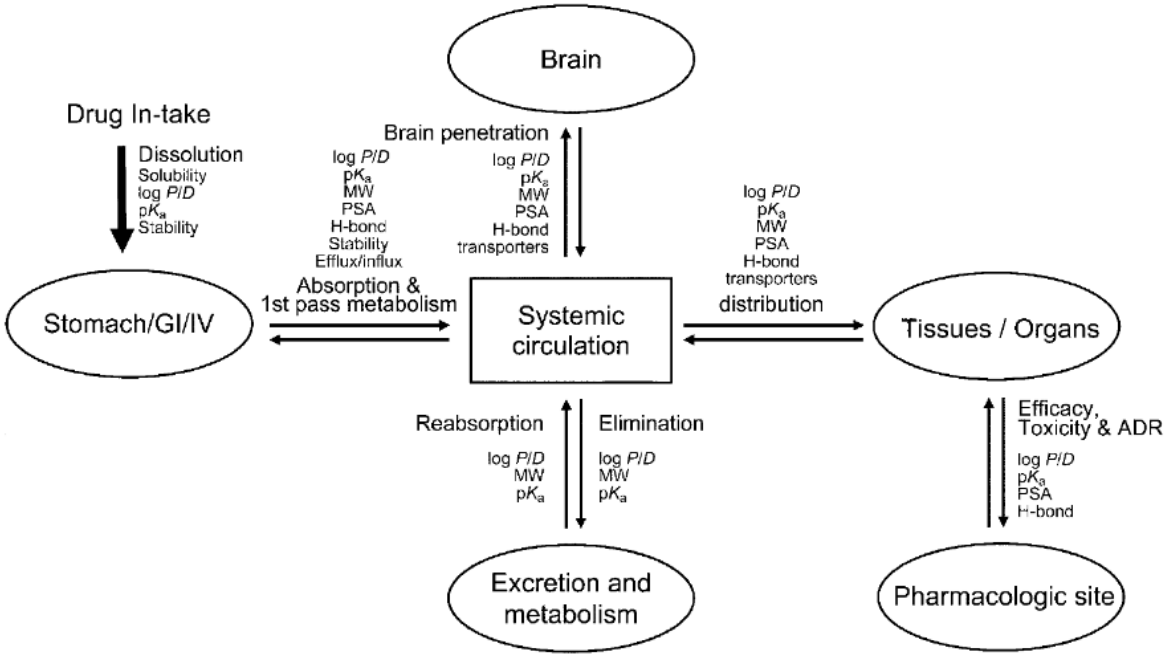
- ABSORBTION
- DISTRIBUTION
- METABOLISM
- EXCRETION



http://blog.gyrosproteintechnologies.com/spinblog/adme-of-therapeutic-proteins

CHEMICAL PROCESSES IN ADME

GREEN CHEMISTRY



Source: Wang and Skolnik, Chemistry and Biodiversity, 2009

ABSORPTION

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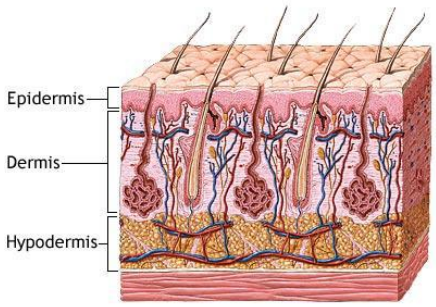
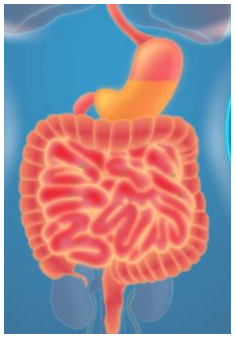


Dermal

Skin is the first barrier to absorption for the chemical. The skin can keep chemicals out of the body, or it can let them in, depending on the physical and chemical properties of the chemical. Skin absorption depends on molecular weight, lipid solubility (log P), and physical state. These parameters determine if the chemical passes through the skin cell membranes into the body. Absorption of a chemical will result in the chemical circulating inside the body and perhaps causing adverse effects.

Respiratory

As chemicals are inhaled, they may reach the lungs. The lung surface is a poor barrier against the entry of many chemicals into the body, which means that absorption of chemicals into the lung can be rapid and efficient. Respiratory absorption depends on many factors such as molecular weight, log P and vapor pressure.



Digestive

If chemicals are swallowed, either intentionally or unintentionally, they enter the gastrointestinal tract (GI). From there, they may either pass through the body or be absorbed into the body. GI absorption depends on many factors such as molecular weight, log P and physical state.

ABSORPTION

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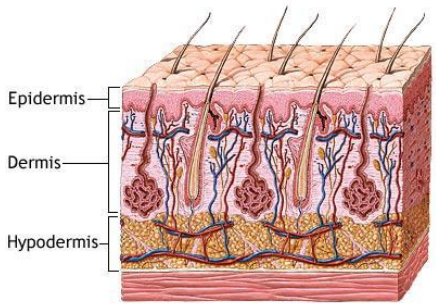

Dermal

Parameter	Preferred	Not Preferred
Physical state	solid	liquid
LogP	Less than 0 or greater than	Between 0 and 5
Molecular weight	More than 400 Da	Less than 400 Da

Respiratory

Parameter	Preferred	Not Preferred
Particle size [nm]	More than 5	Less than 5
LogP	Less than 0 or greater than 5	Between 0 and 5
Molecular weight [Da]	More than 400	Less than 400
Vapor pressure [mmHg]	Less than 0.001	More than 0.001

Digestive

Parameter	Preferred	Not Preferred
Particle size [nm]	More than 100	Less than 100
LogP	Less than 0 or greater than 5	Between 0 and 5
Phase	solid	liquid
Molecular Weight [Da]	More than 500	Less than 400

DISTRIBUTION

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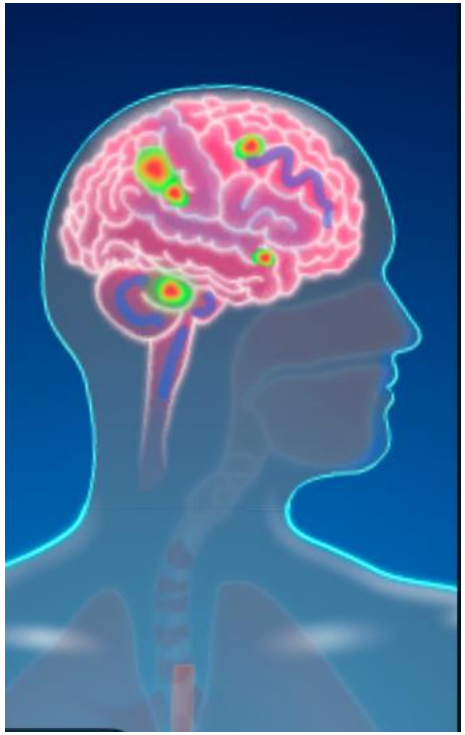

Distribution is the movement of a chemical throughout the bloodstream and into other organs, such as the brain and the bones. Pharmaceuticals such as antibiotics and painkillers are designed to have high distribution rates so they can reach their target organs and have therapeutic effects. For chemicals such as detergents, distribution should be limited.

Distribution depends on many factors such as log P, polar surface area, acidic/basic properties, and molecular weight.

Distribution as opposed to absorption is more difficult to control.

Courtesy of Molecular Design Research Network and Dr. Karolina Mellor

METABOLISM

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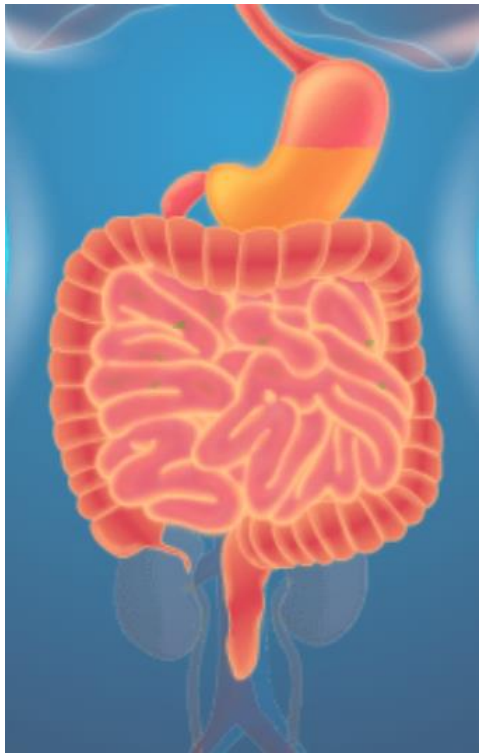

Courtesy of Molecular Design Research Network and Dr. Karolina Mellor

As a chemical is distributed through the body, it will most likely undergo metabolism. Metabolism is the body's way of facilitating the excretion (removal) of the detergent through the kidneys. The rate at which a chemical is metabolized is usually dependent on its accessibility to enzymes.

Metabolism is more difficult to control than Absorption, and it can lead to detoxification or toxification of the organism.

ELIMINATION

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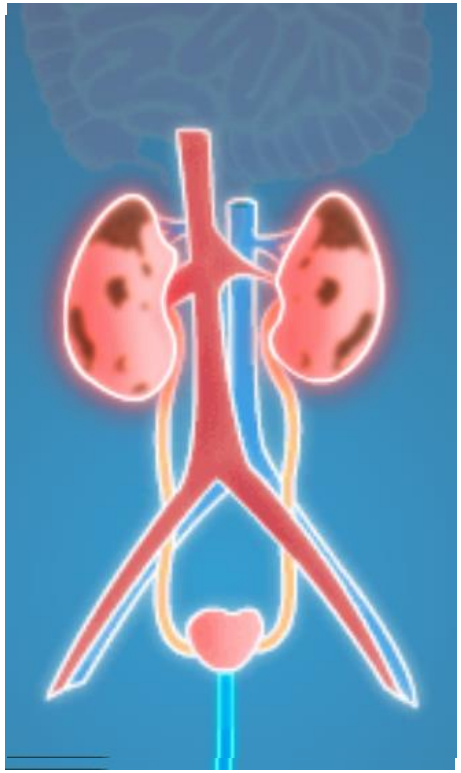

Courtesy of Molecular Design Research Network and Dr. Karolina Mellor

After the chemical is absorbed, the body can eliminate it by a process called excretion which can occur through the kidneys, the skin, the GI tract, and the lungs. If the detergent is not eliminated from the body, it can accumulate, or stay in the blood, which can lead to disease.

Excretion as opposed to absorption is more difficult to control.

IN-CLASS EXERCISE

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- Go to chemspider.com and put in following CAS number:
  - Benzene **71-43-2**

- Using discussed parameters, predict respiratory, dermal and digestive absorption of compounds.

Benzene:

- Colorless sweet smelling liquid; highly flammable
- Used as precursor to many complex chemicals: polystyrenes, polycarbonates, epoxy resins, nylon
- Toxic- known carcinogen

DERMAL	
	71-43-2
LogP	
Molecular weight [g/mol]	
Phase	

RESPIRATORY	
	71-43-2
LogP	
Molecular weight [g/mol]	
Vapor pressure [mmHg]	

DIGESTIVE	
	71-43-2
LogP	
Molecular weight [g/mol]	
Phase	

DERMAL	
	71-43-2-Benzene
LogP	2.22
Molecular weight [g/mol]	78.112
Phase	liquid

RESPIRATORY	
	71-43-2-Benzene
LogP	2.22
Molecular weight [g/mol]	78.112
Vapor pressure [mmHg]	100.9

DIGESTIVE	
	71-43-2-Benzene
LogP	2.22
Molecular weight [g/mol]	78.112
Phase	liquid

CONCLUSIONS

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- Benzene is volatile–it will absorb through the respiratory system
- Once benzene is in the body, it has a moderate lipid and water solubility, therefore some of it will absorb in digestive track
- Since it is a liquid, it will absorb easier than solid
- Skin absorption is also probable

FOR ADDITIONAL PRACTICE: SAFER CHEMICAL DESIGN GAME

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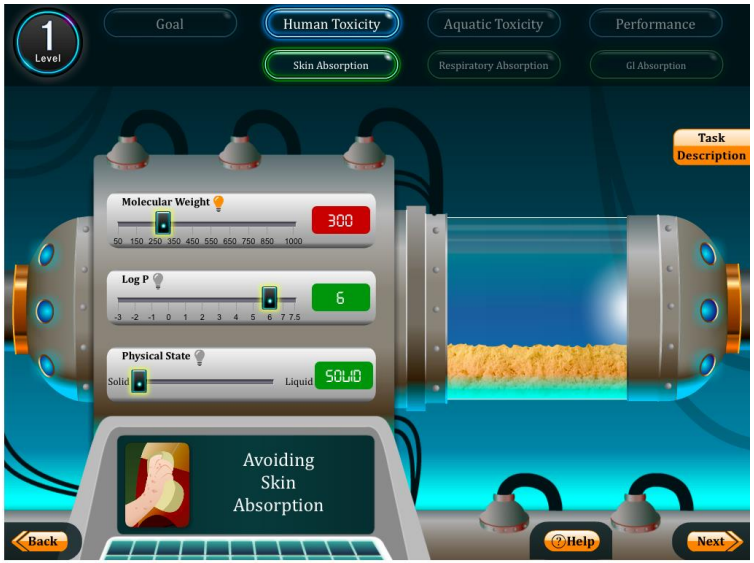
Educational game based on ADME and scientific data for surfactants to make connection between physico-chemical properties and health.



http://gwiz.yale.edu

Courtesy of Molecular Design Research Network and Dr. Karolina Mellor

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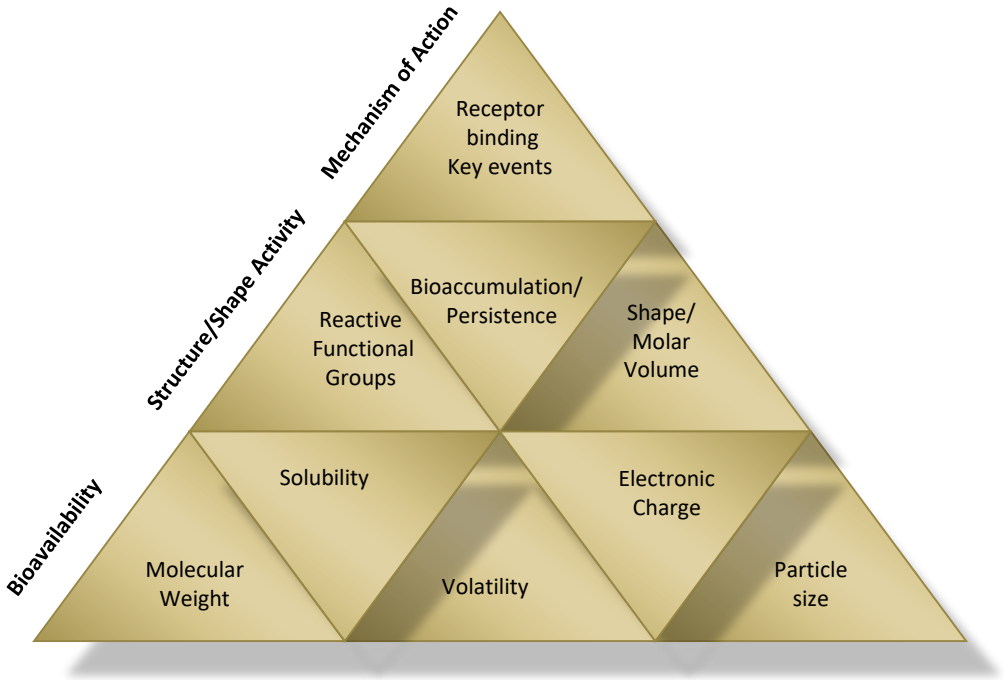
Approaches to Hazard Minimization through Molecular Design

GREEN CHEMISTRY MOLECULAR DESIGN PYRAMID

GREEN CHEMISTRY



Toxicodynamics

Not well understood and relatively complex

That's what we want to target

Chemists can control quite well

Toxicokinetics

APPROACHES TO HAZARD MINIMIZATION THROUGH MOLECULAR DESIGN

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A. Elimination of the molecular initiating event that activates pathway
B. Changing reactive functional groups
C. Reducing or eliminating bioavailability
D. Reduction of need for associated hazardous substances
E. Design for End-of-Useful product life

A. ELIMINATION OF THE MOLECULAR INITIATING EVENT THAT ACTIVATES PATHWAY

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Where the mechanistic pathway of action is known, molecular structures can be design such that the necessary reactions necessary are either impossible or highly disfavored resulting in significant toxicity reduction.

B. CHANGING REACTIVE FUNCTIONAL GROUPS

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In the absence of specific mechanistic information, chemists can modify structure such that certain reactive functional groups, e.g., cyano, electrophilic, etc., can be minimized or eliminated from the chemical structure where feasible.

C. REDUCING OR ELIMINATING BIOAVAILABILITY

GREEN CHEMISTRY

In order for a chemical to manifest its intrinsic hazard, it must be able to reach the toxicological target, human, animal, environmental or global. Through structural molecular design, properties such as solubility, log Kow, and volatility can adjusted to reduce hazard manifestation.

D. REDUCTION OF NEED FOR ASSOCIATED HAZARDOUS SUBSTANCES

GREEN CHEMISTRY

Many chemical substances, if not hazardous themselves, require the use of other hazardous substances e.g., paints with VOCs, surfaces requiring specific cleaners, plastics with various additives.

Through molecular design, these associated substances can be eliminated by making the desired properties integral to the product

E. DESIGN FOR END-OF-USEFUL PRODUCT LIFE

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Persistence of chemical in the environment is a problem that can be designed out of molecular structure.

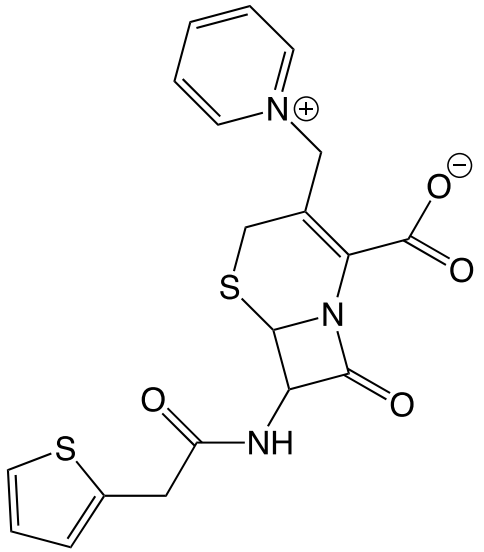
By creating products that degrade to innocuous by-products under designed conditions, e.g., heat, light, time one a can reduce or eliminate this hazard.

Design for utilization of waste as a feedstock is an important goal.

BY CHANGING THE MOLECULAR CHARGE: CEPHALOSPORINS

GREEN CHEMISTRY

- Clinical nephrotoxicity was recognized early – damage to proximal tubular epithelia.
- Mechanism: the drug is rapidly transported across basolateral membrane via the organic anion transporter, OAT1. Transport out of cell into lumen is less well characterized (involves other OAT, OAT4).
- Cephalosporin has a very low affinity for OAT4 due to its zwitterionic character, resulting in considerable intracellular accumulation

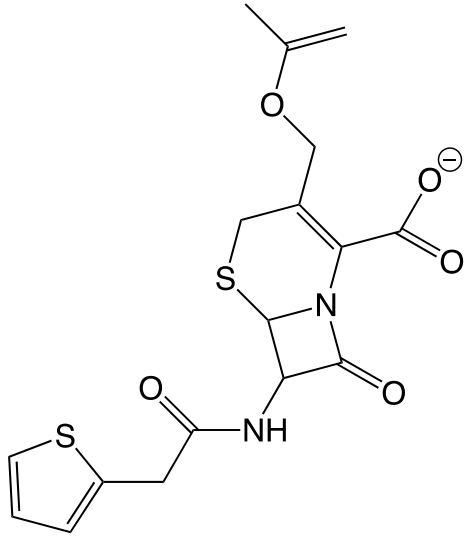


Cephaloridine

CEPHALOTHIN

GREEN CHEMISTRY

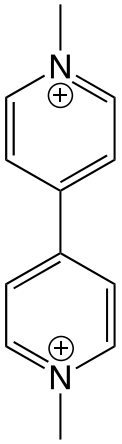
- In contrast, cephalothin, an anionic analog of the original zwitterionic drug, rapidly moves across the epithelia from blood into urine
- Is thus not a neurotoxin



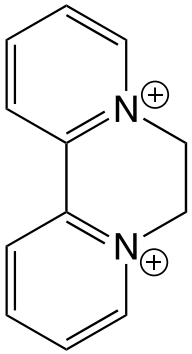
Cephalothin

BY MANIPULATING STERICS: PARAQUAT AND DIQUAT

GREEN CHEMISTRY



Diquat



Paraquat

Mechanism: After oral ingestion, a very small fraction is absorbed, but the blood levels remain constant for many hours as paraquat is not metabolized by the liver. Instead, it accumulates in the lung and is retained there even after blood concentrations decrease.

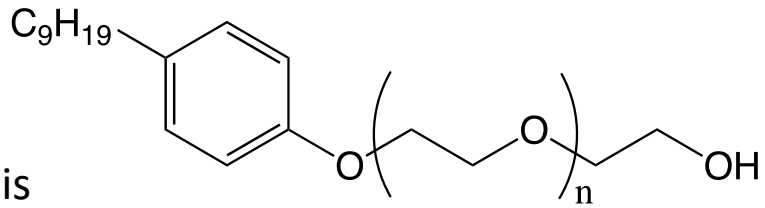
Paraquat was found to enter the lung via carrier-mediated transmembrane transport, specifically the polyamine transport system.

THROUGH SAR DATA: NONYLPHENOLS AND GLYCIDYL ETHERS

GREEN CHEMISTRY

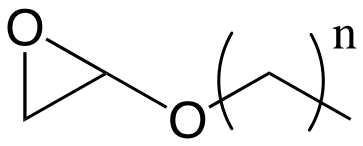
Polyethoxylatednonylphenols

- Emulsifiers, surfactants
- When n = 14-19, intense myocardial necrosis at 40 mg/kg day in dogs and guinea pigs
- When n<14>19, no myocardial effects



Glycidyl ethers

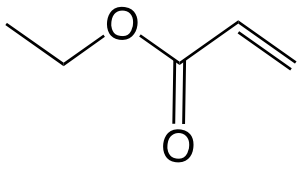
- When n = 7-9, mutagenic, cause testicular lesions
- When n = 11-13+, non-mutagenic



BY MANIPULATING ELECTROPHILICITY: ACRYLATES

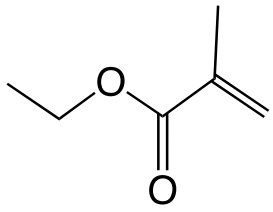
GREEN CHEMISTRY

- Acrylate is understood to be carcinogenic because it can readily undergo Michael addition reactions
- The addition of a methyl group to form methacrylate decreases the electrophilicity of the b-carbon, and decreases tendency for Michael reactions.
- While this does not reduce the commercial efficacy, but whereas acrylate causes cancer is experimental assays, methacrylate does not.



Acrylate

carcinogenic



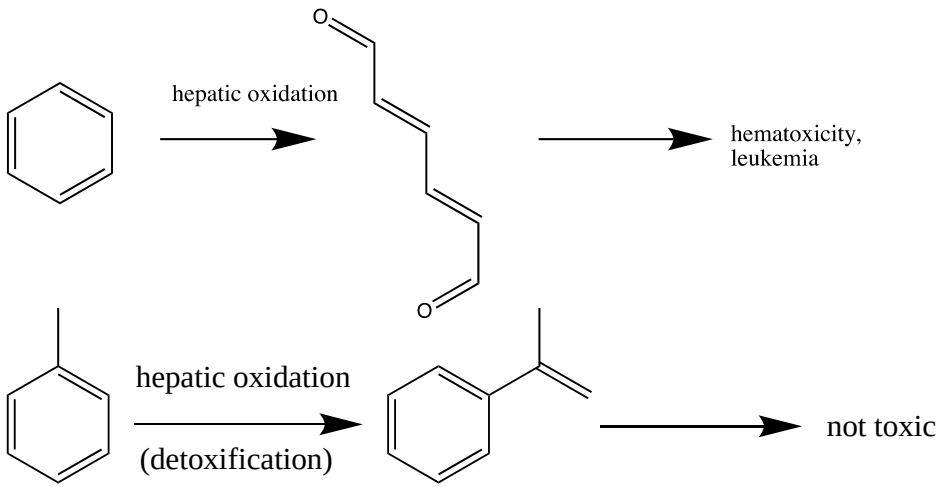
Methacrylate

non-carcinogenic

BY FACILITATING DETOXIFICATION: BENZENE

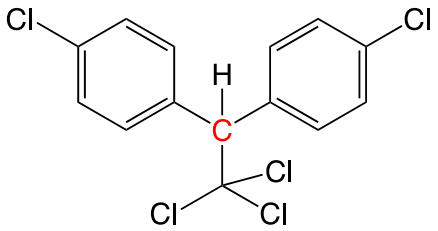
GREEN CHEMISTRY

- Benzene is known to cause hematoxicity and leukemia in humans
- This is understood to be due to one of its metabolites, (E,E)-muconaldehyde.
- Toluene is comparatively much less toxic, as the methyl group is oxidized more easily than the benzene ring to give benzoic acid

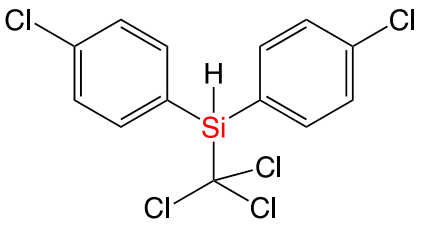


BY ISOSTERIC SUBSTITUTION: CARBON WITH SILICON

GREEN CHEMISTRY



DDT
(Toxic to insects)



Si-DDT Analog
(Non-toxic to insects)

- DDT is well known to be environmentally persistent
- DDT analog with Silicon above was synthesized.
- While less persistent, the analog turned out to be non-toxic to insects
- This is due to the more readily oxidized (metabolized) Si-H bond compared to C-H and also the larger size of the molecule

DESIGNING NEW MOLECULES IS NOT A TRIVIAL TASK

GREEN CHEMISTRY

Even if chemists design one chemical, it has to undergo tests

14-day studies.

Parameter	Animals	Species	Sex	Exposure levels	Totals
Exposure group	5	2	2	5	100
Controls	5	2	2	1	20
Total					120
Exposure duration	14 days				
Toxicity end points	Mortality, clinical signs of toxicity, body weights, food and water consumption, selected organ weights, gross pathology, histopathology on selected organs.				

90 day toxicity assays

Parameter	Animals	Species	Sex	Exposure levels	Totals
Exposure group	10	2	2	5	200
Controls	10	2	2	1	40
Total					240
Exposure duration	90 days				

Two-year toxicology and carcinogenesis studies.

Parameter	Animals	Species	Sex	Exposure levels	Totals
Exposure groups	60	2	2	3	720
Controls	60	2	2	1	240
Sentinel	15	2	2		60
Total					1020
Exposure duration	104 weeks				
Interim evaluations	Week 65				
Toxicity end points	Chronic toxicity, carcinogenicity				

Too many animals

Takes too long

Too expensive

1380 animals/chemical

Do comprehensive pathology analysis looking for tissue toxicity and cancer

- Current complete acute and chronic toxicity costs about $2 million per chemical (and that's just mammalian toxicity)

QSAR-QUANTITATIVE STRUCTURE ACTIVITY RELANTIONSHIP

GREEN CHEMISTRY

- Assumes that similar chemicals behave similarly
- Behavior of the chemical is derived from the structure
- QSAR seeks for a relationship between chemical structure and activity
- Identifies changes that lead to different activity (activity to avoid or keep)

WHEN TO USE QSAR?

GREEN CHEMISTRY

- Not sufficient data on majority of chemicals
- Not all chemicals will be tested
- QSAR has been used for over 60 years
- Better to predict than have nothing

QSAR BASICS

GREEN CHEMISTRY

- They are associated with a specific endpoint [like LC50 or oxidative stress]
- They ‘group’ chemicals based on activity like toxicity
- Predict endpoints directly from chemical structure

PREDICTORS OF FUNCTION, TOXICITY, PROPERTIES

GREEN CHEMISTRY

- Lipinski rule of five
- Number of rings
- Number of rotatable bonds
- Degree of branching
- Connectivity
- Overall shape

EXAMPLES OF POPULAR TOXICITY PREDICTION TOOLS

GREEN CHEMISTRY

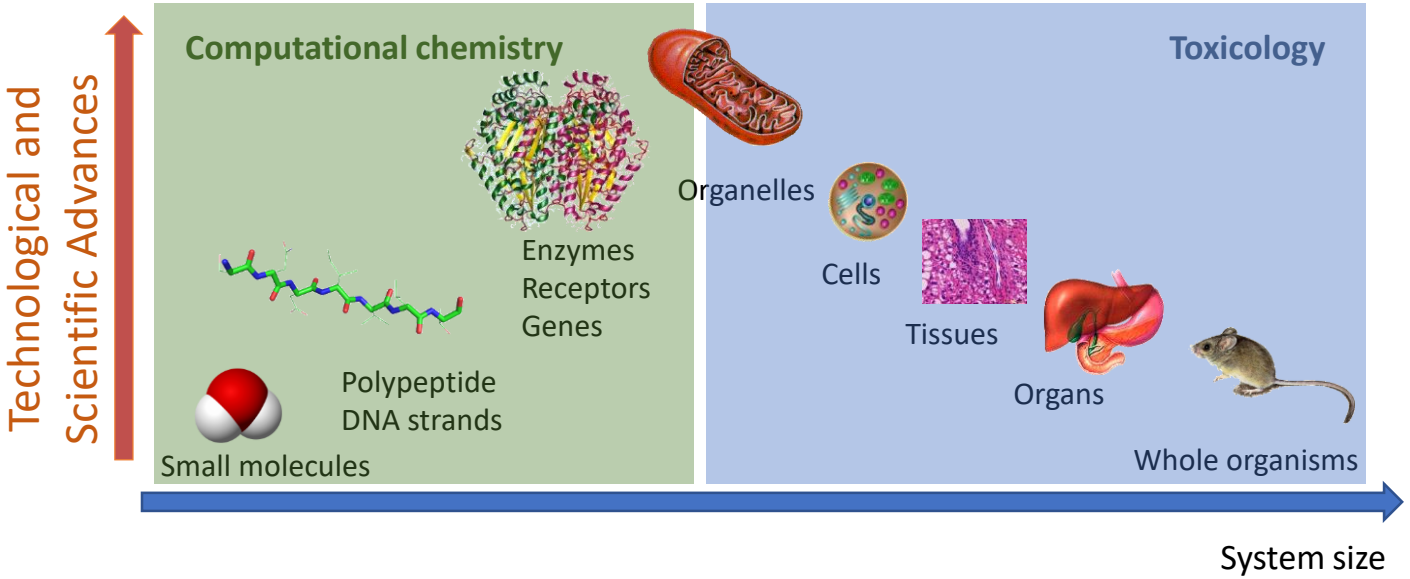
Current limitations

- Prediction accuracy not higher than 65-70% for non-carcinogenic chemicals.
- Lack of validation with up-to-date data
- Application to a narrow range of chemical structures
- Qualitative output

Program	Originators	Now licensed by
TOPKAT	Enslein, 1970s	Accelrys Inc.
LAZAR	Helma, 2006	In silico Toxicology (Free)
DEREK	Schering Agrochemicals	Lhasa Ltd (non-profit)
ADAPT		Compudrug
OncoLogic	US EPA	Free
MULTICASE	Klopman, Case Western Reserve Univ., 1980s	Multicase
ToxBoxes		Pharma Algorithms Inc. (Free or fee-based)
TOXTREE	Ideaconsult Ltd. (EU REACH)	European Commission
EPA PBT Profiler	US EPA	Free
OECD QSAR Toolbox	Oasis LMC (OECD)	Free

NEW APPROACH: CROSSROADS OF COMPUTATIONAL CHEMISTRY & TOXICOLOGY

GREEN CHEMISTRY



As toxicology has increased its understanding of underlying biological processes leading to toxicity, computational chemistry can now describe the chemical transformations involved in these processes

UNDERSTANDING PHYSICOCHEMICAL PROPERTIES ASSOCIATED WITH REDUCED HAZARD

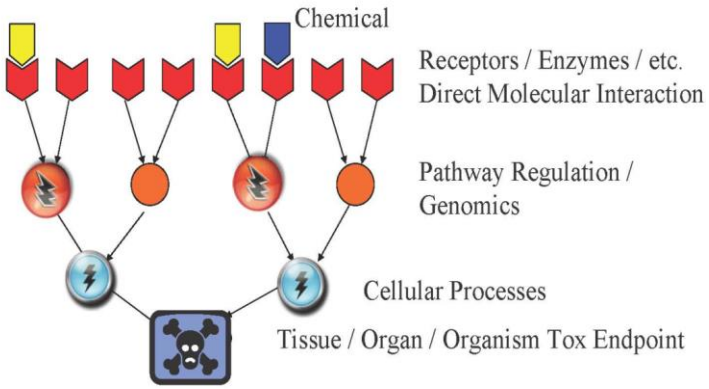
GREEN CHEMISTRY

DESIGN

Chemical and Physical Properties

pKa chain branching log P molecular refractivity mol. wt. hydrolyzable groups

E_{HOMO} E_{LUMO} electronegativity hardness dipole log $D_{7.4}$ # H-bond accep/donor

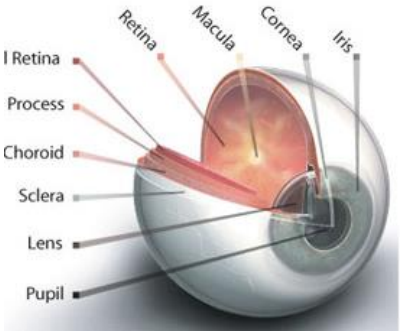


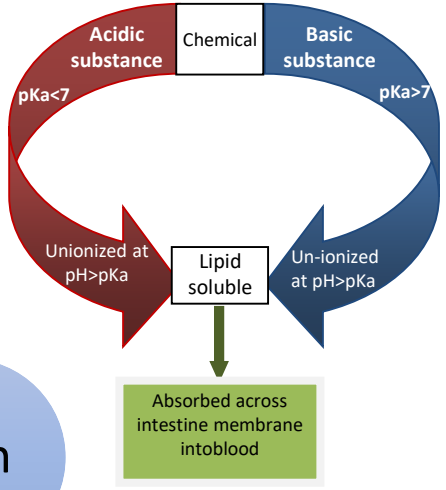
- Flammability
- Radioactivity
- Risk of Explosion
- Chemical Reactivity

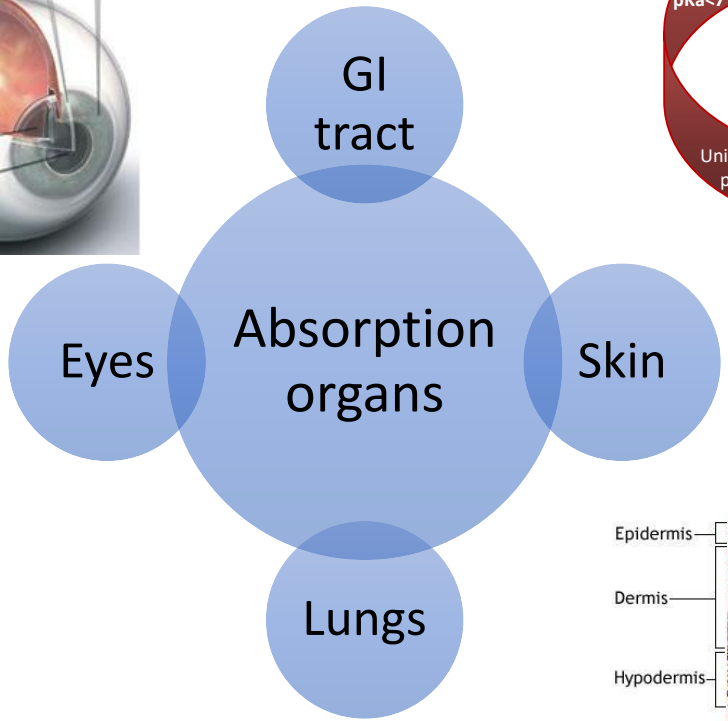
- Pollution
- Persistence
- Depletion of resources

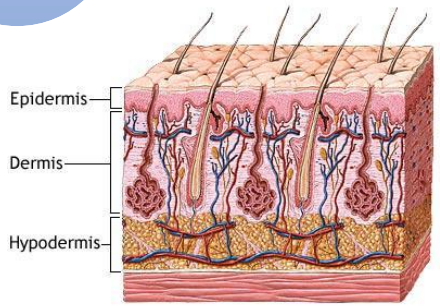
PROPERTY-BASED GUIDELINES FOR BIOAVAILABILITY

GREEN CHEMISTRY



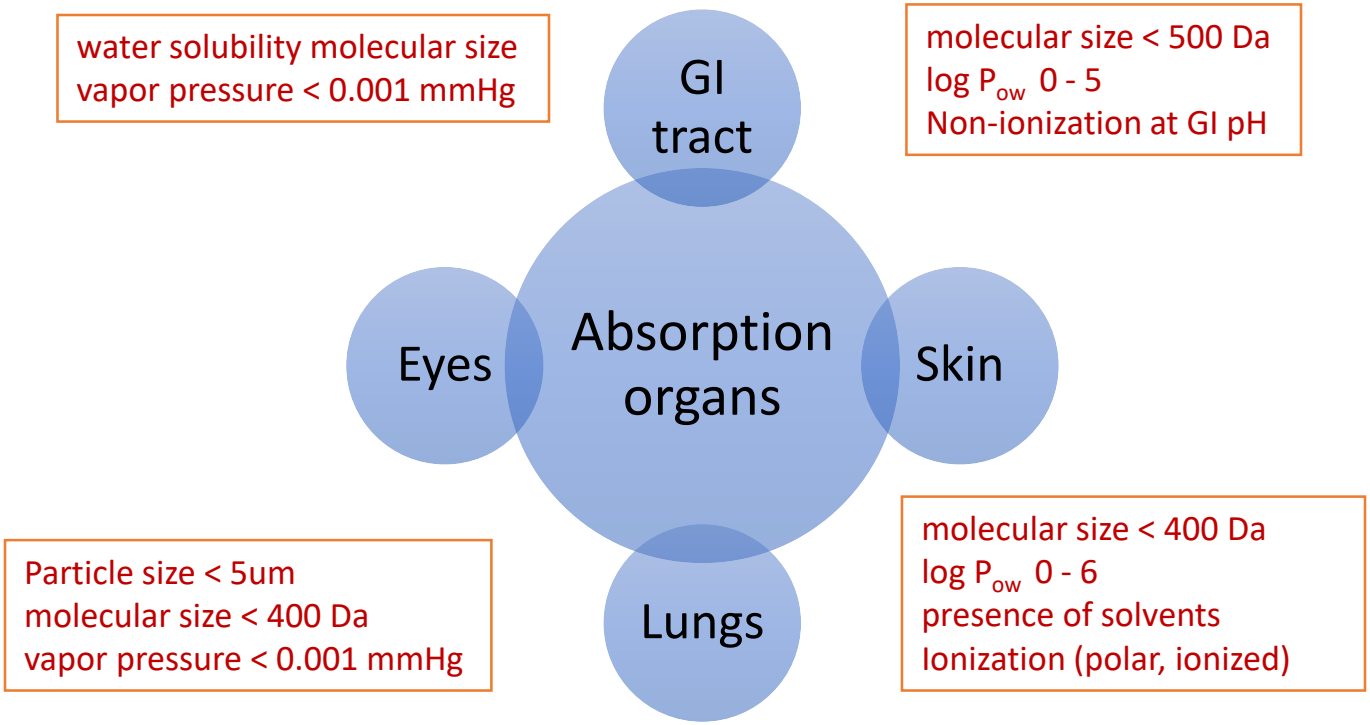






PROPERTY-BASED GUIDELINES FOR BIOAVAILABILITY

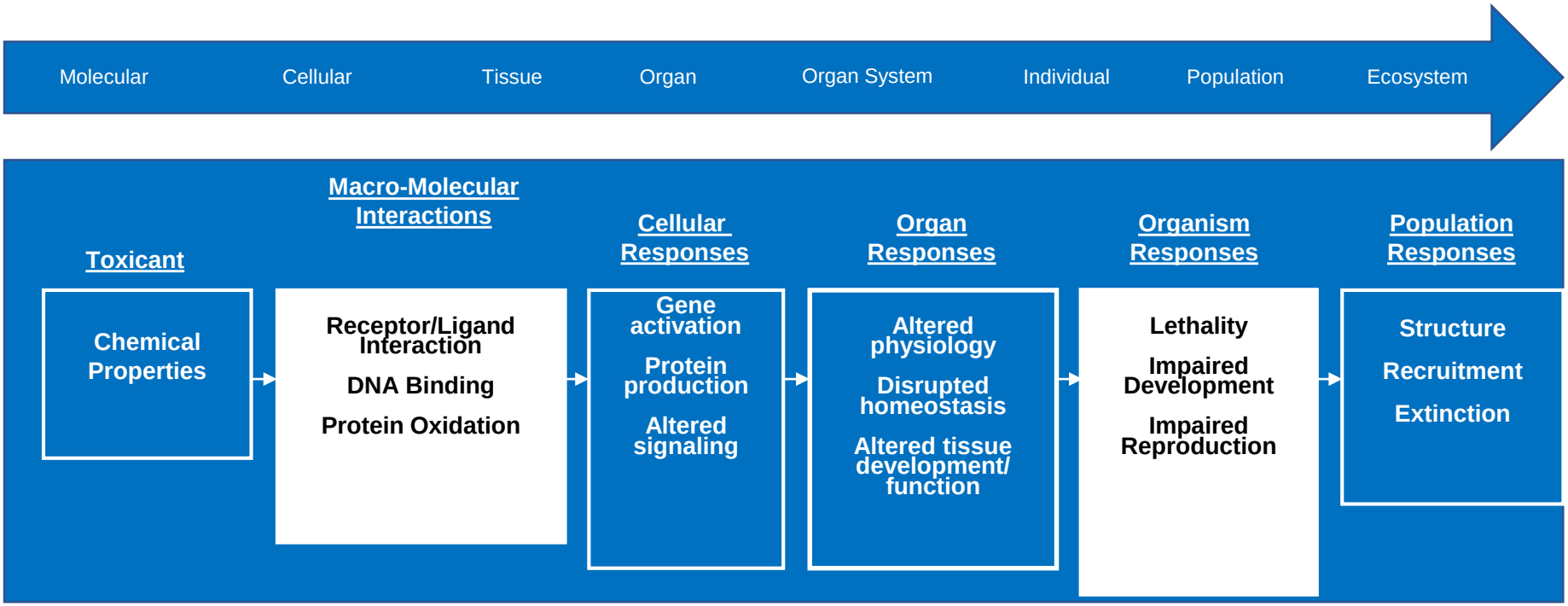
GREEN CHEMISTRY



Voutchkova, A.; Osimitz, T.; Anastas, T. Chem. Rev. 2010, 110, 5845

ADVERSE OUTCOME PATHWAYS

GREEN CHEMISTRY



- Mechanistic understanding is critical for evaluating toxicity pathways
- Design guidelines will be rationalized according to molecular initiation events

Ankley et al. 2010 *ET&C;* Source: Gary Ankley & Dan Villeneuve, EPA

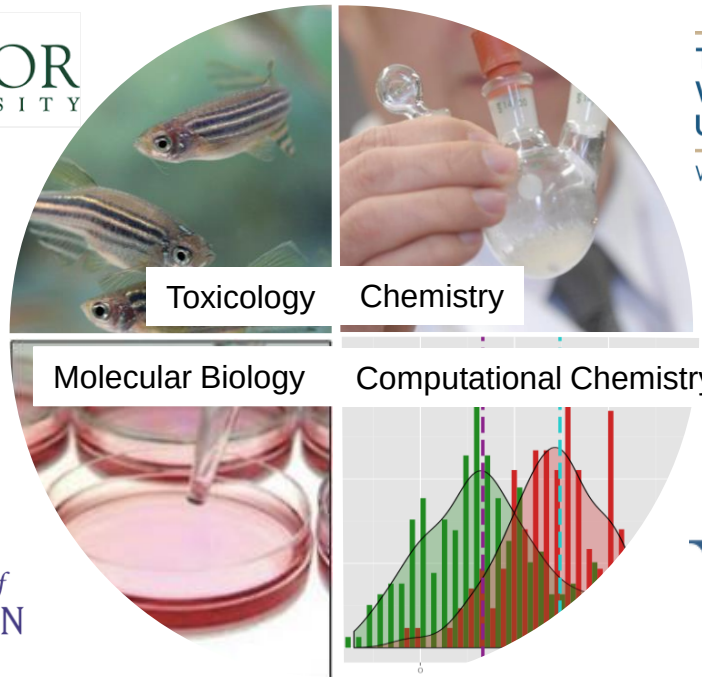
Create a reliable tool for chemists which will not only predict the toxicity of existing chemicals but will allow a design of future molecules with reduced hazard

MOLECULAR DESIGN RESEARCH NETWORK

GREEN CHEMISTRY

BAYLOR UNIVERSITY

THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC



UNIVERSITY of WASHINGTON

Yale

WHERE IS DATA COMING FROM?

GREEN CHEMISTRY

- EPA ToxCast
- Tox21

High throughput assay

- Network lab assays

Low throughput assay

WHAT IS AN ASSAY?

GREEN CHEMISTRY

Assay can test almost any biological effect

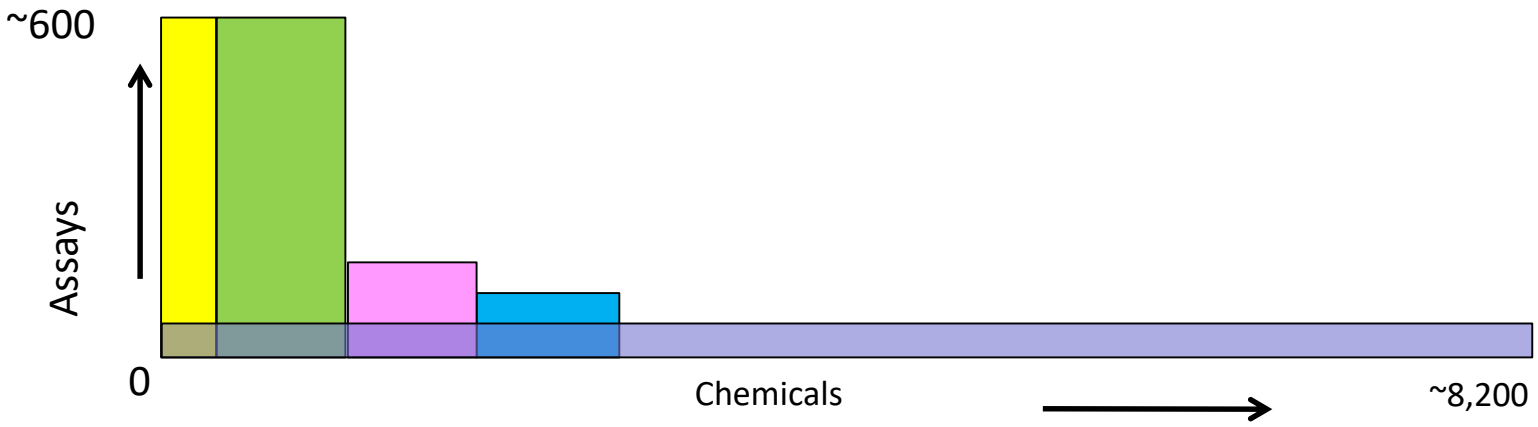
In vitro assay →in cell
In vivo assay →outcome in organism

Ideal assay is:
Reproducible: same result when repeated
Reliable: same result with different people repeat it
Sensitive: won't miss an effect
Specific: won't say there is an effect if there is not
Predictive of outcome of interest

DATA FROM TOXCAST

GREEN CHEMISTRY

Set	Chemicals	Assays	Endpoints	Completion	Available
ToxCast Phase I	293	~600	~700	2011	Now
ToxCast Phase II	767	~600	~700	03/2013	10/2013
ToxCast Phase IIIa	1001	~100	~100	Just starting	2014
E1K (endocrine)	880	~50	~120	03/2013	10/2013
Tox21	8,193	~25	~50	Ongoing	Ongoing

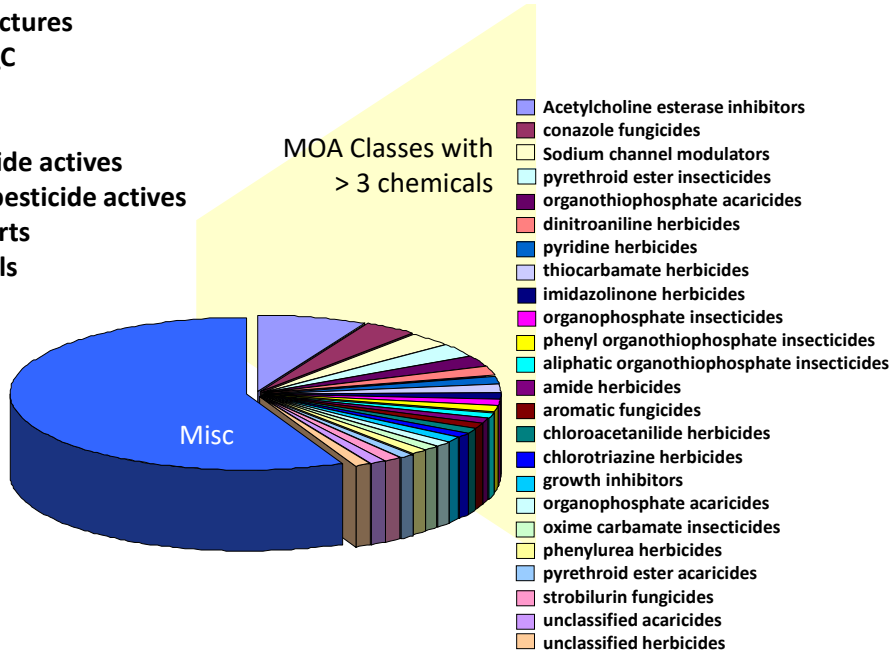


DATA FROM TOXCAST

GREEN CHEMISTRY

309 unique structures
Replicates for QC
8 metabolites

291 total pesticide actives
273 registered pesticide actives
22 pesticide inerts
33 antimicrobials



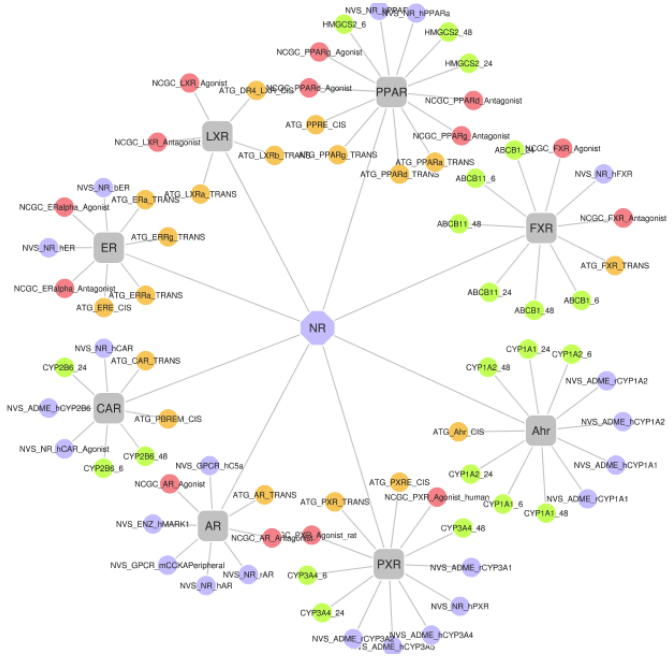
- ToxCast phase I: primarily pesticides
- ToxCast phase II: industrial chemicals
- ToxCast phase III: diverse chemical space; high production

DATA ENDPOINTS

GREEN CHEMISTRY

- Cell cytotoxicity (High Content Screening)
- Cell free assays of protein function
- Cell-based transcriptional reporter assays
- Gene expression in primary human cell cultures
- Developmental assays in zebrafish embryos

~624 assays
Redundant assays
for some "target" endpoints



Judson et al. (2010) "In Vitro Screening of Environmental Chemicals for Targeted Testing Prioritization - The ToxCast Project" Environmental Health Perspectives DOI:10.1289/ehp.0901392

TOPICS COVERED

GREEN CHEMISTRY

1. Hazard and Risk – Past and Present
2. Toxicology
3. Assessing Hazards and Exposure
   - What Happens When You're Exposed?
4. Hazard Minimization Through Molecular Design
5. QSAR - Quantitative Structure Activity Relationship
6. Molecular Design Research Network (MoDRN)

UNITED NATIONS
INDUSTRIAL DEVELOPMENT ORGANIZATION

GREEN CHEMISTRY

THANK YOU!

QUESTIONS?

This training material was developed in close collaboration with the Center for Green Chemistry and Green Engineering at Yale University.

www.greenchemistry-toolkit.org