POLITECNICO DI MILANO

School of Industrial and Information Engineering

Course 096125 (095857)

Introduction to Green and Sustainable Chemistry





Toxicology.

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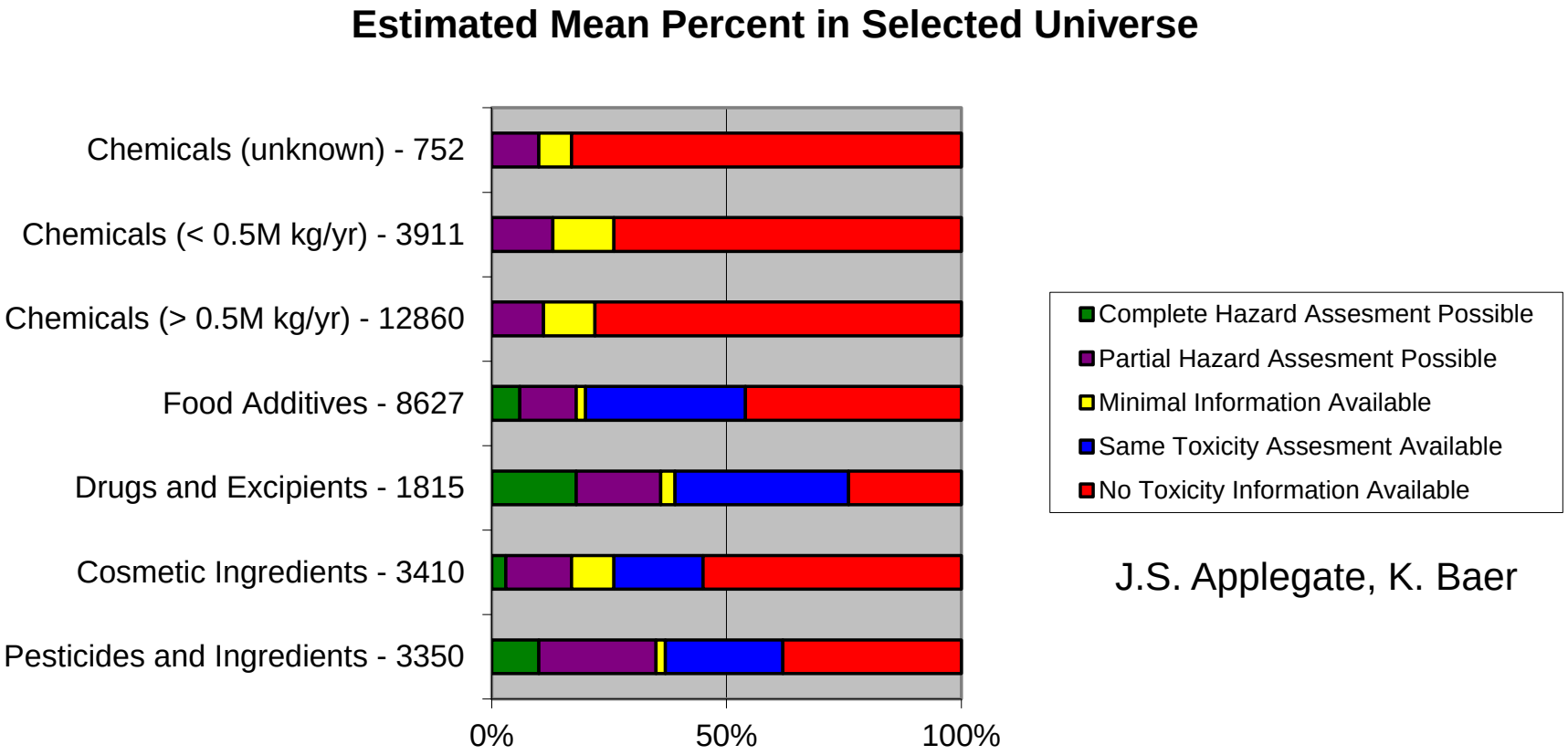
http://iscamapweb.chem.polimi.it/citterio/education/**course-topics/**

General aspects:

- Toxicological Risk : dose-response
- Toxicology vs. epidemiology
- Physiological effects on man
- Environmental effects

Toxicity Assessment Data Gaps.



- As of August 2011, ~ **30 million** organic and inorganic substances were documented
  (indexed by the American Chemical Society's Chemical Abstracts Service in their CAS Registry; excluding bio-sequences such as proteins and nucleotides)
- Of these chemicals, ~ **10 million** were commercially available.

What does Toxicology Means?

- *Evaluate the **HAZARD** (danger) of new/old substances*
- *Propose measures for preventing and contain the risk associated with the **EXPOSURE***
- *Calculate the **RISK = f (hazard , exposure)***

E.g.

We handle (or we are exposed) to many chemicals in our everyday lives.

Gasoline is a good example. We know that it is toxic if ingested or inhaled, but if we take care to limit our exposure to it and handle it safely, we take little risk in using it.

Definitions.

Hazard

The inherent toxicity of a substance, based on appropriate models (*in-vivo, in-vitro, in-silico*) or information from human epidemiologic studies.

Exposure

- *Route of entry*:

Oral	=	Ingestion by mouth
Dermal	=	Skin exposure
Inhalation	=	Absorbed by lungs
Ocular	=	Eye exposure

- *Probability of contact*;
- Use of safety equipment (individual: e.g. gloves, collective: e.g. cabinet);
- ….

Risk

The probability of adverse effect due to exposure of a chemical substance IN PARTICULAR CIRCUMSTANCES

Toxicity Testing in the Twenty-first Century.

NAS PANEL SEEKS MAJOR SHIFT IN HOW EPA ASSESSES CHEMICALS' TOXICITY

Date: June 22, 2007 -

Inside EPA
Online access provided by InsideEPA.com

A National Academy of Sciences (NAS) panel is calling for a major shift in how EPA assesses chemicals' toxicity, recommending that the agency base its toxicological research and regulatory processes on how substances affect biological pathways -- which send information within and between cells -- rather than so-called health endpoints, such as cancer.

The new studies envisioned by the panel would evaluate chemicals' effects on biological processes using cells or cell lines, preferably human, to examine how they react to exposure to different substances. Rather than focusing research and basing regulations on endpoints, such as a substance's apparent ability to create tumor cells or harm brain development in fetuses, EPA should center toxicity testing around "the perturbations in toxicity pathways that are expected to lead to adverse effects," the report says.

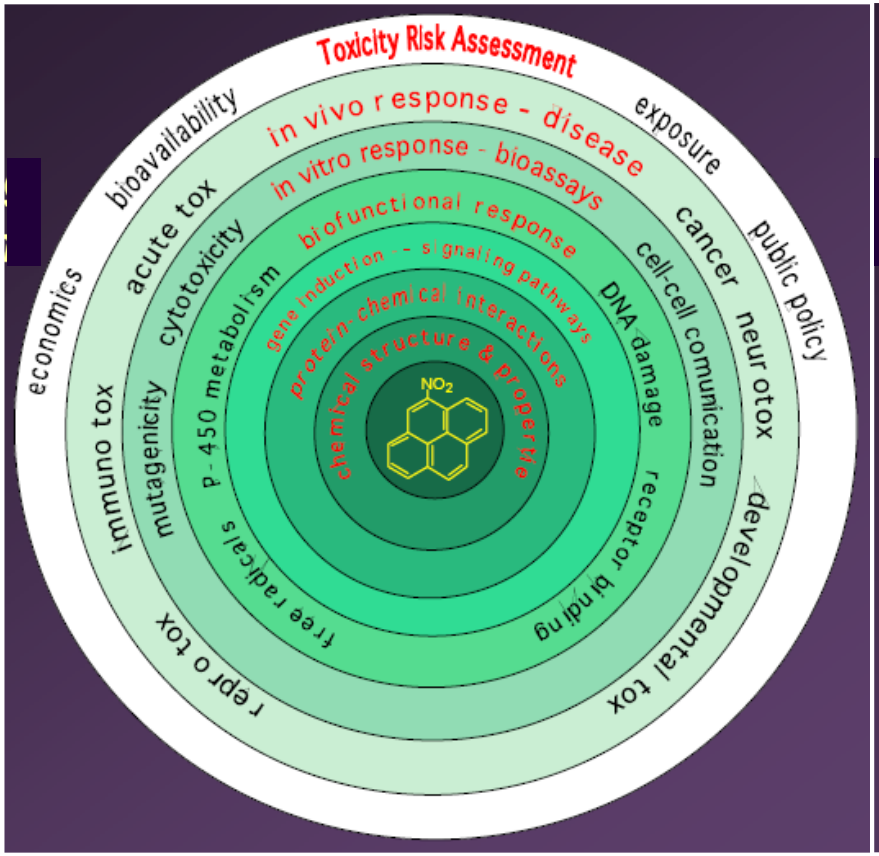
"In this framework, the goals of toxicity testing are to identify critical pathways that when perturbed can lead to adverse health outcomes and to . . . understand the effects of perturbations on human populations," says the report, *Toxicity Testing in the Twenty-first Century: A Vision and a Strategy* .

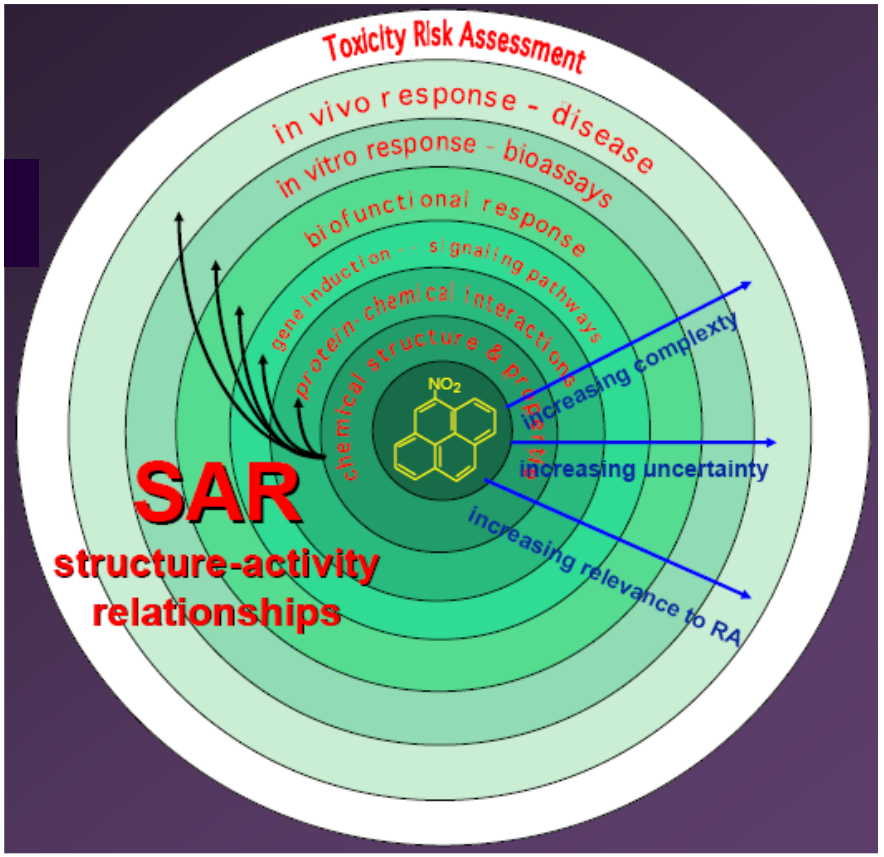
National Academy of Sciences Report (2007) Toxicity Testing in the Twenty-first Century: A Vision and a Strategy

On 11 March 2013 the **full ban on animal testing** for cosmetic products within the European Union entered into force.

http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2013:0135:FIN:EN:PDF

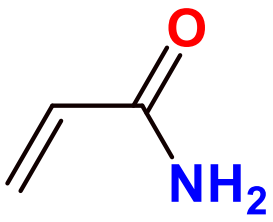
Toxicity Modeling Problem.





Legislation related to toxicity and risk of chemicals:
http://www.hse.gov.uk/chemicals/index.htm

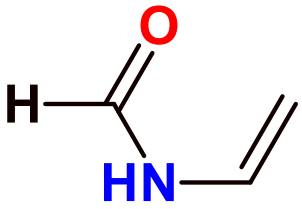
Example: Acrylamide vs. N-vinyl-Formamide.



Polyacrylamide, used in papermaking, oil recovery, personal care, concrete, water treatment.

Highly toxic, causes CNS paralysis **~ $ 1/kg** capacity > 500 000 t/y

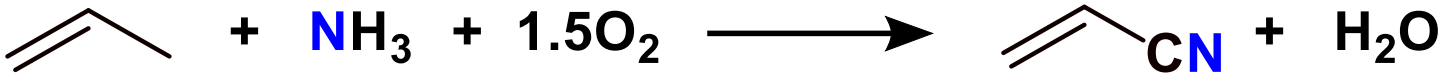
MW = C_3H_5NO

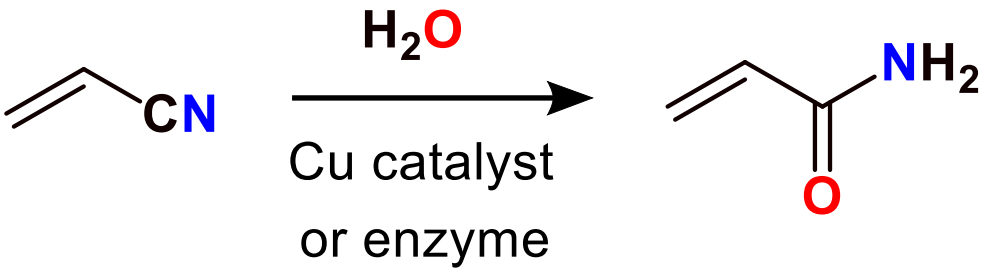


Poly(N-vinyl formamide), many of the same uses, hydrolyzed to polyvinyl amine.

Acute oral, > 1400 mg/Kg, not a neurotoxin **~ $ 4.50/kg**

Two Alternative Acrylamide Synthesis.

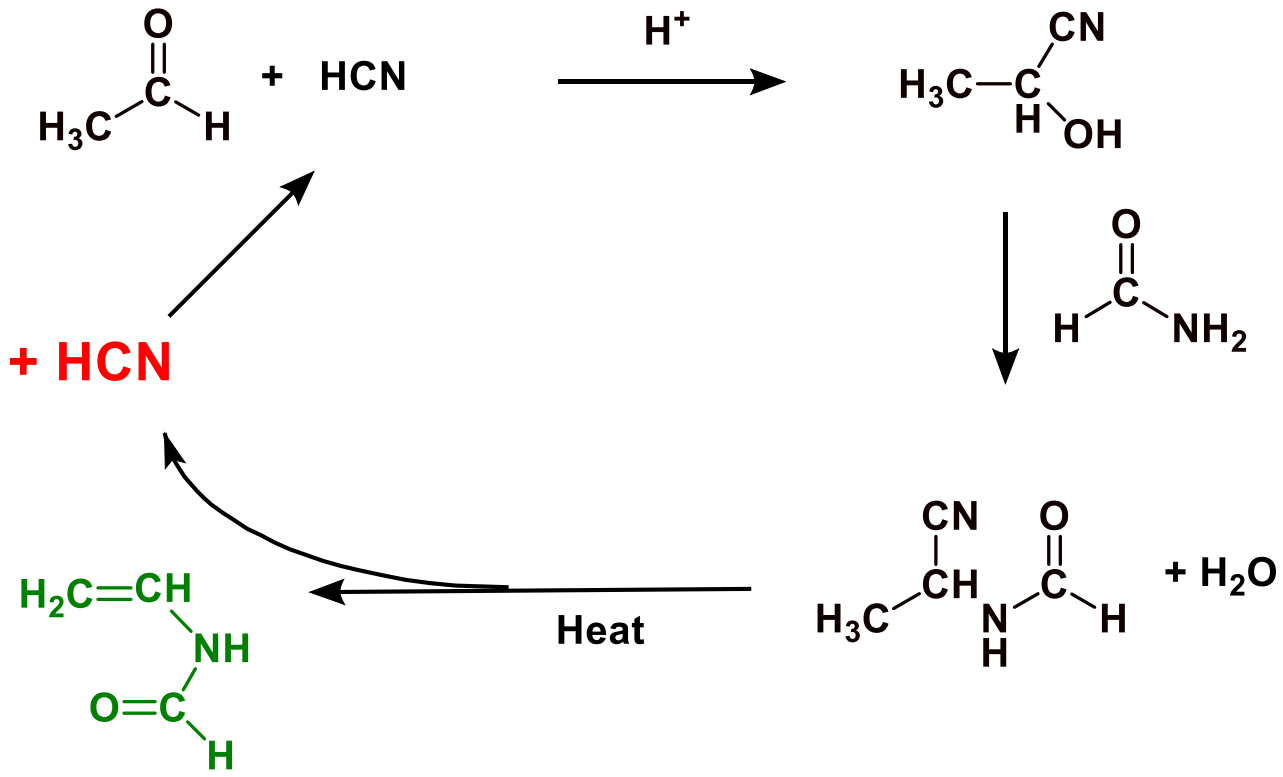
a) 

b) 

Enzymatic route newest, greenest approach.

Process green, Product not

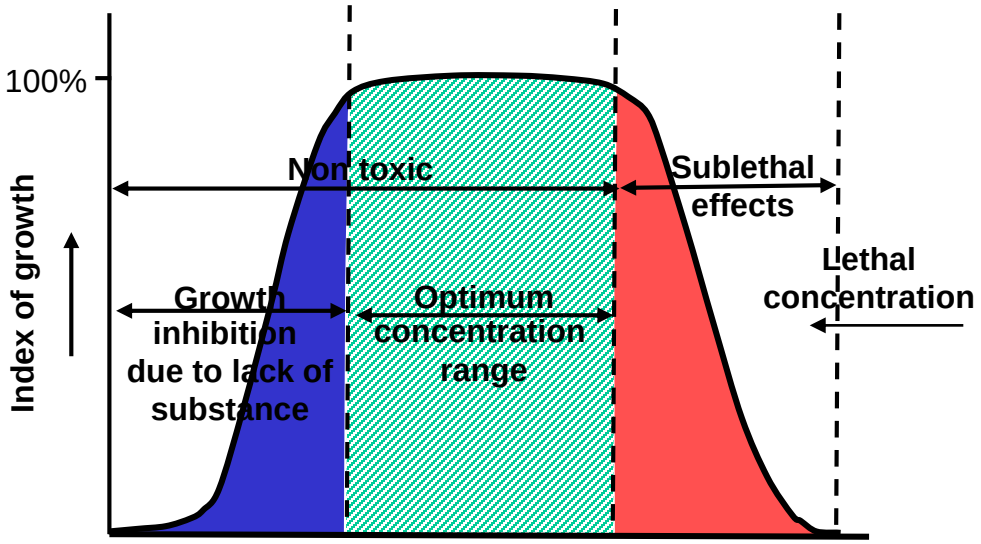
N-Vinylformamide Synthesis.



HCN, an inherent hazard, raises costs.

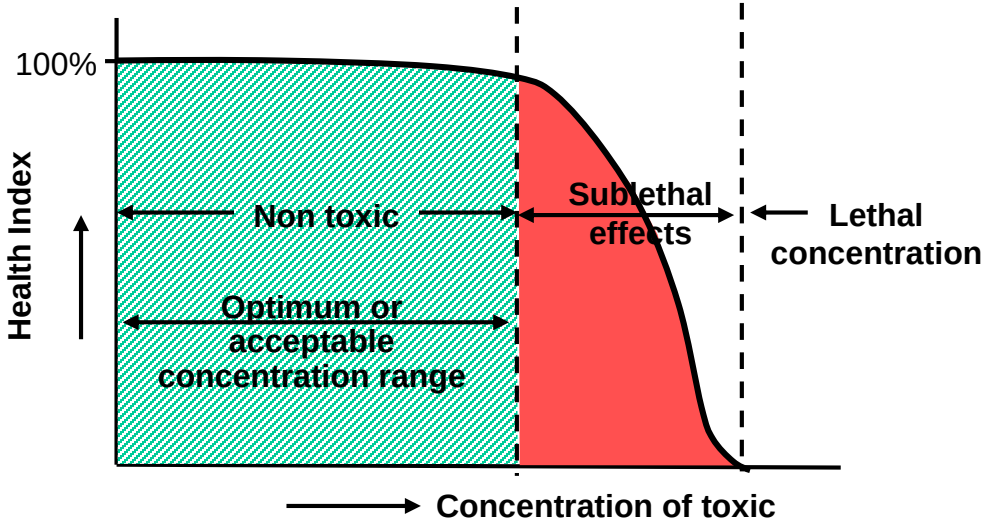
Product green, Process not

Essential versus Nonessential Nutrients.

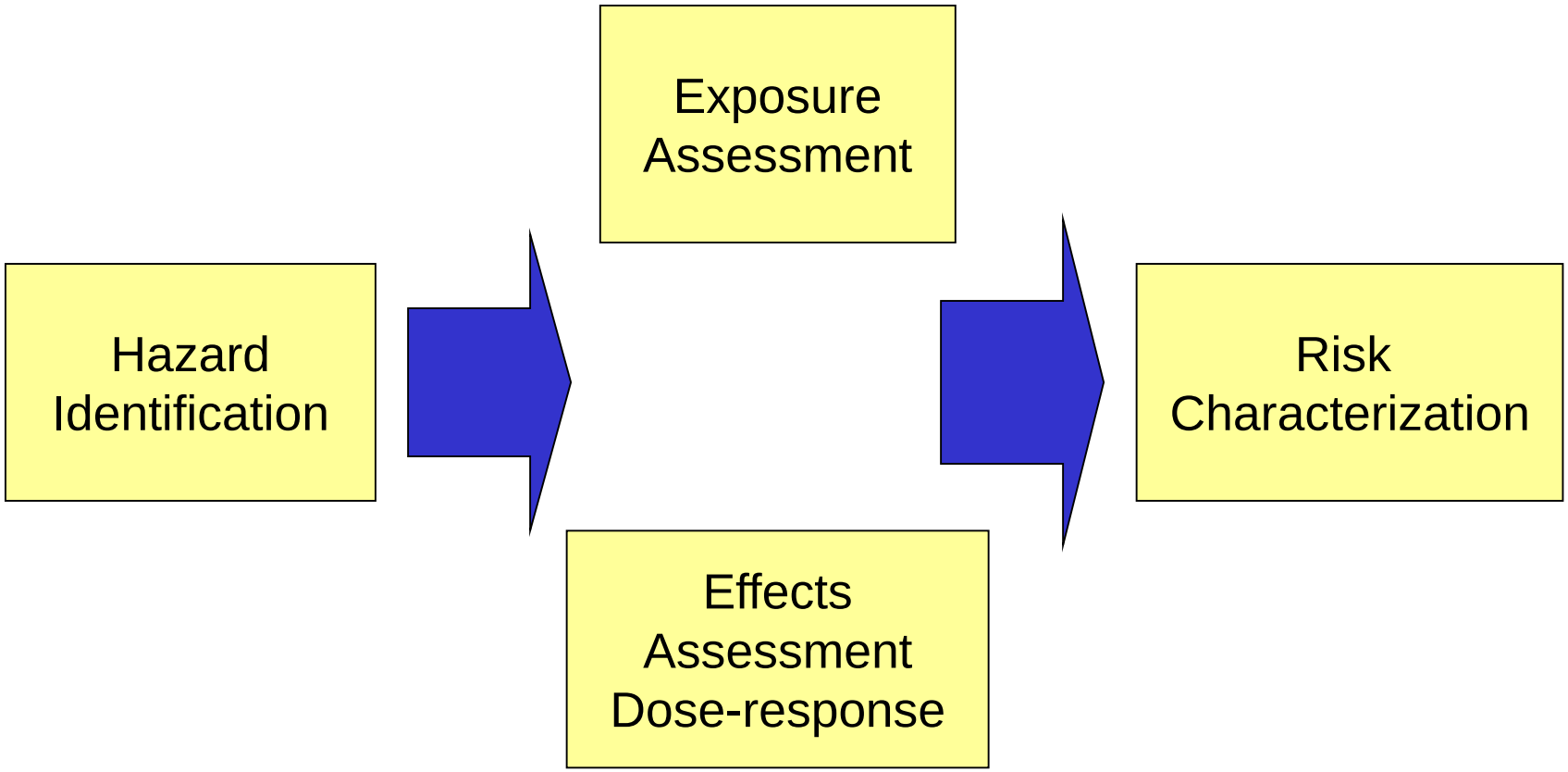


Essential elements are elements like nitrogen, phosphorus, magnesium and zinc. They are necessary to life, but they are also toxic at high concentrations

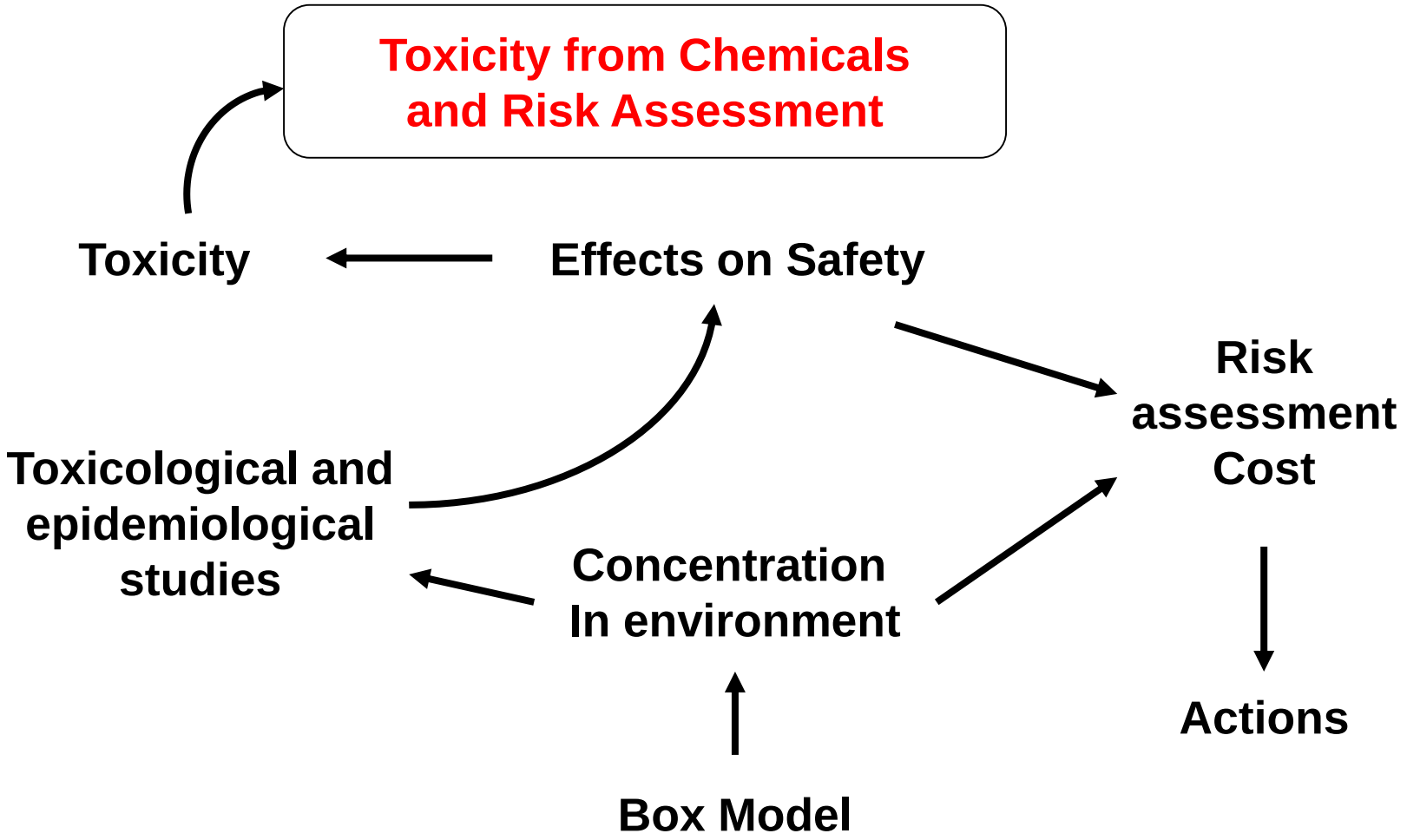
Non-essential elements are elements like mercury, tin, arsenic, cadmium, boron, lithium and nickel. At lower concentrations they may be acceptable, but eventually they will become toxic



Exposure to Exogenous Agents.



Toxicity and Risk.

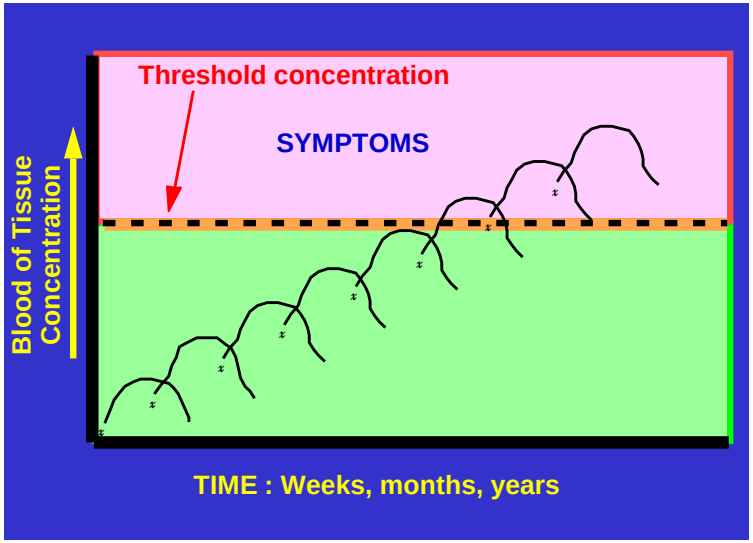


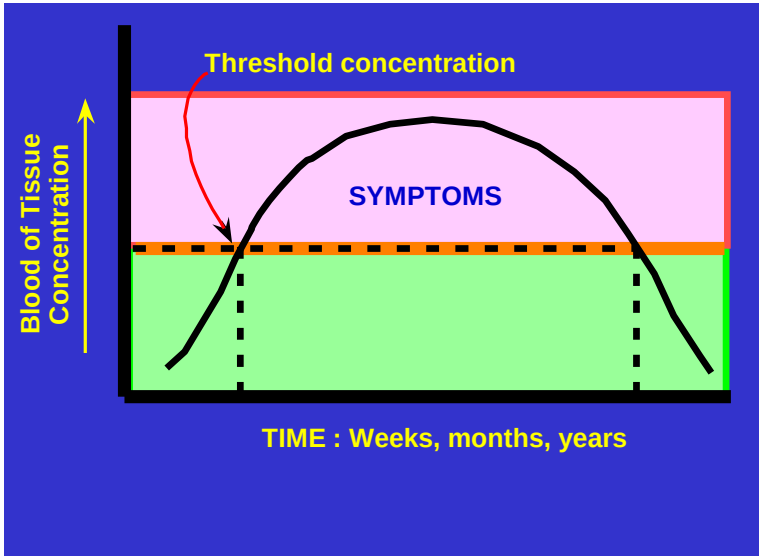
Toxicity Risk Assessment.

- Identify toxins
- Correlate entity of exposure to effects on health
  - Evaluation dose-response
  - Evaluation of exposure
- Evaluate the levels of acceptable risk
  - Quantify dead/diseases per million
- Estimate cost of controls
  - Economic costs of control vs. social costs or benefit.

Health Effects of Pollutants.

- *Acute Toxicity:* Short term exposure to high concentrations
- *Chronic Toxicity:* Long term exposure to low concentrations
  - Dose-response relationship
    - Threshold like
    - Non threshold like





Dose.

- Dose: combination of environmental concentration and exposure time

Effect

High concentration,
Low exposure time — *Acute*

Low concentration,
High exposure time — *Chronic*

Exposure Time.

It is NOT equal to the residence time in the box model!

Exposition Time ≡ time of contact with toxin

- Acute: short time exposure (normally high concentration)
- Chronic: long time exposure (normally low concentration). It is NOT equal to the residence time in the box model!

Dose-response relationship:

- Threshold type
- Non threshold type

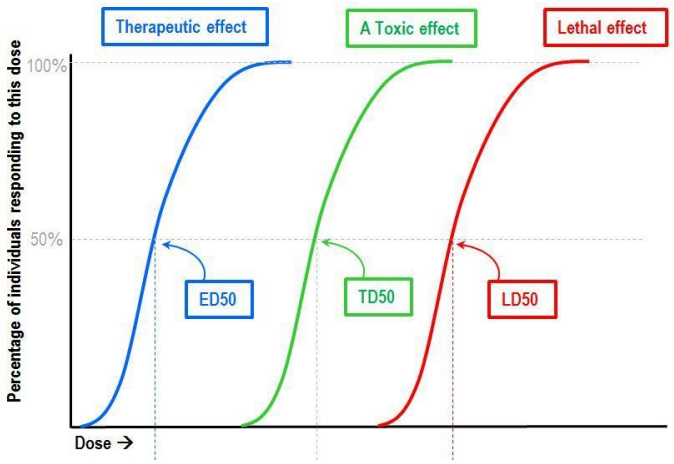
Toxicity Measure.

LD_{50} : the dose that produces 50% mortality in a test population.

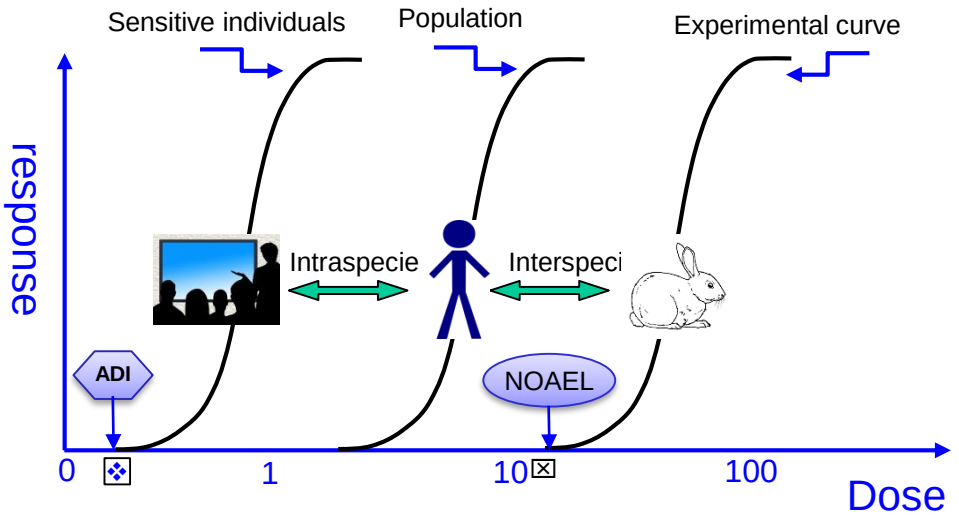
E.g. LD50 can be expressed in milligrams of substance per kilogram of test animal body weight (mg/kg).

NOAEL : No Observable Adverse Effect Level

DNEL : the Derived No Effect Level = $\frac{\text{NOAEL}}{\text{Assessment factors}}$

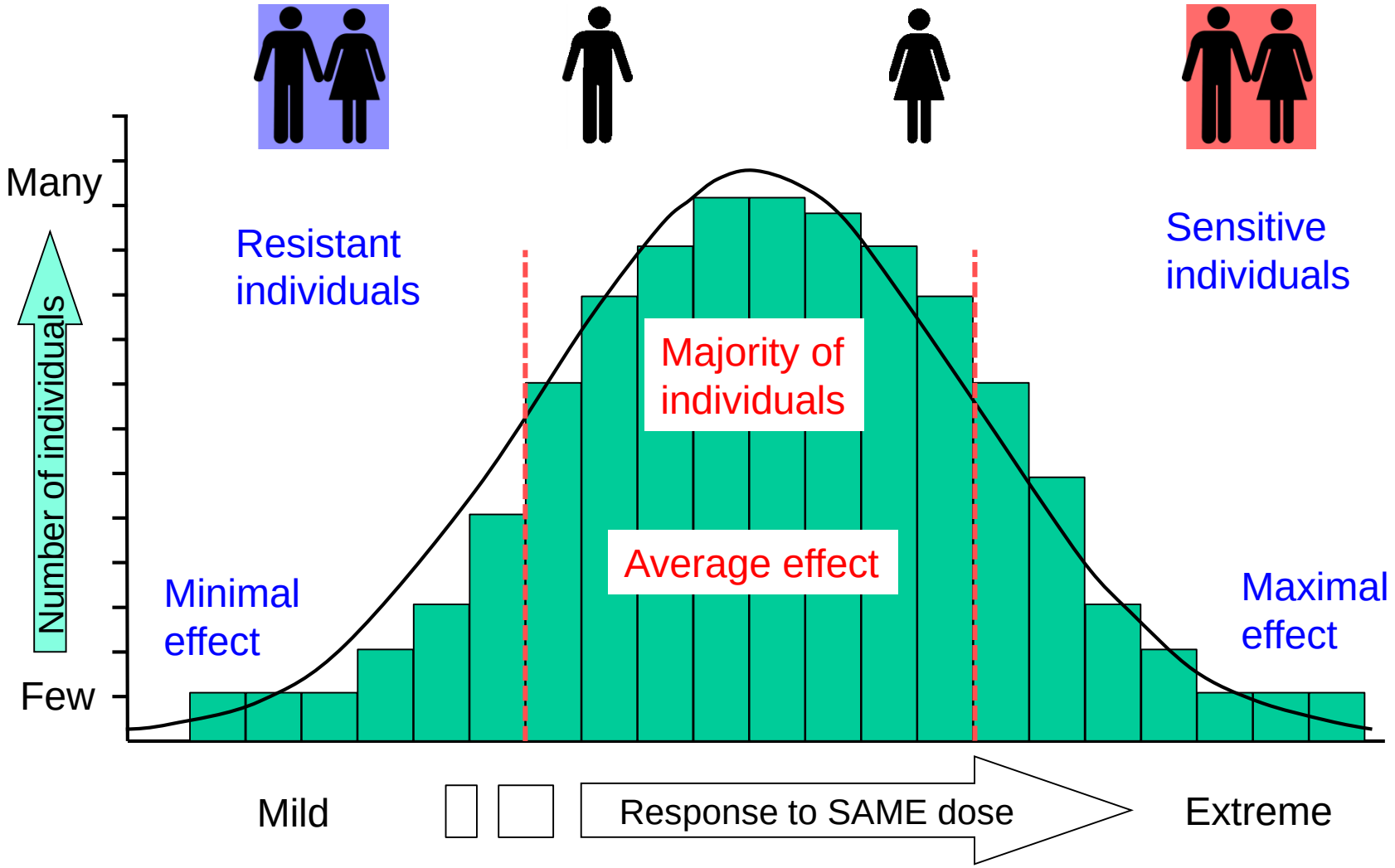


- Human assessment
- Environmental assessment

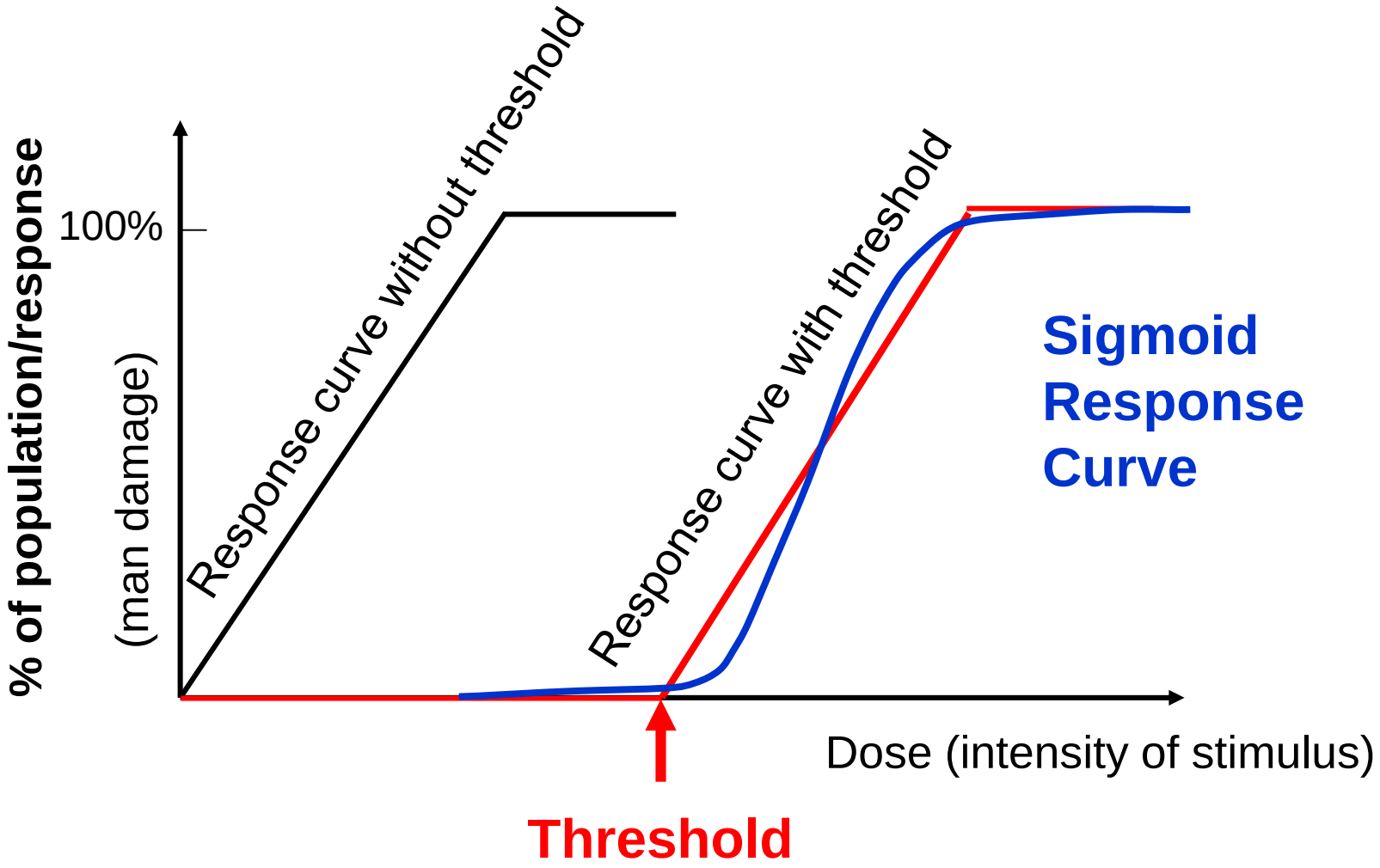


ADI, Acceptable Daily Intake

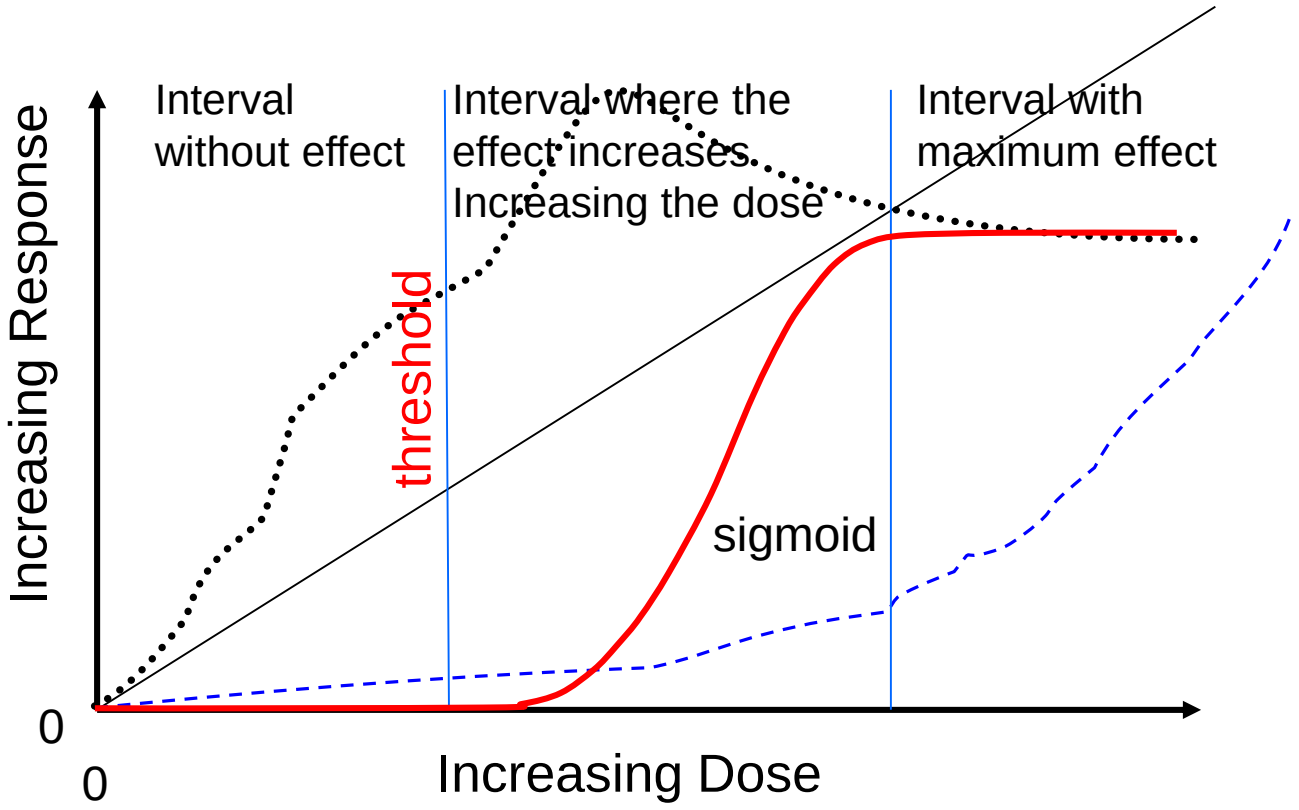
Population Dose-Response.



Response Curve with and without Threshold.

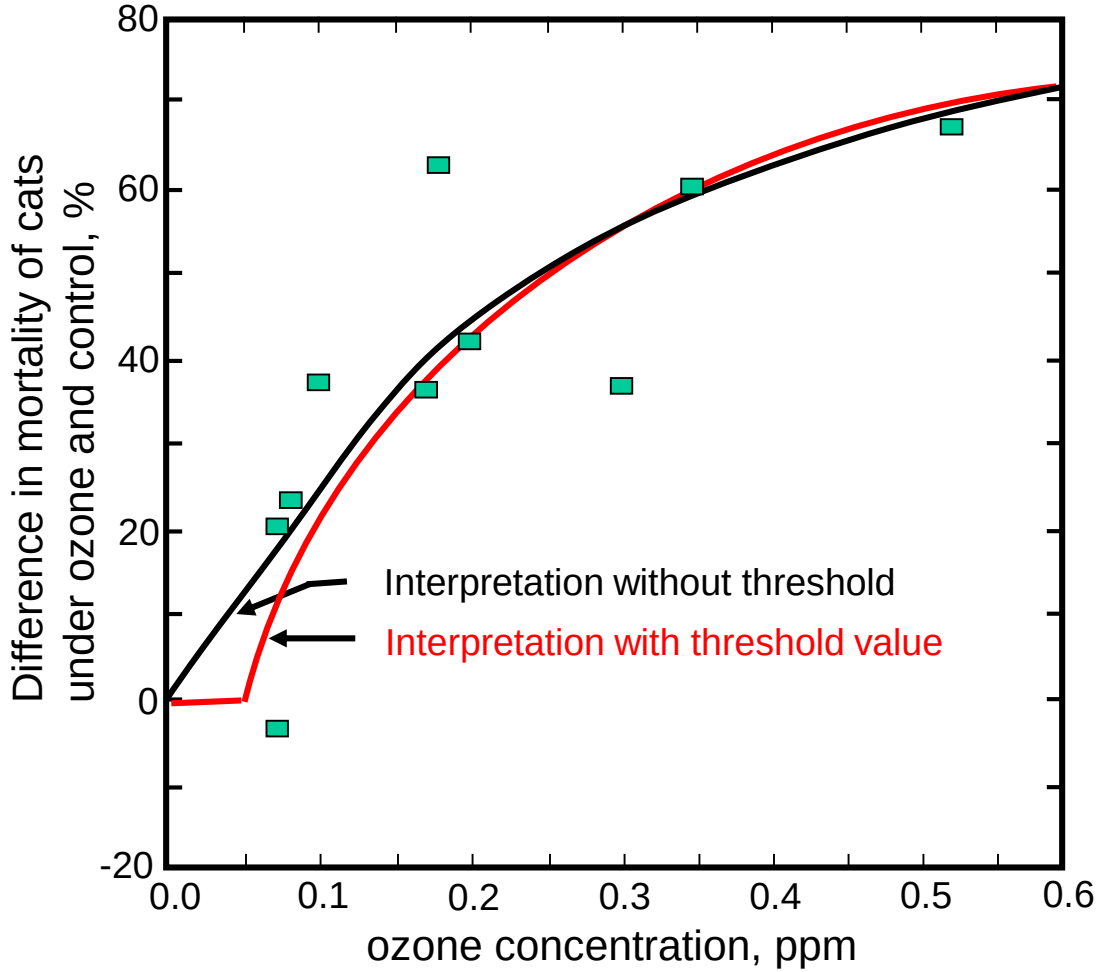


Dose-Response.



Casarett e Doull, Cap. 2, pp. 18-27
Timbrell Cap. 2 (pp. 7-25)

Exposure to Ozone (cat).



Some Acronyms.

- NEL, No Effects Level
- NOEL, No Observed Effects Level
- NOAEL, No Observed Adverse Effects Level
- ADI, Acceptable Daily Intake
  - AWI, AMI, etc.
- TDI, Tolerable Daily Intake
- MCL, Maximum Contaminant Level (SDWA)
- SF, UF, MF: safety, uncertainty, modifying factors

Pollutants and Effects.

- Relation between high concentrations of pollutants and respiratory problems, *morbidity*
- Relation between high concentrations of pollutants and daily dead, *mortality*
- Relation between high concentrations of pollutants and mean life, *cancer risk*
- Risk population

Concentration, Dose, Exposure.

- Dose = $C \times V$
  - C : Pollutant concentration, mass/volume normally a time function.
  - V : volume of inhaled air
    dV/dt, inhalation rate is function of the activity of the organism.
- Integrated Dose = $\int C\left(\frac{dV}{dt}\right)dt$
- Exposure = $\int C\,dt$

Assessment of Effects on Health

Correlation between exposure and specific response.

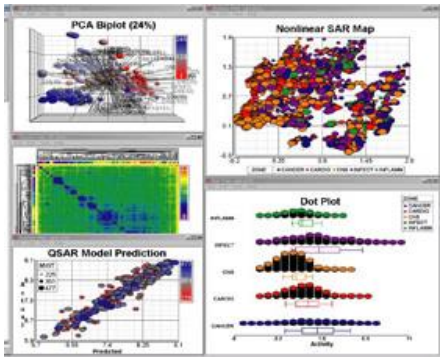
- Toxicological studies on animals
  - expose animals (cat, mouse) to pollutant of concern in controlled conditions and see the effects, then extrapolate the results to man
- Epidemiologic studies
  - analyze the effects on populations with similar characteristics unless exposition to pollutant of concern
- In vitro studies
  - verify on model system the relationship exposure/response
- In silico studies
  - predict the effects based on structural models

Toxicity Evaluation.

***In-vivo* models**

***In-vitro* models**

***In-silico* models**



“Toxicological” Studies.

Clinical/laboratory experiments:

- **Advantages**
  - Controlled change of exposure
  - Controlled environment of individuals
- **Disadvantages**
  - Small samples
  - Short testing periods
  - Not humanoid subjects
  - High costs

Epidemiology Basics.

Measures of disease occurrence

- *Cumulative Incidence*, CI, the proportion of healthy individuals who get the disease
  - CI = Number of individuals who get the disease during a period / number of individuals in the population

Disadvantages:

- Wide dimension of individuals sample
- Possible long term studies
- Absence of control on exposure and environment
- Unknown history, behavior of individuals
- Mobility of individuals

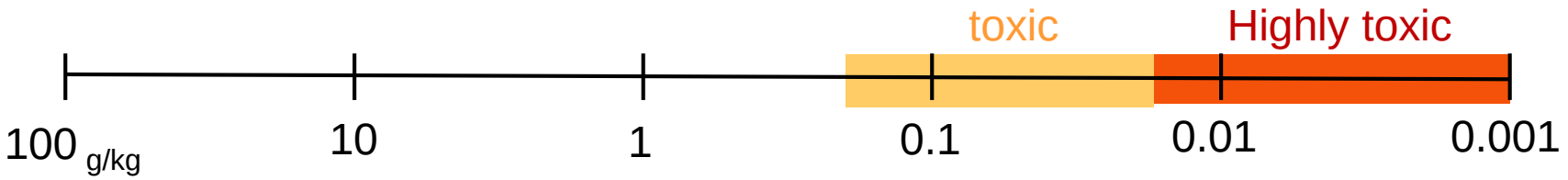
Toxic Effects.

When toxic compounds enter the body, they may have a range of effects.

- At low levels, there may be no effect. This "threshold" may be considered a "safe" level of exposure.
- Chemicals may have acute effects, the result of a high dose in a short period of time. Most animal experiments are simple acute toxicity studies.
- Chemical may also have chronic effects, caused by a low-level dose over a long period
  - Acute / chronic
  - Reversible / irreversible
  - Immediate / delayed
  - Idiosyncratic - hypersensitivity
  - Local / systemic
  - Target organs

Acute Mammalian Toxicity Criteria for Hazard Designation (LD_{50} (Oral, Rat), g/kg).

Acute Mammalian Toxicity	Very high	High	Moderate	Low
Oral LD_{50} ($mg \cdot kg^{-1}$)	≤ 50	> 50 - 300	> 300-2000	> 2000
Dermal LD_{50} ($mg \cdot kg^{-1}$)	≤ 200	> 200 - 1000	>1000-2000	> 2000
Inhalation LC_{50} (vapor/gas) ($mg \cdot L^{-1}$)	≤ 2	> 2 - 10	> 10 - 20	> 20
Inhalation LC_{50} (dust/mist/fume) ($mg \cdot L^{-1}$)	≤ 0.5	> 0.5 – 1.0	> 1.0 - 5	> 5



Acute mammalian toxicity criteria differentiate compounds based upon a common measure of short term exposure toxicity, the median lethal dose or concentration (LD_{50} or LC_{50}), through oral, dermal, and respiratory routes. These values were derived from the GHS criteria [GHS, Chapter 3.1: Acute Toxicity. 2009, United Nations].

EPA Threshold-Based Criteria for Toxicity.

Endpoint (LOAEL, NOAEL)	High	Moderate	Low	Very Low
Oral (mg/kg-bw/d)	<50	50-250	>250-1000	> 1000
Dermal (mg/kg-bw/d)	<100	100-500	>500-2000	> 2000
Inhalation (vapor, mg/L/d)	<1	1-2.5	>2.5-20	> 20
Inhalation (dust, mg/L/d)	<0.1	0.1-0.5	>0.5-5	> 5

- Chemicals with data
- Considers exposure route
- Examples of threshold-based criteria:
  - *Acute toxicity*
  - *Acute aquatic toxicity*
  - *Bioaccumulation*
  - *Repeated dose toxicity*
  - *Reproductive & developmental toxicity*

Health Hazard Endpoints.[1]

Acute Toxicity
- Oral (LD_{50}), Dermal (LD_{50}), Inhalation (LC_{50})

- Skin Irritation or Corrosion
- Eye irritation or Corrosion
  - Serious Eye Damage
- Sensitization
  - Dermal and Respiratory
- Genotoxicity/Mutagenicity
  - Germ Cell Mutagenicity
- Carcinogenicity

- Reproductive Toxicity
- Specific Target Organ Toxicity - Single Exposure
- Specific Target Organ Toxicity - Repeated Exposure
- Aspiration Hazard

[1]See : Appendix A to 2012 OSHA HazCom Standard (1910.1200) and GHS (5th edition; 2013) for more detailed information on each endpoint

Human Toxicity by Ingestion.

$$INGTP_i = \frac{C_{i,w} / RfD_i}{C_{tot,w} / RfD_{tot}} \quad \text{or} \quad INGTP_i = \frac{C_{i,w} / LD_{50}}{C_{tot,w} / LD_{50,tot}}$$

$$I_{ING} = \sum_i INGTP_i \cdot m_i$$

Compd.	RfD, mg/kg/d	LD_{50}, (rat) mg/kg	P_{vap} at 25˚C, mbar	RfC, mg/m^3	LC_{50}, g/m^3 4h (rat)	INGTP
toluene	0.08	636	38	5	49	1.0
CH_2Cl_2	0.06				76	0.64
hexane		28,700	200	0.2		7.2

RfD and RfC data available on the IRIS website. http://cfpub.epa.gov/ncea/iris/index.cfm?fuseaction=iris.showSubstanceList
LD_{50} and LC_{50} data available on NTP website. http://ntp.niehs.nih.gov:8080/index.html?col=010stat
(search for the compound, select it, then select Toxicity Effects on the left)

Basic Assumptions.

(a) The response is causally related to the compound administered

(b) The response is a function of the concentration at the site of action

(c) The concentration at the site of action is related to the external dose

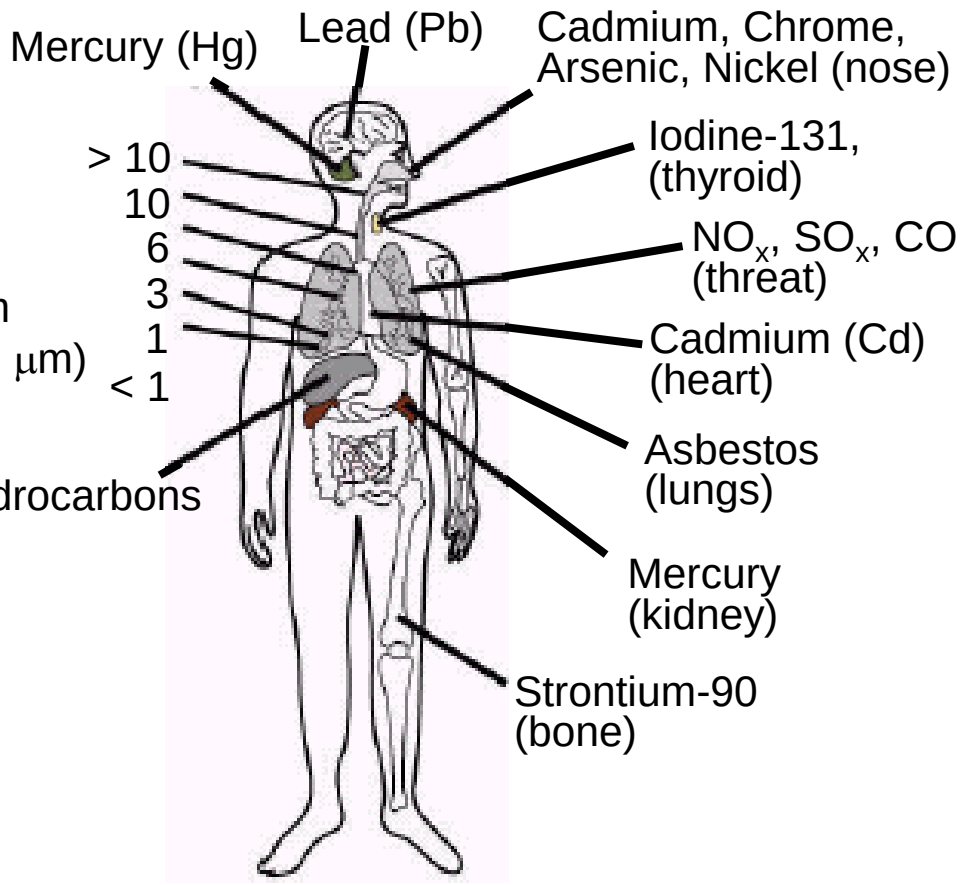
(d) An interaction at the site of action initiates a proportional response

(e) The crucial interaction involves reversible formation of a receptor-toxin complex

Effects on Health from Air Pollution Exposure.

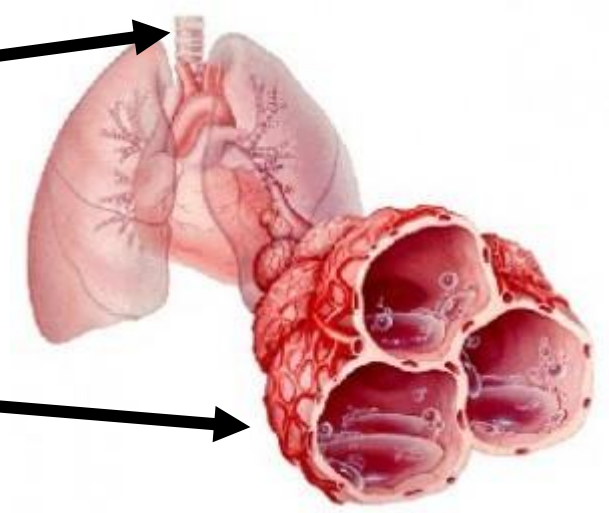
- **Respiratory System**
- **Circulatory System**
- **Central nervous System, Organs**
- **Carcinogenic Aerosol**
- **Ionizing Radiations**

Aerosol particles introduced in the respiratory system (particle diameter, μm)



Respiratory Diseases.

- Bronchitis
  - Inflammation of bronchial ducts
- Pulmonary Emphysema
  - Destruction of alveolar sacs
- Silicosis
  - Internal covering of lungs with particles



Alveolar Sacs

Effects on Respiratory System.

- Smell
  - i.e.: Hydrogen sulfide
- Mucous irritation, inflammation
  - i.e.: Ozone, Asbestos
- Mutagen agents
  - i.e.: Radioactive particles, Nanomaterials

Effects on Circulatory System.

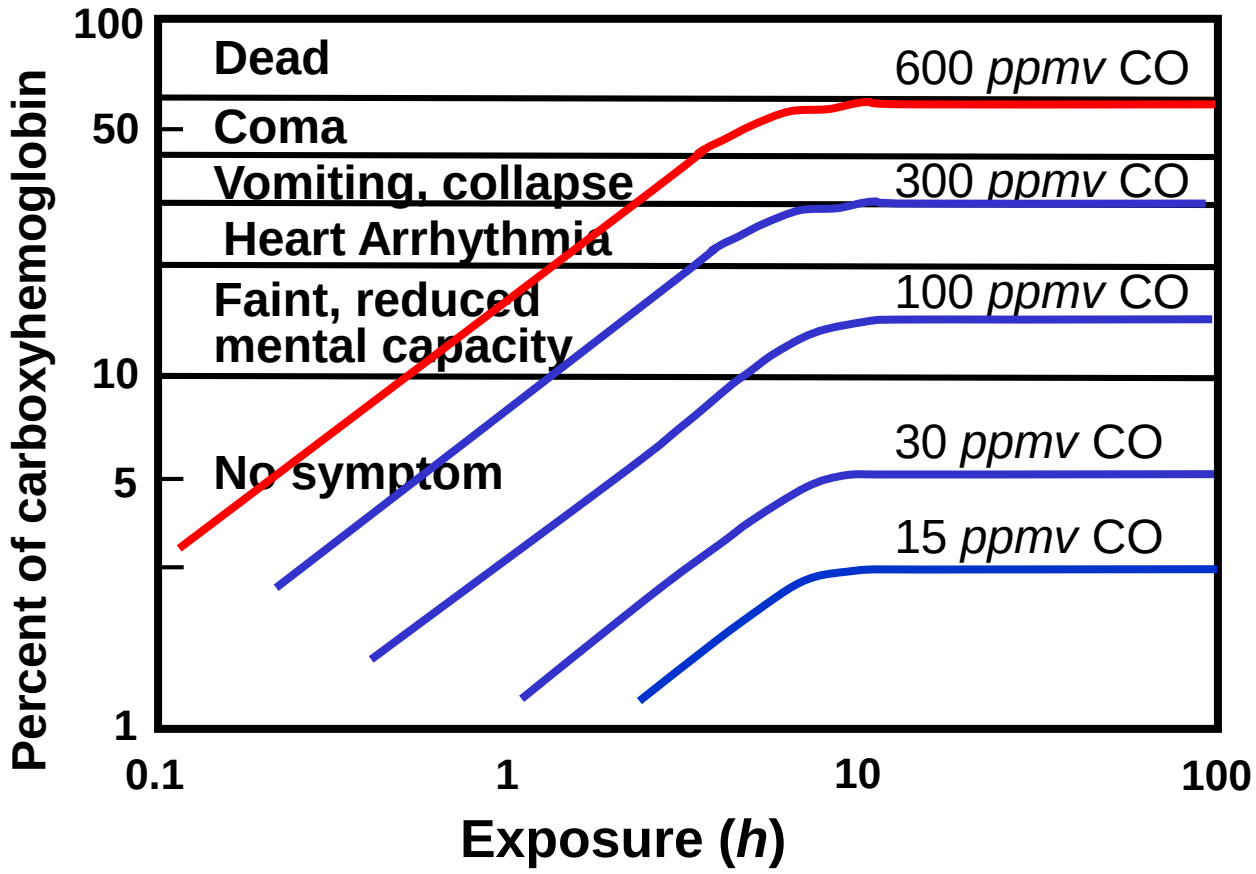
- Blood Poisoning by CO
  - Oxygen uptake is limited

    CO + hemoglobin ⇄ CO·Hb (carboxyhemoglobin)

    - CO fits in the site of Hb normally used to transport oxygen to body tissues
    - The exposure to CO is cumulative and reversible

- Lead Poisoning
  - Red blood cells transport Lead along the body

Effects of CO Exposition.



Organs, Central Nervous System.

Heavy Metals:

- Lead
  — cerebral damages, anemia, bones, immune system
- Mercury
  — CNS attack, immune system, cell membranes
- Cadmium
  — kidney, heart, CNS centers of odor, cancer promoter
- Arsenic
  — cell metabolism
- “Aluminum”
  — stomach, bones, cell metabolism

Carcinogens.

Materials inhaled or ingested which induce cellular mutations

- Heavy metals
  - Arsenic, Chrome, Cadmium
- Volatile Organic Solvents
- Polycyclic aromatic compounds
- Aromatic amines
- Dioxins
- …….

Carcinogens (2).

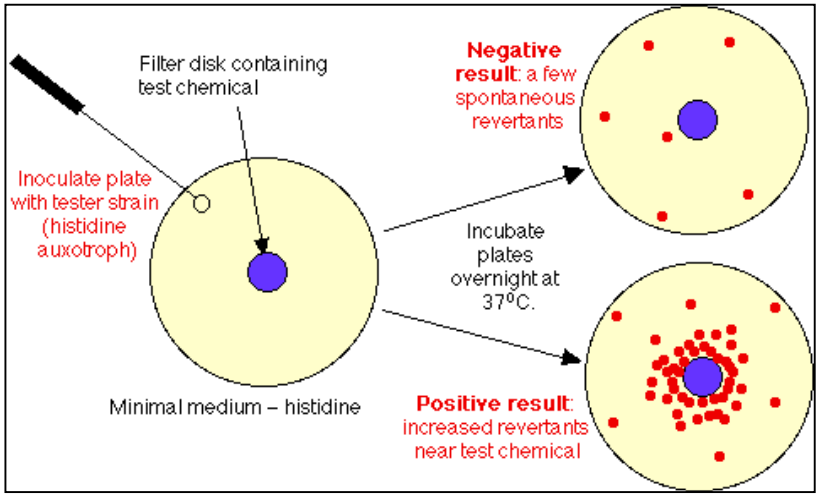
Carcinogenicity demands further deliberation.

- Many chemicals have the potential to cause cancer
- Only a relatively few are known human carcinogens
  - http://ehp.niehs.nih.gov/roc/toc10.html
    - "reasonably expected" to cause human cancer = 174 agents
    - "known" to cause human cancer = 49 agents
  - http://monographs.iarc.fr/monoeval/crthgr01.html
    - 75 agents known to cause human cancer
- High-dose animal studies identify potential carcinogens, but the results may not apply to humans, especially at low doses.
- The carcinogenic effects of naturally occurring chemicals is often overlooked.

Carcinogens (3).

Dr. Bruce Ames, author of the Ames mutagenicity test, suggest we take a more reasonable approach to carcinogens.

- HERP index (Human Equivalent Rodent Potential) ranks carcinogens in our environment according to the dose that caused cancer in rodents.



http://pubs.acs.org/hotartcl/chas/96/julaug/ames/ames.html

EPA Carcinogenicity Criteria for Hazard Designation.

Carcinogenicity	Very high	High	Moderate	Low
Carcinogenicity	Known or presumed human carcinogen (equivalent to GHS Category 1A and 1B)	Suspected human carcinogen (equivalent to GHS Category 2)	Limited or marginal evidence of carcinogenicity in animal (and inadequate evidence in humans)	Negative studies or robust mechanism based SAR

These criteria mirror the classification approach used by the International Agency for Research on Cancer (IARC),* and incorporate the Globally Harmonized System (GHS) classification scheme.** Authoritative lists can supplement these criteria.

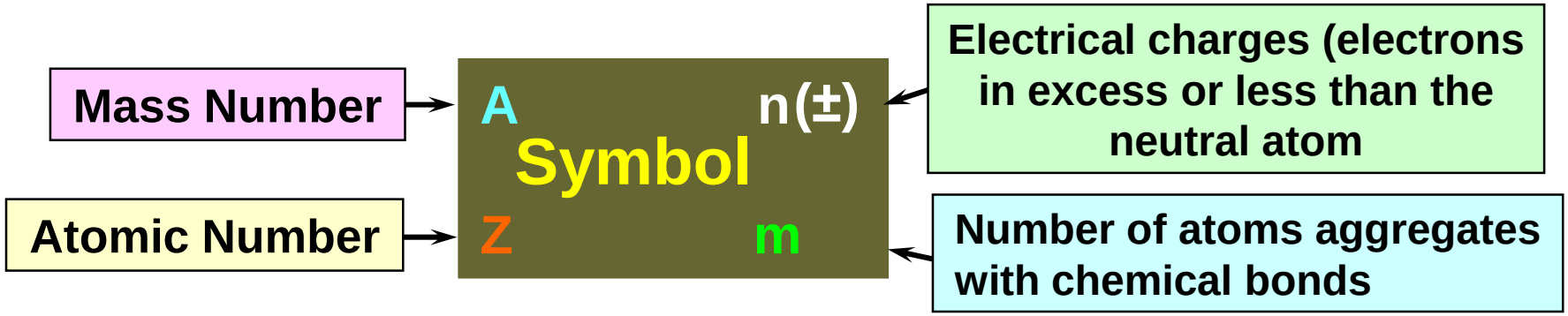
*[http://monographs.iarc.fr/ENG/Preamble/currentb6evalrationale0706.php.
**GHS, Chapter 3.6: Carcinogenicity. 2009, United Nations.

Other Toxicity Criteria for Hazard Designations.

- Mutagenicity/Genotoxicity
- Reproductive and Developmental Toxicity
- Reproductive and Developmental Toxicity (including Developmental Neurotoxicity)
- Neurotoxicity
- Repeated Dose Toxicity
- Respiratory and Skin Sensitization
- Eye and Skin Irritation / Corrosivity
- Endocrine Activity

Radiation Toxicity.

- **Radioisotopes: an unstable form of an atom (with propensity to "decay" spontaneously)**
- **Nuclear symbol:**



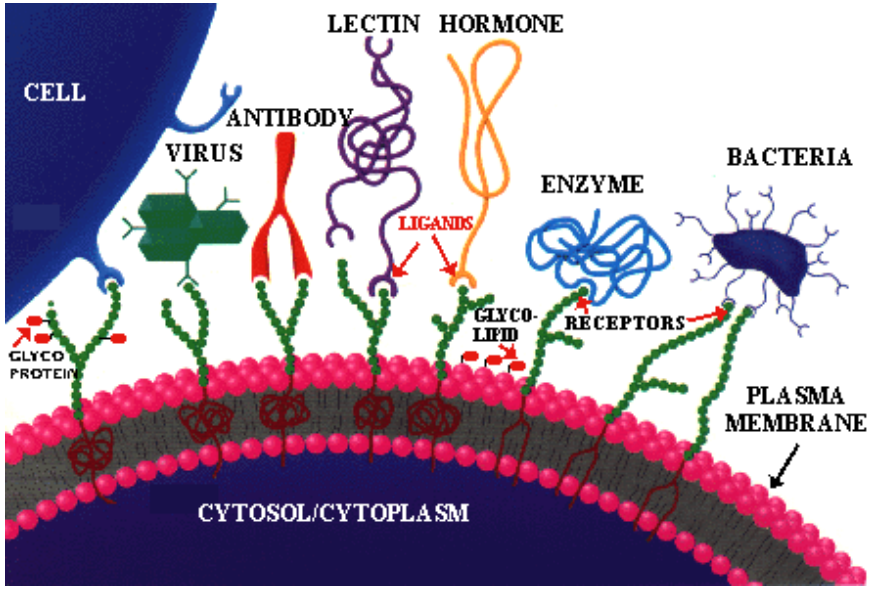
Es. : ${}^{1}_{1}H$; ${}^{12}_{6}C^{3+}$; ${}^{127}_{53}I^{-}_{3}$

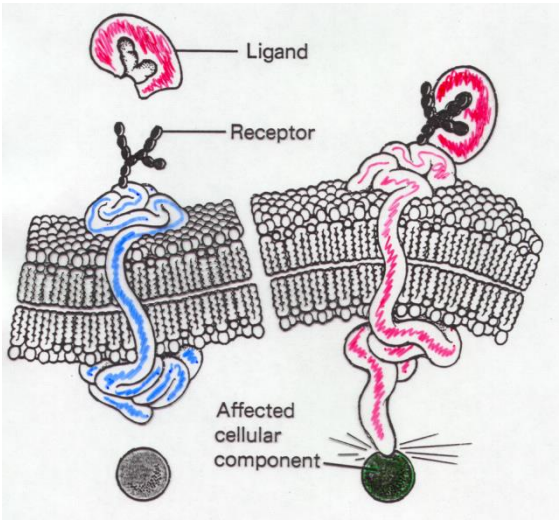
- **Alfa and Beta particles, Gamma rays: high-energy products of radioactive decay**
- **Half-life: time to reduce to an half the mass of radioisotope by decay**

Receptors : Molecular Targets of Chemical Compounds.

Receptors

- Ion Channel Receptors
- Carrier Proteins
- G-Protein Coupled Receptors
- Tyrosine-Kinase Receptors
- Ah Receptors
- Steroid Hormone Receptors





Usually proteins:

- Located on outside of cell wall, or inside cell
- Interact with ligands

Receptors Important in Pharmacology.

- **Agonists and antagonists of neurotransmitters:**
  - *cholinergic receptors*: acetylcholine;
  - *nicotinic receptors*: skeletal muscle, autonomic ganglia;
  - *muscarinic receptors*: smooth muscle, heart, exocrine glands
- **Adrenergic receptors** : dopamine, endorphins, encephalins, histamine
- **Hormone receptors** : Insulin, cortisone (glucocorticoids), estrogen, progesterone, testosterone, prostaglandins
- **Drug receptors**: Benzodiazepines

Receptors Important in Toxicology.

- Ah (TCDD) receptor
- Steroid receptors

Reversible formation of a receptor-toxin complex

$$R + T \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R\text{-}T$$

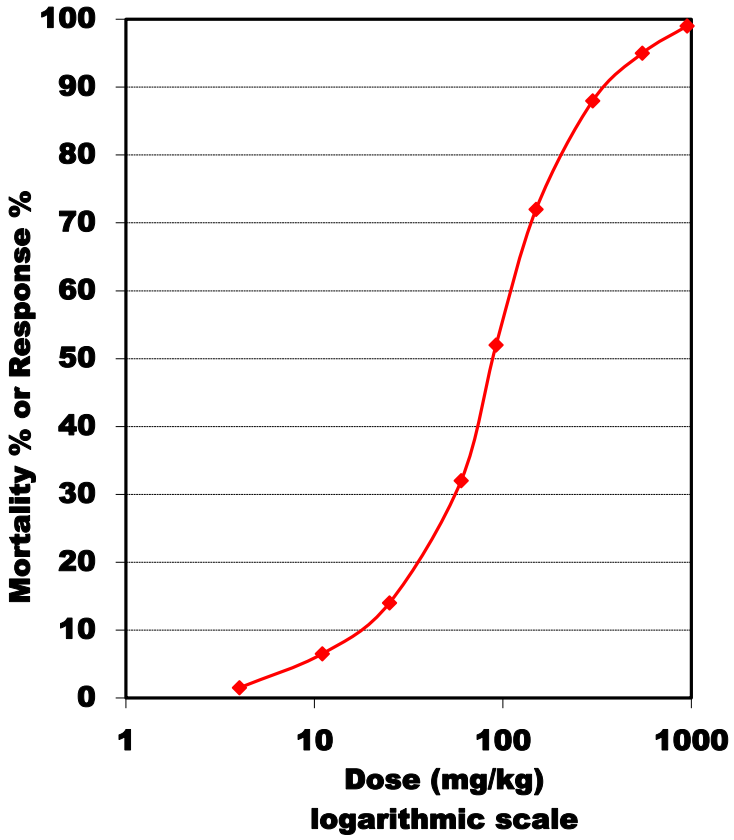
R = receptor

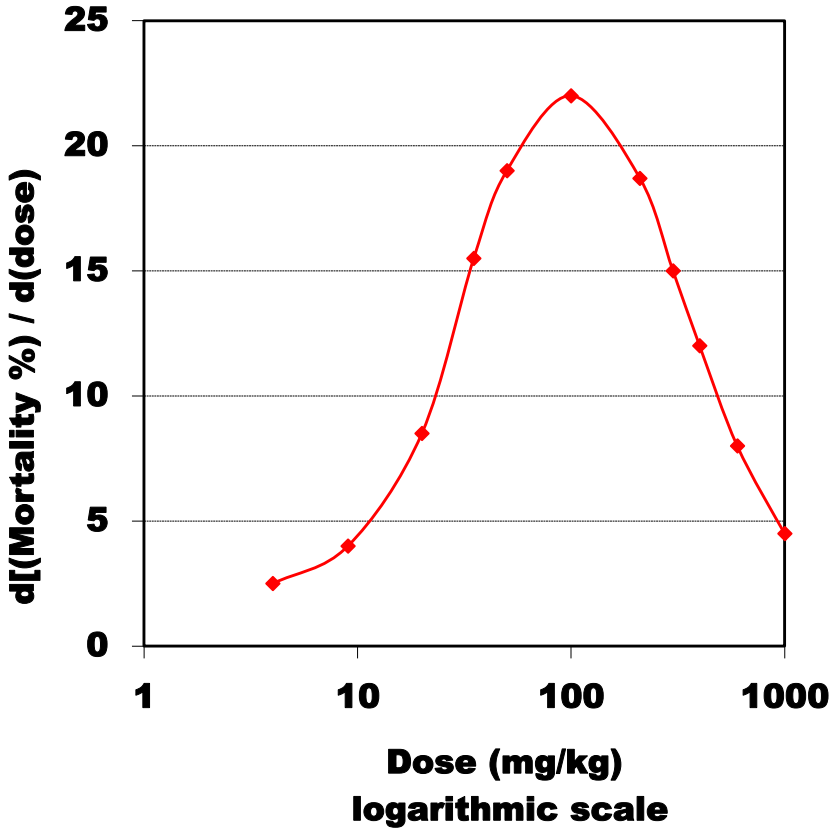
T = toxic compound

R-T = receptor-compound complex

k_1 and k_{-1} are rate constants for formation and dissociation (respectively) of the complex R-T

Dose-Response Relationship





LD_{50} LC_{50} ED_{50}

Common Dose-response Models.

- **Normal:**

$$y_{i,j} = \frac{1}{\sqrt{2\pi\sigma}} e^{\frac{(x-\mu)^2}{\sigma^2}}$$

- **Logistic:**

$$y_{i,j} = \frac{1}{\left(1+e^{\beta_1(dose_i-\beta_0)}\right)}$$

- **Modified Logistic:**
  (e.g. Seefeldt et al. 1995)

$$y_{i,j} = C + \frac{D-C}{\left(1+e^{\left(-B(dose_i-I)\right)}\right)}$$

- **Gompertz:**

$$y_{i,j} = \beta_0 e^{-e^{-\beta_1(dose)}}$$

- **Exponential:**

$$\begin{cases} y_{i,j} = \beta_0 e^{-\beta_1(dose)} \\ y_{i,j} = \beta_0 \left[1-e^{-\beta_1(dose)}\right] \end{cases}$$

Acute Toxicity Studies.

Single dose - rat, mouse (5/sex/dose), dog, monkey (1/sex/dose)

- 14 day observation
- In-life observations (body wt., food consumption, clinical observations)
- Necropsy

Repeated dose studies - rat, mouse (5-10/sex/dose), dog, monkey (2/sex/dose)

- In-life observations
- Necropsy
- Histopathology
- Clinical pathology (optional)

Acute LD_{50} Values vs. Toxicity.

Chemical	LD_{50} (*mg/kg*)	Toxicity
Sodium Chloride	4000	Slightly toxic
DDT	100	Moderately toxic
Picrotoxin Strychnine Nicotine	5 2 1	Highly toxic
Dioxin Botulinum Toxin	0.001 0.00001	Super toxic

Some Acute Oral LD_{50} Values.

Category	Dose (*mg/kg* body weight)	Species	Chemical
Practically nontoxic	15 000		
Slightly toxic	10 000	Mouse	Ethanol
	5 000		
Moderately toxic	4 900	Rat	Glyphosate
	750	Rat	Atropine
	500		
Highly toxic	250	Rat	Carbaryl
	50		
Extremely toxic	13	Rat	Parathion
	5		
Supertoxic	3	Rat	Warfarin
	0.4	Duck	Aflatoxin B_1

Species Differences in the Acute Toxicity of Dioxin.*

Species	LD_{50} (*μg/kg* body weight)
Guinea-pig	0.5-2
Rat	20 -100
Mouse	114-284
Rabbit	10-115
Chicken	25-50
Rhesus monkey	< 70
Dog	>30-100
Hamster	5051

*Dioxin: 2,3,7,8-tetrachlorobenzodioxin: TCDD

Other Factors.

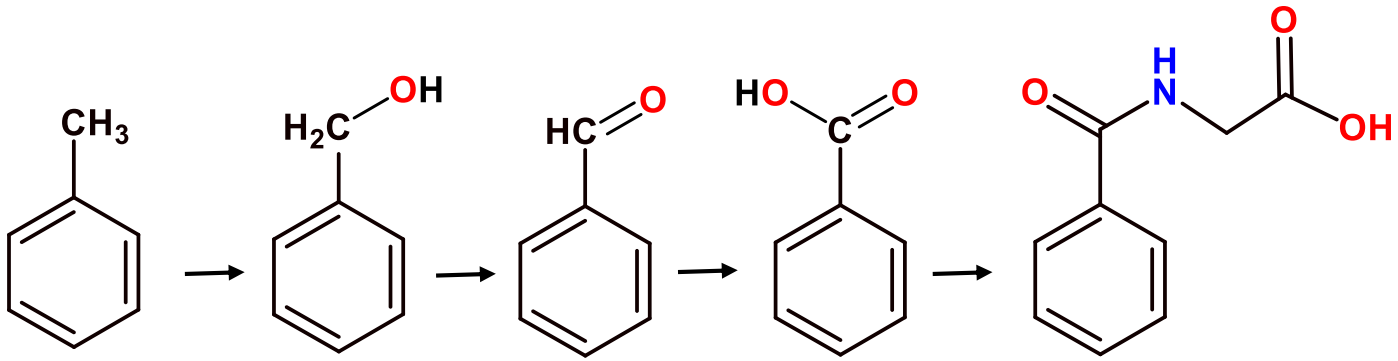
- Interval of exposure
- Interaction may be not reversible
- Repair or removal of complex R-T may be important
- Response may be multi-step, binding of T to R may not be the rate-limiting step
- Assumes normal (Gaussian) distribution
- Uniform population - no significant inter-individual differences in response
- Dichotomous (quantal) response, e.g. tumor frequency.

Effect Factors (EF) and Hazard.

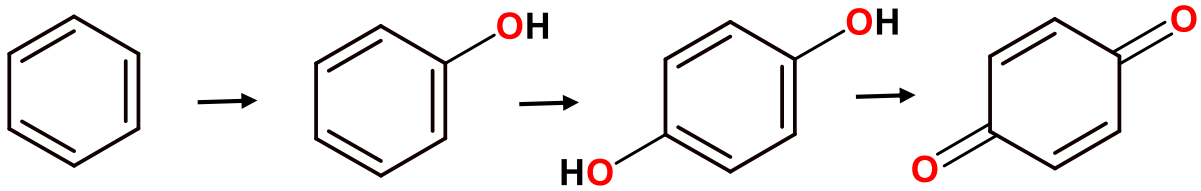
Risk factors after TRGS 440 *(GER 2001)*

Risk phrases	*Hazards*	*effect factor*
R45, R46, M1, M2, K1, K2	carcinogenic or mutagenic	50,000
R26, R27, R28 or LGW < 0,1 mg/m^3	highly toxic	1,000
R32, R60, R61, RE1, RE2, RF1, RF2	potential reproduction toxicity or teratogenic, formation of highly toxic gases in contact with acids	1,000
R35, R48/23, R48/24, R48/25, R42, R43	highly corrosive, high chronic toxicity, potentially sensitizing	500
R23, R24, R25, R29, R31, R34, R41, H	toxic, generation of toxic gases in contact with water or acids, cauterizing for eyes, skin absorption	100
R33, R40, K3, M3, pH < 2 or pH > 11,5	risk of cumulative effects, potentially irreversible damages, suspected mutagenic or carcinogenic effects	100
Not tested sufficiently	= No LGW, no risk phrases	100
R48/20, R48/21, R48/22, R62, R63, RE3,	chronically harmful, suspected reproduction toxicity or teratogenic effects	50
R20, R21, R22	harmful	10
R36, R37, R38, R65, R67	irritating, narcotic	5
other risk phrases or LGW > 100 mg/m^3		1

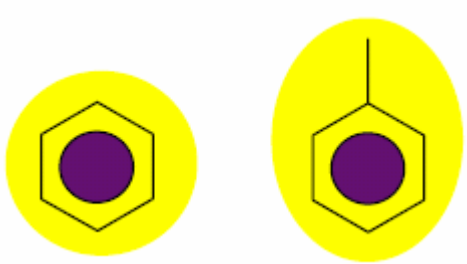
Toxicity Trends in Similar Molecules.



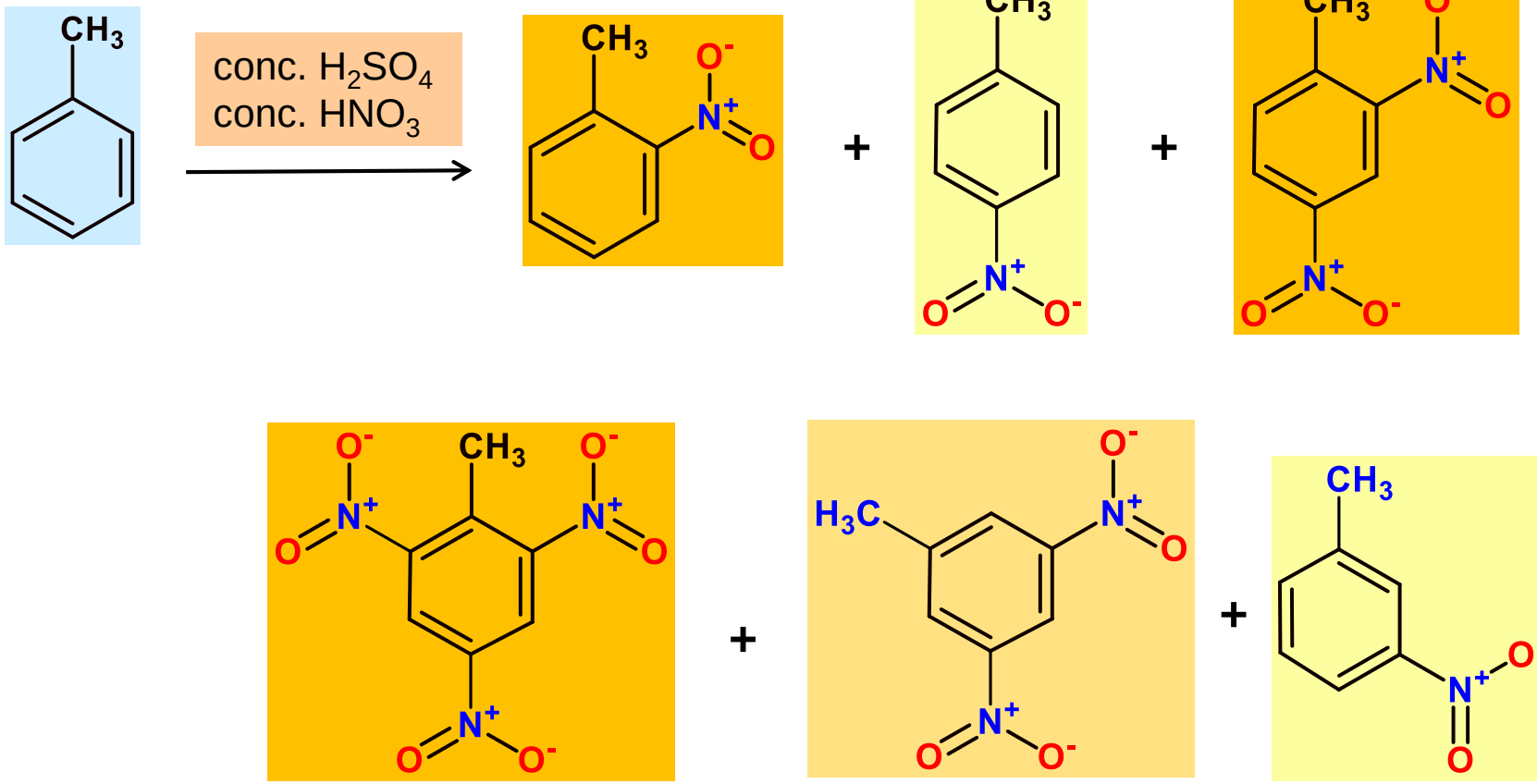
DL_{50} (mouse, oral) 54.3 mmol/kg 133 mmol/kg 12.3 mmol/kg 13.9 mmol/kg



DL_{50} (mouse, oral) 43.5 mmol/kg 29.8 mmol/kg 2.74 mmol/kg 1.20 mmol/kg



Toxicity Trends in Reaction Products.



- Effect factor > 1000
- Effect factor > 100 – 1000
- Effect factor > 10 – 100
- Effect factor 0 - 10

Sub-Acute Toxicity.

- 28 week study (3 doses and control)
- Species – rat (10/sex/dose), dog or monkey (2/sex/dose)
- In-life observations
- Clinical pathology
- Necropsy
- Histopathology

Sub-Chronic Toxicity.

- 13 week study +/- 4 wk recovery (3 doses and control)
- Species - rat (10/sex/dose), dog or monkey (2/sex/dose)
- In-life observations (+/- ophthalmology)
- Clinical pathology
- Necropsy
- Histopathology

Chronic Toxicity.

- 1 year study +/- 4-13 wk recovery (3 doses and control)
- Species - rat (10-15/sex/dose), dog or monkey (2-3 /sex/dose)
- In-life observations including ophthalmology
- Necropsy
- Histopathology

Endocrine Disrupting Compounds (ED).

Any exogenous agent that causes adverse health effects in an intact organism, or its progeny, consequent to changes in **endocrine function**.

Specifically:

Any exogenous chemical that interferes with the production, release, transport, binding, action, or elimination of natural hormones responsible for the maintenance of homeostasis and regulation of development.

The WHO/IPCS definition is characterised by three elements: a chemical can be defined an ED;

1. if it shows an adverse effect in an intact organism (generally from in vivo animal testing);
2. if it is able to interfere with the endocrine/hormonal system (mechanistic data show the substance can act via an endocrine/hormonal mode of action); and
3. if a plausible link can be established between the endocrine mode of action and the adverse effect observed for the substance.

The EU List of Potential Endocrine Disruptors.

- Category 1: Substances for which endocrine activity have been documented in at least one study of a living organism. These substances are given the highest priority for further studies. Category 1 contains 194 substances.
- Category 2: Substances without sufficient evidence of endocrine activity, but with evidence of biological activity relating to endocrine disruption.
- Category 3a and 3b: Substances for which there are no indications of endocrine-disrupting properties or which cannot be evaluated due to a lack of data.

Evaluations are based on various endocrine modalities: the androgen (A), the oestrogen (E), the thyroid (T) and the (S) steroidogenesis modalities (often referred to as EATS modalities) (OECD 2012*; EFSA 2013**)

*http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2012)22&doclanguage=en

**EFSA Journal 2013;11(3):31323. doi: 10.2903/j.efsa.2013.3132

Endocrine Disruptors.

At Least 4 Modes of Action

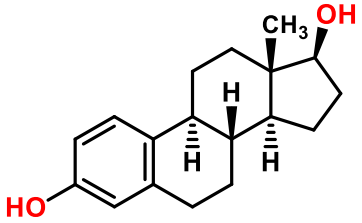
- Serving as steroid receptor ligands.
- Modifying steroid hormone-metabolizing enzymes.
- Perturbing hypothalamic pituitary release of trophic hormones.
- Miscellaneous or unknown.

Chemicals: Wide Variety

- Pesticides
- Herbicides
- Fungicides
- Plasticizers
- Surfactants
- Organometals
- Halogenated PAHs
- Phytoestrogens

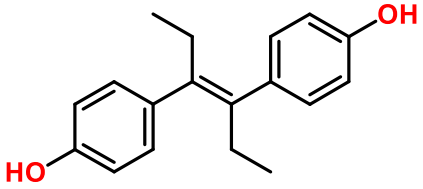
Prototypical Exo-estrogens: Note the Diverse Chemical Structures.

Endogenous ligand

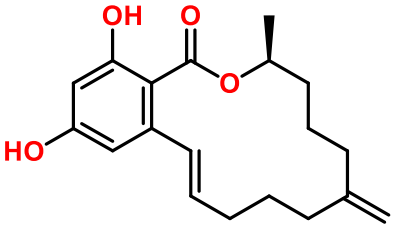


17β-Estradiol

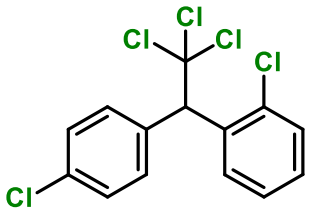
Synthetic estrogen



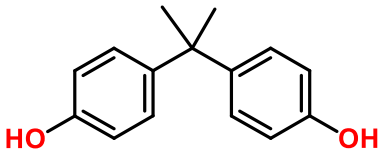
Diethylstilbesterol



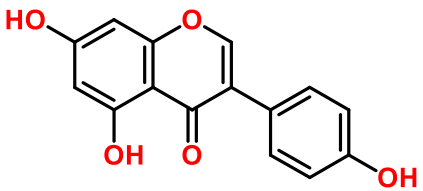
Zearalenone



o.p'-DDT



Bisphenol-A



Genistein

Specific Examples of Endocrine Disruption.

Natural Products	Environmental pollution	Industrial products	Pharmaceutical	Complex mixtures
Genistein	DDT	Bisphenol-A	Etinyl estradiol	Effluents
Naringenin	Kepone	Nonionic surfactants	Diethylstilbestrol	Sediment extracts
Coumestrol	PCBs/HO-PCBs	Phthalate esters	Gestodene	Air particulate matter
Zearalenone	PAHs and dioxins	Endosulfan	Norgestrel	Tissue extracts

*DDT = dichlorodiphenyltrichloroethane, PCBs = polychlorinated biphenyls, HO-PCBs = hydroxylated PCBs

Environ. Toxicol. Chem. 17, 1998, 5.

Tributyltin

Causes imposex and intersex in gastropod mollusks.

Neogastropods have separate sexes but it was observed that many female dogwhelk from some areas of the UK had a penis-like structure behind the right tentacle. This was also seen later in other gastropods in the eastern US. These gastropods also had a vas deferens (sperm duct) and a convoluted gonoduct. The term “imposex” was coined to describe the superimposition of male characters onto females. It was demonstrated that levels of imposex were elevated close to marinas, a feature attributed to the presence of anti-fouling paints.

Carcinogens and Carcinogenicity Studies.

- 2 years (3 doses and control)
- Species - rats and mice (50/sex/dose)
- In-life observations
- Clinical pathology (rats, optional)
- Necropsy
- Histopathology

Evaluation Issues

- Survival
- Body weight
- Variability of endpoints
- Pathology Working Group

- MTD
- Statistics vs. biology
- Dose-response
- Mechanistic Factors

Human Health Protection.

- Health and Safety at work
  - Short-term exposure limit (STEL)
  - Time-Weighted Average (TWA)
- Specific quality goals
- Monitoring and Bio-monitoring

Occupational Toxicology

Multidisciplinary field:

- Routes of exposure & uptake
- P450 metabolism & characterization of toxic metabolites
- Phase II metabolism & identification of urinary metabolites
- Characterization of DNA adducts
- Identification of target tissue

Example:
Metal Limits in EU Toy Directive (2009/48/EC)

Element	Requirements (mg/kg)		
	In dry brittle, powder like or pliable toy material	In liquid or sticky toy material	In scraped off toy material
Aluminum	5625.00	1406.00	70000
Antimony	45.00	11.30	560
Arsenic	3.80	0.90	47
Barium	4500.00	1125.00	56000
Boron	1200.00	300.00	15000
Cadmium	1.30	0.30	17
Chromium(III)	37.50	9.40	460
Chromium(VI)	0.02	0.005	0.2
Cobalt	10.50	2.60	130
Copper	622.50	156.00	7700
Lead	13.50	3.40	160
Manganese	1200.00	300.00	15000
Mercury	7.50	1.90	94
Nickel	75.00	18.80	930
Selenium	37.50	9.40	460
Strontium	4500.00	1125.00	56000
Tin (Organic Tin 0.9, 0.2, 12)	15000.00	2750.00	180000
Zinc	3750.00	938.00	46000

Occupational Exposure Limits.

- TLV, Threshold Limit Value
- TWA, Time-Weighted Average (8h/day, 40h/ week)
  - Used for contaminants with longer-term or chronic
    - Lead, carcinogens, etc.
  - "Integrated" exposure over the shift
    - Single sample TWA
    - Multiple samples can be combined

$$TWA = \frac{C_1T_1 + C_2T_2 + \ldots C_nT_n}{T_1 + T_2 + \ldots T_n}$$

- TLV-C, Ceiling level
- STEL, Short-term exposure limit
- IDLH, Dangerous to Life and Health

Example of TWA, STEL, and IDLH Value for Some Chemicals (in ppm)

Substance	TLV TWA	TLV STEL	IDLH
Acetaldehyde	-	25C	2,000
Acetic Acid	10	15	50
Acetone	500	750	2,500
Acrolein	-	0.1C	2
Acrylonitrile	2	-	85
Ammonia	25	35	300
Arsine	0.05	-	3
Benzene	0,5	2,5	500
Boron Trifluoride	-	1C	25
Bromine	0.1	0,2	3
1,3 – Butadiene	2	-	2000
Butane	1000	-	-
n-Butyl Acrylate	2	-	-
n-Butyl Alcohol	20	-	1400
Butyl Mercaptan	0.5	-	500
Carbon Dioxide	5000	30000	40000
Carbon Disulfide	10	-	500
Carbon Monoxide	25	-	200
Carbon Tetrachloride	5.1	1	10

Data from 2005 Threshold Limit Values & Biological Exposure Indices, copyright 2005 by the American Conference of Governmental Industrial Hygienists (ACGIH). IDLH values extracted from the NIOSH Pocket Guide to Chemical Hazards, 2004 published by the National Institute for Occupational Safety and Health (NIOSH). “C” indicates Ceiling Limit.

TWA Example.

Assume 4 exposure samples

1. 1 hour, 10 *ppm*
2. 3 hours, 20 *ppm*
3. 3 hours, 30 *ppm*
4. 1 hour, 100 *ppm*

$$TWA = \frac{(1\times 10)+(3\times 20)+(3\times 30)+(1\times 100)}{(1+3+3+1)} = 32\ ppm$$

(straight average = 40 *ppm*)

Interactions.

- **Additivity** Chemicals A, B, C…N are all toxic

  Potency of mixture = Sum of potencies of constituents

  $Effect_{total} = Potency_A \times Dose_A + Potency_B \times Dose_B + Potency_C \times Dose_C + \ldots.. + Potency_N \times Dose_N$

- **Synergism** Potency of the whole is greater than the sum of the potencies of the individual constituents

  $Effect_{total} >> Potency_A \times Dose_A + Potency_B \times Dose_B \ldots + \ldots + Potency_N \times Dose_N$

- **Potentiation** One constituent is toxic, the other is not. Potency of the combination is greater than the potency of the active constituent

  $Effect_{total} >> Potency_A \times Dose_A$ where $Potency_B = 0$

- **Antagonism** Potency of the whole is less than the sum of the potencies of the individual components

  $Effect_{total} << Potency_A \times Dose_A + Potency_B \times Dose_B \ldots + \ldots + Potency_N \times Dose_N$

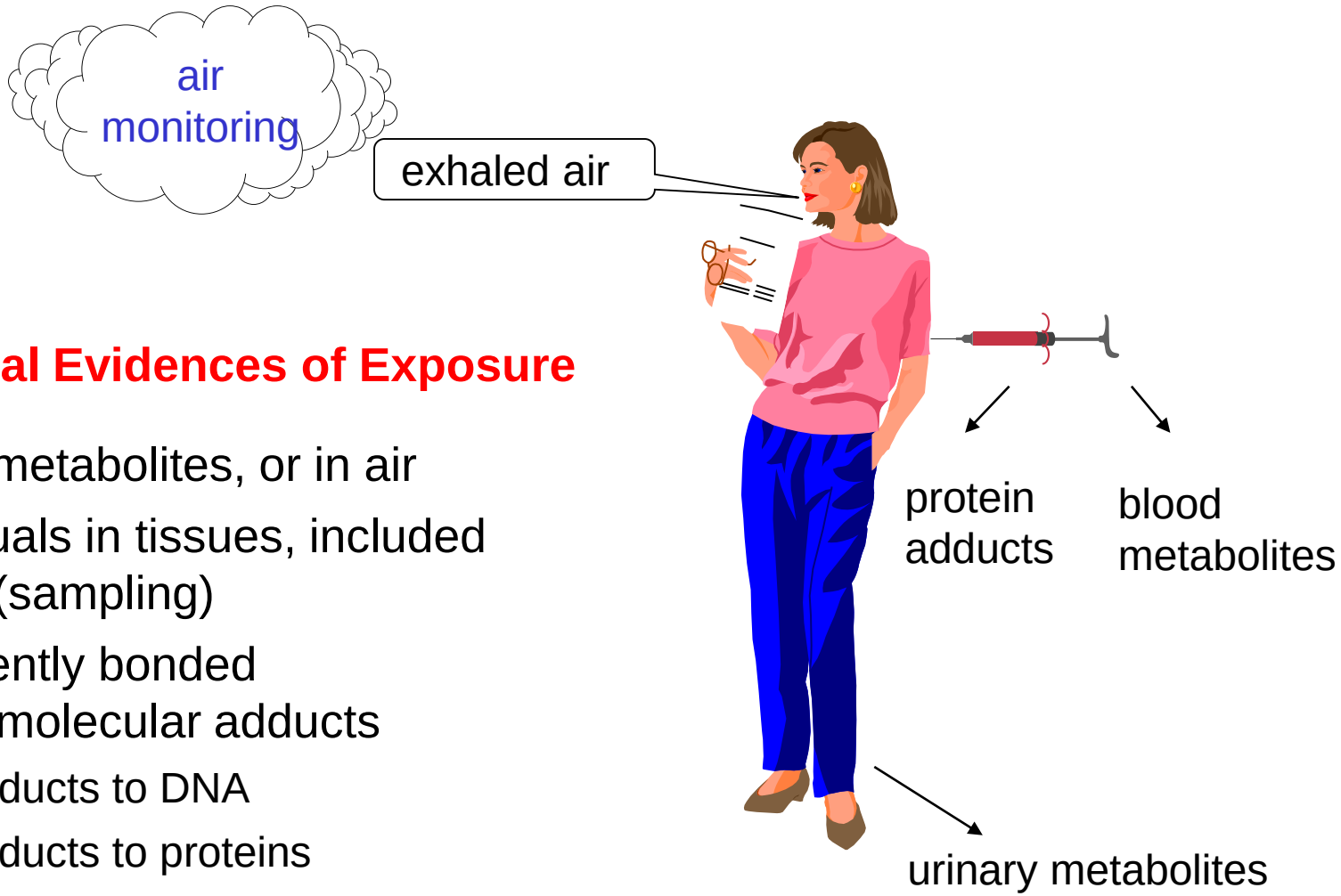
Routes of Exposure.

- Airborne (dusts, fibers, particulate matter, aerosols, gases)
- Waterborne (solution, suspension, emulsion)
- Foodborne (solids, liquids)

Portals of Entry

	Experimental equivalents
➢ Skin (percutaneous)	Skin-painting
➢ Respiratory tract (inhalation)	Intra-tracheal instillation
➢ Gastrointestinal tract (ingestion)	Oral gavage
➢ Trans placental	Administration to dam
➢ Injection	Injection

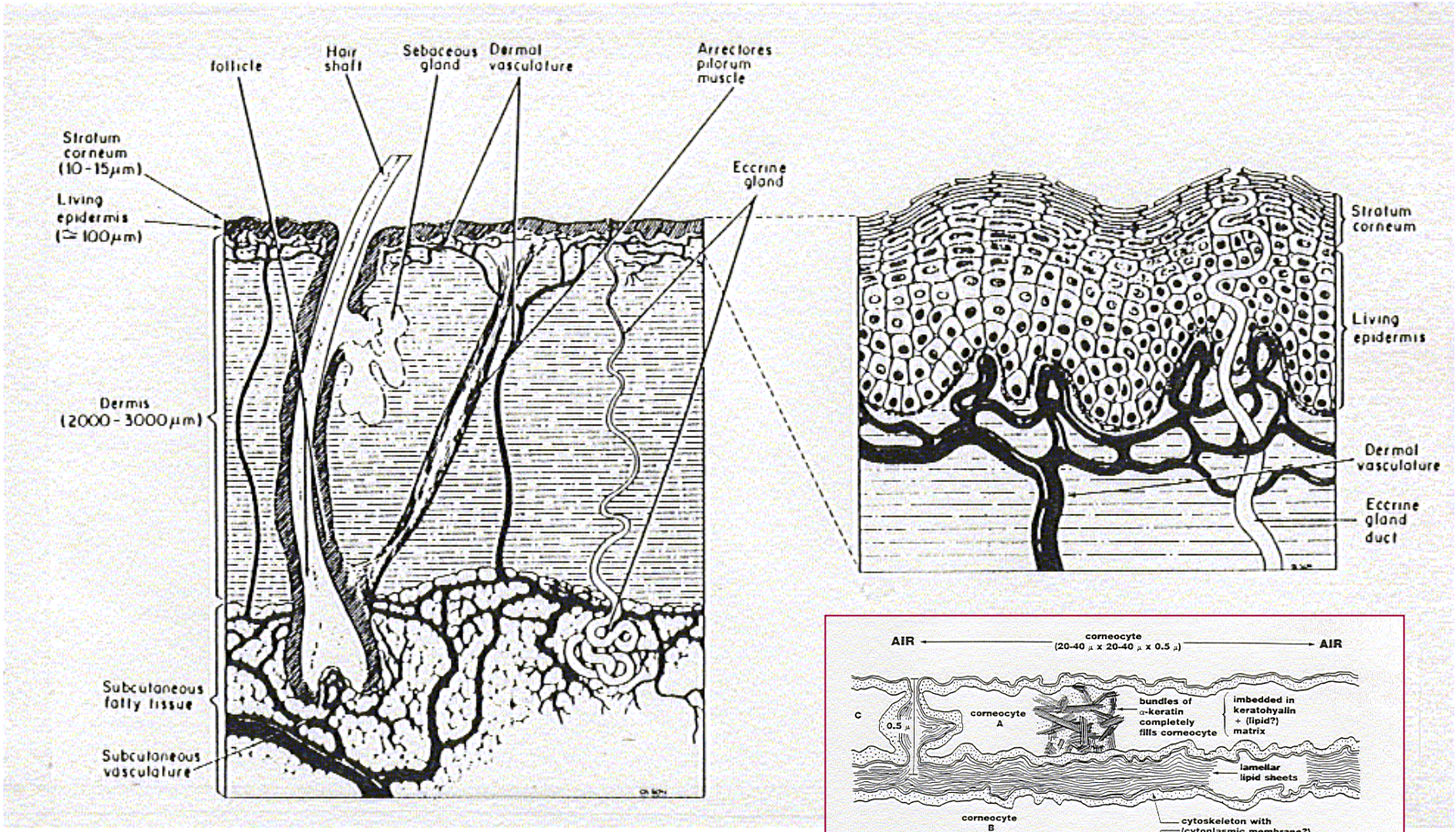
Exposure Assessment.



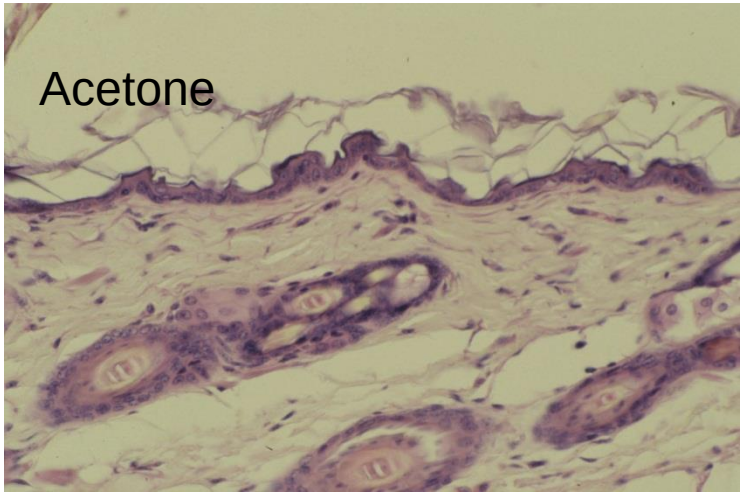
Chemical Evidences of Exposure

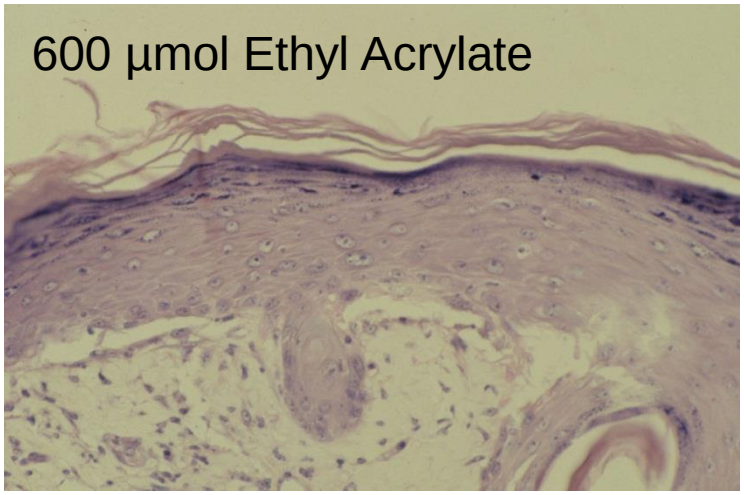
- Urine metabolites, or in air
- Residuals in tissues, included blood (sampling)
- Covalently bonded macromolecular adducts
  - Adducts to DNA
  - Adducts to proteins
- Antibody

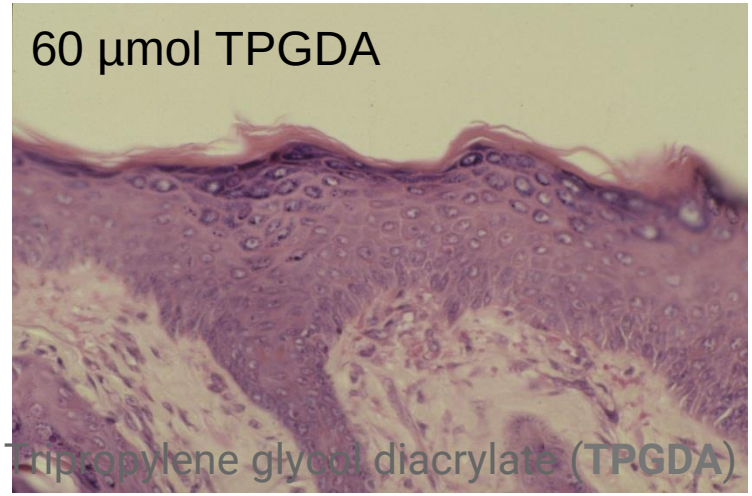
The Major Structures of the Skin.

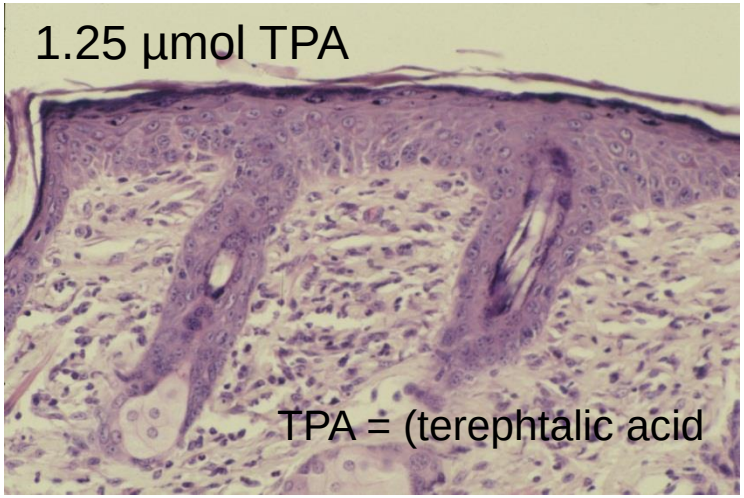


Effect on Skin of Contact with Solvents.









Exposition Phases.

Absorption

Distribution

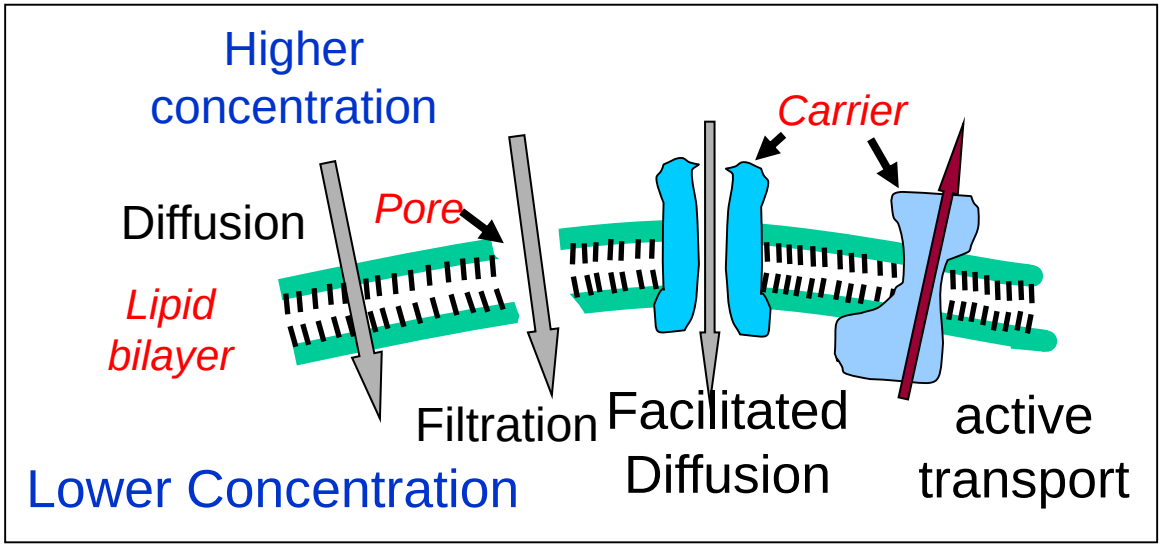
Metabolism

Elimination

Mechanisms of Uptake.

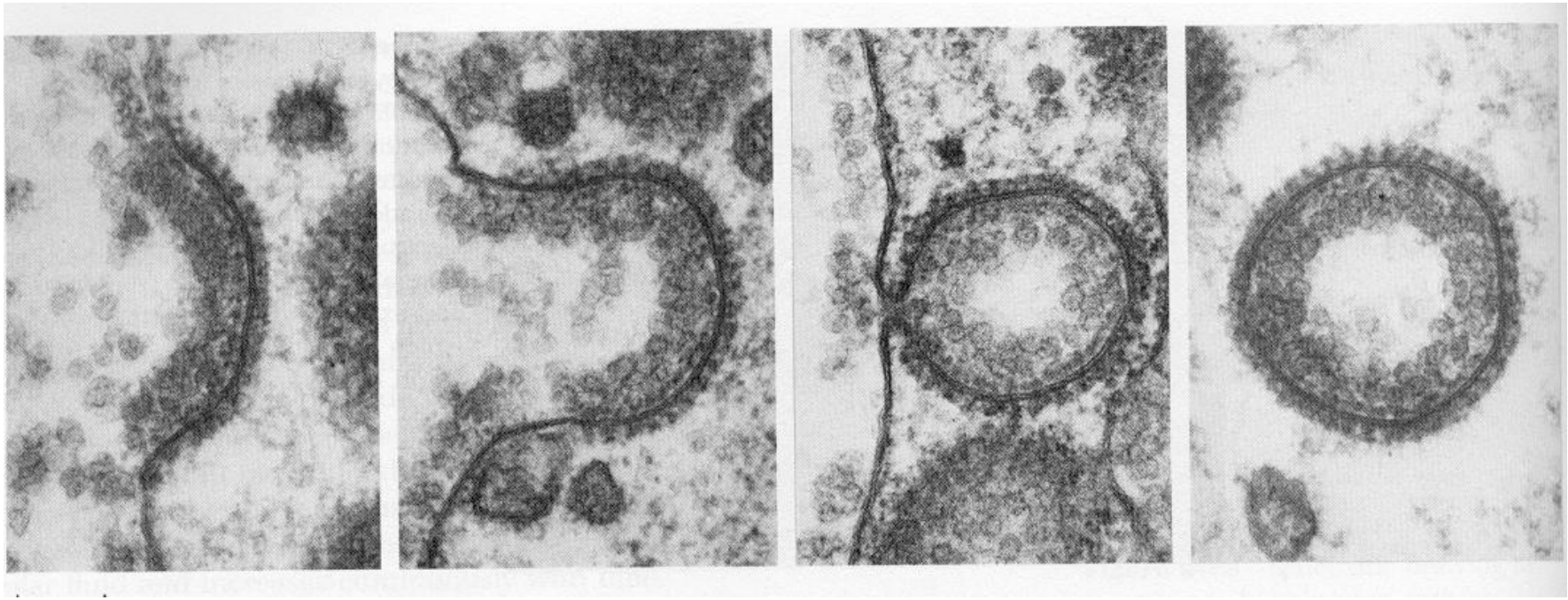
- Passive diffusion
- Filtration
- Carrier-mediated transport
  - Facilitated diffusion
  - Active transport
- Engulphment
  - Pinocytosis
  - Phagocytosis

Chemical uptake mechanism



Engulphment

The cellular mechanism that involves the internalization of extracellular components (solid and liquids).



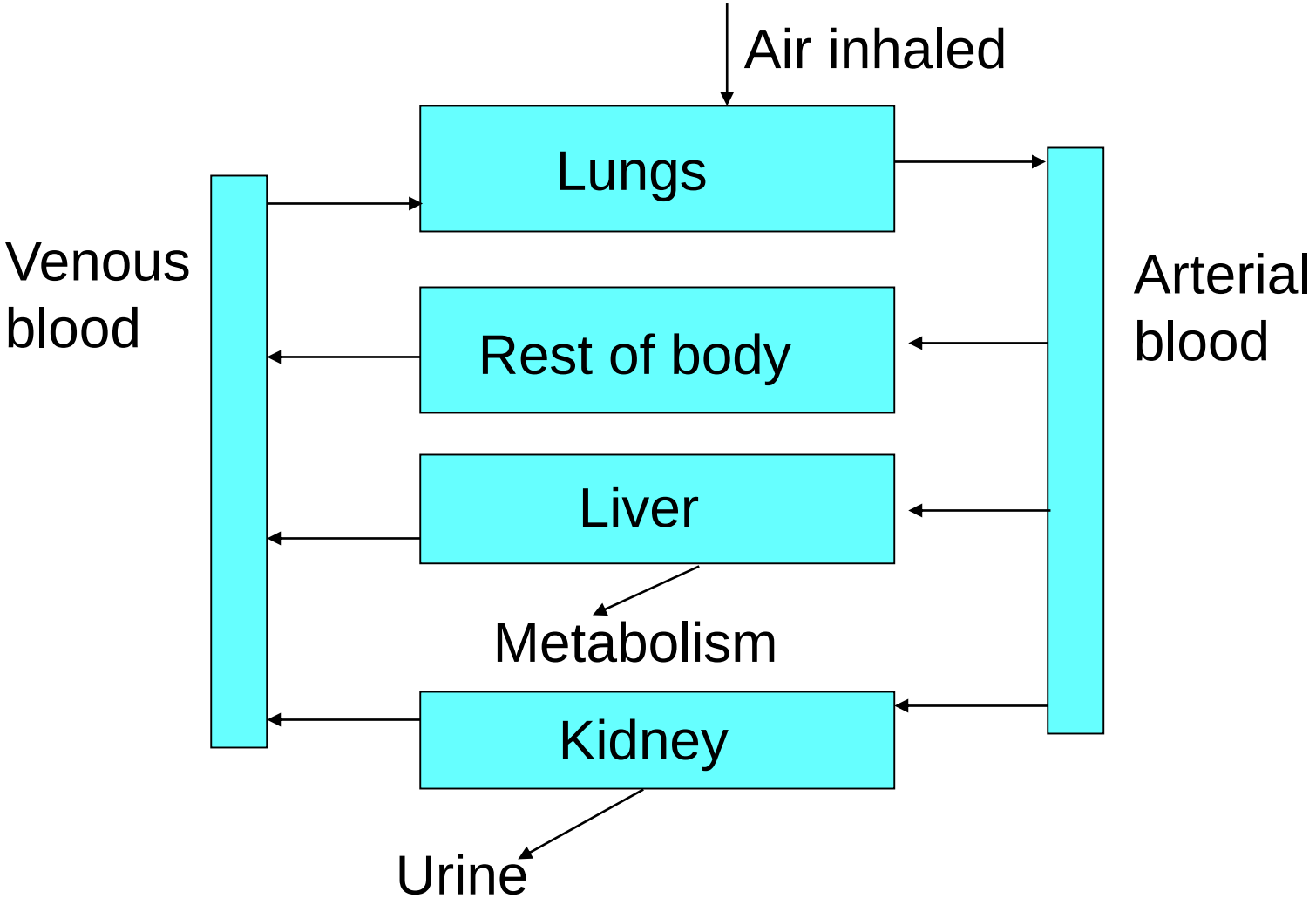
Factors Influencing Route and Uptake Rate.

- Properties of the chemical
  - Size and shape
  - Similarity to “endogenous” molecules
  - Solubility
    - Hydrophilicity / hydrophobicity
    - Lipophilicity / lipophobicity
    - Partition coefficient: K_{ow}
      - Log10 of [octanol]/[water]
  - Charge
    - Ionization state

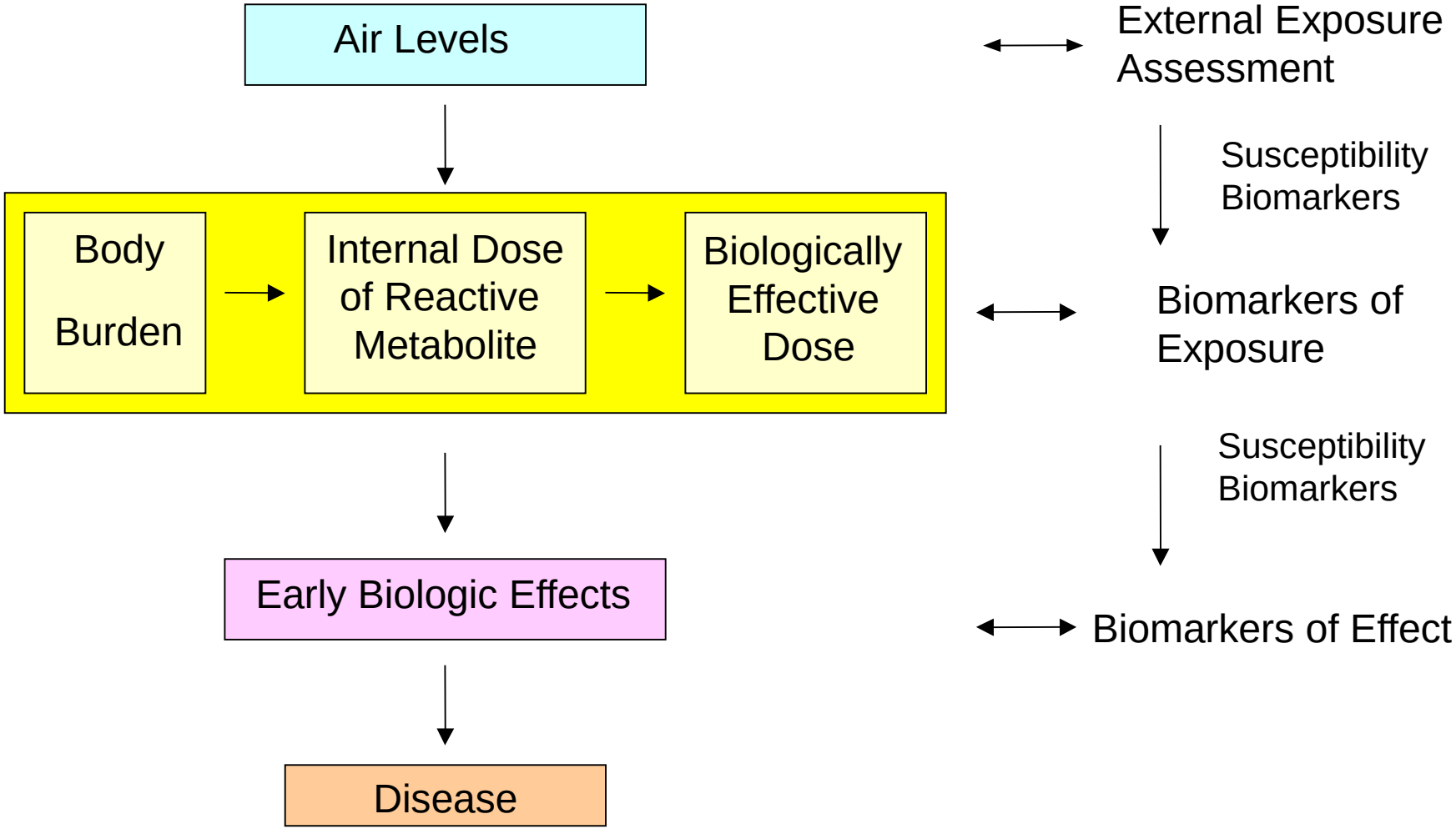
Physiologically-Based Pharmacokinetics Modeling.

- Each relevant organ or tissue is a compartment
- Material flows into compartment, partitions into and distributes around compartment, flows out of compartment usually in blood
- If blood flow rates, volume of compartment and partition coefficient are known, can write an equation for each compartment
- Assuming conservation of mass, solve equations simultaneously – can calculate concentration (mass) in each compartment at any time

Example of a Model.



Biomarker Types.



General Examples of Biomarkers.

Please note that these categorizations are NOT exact - they are just meant to provide a framework for understanding. (E.g., DNA adducts may be considered a measure of early effect rather than of exposure.)

Biomarkers of Exposure

- Body Burden
  - Exhaled breath
  - Blood or urinary levels
- Internal Metabolite Dose
  - Blood metabolite levels
  - Protein adducts
  - Urinary metabolite levels
- Biologically-Effective Dose
  - DNA adducts

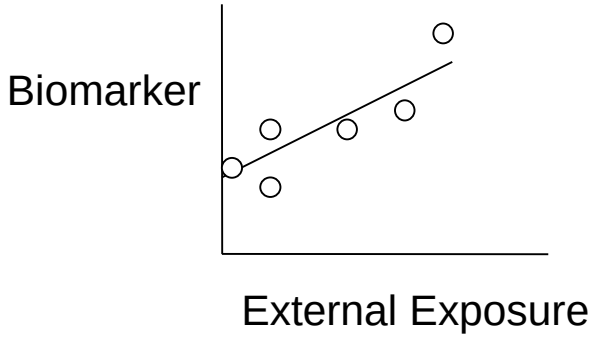
Biomarkers of Effect

- Sister chromatid exchanges
- Micronuclei
- Chromosomal damage

Biomarkers of Susceptibility

- Breathing rate
- Enzyme genotype (DNA sequence) or phenotype (activity)
  - P450s
  - Glutathione S-transferase
  - Epoxide hydrolase
  - DNA repair enzymes

Biomarker - Exposure Relationships.



R^2 represents the % variation in the biomarker (e.g., tissue dose) that can be explained by exposure

High R^2

- external exposition is linearly related to dose
- low inter-individual variability in uptake & metabolism
- biomarker is specific
- sample size is adequate

Low R^2

MORE DIFFICULT TO INTERPRET

- external exposure is not linearly related to dose
- high inter-individual variability in uptake & metabolism
- biomarker is non-specific
- sample size is inadequate

Biomarker Choice.

The choice is dependent upon a number of factors:

- Time frame (short or long-term effects? latency of disease?)
- Is exposure constant or highly variable over mins/hrs/days/weeks/months?
- Number of subjects?
- Budget/time constraints?
- Toxic metabolite known?
- Mechanism of toxicity known or not?
- Route of exposure (just inhalation, or also dermal/oral)?
- Inter-individual differences in uptake (protective equipment) or metabolism?
- Source of exposure (just work?)
- What (bio)monitoring techniques are available?

Ambient Monitoring vs. Bio-Monitoring.

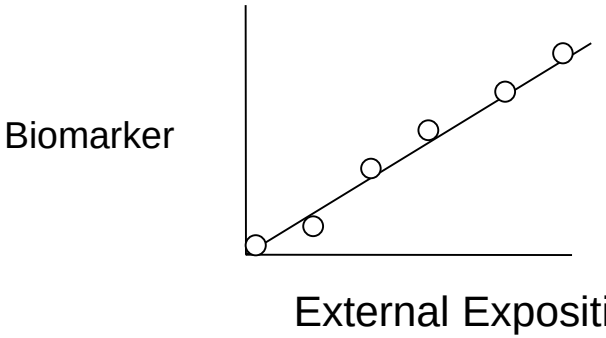
External Monitoring

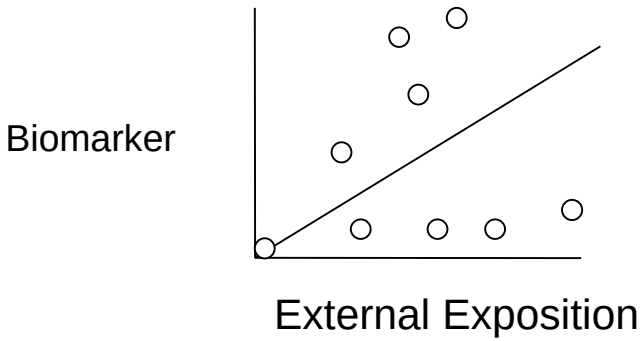
- Can compare to old records
- Lower cost
- Less skilled labor
- Larger number of samples
- Easier to obtain (air)
- Just inhalation exposure
- Just work exposures
- Short time period (mins-hrs)
- Air levels of compound

Exposure Biomarkers

- New techniques, little historical data
- Higher cost
- Highly skilled labor
- Smaller number of samples
- Harder to obtain (blood, urine, tissue)
- All routes of exp (inhalation, dermal, oral)
- Reflects ALL exposures (hobbies, diet)
- Short to long time periods (mins-weeks)
- Tissue levels of reactive metabolite
  - Accounts for personal habits (hand washing, use of protective equipment)
  - Inter-individual differences in metabolism (both activation & detoxification) and repair

Biomarker Choice.





- Good relationship between biomarker and exposure
- High R^2
- No need for a biomarker - choose whichever is cheaper/easier (generally the external measure)

- Poor relationship
- Low R^2
- Looks like 2 distinct populations - indicative of differences in either
  - uptake (protective equipment)
  - metabolism
  - repair
- Biomarkers helpful in this case

Protein Adducts.

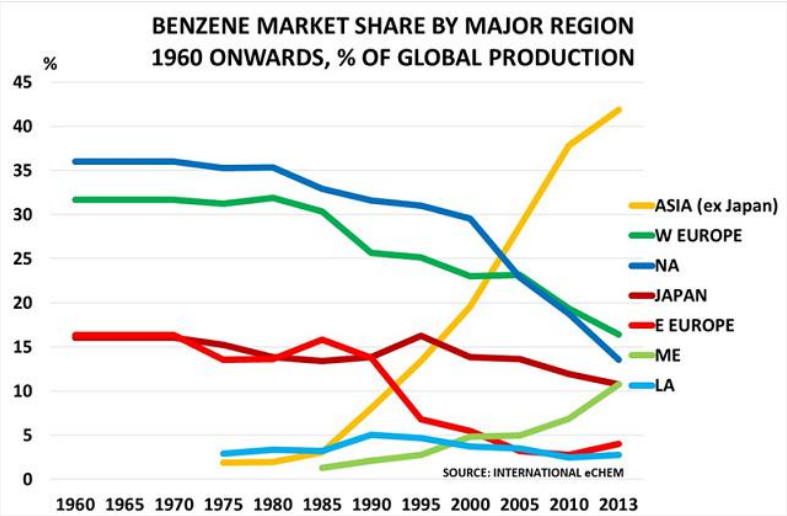
Proteins used:

- Hemoglobin (Hb)
  - 120 day lifespan of the red blood cell
  - 150 *mg/mL* blood
- Albumin
  - 20-25 day half-life
  - 18-25 *mg/mL* blood
- Target tissue protein

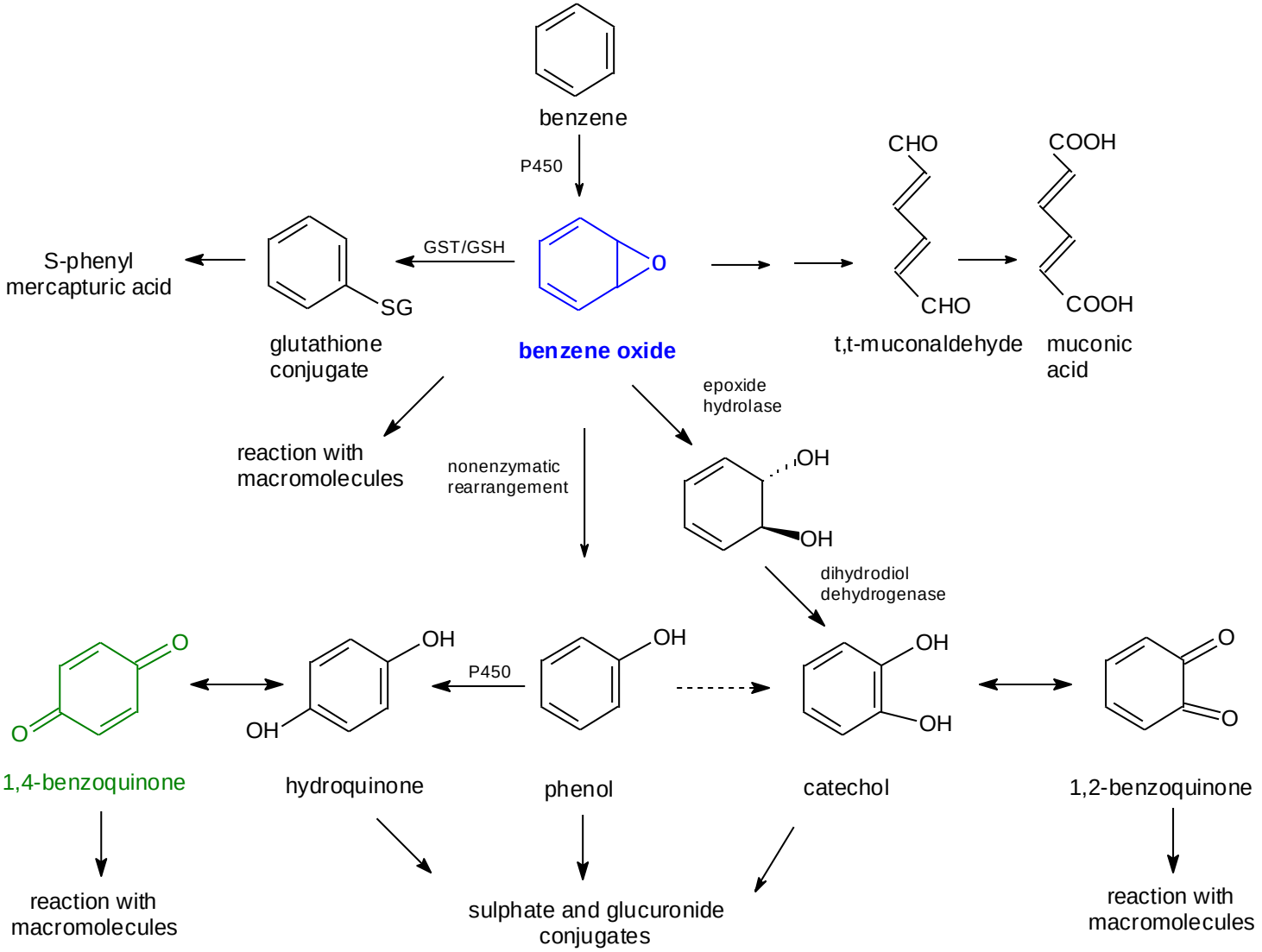
- Protein adducts can be used to predict the average blood concentration (blood dose) of the reactive metabolite over the lifespan of the protein. Regardless of which protein is used, the predicted dose should be the same.

Benzene.

- 48 billion kilo produced in the world in 2016
- human exposures due to cigarette smoking, gasoline & processing of petroleum products
- highest exposures occur in countries such as China and Turkey
- causes cancer in rodents and hematotoxicity and leukemia in exposed humans
- metabolite(s) responsible for benzene toxicity are still unknown; possibilities include:
  - **benzene oxide (BO)**
  - **1,2-or 1,4-benzoquinone**
  - **hydroxybenzoquinone**
  - ***trans,trans*-muconaldehyde**
  - **reactive oxygen species**



Benzene Metabolism.



Example of Exposure Evaluation: Alcohol Ethoxysulphates, AES.

Typical Distribution of Ethoxylate Adducts:

$CH_3(CH_2)_xO(CH_2CH_2O)_nSO_3Na$

x = 7 – 15, typically 11.

90-40% of the carbon chains are linear, the remainder being mono-branched 2-alkyl isomers, predominantly 2-methyl.

n ranges from 0-8.

Used as detergent/cleaning agent. Ethoxylation of alcohols is carried out by base catalyzed reaction with ethylene oxide. The *n* average for the important sulphation grades is 1-3 moles EO per mole alcohol. Toxic dioxane must be removed.

Average EO Groups	**3**	**2**	**1**
Oligomer distribution, %m/m, of $RO(CH_2CH_2O)_nH$ where n=			
0	13.1	23.5	42.9
1	9.1	12.8	20.3
2	11.9	15.6	14.9
3	12.9	13.4	8.8
4	11.8	10.1	5.1
5	10.3	7.5	3.0
6	7.9	5.0	1.9
7	6.5	4.0	1.4
8	4.8	2.9	0.9
9	3.9	1.8	0.5
10	2.9	1.4	0.3
11	1.9	0.9	0.1
12	1.3	0.6	
13	0.7	0.3	
14	0.5	0.2	
15	0.3		
Average EO Number	**3.1**	**2.1**	**1.0**

Source: Hera 2003

Direct Skin Contact from Hand-washed Laundry.

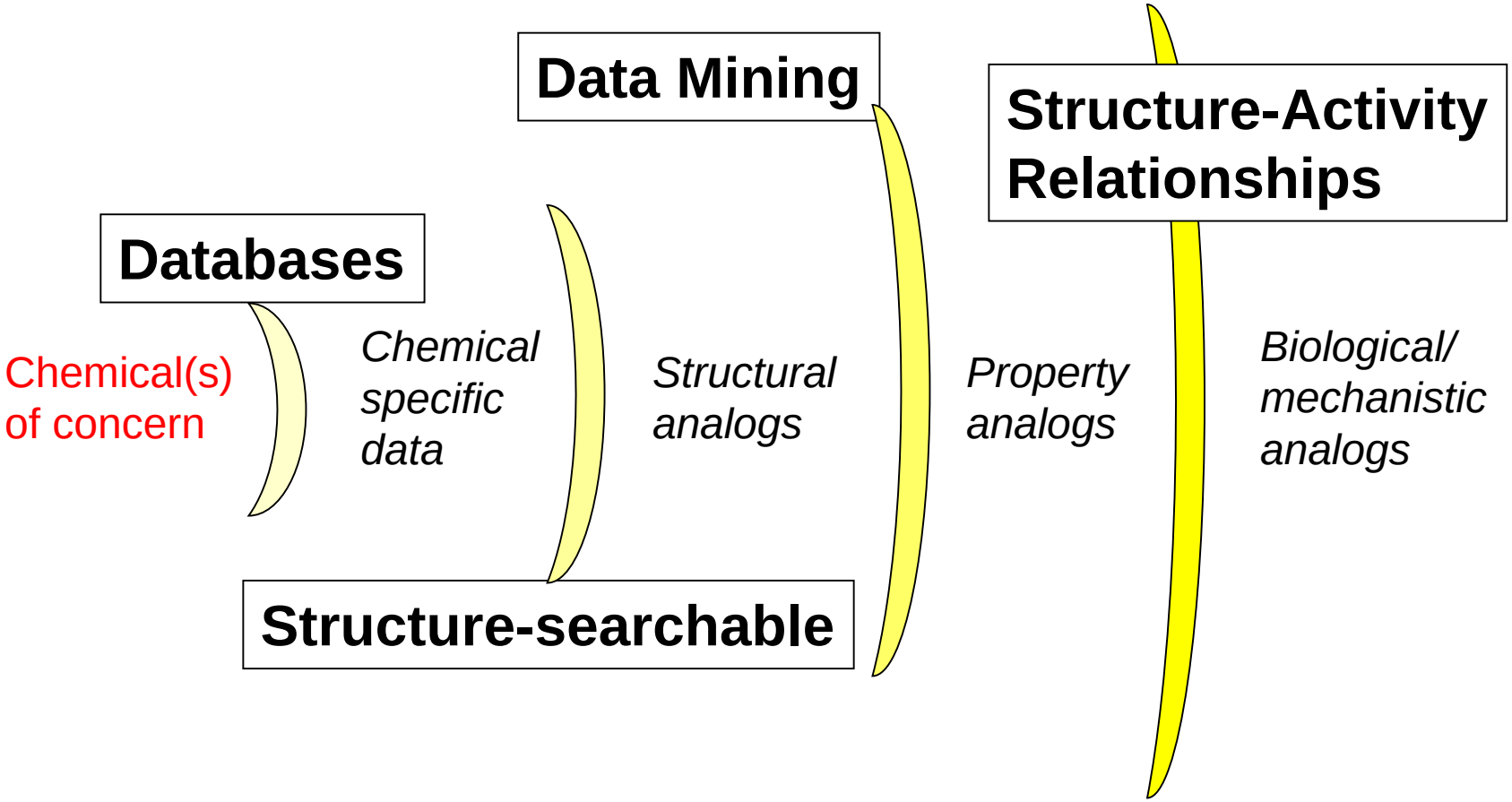
$$Exp^{sys} = F^1 \times C \times K_p \times t \times S^{der} \times n / BW$$

F^1 % weight fraction of substance in product	***20%*** (0.2) [AISE Internal data]
C product concentration in mg/ml:	***10 mg/ml*** [AISE/HERA Table of H&P, 2002]
K_p dermal penetration coefficient	***1.62×10^{-4} cm·h^{-1}**** [Black et al. 1979]
t duration of exposure or contact	***10 min (0.167h)*** [AISE/HERA Tab 2002]
S^{der} surface area of exposed skin	***1980cm²*** [TGD, 1996]
n product use frequency (tasks per day)	***3*** [AISE/HERA 2002]
BW body weight	***60 kg***

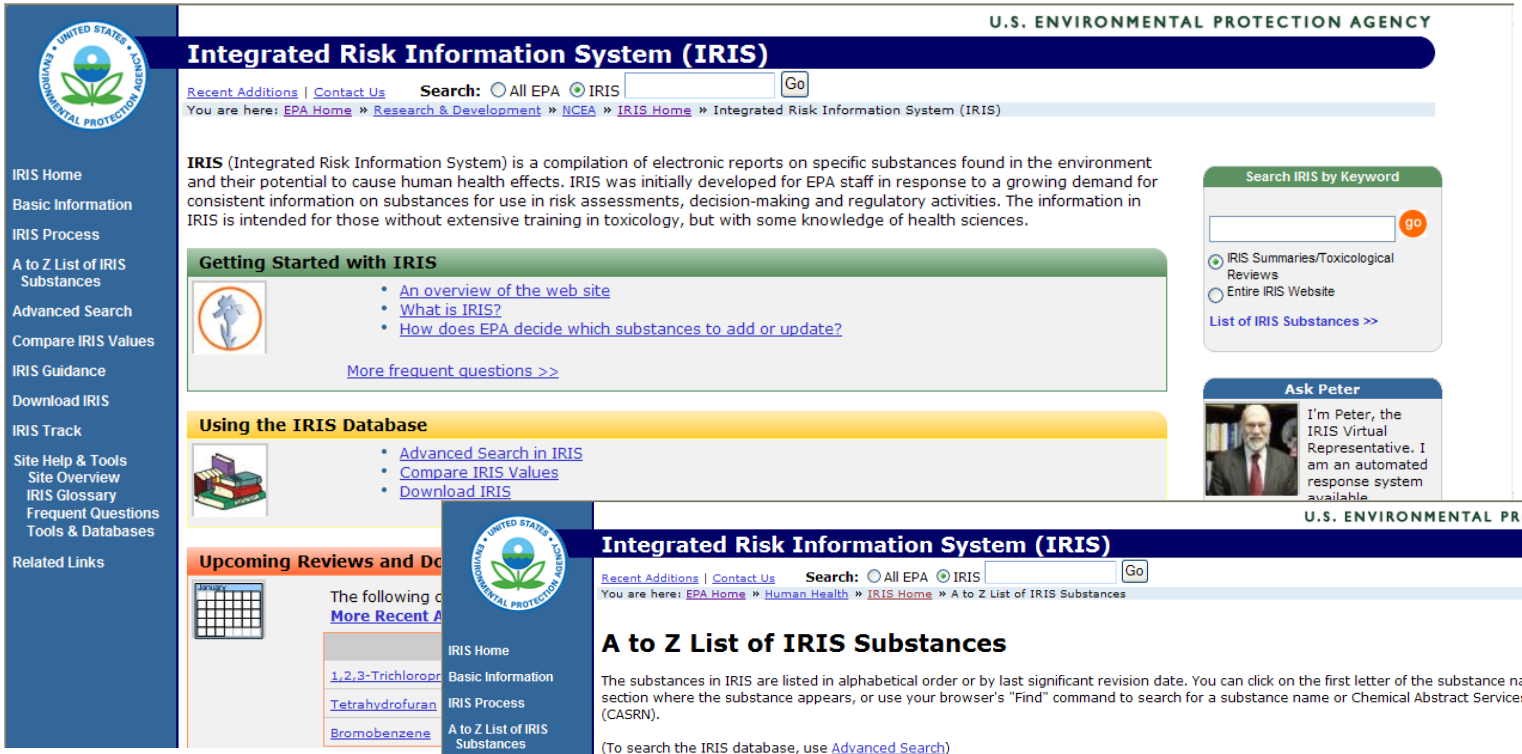
$$Exp^{sys} = [0.2 \times (10\ mg/ml) \times (1.62 \times 10^{-4}\ cm/h) \times (0.167h) \times 3 \times (1980\ cm^2)] / 60\ kg =$$
$$= 5.4\ \mu g \cdot kg^{-1}\ bw/day$$

* the dermal penetration coefficient calculated from the dermal flux (0.39 µg/cm²) which was determined in an in vivo dermal penetration experiment conducted by Black and Howes according to the following algorithm: Kp = dermal flux/exposure time x concentration of solution; Kp = 0.00039 mg/cm²/24h □ 10 mg/cm³ = 1.62 □ 10^{-4} cm/h

Chemistry-based Data Mining & Exploration.

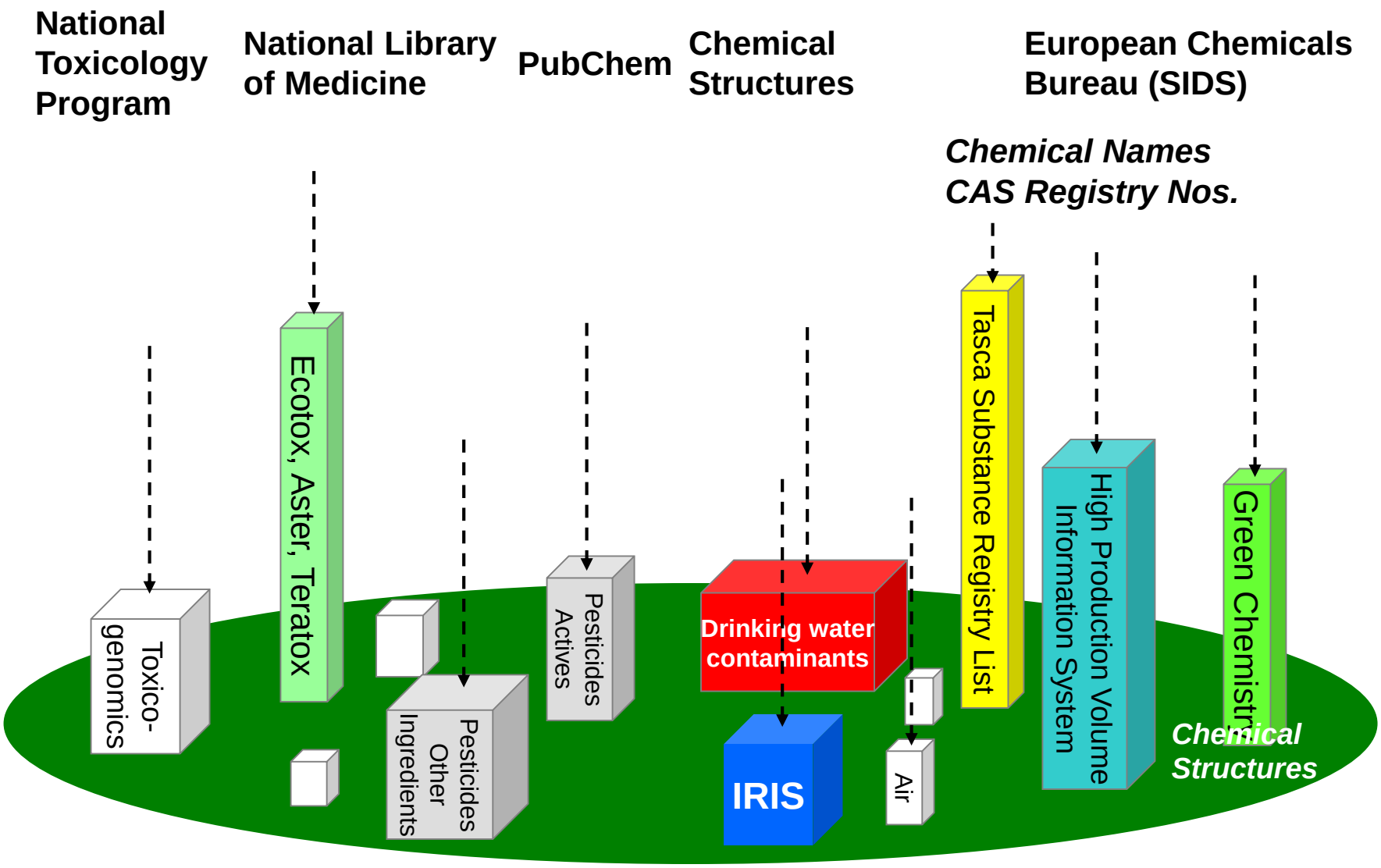


Search by: Chemical Name CAS Registry #.



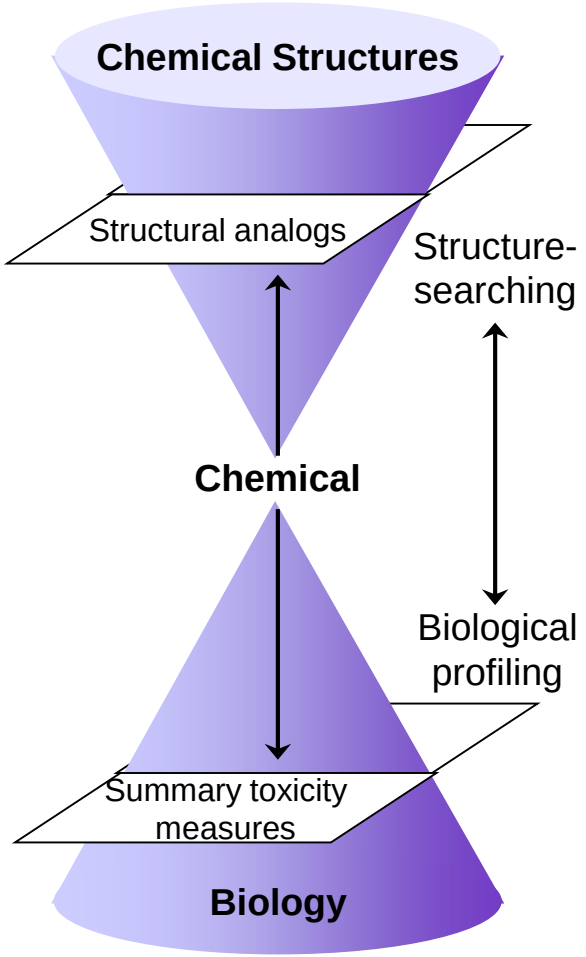
http://cfpub.epa.gov/ncea/iris/index.cfm

EPA's Chemical Data Islands.



http://ntp.niehs.nih.gov/

Toxicity Experimental Data → Summary Data.



Yang et al (2006) Landscape of current toxicity databases and database standards. *Curr. Opinion Drug Discov. Develop.* 9(1),124-133.

Yang et al (2006) The art of data mining the minefields of toxicity databases to link chemistry to biology. *Curr. Comput-Aided Drug Design.*, 2(2), 135-150.

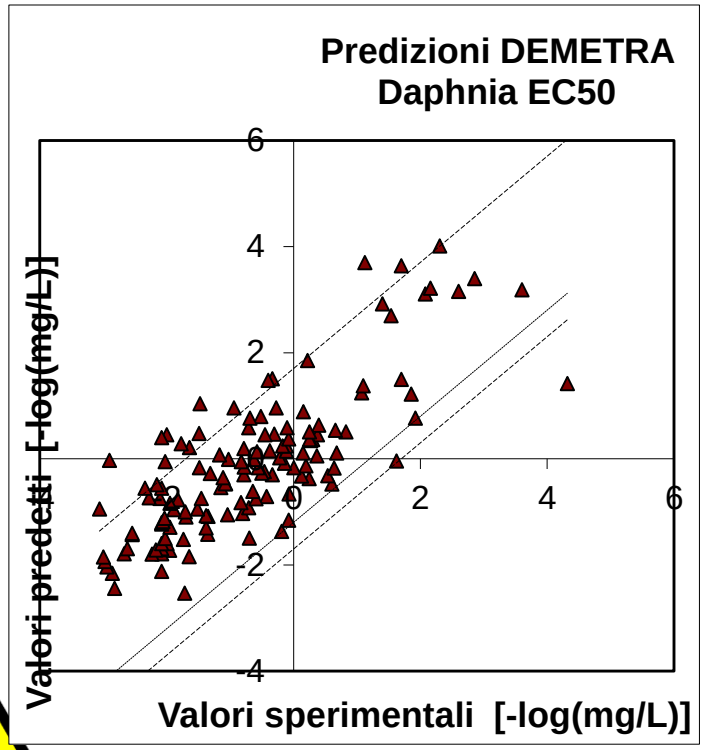
Strategy for Compounds Evaluation.

$$\left[\ \text{T+}\ \right] = f\left(\ \right)$$

1. In Silico screening

a) *Epi-suite* (US EPA)
b) *Toxtree* (JRC)
c) *Demetra/Caesar* (EU funded prj)
…

Toxtree descriptors:
- MW
- LogP
- Vapor Pressure
- Water Solubility
- **Lipid Solubility**
- Melting Point
- **Surface Tension**

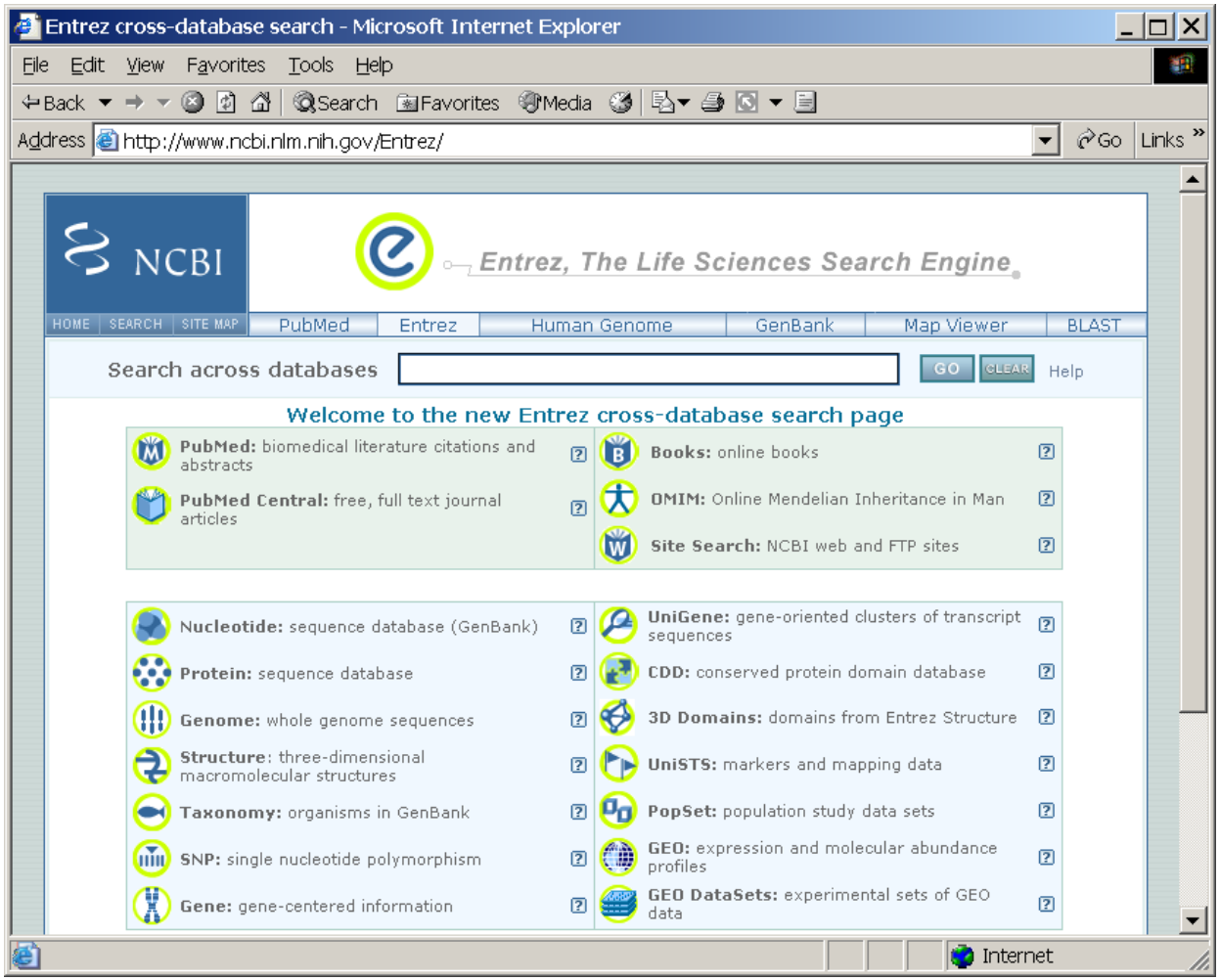


PubChem - Entrez Retrieval System ...

PubChem is a component of National Institutes of Health (NIH) Roadmap Molecular Libraries Initiative.

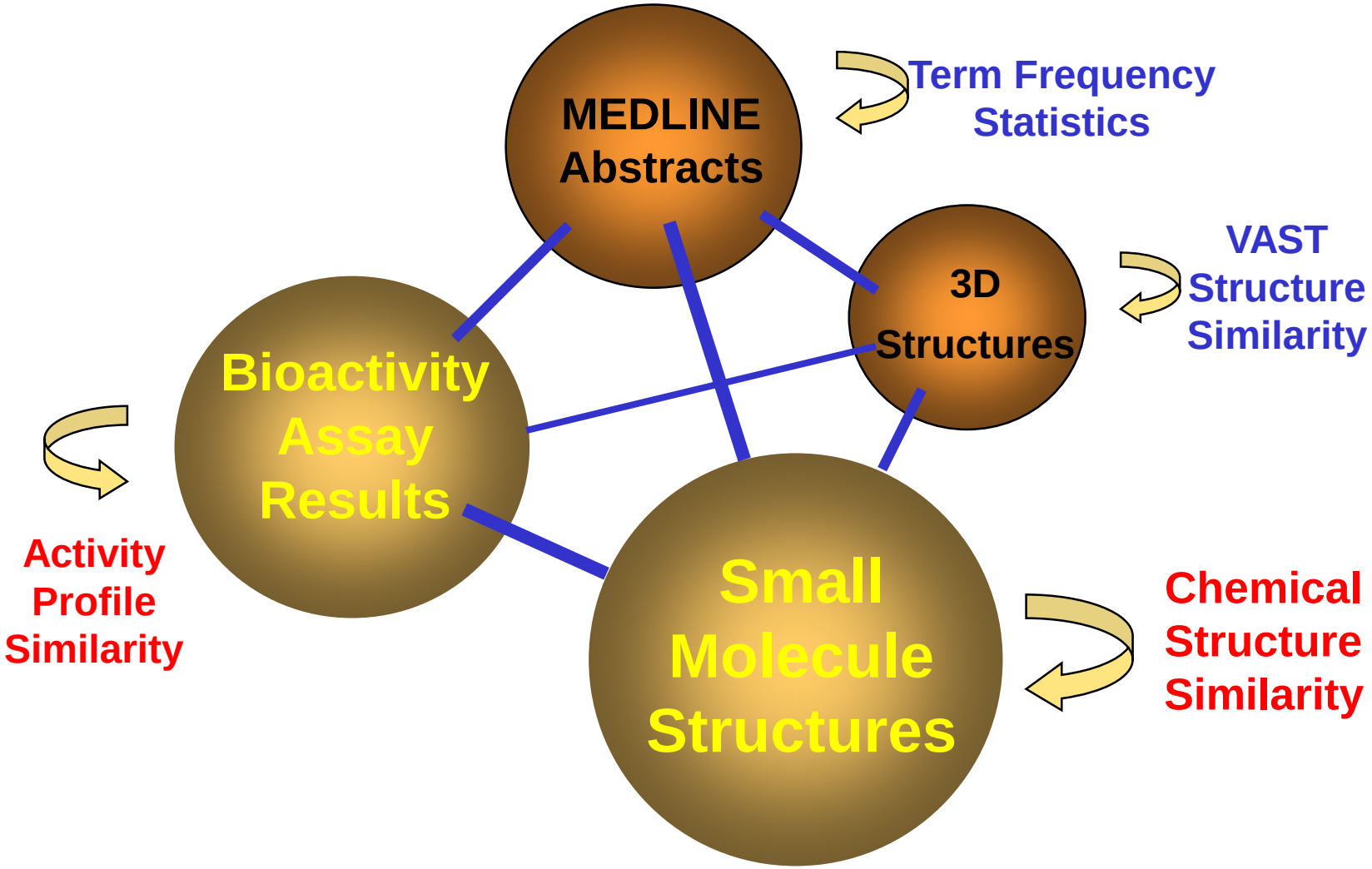
PubChem contains information on substances, compound structure and bioactivity data.

PubChem is integrated with Entrez, the main research engine of NCBI.

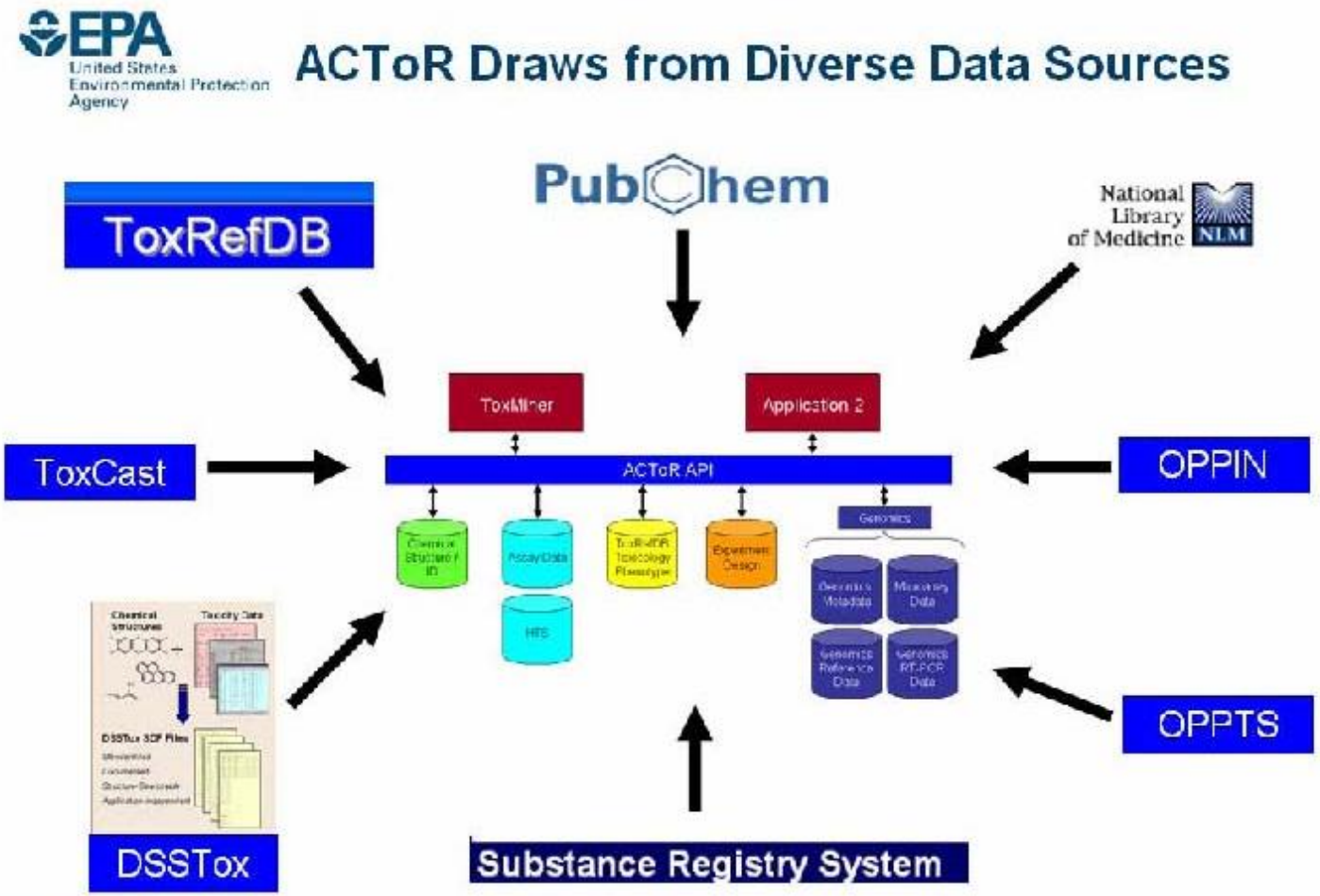


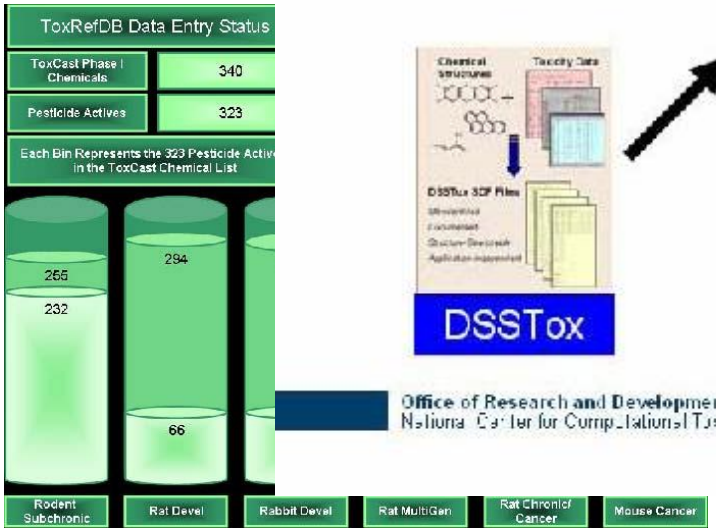
- 3 main database : PC Substance; PC Compound; PC BioAssay.

Entrez with PubChem ...

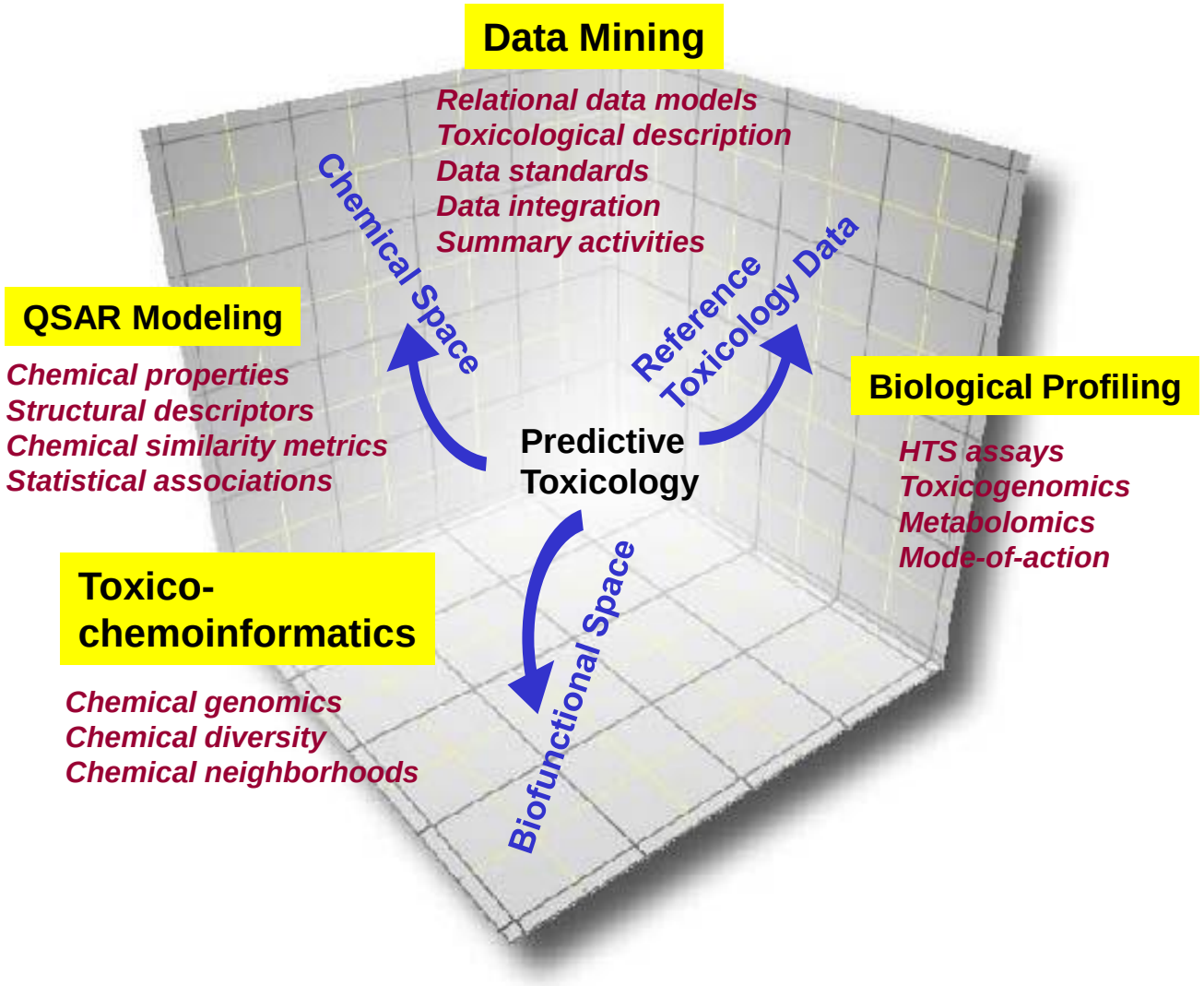


Toxicological Data Banks.





Correlating Domain.

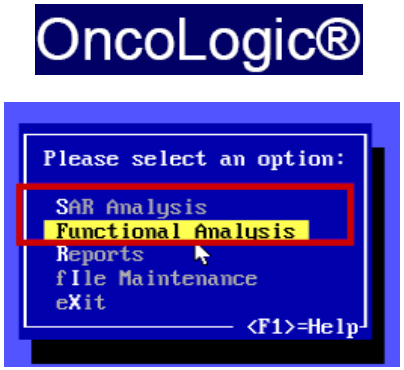


Development of Alternative Toxicity Tests.

REACh, Art.1: “The purpose of this Regulation is to ensure a high level of protection of human health and the environment, including the promotion of alternative methods for assessment of hazards of substances…”

Art.13: “…In particular for human toxicity, information shall be generated whenever possible by means other than vertebrate animal tests, through the use of alternative methods, for example, in vitro methods or qualitative or quantitative structure-activity relationship models or from information from structurally related substances (grouping or read-across)…”

Use of expert system tools for predicting toxicity



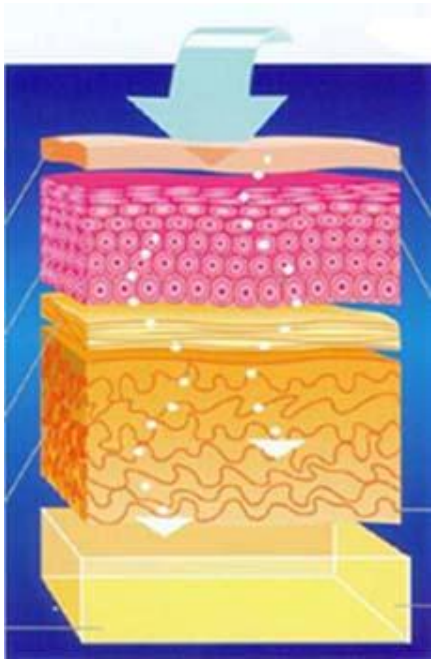
Episkin: Reconstructed Human Skin Model.

TARGET: human skin artificial multilayer

OECD 431

in vitro method where test substance is applied to stratum corneum of the epidermal model at different time of exposure.

Detection throughout mitochondrial activity analysis

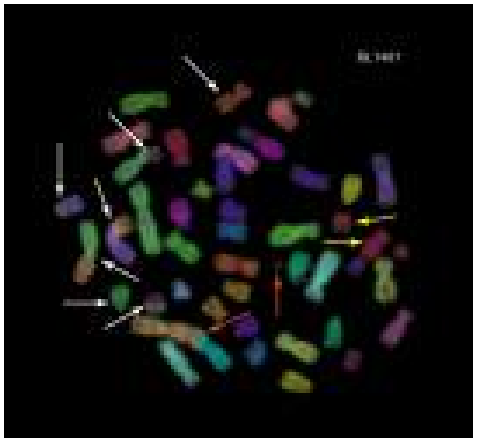


Replacement for the in vivo corrosivity test for hazard identification and classification corrosive potential

Chromosomal Aberration.

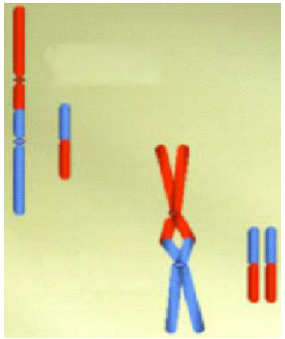
TARGET: human PBMC (Peripheral Blood Mononuclear Cell)

OECD 473



Mutagen-induced aberrations include:

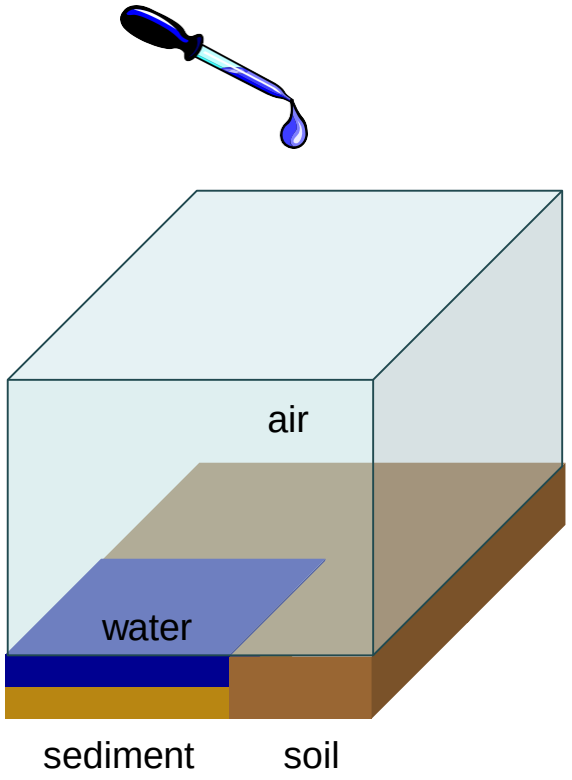
- Gaps
- Breaks
- Dicentric chromosomes
- Ring Chromosomes



ECOTOXICITY.

Where Does a Pollutant Go?

Before assessing impact of a pollutant, we need to find out where it goes.

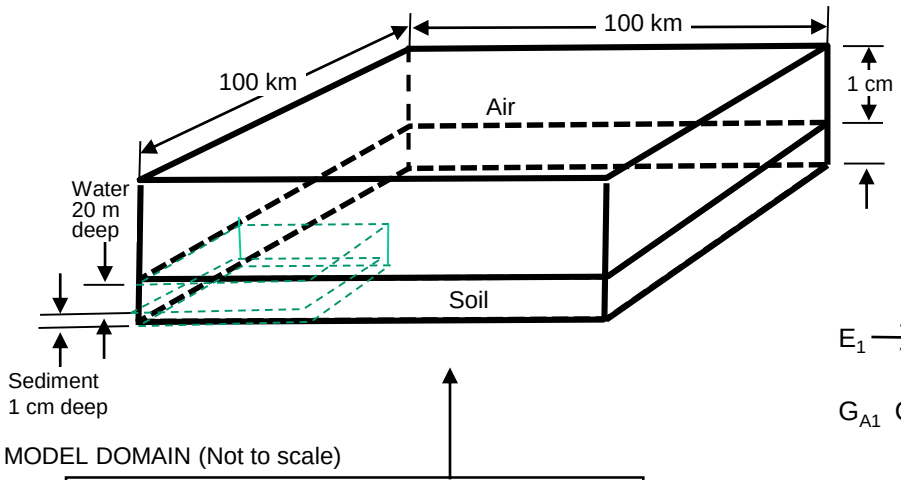


Need to define:

1. K_{ow}
2. K_{oc}
3. Henry's Law Constant
4. Multimedia Compartment Model

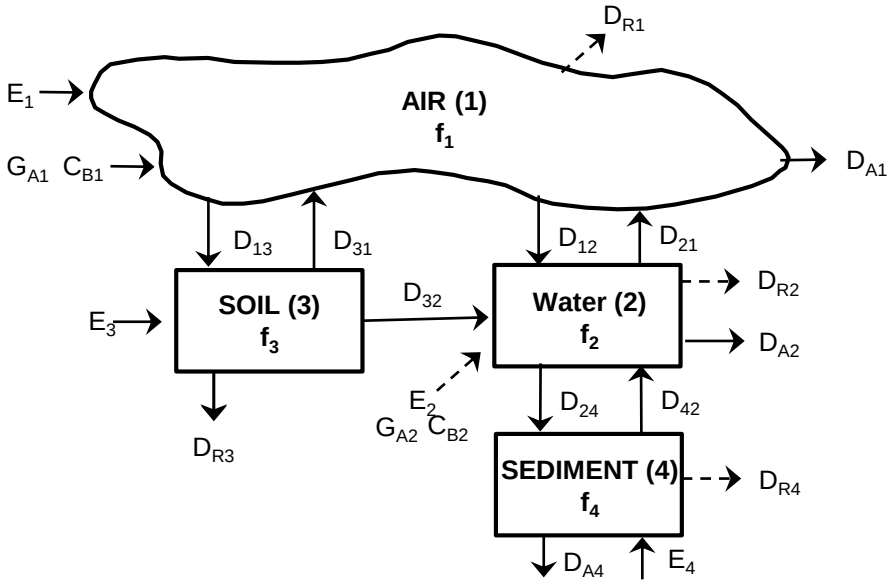
Multimedia Compartment Model Formulation.

Multimedia compartment model



Processes modeled

- emission inputs, E
- advection in and out, D_A
- intercompartment mass transfer, $D_{i,j}$
- reaction loss, D_R



Model Domain Parameters

- surface area - 10^4 -10^5 km^2
- 90% land area, 10% water
- height of atmosphere - 1 km
- soil depth - 10 cm
- depth of sediment layer - 1 cm
- multiphase compartments

Mackay, D. 1991, "Multimedia Environmental Models", 1st edition,, Lewis Publishers, Chelsea, MI

Multimedia compartment model input data.

Environmental Property	*Unit*	*Spreadsheet Location*	*Benzene*	*Ethanol*	*PCP**
Molecular Weight	g/mole	C6	78.11	46.07	266.34
Melting Point	˚C	C7	5.53	115	174
Dissociation Constant	log pK_a	C8			4.74
Solubility in Water	g/m^3	C11	1.78E+2	6.78E+5	14
Vapor Pressure	Pa	C12	1.27E+4	7.80E+3	4.15E-3
Octanol-Water Coefficient	log K_{ow}	C13	2.13	-0.31	5.05
Half-life in air	hr	C33	1.7E+1	5.5E+1	5.50E+2
Half-life in water	hr	C34	1.7E+2	5.5E+1	5.50E+2
Half-life in soil	hr	C35	5.5E+2	5.5E+1	1.7E+3
Half-life in sediment	hr	C36	1.7E+3	1.7E+2	5.50E+3

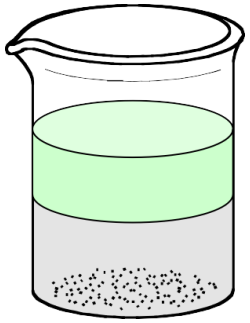
*PCP = Pentachlorophenol

Multimedia compartment model input data.

Chemical (emission scenario)	Total mass (kg)	Percentage (%) Air	Water	Soil	Sediment
Benzene (a)	1.98×10^{4}	99.59	0.29	0.12	1.0×10^{-3}
Benzene (b)	1.41×10^{5}	4.48	95.17	5.5×10^{-3}	0.35
Benzene (c)	6.86×10^{4}	20.61	1.61	77.78	5.8×10^{-3}
Ethanol (a)	4.56×10^{4}	92.87	3.85	3.28	2.9×10^{-3}
Ethanol (b)	7.35×10^{4}	0.22	99.7	7.8×10^{-3}	0.08
Ethanol (c)	7.84×10^{4}	0.92	5.64	93.42	0.02
Pentachlorophenol (a)	2.07×10^{6}	0.26	2.56	97.07	0.11
Pentachlorophenol (b)	4.59×10^{5}	$7.2\text{x}10^{-5}$	96.19	0.03	3.78
Pentachlorophenol (c)	2.39×10^{6}	$2.9\text{x}10^{-4}$	0.54	99.44	0.02

a) 1000 kg/hr emitted into the air compartment
b) 1000 kg/hr emitted into the water compartment
c) 1000 kg/hr emitted into the soil compartment

K_{ow} and Bioaccumulation.

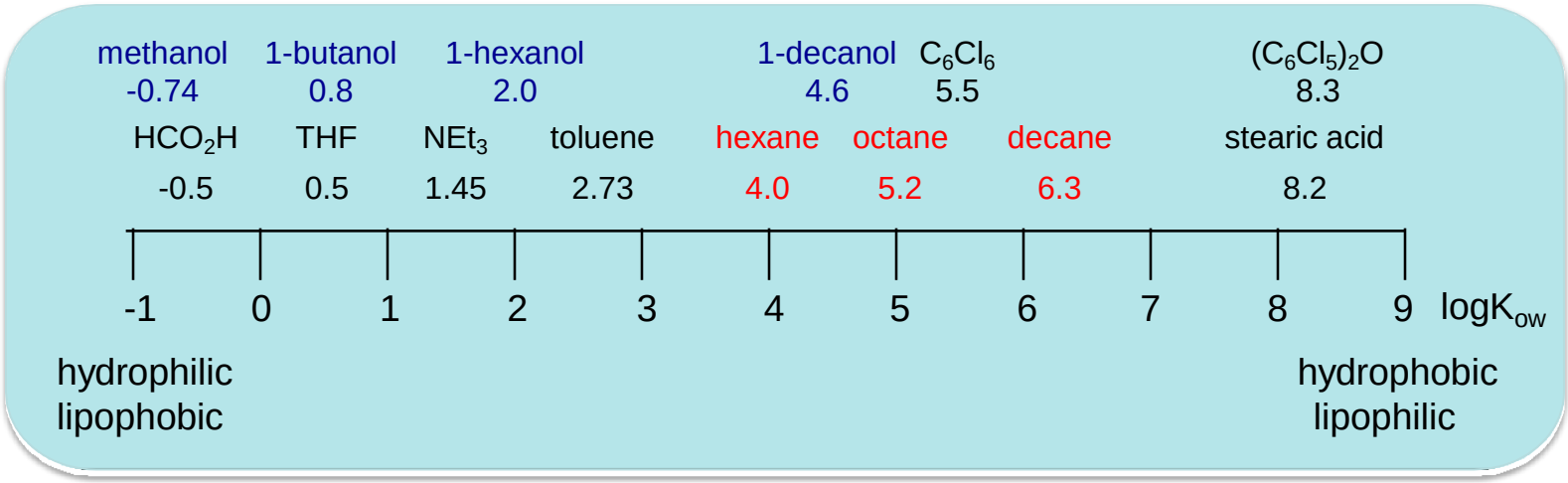


1-octanol

water

$$K_{ow} = \frac{[solute]_{octanol}}{[solute]_{water}}$$

Compound	K_{ow}	$\log K_{ow}$
methanol	0.18	-0.74
benzene	148	2.17
toluene	537	2.73
decachloro-biphenyl	182,000	8.26



K_{ow} data available from CRC Handbook of Chemistry and Physics.
Estimates from ChemDraw or from http://www.vcclab.org/lab/alogps/start.html

Estimation of EC_{50}.

$$\log EC_{50} = a + b \cdot \log K_{ow}$$

- A key parameter in the assessment of environmental risk and in the prediction of the fate of chemicals in the environment.
- Describes the hydrophobicity or hydrophilicity of a compound.
- It can be used to estimate EC_{50} for *simple organisms* because K_{ow} is the basis of correlations to calculate bioaccumulation and toxicity.
- Log K_{ow} can be estimated using several programs such as KowWIN Program (atom/fragment contribution method).
  http://www.epa.gov/opptintr/exposure/docs/episuite.htm

- Group contribution methods:

Studies have been performed on the relationship between toxicity and chemical structure for several compounds.

Henry's Law Constant.

P = H×C

hints:

$H = 2479 / 10^{CD}$

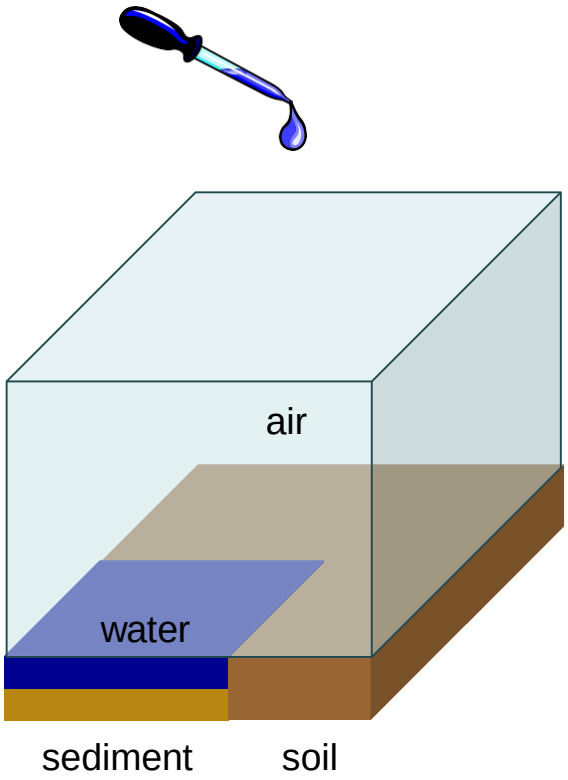
divide by 101,325 Pa/atm

Compd.	H (25 ˚C), mol·kg^{-1}· bar^{-1}	H (25˚C), Pa·m^3· mol^{-1}	H (25˚C), atm·m^3·mol^{-1}
hexane	0.00060	170,000	1.7
toluene	0.16	677	6.7×10^{-3}
benzene	0.18	557	5.5×10^{-3}
CH_2Cl_2	0.36	290	2.9×10^{-3}
ethyl acetate	6.4	16	1.6×10^{-4}
1-propanol	140	0.73	7.2×10^{-6}
ethanol	200	0.51	5.0×10^{-6}

Henry's Law Constants available from CRC Handbook of Chemistry and Physics and from the NIST website:. http://webbook.nist.gov/chemistry/

Unit conversion calculator for Henry's Law constants: http://www.mpch-mainz.mpg.de/~sander/res/henry-conv.html

Multi-Compartmental Models.



1. Acidification potential
2. Ozone depletion potential
3. Smog Formation Potential
4. Global warming potential
5. Human toxicity potential (inhalation)
6. Human toxicity potential (ingestion)
7. Persistence
8. Bioaccumulation
9. Resource depletion

EXAMPLE:
Estimate the four Z factors for DDT, and then calculate the concentration of DDT in each of the phases, If 1 mole of DDT were released into the environment, what % of the DDT would go into each phase? Assume the following data:

$K_{oc} = 2.04 \times 10^5$ m^3/ton
$H = 9.57 \times 10^{-6}$ atm m^3/mol
$V_{air} = 10^{10}$ m^3
$V_{water} = 7 \times 10^6$ m^3
$V_{soil} = 9 \times 10^3$ m^3
$V_{sediment} = 2 \times 10^4$ m^3

See: Life cycle assessment file

Books on Toxicity and Eco-toxicity of Chemicals.

Endocrine Disruption:

- Theo Colborn, Dianne Dumanoski, John Peterson Myers *Our Stolen Future: Are We Threatening Our Fertility, Intelligence, and Survival?—A Scientific Detective Story,*.

Toxicity and Eco-toxicity:

- Mark Cronin, Judith Madden, Steven Enoch, David Roberts *Chemical Toxicity Prediction; Category Formation and Read-Across* 2013 SBN: 978-1-84973-384-7
- W. Karcher, J. Devillers , Ph. Garrigues, J. Jacob *Spectral Atlas of Polycyclic Aromatic Compounds: Including Information on Aquatic Toxicity, Occurrence and Biological Activity* 2014, Springer-Verlag.
- Ernest Hodgson Ed. A Textbook of Modern Toxicology, 4th Ed. 2010 Wiley Ed. ISBN: 978-0-470-46206-5.
- SETAC, Toxicity Reduction and Toxicity Identification Evaluations for Effluents, Ambient Waters, and Other Aqueous Media, Volume 1 (2005).
- Joe Thornton, *Pandora's Poison: Chlorine, Health, and a New Environmental Strategy*, MIT Press, Cambridge, 2000.