

CVEN 4474/5474 Haz Waste Outline

- Toxicity

Paracelsus: "All substances are poisons. The right dose differentiates a poison and a remedy."

• Examples

Substance	RDA (mg/day)	Toxic Level (mg/day)
Zinc	15	60 (LOAEL)
Selenium	0.05-0.2	0.8-1.0 0.35 RfD
Chromium	0.05-2 (+3)	70 (+3) RfD 0.35 (+6) RfD

RDA = Recommended Daily Allowance
LOAEL = lowest observed adverse effect level
RfD = reference dose for oral intake by 70 kg person

- Toxicology = study of adverse effects to organisms due to chemical exposure
 - Controlled; lab; animals
- Epidemiology = study of distribution of diseases and causes in humans
 - Avoids extrapolation from animals
 - Observational - correlation but not causation
 - Sensitivity problems - population or dose too small to see effect
 - Months, years, or lifetimes req'd for study

- Few compounds have enough human data to quantitatively determine negative effects
 - Worker exposure
 - Miners, hat makers, manufacturing,....
 - Accidental catastrophes
 - Bhopal, Sveso Italy,
- Most toxicity data based on animal studies

Toxic Effects of Chemicals

- Exposure to chemical
 - 3 routes: skin absorption, inhalation, ingestion
 - Uncertainty: conc in soil, air, water, food; contact time, cumulative over time?
- Dose of chemical
 - Amount in body to target organs
 - Net = input - elimination
- Response to chemical
 - Death, illness, cancer, sensory effects,.....

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Response vs Dose

- Non-carcinogenic effects
 - Assume a "threshold" below which no adverse effects
- Definitions
 - ADI = acceptable daily intake
 - LOAEL = lowest observed adverse effect level
 - NOAEL = no observed adverse effect level
 - RfD = Reference Dose; "safe", ~ ADI
 - NOAEL/UF where UF = uncertainty factor

Extrapolate from lab study with animals to humans

- NOAEL ADI 1-10x (*UF 1-10*)
–Quality of study
- LOAEL NOAEL 1-10x
- Subchronic animal study chronic effect 10x
- Chronic ave animal Ave human 10x
- Ave human Sensitive human 10x
- Multiple cmpd exposures 1-100x

Example

Data from toxicity study with rabbits and malathion.
50 rabbits per dose group
2 yrs

Dose, mg/kg-d	# Dead
0	2
4	2
7	7
14	17
23	26

What is LD50 (lethal dose to 50% of population)?
What is NOAEL?
What is LOAEL?
What is safe dose for humans?

Putting it together: Which of the compounds is more toxic?

CMPD A	CMPD B
LD50 10 mg/kg	LD50 100 mg/kg
CPF 10 kg-d/mg	CPF 100 kg-d/mg
NOAEL 0.1 mg/kg	NOAEL 1 mg/kg

CPF = carcinogenic potency factor

What is the combined toxicity of A and B?

- What is the LD50 if the total dose to which an organism is exposed is 50% A and 50% B by mass ?
- What is the LD50 if the total dose to which an organism is exposed is 25% A and 75% B by mass?

ANSWER: Depends on assumptions made!

- Assume ADDITIVE toxicity, then
–50% each: LD50 = 18
• $(0.5/LD50_1 + 0.5/LD50_2 = 1/LD50_{mix})$
– 25A/75B: LD50 = 31
- Assume SYNERGISTIC toxicity, then
–50% each: LD50 < 18
- ASSUME ANTAGONISTIC toxicity, then
–50% each: LD50 > 18

Which interaction is most likely?

- If similar mechanism may be additive
- Synergistic if:
 - affect the same organ in different ways
 - Chemical reactions
(nitrites+amines=nitrosamines; carcinogen!)
- Antagonistic if:
 - Chemicals react together (EDTA + metals)
 - Opposite effects of toxins (stimulant vs depressant)
 - Competition for the same enzymes or receptors

However, unfortunately....

- Interactions of mixtures are difficult to predict
- Optimally have data
 - Ex: tobacco smoke & asbestos on lungs
 - Ex: ethanol and CT on liver
- Most often do not have data
 - Too many chemicals and potential combinations!

Further complications....

- Not a single value
 - Ex: LC50 for endosulfan toxicity to fish ranged from 0.68 to 3.30 mg/L in 4 different labs (5x)
- Different organisms respond differently
- Low level effects difficult to detect
 - Ex: 24,000 mice tested, couldn't detect 1% excess risk (1/100 incidence)
 - \$1.5M for rodent sty of 1 chemical @ >5%