(Food) Toxicology and Risk Assessment

DR. KATHERINE FLYNN, PH.D.
SCIENTIFIC SECRETARY, SAFE CONSORTIUM BRUSSELS
ASSOCIATE PROFESSOR OF BIOLOGY, PACE UNIVERSITY NYC

QUESTIONS? COMMENTS? CONTACT ME AT KATHERINE.FLYNN@SAFECONSORTIUM.ORG

Today's Outline

- **Toxicology: Introduction**
- Determining Toxicity
- Some Possible Food Toxicants: Pesticide Residues, Food Additives, Food Packaging
- Risk Assessment: Hazards, Exposure, Characterisation

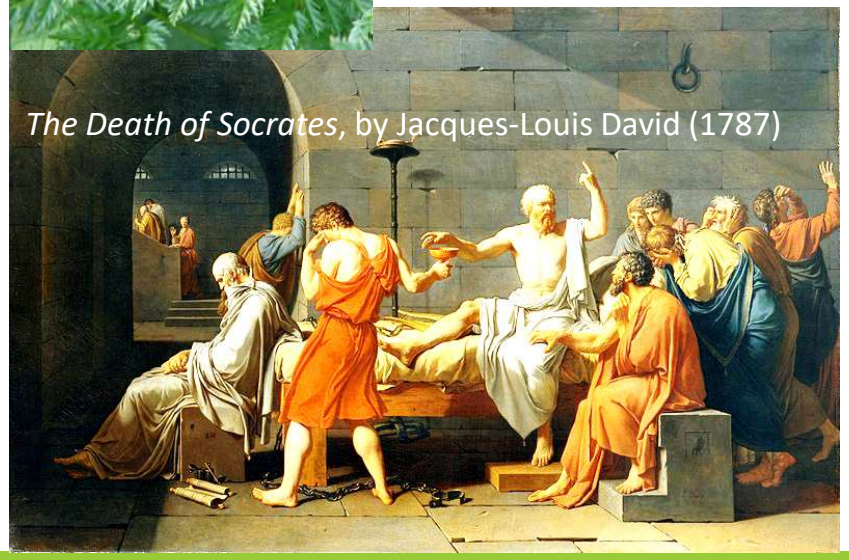
Toxicology: What is it?

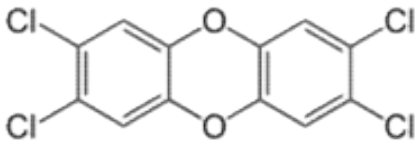
- A relatively new scientific discipline
  - Though many of its principles have been known for a long time
- View of toxicology has changed over time
- Six areas of Applied Toxicology recognised today
  - Analytical, Clinical, Environmental, Forensic, Occupational, **Regulatory**
- Toxicology's Basic Principle: **« The dose makes the *poison* »**

Egyptian Medical Papyrus (1500 BC) discussing poisonous plants therapeutic agents

Old and New Poisons:

Hemlock. Execution of Socrates in 399 BC
Dioxin. Disfigurement of Viktor Yushchenko in 2004


The Death of Socrates, by Jacques-Louis David (1787)



2,3,7,8-Tetrachlorodibenzodioxin

Toxicology definition:

the study of *adverse effects*

of chemical, physical or biological agents

on living organisms and the ecosystem,

including the prevention and amelioration of such effects

Adverse effect

A change in morphology, physiology, growth, reproduction, development or lifespan of an organism

which results in an impairment of functional capacity

or impairment of capacity to compensate for additional stress

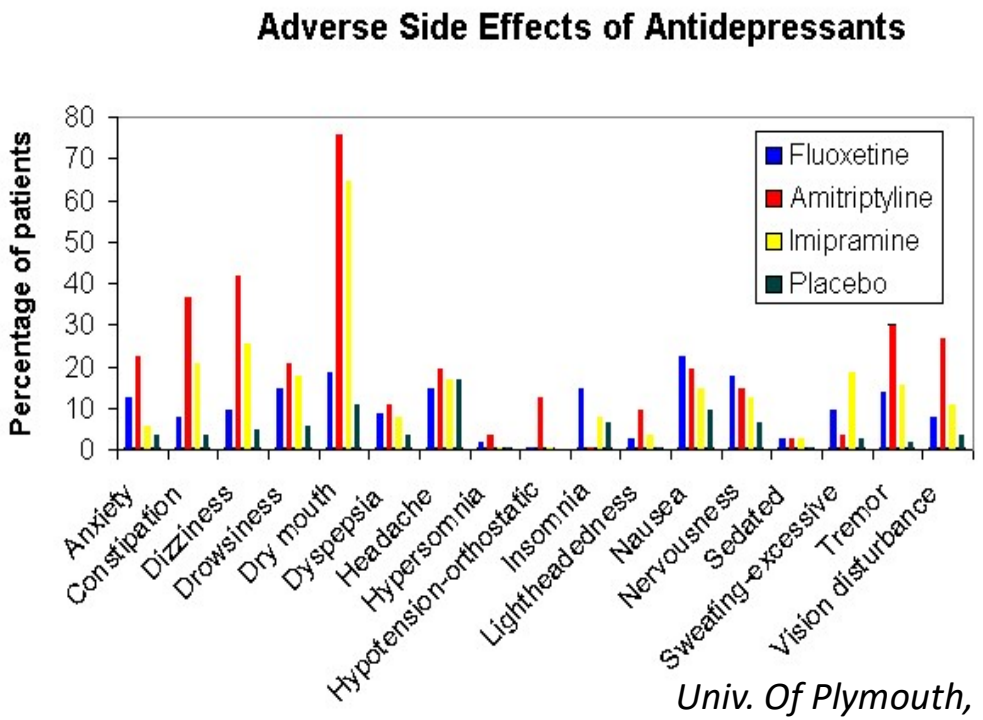
or increased susceptibility to the harmful effects of other environmental influences.

World Health Organization, 2004

The range of adverse effects is enormous:
From immediate death
to subtle molecular or behavioral changes in the next generation

Unintentional Toxicants

- When dangers are « not known » and benefits are many
  - Pharmaceuticals
  - Household chemicals
  - Cosmetics
  - Food Toxicants
    - Natural or deliberate or accidental
- Workers
- Natural and Industrial disasters



Univ. Of Plymouth, UK

Unintentional Toxicants

- **Since WWII more than 80.000 new chemicals have been invented**
- **Many of these are widely dispersed in the environment**
  - In the US, more than 4 billion pounds (1.8 trillion kg) of synthetic chemicals are released into the environment every year by industry.
    - 72 million pounds are known carcinogens. (Mt.Sinai Med Center, USA)
- **Many of these are ingested with our food**
- **Only a fraction have been tested**

Toxicology Testing

- **Many scientific specialties are involved**
  - Biology, chemistry, environmental science, epidemiology, genetics, physiology, pathology

- **The aim is to determine how an organism is affected by a substance**
  - How the substance enters the body
  - How it moves throughout the organism
  - How it may be changed within the organism, metabolised
  - What parts of the organism are affected
  - The health outcomes of exposure
  - How the substance is excreted

QUESTION

Which of the following news headlines are concerned with issues relating to toxicology?

- ❑ Arsenic Widespread in Bangladeshi Water
- ❑ Sarin Gas Attack on the Tokyo Subway
- ❑ Gas Leak Accident in Bhopal: An Indian Tragedy
- ❑ Hormone Disrupters in Everyday Foods
- ❑ Toxic Chemicals in One-Third of Fast Food Packaging
- ❑ Adults and Children Suffer Lead Posioning From Public Water in Flint Michigan
- √ All of the above

Today's Outline

- Toxicology: Introduction
- **Determining Toxicity**
- Some Possible Food Toxicants: Pesticide Residues, Food Additives, Food Packaging
- Risk Assessment: Hazards, Exposure, Characterisation

Determining Toxicity: Dose

"All substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy."

The dose makes the poison

« Alle Dinge sind Gift und nichts ist ohne Gif. Dosis macht, dass ein Ding kein Gift ist. »

Substance	Non-Toxic or Beneficial Dose	Toxic Dose	Lethal Dose
Alcohol *ETHANOL BLOOD LEVELS*	0.05 %	0.1 %	0.5 %
Carbon Monoxide *% HEMOGLOBIN BOUND*	< 10 %	20 - 30 %	> 60 %
Secobaraital *(sleep aid)* *BLOOD LEVELS*	0.1 mg/dL	0.7 mg/dL	> 1 mg/dL
Aspirin	0.65 gm *(2 tablets)*	9.75 gm *(30 tablets)*	34 gm *(105 tablets)*
Ibuprofin *E.G., ADVIL & MOTRIN*	400 mg *(2 tablets)*	1,400 mg *(7 tablets)*	12,000 mg *(60 tablets)*

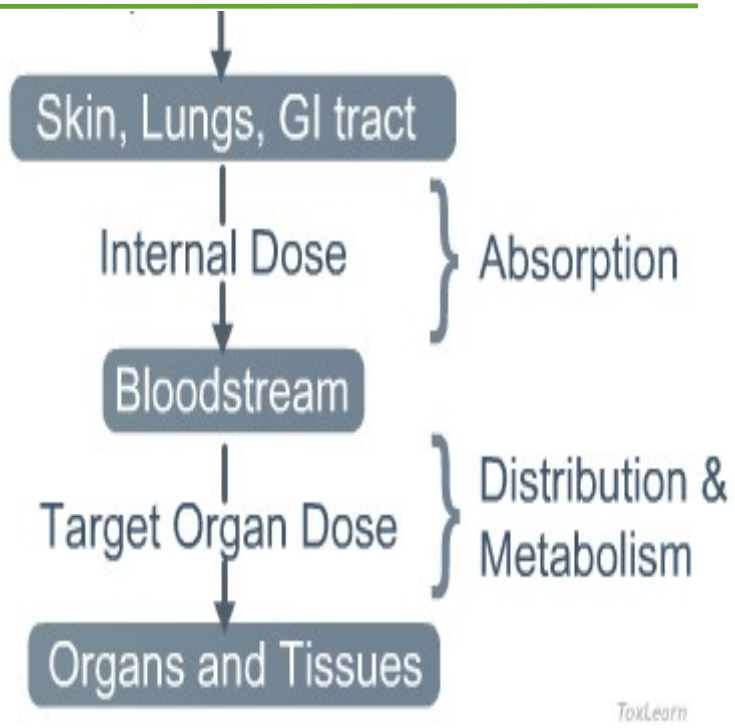
Principles of Clinical Toxicology *(T. Gossel and J. Bricker, eds)*

- There are not good chemicals and toxic chemicals (substances).
- Anything can be toxic.
- The degree of toxicity varies and the **dose** which causes toxicity varies.

Determining Toxicity: Dose has many meanings

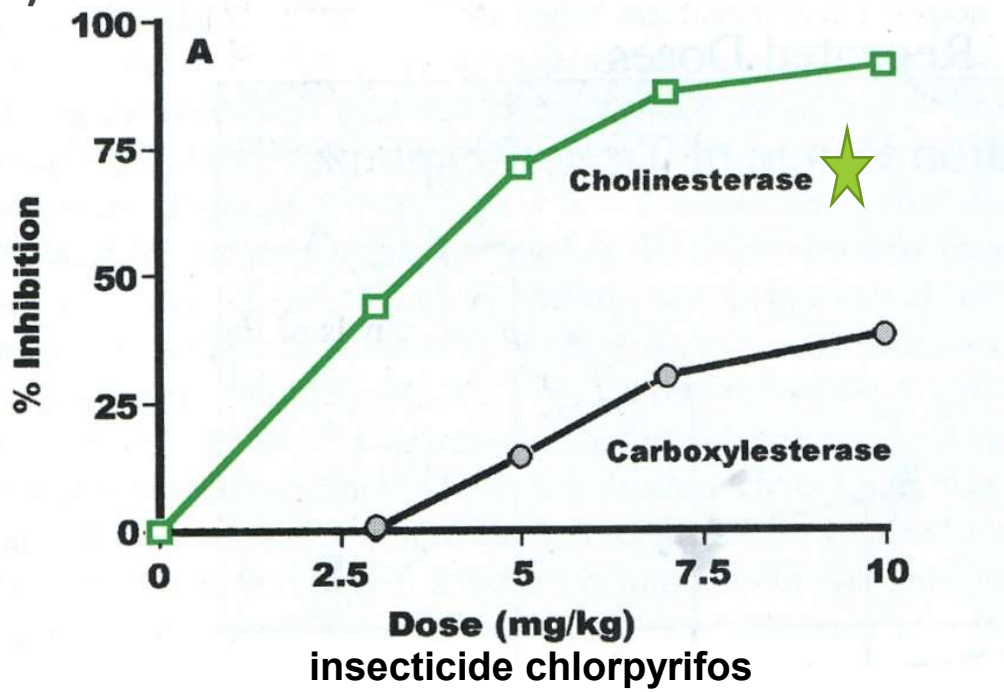
- **Exposure** (or Administered) Dose
- **Absorbed Dose:** what enters the body
- **« Effective » Dose:** what is at the site of action and active
- **Total Dose:** considers amount, frequency, length of time

Dose may be measured in amount (mg) or in amount per weight of the individual (mg/kg) or, for chronic exposure such as foods, in ***amount per weight of the individual per time (mg/kg/day)***



Determining Toxicity: The Dose-Response Relationship

- **Correlates exposure (dose) and effect (response)**
  - Generally, more exposure = more effect
- **Based on observational data**
- **Fundamental toxicology concept**
  - Quantifies toxicity
- **Individual D-R curves show strength of effect**
  - Population D-R curves show percent effected



insecticide chlorpyrifos

Many possible « responses » in a Dose-Response study!

Enzyme Inhibition

Inflammation

Cell death (necrosis)

Biochemical uncoupling or lethal synthesis

Covalent bonding

Free radical oxidation of lipids

Receptor interactions

Other possible responses to measure (7):

Allergy (immune hypersensitivity)

Behavioural changes

Cancer (aberrant cell division)

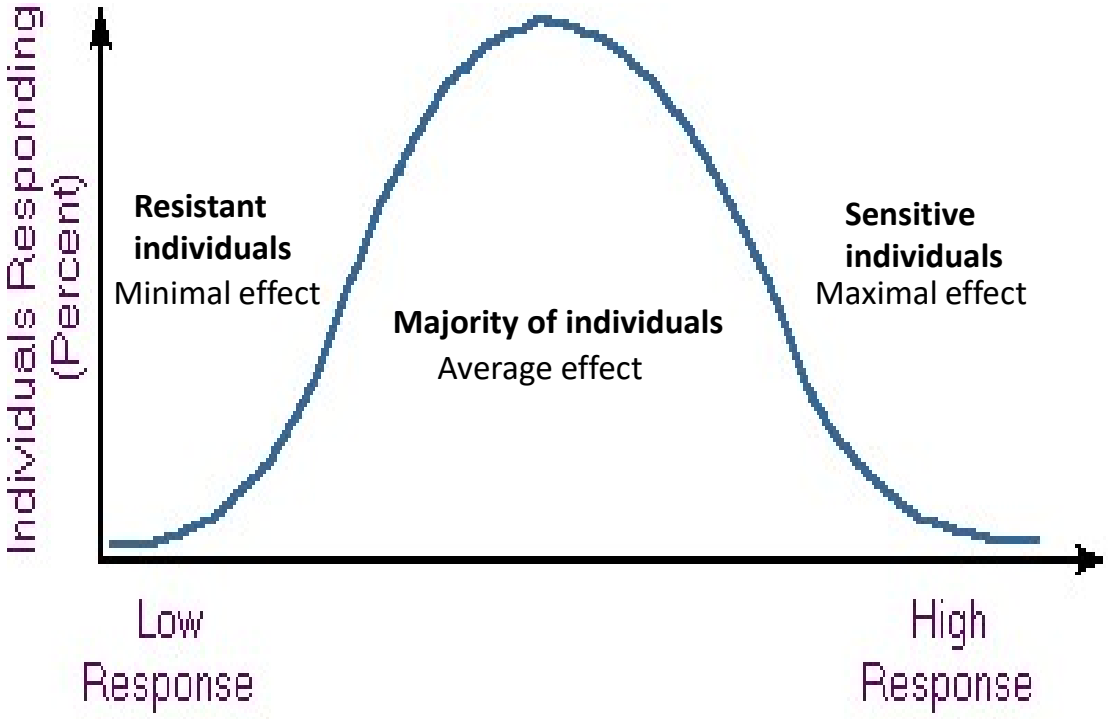
Developmental (effects on fetus)

Immune supression

Mutation (genotoxicity or DNA interference)

Reproductive (effects on conception)

Population Dose-Response Curve



Shows what percentage of a population have **a given response to a given dose**

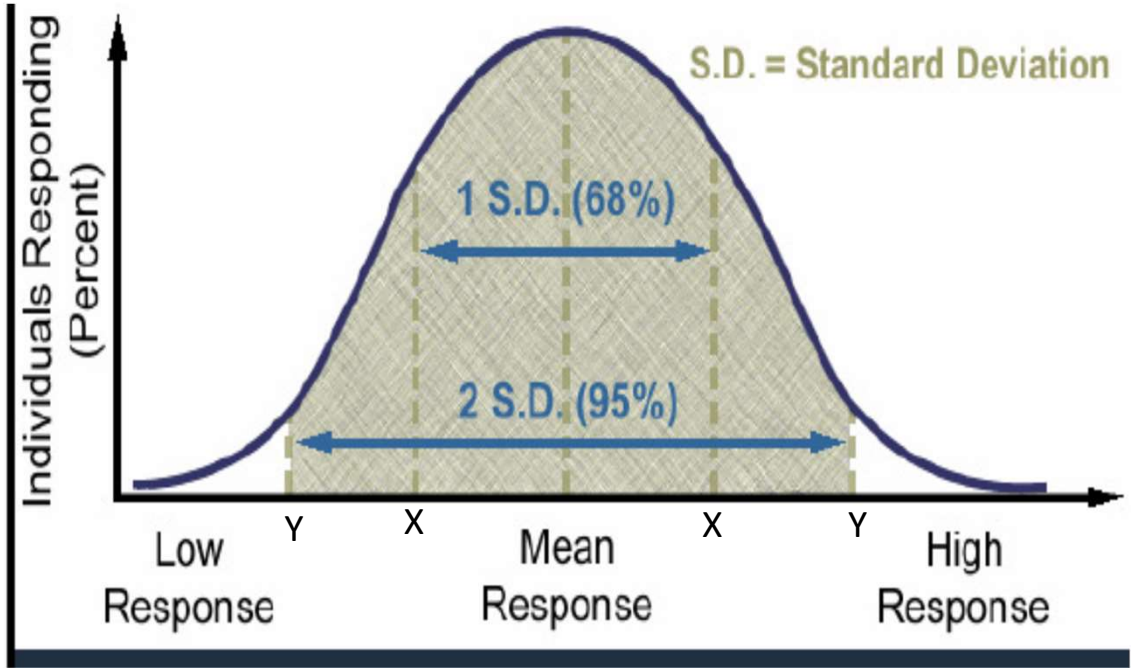
- Choice of what dose to give and which response to measure is up to the researcher

A Bell curve

A Gaussian or normal distribution

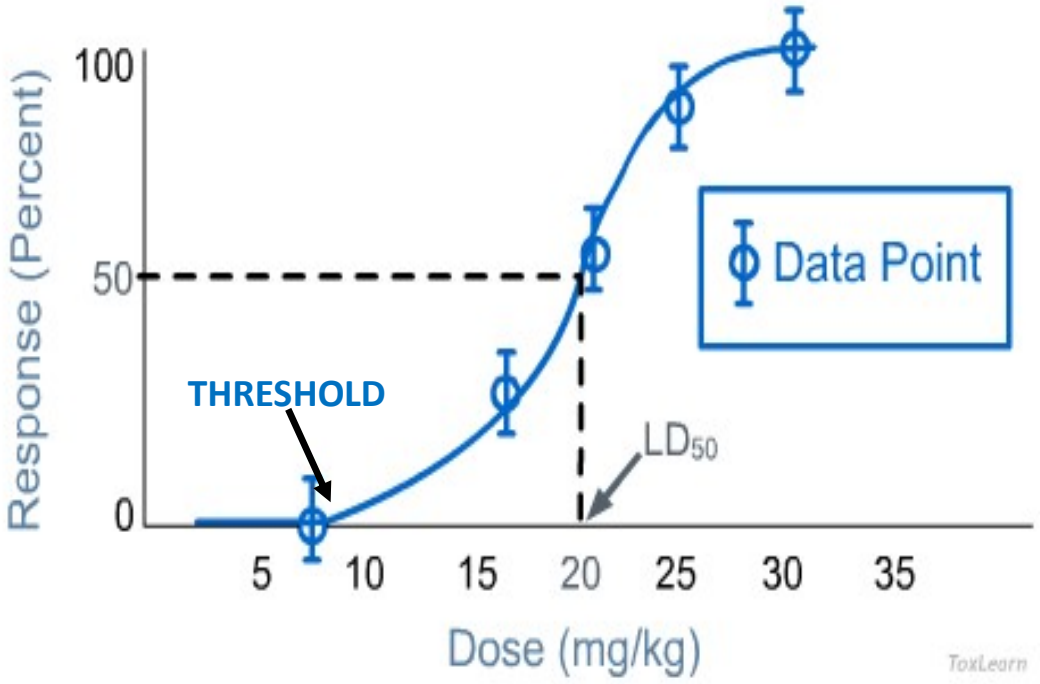
Inter-individual variability

Normal distribution parameters



*Change percent responding to **cumulative responding** at different doses and Bell curve becomes sigmoid…*

Classic D-R curve



- **On the x axis:** the dose
- **On the y axis:** the proportion of animals exhibiting a particular response, here *death*

LD_{50}: Lethal Dose 50 or dose which kills one half of the animals.

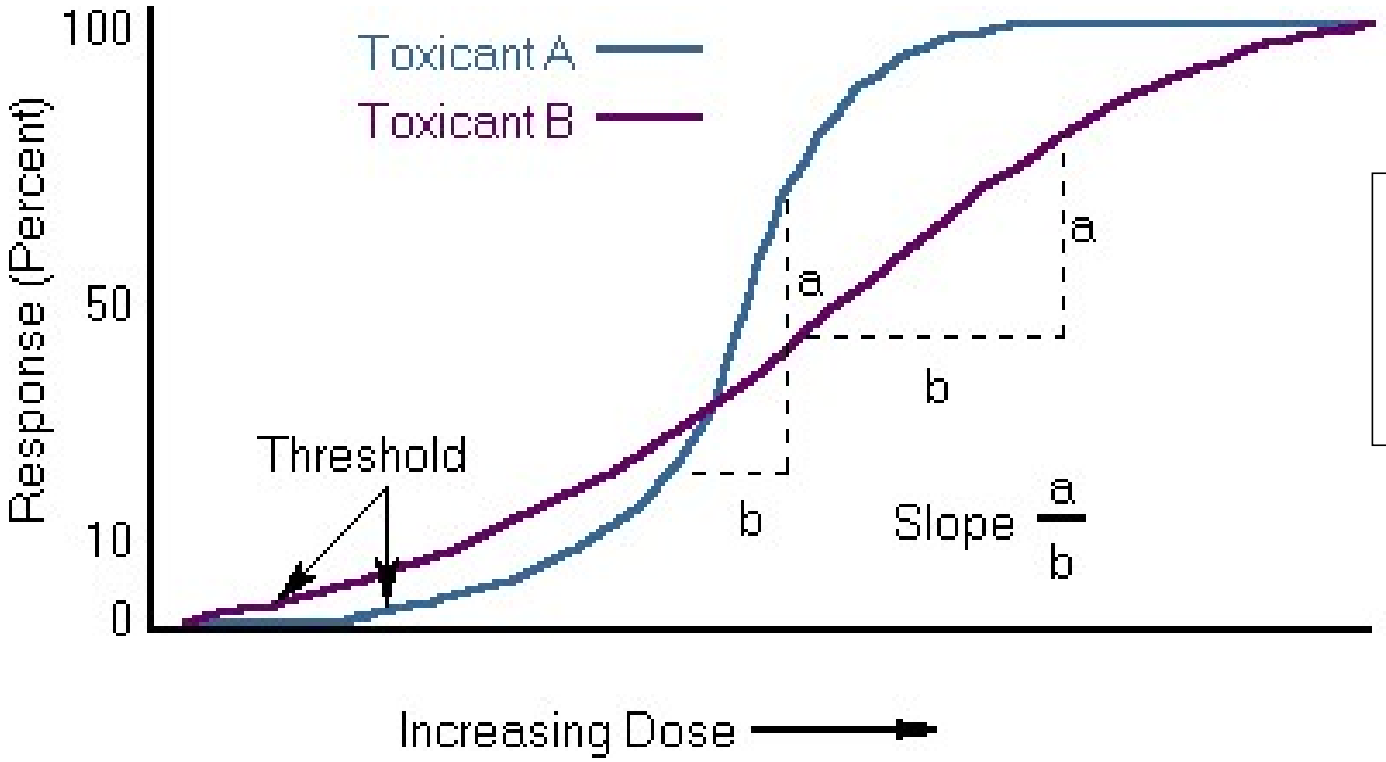
THRESHOLD: lowest dose at which there is an effect.

QUESTION

Which substance is more dangerous?

- [x] One with an LD_{50} of 5 mg/kg
- [ ] One with an LD_{50} of 50 mg/kg

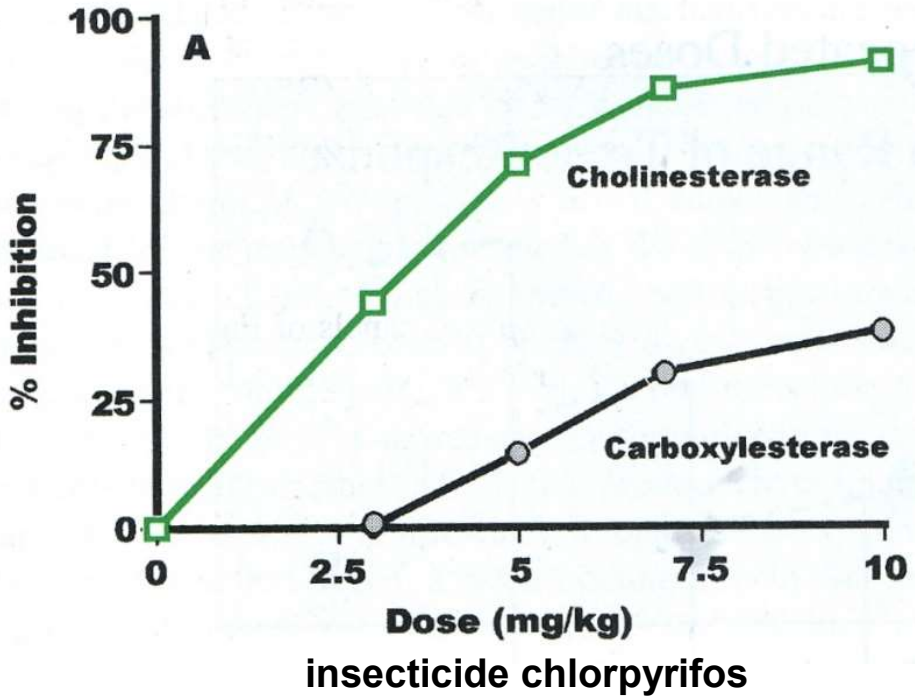
Different substances have different D-R curves



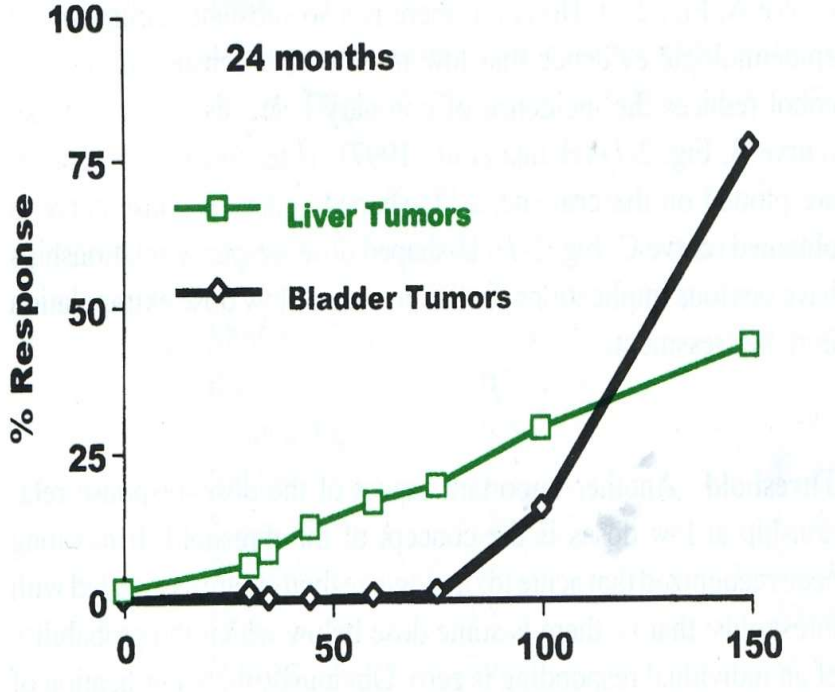
Which is more dangerous Toxicant A or Toxicant B ?

WHY ?

Same substance may have different D-R curves for different endpoints

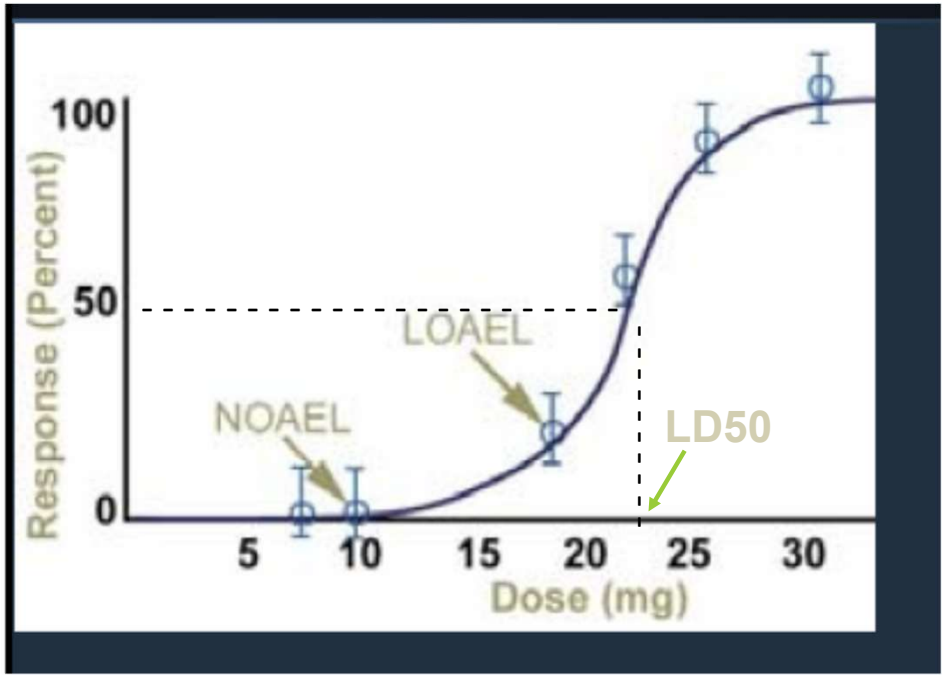


insecticide chlorpyrifos



(2-acetylaminoflourene)

Important points on a D-R curve

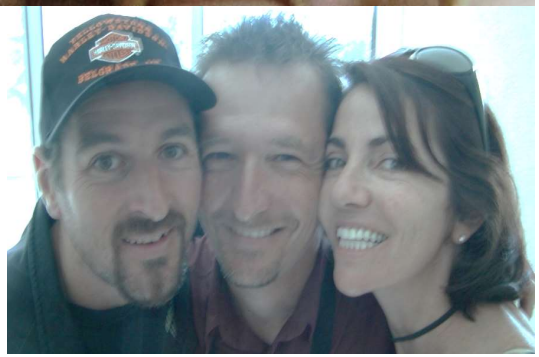


- **LD50**
  - Lethal Dose 50.
- **NOAEL**
  - No Observed Adverse Effect Level. The highest tested dose at which no effect was observed. **THRESHOLD** is just after this point
- **LOAEL**
  - Lowest Observed Adverse Effect Level. The lowest tested dose at which an effect was observed.

The NOAEL or LOAEL in animals is often used to make decisions on maximum recommended exposures for humans.

Many factors can affect response to a toxicant

•Species

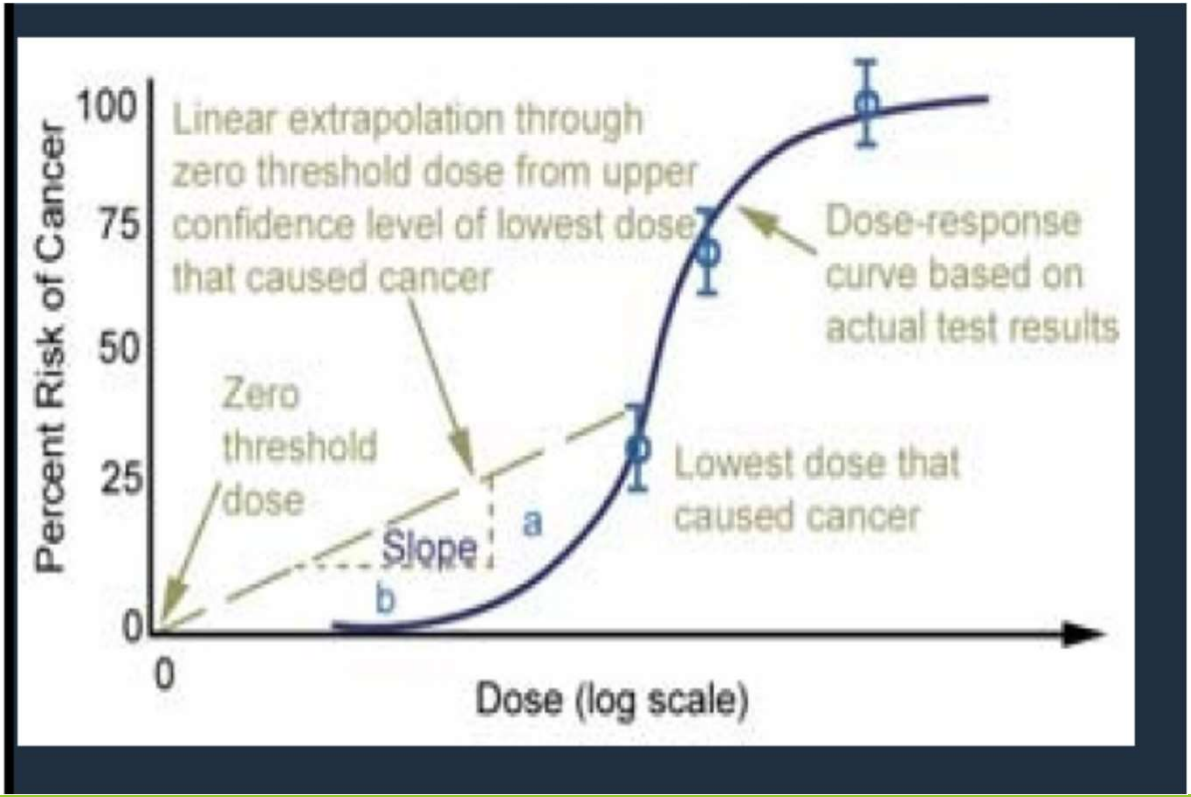


Some others (12):

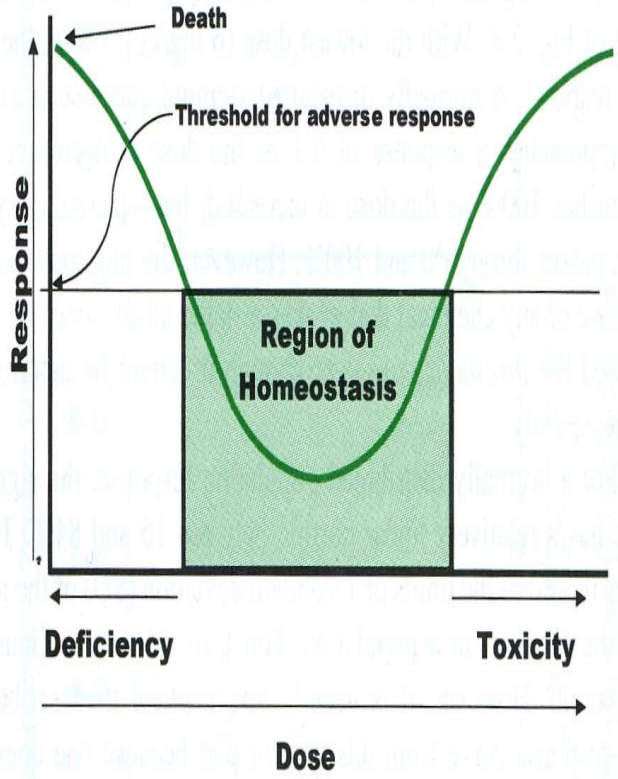
- Age
- Weight
- Gender
- Overall health
- Nutrition
- Other exposures
- Route of administration
- Temperature
- Time of day
- Season
- Gut contents
- Sex life

Determining Toxicity. Cancer D-R Curve

- The D-R model here assumes **no threshold**. That is no dose is without effect.
- Starting from a threshold of zero, a line is drawn to reach the lowest dose that caused cancer in an animal study.
- This is used to predict cancer risk at specific doses in humans.



Atypical D-R Curves: U-shaped



- **Vitamins and trace elements have U shaped D-R curves**
  - Toxicity from too little, « Deficiency »
  - Toxicity from too much, « Hypervitaminosis »
  - A range of homeostasis

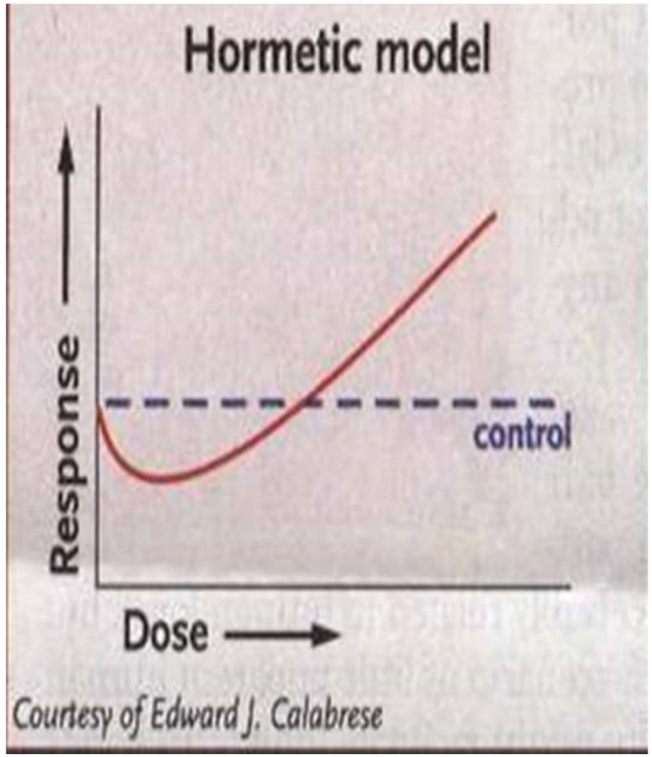
Often too little and too much have unrelated effects

Vitamin A

- Deficiency is the leading cause of preventable blindness in children in poor counries
- Vit A needed for RHODOPSIN

- Hypervitaminosis A causes central nervous system effects: headaches, nausea, irritability
- Vit A is fat soluble and crosses the BBB

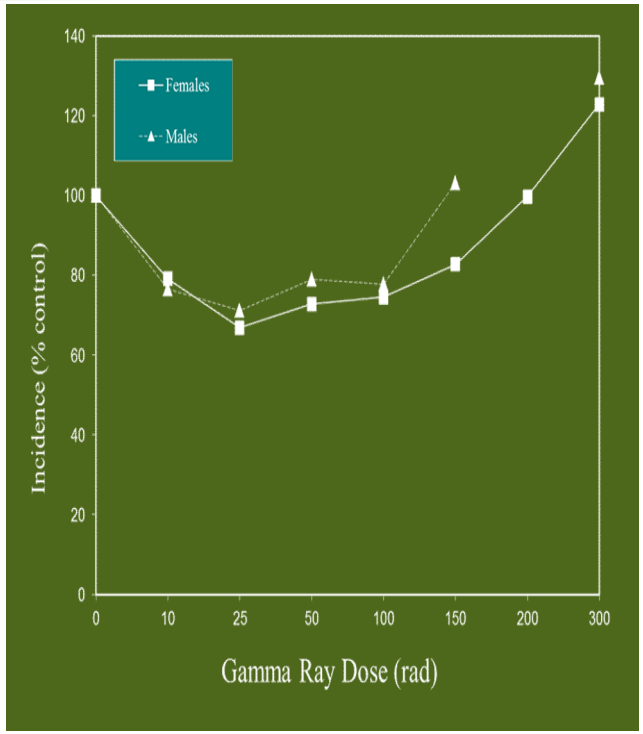
Atypical D-R curves: Hormesis



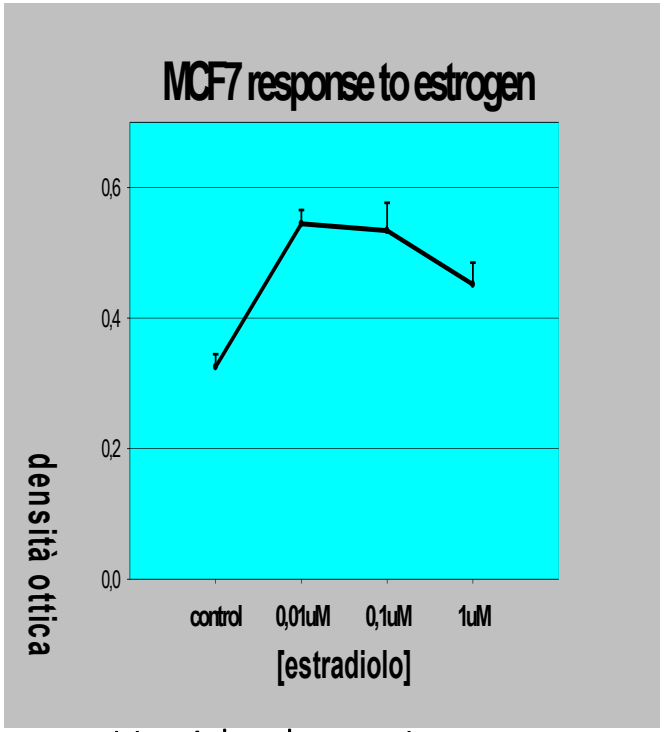
J-Shaped D-R Curve

- Opposite effect at low dose
  - Not a different response
  - Not a deficiency
  - Not beneficial then adverse
- Counter-intuitive

Many substances have hormetic D-R curves



J curve



Upside down J curve

QUESTION

The dose level at which a toxic effect is first encountered is known as the

- [x] Threshold dose
- [ ] First dose
- [ ] Median toxic dose
- [ ] LD50 dose

QUESTION

Which of the following does not affect toxicity?

- A Whether the agent is inhaled or ingested
- B Whether the exposed organism is male or female
- √ C Whether the agent is synthetic or naturally occurring
- D Whether the exposure is continuous or sporadic
- E Whether the exposed organism is a child or an adult

Today's Outline

- Toxicology: Introduction
- Determining Toxicity
- **Some Possible Food Toxicants: Pesticide Residues, Food Additives, Food Packaging**
- Risk Assessment: Hazards, Exposure, Characterisation

Pesticide Residues

Pesticides are poisons. Used as directed, they kill

- Fungicides kill fungi
- Insecticides kill insects
- Herbicides kill plants
- Rodenticides kill rodents
- Bactericides kill bacteria
- etc.

Pesticides are meant to be species-specific toxicants. Do they have effects on non-target organisms?

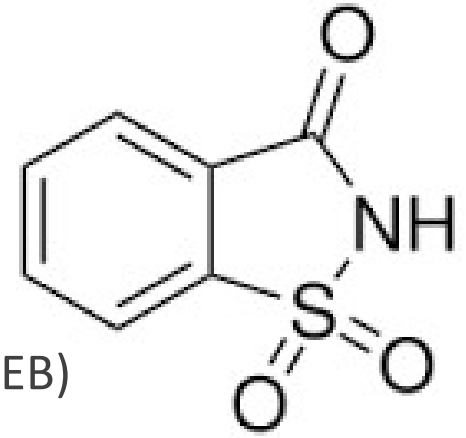
Personal protection equipment required for pesticide application

Food Additives

any substance intentionally added to food

Many agencies study the safety of food additives

- Joint FAO/WHO Expert Committee on Food Additives (JECFA)
  - Established in 1950
  - Assesses safety, internationally, of chemical food additives
- Codex Alimentarius Commission
  - Established in 1960
  - Has an on-line database of General Standard for Food Additives
    - http://www.fao.org/fao-who-codexalimentarius/standards/gsfa/en/
- Federation of American Societies for Experimental Biology (FASEB)
  - Does safety evaluations for the FDA
- European Scientific Committee for Food (SCF)
  - Similar to FDA



Saccharin is the name given to benzoic sulfimide in 1869

Food Packaging

Mail Online health

Home | News | U.S. | Sport | TV&Showbiz | Australia | Femail | Health | Science | Money | Video | Travel | Fashion Finder

Latest Headlines | Health | Health Directory | Diets | Discounts | Login

Ad closed by Google

Stop seeing this ad | Why this ad?

The hidden toxins in YOUR takeaway: Fast-food packaging contains harmful compounds that may lower fertility and cause cancer

- US study found evidence of polyfluoroalkyl substances in junk-food packaging

Site | Web | Enter your search | Search

Like Daily Mail | Follow @MailOnline

Follow Daily Mail | +1 Daily Mail

DON'T MISS

EDITION: UNITED STATES

REUTERS

Business | Markets | World | Politics | Tech | Commentary | Breakingviews | Money | Life

Votre prochain voyage à nos meilleurs prix

Copenhague

Vol direct depuis Paris

À partir de/aller simple

31,70€

HEALTH NEWS | Wed Feb 1, 2017 | 3:40pm EST

Toxic chemicals in one-third of fast food packaging

By **Lisa Rapaport**

(Reuters Health) - Fast food isn't exactly known for its health benefits, but a new U.S. study suggests even the packaging may be harmful.

That's because the study found one-third of fast food packaging contains chemicals known as PFASs (for polyfluoroalkyl and perfluoroalkyl substances) that give it stain-resistant, water-

Current Food Safety Concerns

- Safe, alternative and innovative manufacturing processes
- Safely reducing food waste, from producer through consumer
- Safe valorisation of by-products into foods
- Emerging chemical and biological food safety, including toxins and contaminants
- Traceable, safe and authentic products for consumer confidence

Today's Outline

- Toxicology: Introduction
- Determining Toxicity
- Some Possible Food Toxicants: Pesticide Residues, Food Additives, Food Packaging
- **Risk Assessment: Hazards, Exposure, Characterisation**

Risk Assessment is a part of Risk Analysis

4 STEPS OF RISK ANALYSIS

- Risk Assessment
- Risk-Benefit Analysis
- Risk Management
- Risk Communication

Risk Assessment

RISK:
THE PROBABILITY THAT AN EVENT (HAZARDOUS) WILL OCCUR.

RISK ASSESSMENT:
The process of gathering all available information
on the toxic effects of a substance
and evaluating it
to determine the possible risks associated with exposure.

- Risk Assessment may be performed for a single substance or, more realistically, for a complex « cocktail » of chemicals.
- For exposure to complex mixtures, the risk assessment itself becomes quite complex.

> *Greenpeace affirme que des cocktails de pesticides continuent d'être utilisés par les producteurs de pommes dans de nombreux pays européens, en particulier par les agriculteurs fournissant la grande distribution.*
>
> Le Parisien | 16 Juin 2015

Risk Assessment: 4 steps

1. Identify the **hazard**. What is the danger? What will be lost?
2. Evaluate the hazard by dose-response analysis.
3. Assess the exposure: Who is exposed and to how much?
4. Characterise the risk: **probability** (Frequent, Occasional, Improbable) and **severity** (Catastrophic, Critical, Negligible)

The probability of « losing » is important
The severity of the « loss » is important

Russian Roulette

Roulette Wheel

RISK ASSESSMENT MATRIX				
SEVERITY / PROBABILITY	Catastrophic (1)	Critical (2)	Marginal (3)	Negligible (4)
Frequent (A)	High	High	Serious	Medium
Probable (B)	High	High	Serious	Medium
Occasional (C)	High	Serious	Medium	Low
Remote (D)	Serious	Medium	Medium	Low
Improbable (E)	Medium	Medium	Medium	Low
Eliminated (F)	Eliminated			

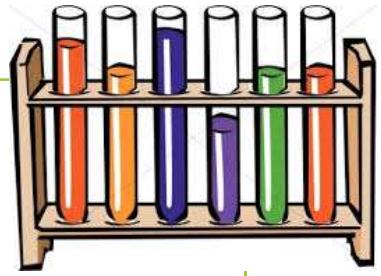
Risk Assessment:
1. Hazard Identification

AIM IS TO IDENTIFY:

- The innate adverse toxic effects of the agent
- The **primary hazard of concern**. Is it cancer?

Laboratory Studies

- *In vitro*
- *In vivo*
  - Acute
  - Chronic



Epidemiological Studies

- Retrospective.
  - Look back. Gather information from the past
- Prospective.
  - Look ahead, follow a population for a given amount of time.

Home 〉 Good Living

What's deal with non-stick cookware? Is it safe?

FRANKI HOBSON August 2 2016

SHARE PIN PRINT MAKE A COMMENT

Hazard Identification

Human epidemiology data are the most desirable source of data

But they are difficult to obtain

Often studies aren't available

When they are they are often incomplete or unreliable

Usually human studies provide qualitative data only

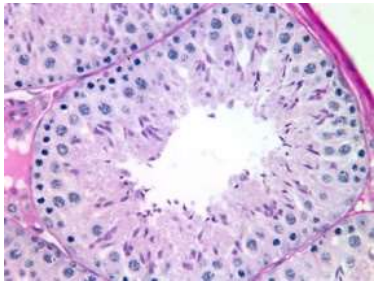
***In vivo* animal studies are the most common source of data**

Experiments are well controlled, exposures are known and clinical and pathological exams follow

The use of lab animals is necessary and accepted

Animals with physiology similar to humans are used.

In vitro studies are done on cells or isolated cellular molecules and provide supporting data particularly about the mechanism of action. **Structure-Activity Relationships (SAR) to prioritise testing.**



QUESTION

The definition of risk is:

- the capacity of a substance to cause an adverse effect in a specific organ or organ system

- √ the probability that a hazard will occur under specific exposure conditions

- the weighing of policy alternatives and selection of the most appropriate regulatory actions