foodregsci

STARTING THE RISK ASSESSMENT APPROACH

Prof. Samuel Godefroy, Ph.D. *| Full Professor, Food Risk Analysis and Regulatory Policies*

Review of a Risk Assessment Approach…

Reviewing the notions of Hazard and Risk

Reviewing the various approaches to achieve hazard characterization for chemicals in food

Studying the Hazard for Chemicals : TOXICOLOGY

Definition :

- From the Greek words τοξικός - toxicos "poisonous" and logos. Studies the adverse effects of chemicals on living organisms.

Mission:

- To identify possible hazards of chemicals and to investigate deleterious effects of chemicals on living organisms

Paracelsus (1493-1541)
The founder of toxicology

Dosis sola facit venenum

It is the dose that makes the poison

Chemical	poisonous	mortal
Water		17 L
Kitchen salt		200 g
Ethanol		175-300 mL
Solanin	25 mg	400 mg

Toxic Effects of Substances

Reversible:

- ❑ Effects are completely reversible: when the toxicant is eliminated, the effect disappears
  - E.g. trichothecene – local on the skin - skin irritation (red discoloration)

Irreversible:

- ❑ Compound is not (or very slowly) eliminated or degraded: action persists because agent persists
  - E.g. chlorinated hydrocarbons
    - TCCD (= dioxin) => persistent chloracne
- ❑ Toxin binds covalently to essential macromolecules: action persists because the toxic effect persists even after elimination or degradation of the agent.
  - E.g. Aflatoxin-B1-8,9-oxide forms stable DNA-adducts lead to mutations and possibly cancer

Viktor Juschtschjenko (Ukrainian President) 2006: poisoned with TCCD in 2004 (chloracne)

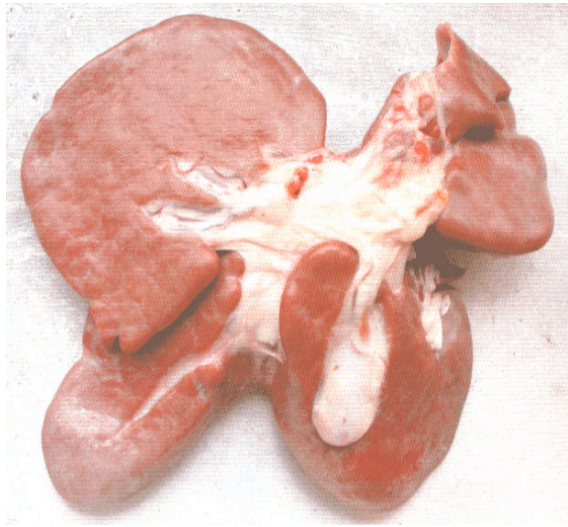
Toxic Effects of Substances (2)

Acute effects:

- ❑ Short exposure time (seconds to hours)
  - High dose: cause is easily recognizable, dramatic symptoms
    - E.g. deoxynivalenol may cause vomiting (vomitoxin)

Chronic effects:

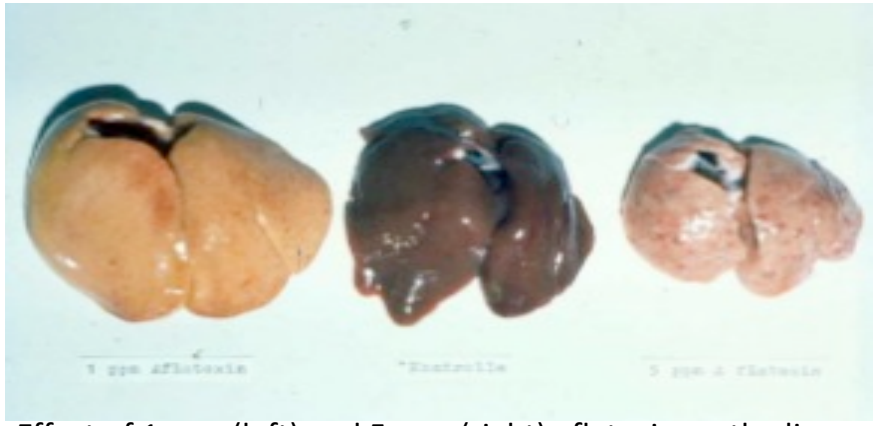
- ❑ Long exposure (weeks to years)
  - Low dose can cause effects that are not easy recognizable. Symptoms may initially not be present or weak
    - e.g. ethanol –> stomach (local) –> gastritis –> cirrhosis of liver (replacement of liver tissue by fibroid and scar tissue)



Example : Aflatoxin

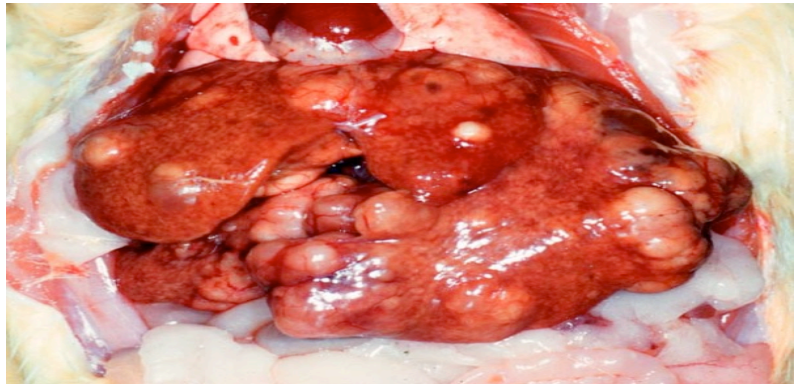
Acute Toxicity ⟷ **Chronic Toxicity**

- ❑Deterioration of liver and kidney function
- ❑Jaundice (yellow skin)
- ❑Emesis (vomiting)
- ❑Anorexia (no appetite)
- ❑Ascites (fluid in the peritoneal cavity)
- ❑Gastrointestinal haemorrhage (bleeding)



Effect of 1ppm (left) and 5ppm (right) aflatoxin on the liver (control in the centre)

- ❑Liver cancer
- ❑Chronical hepatitis (inflammation)
- ❑Jaundice
- ❑Hepatomegalie (abnormal size)
- ❑Liver cirrhosis*
- ❑Immune suppression

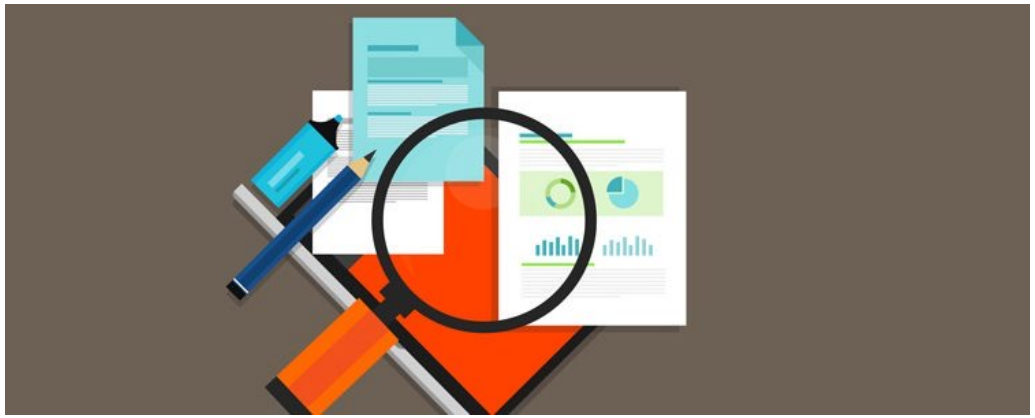


Rat liver tumors (AfB1)

* replacing organ tissue by connective tissue

Assessing the Toxicity of Chemical: Methods

- ❑General acute irritation and sensitization
  - Acute toxicity studies:
    - Acute oral toxicity
    - Acute dermal toxicity
    - Acute inhalation
  - Irritation:
    - Skin irritation in vitro
    - Skin corrosion in vitro
    - Skin irritation in vivo
    - Chorioallantoic Membrane Vascular Assay (CAMVA) (replacement of the ocular irritation test)
    - Sensitization (skin)



- ❑Studies with multiple application: subacute, subchronic and chronic studies
- ❑Reproduction and teratogenicity studies
- ❑Mutagenicity studies
- ❑Carcinogenicity
- ❑Special studies
  - Immune toxicity, neurotoxicity etc.
- ❑Toxicokinetics and metabolism

Assessing Acute Toxicity of Chemicals – *in vivo*

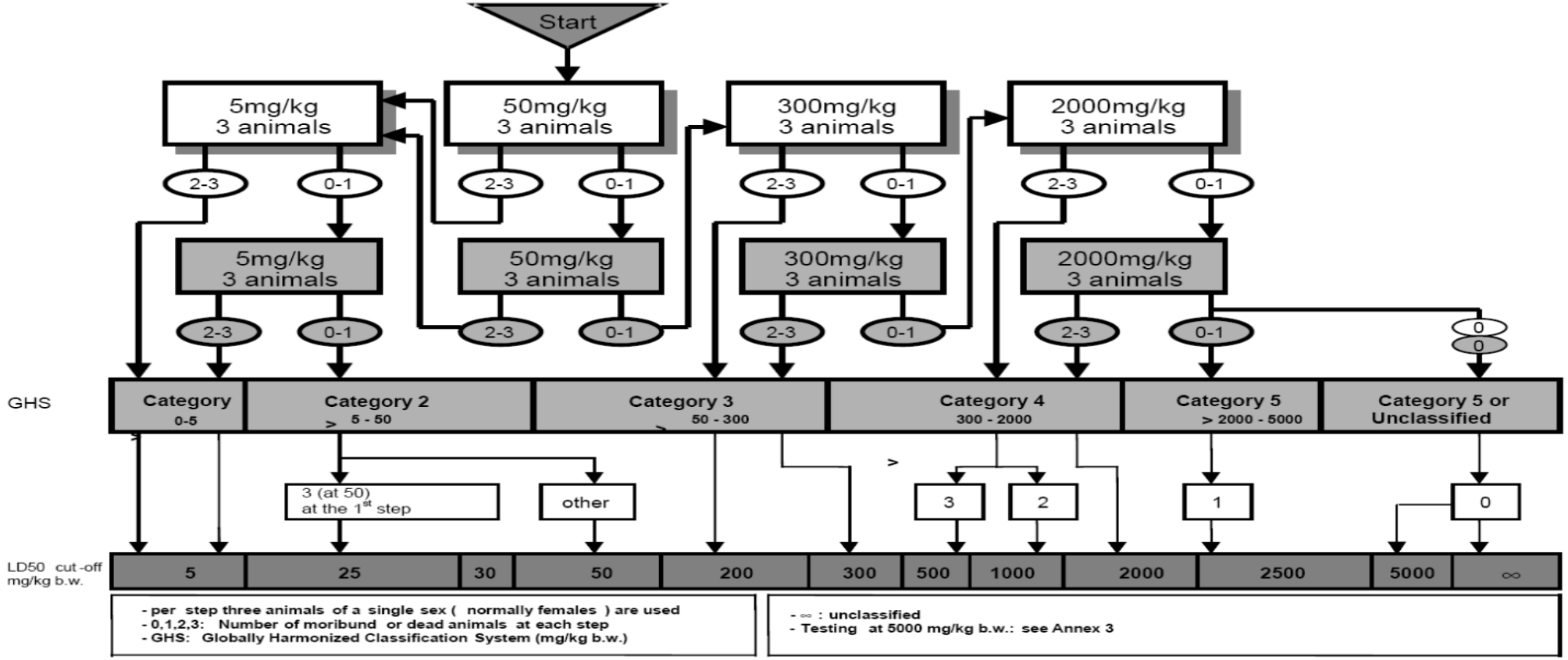
- Goal: assess the risk of a single high dose of a substance
- May occur for example in an accident at work, after food poisoning….
- Endpoint = LD_{50} or LC_{50} (lethal dose, lethal concentration, killing 50% of the animals)
- Classically LD_{50} with many animals/concentrations to assess 50% mortality exactly
- LD_{50} determination is now prohibited and replaced with tests using less animals

Exposition	Animals	Treatment	Remarks
Oral	one species (rat/mouse) 3-10 animals (female)	Single gavage ≠ [ ]	3 OECD guidelines Observation: 2 weeks Then killed and examined
Dermal	5 animals of each gender (rat, guinea pigs, rabbits)	during 24 hours (acute) ≠ [ ]	On shaved back (at least 10% body surface)
Inhalation	rodents* 5 animals of each sex	during 4 hours ≠ [ ]	Gas, vapor, aerosol (dust or mist: particle diameter 1-4µm)

* = rat, mouse, guinea pig, hamster. Rabbits are not rodents!

Determination of Acute Oral Toxicity According to OECD Guideline 423

ANNEX 2b: TEST PROCEDURE WITH A STARTING DOSE OF 50 MG/KG BODY WEIGHT



foodregsci

Subacute, Subchronic and Chronic Studies

Goal:

- ❑ To investigate the effect of a “normal” exposure to a substance
- ❑ Mimics the effect of a sporadic (e.g. suncream), daily (medicine, aftershave) or whole life time (environmental or food contaminant (e.g. in bread)) contact with a substance

Duration of the study:

- ❑ Depends on the duration of exposure to a specific substance:
  - E.g. medicine: normal therapy period
  - E.g. environmental contaminant: whole lifetime
- ❑ Subacute, ≤ 28 days; subchronic, < 1 year; chronic >1 year
  - E.g. a carcinogenic study goes over the whole lifetime of the animal – for rat 24 months, for mice 18-24 months

Dose:

- ❑ Specific range-finding experiments can be carried out in a preliminary test
- ❑ One dose where no symptoms should occur (NOAEL)
- ❑ Second dose where only weak toxic relevant symptoms should occur
- ❑ Third dose should show clear toxic relevant effects (maximal tolerable dose = MTD, with weight reduction of ca. 10%)
- ❑ Control group and satellite groups (for example to test recovery) are added

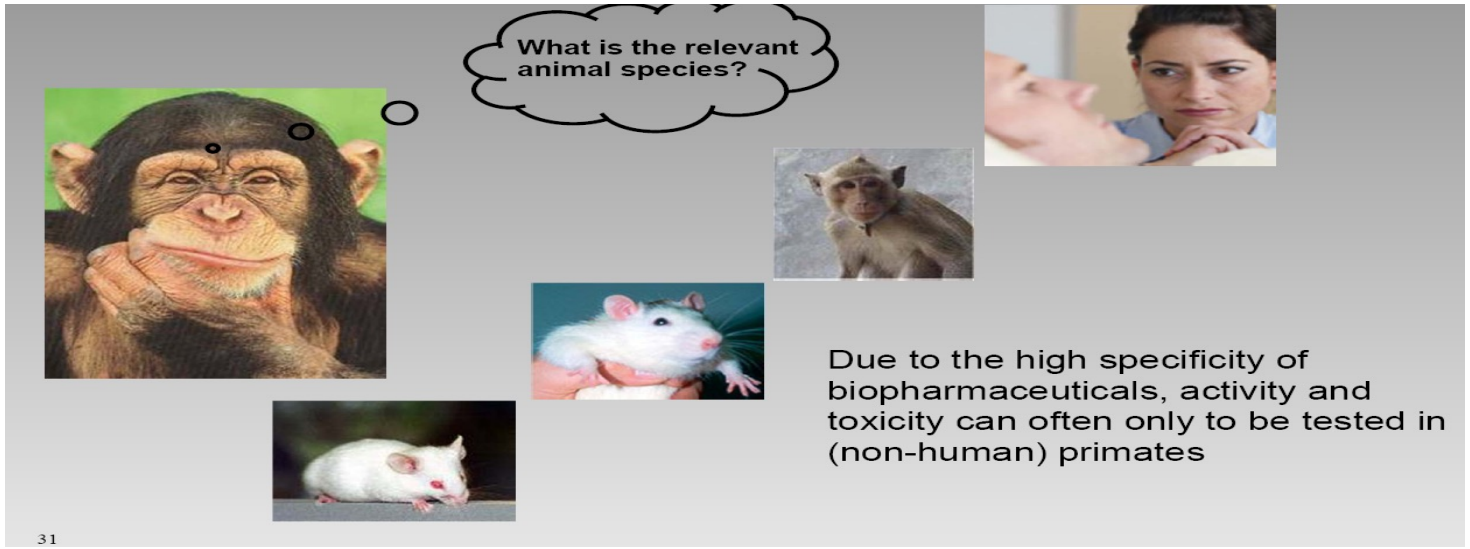
Application method of the substance:

- ❑ According to the way of uptake in humans
  - E.g. food contaminants applied in the feed of the test animals
  - E.g. dust particles (workplace) applied via inhalation

Subacute, Subchronic and Chronic Studies (2)

Animals:

- ❑Mostly rats: most endpoints are determined with this species
- ❑Mouse or other rodents only if rat is not suitable (physiological reasons for example)
- ❑Guidelines may require a second non-rodent species: e.g. canine (=dog) for pesticides or primates for (human) drugs



Subacute, Subchronic and Chronic Studies (3)

Number and gender of animals:

- Depends on the guidelines. For rodents:
  - subacute and subchronic studies 5 to 10 animals in each group and for each gender
  - chronic studies 20 animals/group and/gender
  - cancerogenic studies 50 animals/group and/gender
  - For non-rodents (canine, monkey) less animals are used (3-4/group and/gender)

Observations:

- Are assessed regularly (daily, ¼ year….) depending on the parameter
  - clinical pathology/symptomatology:
    - E.g. wounds, lethargy, drinking and feeding behavior, bodyweight
  - ophtamology: eye check
  - haemathology: red and white blood cells…..
  - clinical chemistry: organ specific parameter of liver and kidney
  - analyses of the urine
  - necropsy, weight of animals/organs (organ toxicity), histopathology (e.g. tumors)

Evaluation of the experiment (endpoints):

- Repeated dose studies suitable for the derivation of dose response curves
- Is effect reversible?
- Determination of the Lowest Observed Adverse Effect Level (LOAEL)
- Determination of the No Observed Adverse Effect Level (NOAEL)


thank you
danke
謝謝
рахмат
ngiyabonga
teşekkür ederim
Баярлалаа
спасибо
mersi
kia ora
barka
welalin
tack
spas
faafetai lava
vinaka
blagodaram
dank je
misaotra
matondo
paldies
grazzi
mahalo
tapadh leat
gracias
спасибі
kiitos
dankie
nanni
nandri
dhanyavad
mauruuru
köszönöm
dankon
aĉiū
akun
хвала
asante
manana
obrigada
murakoze
tenki
bedankt
bayarlalaa
gràcie
hvala
enkosi
dziękuję
djiere dieuf
tau
mochchakkeram
дякую
mamnun
chokrane
chnorakaloutioun
gratias ago
gràcies
sulpáy
taiku
go raibh maith agat
sobodi
děkuji
obrigado
sagolun
sukriya
kop khun krap
arigatô
takk
dakujem
trugarez
mèsi
didi madloba
najis tuke
ありがとう
tanemirt
grazie
rahmet
kam sah hamnida
rahmat
terima kasih
diolch
dhanyavadagalu
shukriya
mercé
мерси
তোমাকে ধন্যবাদ
감사합니다
xièxie
ευχαριστώ
merci