Toxicology and Safety in III V epitaxy

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Arsenic compounds in nature

Earth crust ~ 2mg/kg (2 ppm in weight)

Volcano activity (gas, particles, dust) and geological layers

Minerals : FeAsS (mispickel), As_4S_4 (realgar),As_4S_6 (orpiment)

Impurity in minerals based on Cu, Sn, Pb, Zn, Co, Au...

Water : ocean, river, drinking (mineral As)

Food : fish & sea food [metalorganics : arsenobetaine R-As-$(3CH_3)_3$], residues of chemical treatment (mineral or not)

Use of Arsenic compounds

- Lead battery : As-Sb-Pb
- Hunting items (shots round and hard Pb-As)
- Pesticide, insecticide, herbicide, defoliant (cotton)
- Wood preservative : CCA (Cr, Cu, As) [forbiden now]
- Electronics : GaAs [As sources : arsine and metalorganic substitutes, $AsCl_3$ or As), As (dopant for Silicon)
- Medicine & veterinary applications, still used as antiparasitic agents (amebiasis)
- Chemical weapon : LEWISITE, a blistering poison gas, prepared but not used during World War I. Its antidote is available (British Anti Lewisite : BAL)
- Green colorants : (Cu arsenites) (green of Paris, green of Scheel)

Occupational, environmental, nutritional exposure

- In all industries listed before
- In waste treatment industry : recycling of lead batteries
- In mines : extraction of Au, As from its minerals
- In metal manufacturing : Co, Zn, Pb and Cu minerals in which As is an impurity
- Fossil coal burning (coal-fired power plant, domestic use…)
- Agricultural products, wood preservation CCA
- From food : water, fish and sea food, residues from plant and fruit treatments

Massive intoxications related to Inorganic arsenic in 1998

Natural contamination of drinking water (sources from specific geological layers).

- TAIWAN (since a long time) epidemiological study on 40 000 people.
- ARGENTINA, MEXICO, CHILE (since a long time).
- MONGOLIA, WEST BENGAL (India), BENGLADESH (since many years) in 1998, millions of persons were concerned.

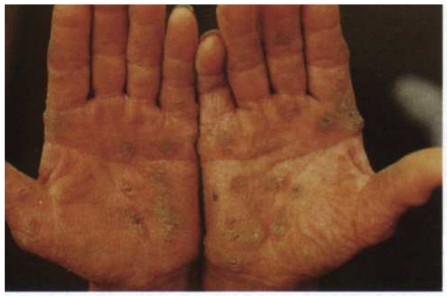
Skin cancer, internal organ cancer, not lung cancer.

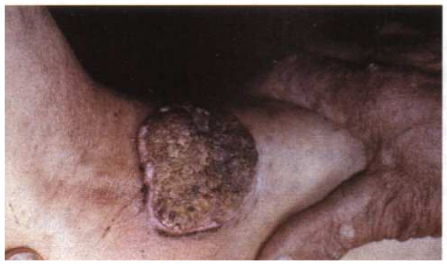
Circulatory track problem (black foot disease).

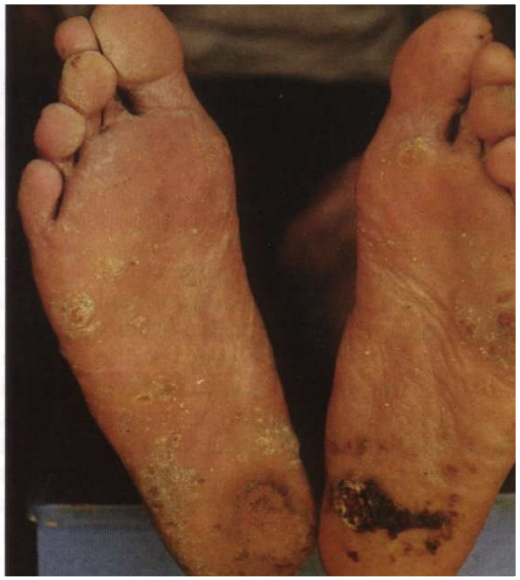
WHO Alert : end of 2000

Tap water legislation (EC) => Concentration of As per liter of water **< or = 10µgAs/liter**

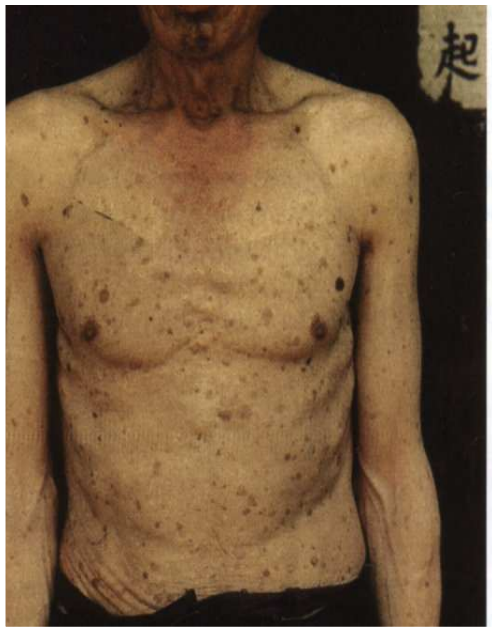
Massive intoxications related to Inorganic arsenic in 1998

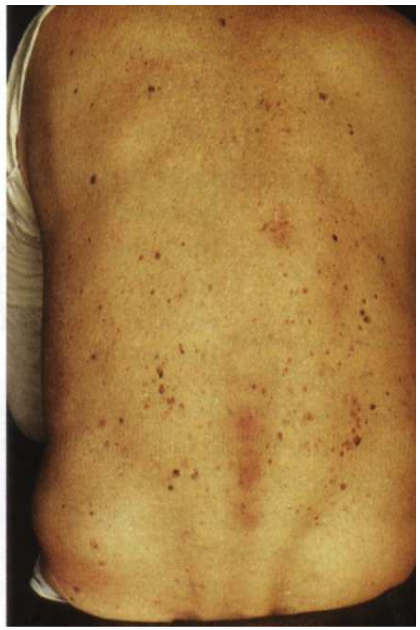






Examples





Skin cancer

Some mineral and metalorganic As compounds

MINERAL COMPOUNDS

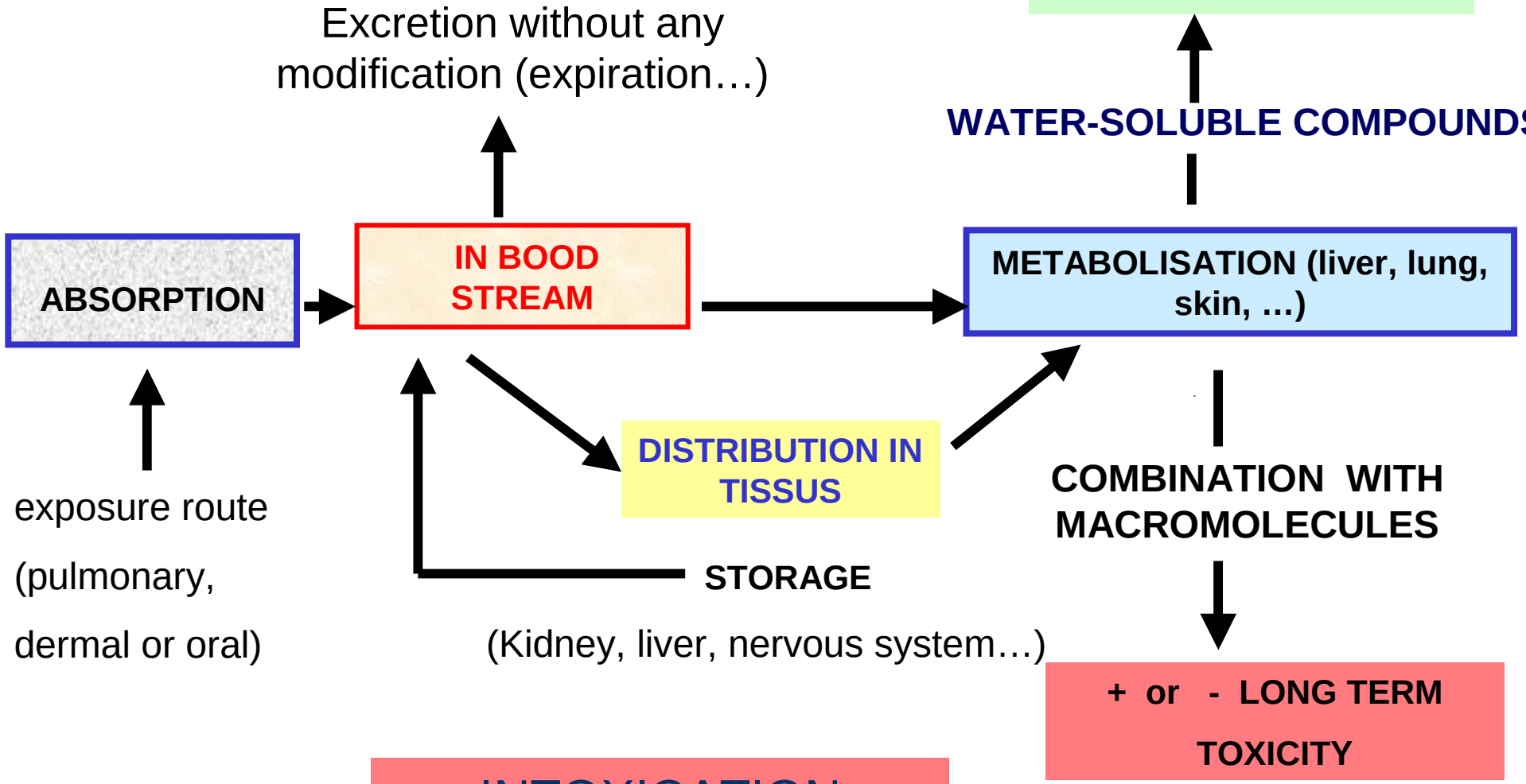
- Arsine As
- As_2O_3 As_2O_5
- As_4S_4 GaAs InAs…

METALORGANICS

- TBA : $AsH_2C(CH3)_3$
- MMA : $CH_3AsO(OH)_2$
- DMA : $(CH_3)_2AsOOH$
- TMA : $As(CH_3)_3$
- DMAAs : $AsN_3(C_2H_6)_3$
- Arsenobetaine : R-As-$(CH_3)_3$

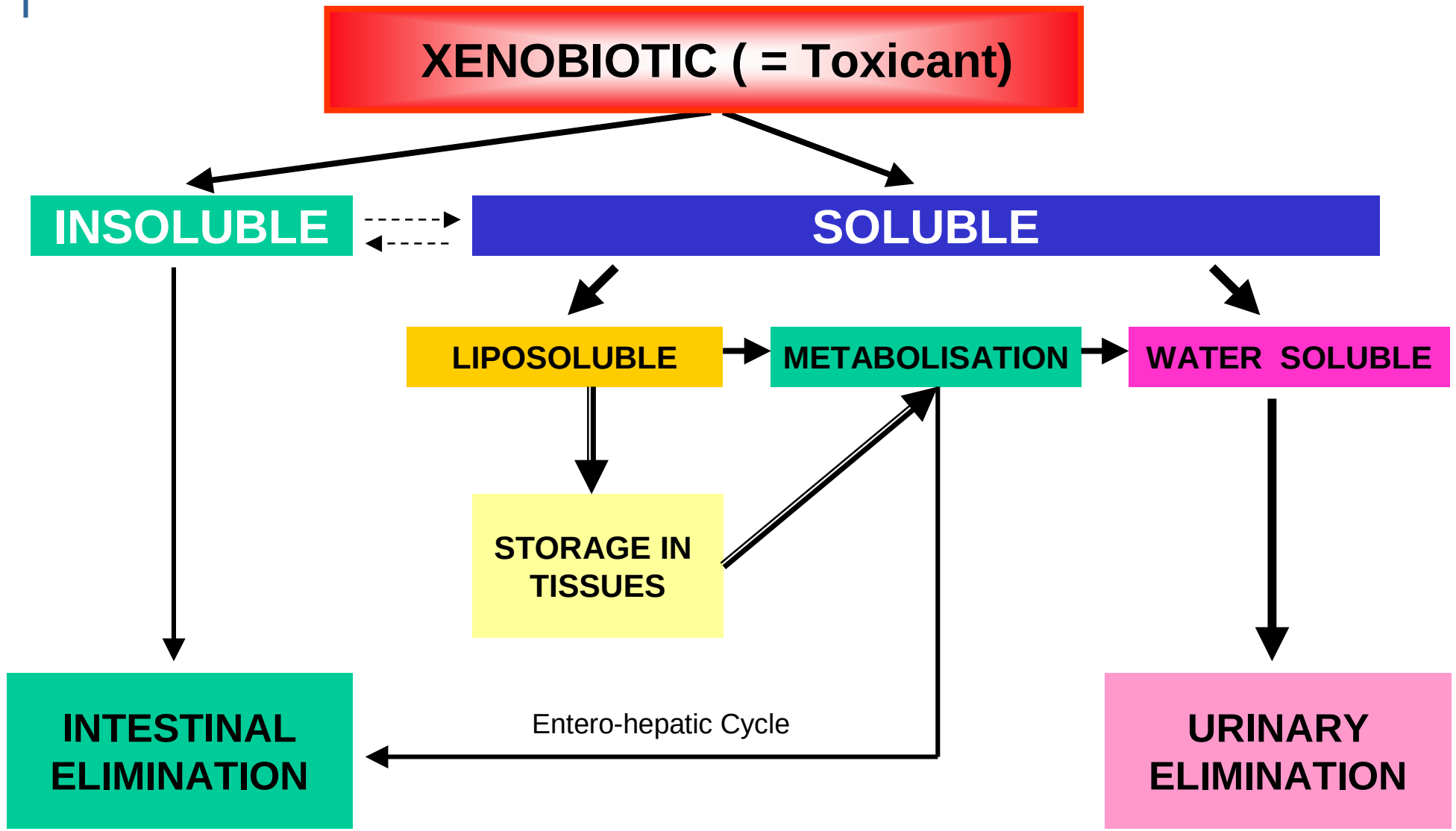
SPECIATION is very important for exposure, toxicity, metabolisation, excretion and biometrology

DETOXICATION

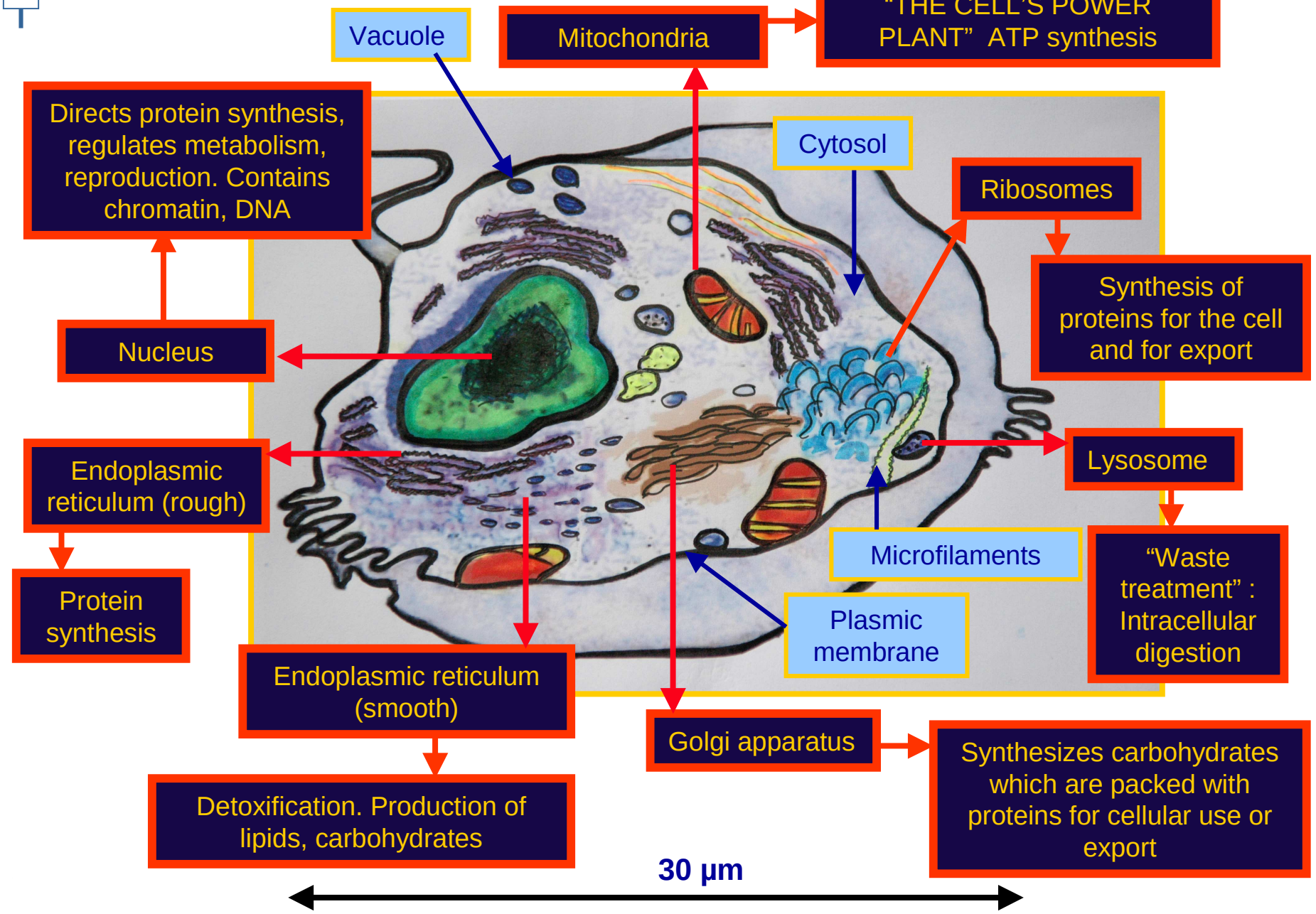


INTOXICATION

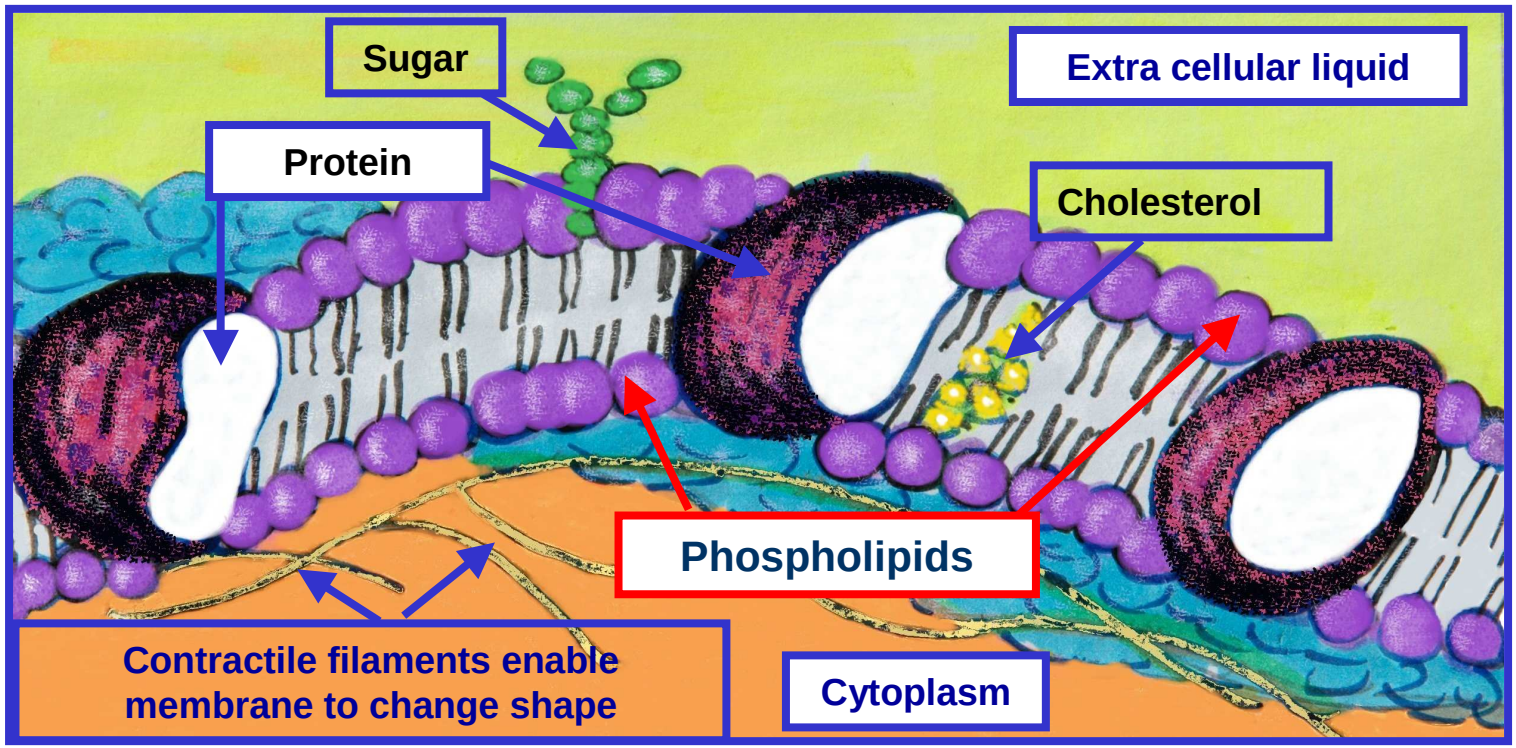
Solubility importance



A typical cell. Sites where toxicants have their impact



Cell membrane arrangement and structure



Phospholipid molecules (phosphates + lipids). - Phosphate head is hydrophylic (attraction for water) Lipid tail is hydrophobic (no attraction for water) and lipophilic (attractive to lipid soluble substances).

Cell membrane (semipermeable) = a sandwich of 2 layers of phospholipids (phosphate heads => outer regions exposed to water)

Processes of cellular absorption

Substances use different passive or active transport mechanisms to enter into the cell

1- Passive or spontaneous : without energy, based on simple diffusion (gradient of concentration, from high to low concentration until equilibrium). If no gradient no movement.

2- Facilitated diffusion : assistance of specific carrier proteins on the outer surface of the cell to which molecules will be bounded in order to be passively transported into the cell

3- Active transport with energy, Based on the consumption of cellularly produced energy (Adenosine triphosphate or ATP). Against gradient of concentration.

2 & 3 : said of few importance to introduce toxicant into the cell, but 2 &3 important for elimination of metabolites out of the cell

Solubility and excretion

Substances absorbed into the body that are fat soluble or lipophilic or lipid soluble are difficult to excrete

To remove fat soluble substances from the body, they are transformed in the liver by the phase I and phase II reactions, producing **more water-soluble compounds** called metabolites

Phase 1 reactions (mainly catalyzed by Cytochrome P 450) : oxydation, hydrolysis, reduction

Phase 2 reactions = conjugation of phase 1 metabolite : sulfate conjugation, methylation, glucuronidation (in liver)...

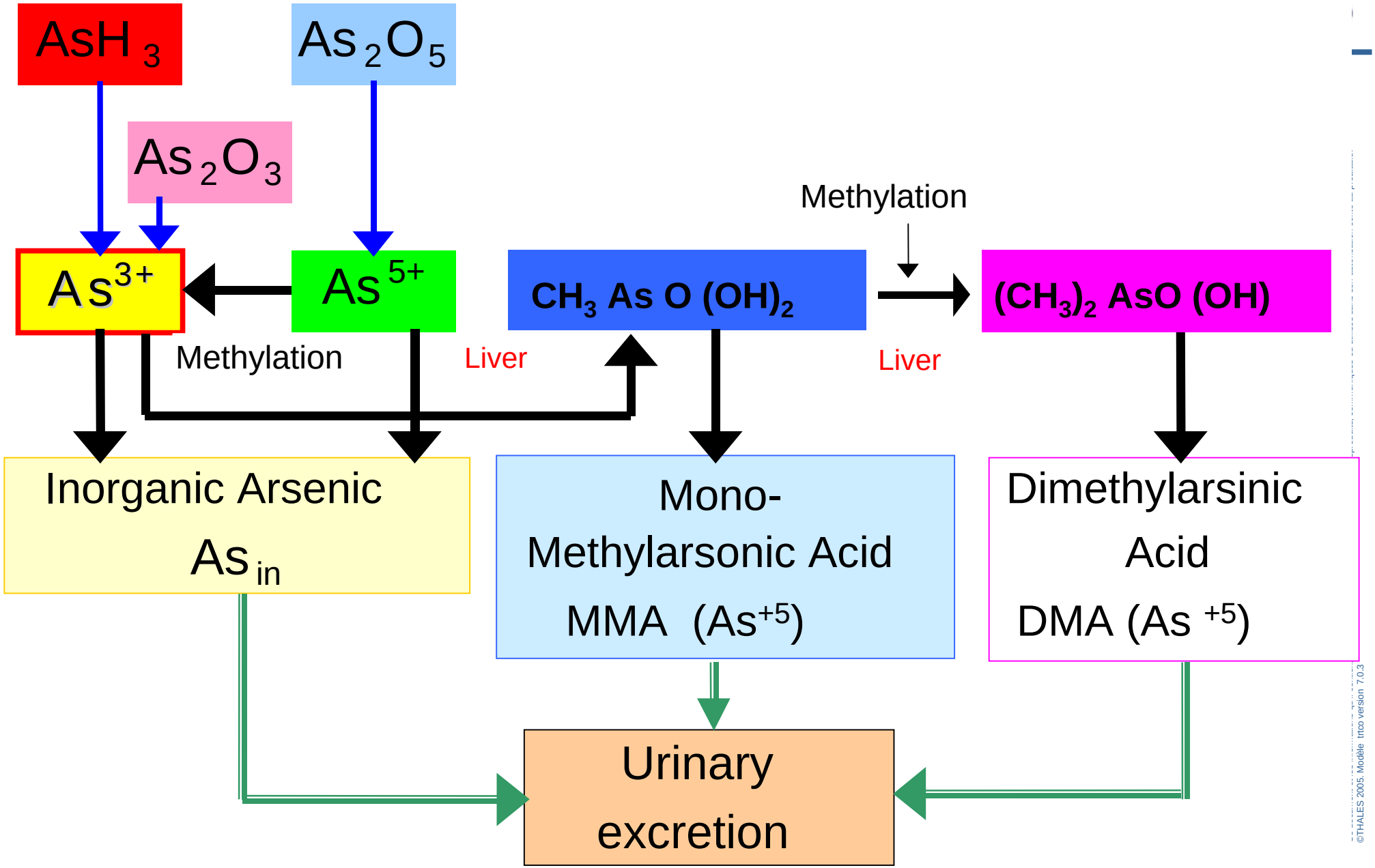
Arsine toxicity

Lipid soluble gas, well absorbed in lung => easy to enter the blood stream

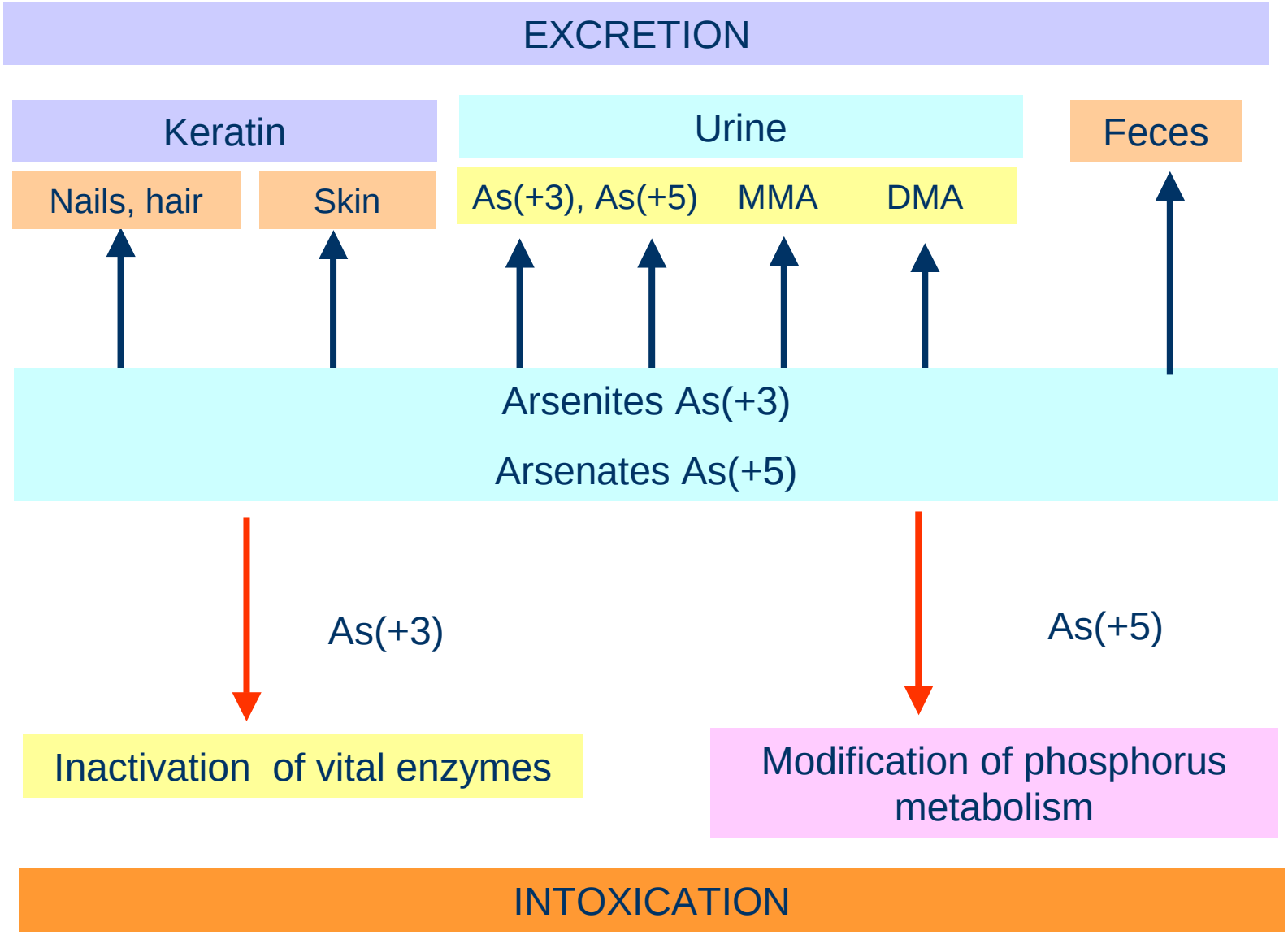
HEMOLYSIS :

red blood cell destruction by oxygen based reactive species (H_2O_2 …) ➔ destruction of cell membranes ➔ free hemoglobin

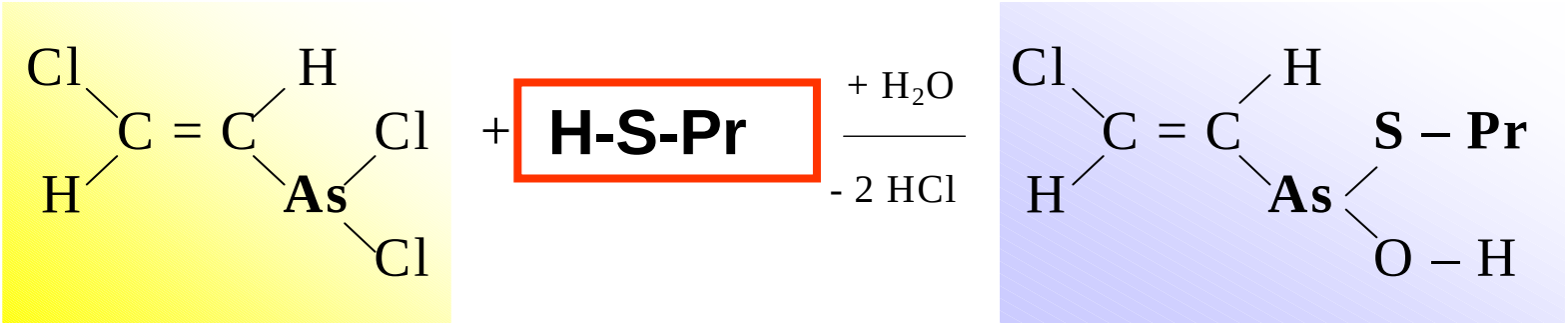
Then toxicity of inorganic arsenic (As valence +3), inactivation of many and important enzymes and proteins with sulphydryl groups SH (biological cell life and toxicant metabolisation affected)…



Excretion, intoxication after exposure to arsenites and arsenates



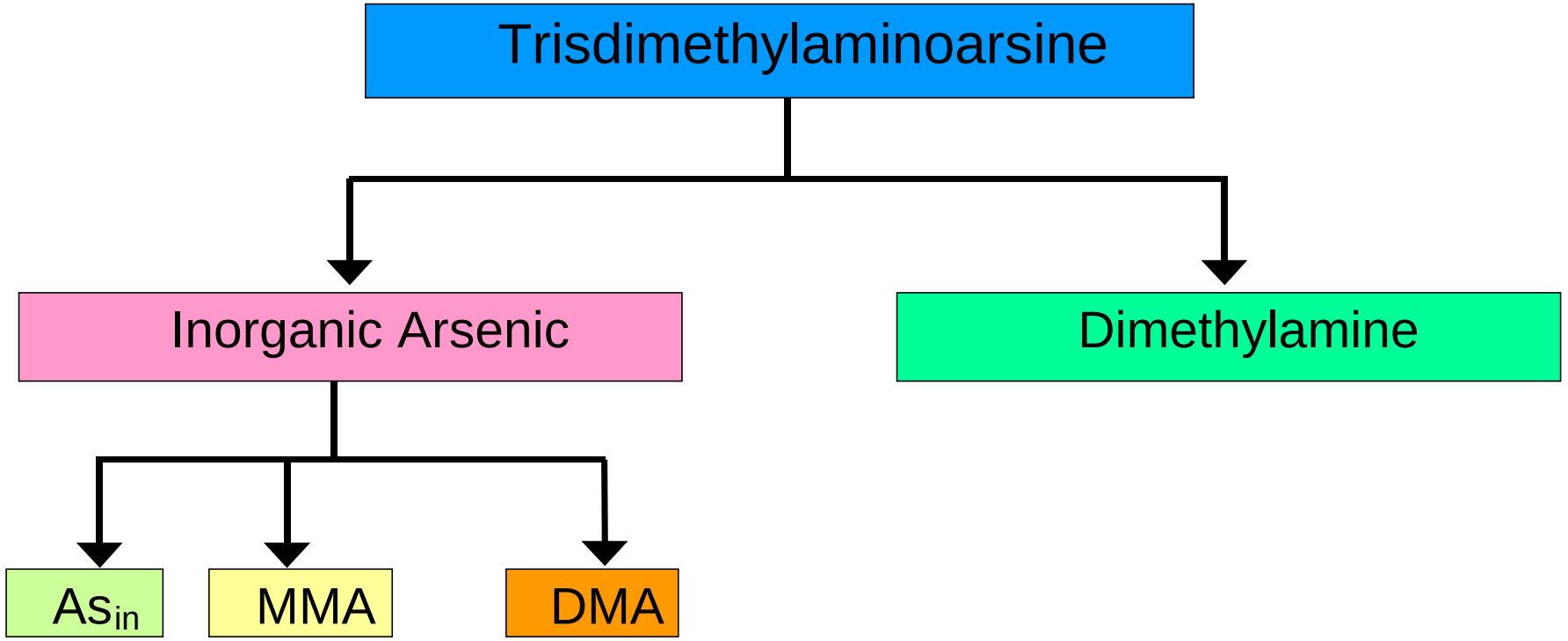
Dichloroarsines, such as the chlorovinyldichloroarsine or Lewisite, (chemical weapon from the World War I) are very toxic at the cellular level as they are attracted by protein with thiol S-H (protein and enzyme inhibition...).



Lethal Dose$_{50}$ or LD$_{50}$ arsenic compounds

Arsenic compounds	LD_{50} (mg/kg)	Animal / Administration mode
Arsenite : arsenic trioxide	**34,5**	**mice / oral**
Arsenite : sodium arsenite	**4,5**	**rat / intraperitoneal**
Arsenate : sodium arsenate	**14 - 18**	**rat / intraperitoneal**
MMA : monomethylarsonic acid	1 800	mice / oral
DMA : dimethylarsinic acid	1 200	mice / oral
Arsenobetaine	**> 10 000**	**mice / oral**
Trimethylarsine oxide	**10 600**	**mice / oral**
Trimethylarsine	**8 000**	**mice / subcutaneous**
Trisdimethylaminoarsine	**15**	**mice / subcutaneous**

DMAAs In vivo metabolism

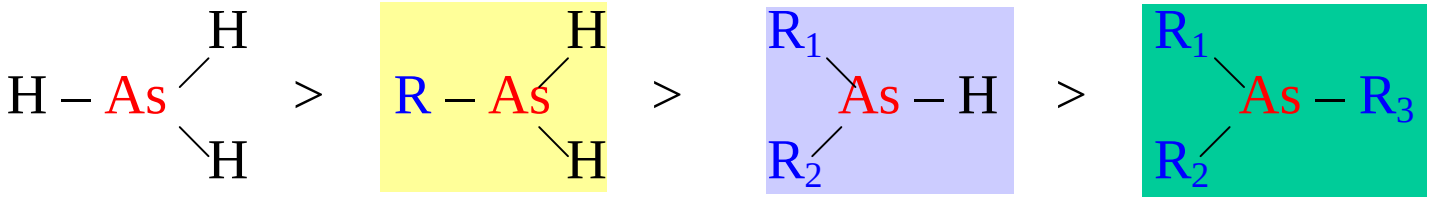


Metabolism of trisdimethylaminoarsine in vivo

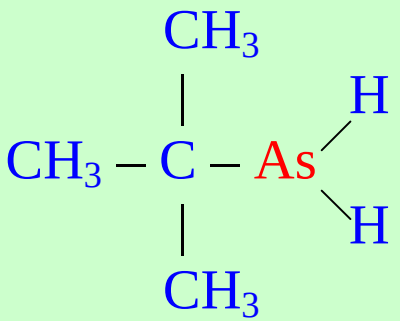
Arsine and substitutes

3 hydrogen can be substituted and replaced by organic groups to decrease toxicity

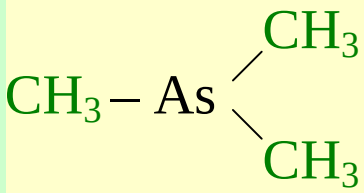
Decreasing toxicity (not always true!)



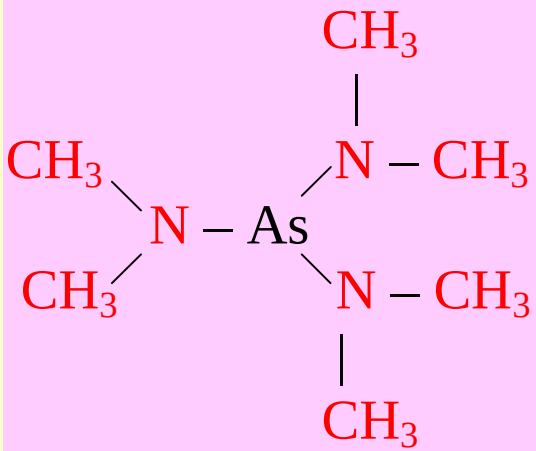
Arsine LC_{50} = 5 to 10 ppm



Tertiarybutylarsine
LC_{50} = 70 ppm



Trimethylarsine
LD_{50} = 8000 ppm (mg/kg)
LC_{50}= 20 000 ppm



Trisdimethylaminoarsine
LD_{50} = 15 ppm (mg/kg)

As & As compounds : carcinogens for Human

ACUTE, LONG TERM TOXICITY

As TARGET ORGANS

- Skin, Kidney, Liver
- Blood
- Respiratory system
- Gastrointestinal tract
- Nervous system
- Cardiovascular system

IARC, As & As compounds : Group 1 = carcinogens for Human

***** IARC end 2003, GaAs (Group1) this is due to Ga!…**

Experiments on animals

For As compounds : hard to find the adapted model as humans are much more reactive and sensitive than rodents

The rat is not the right model, the hamster or the rabbit is more convenient

GaAs, InAs excretion

GaAs (intraperitoneal) ➔ after 5 days 0,3% of the dose in urine

InAs (subcutaneous) ➔ after 5 days 0,25% of the dose in urine

Excretion : urine, feces, fur… Organ deposition

Difficulty to identify acute and long term toxicity

In vivo slow dissolution

GaAs / InAs => As, Ga, In mineral compounds =>

As_2O_3 ? Ga_2O_3? In_2O_3? or others

Kinetics of excretion not the same for As, In or Ga

As biological monitoring (urine) not possible

No biological monitoring for In and Ga

Biological monitoring => **As in urine**

SPECIATION : As_{inorg} + MMA + DMA

As in urine = As_{inorg} + MMA + DMA + TMA (TRIMETHYLATED)

No measurement of total As which includes (TMA)

- Measurement by a combination of hydride generation and atomic absorption spectrometry - External quality control program

BIOLOGICAL EXPOSURE INDICATOR (BEI) = GUIDELINE

Non exposed people < 10 µg As / g creatinine

Metabolites in urine after exposure

MINERAL COMPOUNDS :

- ARSINE, As_2O_3, As_2O_5…=> As_{inorg} + MMA + DMA
- GaAs, InAs => As_{inorg} + MMA + DMA (slow kinetics)

METALORGANICS :

- TBA => As_{inorg} + MMA + DMA
- DMAAs => As_{inorg} + MMA + DMA + DIMETHYLAMINE METABOLITES
- ARSENOBETAINE => ARSENOBETAINE

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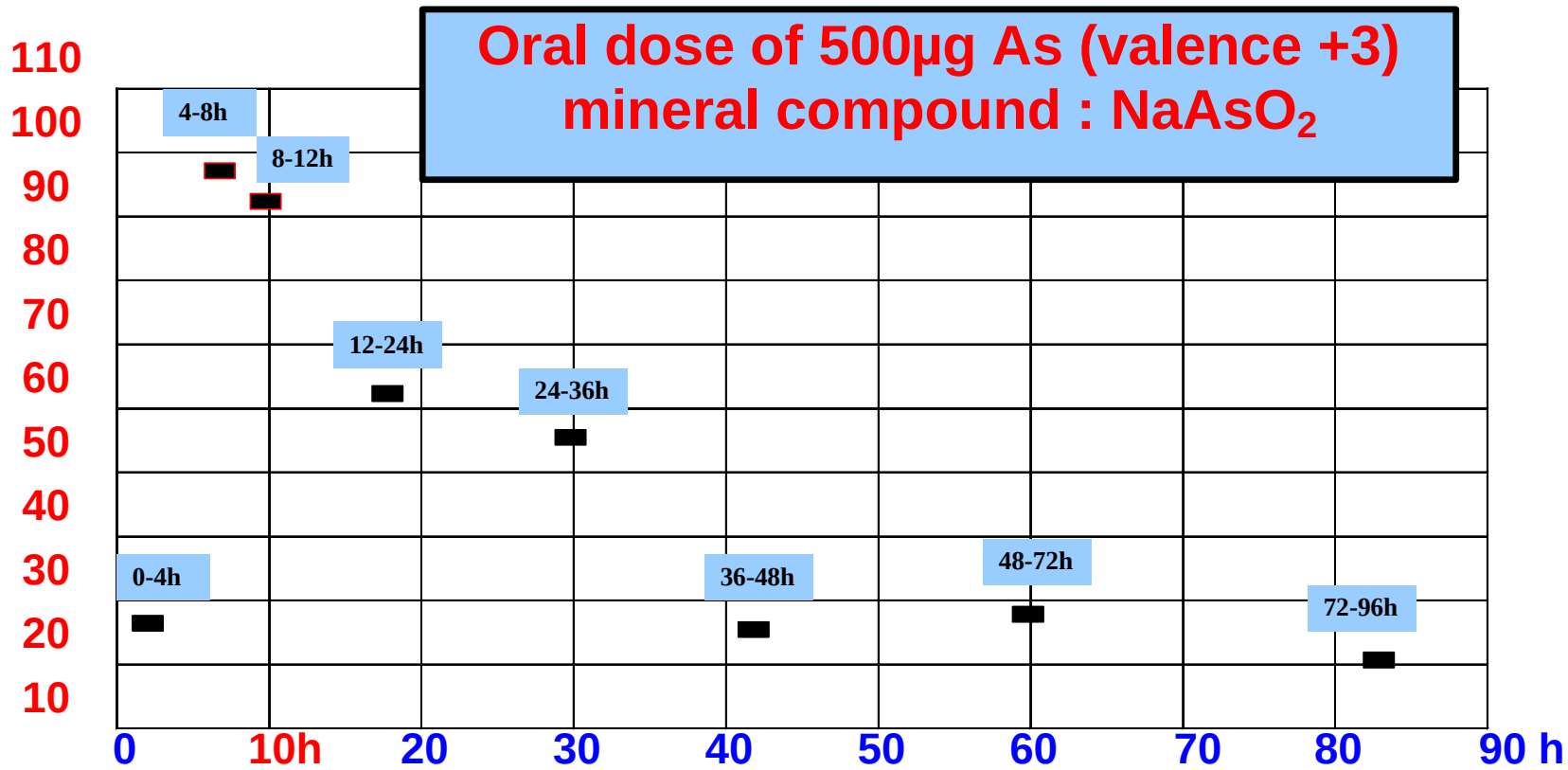
J P BUCHET study on Humans



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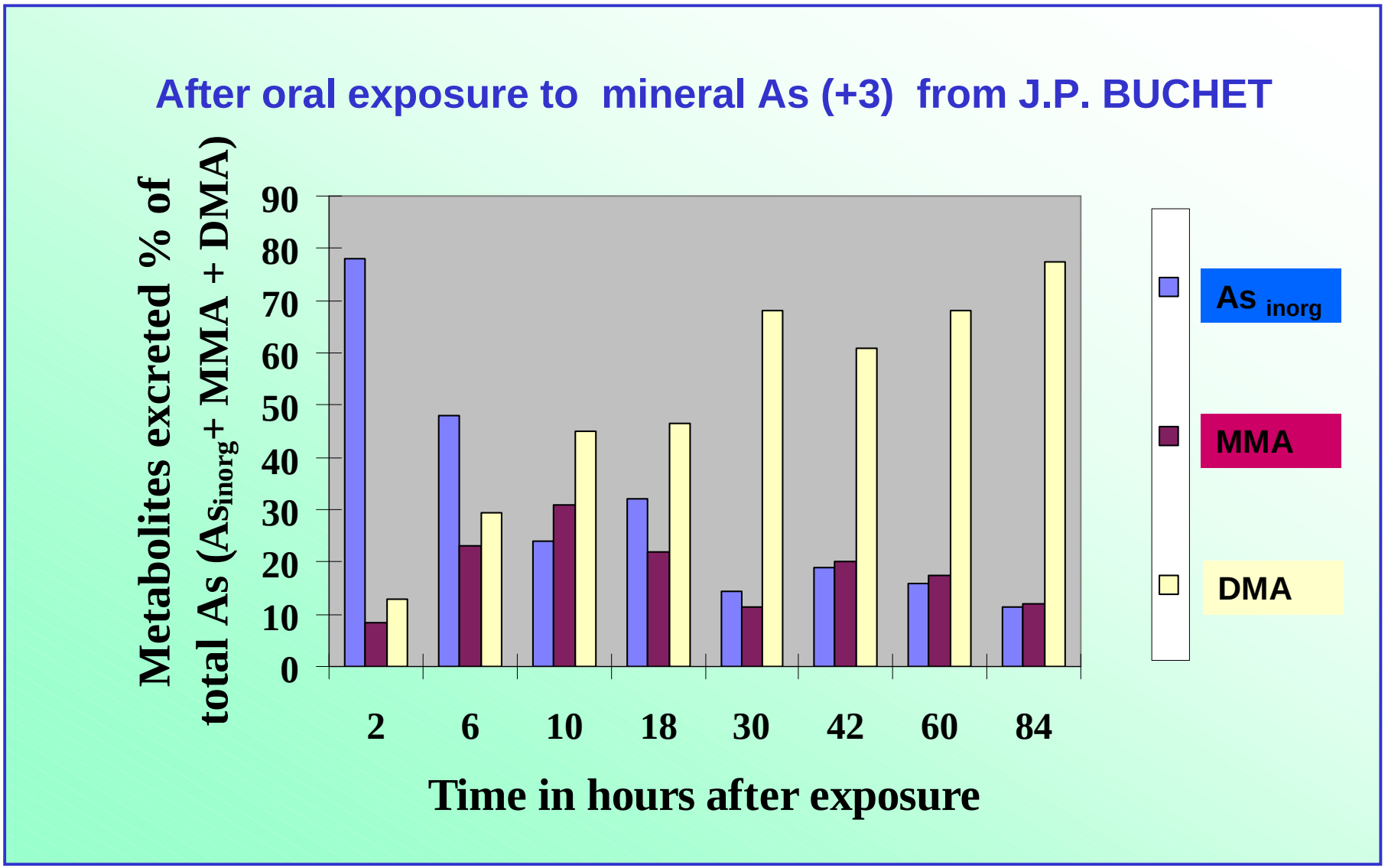
WWW BRIGHTER EU

THALES

J P BUCHET study on Humans



Studies on Humans : summary

1 - INORGANIC As : $NaAsO_2$ (Buchet study)

46% dose excreted in 4 days

1/2 excretion (23%) in 28h (1/2 biological lifetime)

excretion of 3 metabolites : Asi + MMA + DMA

on 96 h, are excreted : 25% Asi + 21% MMA + 54% DMA

2 - DIMETHYLED As : $(CH_3)_2AsO_2Na$ (Buchet study)

75% dose excreted in 4 days

1/2 excretion en 11h (1/2 biological lifetime)

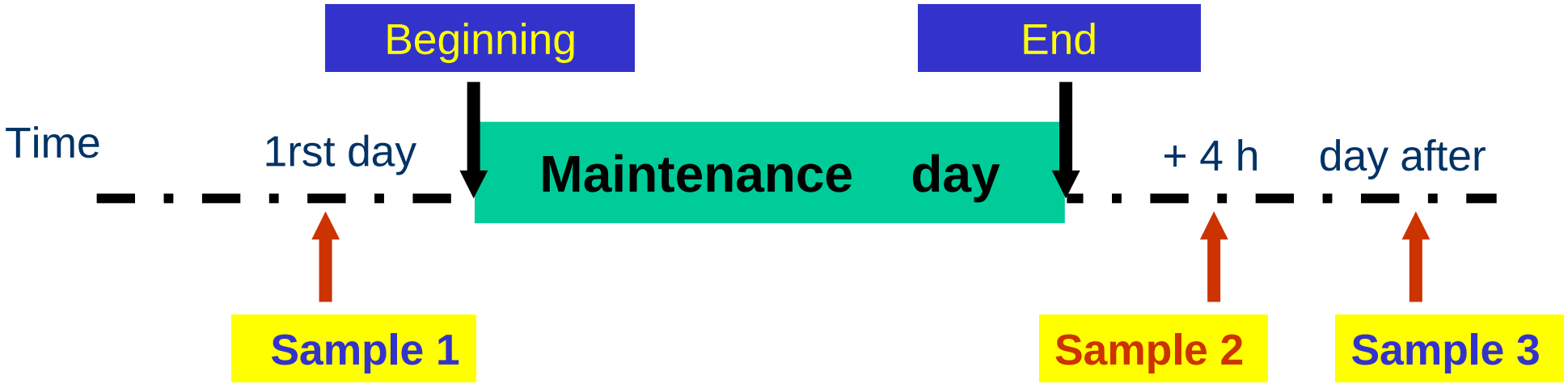
excretion : only DMA

3 - TRIMETHYLED As commonly excreted without any transformation (arsenocholine, arsenobetaine, ...)

78 % dose in 1,5 day

Urine sampling : a new protocol defined by the doctor

Recommendations to avoid diet interferences!



- Sample 1 : morning urine before starting work
- Sample 2 : urine collected 4 hours after the end of exposure
- sample 3 : 1rst morning urine the day after exposure

Arsenic hazards in brief in epitaxy maintenance

Arsine (and other As compounds) can be released from :

- pump oil
- some solid materials deposited at low temperature
- waste
- paper used during maintenance …

Each system has to be characterized to evaluate hazard sources : results dependent on the machine.

MBE is different from MOCVD

Similar hazards related to P compounds can be mentioned

- In Microelectronics, potential exposure (variable time and intensity) to arsine and/or As metalorganics and As based particles (during the maintenance the GaAs deposition system)

- Speciation on As molecules in air necessary to identify all the gaseous species emitted during maintenance.

- Speciation on As in urine necessary to check if there was exposure. Collect urine at the right time.

Possible interferences (due to the diet).

- Exposure level seems to be low as shown by speciation results on urine. (People well protected and adequate workstations)