Toxicology
An Introduction

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General considerations

- Toxicology is the science which lets us know how substances can harm life by physico-chemical reactions with living cells
- All substances, whether synthetic or natural, can cause harm to people, animals, plants, micro-organisms, and their environment

General considerations

- There are naturally occurring substances which are as poisonous as or more poisonous than the most toxic synthetic chemicals
- For example - ricin, *Clostridium botulinum* toxin, saxitoxin

Toxicity and dose

- The toxicity (poisonous nature) of any substance is inversely related to the amount (dose) required to cause harm
  - The more that is required, the lower the toxicity
- But – all substances are toxic at a high enough dose

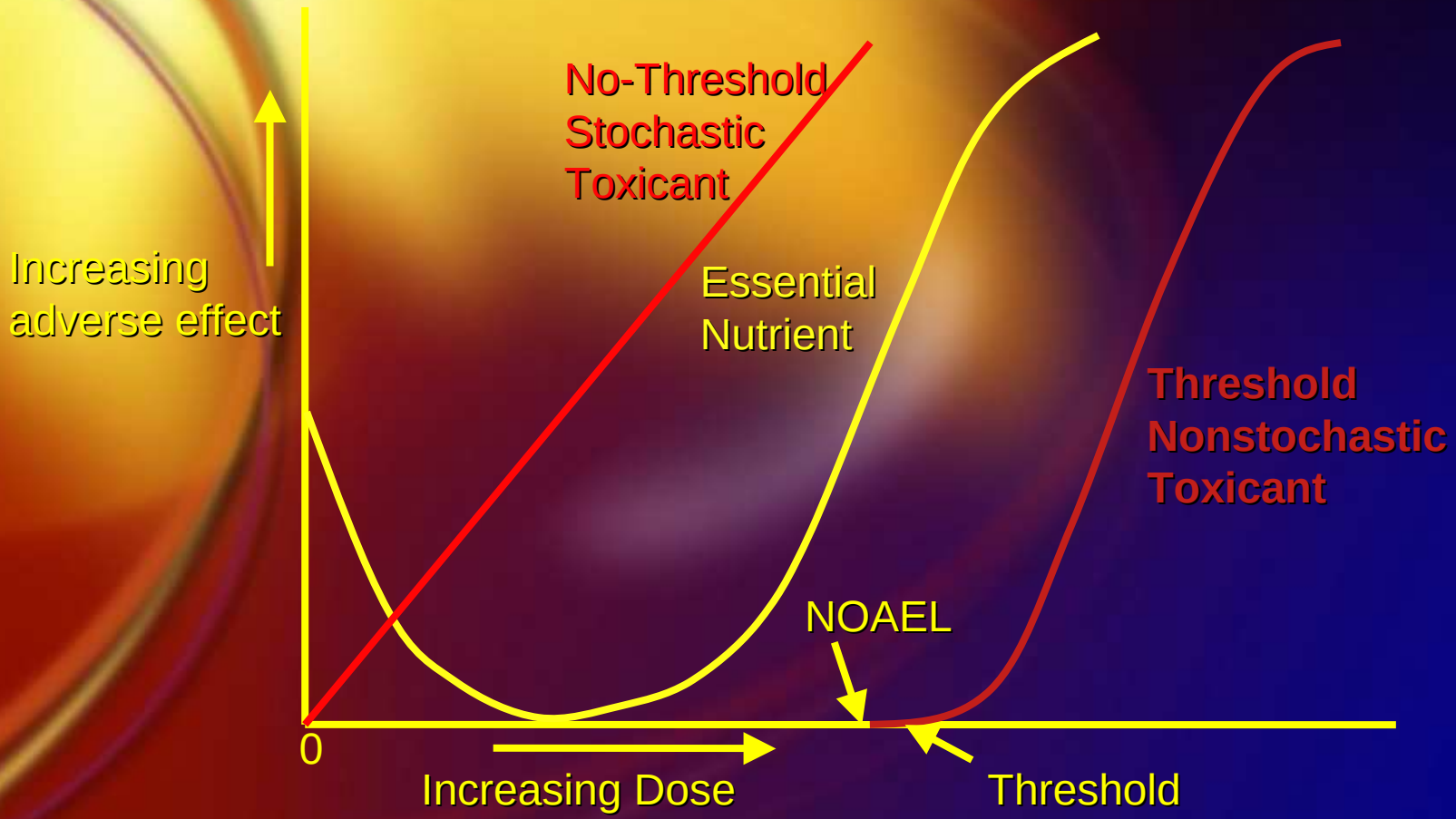
Toxicity and dose

- Substances that can cause harm following exposure to very small amounts, sometimes no more than a few molecules, are said to be extremely toxic
- Substances that require exposure to many grams before harm results are said to have low toxicity

Toxicity and Dose

- Even essential nutrients become toxic if the amount ingested is above a certain acceptable dose
- Some substances such as oxygen are toxic (harmful) at the dose which is essential for life! We are protected by anti-oxidants
  - Oxygen is toxic at all levels to obligate anaerobes (toxicity classification?)

Dose-effect curves



What is a poison?

- 500 years ago, a physician called Paracelsus wrote the following fundamental rule of toxicology:
  - "Only the dose required makes the difference between a cure and a poison"
- Note: Paracelsus is the name given to **Theophrastus Phillippus Aureolus Bombastus von Hohenheim**

What is a poison?

- Water ? - essential for life but people have died from drinking too much pure water, washing out essential salts such as sodium chloride and potassium chloride
- Fresh water fish rarely survive in salt water or salt water fish in fresh water and so both could be classified as “poisons”

What is a poison?

- Vitamin A ? - essential for human health; it is fairly easy to exceed the required dose and people have died from eating too much
  - It may also cause developmental abnormalities in babies if their mothers consume too much while carrying them during pregnancy

What is a poison?

- Oxygen ? - essential for aerobic life but destroys essential molecules by oxidation; protective mechanisms involving compounds such as vitamin C, vitamin E, and glutathione have evolved
- Reactive oxygen species (ROS) have been implicated in mutagenesis and carcinogenesis

Natural and synthetic chemicals

- Aflatoxin, from the fungus *Aspergillus flavus*, is one the most potent carcinogens known, causing liver cancer in people, birds and fish after eating food made from contaminated cereals such as rice

Natural and synthetic chemicals

- The distinction between naturally occurring substances and synthetic substances is of little value in considering toxicity
- Pure natural vitamin C and pure synthetic vitamin C are identical molecules and equally good for people

Movement through the environment

- Substances in the environment, whether toxic or not, may enter living organisms directly - by inhalation (lungs or gills), ingestion, by skin contact, through wounds, or through the eyes
- Or indirectly from food or through the environmental media - air, soil, sediments, or water

Routes of human exposure from the environment

- Each route of exposure must be considered separately although the effects may be interactive

Routes of direct human exposure

Eyes

Respiration through nose and mouth

Ears

Ingestion through mouth*

Absorption through skin, wounds

Exposure of baby in the womb through the placenta

*Do not forget exposure of babies through mother's milk

Different routes - different effects?

- Different routes of exposure may cause different effects from the same substance
  - Sometimes only one route of exposure is harmful
  - For example, organophosphate pesticides are highly toxic through the lungs but break down in the stomach

Exposure of the child in the womb and babies

- The developing child in the womb may be harmed by substances in the mother's bloodstream which can pass across the placenta into the baby's blood circulation
  - An example is methylmercury chloride, found naturally in tuna and swordfish, which can kill a baby in the womb at levels which do not harm the mother

Exposure of the child during breast feeding

- The breast feeding child may be harmed by substances in mother's milk
  - Particularly dangerous in this respect are persistent fat-soluble compounds such as organochlorine pesticides which can accumulate in the breast; they are included in the United Nations list of persistent organic pollutants (POPS), banned in many countries

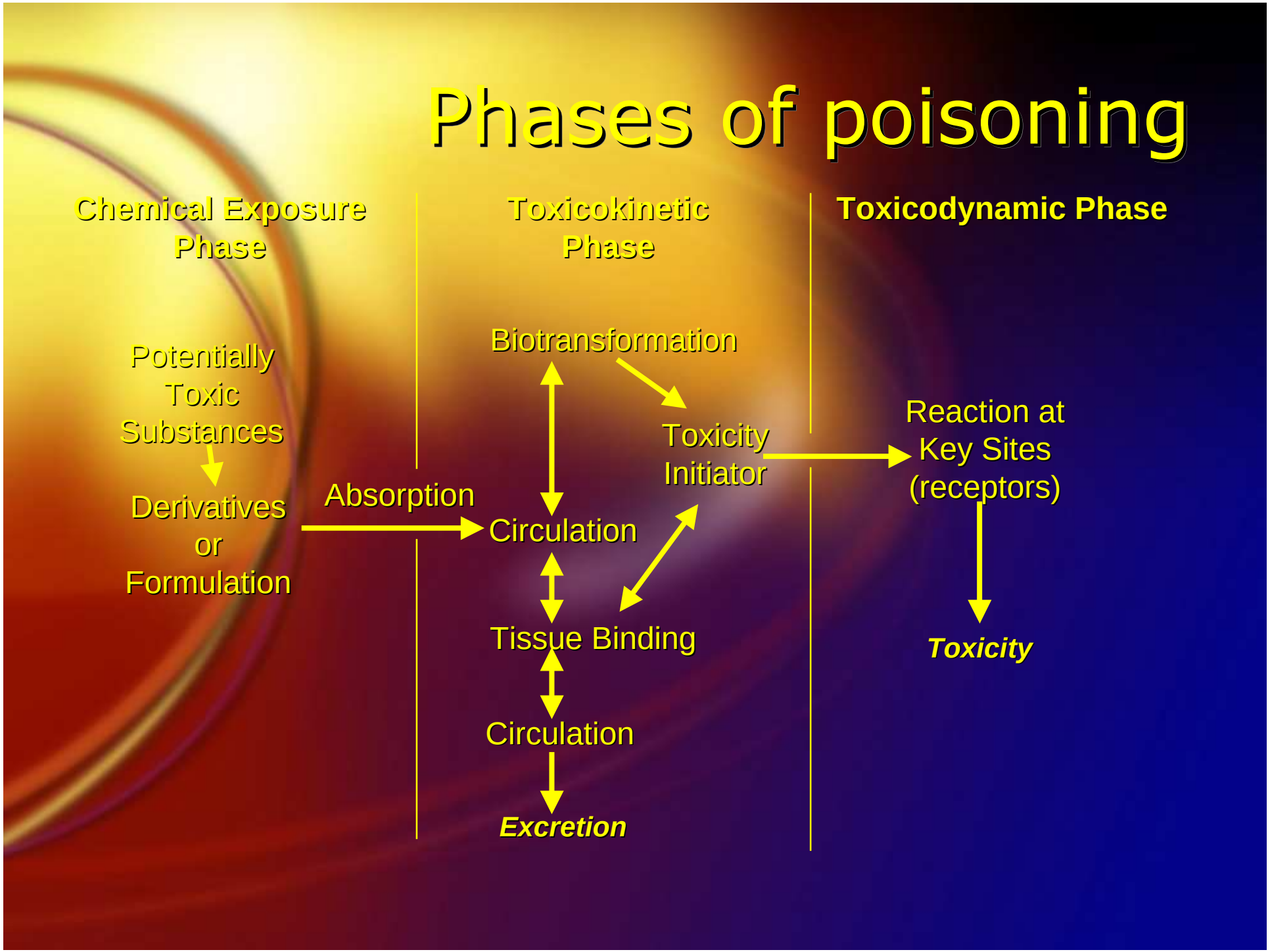
Nanoparticles

- Particles smaller than 2.5 μm and particularly nanoparticles, previously called ultrafines (<100 nm), may lodge permanently in the alveoli and cause chronic problems; nanoparticles may move through cell junctions into the body and affect the heart

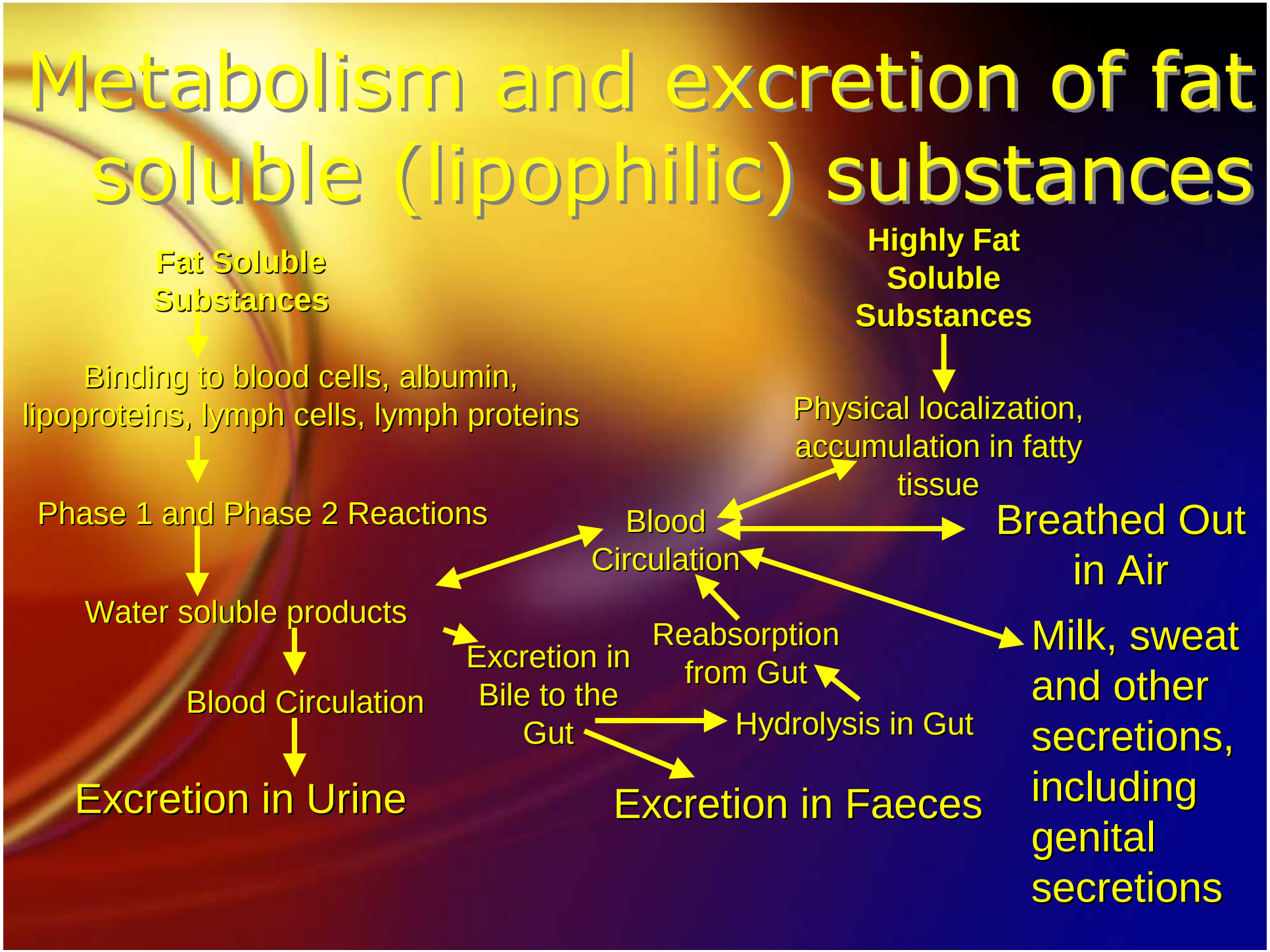
Phases of poisoning

- Exposure (already discussed) is the first phase
- The toxicokinetic phase covers uptake to excretion
- The toxicodynamic phase covers all aspects of the way in which a substance causes harm once it reaches its "target" in the body

Phases of poisoning

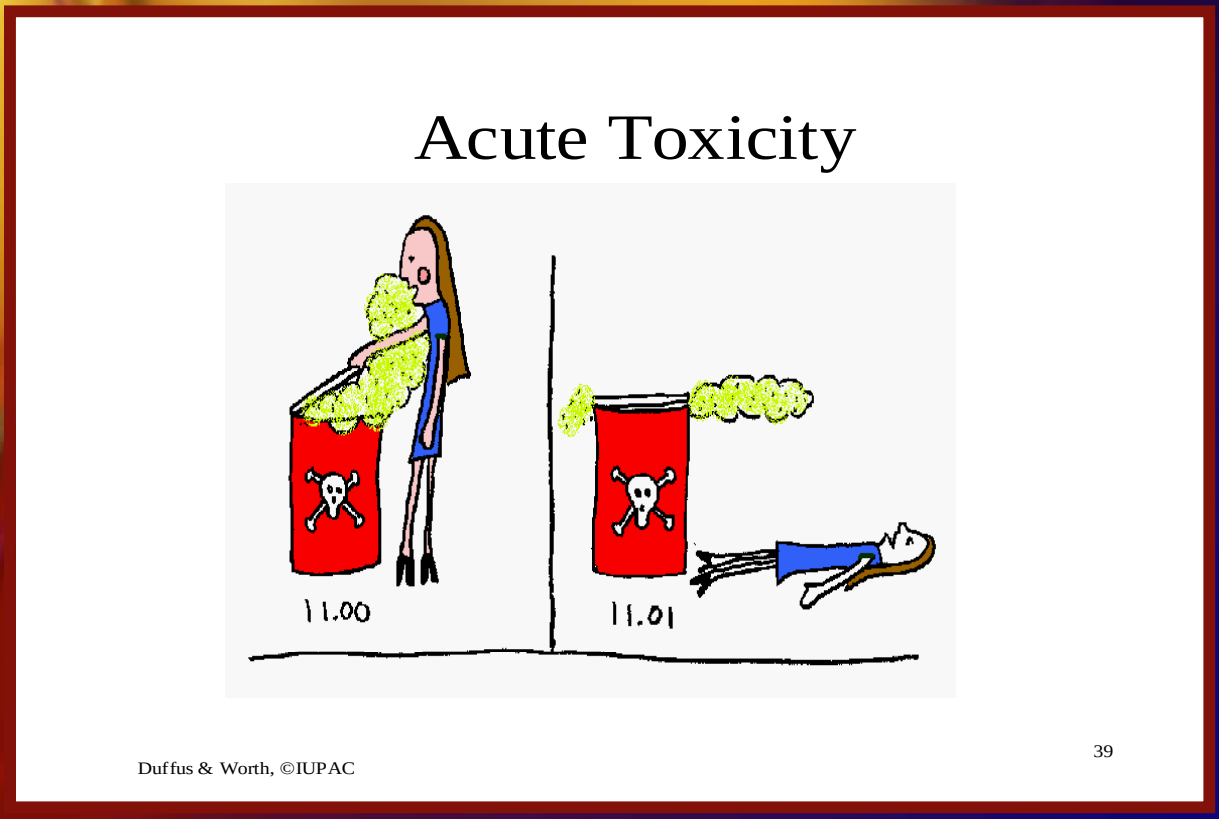


Metabolism and excretion of fat soluble (lipophilic) substances



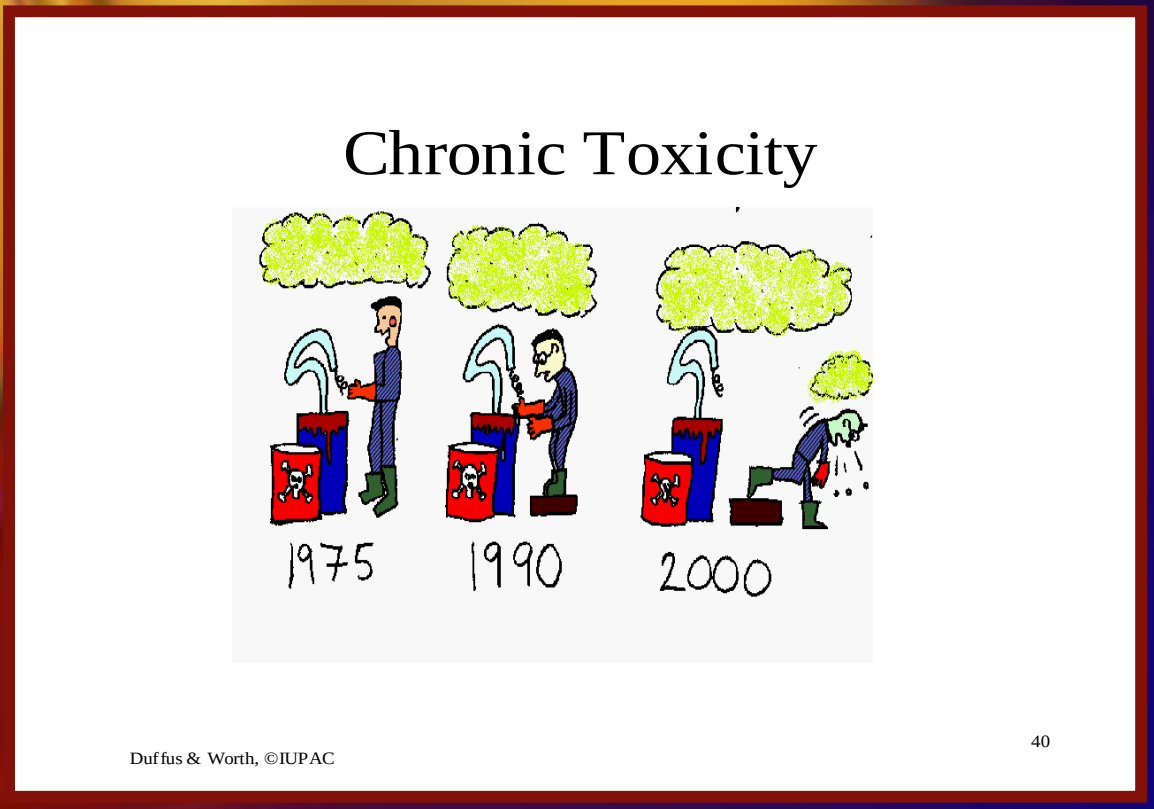
Acute toxicity

- Toxicity resulting from short exposure is called acute toxicity



Chronic toxicity

- Toxicity resulting from long term exposure



Chronic toxicity follows accumulation of toxicants or effects

- Accumulation by storage in:
  - Fat– DDT, PCBs, tetraethyl lead etc
  - Bone– Lead ions, calcium ions, strontium ions etc
  - Liver and kidney-bind and trap both organic and inorganic toxicants
  - Plasma proteins- especially albumin, bind both organics and inorganics; competition for binding may displace a large dose causing toxicity

Important aspects of chronic toxicity

- Chronic toxicity includes the production of cancer (carcinogenicity) and possibly senile dementia and other diseases of old age
- Note the special problem of brain cells where normal decrease through life may be accelerated by exposure to toxicants

Exposure to mixtures

- Living organisms are exposed to mixtures of potentially harmful substances
- There are four types of effects chemicals can have on each other: exposure to two or more substances simultaneously may produce effects that are independent, additive, synergistic, or antagonistic

Effects of exposure to mixtures

- Independent – substances do not interfere with each other or enhance each other's effect on simultaneous exposure
- Additive - have the same effect independently and any combined exposure produces a total effect equal to the sum of the effects of separate exposure to each substance

Effects of exposure to mixtures

- **Synergistic – substances** have the same effect or different effects but the final effect observed is greater than the sum of the effects of separate exposure to each substance
- **Antagonistic -** effect of one substance counteracts the adverse effect of another; exposure to the substances together has less effect than the sum of the effects of independent exposures

Chemical Speciation

- The chemical species of an element is the specific form in which it exists, defined as to isotopic composition, electronic or oxidation state, and/or complex or molecular structure
- Thus, organic chemistry is the study of the nature and properties of all the chemical species of carbon

Why is speciation important?

- Consider mercury.
  - It can exist as the pure metal which is an electrically neutral volatile liquid
  - The vapour is fat soluble, the liquid metal is neither fat soluble or water soluble
  - It can also exist as Hg^{+} or Hg^{2+} ions that are sparingly soluble. However $HgCl_2$ in seawater is largely unionized and therefore fat soluble
  - Methylmercury chloride is sparingly water soluble and very fat soluble

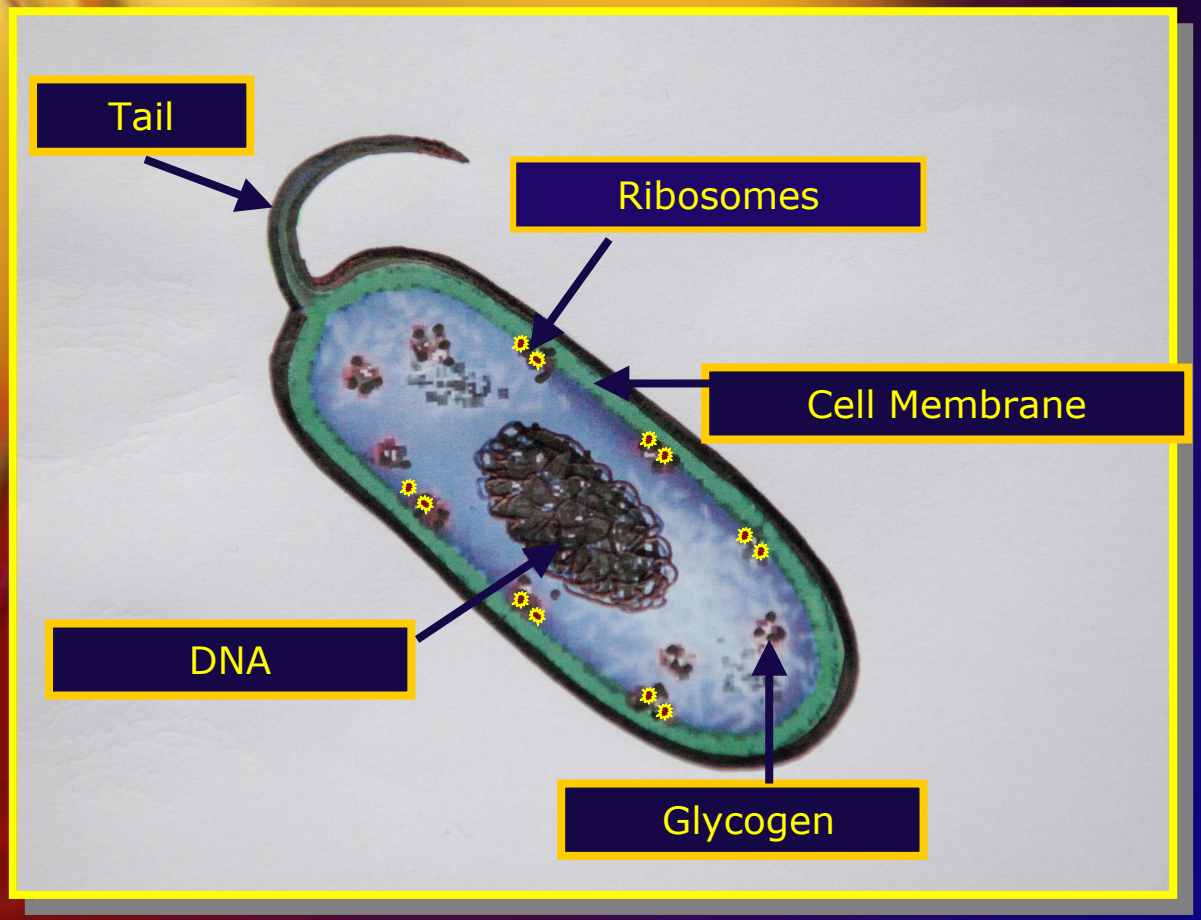
Why is speciation important?

- Mercury (continued)
  - Fat soluble mercury vapour and mercuric chloride enter cells easily through the phospholipid membrane
  - Liquid mercury is not absorbed by cells.
  - Ionized mercurous chloride does not enter cells; unionized mercuric chloride does.
  - Fat soluble methylmercury chloride enters cells readily

Why is speciation important?

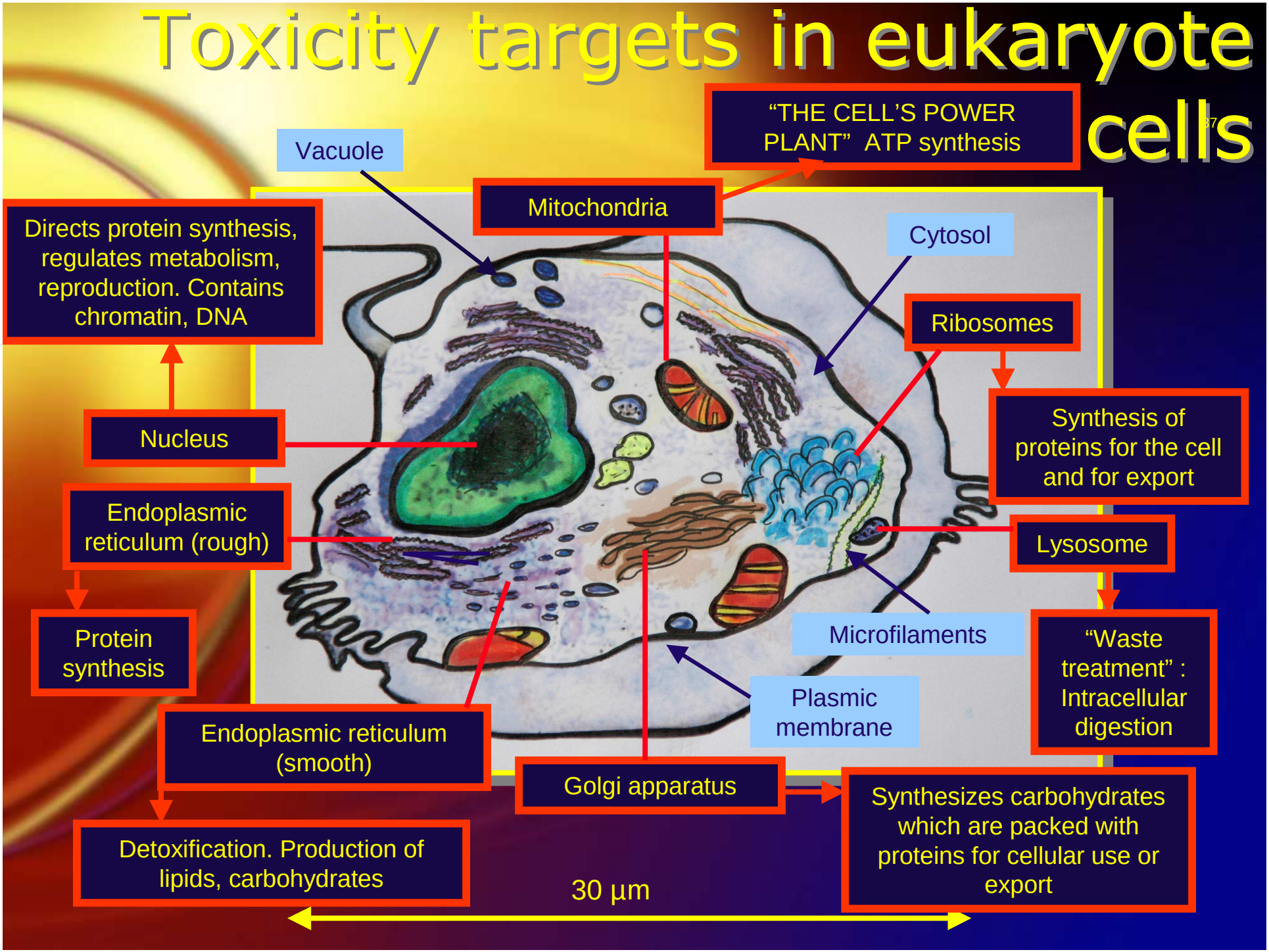
- Mercury continued
  - Fat-soluble mercury species, e.g. mercury vapour, fat-soluble unionized mercuric chloride, and fat-soluble methylmercury chloride are highly toxic
  - Liquid mercury and ionized mercurous and mercuric salts have relatively low toxicity

The biological dimension - prokaryotes (e.g.bacteria) – no nuclear membrane

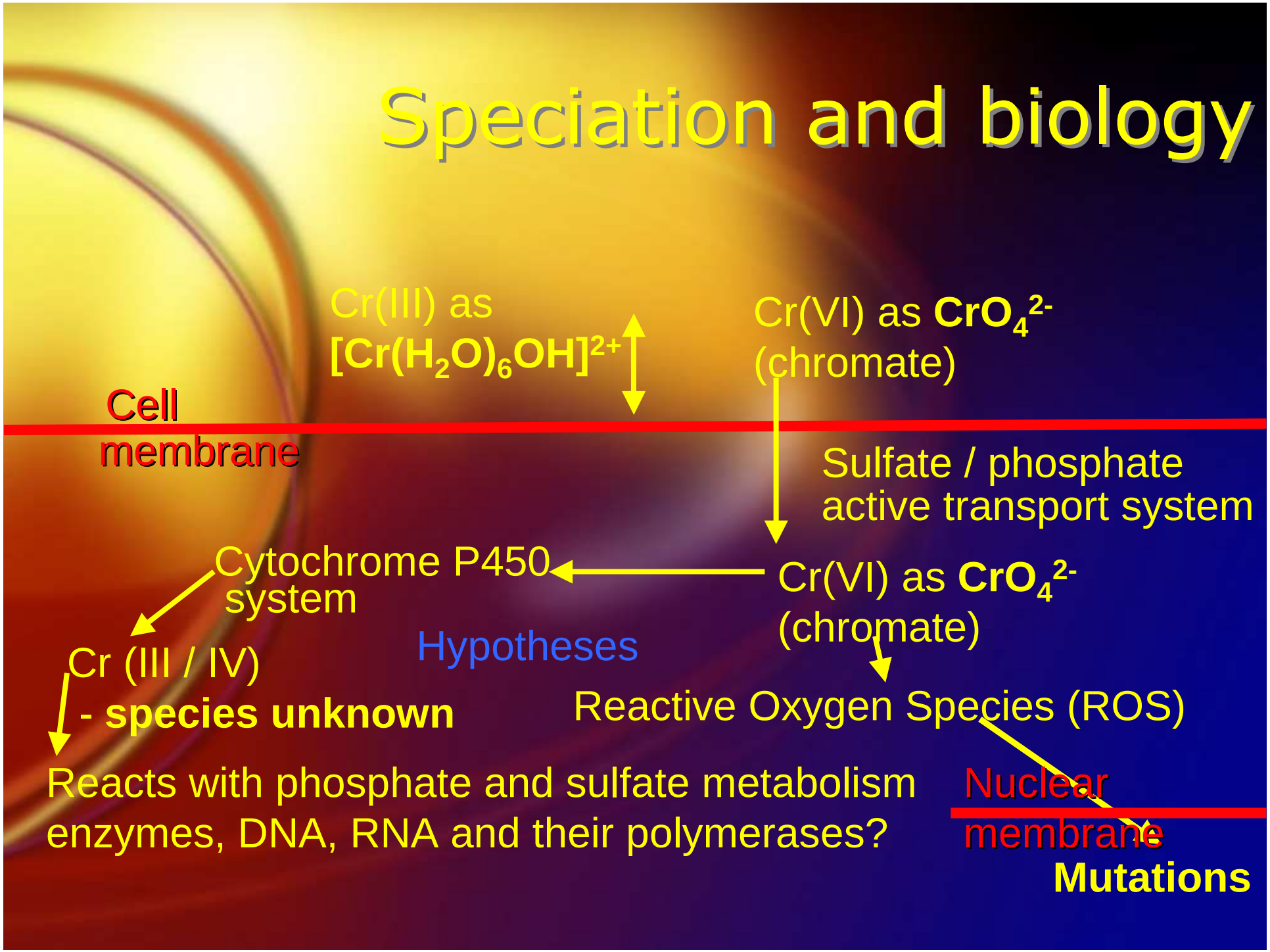


The biological dimension – eukaryotes, e.g., human cells, note the nuclear membrane

Toxicity targets in eukaryote cells



Speciation and biology



The End

- Thank you very much for your attention