The Science of Chemical Safety
Essential Toxicology - 2

Factors Affecting Risk of Poisoning

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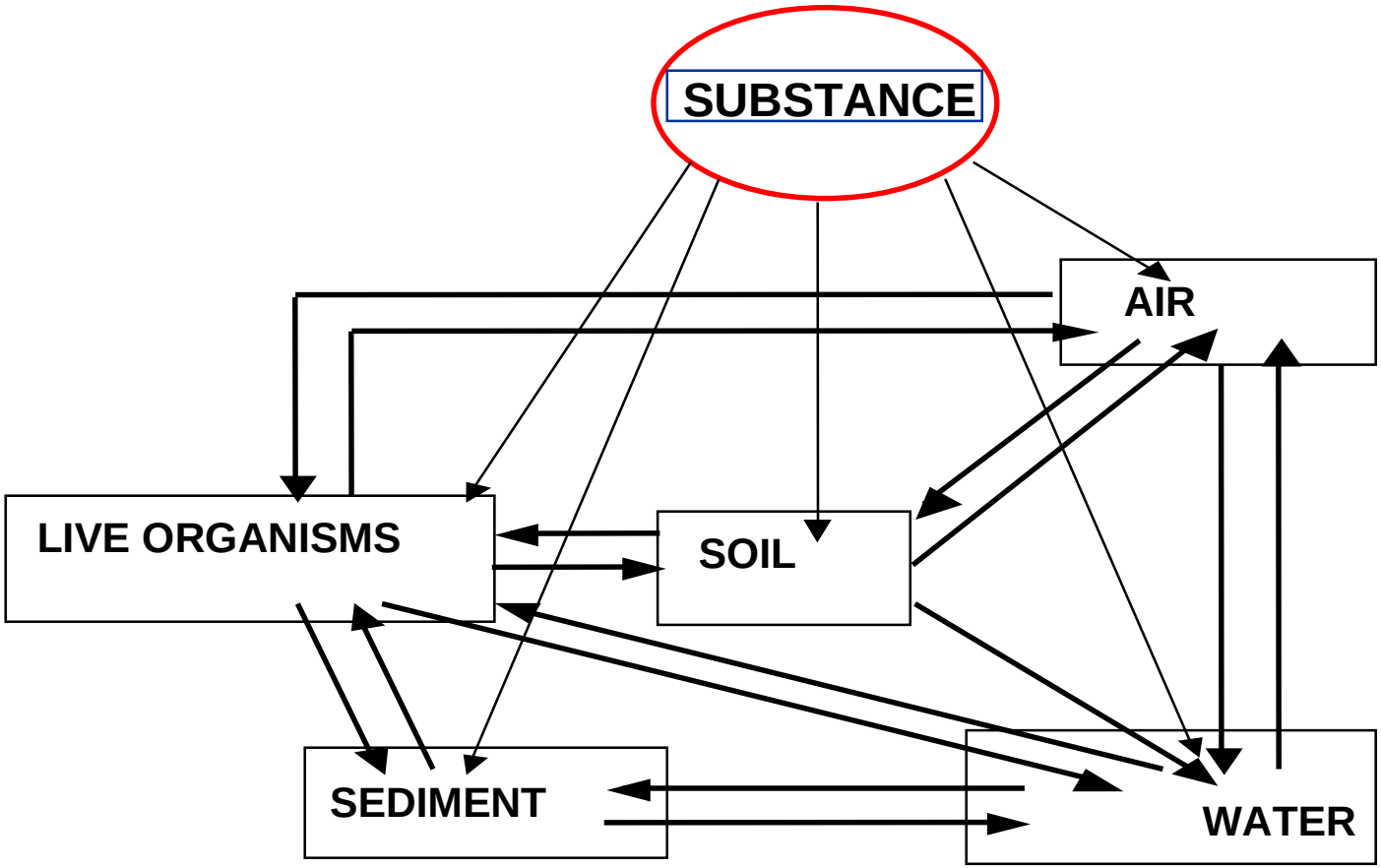
IUPAC Educators' Resource Material

Movement Through the Environment

- Substances in the environment, whether toxic or not, may enter living organisms directly, or through the environmental media - air, soil, sediments, or water
- There is also transfer between these components of the environment, sometimes after chemical change and conversion into derivatives has happened

Movement Through the Environment



Routes of Human Exposure from the Environment

- People may be exposed to any of the environmental media
- Exposure may be through the skin, through the gut (ingestion), through the lungs (inhalation), or may affect the eyes
- Different routes of exposure may result in different effects from the same substance
  - Sometimes only one route of exposure is harmful

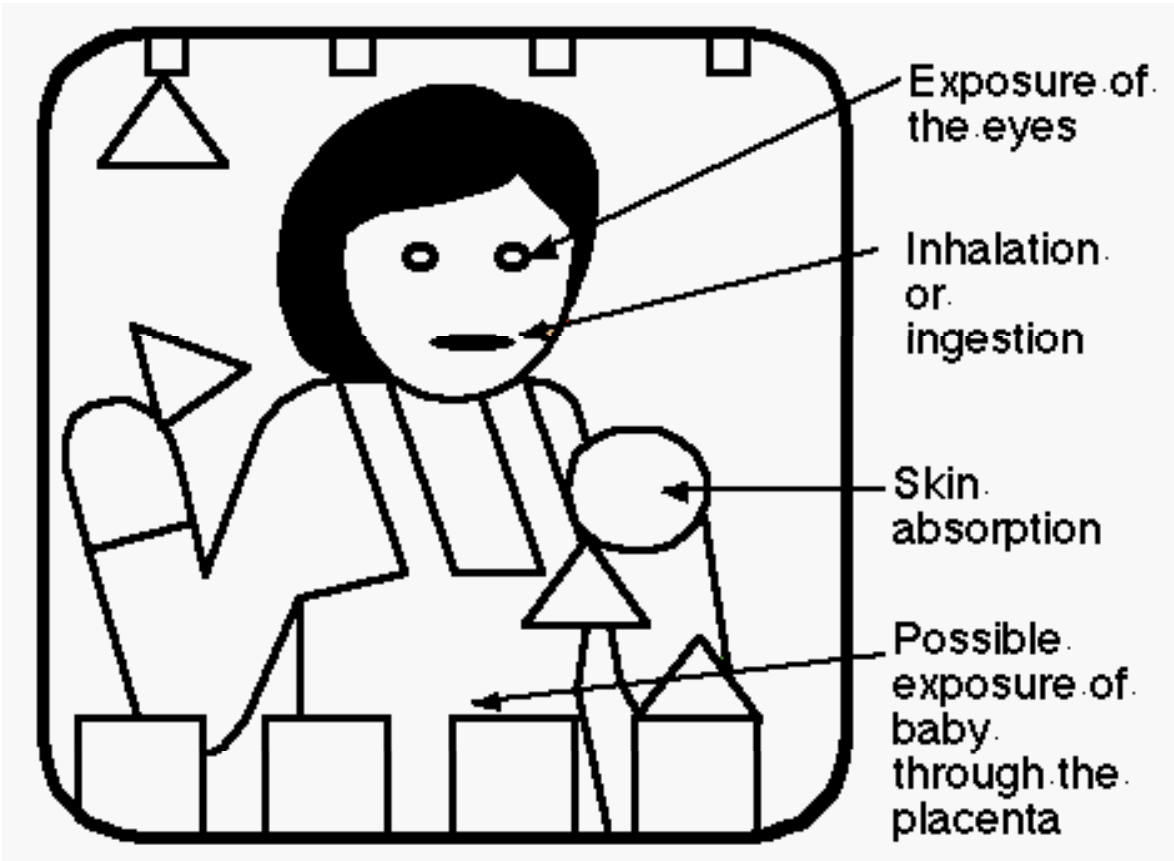
Exposure of the Child in the Womb and Babies

- The developing child in the womb may be harmed by substances in the mother's bloodstream which can pass the placenta into the baby's blood circulation
  - An example is methylmercury which can kill a baby 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)

Routes of Direct Human Exposure

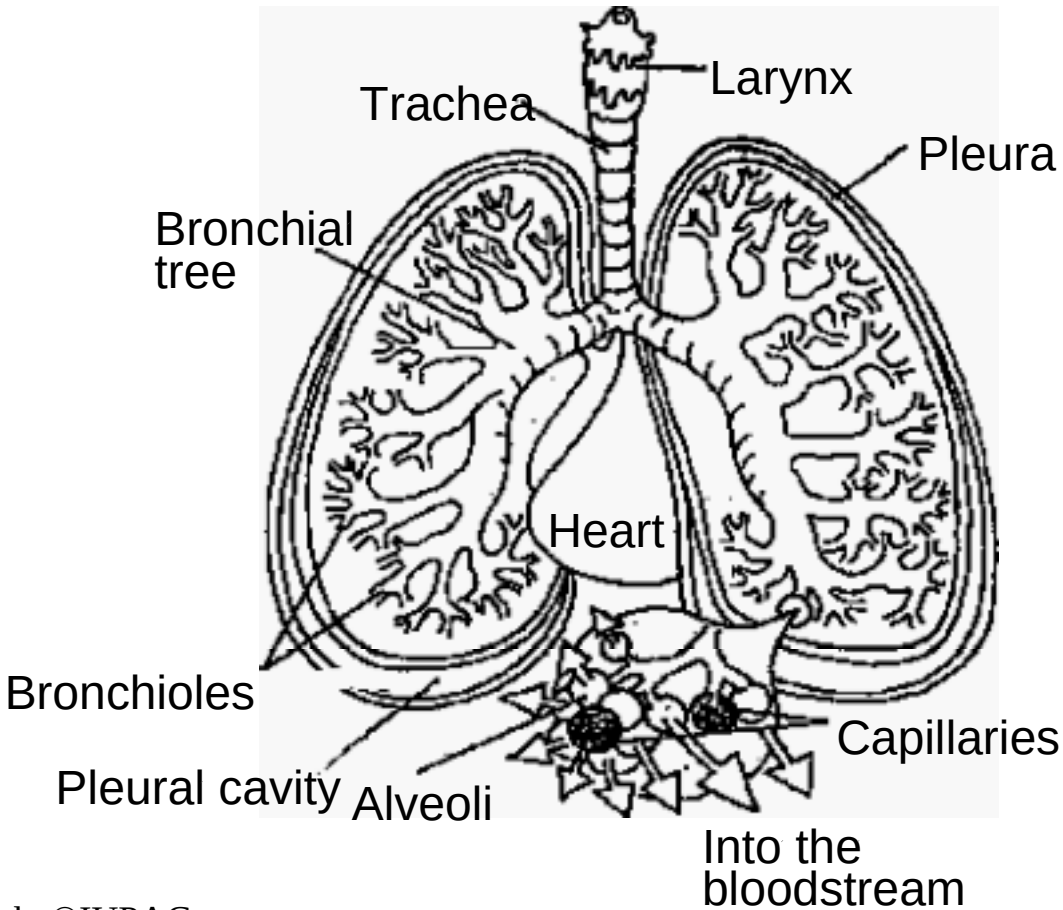


Uptake from the Lungs

- The lungs have evolved to absorb and excrete gases
- Particles can only reach the bottom of the lungs (alveoli) if they are small enough (less than 10 μm aerodynamic diameter - the so-called PM10 fraction)
  - Some particles such as asbestos fibres and crystalline silica can cause lung cancer
  - Even wood dust can cause nasal and lung cancers
- Inhaled particles larger than the PM 10 fraction enter the gut either directly after deposition before entering the lungs or indirectly in mucus from the lungs

The Lungs

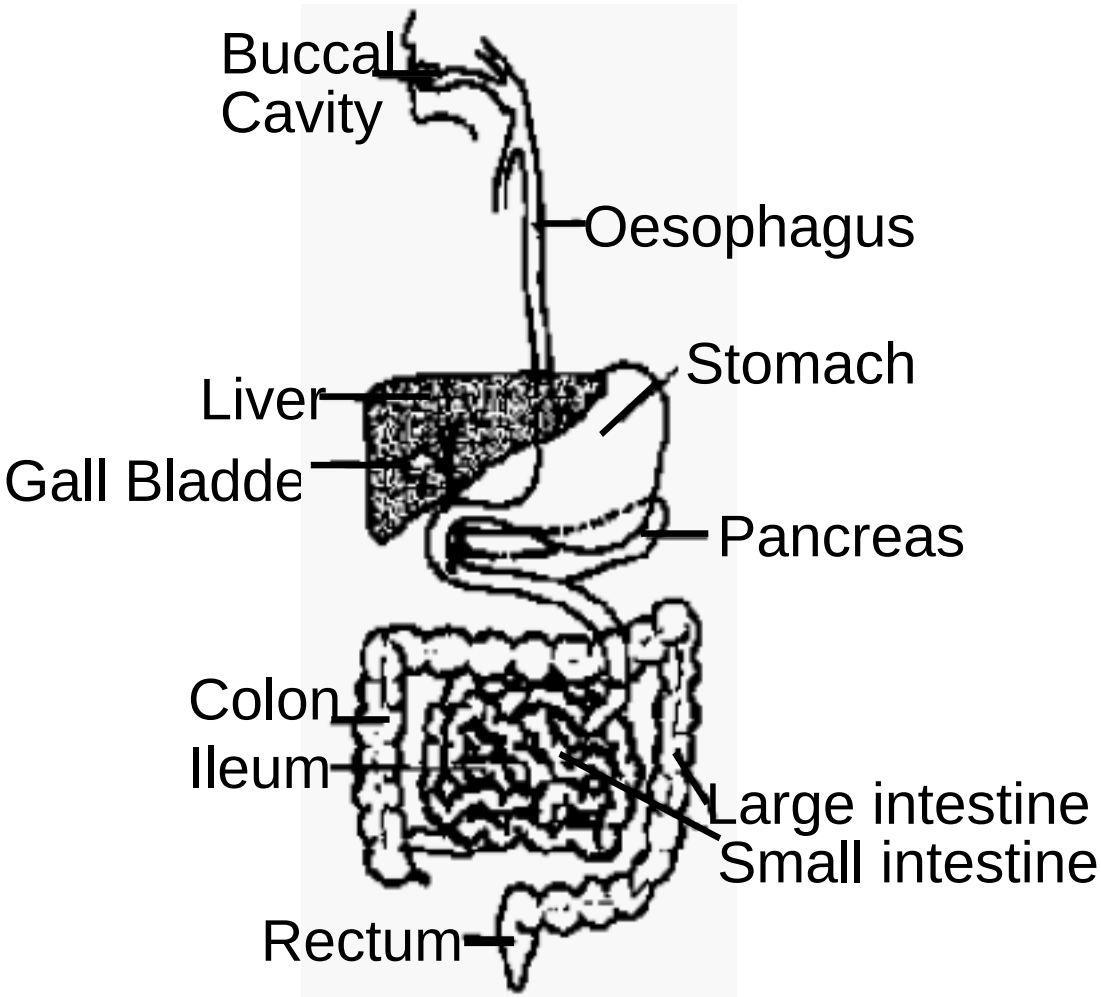
In general, absorption from the lungs is greater than from the mouth or gut, which is greater than through the skin.



Uptake From the Gastro-intestinal Tract (Gut)

- Substances are absorbed mostly from the small intestine and transferred to the liver where derivatives may be produced (see later)
- Substances absorbed from other parts of the gut may enter the general circulation and pass round the body in their original form

The Gastro-intestinal Tract (Gut)



Ionization and Uptake from the Gastro-intestinal Tract (Gut)

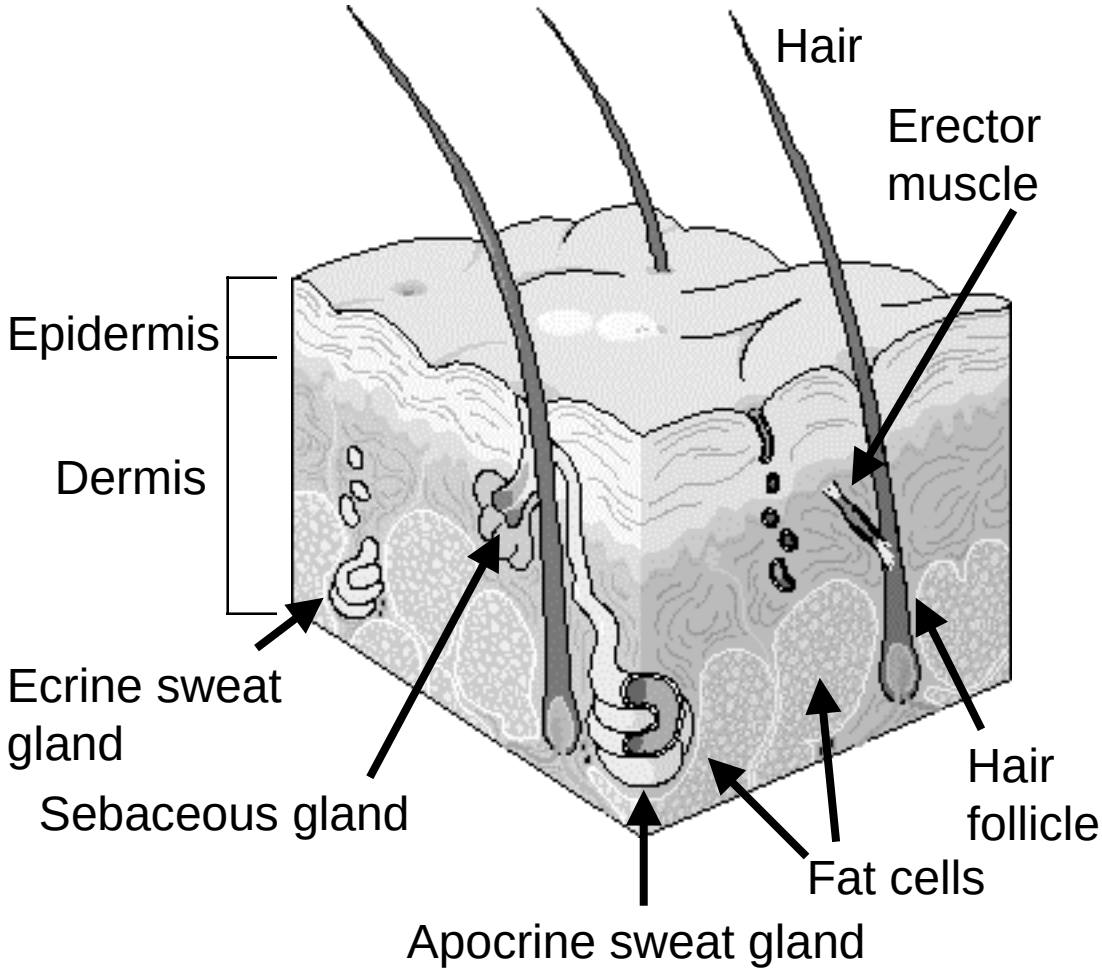
- Absorption from the mouth or gut is strongly influenced by ionisation.
- Un-ionised fat-soluble substances are generally absorbed much better than ionised substances.
- Ionisation varies with pH in the gut. Weakly acidic substances are un-ionised in the acid of the stomach (facilitating absorption) but ionise in the small intestine which is slightly basic in pH.

Absorption Through the Skin

- Absorption through the skin, as with other body barriers including cell membranes, mostly reflects fat solubility and permits circulation of the unmodified substance
- Uptake through the skin varies from one part of the body to another, generally being greatest where the skin is thinnest
- Phenols pass through the skin easily and may be lethal

Skin

Absorption through the skin may take the substance to the underlying capillaries and the central blood circulation with little modification and may reach sensitive organs quickly if they are close to the point of absorption



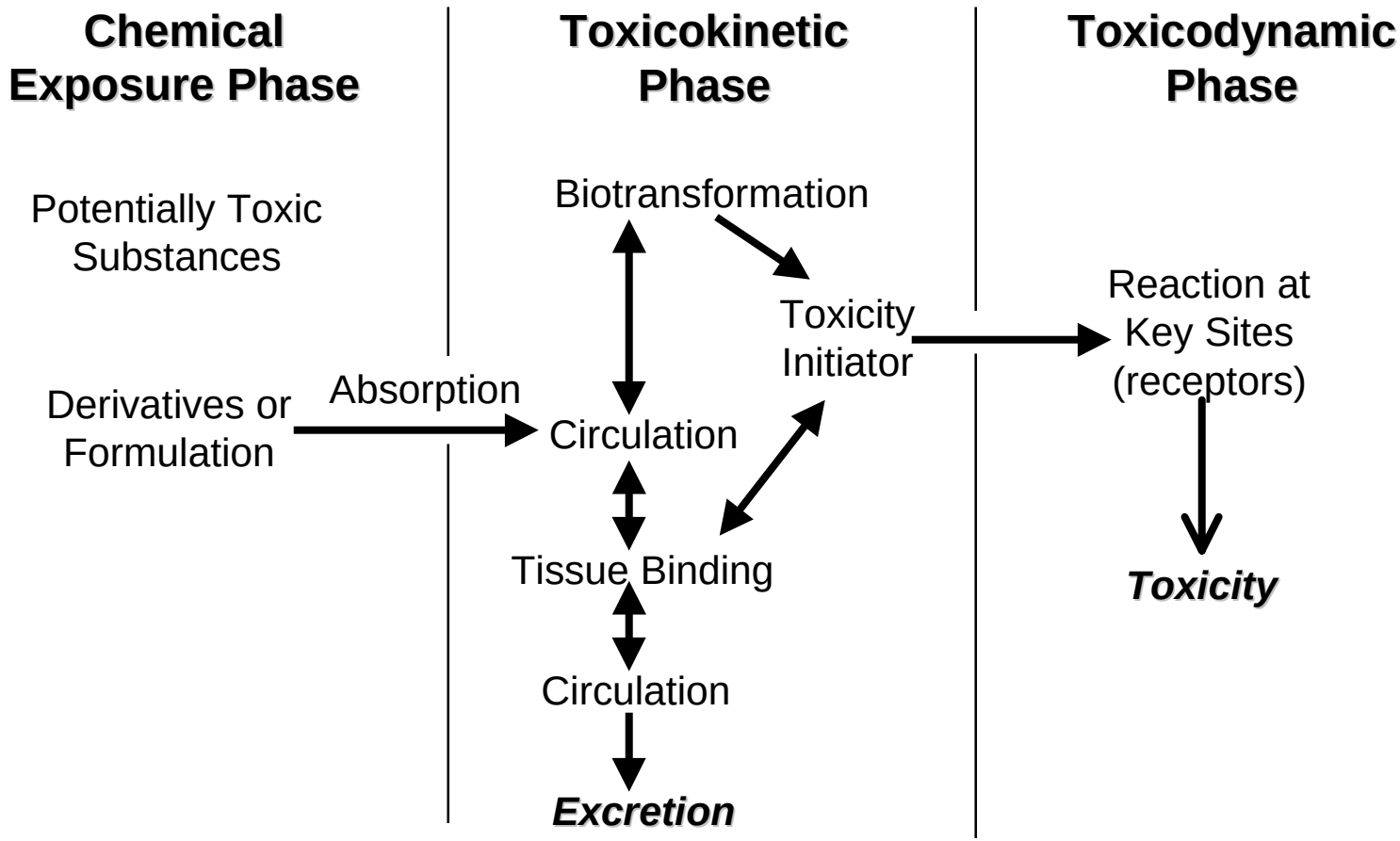
Toxicokinetics

- Toxicokinetics describes the uptake and distribution of a substance through the body
  - It includes absorption, distribution, storage, metabolism and excretion
- Absorption from the lungs takes the substance to the heart and directly to the central blood circulation
  - In this way, it may quickly reach sensitive organs such as the brain without any modification, especially if it is fairly fat soluble and can pass the protective blood-brain barrier easily

Phases of Poisoning

- Exposure (already discussed) is the first phase
- The toxicokinetic phase covers uptake to excretion (see previous slide)
- 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



The Liver

- Absorption from the small intestine takes most substances to the liver where there is a very active chemical transforming system
- In general, liver chemistry makes substances less toxic by making them more water soluble so that they are easily removed from the body

Liver Biotransformation

- This process is sometimes called “detoxication”. Unfortunately, some of the derivatives produced by these reactions are more toxic. This applies particularly to products of what are called the phase I reactions - see next slide
- Water solubility may also be enhanced by conjugation to water soluble substances such as sugars or amino-acids - phase 2 reactions - see next slide

Phase 1 and Phase 2 Reactions

- Phase 1 reactions introduce a polar (water soluble) reactive group into fat soluble compounds
  - In most cases this becomes the site for conjugation in phase II reactions (next slide)
  - The products of phase I reactions may be powerful electrophiles which react with nucleic acids and proteins causing serious cell damage which may sometimes lead to cancer

Phase 2 Reactions

- Phase 2 reactions cause the conjugation of phase 1 products and similar compounds with metabolites such as sugars, amino-acids, glutathione and sulfate making them easier to excrete

Local and Systemic Effects

- Local effects occur if the effect of a chemical is limited to the area of contact
- Systemic effects occur if a substance is absorbed into the general blood circulation and carried to various organs throughout the body causing effects on these organs

Systemic Effects

- Systemic effects may have organ specific names, for example:
- Hepatotoxic - damaging the liver
- Nephrotoxic - damaging the kidneys
- Neurotoxic - damaging the nervous system
- Cardiotoxic - damaging the heart
- Immunotoxic - damaging the immune system

Fat Solubility and Water Solubility

- Substances absorbed into the body that are fat soluble or lipophilic are difficult to excrete
- To remove fat soluble substances from the body, they are altered in the liver by the phase I and phase II reactions, producing more water-soluble compounds called metabolites

Water Soluble Compounds

- Water-soluble substances can be excreted from the body more easily than fat soluble substances and are therefore usually less toxic to us than any fat soluble substance from which they can be produced
  - This is because they are readily transported dissolved in the blood to the kidneys from which they are excreted dissolved in the urine

Very Fat Soluble Compounds - 1

- Absorption of some very fat soluble compounds from the small intestine takes them into the lymphatic system where they may affect our active protection against disease through the immune system or provoke an allergic (hypersensitivity) effect

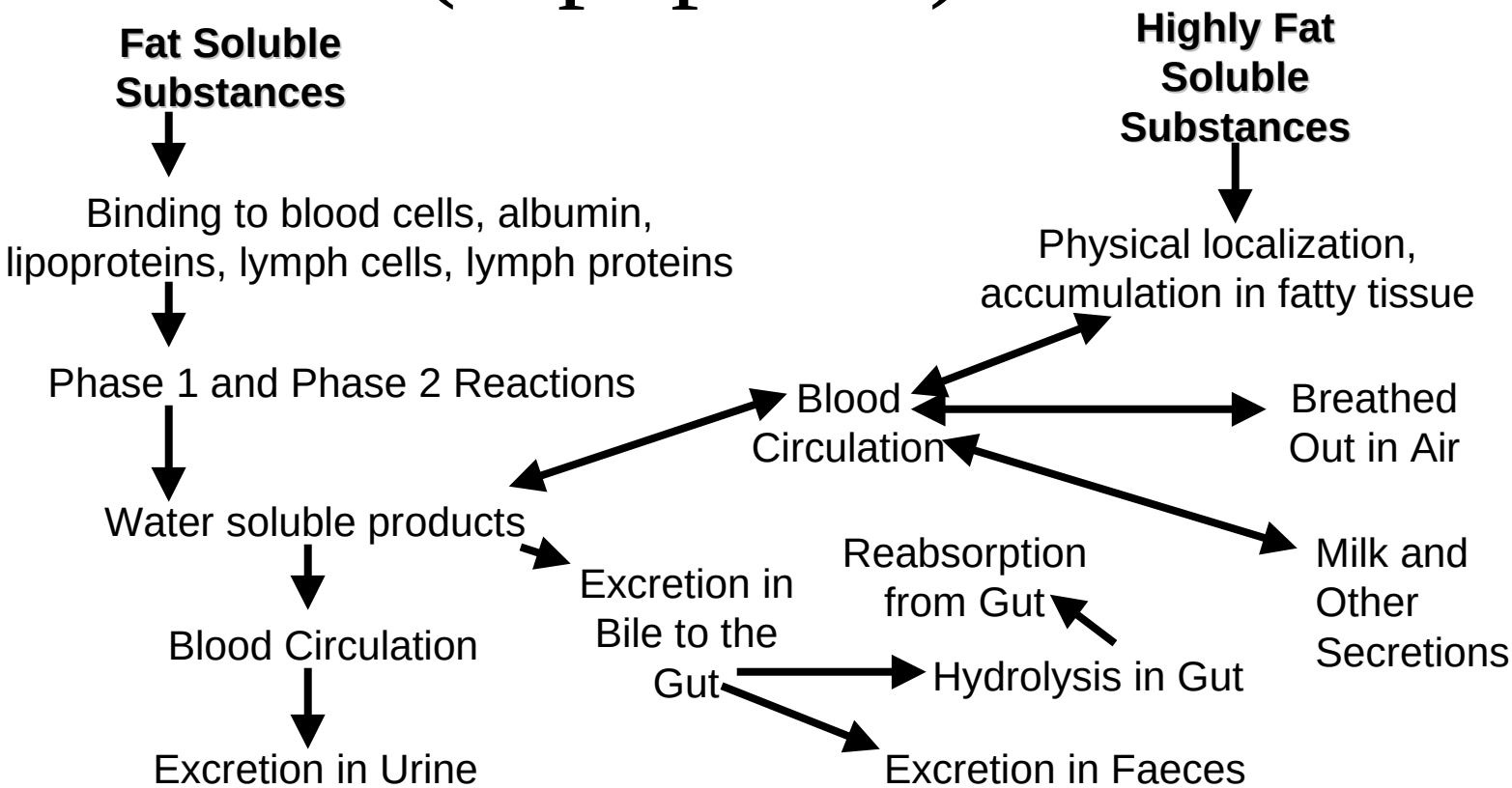
Very Fat Soluble Substances - 2

- Chemically stable fat soluble substances, like DDT, DDE (the main natural decomposition product of DDT), or dioxin (TCDD), may never be excreted but may accumulate in the fatty (adipose) tissues of the body
  - These compounds may accumulate to harmful levels even if daily exposure is low
  - Such substances are called persistent organic pollutants (POPs) and have been banned in many countries

Very Fat Soluble Substances - 3

- When the human body is stressed by pregnancy, illness or old age, fatty tissues containing dissolved toxicants may break down quite quickly releasing those toxicants in sufficient quantity to cause harm; thus the toxic effect may occur long after exposure has ceased

Metabolism and Excretion of Fat Soluble (Lipophilic) Substances



Exposure to Mixtures

- Normally we 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 (see slides 31, 32), additive (see slide 33), synergistic (see slide 34) or antagonistic (see slide 35)

Independent Effects

- Effects are independent when substances produce different effects or have different modes of action and thus do not interfere with each other or enhance each other's effect on simultaneous exposure.
- Cigarette smoke contains carbon monoxide, cadmium, benzo[a]pyrene, and nicotine, all of which act independently

Independent Effects in Cigarette Smoke

- Carbon monoxide prevents uptake of oxygen by the blood, inhibiting nerve and brain function, leading ultimately to unconsciousness and death
- Cadmium accumulates and damages the heart and the kidneys
- Benzo[a]pyrene causes lung cancer
- Nicotine reacts with nerve receptors, blocking nerve function, leading ultimately to unconsciousness and death

Additive Effects

- Effects are additive when substances 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.
- An additive effect occurs in the reproductive effects on birds following exposure to PCB's (polychlorinated biphenyls) and the insecticide DDT.

Synergistic Effects

- Effects are synergistic when 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.
- A synergistic effect occurs when people get lung cancer following exposure to crocidolite asbestos and cigarette smoke; incidence of cancer is 40 times greater than with exposure to either alone

Antagonistic Effects

- Effects are antagonistic when the effect of one substance counteracts the adverse effect of another and so exposure to the substances together has less effect than the sum of the effects of independent exposures.
- Antagonism between mercury and selenium has been observed in populations eating seal meat containing both mercury and selenium; selenium appears to protect against nervous system damage caused by mercury

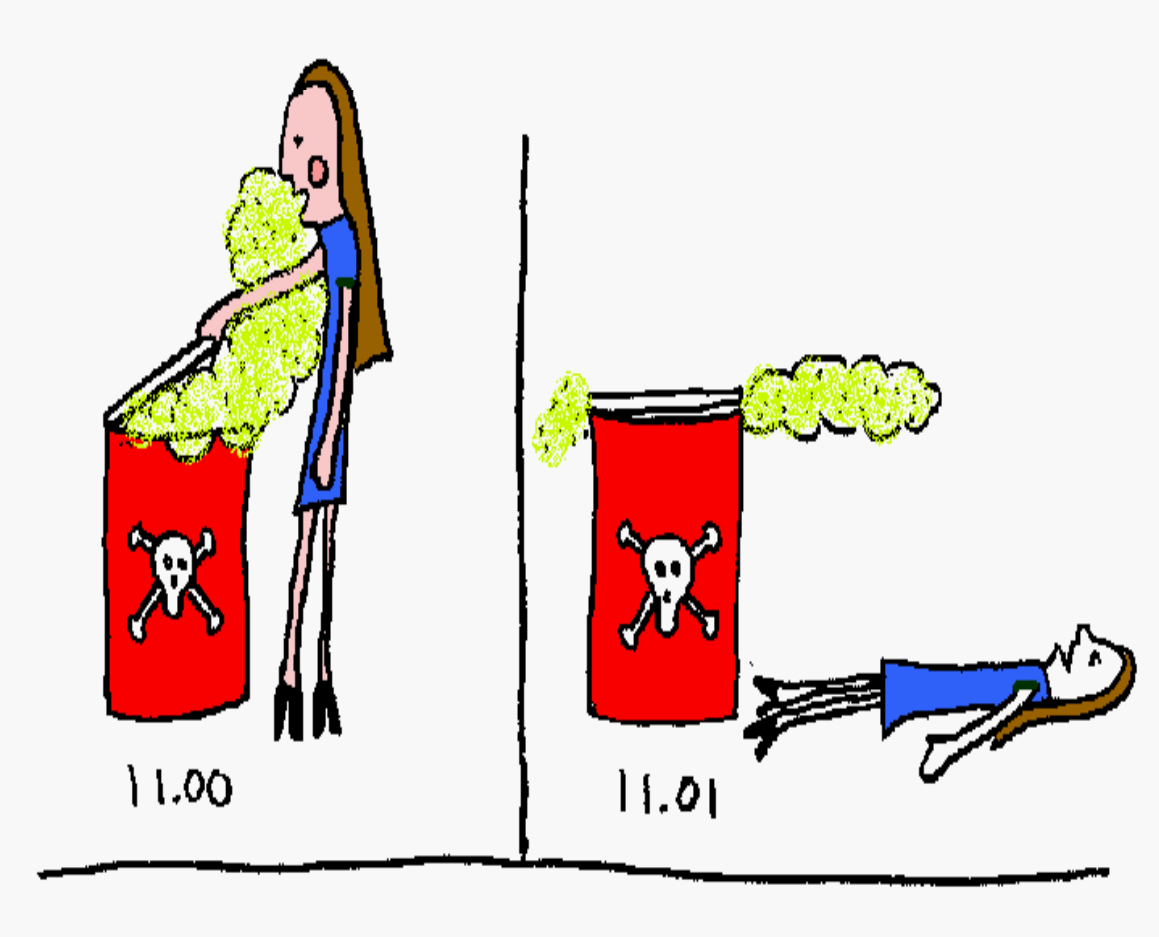
Acute and Chronic Toxicity

- Toxicity resulting from short exposure is called **acute toxicity:** a short exposure may be anything from a few minutes for an accident up to 96 hours for testing purposes
- Toxicity resulting from long term exposure (repeated or continuous for a period of more than 3 months) is called **chronic toxicity: f**or human beings, this may be a lifetime of about 70 years

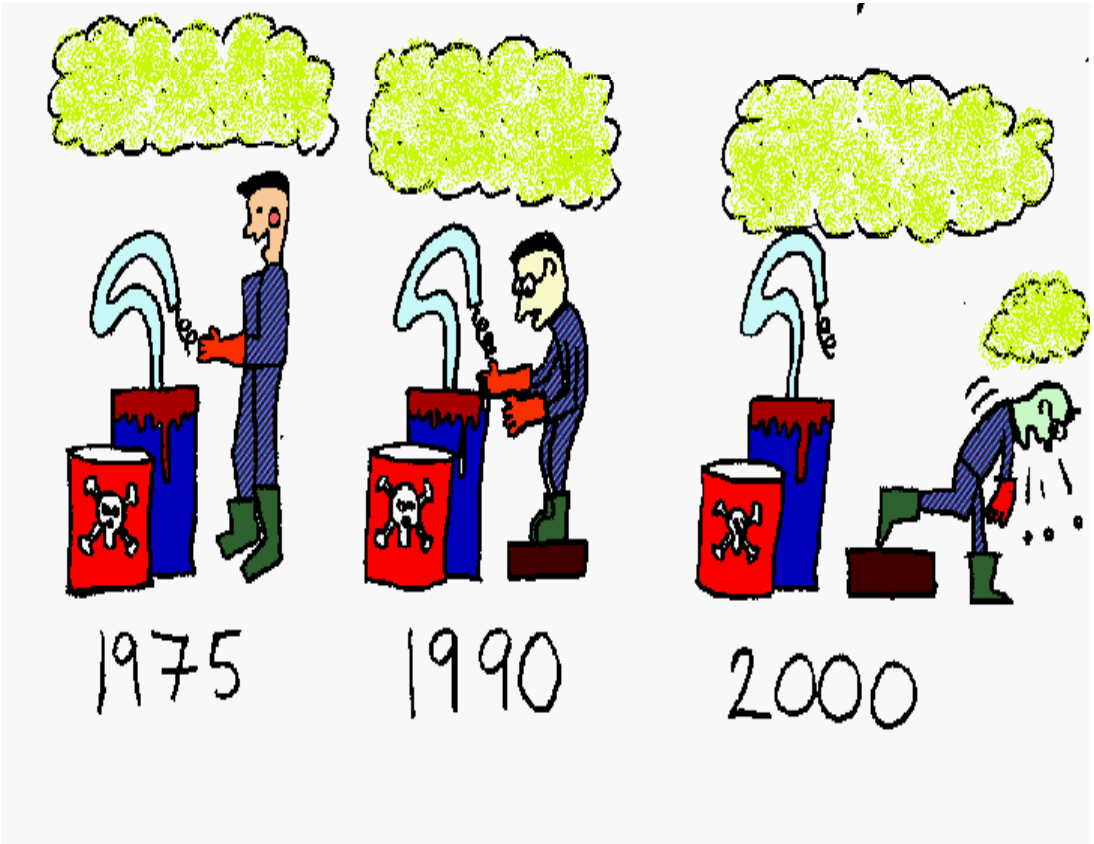
Dose and Time of Exposure

- Chronic toxicity includes the production of cancer (carcinogenicity) and possibly senile dementia
- Severity of toxicity is dependent on both dose and time of exposure: exposure to a small dose continuously for a long time may have similar effects to exposure to a large dose for a short time
- A dose versus time curve for a given effect and dose can give important information for regulatory purposes

Acute Toxicity



Chronic Toxicity



Harmful Effects of Some Toxic Substances - 1

- Carbon monoxide
  - reduced blood O_2-carrying capacity, leading to depression of the nervous system, gradual unconsciousness, and death
- Lead
  - Damage to the central nervous system, anaemia

Harmful Effects of Some Toxic Substances - 2

- Aldehydes, nitrogen dioxide, nitric oxide, ozone, sulfur dioxide, suspended particulates
  - asthma, bronchial and eye irritation, heart problems
- Polycyclic aromatic hydrocarbons
  - lung cancer

Self Assessment - 2.1
True or False?

- Any substance released into the environment may move from one place to another and from one environmental medium to another - see slide 2
- Human exposure through the lungs may cause a harmful effect even when ingestion is harmless - see slide 4
- The child in the womb may be poisoned by substances in the mother's bloodstream which do not affect the mother herself - see slide 5

Self Assessment - 2.2
True or False?

- Mother's milk may carry organic toxicants to her child - see slide 6
- Only gases cause harmful effects on the lungs - see slide 8
- Large particles (more than 10 μm in aerodynamic diameter) are unlikely to cause problems of toxicity in the lungs - see slide 8
- Substances absorbed from the small intestine are transferred directly to the liver - see slide 10

Self Assessment - 2.3
True or False?

- Suppression of ionisation of substances reduces their uptake by living organisms - see slide 12
- Uptake through the skin is not a serious problem - see slide 13
- The liver can make foreign organic substances more water soluble, ensuring their excretion - see slide 18
- Some liver chemical transformations make substances more poisonous - see slide 20

Self Assessment - 2.4
True or False?

- Fat soluble, chemically stable organic compounds are referred to as persistent organic pollutants (POPs) - see slide 27
- Harmful effects of exposure to chemicals may be less than, equal to, or more than the sum of the effects of the chemicals separately - see slides 30-35
- Timelength of exposure is less important than dose in determining the final toxic effect of a chemical - see slides 36-39

Self Assessment - 2.1 Checklist

- Any substance released into the environment may move from one place to another and from one environmental medium to another - True
- Human exposure through the lungs may cause a harmful effect even when ingestion is harmless - True
- The child in the womb will not be affected by substances in the mother's bloodstream which do not affect the mother herself - False

Self Assessment - 2.2 Checklist

- Mother's milk may carry organic toxicants to her child - True
- Only gases cause harmful effects on the lungs - False
- Large particles (more than 10 μm in diameter) are unlikely to cause problems of toxicity - False
- Most substances absorbed from the small intestine are transferred directly to the liver - True

Self Assessment - 2.3 Checklist

- Suppression of ionisation of substances reduces their uptake by living organisms - False
- Uptake through the skin is not a serious problem - False
- The liver can make foreign organic substances more water soluble, ensuring their excretion - True
- Some liver chemical transformations make substances more poisonous - True

Self Assessment - 2.4 Checklist

- Fat soluble, chemically stable organic compounds are referred to as persistent organic pollutants (POPs) - True
- Harmful effects of exposure to a mixture of chemicals may be less than, equal to, or more than the sum of the effects of the chemicals separately - True
- Timelength of exposure is less important than dose in determining the final toxic effect of a chemical - False