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PHARM

Toxicologically important organic substances

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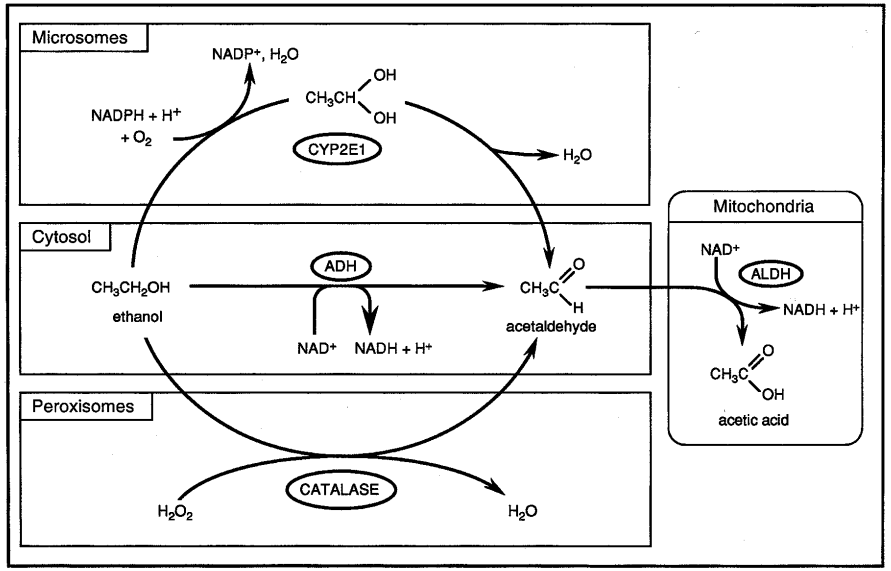
Ethanol

- Alcoholic beverages
- Present also in fermented fruits, dough containing yeasts, disinfectants, cosmetic products etc.
- Rapidly absorbed from GIT (20% stomach, 80% intestine) and lungs, partially from skin
- Detoxification has a constant rate
- Non-specific mechanism of action – osmotic activity + dissolves lipids in membranes, thus disturbs many neuronal functions – e.g. interaction with many neurotransmitters (influences GABA and NMDA receptors), disturbs thermoregulation, blocks production of adiuretin
- First excitation, then depression of CNS, causes hypoglycaemia

Ethanol

- Its metabolite acetaldehyde is also toxic - metabolic acidosis



- In 1 ‰ – excitation of CNS, muscle incoordination, diuresis = dehydration, thirst (due to the lack of antidiuretic hormone – hangover next day)
- In 2 ‰ – strong inebriety, inability to move exactly, metabolic acidosis – tachycardia, tachypnoea
- In 3-4 ‰ – coma, decrease of temperature (vasodilatation of skin capillaries), blood pressure, respiration

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Ethanol

Chronic intake: gastritis (increased secretion of digestive juices, vasoconstriction in GIT), stomach ulcers, steatosis and cirrhosis of liver (acetic acid used for the synthesis of fatty acids), polyneuritis, worse immune reactions, deficit of thiamine

Treatment:

- Symptomatic and supportive
- Liquids, glucose, correction of acid-base balance, monitoring of heart function and respiration
- In chronic poisoning supplementation of thiamine.

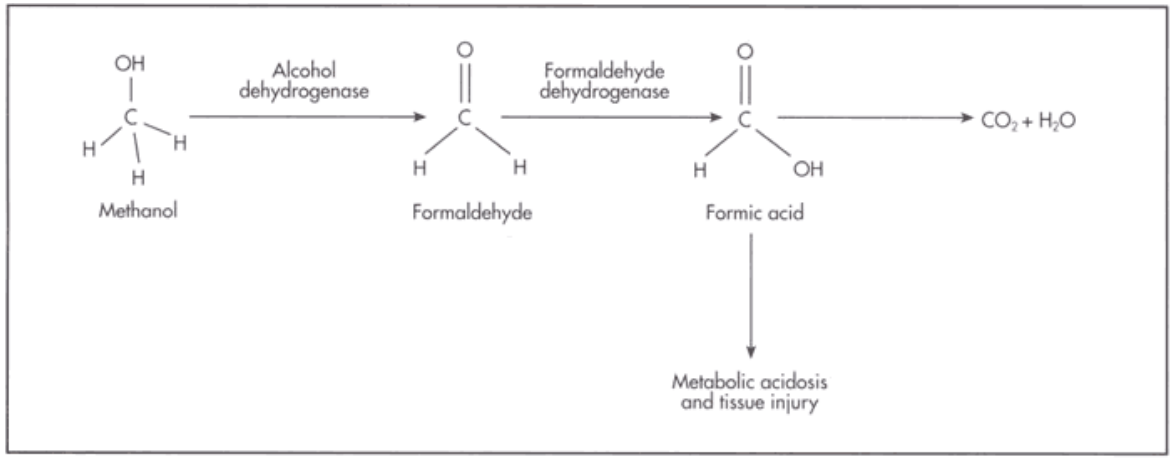
Activated charcoal is not effective!

It is possible to perform haemodialysis

Methanol

- Colourless liquid
- Used as a solvent, antifreeze, fuel, released from artificial sweetener aspartam
- Absorbed after ingestion, inhalation, via skin
- Methanol itself has only osmotic activity
- In organism converted to formaldehyde (by alcohol dehydrogenase) and formic acid (by aldehyde dehydrogenase) These products are toxic!
- Formic acid degraded to CO_2 and H_2O, but folic acid is necessary for this process – after a short time, depletion of folic acid! and cummulation of toxic formic acid = tissue damage

Methanol



- Low activity of folate dependent enzymes necessary for the conversion to CO_2 is known for humans, apes/primates and pigs (LD approx. 0,5-1,5 ml/kg). Other species less sensitive (e.g. dog 5-11 ml/kg).
- Formic acid binds to Fe3+ in breathing enzymes and inhibits cytochrome oxidase – damage of tissues with high ATP requirements (mainly CNS). Specifically cumulated in optical nerve.

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Methanol

Clinical signs:

- First nausea, vomiting, headache, dizziness, ataxia – similar to inebriety
- Other symptoms after a several hours' latency, mainly in humans - atrophy of optic nerve – blindness, decreased heart function, incoordination, cyanosis, seizures, death

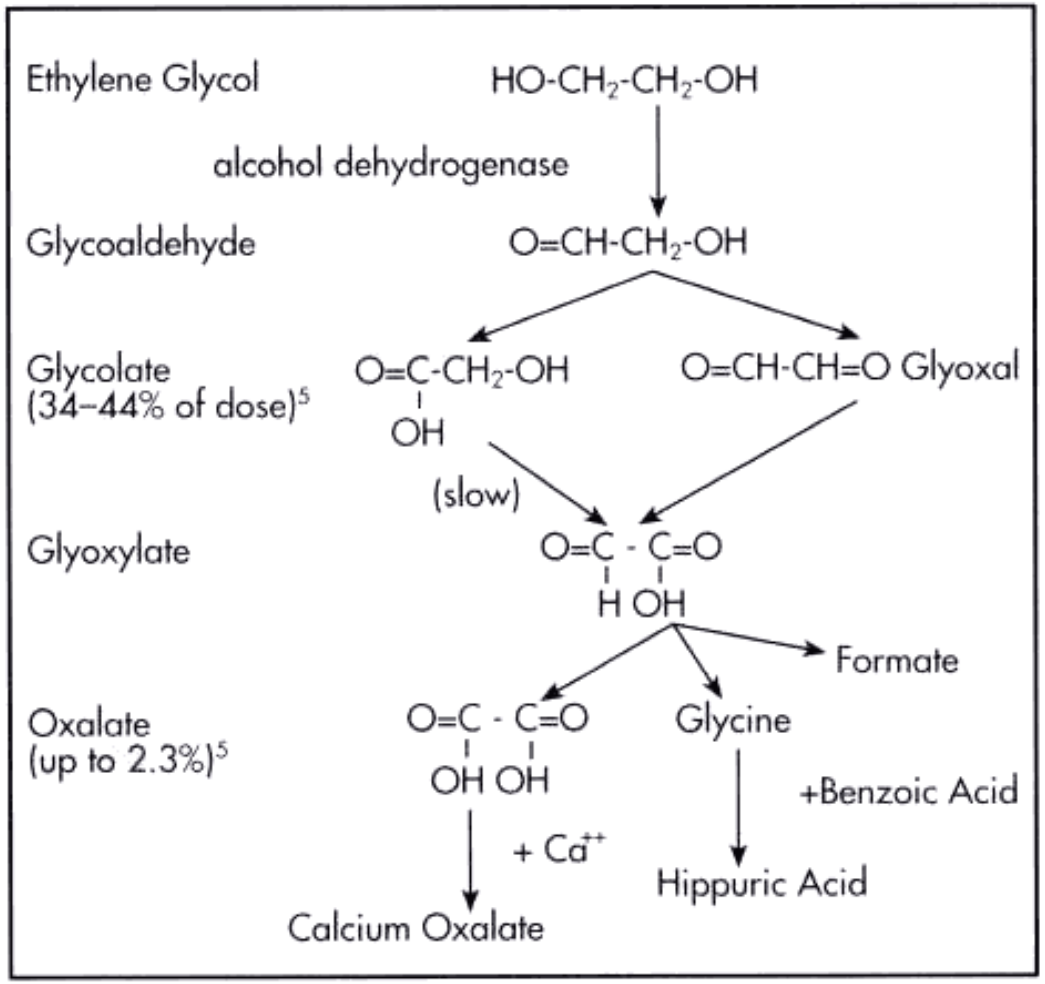
Treatment:

- Ethanol – is first metabolised and methanol can be excreted unchanged (especially by lungs) – competition for alcohol dehydrogenase
- 4-methylpyrazole = fomepizole – inhibitor of alcohol dehydrogenase
- Bicarbonates to control acidosis, haemodialysis, folate
- Activated charcoal ineffective!

Ethylene glycol

- Colourless, odourless, syrupy liquid with a sweet taste (now Bitrex is usually added)
- Coolant or antifreeze in automobiles and personal computers, important in the plastics industry for the manufacture of polyester fibres and resins, in cleaning products etc.
- Rapid absorption via GIT and inhalation, quick metabolism, acute poisonings
- Ethylene glycol has only osmotic activity, but again it is metabolized to toxic products!
- Extremely toxic to cats (LD50 0,9 ml/kg) and humans (LD50 1,4 ml/kg)

Ethylene glycol



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Ethylene glycol

- Clinical signs of ethylene glycol poisoning usually follow a three-step progression:

Stage 1: (1-3h after ingestion, EG itself)

- neurological symptoms, dizziness, headaches, confusion, ataxia, polyuria/polydipsia (PU/PD)
- Over time, the body metabolizes ethylene glycol into other toxins

Stage 2: (3-6h, mainly glycoaldehyde, glycolic acid)

- result of accumulation of these metabolites - metabolic acidosis = tachycardia, hypertension, hyperventilation, sometimes coma. Oxalate crystals in urine (6-8h)! Hypocalcaemia may occur

Stage 3: (6-48h) glyoxylic acid, oxalic acid, calcium oxalate

- renal oedema + damage by crystals = oliguric kidney failure - uraemia, vomiting, oral ulceration, seizures, death

Ethylene glycol

Treatment:

- Quick and aggressive fluid therapy for at least 48h
- The antidotes for ethylene glycol poisoning are ethanol or fomepizole, efficient in first 4 hours, later not (EG already metabolized)
- Ethanol (usually given i.v. as a 5 or 10% solution in 5% dextrose)
- Fomepizole (4-methylpyrazole)
- Haemodialysis, bicarbonates, glucose, monitoring of heart function and breathing

Aldehydes (formaldehyde = methanal)

- Gas - colourless, flammable, heavier than air, pungent (may not provide adequate warning of hazardous concentrations - odour adaptation can occur)
- Usually sold ad 36-38% solution in water = formalin (4-10% for histology) – may contain methanol as stabiliser
- Exposure – all routes (GIT, lungs, skin)
- Use: bactericide, fungicide, for histological sample preparation, production of resins,as embalming fluid, textile treating - wrinkle-resistence, etc.
- Carcinogenic, sensitizer
- **LD:** as little as 30 milliliters ingested (adult; metabolic acidosis, circulatory shock, respiratory insufficiency, acute renal failure). Inhalation - 100 ppm.
- **Clinical signs**: irritation of eyes, nose, throat and chest, asthma, dermatitis, corrosive effects. Systemic effects due to its metabolic conversion to formate
- **Do not induce vomiting**, rather no charcoal, symptomatic treatment

Ketons (acetone)

- Man-made chemical, also found naturally in the environment and organisms (in traces in animal and plant metabolism – lipid degradation (see diabetes), isopropyl alcohol is converted to acetone in the body, etc.)
- Colourless liquid with a distinct (fruity) smell and taste
- Volatile, flammable, dissolvees in water
- Used as solvent (laboratories, nail polish removers etc.), in production of plastics, paints and coatings, cleaning and personal care products.
- Mechanism of action not known (decreased surface tension, ketoacidosis?)

Clinical signs: nose, throat, lung, and eye irritation, dry, irritated, and cracked skin, gastrointestinal upset. High ingested doses - GIT erosions, hypotension, cardiopulmonary arrest, tachycardia, hyperglycemia, acute kidney injury. High doses inhaled - nauzea, vomiting, heavy breathing, unconsciousness. Long-term effects - in animals (kidney, liver, nerve damage, birth defects, male infertility)

- **Do not induce vomiting**, activated charcoal probably ineffective

Hydrocarbons

- Hydrocarbons are organic compounds that consist of hydrogen and carbon
- Generally liquid at room temperature, such as gasoline
- Common uses:
  - industry for production of plastics, varnish, paint, glue, solvents, degreasers, and lubricants – aromatic substances as benzene, toluene, naphthalene, xylene, and n-hexane (mostly from petroleum)
  - Primary energy and combustible fuel sources – aliphatic saturated as gasoline (C5-C8), diesel + kerosine (C9-C16) (from petroleum = crude oil = naphtha)
- Some also agents of abuse and typically inhaled for their euphoric effects

Hydrocarbons

- Poisonings by inhalation or ingestion (animals also from dermal exposure – e.g. oil spills on the water and death of birds and fish)
- Lower viscosity, lower surface tension, and higher volatility all increase the risk of aspiration and subsequently, increase the risk of toxicity

Mechanisms of action:

- Trigger oxidative stress
- Lower alveolar surfactant
- Interfere with gas exchange and cause impaired diffusion
- Decreases partial pressure of oxygen in inhaled air
- Disrupt lipid membranes of the microvasculature
- Exact mechanism of CNS effects unknown (they affect NMDA, dopamine, and GABA receptors; may be secondary to relative hypoxia)

Hydrocarbons

- The pulmonary system - affected by inhalation or aspiration - direct toxicity
- Hydrocarbon pneumonitis is caused by the destruction of alveolar and capillary membranes as well as alteration of surfactant function and production
- This can lead to ARDS due to increased vascular permeability and oedema. Progression to necrotizing pneumonitis and haemorrhagic pulmonary oedema is ultimately possible
- Cardiac toxicity is also possible - life-threatening dysrhythmias = ventricular tachycardia or fibrillation (so called “Sudden sniffing death syndrome”)
- The primary CNS effect is a decreased level of consciousness – crossing of the blood-brain barrier causing direct toxicity. Also indirect CNS effects as a result of severe hypoxia from lung injury or oxygen depletion
- Repetitive exposure = white matter degeneration as well as peripheral demyelination

Hydrocarbons

- Hydrocarbons are gastrointestinal irritants which lead to burning abdominal pain, vomiting or even gastric perforation
- Toluene causes renal tubular acidosis or severe hypokalaemia, similar to hypokalaemic periodic paralysis
- Benzene and naphthalene associated with hematologic disorders (intermediate product of benzene = benzenepoxide is haematotoxic and carcinogenic)
- Methaemoglobinaemia and delayed carboxyhaemoglobinemia are specifically associated with exposure to hydrocarbons containing amine and nitro groups in their molecule

Clinical signs:

- Symptoms usually occur within 30 min, but may be delayed for hours
- Coughing, choking, or vomiting with aspiration, hypoxia and laboured breathing
- Initial neurologic symptoms may be agitation, hallucinations, tremors, but generally, hydrocarbons are neurologic depressants

Hydrocarbons

Treatment:

- Symptomatic and supportive
- No specific quantitative/qualitative tests for hydrocarbons available (anamnesis)
- Immediately place patient on a cardiac monitor, start pulse oximetry
- Chest radiograph is indicated if inhalation or aspiration is suspected
- ECG, basic metabolic profile, hepatic function tests, complete blood count
- Carboxyhemoglobin or methemoglobin levels may also be helpful
- Supplemental oxygen is often required, exogenous surfactant has been used with success, in case of hypotension - aggressive fluid resuscitation
- In the case of ingestion - **no vomiting, gastric lavage or charcoal** (substances are quickly absorbed). Vomiting and charcoal contraindicated due to the high risk of aspiration

Hydrocarbons

Styrene (vinylbenzene)

- Industrial chemical (mainly polystyrene manufacturing)
- Readily absorbed and distributed throughout the body tissues following inhalation and dermal exposure
- Repeated exposure to styrene leads to a gradual accumulation in the adipose tissue, suspected carcinogen
- Extensively metabolised by cytochrome P450 oxidation to styrene 7,8-oxide, which is further metabolised, in the urine mandelic acid can be detected (see BET slide at the end of presentation)
- Acute (mostly inhalation, but also ingestion and skin) contact: irritation of the nose and throat, increased nasal secretion, wheezing, coughing, pulmonary oedema, cardiac arrhythmias, headache, nausea, vomiting, weakness, fatigue, dizziness and ataxia CNS depression, coma

Chlorinated hydrocarbons

- Simple molecules (do not confuse with chlorinated POPs!)
- Trichlorethylene, tetrachlorethylene, carbon tetrachloride, chloroform, methylene chloride etc.
- All of them very lipophilic, cross blood-brain barrier, neurotoxic (CNS depressants – probably interference with neuronal membrane) and hepatotoxic
- Sensitize the myocardium to catecholamines
- Used as solvents of resins, rubber, tar, degrease agents of metals, fuel additives etc.
- Often inhalation poisonings, treatment is only symptomatic (inducing vomiting is forbidden – aspiration of vapours!)
- Rapidly absorbed, slowly oxidized in liver via CYP 450 (high ROS production), accumulate in the body

Chlorinated hydrocarbons

Trichlorethylene

- Colourless liquid of sweet taste and smell, Water insoluble, non-flammable
- Necrotic effect, irritating mucosas, damage CNS - depressant, strong carcinogen!

Tetrachlorethylene

- Similar effect as trichlorethylene
- Hepato- and nephrotoxic, suspected carcinogen

Trichlormethane (chloroform)

- Excitement, nausea and vomiting followed by ataxia, dizziness, drowsiness
- Toxic to liver, kidneys. Exposure to chloroform may also cause cancer

Carbon tetrachloride

- Colourless, volatile liquid of sweet smell
- Very toxic, damages liver and kidney, narcotic, strong carcinogen!

Ethers

Diethyl ether

- Volatile and extremely low flashpoint temperature (40°C) - one of the greatest fire hazards commonly encountered in the laboratory
- Sweet smelling
- Inhibits alcohol dehydrogenase (slows the metabolism of ethanol). Interferes with CYP450 (induces oxidative stress, inhibits metabolism of other substances). Slowly eliminated from fatty tissue.
- Anaesthetic, stimulates the sympathetic nervous system leading to hypertension and tachycardia, addictive
- First excitement and inebriation, then salivation, irregular breathing, sedation, unconsciousness and respiratory paralysis! Kidney damage may occur.
- Irritating to the eyes, respiratory system and skin

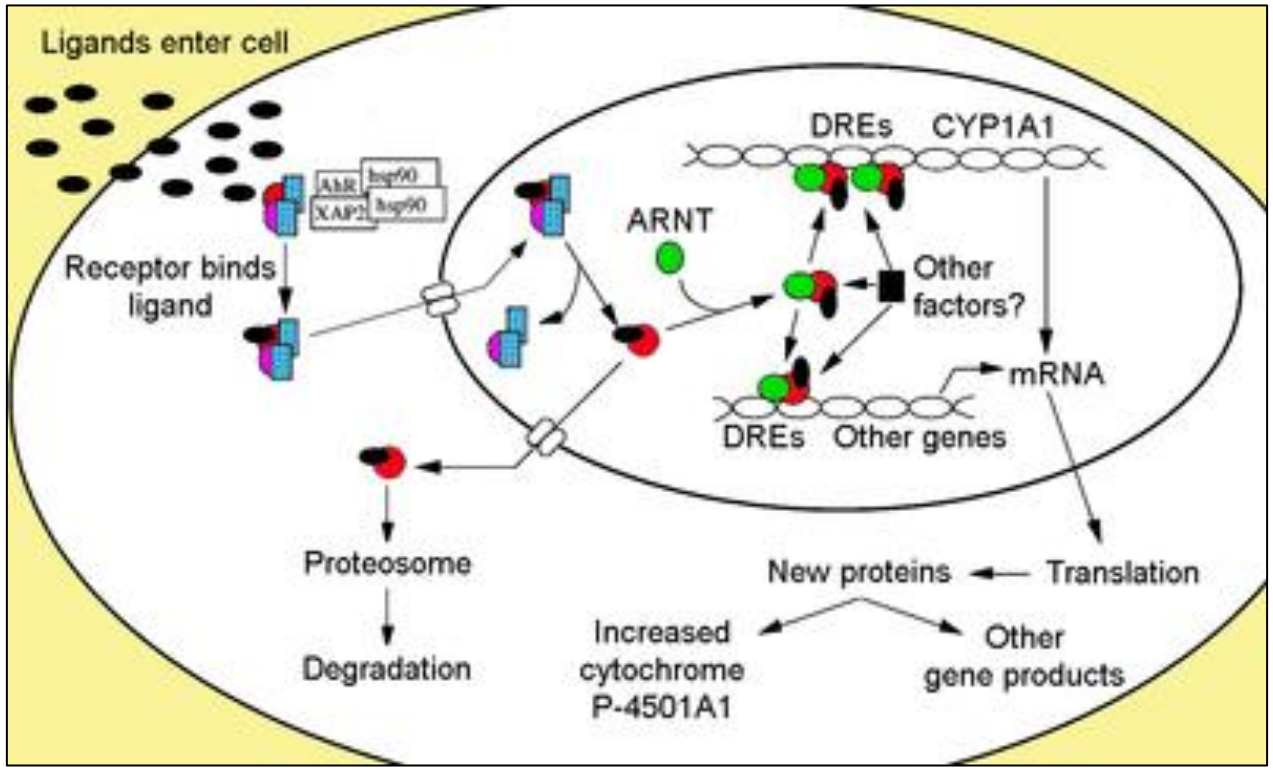
Dimethyl ether – low toxicity; **Dioxan** - carcinogenic

Polycyclic aromatic hydrocarbons - PAHs

- Do NOT contain chlorine, thus are NOT persistent (not POPs)!!!
- Formed during the incomplete burning of coal, oil and gas, garbage, tobacco, cuisine procedures – barbecuing, smoking of meat
- Some PAHs are manufactured, others are found in coal tar, crude oil, creosote, and roofing tar. A few are used in medicines (coal tar, beech tar) or to make dyes, plastics, and pesticides
- Enter the air from volcanoes, forest fires, burning of fossil fuels, automobile exhaust, industry
- 16 so called priority PAHs (have negative effects on mammals and fish) – indicators of environment contamination (e.g. naphthalene, fluorene, fenanthrene, anthracene, benzo(*a*)pyrene).
- Broken down by sunlight within a few weeks, quickly metabolized by liver, but cumulate in the sediments (enter food chain)

PAHs

- Enter organisms via inhalation, GIT or skin (phototoxicity)
- In vertebrates metabolised in liver by cytochrome P450 – carcinogenic epoxydiol (DNA adducts), then conjugation. No deposition in body, excreted in bile as 1-hydroxypyrene (biomarker)
- Slow metabolism in invertebrates
- Act via Ah receptor
- Carcinogenic, mutagenic, teratogenic, genotoxic, reproductive problems, endocrine disruptors, etc.



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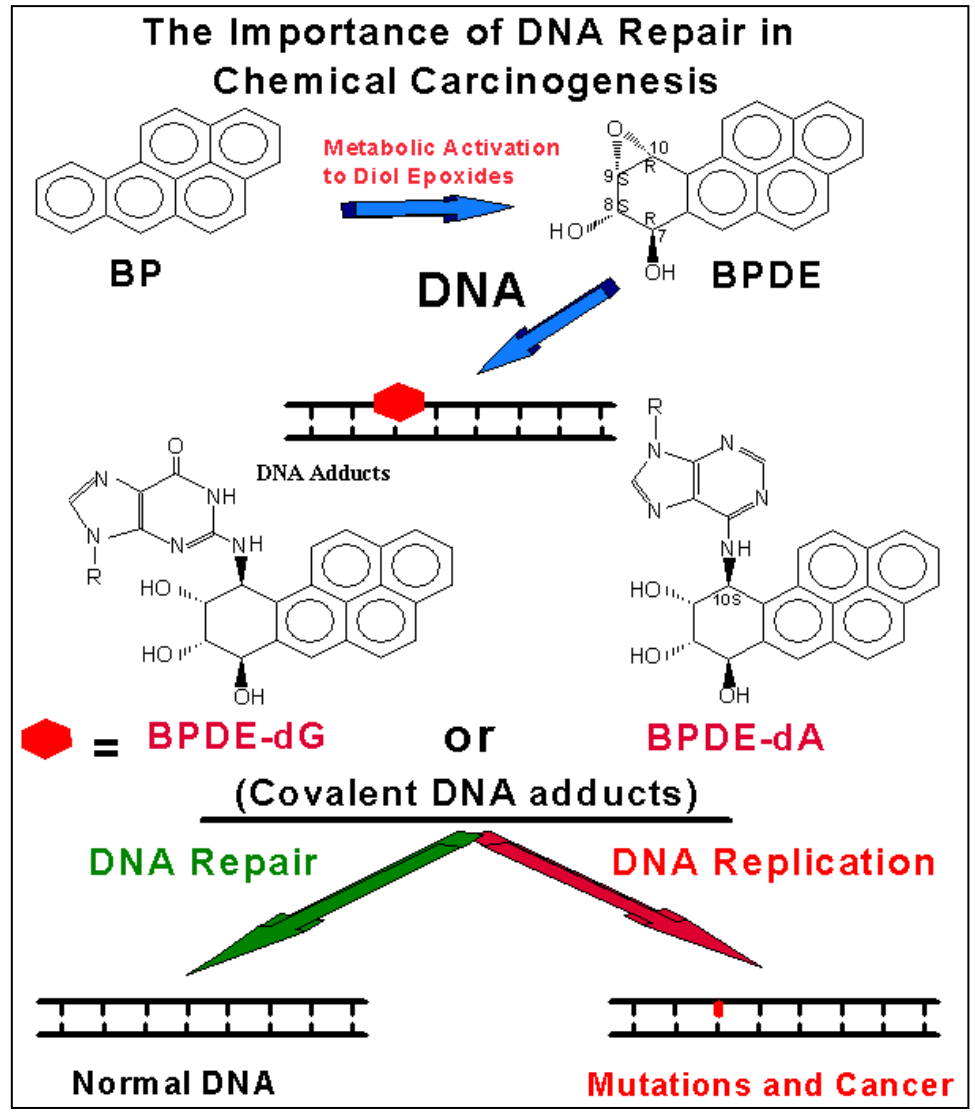
PAHs



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Polychlorinated dibenzodioxins – PCDDs, polychlorinated dibenzofurans – PCDFs = generally called dioxins

- Global pollutants
- Not produced intentionally, but by-products of anthropogenic activity, only minority created in environment (bacterial function etc.)
- One of the most toxic chemicals, belong to POPs (Persistent organic pollutants)
- Planar molecules (important for their mechanism of action)
- We know 75 congeners of PCDDs and 135 PCDFs. Only 17 of them are of toxicological importance
- Most toxic is 2,3,7,8-TCDD (tetrachlorodibenzodioxin), a standard for comparison of effect: TEF = EC50 of TCDD/EC50 of assessed congener (Toxic Equivalence Factor for TCDD is 1, other have lower)

Dioxins

Sources:

- Industrial processes involving chlorine, chemical and pesticide manufacturing, pulp and paper bleaching
- Thermic reactions, where organic matter with chlorine is involved (e.g. PCB combustion at temperatures bellow 1400°C, PVC combustion etc.)
- Created in municipal waste water contaminated by chlorphenols (e.g. chlorhexidine) – due to biosynthesis mediated by microbial peroxidases

- Fat-soluble, stable, mainly not volatile (the more chlorines, the less volatility), persistent and accumulated
- Half life in soil is ten and more years, in sediments even more
- Almost not metabolised. Go to milk, eggs, embryos.

Dioxins

Mechanism of action:

- Act via AhR (see PAHs)
- Cytochromes P450 produced in increased amounts are oxidases, by their function high concentration of free radicals is released

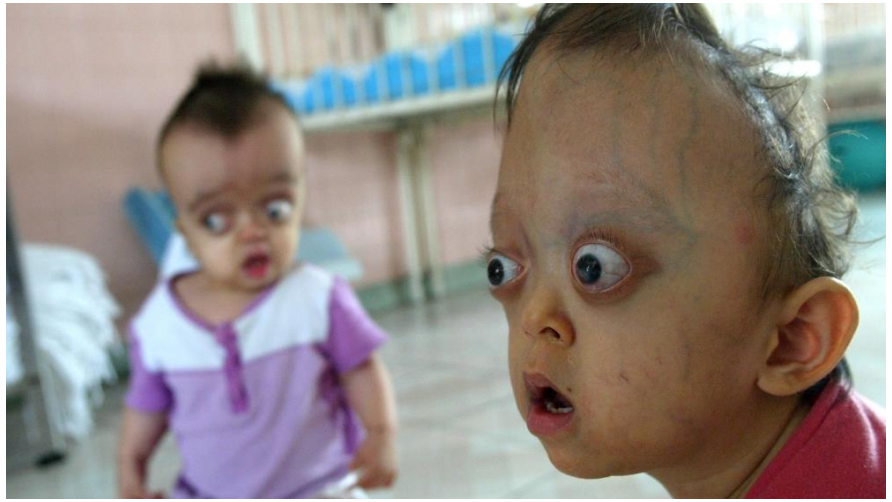
- Also testosterone synthesis is inhibited, oestrogen receptors are down-regulated, phosphorylation of amino-acids appears
- Some effects are not mediated via AhR, e.g. inflammatory effects

Clinical signs:

- carcinogenity, birth defects, inability to maintain pregnancy, decreased fertility, reduced sperm counts, endometriosis, diabetes, learning disabilities, immune system suppression, lung problems, skin disorders, lowered testosterone levels etc.

Dioxins

- Agent Orange, Victor Yuschenko, Seveso industrial catastrophe



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Polychlorinated biphenyls - PCBs

- Polychlorinated biphenyls
- 1-10 chlorines on biphenyl nucleus
- 209 derivates (congeners)
- Toxic congeners - 77, 81, 126, 169 - coplanar, chlorine in non-ortho position – minor congeners (so called dioxin-like PCBs)
- Indicator congeners – majority (six, their ratio predicts also occurrence of toxic ones)
- Thermostable, photostable, chemically inert
- Classified as persistent organic pollutants – POPs
- Manufacturing started in 1929, lasted till late 1970´s

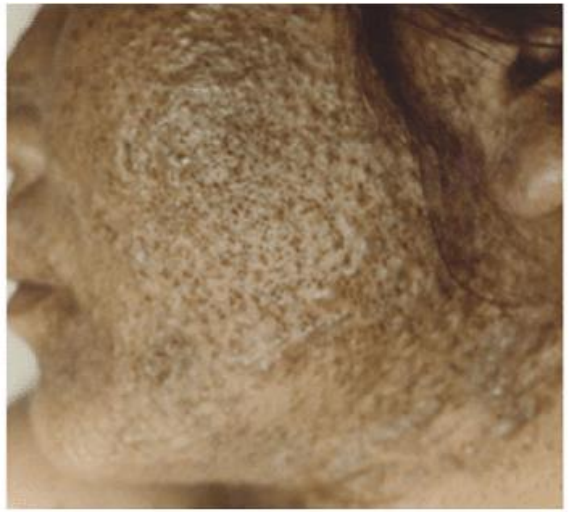
PCBs

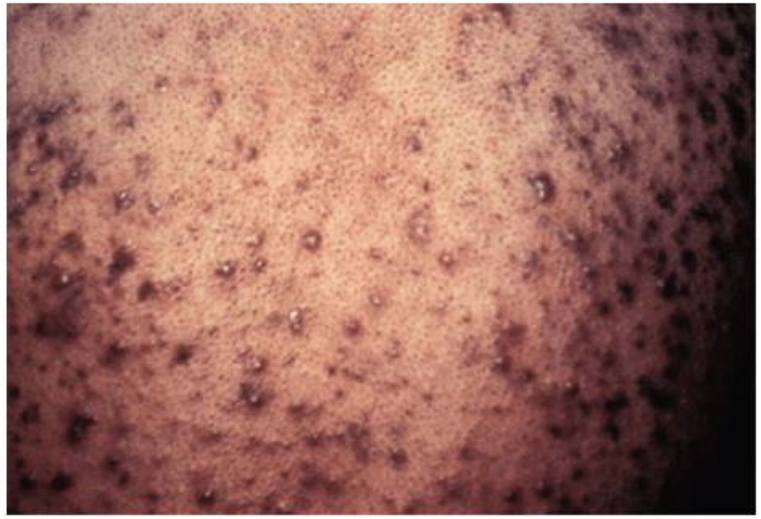
Closed systems: transformators, cooling liquids, hydraulic liquids (no new production, but still used)

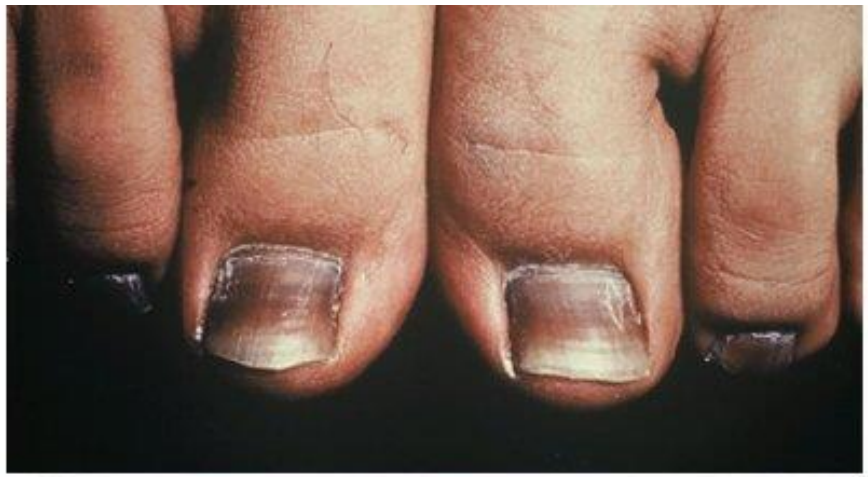
Opened systems: flame retardants, as additives in inks, adhesives, paints and dyes, as plasticisers etc. - banned

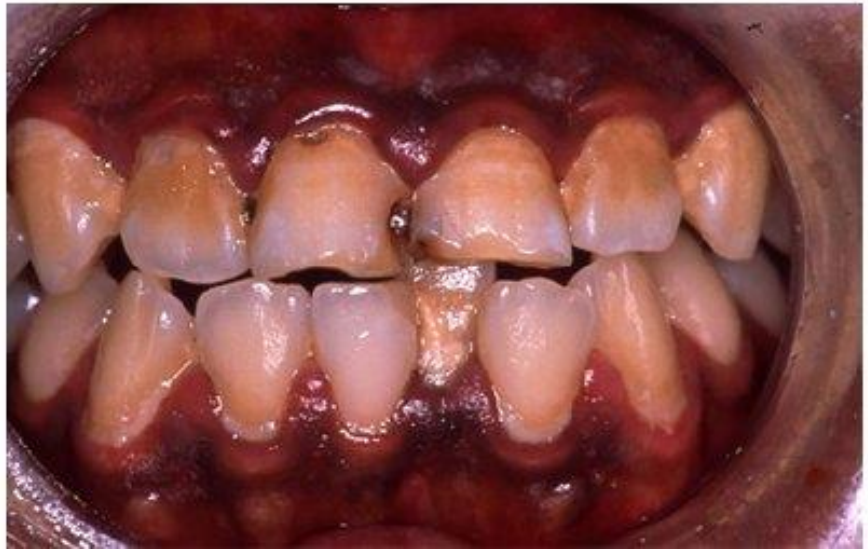
- high concentrations in aquatic organisms because of their deposition in sediments – incorporation to food chain
- Absorbed both orally and via skin
- Very lipophilic, accumulate in fatty tissues, metabolism is very slow, cytochrome P450 1A is involved
- Mechanism of action mainly through AhR (see PAHs, dioxins)
- Some effects not mediated via: induction of CYP 2 and 3, activation of pregnane-X-receptor, imbalance in dopamine and serotonin in CNS during brain development, etc.
- In Japan disease from rice oil – Yusho disease

PCBs









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Phthalates

- Salts of phthalic acid
- Used as plasticizers in polyvinyl chloride (PVC) industry - in toys and containers, in nail polish, paint pigments and inks, as viscosity control agents etc.
- In EU banned esp. in toys for toddlers (oral contact)
- Easily released from plastic toys or from containers to food (mainly in higher temperature), no covalent bond with plastic, some of them volatile
- Form up to 60 % of the product weight!
- Low phthalates (C3-8) replaced by high phtalates (>C9) – more stable, less toxic
- Lipophilic, found mainly in soil and sediments, food chain

Phthalates

- Absorbed orally and via skin
- Degradation in an organism – no oxidation/reduction, only conjugation
- 80 % excreted in urine and bile, rest accumulated in fatty tissue
- Have xenoestrogenic (antiandrogenic) and carcinogenic effect (found only animals – mainly rodents, not proved for humans),
- **Acute toxicity:** tiredness, blurred vision, lacrimation
- **Chronic toxicity:** damage of liver, kidneys, increased pigmentation, disturbances of reproduction, risk of allergies in children, increased risk of diabetes and/or obesity development

Bisphenol A (but probably also S, F etc.)

- Plasticizer – no colour, to make polycarbonate bottles, CDs and DVDs, coating in waterpipes, cans etc. (hard plastics)
- Now banned in baby products, but other bisphenols still used
- Endocrine disruptor:
  - binds to oestrogen receptor – hyperoestrogenism, reproductive problems
  - increased risk of obesity
  - thyroid function interference
  - brain development disturbances (epigenetic modification of DNA)
- Interferes with nitrogen fixation at the roots of leguminous plants – at higher concentration of BPA bad growth of plants

Musk compounds

- Nitro and polycyclic synthetic musks (E.g. tonalide, galaxolide etc.)
- Frequently used as fragrance ingredients in personal care products and household products
- Lipophilic, slower degradation (weeks to months) in water
- Found in humans and aquatic organisms
- Inhibit the activity of multidrug efflux transporters responsible for multixenobiotic resistance (MXR) = other xenobiotics are able to enter the cell and induce toxic effects. Transporter proteins responsible for MXR include e.g. P-glycoprotein
- Low binding affinity to oestrogen receptors – also weak xenoestrogens

Biological exposure tests (BET)

- based on the detection of the substance from the given compartment and serve to determine the concentration of the given toxic substance in the organism.

- **Direct exposure tests** are based on the detection of the given noxae or the product of their biotransformation in the body (e.g. lead in the blood - plumbemia, styrene - mandelic acid in the urine, oxalate crystals in the urine - ethylene glycol)
- **Indirect exposure tests** are based on the finding of the substance to which noxa binds (e.g. mercapturates in urine after exposure to alkylating agents)
- **False exposure tests** are based on the detection of a substance that is changed or affected by the effect of noxa (e.g. decreased concentration of 5-ALA-dehydrogenase after exposure to Pb).

Thank you for your attention

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