Chemical carcinogenesis

About 80% of human tumors are caused by environmental factors, especially chemicals. Exposure to these compounds occurs due to:

- employment (e.g. benzene, asbestos...)
- diet (e.g. aflatoxin B1, which is produced by the fungus *Aspergillus flavus* and is occasionally found as a contamination of peanuts and other foods; furthermore, the most risky foods include animal fats and foods containing them; inappropriate food preparation - frying, baking, smoking, etc., which increases the content of carcinogenic substances)
- lifestyle (smoking cigarettes...)

Classification of chemical carcinogens

1. **primary carcinogens:** active without metabolic activation
2. **secondary carcinogens:** at first they must be activated by biotransformation → procarcinogens
3. **carcinogens:** directly increase the carcinogenic effect (by inducing biotransformation enzymes)
4. **promoters:** indirectly increase the carcinogenic effect by stimulating proliferation

Procarcinogens

náhled|Mechanismus chemické kancerogeneze

- metabolic activation to ultimate carcinogens catalyzed by one or more enzymes is required => possible sequence: *procarcinogen – intermediate carcinogen – final carcinogen*
- metabolism of chemical carcinogenesis: metabolism procarcinogens and other xenobiotics includes monooxygenases a transferases – enzymes responsible for the metabolic activation of procarcinogens are part of the system cytochrom P-450 in endoplasmic reticulum. Their activity is influenced by a number of factors, such as species influences, genetic factors, age or gender
- oespecially monooxygenase involved in the metabolism of polycyclic aromatic [[hydrocarbons] (playing an important role in chemical carcinogenesis) is often called cytochrome P-448 or hydroxylase of aromatic hydrocarbons

1. **polycyclic aromatic hydrocarbons – PAH** – benzanthracene (1. pure carcinogen) – 3,4-benzopyrene (from coal tar) – 3-methylcholanthrene (prepared from steroids, deoxycholic acid) – 7,12-dimethylbenzanthracene (the most effective carcinogen)
2. **aromatic amines and azo dyes**– 2-naftylamine (causes bladder cancer) – 2-acetylaminofluorene – 4-dimethylaminoazobenzene (causes hepatomas)
3. **natural substances – products of fungi and plants** – aflatoxin B1 (hepatokarcinogen, food contamination, causes mutations in DNA, G → T conversion in the p53 molecule, HBV is a synergistic factor in the carcinogenesis of aflatoxin B1) – mitomycin C-cytostatic
4. **others** – nitrosamines (can be formed by the action of bacteria on nitrites in food) – insecticides (chlordane) – tetrachlormethane – ethylene oxide – some metals

Direct carcinogens

- they react directly with DNA

1. alkylating agents – cytostatics and immunosuppressants – beta-propiolaktone – bis-chloromethyl ether
2. acetylating agents – 1-acetylimidazole

Other possible divisions of chemicals with mutagenic effect

1. substances that induce mutations only during replication (= base analogues (5-bromouracil – zcauses base mismatches) and acridine dyes (acridine orange - induces reading frame shift))
2. substances that are mutagenic in action on non-replicating DNA (substances causing alkylation (sulfur mustard – alkyl group donor), deamination (nitrous acid and nitrites), hydroxylation (hydroxyamine))

Factor	Environment	Tumor localization
Polycyclic hydrocarbons - in soot, tar, oils	Chimney sweeps, gas workers, asphalters	Scrotum, skin, bronchi
2-naphthylamine, 1-naphthylamine	Chemists, rubber workers, smokers	Bladder
Benzidine, 4-aminobiphenyl	Chemists	Bladder
Asbestos	Asbestos workers, shipyards, insulators	skin, bronchi
Benzene	Workers with adhesives, laboratory technicians	Bone marrow (leukemia)
Nitrogen mustard	Production of toxic gases	Bronchi, larynx, nasal sinuses
Vinyl chloride	PVC production	Liver

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