



Molecular principles of specific toxicants & PAH



3/25/2024

1

Types of Carcinogens

Carcinogens are grouped into the following 4 categories.

- Incomplete carcinogens (Pre-carcinogens)
- Partial carcinogens (Proximate carcinogens)
- Complete carcinogens (Ultimate carcinogens)
- Tumor promoters and cocarcinogens.

3/25/2024

2

Types of Carcinogens (cont.)

- Pre-carcinogens are inactive carcinogenic compounds. They require promoting agents or metabolic activation through normal enzyme-catalyzed reactions to provide a proximate or ultimate carcinogen.
- Proximate carcinogens are substances that are more closely related to the actual active form of the carcinogen (ultimate carcinogen) than are the parent compound (pre-carcinogen).
- Ultimate carcinogens can produce tumors on their own. Ultimate carcinogens are generally electrophilic agents that have the potential to interact directly with DNA.

3/25/2024

3

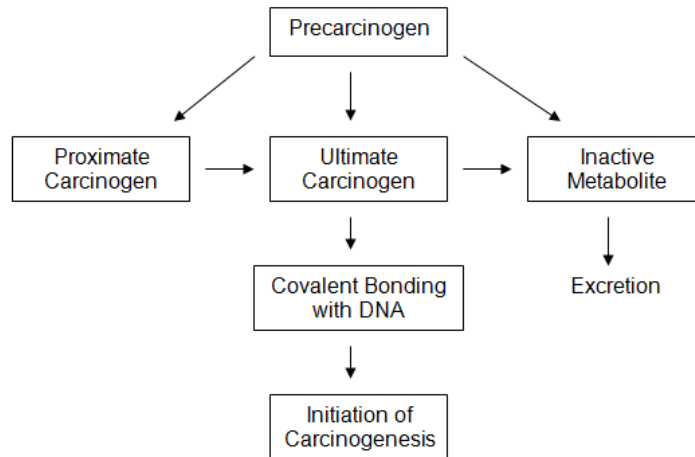
Types of Carcinogens (cont.)

- Co-carcinogens are not carcinogenic in themselves but serve to enhance the effect of pre-carcinogens or ultimate carcinogens. They can lead to the development of tumors when applied to tissues previously treated with pre-carcinogen or a sub-threshold dose of ultimate carcinogen.
- All promoting agents appear to act, at least in part, through their ability to cause irritation or inflammation.
- Natural enzymatic defense processes can deactivate either the pre-carcinogen or ultimate carcinogen to an inactive metabolite that is excreted.

3/25/2024

4

Types of Carcinogens (cont.)



3/25/2024

5

Mechanism of Chemical Carcinogenesis

Carcinogenesis is a multistage process, and the first step is the initiation which is followed by one or more promoting events.

Carcinogenesis in mouse skin is the classic model system in which two stages in cancer development (initiation and promotion) were first described.

With a single application, applying ultimate carcinogen (UC) to the shaved back skin results in the initiation process. If the animals are left without further treatment, they will persist for a long time without showing tumors. Multiple exposures to UC will reduce the onset time of tumors.

3/25/2024

6

What are reproductive toxins?

Mutagens

- ⚡ Cause damage to chromosomes by introducing changes to DNA.
- ⚡ Have adverse effects on fertility and general reproductive performance.
- ⚡ Are chronic toxins

Teratogens

- ⚡ Act during pregnancy to cause adverse effects on the embryo or fetus including malformations, retarded growth and post-natal deficiencies.
- ⚡ Reproductive toxins can affect both men and women.

3/25/2024

7

From the Reproductive Toxins Fact Sheet

There are three categories for reproductive toxins, Category 1A, 1B and 2, that you may see on safety data sheets (SDS) or on a chemical bottle. In Section 2–Hazard Identification of the safety data sheets (SDS), a combination of the following hazard classifications, pictograms and hazard statements will be listed indicating a reproductive hazard.

| Hazard Classification and Category | Pictogram | Hazard Statement |
|-----------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Toxic to Reproduction – Category 1A, 1B and 2 |  | May damage fertility or the unborn child Suspected of damaging fertility or the unborn child May cause harm to breast-fed children |

<https://essr.umd.edu/sites/default/files/2021-11/ReproductiveToxinsFactSheet.pdf>

3/25/2024

8

What is a chemical carcinogen?

- ⌘ Any discrete chemical compound which has been shown to cause cancer in human or animal studies.
- ⌘ Hundreds of individual compounds have been shown to induce cancers. Many thousands of additional compounds are “suspect” carcinogens.
- ⌘ Many are commonly used in laboratory operations, shops and art studios.

What is a chemical carcinogen?

Which classes of chemicals tend to be carcinogens?

- ❖ **Epoxides:** Ethylene oxide
Propylene oxide
- ❖ **Organ halogen comp.:** Vinyl chloride, Chloroform
Carbon tetrachloride
Hexachlorobenzene
Trichloroethylene
- ❖ **Hydrazine:** 1,2-Dimethylhydrazine

Miscellaneous organic and inorganic compounds

❖ Organic compounds:

Formaldehyde
 Acetaldehyde
 1,4-Dioxane
 Ethyl carbamate
 2-Nitropropane
 Styrene
 Thiourea
 Thioacetamide

❖ Inorganic compounds

Arsenic and compounds
 Chromium and comp.
 Thorium dioxide
 Beryllium and compounds
 Cadmium and compounds
 Lead and compounds
 Nickel and compounds
 Selenium sulfide

What is a chemical carcinogen?

Which classes of chemicals tend to be carcinogens? (Cont.)

❖ Polycyclic Aromatic Hydrocarbon (PAH)

Dibenzo-pyrene, Benzo[α]anthracene, Benzo[α]pyrene.

❖ Alkylating agents:

Sulphur mustard, Lactones, Nitrosamine

❖ Aromatic Amines:

Benidine, Aniline, 2-Naphthaylamine.

❖ N-Nitroso compounds:

N-Nitroso-dimethylamine

What factors influence the development of cancer?

- ⌘ Dose--amount and length of exposure. The lower the dose you are to develop cancer, the least likely _____
- ⌘ Environmental or “lifestyle” factors.
 - ✓ Cigarette smoking (co-carcinogen)
 - ✓ Alcohol consumption (co-carcinogen)
 - ✓ Diet--high fat consumption, natural antioxidants
 - ✓ Geographic location--industrial areas, UV light
 - ✓ Therapeutic drugs--some are known carcinogens
 - ✓ Inherited conditions

3/25/2024

13



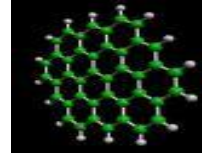
Polycyclic Aromatic Hydrocarbons (PAH)



3/25/2024

14

Polycyclic Aromatic Hydrocarbons

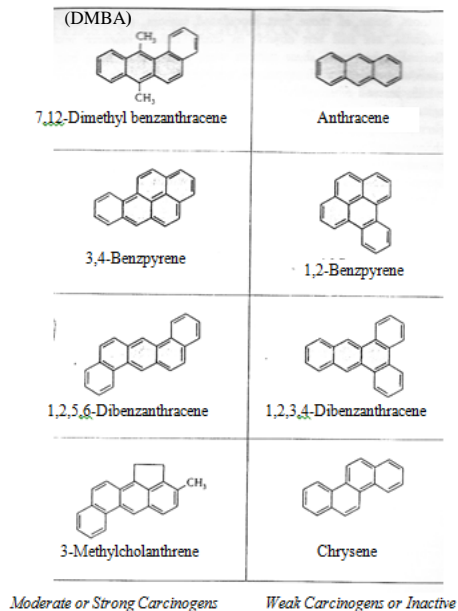


The carcinogenic activity of polycyclic aromatic hydrocarbons (PAH) was first reported in 1915 by two Japanese, Yamagiwa and Ichikawa. They induced the first experimental tumors by the application of tar, 2-3 times a week to the inside of rabbit ears. After 3 months proliferations were developed, which later turned to cancerous growth.

3/25/2024

15

Names and structures of some PAH with variable carcinogenic activities



3/25/2024

16

Tumor Induction by DMBA

- ❖ A single subcutaneous injection of 7,12-dimethylbenzanthracene (DMBA) leads to sarcomas after a long latent period (3-4 months).
- ❖ If DMBA is injected subcutaneously in newborn mice, multiple lymphomas (lymph gland tumors) occur and the usual sarcomas at the injection site are seldom found.
- ❖ Multiple intravenous injections of DMBA in both rats and mice lead to leukemia.

General Description of PAH

- ❖ Polycyclic aromatic hydrocarbons (PAHs) are a large group of organic compounds with two or more fused aromatic rings.
- ❖ They have a relatively low solubility in water but are highly lipophilic.
- ❖ PAHs can undergo photodecomposition when exposed to ultraviolet light from solar radiation.

General Description of PAH (cont.)

- ❖ In the atmosphere, PAHs can react with pollutants such as ozone, nitrogen oxides and sulphur dioxide, yielding diones, nitro- and dinitro-PAHs, and sulfonic acids, respectively.
- ❖ PAHs may also be degraded by some microorganisms in the soil

Relative significance of different routes of exposure

- ❖ Estimates were made for a "reference man" aged between 19 and 50 years and presented on a total body basis.
- ❖ In non-smokers a mean total intake of 3.12 mg/day was estimated, of which food contributed 96.2%, air 1.6%, water 0.2% and soil 0.4%.
- ❖ Smokers consuming one pack of non-filtered cigarettes per day had an estimated additional intake of 1–5 µg/day.

How might I be exposed to PAHs?

- Breathing air containing PAHs in the workplace of smoke houses coal-tar, aluminum and asphalt production plants.
- Coming in contact with air, water, or soil near hazardous waste sites.
- Drinking contaminated cow's milk.

How might I be exposed to PAHs?(cont.)

- PAHs are found in substantial quantities in some foods, depending on the mode of cooking, preservation and storage, and are detected in a wide range of meats, fishes, vegetables and fruits.
- Nursing infants of mothers living near hazardous waste sites may be exposed to PAHs through their mother's milk.

How might I be exposed to PAHs?(cont.)

- Benzopyrene as the most important PAH is produced by pyrolysis of fat dripping on hot-charcoal. i.e., pyrolysis is conversion of substance to another by heat only.



3/25/2024

23

Metabolism and activation

- The enzyme system primarily responsible for PAH metabolism is the microsomal mixed function oxidase system, which converts the non-polar PAHs into polar **hydroxy** and **epoxy** derivatives.
- The enzyme systems that metabolize PAHs are widely distributed in the cells and tissues of humans and animals.

3/25/2024

24

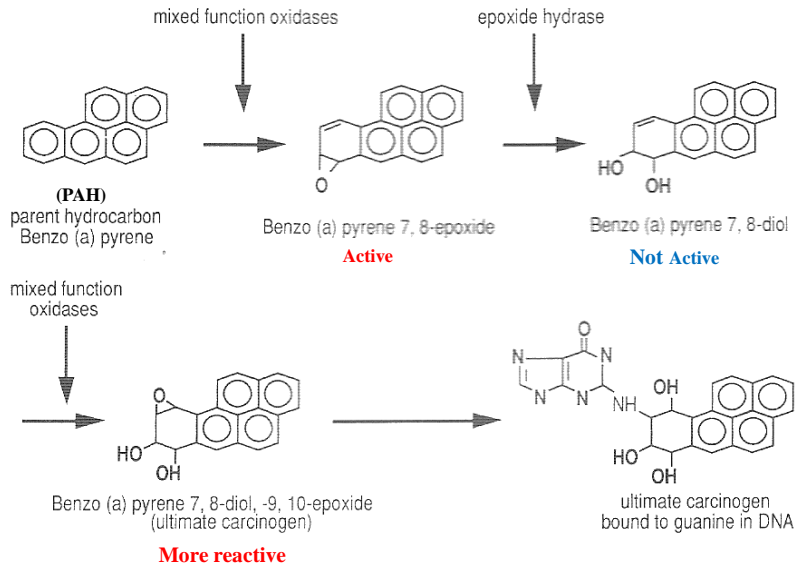
Metabolism and activation (cont.)

- Epoxides are the major intermediates in the oxidative metabolism of aromatic double bonds.
- The epoxides are reactive and enzymatically metabolized to other compounds such as dihydrodiols and phenols.
- Animal and human fetal tissues have the capacity to metabolize PAHs, but at a low rate compared to the adult tissues.

Metabolism and activation (cont.)

- The highest metabolizing capacity is present in the liver, followed by lung, intestinal mucosa, skin and kidneys, but metabolism may also take place in nasal tissues, mammary gland, spleen, brain, hair follicles, erythrocytes, platelets, leukocytes, placenta and uterus.

Metabolic Activation of Benzopyrene

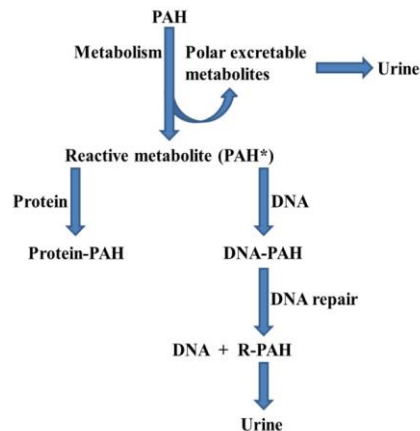


3/25/2024

27

Polycyclic Aromatic Hydrocarbons activation

The DNA binding of activated PAHs is considered to be essential for the carcinogenic effect.



3/25/2024

28

Polycyclic Aromatic Hydrocarbons metabolism (cont.)

- Active epoxides can be inactivated by many enzymes e.g:
 1. Glutathion-S-transferase
 2. UDP-glucuronic acid-epoxide transferase
 3. Epoxide reductase
 4. Epoxide-hydratase that converts the active epoxide to noncarcinogenic dihydrodiol metabolite.