# Environmental Health

Carcinogenesis

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Neoplasia is new **growth or autonomous growth of tissue**. The resulting neoplastic lesion is referred to as a neoplasm. Both benign and malignant neoplasms can be induced by chemical carcinogens

The term "**tumor**" describes a lesion that may or may not be neoplastic ,and is characterized by **swelling or an increase in size**

The term "**cancer**" describes the subset of **neoplasia** that represents **malignant neoplasms**. A carcinogen is an agent, chemical or physical, that causes or induces neoplasia

**Carcinogens** can be chemicals, viruses, hormones, radiation, or solid material

# Malignant vs. Benign Neoplasms

- **Benign**
  - Usually encapsulated
  - Usually non-invasive
  - Highly differentiated
  - Rare mitoses
  - Slow growth
  - Little or no anaplasia
  - No metastases
- **Malignant**
  - Encapsulated
  - Invasive
  - Poorly differentiated
  - Mitoses relatively common
  - Rapid growth
  - Anaplastic to varying degrees
  - Metastases

**Cancer** is therefore the malignant uncontrolled proliferation of neoplastic cells. Also a description of a multitude of different disease states (~200)

# Cancer is the leading disease-related cause of years of life lost in the US.

| • **Causes of Death** | • **Years of Life Lost*** |
|---|---|
| – All causes | – 11,761,000 |
| – Unintentional injuries | – 2,306,000 |
| – Cancer | – 1,803,000 |
| – Heart disease | – 1,563,000 |
| – Suicide, homicide | – 1,247,000 |
| – Congenital anomalies | – 584,000 |

* Estimated years of life lost before the age of 65

## Features of Genotoxic and Nongenotoxic Carcinogens

**Genotoxic carcinogens** Mutagenic Can be complete carcinogens

**Nongenotoxic** carcinogens **Nonmutagenic**, reversible Tumorigenicity is dose responsive No direct DNA damage Species, strain, tissue specific

## MULTISTAGE CARCINOGENESIS

### Initiation

The first stage of the cancer process involves initiation, a process that is defined as a stable, heritable change. This stage is a rapid, irreversible process that results in a carcinogen-induced mutational event.

Initiating agents lead to genetic changes including mutations and deletions. Chemical carcinogens that covalently bind to DNA and form adducts that result in mutations are initiating agents.

**Included among chemicals** classified as initiating carcinogens are compounds such as polycyclic hydrocarbons and nitrosamines, biological agents such as viruses, and physical agents such as X-rays and UV light.

Most chemical carcinogens that function at the initiation stage of the cancer process are indirect-acting genotoxic compounds that require metabolic activation in the target cell to produce the DNA-damaging event.

The **ultimate** form of the carcinogen is then able to bind to nuclear DNA, resulting in adduct formation. The initiating event becomes "fixed" when the DNA adducts or other damage to DNA are not correctly repaired.

**Promotion**

Derived from either endogenous or exogenous stimuli of cell growth, the second stage of the carcinogenesis process involves the selective clonal expansion of initiated cells to produce a **preneoplastic lesion**.

Tumor promoters are not mutagenic and generally are not able to induce tumors by themselves; rather they act through several mechanisms involving gene expression changes that result in **sustained** cell proliferation, either through increases in cell proliferation and/or the inhibition of apoptosis.

Promotion is a **reversible** phenomenon where by upon removal of the promoting agent, the focal cells may return to single initiated cell threshold

Tumor promoters in general **show organ-specific effects** , e.g.,a tumor promoter of the liver, such as **phenobarbital** will not function as a tumor promoter in the skin or other tissues.

**Progression**

The final stage of the carcinogenesis process, progression, involves the conversion of benign preneoplastic lesions into neoplastic cancer. In this stage , due to increase in DNA synthesis, cell proliferation in the preneoplastic lesions, additional genotoxic events may occur resulting in additional DNA damage including chromosomal aberrations and translocations. These events result in the transfer from **preneoplastic**, clonally derived cell populations into **neoplastic cell** populations

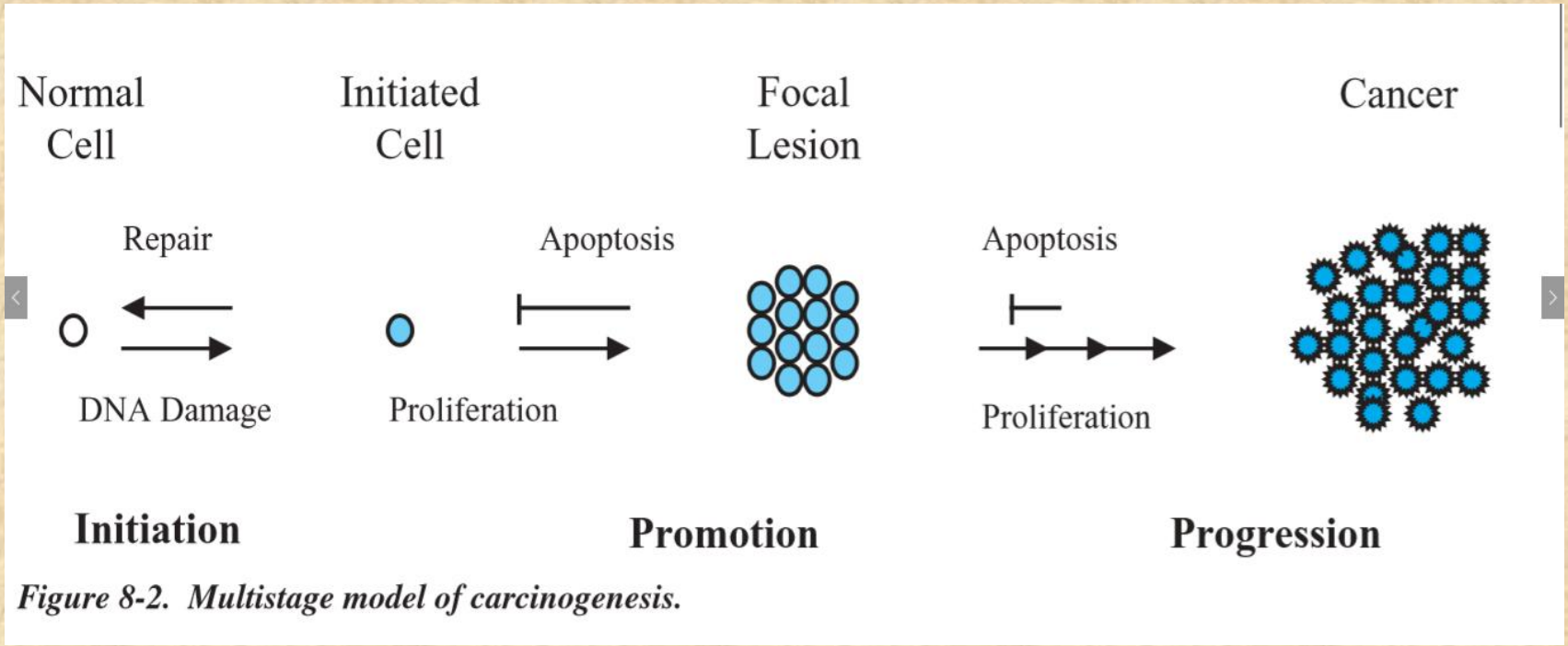



*Figure 8-2. Multistage model of carcinogenesis.*

# MECHANISMS OF ACTION OF CHEMICAL CARCINOGENS

The development of neoplasia requires two major events: the formation of an initiated, mutated cell and the selective proliferation of the mutated cell to form aneoplasm

## Genotoxic Carcinogens

Genotoxic carcinogens initiate tumors by producing **DNA damage**.

**Examples of Genotoxic Carcinogens**

| |
|---|
| Direct-acting carcinogens |
| Nitrogen or sulfur mustards |
| Propane sulfone |
| Methyl methane sulfonate |
| Ethyleneimine |
| B-Propiolactone |
| 1,2,3,4-Diepoxybutane |
| Dimethyl sulfate |
| *Bis*-(Chloromethyl) ether |
| Dimethylcarbamyl chloride |
| Chemicals requiring activation (indirect-acting carcinogens) |
| Polycyclic aromatic hydrocarbons and heterocyclic aromatics |
| Aromatic amines |
| *N*-Nitrosoamines |
| Azo dyes |
| Hydrazines |
| Cycasin |
| Safrole |
| Chlorinated hydrocarbons |
| Aflatoxin |
| Mycotoxin |
| Pyrrolizidine alkaloids |
| Bracken fern |
| Carbamates |

**Direct-Acting(Activation-Independent)Carcinogens**

A variety of carcinogens do not require metabolic activation or chemical modification to induce cancer, and are termed direct acting or activation independent carcinogens. These chemicals are also defined as **ultimate carcinogens**. Examination of the chemical structure of these agents reveals that they are highly reactive electrophilic molecules that can interact with and bind to nucleophiles, such as cellular macromolecules including DNA.

**Direct-acting carcinogens include epoxides, imines, alkyl and sulfate esters, and mustard gases**

Direct-acting electrophilic carcinogenic chemicals typically test positive in the **Ames** test without additional bio activation with a liver metabolic fraction. The relative carcinogenic activity of direct-acting carcinogens is dependent upon such competing reactions and also on **detoxification** reactions.

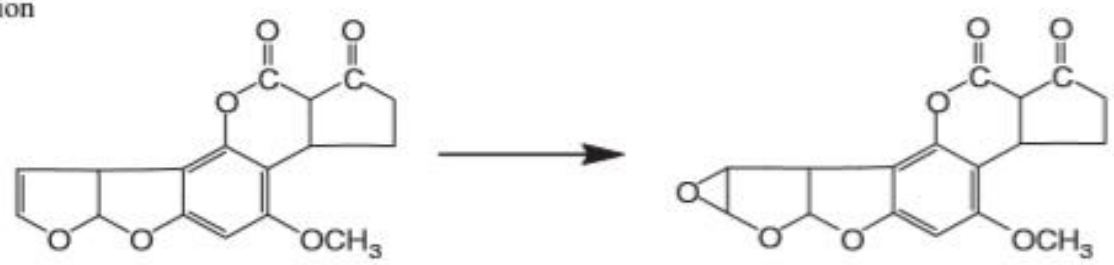
**Indirect-ActingGenotoxicCarcinogens**

An important discovery in the understanding of chemical carcinogenesis came from metabolic activation to be carcinogenic. It has since been shown that the majority of DNA reactive carcinogens are found as parent compounds ,or procarcinogens.**Procarcinogens** are stable chemicals that require subsequent metabolism to be carcinogenic

**The terms procarcinogen, proximate carcinogen, and ultimate carcinogen** have been coined to define the parent compound (procarcinogen) and its metabolite form, either intermediate (proximate carcinogen) or final (ultimate carcinogen) that reacts with DNA .**The ultimate** form of the carcinogen is most likely the chemical species that results in mutation and neoplastic transformation.

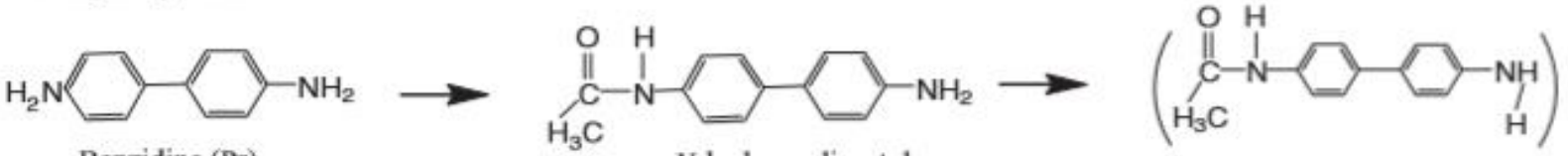
**Procarcinogen** → **Proximate (Px) Carcinogen** → **Ultimate (Ut) Carcinogen**

Direct epoxidation



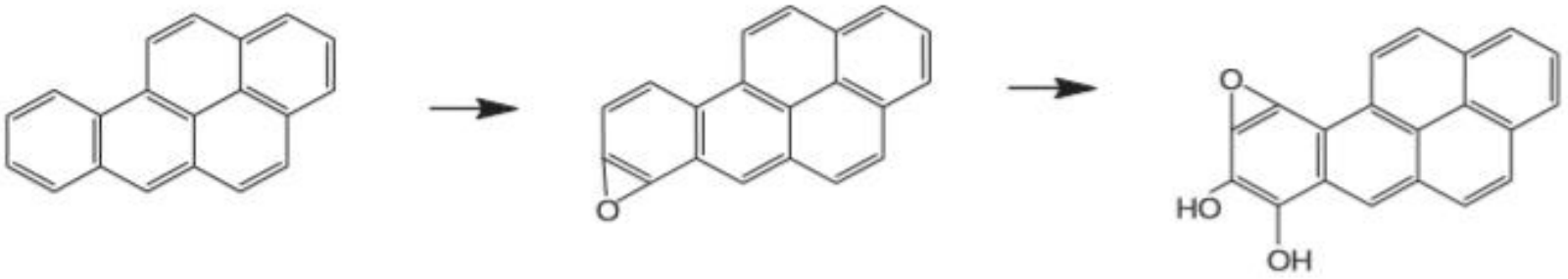
Aflatoxin $B_1$ (Pr) → Aflatoxin $B_1$ 2,3 epoxide (Ut)

*N*-Hydroxylation



Benzidine (Pr) → *N*-hydroxy diacetyl Benzidine (Px) → *N*-Acetyl benzidine Nitrenium ion (Ut)

Two-step epoxidation



Benzo(a)pyrene (Pr) → Benzo(a)pyrene 7,8 epoxide (Px) → Benzo(a)pyrene 7,8 diol-9,10 epoxide (Ut)

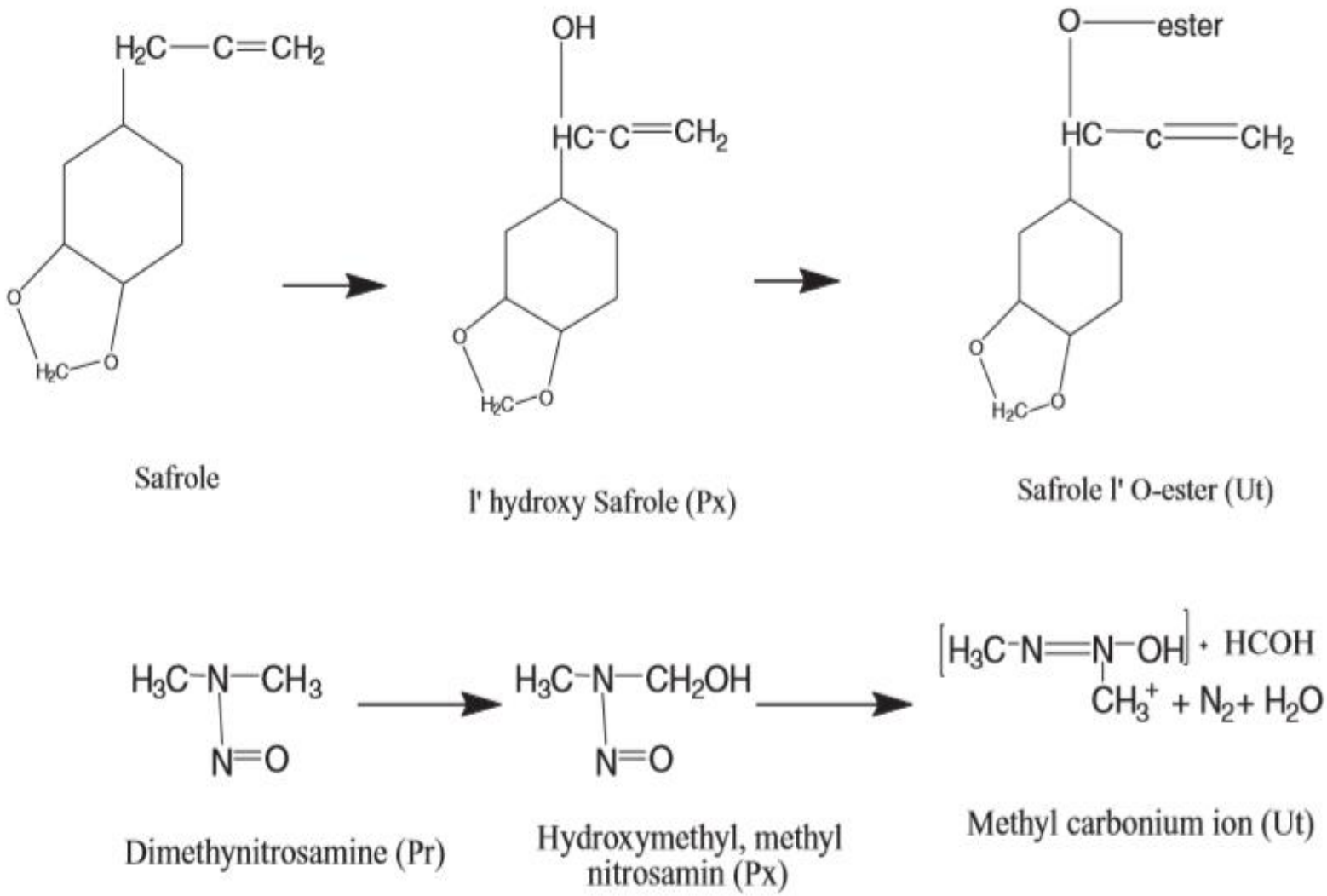



***Figure 8-4. Structures of representative indirect-acting carcinogens and their metabolic derivatives.***

The proximate (Px) and ultimate (Ut) carcinogenic forms result from the metabolism of the procarcinogenic form (Pr).

**Damage by Alkylating Electrophiles**

most chemical carcinogens require metabolic activation to exert a carcinogenic effect. The ultimate carcinogenic forms of these chemicals are frequently strong electrophiles that can readily form covalent adducts with nucleophilic targets. Because of their unpaired electrons, S:, O:, and N: atoms are nucleophilic targets of many electrophiles. The extent of adducts formed is limited by the structure of DNA, where **bulky electrophilic** chemicals can bind, and size of the ultimate carcinogenic form

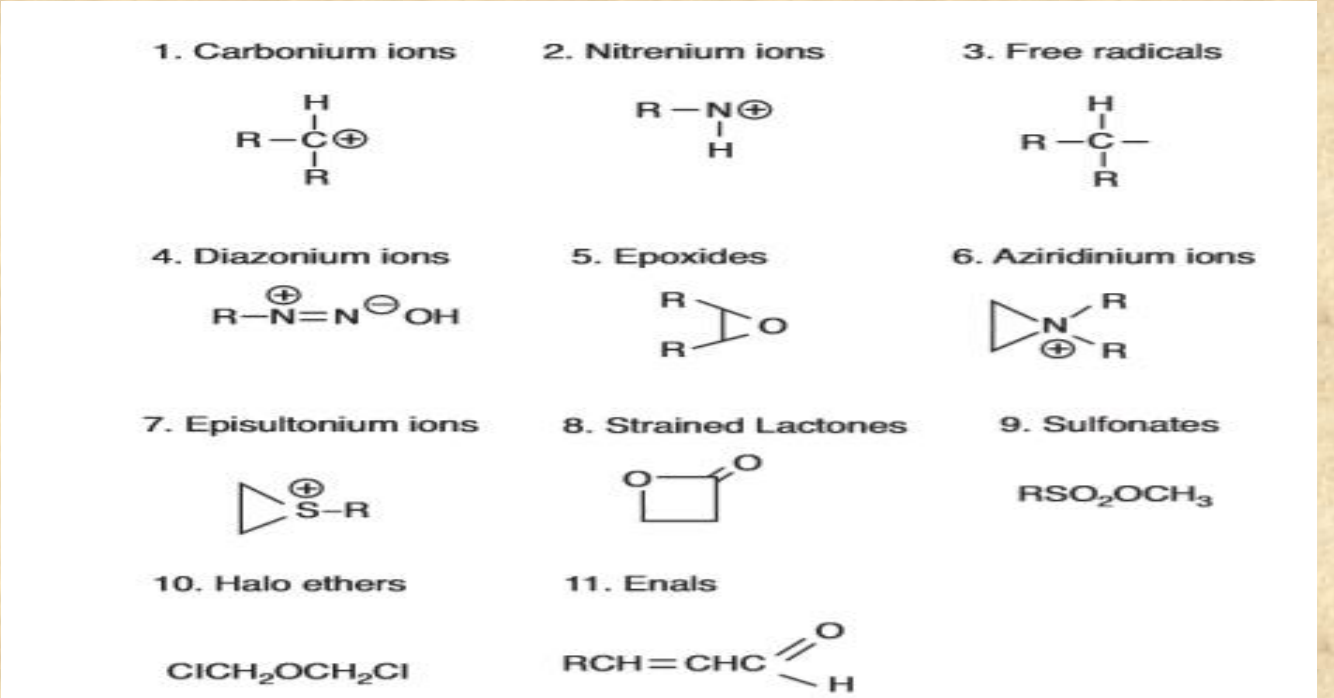
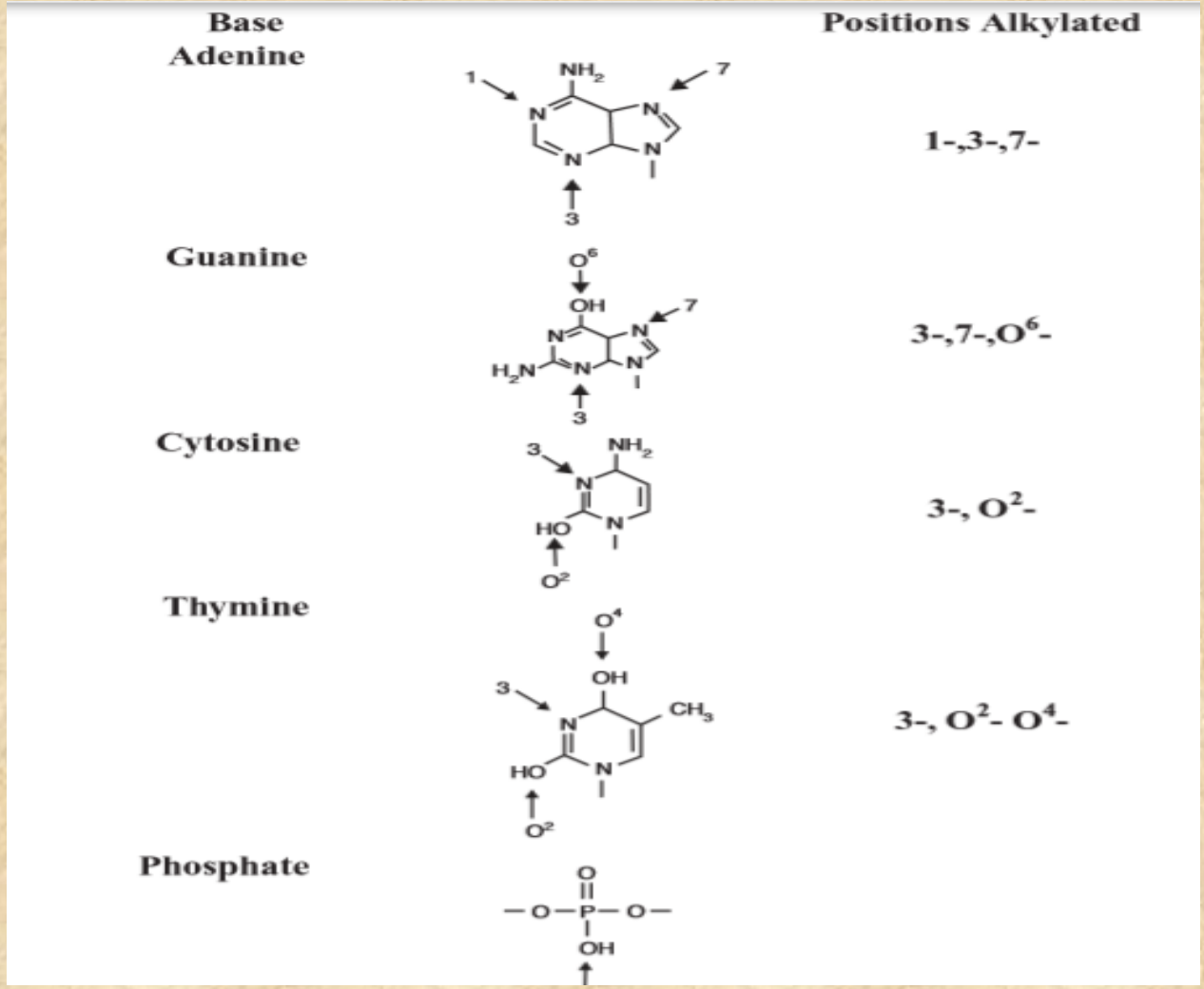
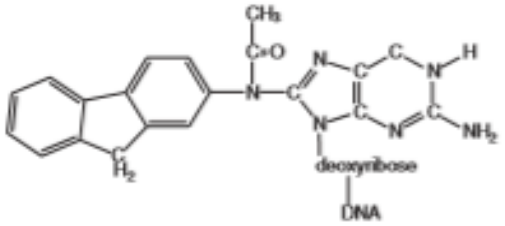


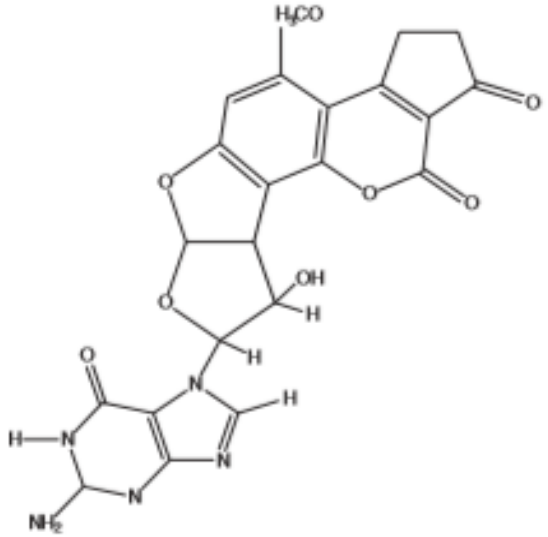

*Figure 8-3. Structures of reactive carcinogenic electrophiles.*

Where as carcinogen DNA adducts may be formed at all sites in DNA, the most common sites of alkylation include the N7 of guanine, the N3 of adenine, theN1 of adenine, theN3 of guanine, and the O6 of guanine. Alkylations of phosphate may also occur at a high frequency

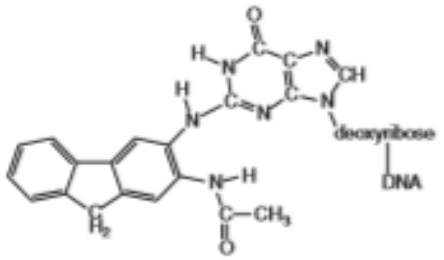




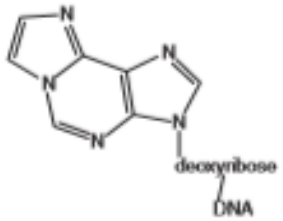

*N*-(deoxyguanosine-8-yl)-acetylaminofluorene in DNA



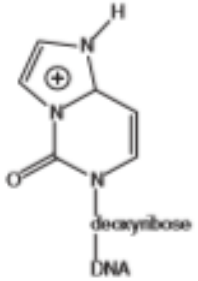

Aflatoxin $B_1$ *N*-7 guanine-adduct



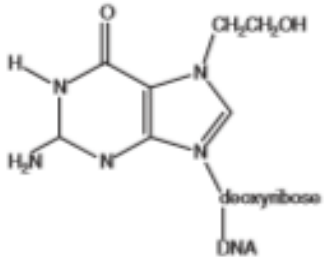

3-(deoxyguanosine $N_2$-yl)-acetylaminofluorene in DNA




1, $N^6$-ethenoadenine in DNA




3,$N^4$-ethenocytosine in DNA




*N*-7-(2-hydroxyethyl) guanosine in DNA

***Figure 8-6. Select structures of protein and nucleic adducts of certain chemical carcinogens.***

Different electrophilic carcinogens will often **display different preferences** for nucleophilic sites in DNA and different spectra of damage. Dimethylnitrosamine and diethylnitrosamine, for example, are metabolized by P450 oxidation to yield a **methyl carbonium ion**

**($CH^+_3$) and an ethyl carbonium ion ($CH_3CH^+_3$),** respectively. Despite the structural similarities of the ultimate electrophiles.

The predominant adduct formed following exposure to methylating chemicals such as methyl methane sulfonate is **7-methylguanin**e.

Another common modification to DNA is the hydroxylation of DNA bases. Oxidative DNA adducts have been identified

The **source of oxidative DNA** damage is typically formed from free radical reactions that occur endogenously in the cell or from exogenous source.

Although a relatively large amount of oxidative DNA adducts have been proposed to be formed per day, repair mechanisms exist that maintain the cellular level at a low rate.

Methylation of deoxycytidine residues is a well-studied DNA adduct. This reaction occurs by the transfer of a methyl group from **S-adenosyl methionine by DNA methyl transferases**

Methylation of DNA results in heritable expression or repression of genes, with **hypomethylation** associated with active transcription of genes, while **hypermethylated** genes tend to be rarely transcribed.

Chemical carcinogens may **inhibit DNA methylation** by several mechanisms including forming **covalent adducts**, **single strand breaks** in the DNA, **alteration of methionine pools**, and inactivation of the DNA methyltransferase responsible for methylation

**DNA Repair Mechanisms**

Although cells possess mechanisms to repair many types of DNA damage, these are not always completely effective, and residual

DNA damage can lead to the insertion of an incorrect base during DNA replication, followed by transcription and translation of the mutated templates

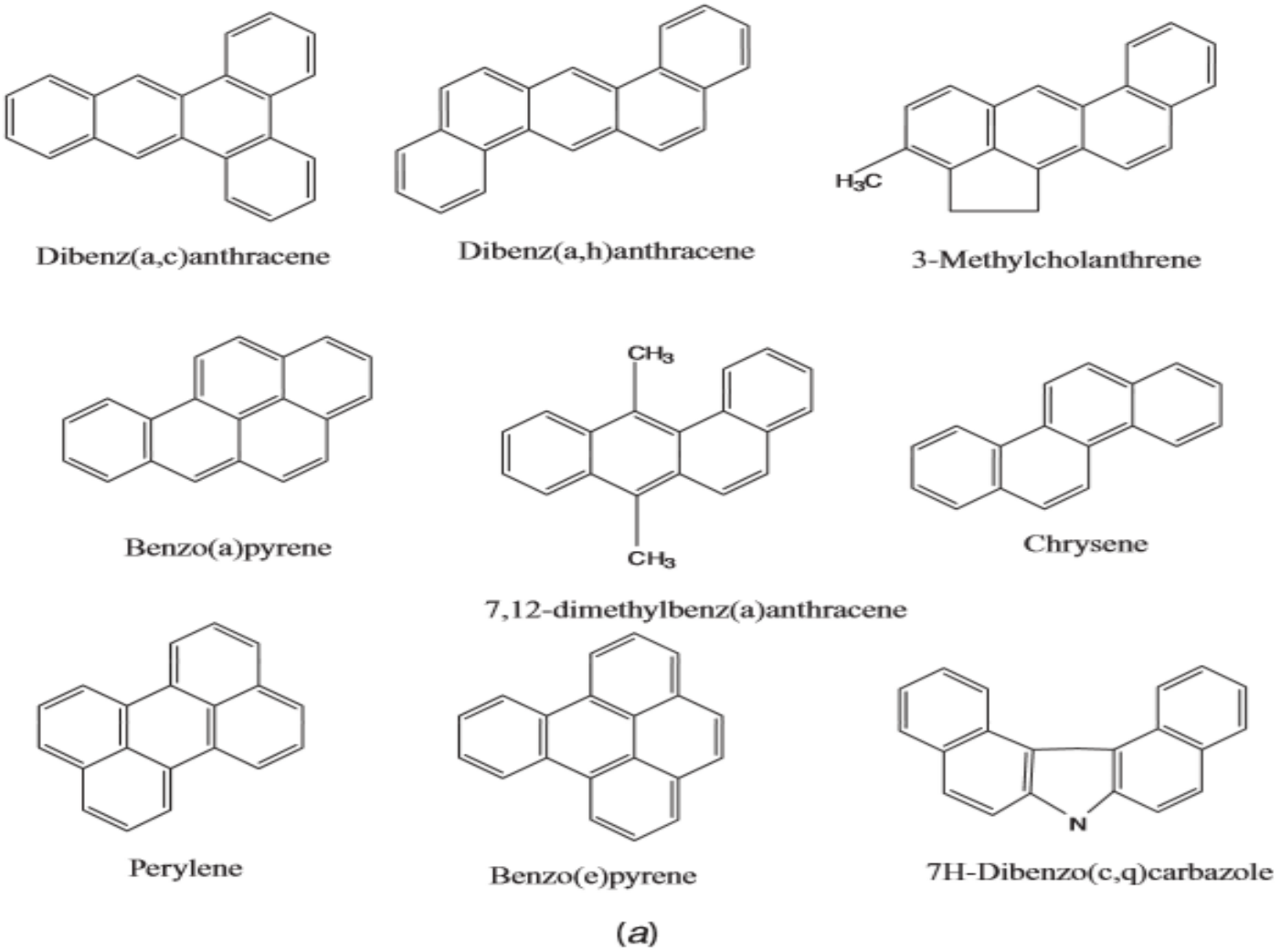
**Table 8-8**

**DNA Repair Pathways**

1. Direct reversal of DNA damage
2. Excision repair systems
   - Base excision repair
   - Nucleotide excision repair
   - Mismatch repair
3. Postreplicational repair (recombination repair)
4. Nonhomologous-end-jointing (NHEJ): double-strand break repair

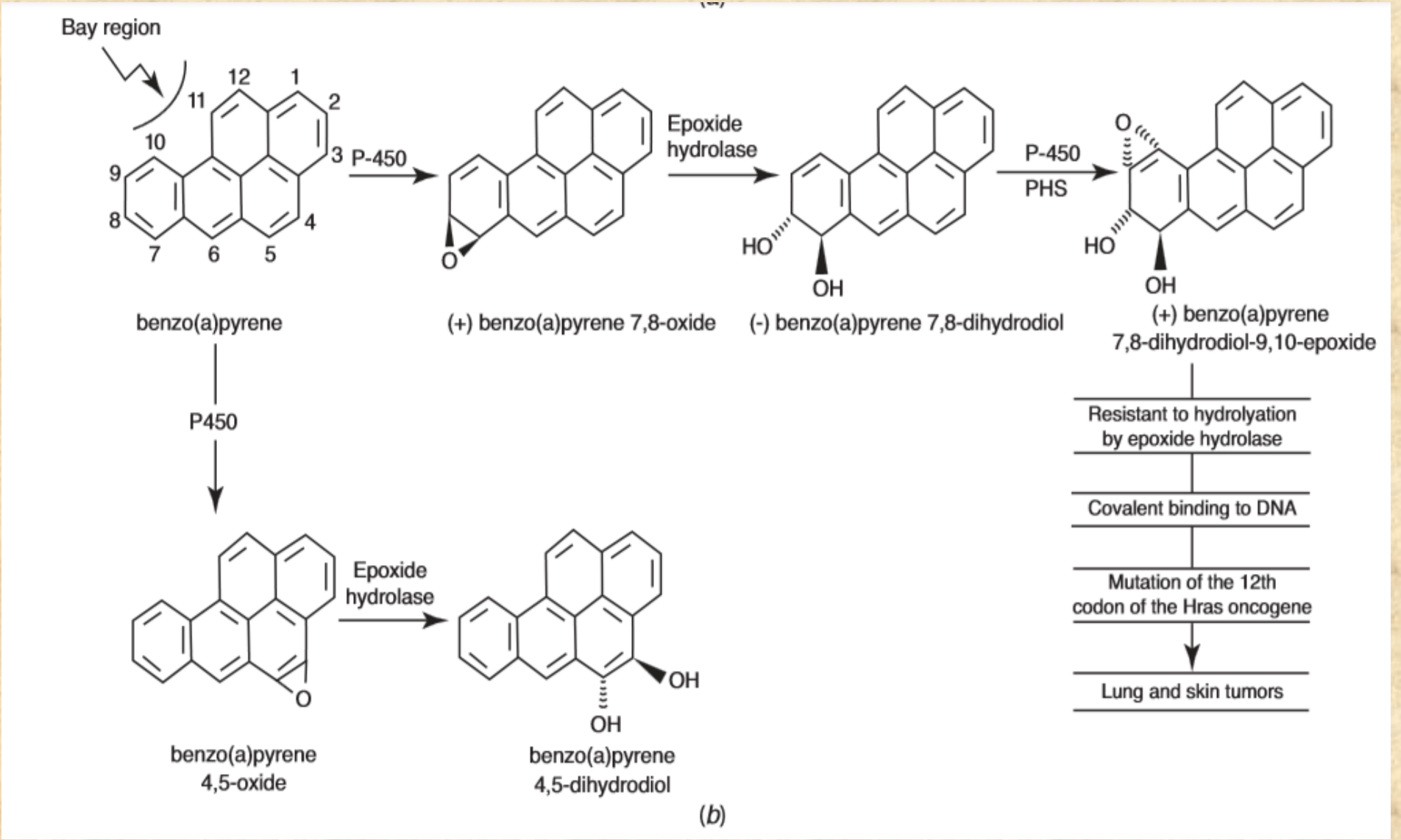
# Classes of Genotoxic Carcinogens

Polyaromatic Hydrocarbons are found at high levels in charcoal




(A) Chemical structures of selected carcinogenic polycyclic hydrocarbons

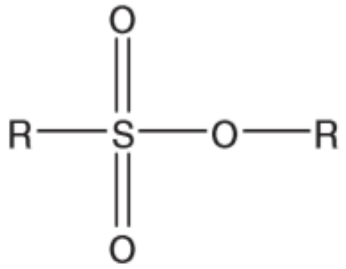
# The metabolism and pathways that lead to tumor formation



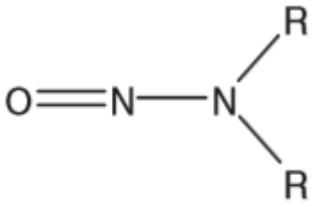

(B) Role of epoxide hydrolase in the activation of benzo[a]pyrene 4,5-oxide and in the conversion of benzo[a]pyrene to its tumorigenic bay-region diole poxide.

**Alkylating Agents** Alkylating chemicals represent an important class of chemical carcinogens. Whereas some alkylating chemicals are direct-acting genotoxic agents, many **require metabolic activation to produce electrophilic metabolites** that can react with DNA. Alkylating agents can be classified into several groups including the **direct-acting** alkylalkane sulfonate
**the indirect-acting nitrosamides**

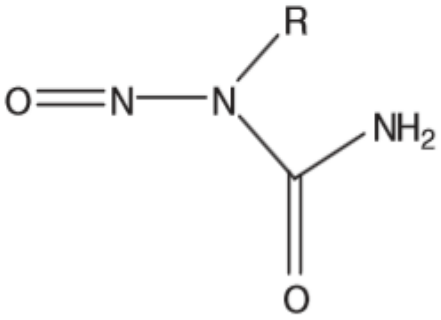
**The alkylating compound diethyl nitrosamine and dimethyl nitrosamine readily react with DNA** at more than 12 sites. The N7 **position of guanine and the N3 position of adenine are the most reactive sites in DNA for alkylating chemicals**. DNA methylation reactions occur more readily and thus exhibit >20 more adducts than with ethylation reactions. However, **ethylation** reactions have a greater affinity for oxygen centers, an event that appears to correlate with the mutagenicity and carcinogenicity of these compounds.



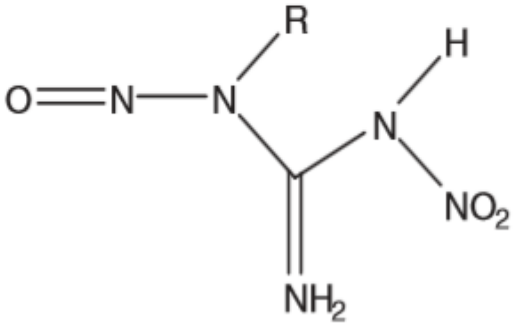

Alkyl alkanesulfonates




Diakyl nitrosamines




*N*-Nitrosoureas




*N*-Alkyl-*N*'-nitro-*N*-nitrosoguanidine

***Figure 8-11. Structures of representative methylating and ethylating agents.***

Alkalating chemicals including the nitrogen mustards (e.g., chlorambucil, cyclophosphamide) have been used in cancer chemotherapy. They produce **DNA adducts as well as induce the formation of DNA strand breaks**.

The alkylation of DNA by nitrogen mustards requires the formation of highly reactive **N-alkyl azirdinium ions** (Fig. below). Nitrogen mustards can produce a wide spectrum of mutations including **base pair substitutions (AT and GC) and deletions. In addition, nitrogen mustards are causing chromosomal aberrations and sister chromatid exchanges**

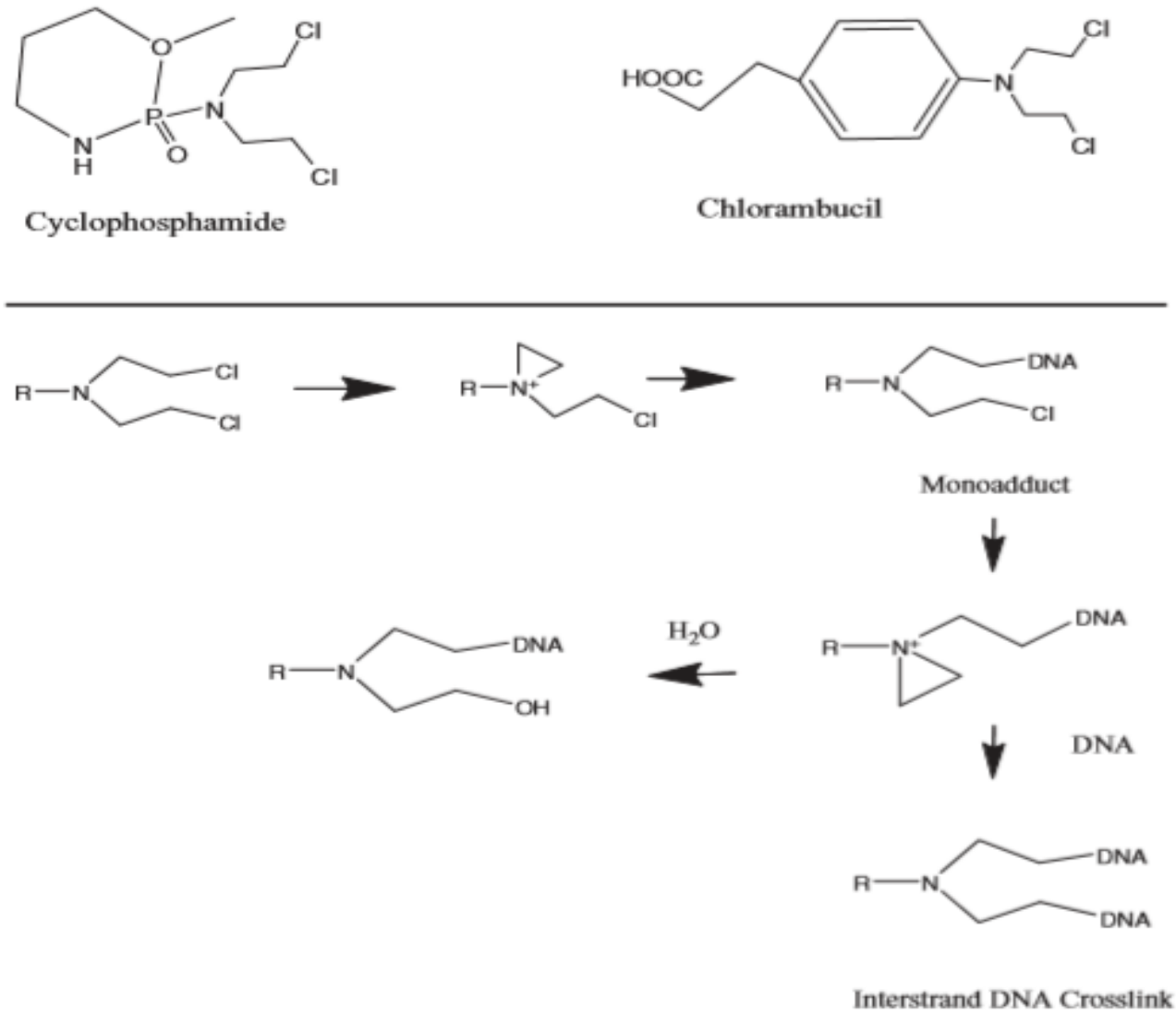



*Figure 8-12. Nitrogen mustards and proposed mechanism for the reaction of nitrogen mustards with DNA.*

**Aromatic Amines and Amides**

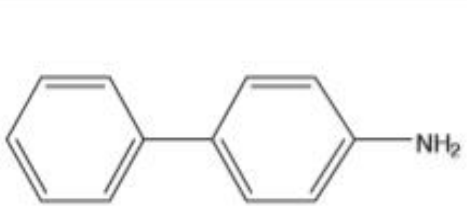
encompass a class of chemicals with varied structures (**aromatic amines, e.g. aniline dyes, 2-naphthylamine, benzidine, 2acetylaminofluorene)** (Fig. below).

Because of their use in the dye industry and other industrial processes their carcinogen potential in humans was realized as early as the late 19th century. **While proper industrial hygiene processes have considerably reduced the human exposure to aromatic amines and amides in the workplace, exposure to these chemicals still occurs through cigarette smoke and environmental sources**. The aromatic amines undergo both phase-I and phase-II metabolism.

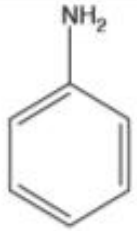
Phase-I reactions occur mainly by cytochrome P450-mediated reactions, yielding hydroxylated metabolites that are often associated with adduct formation in proteins and DNA, and produce liver and bladder carcinogenicity

For example, metabolism of **2-acetylaminofluorene** (AAF) results in the formation of N-hydroxy-AAF, which is a metabolite responsible for the liver tumorigenicity.

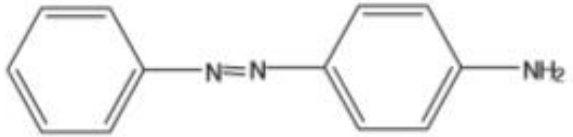
Similarly, 1-napthylamine exhibits carcinogenic activity only in test systems capable of producing the **N-hydroxy metabolite** of naphthylamine. **Aromatic amines are capable of forming adducts with several DNA bases**.




4-Aminobiphenyl (ABP)

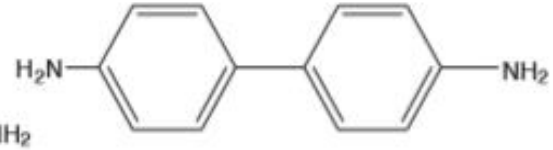



Aniline

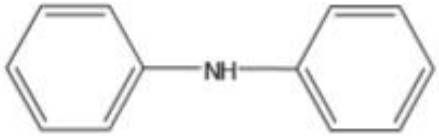



4-Aminoazobenzene

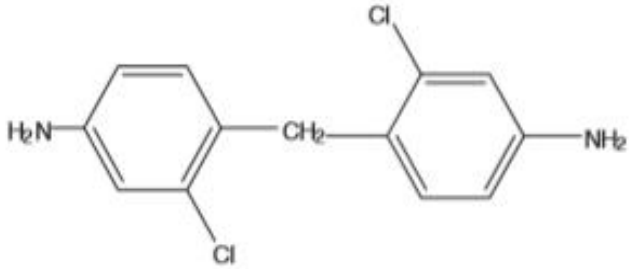

2-Aminophenanthrene



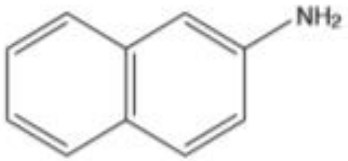

Benzidine



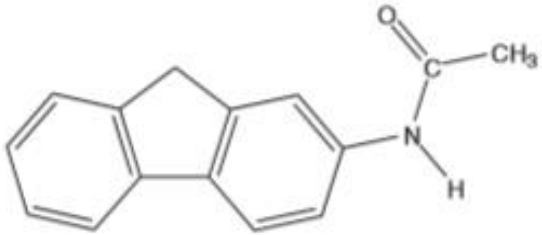

Diphenylamine




4,4'-Methylene-*bis*-2-chloroaniline




2-Naphthylamine




2-Acetylaminofluorene (2-AAF)

***Figure 8-14. Chemical structures of selected carcinogenic aromatic amines.***

## Inorganic Carcinogens

Several metals exhibit carcinogenicity in experimental animals and/or exposed humans. Table a listing of some common metals and their corresponding carcinogenicity in animals and humans.

**Carcinogenicity of Metals**

| | ANIMAL | | | HUMAN | |
|---|---|---|---|---|---|
| METAL | SPECIES | TUMOR SITE | TUMOR TYPE | EXPOSURE | TUMOR TYPE |
| Arsenic | Mice, dogs, rats | None observed | None observed | Cu refinery | Pulmonary carcinoma |
| | | | | As pesticides | Lymphoma, leukemia |
| | | | | Chemical plants | Dermal carcinoma |
| | | | | Drinking water (oral) | Hepatic angiosarcoma |
| Beryllium | Mice, rats, monkeys | Bone | Osteosarcoma | None observed | None observed |
| | | Lung | Carcinoma | | |
| Cadmium | Mice, rats, chickens | Injection site | Sarcoma | CD refinery | Pulmonary carcinoma |
| | | Testes | Teratoma | | |
| Chromium | Mice, rats, rabbits | Injection site | Sarcoma | CR refinery | Pulmonary carcinoma |
| | | Lung | Carcinoma | Chrome plating | Gastrointestinal carcinoma |
| | | | | Chromate pigments | |
| Cobalt | Rats, rabbits | Injection site | Sarcoma | None observed | None observed |
| Iron | Hamsters, mice, rats, rabbits | Injection site | Sarcoma | None observed | None observed |
| Lead | Mice, rats | Kidney | Carcinoma | None observed | None observed |
| Nickel | Mice, rats, cats, hamsters, rabbits Guinea pigs, rats | Injection site | Carcinoma | Ni refinery | Pulmonary carcinoma |
| | | Lung | Carcinoma | | Nasolaryngeal carcinoma |
| | | Kidney | Carcinoma | | Gastric and renal carcinoma |
| | | | | | Sarcoma (?) |
| Titanium | Rats | Injection site | Sarcoma | None observed | None observed |
| Zinc | Chickens, rats, hamsters | Testes | Carcinoma | None observed | None observed |
| | | Testes | Teratoma | | |

**Arsenic**

Arsenic compounds are poorly mutagenic in both bacterial and mammalian cell assays .Metallic arsenic, arsenic trioxide, sodium arsenite, sodium arsenate, potassium arsenite, lead arsenate, calcium arsenate, and pesticide mixtures containing arsenic have been tested for carcinogenicity in experimental animals.

In contrast, inorganic arsenic compounds are known human carcinogens, based on sufficient evidence of carcinogenicity in humans. Inorganic arsenic compounds increases the risk of **cancer in the skin, lung, digestive tract, liver, bladder, kidney, and lymphatic and hematopoietic systems.**

**The mechanisms for cancer** formation are unclear but possibly involve the induction of oxidative stress, altered cell signaling, modulation of apoptosis, and/or altered cell cycle.

The latency period in humans of arsenic-related carcinogenesis is considered to be 30–50 years. The first signs of chronic exposure, frequently seen in water supplies contaminated with arsenic, are skin pigmentation, depigmentation, hyperkeratosis of palms and soles, and skin lesions.

**Cadmium and cadmium compounds** have been classified as known human carcinogens based on evidence of carcinogenicity in humans, including epidemiological and mechanistic information that indicate a causal human cancer.

Many studies have shown that cadmium compounds cause genetic damage, including gene mutations, DNA strand breaks, chromosomal damage, cell transformation, and disrupted DNA repair.

cadmium exposure is associated with elevated **lung cancer** ,prostate cancer

**Lead**

**Lead compounds** also inhibits the activity of DNA and RNA polymerase in cell-free systems and in mammalian cell cultures.

soluble (lead acetate and lead subacetate) and insoluble (lead phosphate, lead chromate) inorganic lead compounds as well as for tetraethyl lead (an organic lead compound), following exposure via oral, injection, and in offspring exposed via the placenta or lactation.

Although kidney tumors (including adenomas, carcinomas, and adenocarcinomas) were most frequently associated with lead exposure, tumors of the brain, hematopoietic system, and lung were reported in some studies.