<table>
<thead>
<tr>
<th><strong>Carcinogenesis</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Definition:</strong> The induction or enhancement of neoplasia</td>
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<tr>
<td><strong>Response of an organism to a carcinogen:</strong></td>
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<tr>
<td>- Increase in frequency of one or several types of tumors</td>
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<tr>
<td>- Development of tumors not seen in controls</td>
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<tr>
<td>- Earlier occurrence than in controls</td>
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<tr>
<td>- Increase in number of tumors in individuals</td>
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<table>
<thead>
<tr>
<th><strong>Human Carcinogen Exposure</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Occupational exposure</strong></td>
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<tr>
<td>- 2-naphthylamine &amp; asbestos</td>
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<tr>
<td><strong>Medical exposure</strong></td>
</tr>
<tr>
<td>- Cyclophosphamide &amp; DES</td>
</tr>
<tr>
<td><strong>Environmental</strong></td>
</tr>
<tr>
<td>- Aflatoxin &amp; arsenic</td>
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<table>
<thead>
<tr>
<th><strong>Weight of Evidence</strong></th>
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<tr>
<td><strong>Sufficient Evidence</strong></td>
</tr>
<tr>
<td>- Benign and malignant tumors in multiple species or strains</td>
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<tr>
<td>- Occurrence of tumors at high rate or of a special type</td>
</tr>
<tr>
<td><strong>Limited Evidence</strong></td>
</tr>
<tr>
<td>- Seen in only one species, strain, or experiment</td>
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<tr>
<td><strong>Inadequate Evidence</strong></td>
</tr>
</tbody>
</table>
Multi-step Carcinogenic Processes

Bioactivation

- Epoxide formation yields reactive metabolites
  - Benzene
  - Vinyl chloride
  - Polycyclic hydrocarbons
  - N-hydroxy derivatives, AAF
  - Aminoazo dyes, Benzidine

Initiation & Promotion Model

- INITIATION — the process of generating DNA damage
  - Protooncogenes → Oncogenes
    - Translocation, gene amplification, base insertion-substitution
    - Dominant mutation
  - (onco-) Suppressor Genes
    - Inactivation
    - Recessive mutation
Cell Cycle Regulatory Mechanisms

Initiation & Promotion Model

- PROMOTION – chemicals that do not cause DNA damage but enhance the expression of damage by acting as:
  - Stimulators of cell proliferation
  - Directly/indirectly affecting gene expression
  - A reversible process
  - Continuous exposure necessary

Targets of Promotional Agents
Conversion and Progression

- Further biochemical and/or morphological changes in the activities or structures of the genome.
  - Combination of genotoxicity & promotion
  - Neoplasm converted to malignant
  - Irreversible

Carcinogen Categories

- Genotoxic agents
  - Direct Acting – Ultimate carcinogens
    - Electrophilic
    - More active *in vitro* than *in vivo*
    - Examples
      - Alkyl & aryl epoxides, lactone, sulfate esters, nitrosamides, nitrosoureas, platinum amine chelates

- Pro- (Pre-) carcinogens
  - Undergo bioactivation
    - Procarcinogen → Proximate carcinogen → Ultimate carcinogen

Polycyclic aromatic hydrocarbons, Aromatic amines, halogenated hydrocarbons, nitrosamines, aflatoxin B1, safrole, thioamides.
Epigenetic Carcinogens

- Mechanisms
- Cocarcinogens – act only when given simultaneously
- Promoters
  - Phorbol esters classic promotor
  - Mechanisms of action

Promotor Actions

- Cytotoxicants – NTA, unleaded gasoline
- Hormones – estradiol, diethylstilbestrol
- Gap junction effects – pesticides (chlordane, DDT, dieldrin) & pharmaceuticals (phenobarbitol, diazepam)
- Immunosuppression – cyclosporin A, azathioprine
- Peroxisome proliferators – phthalate esters, hypolipidemic drugs
- Solid state carcinogens – asbestos, plastics, metals, glass

Other Carcinogens

- Metals & metaloids – As, Cr, Ni
- Mechanisms?
  - Cross links – DNA-protein, DNA-DNA
  - DNA polymerase
  - Cytoskeleton damage
Summary of Chemical & Radiation Induced DNA Lesions