Chemical Carcinogenesis
Proportion of chemicals evaluated as carcinogenic

<table>
<thead>
<tr>
<th>Category</th>
<th>Proportion</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemicals tested in both rats and mice</td>
<td>350/590</td>
<td>59%</td>
</tr>
<tr>
<td>Naturally occurring chemicals</td>
<td>79/139</td>
<td>57%</td>
</tr>
<tr>
<td>Synthetic chemicals</td>
<td>271/451</td>
<td>60%</td>
</tr>
<tr>
<td>Chemicals tested in rats and/or mice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chem. in Carcinogen. Potency Database</td>
<td>702/1348</td>
<td>52%</td>
</tr>
<tr>
<td>Natural pesticides</td>
<td>37/71</td>
<td>52%</td>
</tr>
<tr>
<td>Mold toxins</td>
<td>14/23</td>
<td>61%</td>
</tr>
<tr>
<td>Chemicals in roasted coffee</td>
<td>21/30</td>
<td>70%</td>
</tr>
<tr>
<td>Innes negative chemicals retested</td>
<td>17/34</td>
<td>50%</td>
</tr>
<tr>
<td>Physician’s desk reference PDR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs with reported cancer tests</td>
<td>117/241</td>
<td>49%</td>
</tr>
<tr>
<td>FDA database of drug submissions</td>
<td>125/282</td>
<td>44%</td>
</tr>
</tbody>
</table>

Ames and Gold *Mutat Res* 447:3-13, 2000
CANCER:

“A multicausal, multistage group of diseases the mechanisms of which are still only partially known” (IARC Scientific Publications, 1992)

“Cancer is a group of diseases characterized by uncontrolled growth and spread of abnormal cells […] that can result in death” (American Cancer Society, 2002)
• **Benign** tissue is not cancer. Although the cell growth is moderately increased, the cells do not invade nearby tissue or spread to other parts of the body

• **Malignant** tissue is cancer. The cancer cells divide out of control. They can invade and destroy nearby healthy tissue. Also, cancer cells can break away from the tumor they form and enter the bloodstream and lymphatic system

• **Metastasis**: the spread of cancer beyond the organ of origin
WHAT MAY CAUSE CANCER?

- Hereditary disorders
- Chemicals
- Viruses
- Chronic inflammation
- ???

Interaction of Genes and Environment

From http://www.cancersupportivecare.com/riskintro.html
History of Chemical Carcinogenesis

- Chemical carcinogenesis was first suggested by clinicians 200 years ago
  - Scrotal cancer in chimney sweeps - Potts
  - Nasal cancer and snuff dipping - Hill
  - Today, >50 chemicals are recognized as human carcinogens

- First experimental studies in animals were done ~80 years ago
History of Chemical Carcinogenesis

- Large numbers of chemicals were tested for carcinogenic potential in the 1970-1990s
  - Maximum Tolerated Doses (MTD) were used.
  - 60% of rodent carcinogens were genotoxic
  - 40% of rodent carcinogens were nongenotoxic
  - Some chemicals were single site, single species carcinogens
  - Others were multisite, multispecies carcinogens
  - Dose-response varies from <1/2 MTD to <1/1000 MTD

- Most regulations use straight mathematical extrapolation of high dose rodent data to predict risks
IARC (2004)  
- Carcinogenic to humans (group 1)  
- Probably carcinogenic to humans (group 2A)  
- Possibly carcinogenic to humans (group 2B)  
- Not classifiable as to its carcinogenicity to humans (group 3)  
- Probably not carcinogenic to humans (group 4)  

- Carcinogenic to humans  
- Likely to be carcinogenic to humans  
- Suggestive evidence of carcinogenic potential  
- Inadequate information to assess carcinogenic potential  
- Not likely to be carcinogenic to humans  

- Known to be a human carcinogen  
- Reasonably anticipated to be a human carcinogen  

- Known to the state to cause cancer

Cogliano et al, 2004
<table>
<thead>
<tr>
<th>Agent</th>
<th>Degree of evidence in humans</th>
<th>Degree of evidence in animals</th>
<th>Overall evaluation</th>
<th>Degree of evidence in humans</th>
<th>Degree of evidence in animals</th>
<th>Overall evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,2-Bis(bromomethyl)propan-1,3-diol</td>
<td>I (ND)</td>
<td>S</td>
<td>2A</td>
<td>I (ND)</td>
<td>S</td>
<td>2B</td>
</tr>
<tr>
<td>4-Chloro-ortho-toluidine</td>
<td>L</td>
<td>S</td>
<td>2A</td>
<td>L</td>
<td>S</td>
<td>2A</td>
</tr>
<tr>
<td>5-Chloro-ortho-toluidine</td>
<td>I (ND)</td>
<td>L</td>
<td>3</td>
<td>I (ND)</td>
<td>L</td>
<td>3</td>
</tr>
<tr>
<td>Cinnamyl anthranilate</td>
<td>I (ND)</td>
<td>L</td>
<td>3</td>
<td>I (ND)</td>
<td>L</td>
<td>3</td>
</tr>
<tr>
<td>Coumarin</td>
<td>I (ND)</td>
<td>L</td>
<td>3</td>
<td>I (ND)</td>
<td>L</td>
<td>3</td>
</tr>
<tr>
<td>2,3-Dibromopropan-1-ol</td>
<td>I (ND)</td>
<td>L</td>
<td>3</td>
<td>I (ND)</td>
<td>S</td>
<td>2B</td>
</tr>
<tr>
<td>Diethanolamine</td>
<td>I</td>
<td>S</td>
<td>2B</td>
<td>I</td>
<td>S</td>
<td>3*</td>
</tr>
<tr>
<td>Di(2-ethylhexyl) adipate</td>
<td>I (ND)</td>
<td>L</td>
<td>3</td>
<td>I (ND)</td>
<td>L</td>
<td>3</td>
</tr>
<tr>
<td>Di(2-ethylhexyl) phthalate</td>
<td>I (ND)</td>
<td>S</td>
<td>2B</td>
<td>I</td>
<td>S</td>
<td>3*</td>
</tr>
<tr>
<td>Ethyl benzene</td>
<td>I</td>
<td>S</td>
<td>2B</td>
<td>I</td>
<td>S</td>
<td>2B</td>
</tr>
<tr>
<td>Glycidol</td>
<td>I (ND)</td>
<td>S</td>
<td>2B</td>
<td>I (ND)</td>
<td>S</td>
<td>2A*</td>
</tr>
<tr>
<td>Nitromethane</td>
<td>I (ND)</td>
<td>S</td>
<td>2B</td>
<td>I (ND)</td>
<td>S</td>
<td>2B</td>
</tr>
<tr>
<td>N-Nitrosodiethanolamine</td>
<td>I (ND)</td>
<td>S</td>
<td>2B</td>
<td>I</td>
<td>S</td>
<td>2B</td>
</tr>
<tr>
<td>Pyridine</td>
<td>I</td>
<td>S</td>
<td>2B</td>
<td>I</td>
<td>L</td>
<td>3</td>
</tr>
<tr>
<td>ortho-Toluidine</td>
<td>I</td>
<td>S</td>
<td>2B</td>
<td>I</td>
<td>S</td>
<td>2A</td>
</tr>
<tr>
<td>Triethanolamine</td>
<td>I</td>
<td>S</td>
<td>2B</td>
<td>I</td>
<td>S</td>
<td>3</td>
</tr>
</tbody>
</table>

S, sufficient evidence of carcinogenicity; L, limited evidence of carcinogenicity; I, inadequate evidence of carcinogenicity; ND, no data

Group 1: carcinogenicity to humans
Group 2A: probably carcinogenic to humans
Group 2B: possibly carcinogenic to humans
Group 3: cannot be classified as to its carcinogenicity to humans

*Other relevant data taken into consideration
Cancer Cases Attributable to Environmental Carcinogens (Worldwide, 1990)

- Infections (viruses, parasites, *H. pylori*) 16%
- Tobacco (smoked and smokeless) 14%
- Occupation 4%
- Alcohol drinking 3%
- Diet and dietary components including contaminants 25%
- Pollution 2%
- Reproductive factors 2%

Total: 37%
IARC Group 1 – *Carcinogenic to humans*
Monographs Volumes 1-84 (1972-2002): 89 Agents and Exposures

- Medical drugs and treatments: 24
- Industrial processes: 13
- Infectious agents or processes: 10
- Physical agents: 10
- Industrial chemicals: 7
- Inhaled particulates: 5
- Metals and inorganic salts: 5
- Lifestyle factors (incl. herbal remedies): 7
- Other: 8
# Exposures to Chemicals in the Workplace

<table>
<thead>
<tr>
<th>Agent</th>
<th>Industries and Trades with Proved Excess Cancers and Exposure</th>
<th>Primary Affected Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-Aminodiphenyl</td>
<td>Chemical manufacturing</td>
<td>Urinary bladder</td>
</tr>
<tr>
<td><strong>Asbestos</strong></td>
<td>Construction, asbestos mining and milling, production of friction products and cement</td>
<td>Pleura, peritoneum, bronchus</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Copper mining and smelting</td>
<td>Skin, bronchus, liver</td>
</tr>
<tr>
<td><strong>Alkylating agents (mechloroethamine hydrochloride and bis[chloromethyl]ether)</strong></td>
<td>Chemical manufacturing</td>
<td>Bronchus</td>
</tr>
<tr>
<td>Benzene</td>
<td>Chemical and rubber manufacturing, petroleum refining</td>
<td>Bone marrow</td>
</tr>
<tr>
<td><strong>Benzidine, β-naphthylamine, and derived dyes</strong></td>
<td>Dye and textile production</td>
<td>Urinary bladder</td>
</tr>
<tr>
<td>Chromium and chromates</td>
<td>Tanning, pigment making</td>
<td>Nasal sinus, bronchus</td>
</tr>
<tr>
<td><strong>Isopropyl alcohol manufacture</strong></td>
<td>Chemical manufacturing</td>
<td>Cancer of paranasal sinuses</td>
</tr>
<tr>
<td>Nickel</td>
<td>Nickel refining</td>
<td>Nasal sinus, bronchus</td>
</tr>
<tr>
<td>Polynuclear aromatic hydrocarbons from coke, coal tar, shale, mineral oils, and creosote</td>
<td>Steel making, roofing, chimney cleaning</td>
<td>Skin, scrotum, bronchus</td>
</tr>
<tr>
<td>Vinyl chloride monomer</td>
<td>Chemical manufacturing</td>
<td>Liver</td>
</tr>
<tr>
<td>Wood dust</td>
<td>Cabinetmaking, carpentry</td>
<td>Nasal sinus</td>
</tr>
</tbody>
</table>

Modified from Cullen et al. (1990).
### Carcinogenic Risks of Chemical Agents Associated with Medical Therapy and Diagnosis

<table>
<thead>
<tr>
<th>Chemical or Drug</th>
<th>Associated Neoplasms</th>
<th>Evidence for Carcinogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating agents (cyclophosphamide, melphalan)</td>
<td>Bladder, leukemia</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Inorganic arsenicals</td>
<td>Skin, liver</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Azathioprine (an immunosuppressive drug)</td>
<td>Lymphoma, reticulum cell sarcoma, skin, Karposi’s sarcoma (?)</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Chlornaphazine</td>
<td>Bladder</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Leukemia</td>
<td>Limited</td>
</tr>
<tr>
<td>Diethylstibesterol</td>
<td>Vagina (clear cell carcinoma)</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Estrogens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>Liver cell adenoma</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>Endometrium</td>
<td>Limited</td>
</tr>
<tr>
<td>Methoxypsoralen with ultraviolet light</td>
<td>Skin</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Oxymetholone</td>
<td>Liver</td>
<td>Limited</td>
</tr>
<tr>
<td>Phenacetin</td>
<td>Renal pelvis (carcinoma)</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Phenytoin (diphenyhydantoin)</td>
<td>Lymphoma, neuroblastoma</td>
<td>Limited</td>
</tr>
<tr>
<td>Thorotrast</td>
<td>Liver (angiosarcoma)</td>
<td>Sufficient</td>
</tr>
</tbody>
</table>
## Carcinogenic Factors Associated with Lifestyle

<table>
<thead>
<tr>
<th>Chemical, Physiological Condition or Natural Process</th>
<th>Associated Neoplasm</th>
<th>Evidence for Carcinogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholic beverages</td>
<td>Esophagus, liver, oropharynx, larynx</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Aflatoxins</td>
<td>Liver</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Betel chewing</td>
<td>Mouth</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Dietary intake (fat, protein, calories)</td>
<td>Breast, colon, endometrium, gallbladder</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Reproductive history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late age at first pregnancy</td>
<td>Breast</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Zero or low parity</td>
<td>Ovary</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Tobacco smoking</td>
<td>Mouth, pharynx, larynx, lung, esophagus, bladder</td>
<td>Sufficient</td>
</tr>
</tbody>
</table>

Modified from Pitot (1986a) and Vainio et al. (1991)
Chemical Carcinogenesis in the 21st Century

New perceptions of previously known carcinogens:

Combined effects of multiple exposures

Examples:
- Alcohol drinking and aflatoxins
- Alcohol drinking and HBV/HBC
- Alcohol drinking and tobacco smoking
- Tobacco smoking and asbestos/arsenic/radon
Stages of Carcinogenesis

Initiating Event → Cell Proliferation (clonal expansion) → Second Mutating Event → "N" Mutating Event → Cell Proliferation → Initiation → Promotion → Progression → Malignancy
Cellular and Molecular Mechanisms in Multistage Carcinogenesis: **INITIATION**

Initiating event involves cellular genome – MUTATIONS

Target genes:
- oncogenes/tumor suppressor genes
- signal transduction
- cell cycle/apoptosis regulators

“Simple” genetic changes

From http://newscenter.cancer.gov/sciencebehind/
SOURCES OF MUTATIONS

ENDOGENOUS DNA DAMAGE
- Free Radicals
- Polymerase Errors
- Depurination

EXOGENOUS DNA DAMAGE
- Environmental Agents
- Life Styles

DNA REPAIR

CELL REPLICATION

MUTATION
Chemical Exposure (air, water, food, etc.)

Internal Exposure

Metabolic Activation

Macromolecular Binding

DNA

RNA

Protein (Biomarker)

Detoxication

Biologically Effective Dose

\[ \times \]

Efficiency of Mismatching

\[ \times \]

Cell Proliferation

Initiation
Possible pathways of activation of suspected human carcinogens

Heterocyclic amines
e.g. IQ, PhIP

Aromatic amines
e.g. 4-ABP

PAHs
e.g. B[α]P, DMBA

DNA-reactive products of metabolic activation

Heterocyclic amines (IQ, PhIP) and aromatic amines (4-ABP) are activated by CYP enzymes and other metabolizing enzymes to form reactive intermediates such as N-hydroxy (H-N-OH) or N-oxides (H-N-OSO₃). Heterocyclic amines can also form diazotized compounds and reactive intermediates with DNA. The dihydrodiol epoxide, which is formed from the dihydroxy metabolite, is an electrophile that can react with DNA.

Accumulation of mutations during tumor progression

Loeb L.A. Cancer Res. 61:3230-9 (2001)
Cellular and Molecular Mechanisms in Multistage Carcinogenesis: PROMOTION

Reversible enhancement/repression of gene expression:
- increased cell proliferation
- inhibition of apoptosis

No direct structural alteration in DNA by agent or its metabolites
1. $X \rightarrow$ No Tumors
2. $X \rightarrow$ Tumors
3. $X \rightarrow$ Tumors
4. $X \rightarrow$ No Tumors
5. $X \rightarrow$ No Tumors

$X = \text{Application of Initiator} \quad \Downarrow = \text{Application of Promoter}$

Time
N Basophilic Focus Adenoma Carcinoma

M1 MN

Promotion Regression Progression

No Tumors

Tumors

\( \downarrow \) = Application of Promoter

Cellular and Molecular Mechanisms in Multistage Carcinogenesis: PROGRESSION

- Irreversible enhancement/repression of gene expression
- Complex genetic alterations (chromosomal translocations, deletions, gene amplifications, recombinations, etc.)
- Selection of neoplastic cells for optimal growth genotype/phenotype in response to the cellular environment

"Complex" genetic changes

From http://newscenter.cancer.gov/sciencebehind/
Phenotypic characteristics of cancer cells:

- Immortalization
- Transformation
- Loss of contact growth inhibition
- Autonomy of proliferation
- Avoidance of apoptosis
- Aberrant differentiation
- Induction of angiogenesis
Human Tumors and Stages of Carcinogenesis

- Defects in Terminal Differentiation
- Defects in Growth Control
- Resistance to Cytotoxicity

- Activation of Proto-Oncogenes
- Inactivation of Tumor Suppressor Genes
- Inactivation of Antimetastasis Genes
Multiple Stages of Human Colon Cancer

• It is estimated that by age 70, 50% of the population at large have acquired pre-cancerous adenomas in the colon; 10% of this group will progress to malignancy in the following 10 years.

• **Familial Adenomatous Polyposis (FAP)** is linked to the *APC* gene whose protein is involved in β-catenin signaling. The gene acts as a tumor suppressor, and the loss of function mutation causes development of hundreds to thousands of adenomas, with a consequent high risk of progression to malignancy.

• **Hereditary Non-Polyposis Colon Carcinoma (HNPCC)** is a hereditary predisposition to carcinoma without the prior accumulation of adenoma. HNPCC is caused by a germ line mutation in one set of genes responsible for DNA mismatch repair. To date, there are five genes known to be responsible for causing HNPCC: *MSH2, MSH6, MLH1, PMS1* and *PMS2*. To date, 90% of the inherited mutations in HNPCC are in *MSH2* or *MLH1*.

• **Sporadic colorectal cancer** (i.e., cancer that occurs without any familial predisposition to the disease) is associated with a variety of risk factors. The most prevalent risk factors, besides a personal or family history of colorectal and specific other cancers, are inflammatory bowel disease and age. Most sporadic colorectal cancers occur in women and men over the age of 50. Additional risk factors include diet, less than moderate exercise, and obesity.
# Multiple Stages of Human Colon Cancer

<table>
<thead>
<tr>
<th>Classification</th>
<th>Dukes’ A</th>
<th>Dukes’ B</th>
<th>Dukes’ C</th>
<th>Dukes’ D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Development of Disease</strong></td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
<tr>
<td><strong>Explanation of Cancer Progression</strong></td>
<td>Cancer confined to most superficial cell layers of colon or rectum. (e.g. the top of this polyp).</td>
<td>Cancer may extend completely through wall of colon or rectum, but there is no lymph node involvement.</td>
<td>Cancer may extend completely through wall of colon or rectum and has spread to lymph nodes.</td>
<td>Metastatic disease. The cancer has spread to distant organs, such as the liver.</td>
</tr>
<tr>
<td><strong>Estimated 5-Year Survival Rate</strong></td>
<td>95%</td>
<td>80%</td>
<td>50%</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Percent Diagnosed at Stage</strong></td>
<td>37%</td>
<td>63%</td>
<td>50%</td>
<td>5%</td>
</tr>
</tbody>
</table>

**www.chembio.uoguelph.ca**
**www.exactsciences.com**
Multiple Stages of Human Colon Cancer

**APC protein** (Adenomatous Polyposis Coli) is normally expressed in colorectal epithelial cells, a site of relatively high natural proliferation rates. The epithelium is convoluted into deep recesses called crypts and projections called villi. Crypts contain stem cells for tissue replacement, and the base of the crypt is a site of high mitotic activity. As cells age, they progress up the villus to the tip.

<table>
<thead>
<tr>
<th>Polyps</th>
<th>Adenomas</th>
<th>Progression to cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germline APC+/- FAP</td>
<td>&gt;90% by age 20</td>
<td>50% by age 40</td>
</tr>
<tr>
<td>Germline APC+/+ normal</td>
<td>&gt;90% by age 30</td>
<td>5%</td>
</tr>
<tr>
<td>Cell accumulation and dysplasia</td>
<td>50% by age 70</td>
<td>proliferating, anti-apoptotic, metastatic, angiogenic</td>
</tr>
<tr>
<td></td>
<td>hyperplasia, aneuploidy</td>
<td></td>
</tr>
</tbody>
</table>

www.chembio.uoguelph.ca
Genetic changes underlying development and progression of prostate cancer
Histopathological and molecular events leading to esophageal adenocarcinogenesis

Reflux of gastric and duodenal contents
→ Reflux esophagitis (GERD)
→ Columnar-lined Esophagus (CLE)
→ CLE with Dysplasia
→ Esophageal Adenocarcinoma (EAC)

Local Irritation and inflammation
- gastric acid
- bile acids
- digestive enzymes

Arachidonic Acid Metabolites (PGE₂, LTB₄, etc.)
- recruitment and activation of inflammatory cells
- direct effects on cells expressing respective receptors

Reactive Oxygen Species
- DNA strand breaks
- DNA base modifications
- protein oxidation

Genetic and Epigenetic Changes:
- genomic instability & hyperproliferation
- altered gene expression & cell cycle control
- gene mutation & allelic loss
- altered apoptosis
- gene amplification

Chen and Yang, Carcinogenesis 22:1119-29 (2001)
Classification of Carcinogens According to the Mode of Action

GENOTOXIC       NON-GENOTOXIC

Initiating Event → Cell Proliferation (clonal expansion) → Second Mutating Event → Cell Proliferation → Third Mutating Event → Cell Proliferation → Initiation

Promotion → Progression → Malignancy
Classification of Carcinogens According to the Mode of Action

GENOTOXIC:

- DNA-reactive or DNA-reactive metabolites
- Direct interaction to alter chromosomal number/integrity
- May be mutagenic or cytotoxic
- Usually cause mutations in simple systems

DNA Adduct → Mutation → Cancer
Mechanism of Carcinogenesis: Genotoxic Carcinogens

1. Carcinogen activation
2. DNA binding
3. Cell proliferation (fix mutation)
4. Gene mutation

Chemical → CYP450s → "Activated" carcinogen → DNA binding → DNA Repair → APOPTOSIS
Interaction of the exo-epoxide of aflatoxin B$_{1}$ with DNA

Smela et al., Carcinogenesis 22:535-45 (2001)
Classification of Carcinogens According to the Mode of Action

NON-GENOTOXIC:

- Do not directly cause DNA mutation
- Mechanism of action is not completely understood
- Difficult to detect - requires rodent carcinogen bioassay
Non-Genotoxic Carcinogens

1) Mitogens:
   • stimulation of proliferation
   • mutations may occur secondarily to cell proliferation
   • may cause preferential growth of preneoplastic cells

2) Cytotoxicants:
   • cytolethal
   • induce regenerative growth
   • mutations may occur secondarily to cell proliferation
Tissue Changes with Mitogenic and Cytotoxic Agents

Proliferation

Tissue

Cell Death

Mitogenic Agent

Cytotoxic Agent
Mechanism of Carcinogenesis: Non-Genotoxic Carcinogens

Cell proliferation (to fix “spontaneous” mutation)

APOPTOSIS

CANCER
Mechanisms of Non-Genotoxic Carcinogenesis

(what’s in a “black box” ?)

- Increased cell proliferation
- Decreased apoptosis
- Changes in gene expression
- Induction of metabolizing enzymes
- Activation of receptors (signaling)
- Oxidative stress
- ???
Cell Replication is Essential for Multistage Carcinogenesis

- Decreases time available for DNA repair
- Converts repairable DNA damage into non-repairable mutations
- Necessary for chromosomal aberrations, insertions, deletions and gene amplification
- Clonally expands existing cell populations
Mitogenic Cytokines and Induction of Cell Proliferation

Complete Mitogens:

- Epidermal Growth Factor, Tumor Necrosis Factor α,
- Hepatocyte Growth Factor, etc.

Co-Mitogens:

- Insulin, glucagon, norepinephrin, estrogens

Growth Inhibitors:

- Transforming Growth Factor β, InterLeukin 1β
Reasons That Not All Agents That Increase Cell Proliferation are Carcinogens

- Quality of the data
- Temporal association of the increase in cell proliferation
- Selective cytotoxicity for initiated cells
- Terminal differentiation of proliferating cells
- Maturation arrest
Mutagenesis $\neq$ Carcinogenesis

Cell Proliferation $\neq$ Carcinogenesis

Toxicity $\neq$ Cell Proliferation
Programmed Cell Death (Apoptosis): Active, orderly and cell-type-specific death distinguishable from necrotic cell death (passive process):

- Induced in normal and cancer cells
- Non-random event
- Result of activation of a cascade of biochemical, gene expression and morphological events
- Tissue and cell specific
- Growth factors and mitogens inhibit apoptosis
Alteration of Gene Expression

- Nuclear (hormone-like) receptors
- Kinase cascades
- Calcium-, nitric oxide-mediated signaling
- Transcription factors
- Gene methylation status (hypo -> enhanced gene expression; hyper -> gene silencing)
Induction of Metabolizing Enzymes

- May be a reason for tissue-, and/or species-selectivity of carcinogens
- Metabolites may be ligands for receptors
- Production of reactive oxygen species
Oxidative Stress

- Indirect DNA damage
- Induction of cell proliferation/apoptosis signaling cascades