WASHINGTON STATE UNIVERSITY

Instructor: Allan Felsot
afelsot@tricity.wsu.edu

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ES/RP 531
Fundamentals of Environmental Toxicology

Lecture 15

Soft Tissue Toxicity (Carcinogenicity)

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Daily aspirin use linked with pancreatic cancer

Monday, October 27, 2003 Posted: 9:37 PM EST (0237 GMT)

WASHINGTON (Reuters) -- Women who take an aspirin a day -- which millions do to prevent heart attack and stroke as well as to treat headaches -- may raise their risk of getting deadly pancreatic cancer, U.S. researchers said Monday.

The surprising finding worried doctors, who say women will now have to talk seriously with their physicians about the risk of

Definitions

- **Mutagen / Mutagenicity**
  - **a substance directly interacting with DNA, causing a change in its structure**
- **Oncogen / Oncogenicity**
  - **a substance causing benign or malignant tumors**
  - **chronic disease characterized by benign or malignant tumors**
- **Carcinogen / Carcinogenicity**
  - **substance capable of causing malignant tumors**
  - **a chronic disease marked by malignant tumors**

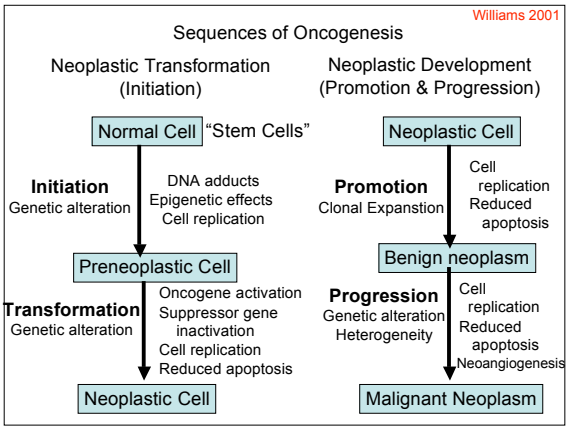
A Few Comments on Carcinogenicity Testing

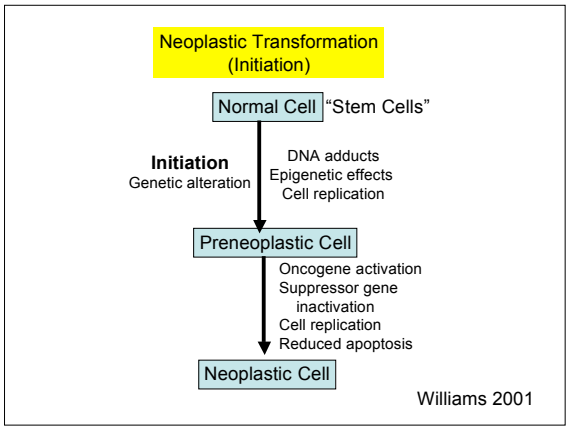
- Battery of tests
  - Mutagenicity
  - Clastogenicity
  - Tumorigenicity
  - Carcinogenicity
- Must use MTD (maximum tolerated dose)
  - Usually use three doses total and a no-dose control
- Modern carcinogenesis theory

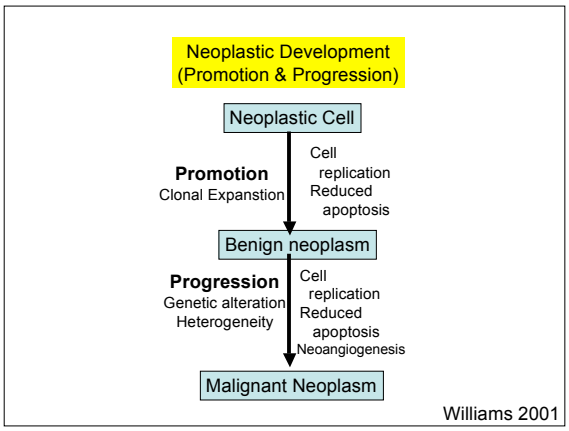
Maximum Tolerated Dose

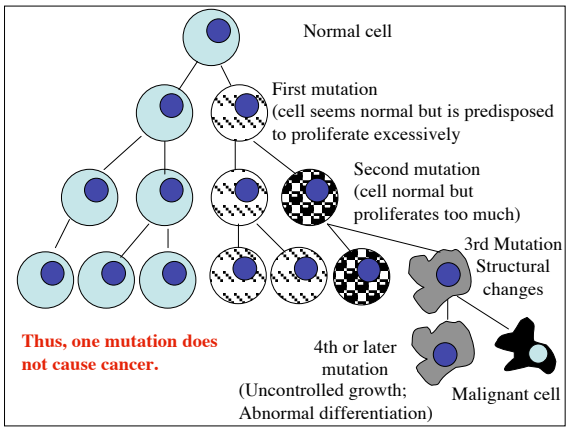
- Highest dose of toxicant during the choronic study that can be predicted not to alter the animal's longevity through effects other than carcinogenicity
- Causes no more than a 10% weight decrement as compared to the non-dosed control group
- Does not produce clinical signs of toxicity
- Doest not cause pathological lesions other than those that may be related to a neoplastic response (i.e., abnormal cell growth)
- Does not shorten animal's life span

Neoplasm ("new growth') = tumor (swelling or mass)









Mutations Are Normal & Frequent

- ~100,000 oxidative DNA hits per day in rat
- ~10,000 oxidative DNA hits per day in human
- Most of these mutations are repaired, but mutations still can accumulate in cell lines during aging

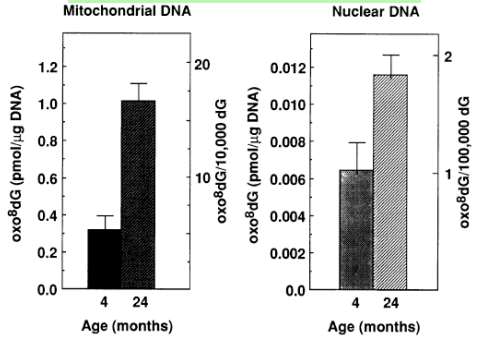
Estimates by Ames et al. 1993

Contraverting Repair Mechanisms

- Mutations normally repaired
- High doses lead to cell death and chronic cell division in an attempt to replace dead cells
  - More probability of mutations because of repair mistakes, especially if cells suffering toxicity

Steady State Oxidative Damage to DNA Increases with Age

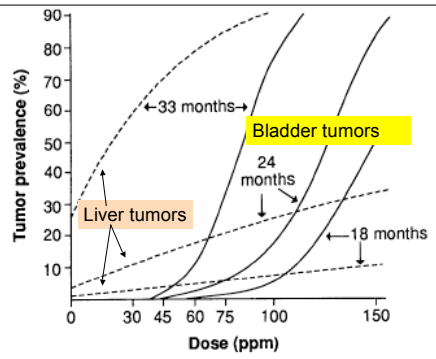
Oxo-guanidine Found in Rat Liver Tissue



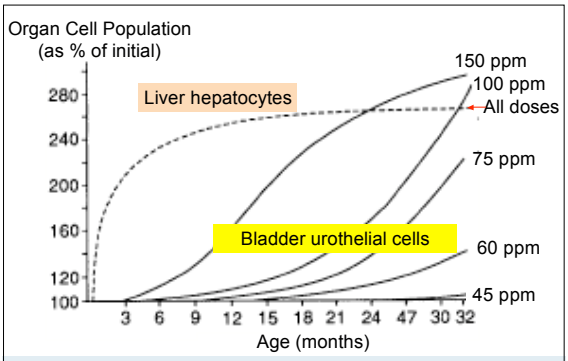
Ames et al. (1993) Proc. Natl. Acad. Sci. 90: 7915

Why Mechanism of Interaction Is Important in Understanding Carcinogenicity and the Relationship to Dose

Ellwein & Cohen 1990
Experiments with Liver and Bladder Cells Exposed to 2-AAF (acetyl aminofluorene)



Liver cells are more sensitive than bladder cells to tumor prevalence; but tumor incidence drops with shorter exposure (Cohen & Ellwein 1990)

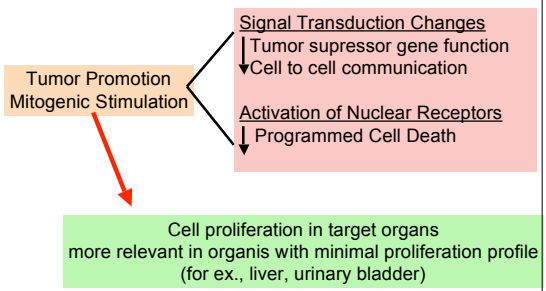


At all doses of 2 AAF (acetyl aminofluorene), liver and bladder cells proliferate in the presence of toxicant; rate of proliferation is related to exposure period (from Cohen & Ellwein 1990)

Mutation vs. Mitogenisis

- 2-AAF is hydroxylated in liver stem cells to an active mutagenic form, but not in older differentiated cells
  - Mutated cells proliferate at same rate as liver's normal growth rate
  - Thus, formation of tumors is related to the probability of mutations in the stem cells
- In bladder, N-hydroxyaminofluorene is formed (highly mutagenic); can mutate any age of cell in the bladder
  - Tumors formed only at doses above 60 ppm as a result of mitogenic (hyperplasia) response
  - Tumors formed only when cell proliferation occurs

Mechanisms of Carcinogenesis by Nongenotoxic Compounds



Lima and Van der Laan 2000

Main Mechanisms of Nongenotoxic Carcinogenicity

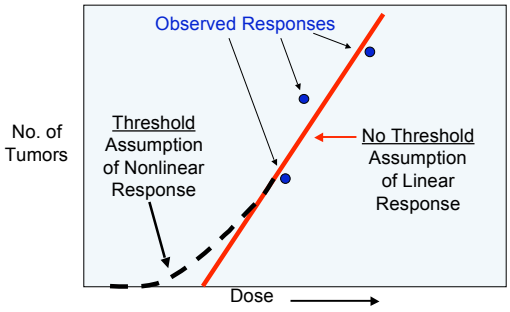
- Chronic cell injury
- Immunosuppression
- Increased secretion of trophic hormones
- Receptor activation
- Other (e.g., cytochrome P450 induction)

Lima and Van der Laan 2000

Biologically Based Classification Scheme for Rat Carcinogens

- Genotoxic
  - Cause DNA mutations
  - Theoretically no threshold
    - ✓ However, dose level can still cause cell toxicity
    - ✓ Depends on metabolism in specific tissues
    - ✓ Effect likely to persist after dosing stops
- Non-genotoxic (epigenetic)
  - Reaction or interference of contaminant with specific cell receptor or growth factor
  - Usually a threshold for an effect
  - Effect related to cell toxicity and regeneration
  - Cells "heal" after dosing

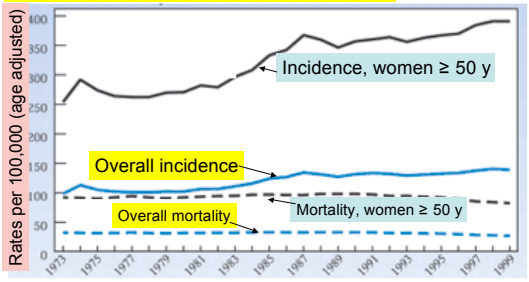
Cancer Testing Dilemma:
Response at high testing doses are extrapolated to low dose exposures. Estimation of hazard depends on knowing the "true" shape of the dose-response curve



Misconceptions About Carcinogenicity

- Cancer rates are soaring
  - Actually, incidence rate of some types of cancer is stable, some is decreasing, and some is rising
    - ✓ For example, NHL (Non-Hodgkin's) lymphoma and prostate cancer rates have increased
    - ✓ Stomach and lung cancer incidence have declined
  - Weir et al. 2003
    - ✓ Cancer incidence rates for all cancer sites combined increased from the mid-1970's through 1992;
    - ✓ Decreased from 1992 through 1995;
    - ✓ Observed incidence rates for all cancers combined were essentially stable from 1995-2000

Incidence & Mortality Rates for Breast Cancer



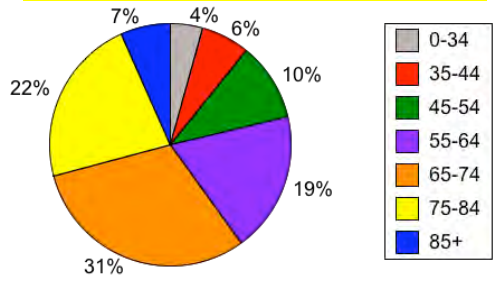
Breast cancer occurs most frequently in women 50-64 y; median age at diagnosis is 63 y. Annual rate of increase in incidence began to diminish in the late 1980s. Overall, breast cancer during 1995-99 accounted for 16.3% of cancer deaths in all women (20.8% in women 50-64 y).

SEER Cancer Statistics Review 1973-2000 (NCI 2002) URL: http://seer.cancer.gov

Misconceptions About Carcinogenicity

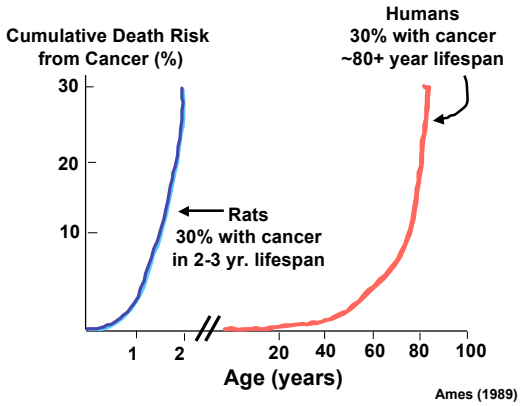
- Cancer rates soaring
  - Cancer is disease of old age

% Incidence of All Cancers by Age Group (1990-1994)



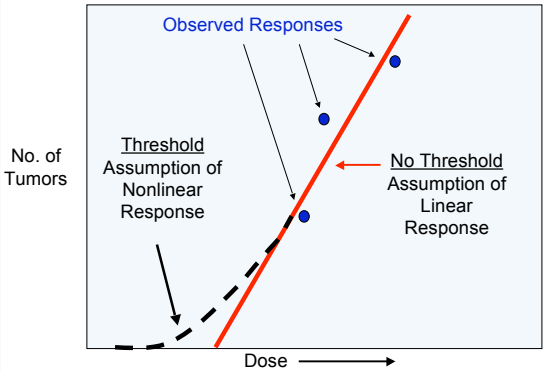
During 1997, 660,000 mean & 596,000 women were diagnosed with cancer in the U.S. Prostate, breast, lung, and colorectal cancers were the most common.

SEER Cancer Statistics Review, 1973-1994; American Cancer Society *Cancer Facts & Figures-1997*



Cancer Misconceptions

- High dose tests with rodents are valid for assessing low dose exposure effects in humans
  - Problems with cell toxicity
  - Leads to cell death, cell proliferation, and proliferation of unrepaired DNA damage



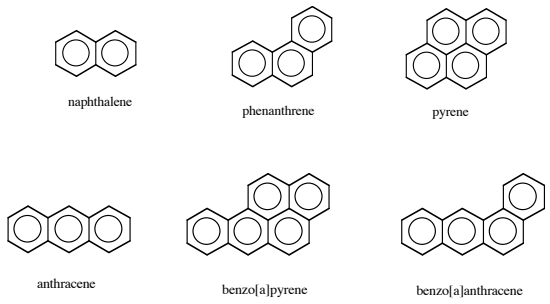
Misconceptions About Carcinogenicity

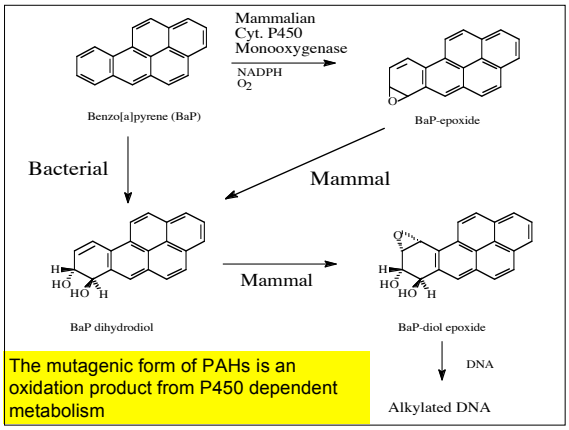
- Most carcinogens are synthetic
  - Half of all compounds tested for cancer and shown to be positive are naturally occurring food biochemicals

Neoplasia in Fish & Mollusks

- Noticed problem in early 1980's especially in contaminated lakes
  - Large oral, dermal, and liver neoplasias
- However, in the 1940's, tumors had been noted in fish
- Polycylcic aromatic hydrocarbons believed to be one of the leading causative factors
- Mollusks on eastern shore of Maryland noted with high incidence of sarcomas in the 1980's
  - Could be related to viral infection or to chemical contamination

Examples of Commonly Detected PAHs



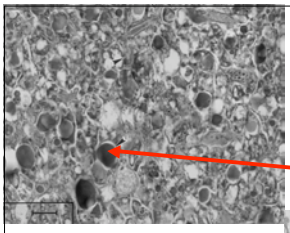


The mutagenic form of PAHs is an oxidation product from P450 dependent metabolism

Endocrine Related Soft Tissue Effects

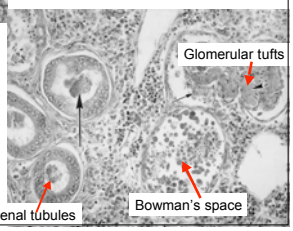
- Male summer flounder injected with estradiol (twice @ interval of two weeks)
- Caused elevation in vitellogenin levels comparable to field-collected fish (carp) near sewage treatment plant outfalls
- Observed hepatocyte hypertrophy, disruption of spermatogenesis, obstruction or rupture of renal glomeruli
- Observed accumulation of hyalin material, protein material that was hypothesized to be partially vitellogenin (based on immunochemical visualization methods)

Folmar et al. 2001 Aquatic Toxicol 51:431-441



Liver pathology in flounder injected twice with 10 mg/kg estradiol; cell structure is disrupted; hyalin material accumulating in cells (red arrow)

Kidney pathology in flounder injected twice with 10 mg/kg estradiol; hyaline material has accumulated in renal tubules, Bowman's space, and glomerular tufts



Folmar et al. 2001