

Introduction to Carcinogenesis

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How do we investigate its cause?

What must be done before we label a compound as carcinogenic?

The Chemical World

- 1. In 2009 There are 50(sept. 09) **MILLION KNOWN CHEMICALS** in the Chemical Abstract service.,
- BOTH NATURAL AND SYNTHETIC;.(ONE MILLION IN 1954).
- 2. MORE THAN 1,000,000 ARE IN WIDESPREAD USE.
- 3. ABOUT 1,000,000 NEW CHEMICALS ENTER OUR ENVIRONMENT EACH YEAR (Based on new CAS Nos.).

CONVERSIONS OF TRACE CONCENTRATION UNITS SET TO MORE USABLE TERMS

Unit +	1 PPB Billion	1 PPB Billion	1 PPB Trillion
Length +	1"/16 miles	1-/16,000 miles	1-/16,000,000 miles (or 6" towards the sun)
Time +	1 min/2 yrs	1sec/32 yrs	1sec/320 centuries
Money +	1c/\$10,000	1c/\$10,000,000	1c/10,000,000,000
Weight +	1oz/21 tons of potato chips	1 pinch salt/20 tons potato chips	1 pinch salt/20,000 tons potato chips
Volume +	1 drop vermouth/50 fifth the gin	1 drop vermouth/500 barrels gin	1 drop vermouth/250,000 hogheads yin.
Area +	1 sq ft/23 acres	1 sq ft/26 sq miles	1 sq ft/250 sq miles
Action +	1 baggy/3,500 golf tournaments	1 baggy/3,500,000 golf tournaments	1 baggy/3,500,000,000 golf tournaments
	1 lb/1,200 tennis matches	1 lb/1,200,000 tennis matches	1 lb/1,200,000,000 tennis matches
Quality +	1 bad apple/2000 barrels	1 bad apple/2,000,000 barrels	1 bad apple/2,000,000,000 barrels
Rate +	1 dented fender/30 car lifetimes	1 dented fender/30,000 car lifetimes	1 dented fender/30,000,000 car-lives.
Other +	1 card/19,231 decks	1 card/19,231,000 decks	1 card/19,231,000,000 decks

Dimensions of a tank to hold 5,000,000 liters = 56.1022 x 56.1022 x 56.1022 feet = 176,579 cu. Ft
5 cc (1 teaspoon) in a tank this size, would be 1 part per million [A James Bond Dry Martini]

METHODS OF DETECTING CARCINOGENS

- IN VIVO:
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- 1. CLINICAL OBSERVATIONS - BY ASTUTE CLINICIANS AND PATIENTS
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- 2. EPIDEMIOLOGIC STUDIES
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- 3. EXPERIMENTAL ANIMAL BIOASSAYS

• SHORT TERM TESTS:

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- 1. MUTAGENESIS ASSAYS ~
 - a. BACTERIA - AMES TEST
 - b. MAMMALIAN CELL CULTURES
 - c. OTHER EUKARYOTES - YEAST
 - DROSOPHILA, MICE
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- 2. ASSAYS FOR CELL TRANSFORMATION
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- 3. ASSAYS FOR DNA BINDING, DAMAGE AND REPAIR - AND BINDING TO OTHER MACRO MOLECULES
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- 4. ASSAYS FOR CHROMOSOMAL ABNORMALITIES AND SISTER CHROMATID EXCHANGE

HOW RELIABLE ARE ANIMAL BIOASSAYS?

- 1. ALL BUT TWO OF THE KNOWN HUMAN CARCINOGENS ARE ALSO CARCINOGENIC IN RODENTS.*
- 2. NONE OF THE APPROXIMATELY 143 "RODENT" CARCINOGENS HAVE BEEN PROVEN TO BE NON-CARCINOGENIC IN HUMANS.
- 3. ANIMAL ASSAYS HAVE PREDICTED SEVERAL HUMAN CARCINOGENS - AFLATOXIN, 4 AMINO-BIPHENYL BIS (CHLOROMETHYL)ETHER, BIETHYLSTIBESTROL MELPHALAN, AND VINYL CHLORIDE.
- 4. FOR SEVERAL CHEMICALS, CARCINOGEN POTENCY IN RODENTS APPROXIMATES THAT IN HUMANS.
- 5. FOR SEVERAL CARCINOGENS, THE TISSUE SPECIFICITY IN RODENTS IS THE SAME AS IN HUMANS, BUT THIS IS NOT ALWAYS THE CASE.

*THE TWO COMPOUNDS ARE BENZENE AND ARSENIC. FURTHER ANIMAL STUDIES OF THESE COMPOUNDS ARE IN PROGRESS. SEE Next TABLE FOR A LIST OF HUMAN CARCINOGENS.

CHEMICAL AND INDUSTRIAL PROCESSES THAT ARE CARCINOGENIC FOR HUMANS

Group 1 - Known Carcinogens

- 4-Aminobiphenyl
- Arsenic; certain arsenic compounds
- Asbestos
- Manufacture of auramine
- Benzene
- Benzidine
- N, N-bis(2-chloroethyl)-2-naphthylamine (chlornaphazine)
- Bis(chloromethyl) ether; technical grade chloromethyl methyl ether
- Chromium; certain chromium compounds
- Diethylstilbestrol
- Underground hematite mining
- Manufacture of isopropyl alcohol by the strong acid process
- Melphalan
- Mustard gas
- 2-Naphthylamine
- Nickel; refining
- Soots, tars, and mineral oils
- Vinyl chloride

Reference – [American Cancer Society](#) (see the updated lists)

- **Group 2 (Probable Carcinogens)**
- **Set – A**
- Aflatoxins
- Cadmium; certain cadmium compounds
- chlorambucil
- Cyclophosphamide
- Nickel; certain nickel compounds
- Tris (l-aziridinyl) phosphine sulphide (thiotepa)
- **Set – B (Possible Carcinogens)**
- Acrylonitrile
- Amitrole (aminotriazole)
- Auramine
- Beryllium; certain beryllium compounds
- Dimethylsulphate
- Carbon Tetrachloride
- Ethylene Oxide
- Iron Dextran
- Oryzathione
- Phenacetin
- Polychlorinated biphenyls
- Look at the [ACS Page on Known & Probable Carcinogens](#).

VARIOUS RESPONSES TO INDUSTRIAL BLADDER CARCINOGENS

SPECIES	2-NAPHTHYLAMINE	BENZIDINE	4-AMINOBIIPHENYL
Mouse	Hepatomata	Hepatomata	Hepatomata
Dog	Bladder tumors	Bladder tumors	Bladder tumors
Monkey	Bladder tumors	Unknown	Unknown
Hamster	Bladder tumors	Liver	Unknown
Mouse	Hepatomata	Hepatomata	Hepatomata
Rat	None	Acoustic Neuroma,	Breast tumors
		intestinal tumors,	mammary tumors
		Hepatomata	

Biologic Properties of Initiating And Promoting Agents

Initiating Agents	Promoting Agent
Carcinogenic by themselves "Solitary" carcinogens	Not carcinogenic alone
Must be given before promoting agent	Must be given after the initiating agent.
Single Exposure Sufficient	Require prolonged exposure
Action "irreversible" and additive	Action reversible (at early stage) and not additive
No apparent threshold	Probable Threshold
Yield Electrophiles – bind covalently to cell macromolecules	No evidence of covalent binding
Mutagenic	Not mutagenic

Considerations in Risk Extrapolation A Dangerous Undertaking.

- Are dose and route of administration comparable?
- Does the chemical have interspecies and organ specificity?
- Is it reasonable to extrapolate from high to low dosage (e.g. 100 cokes a day compared to usual intake)?
- Is there existence of a threshold (How do You Know)?

Extrapolation – Continued

- How sensitive is your assay, how valid is it? What does it really mean to be able to measure parts per billion and parts per trillion.
- What synergy is there between cofactors.?
- Can you really estimate the potency?
- Can you develop a-benefit assessment?
- Can you develop a Risk-Benefit Ratio?