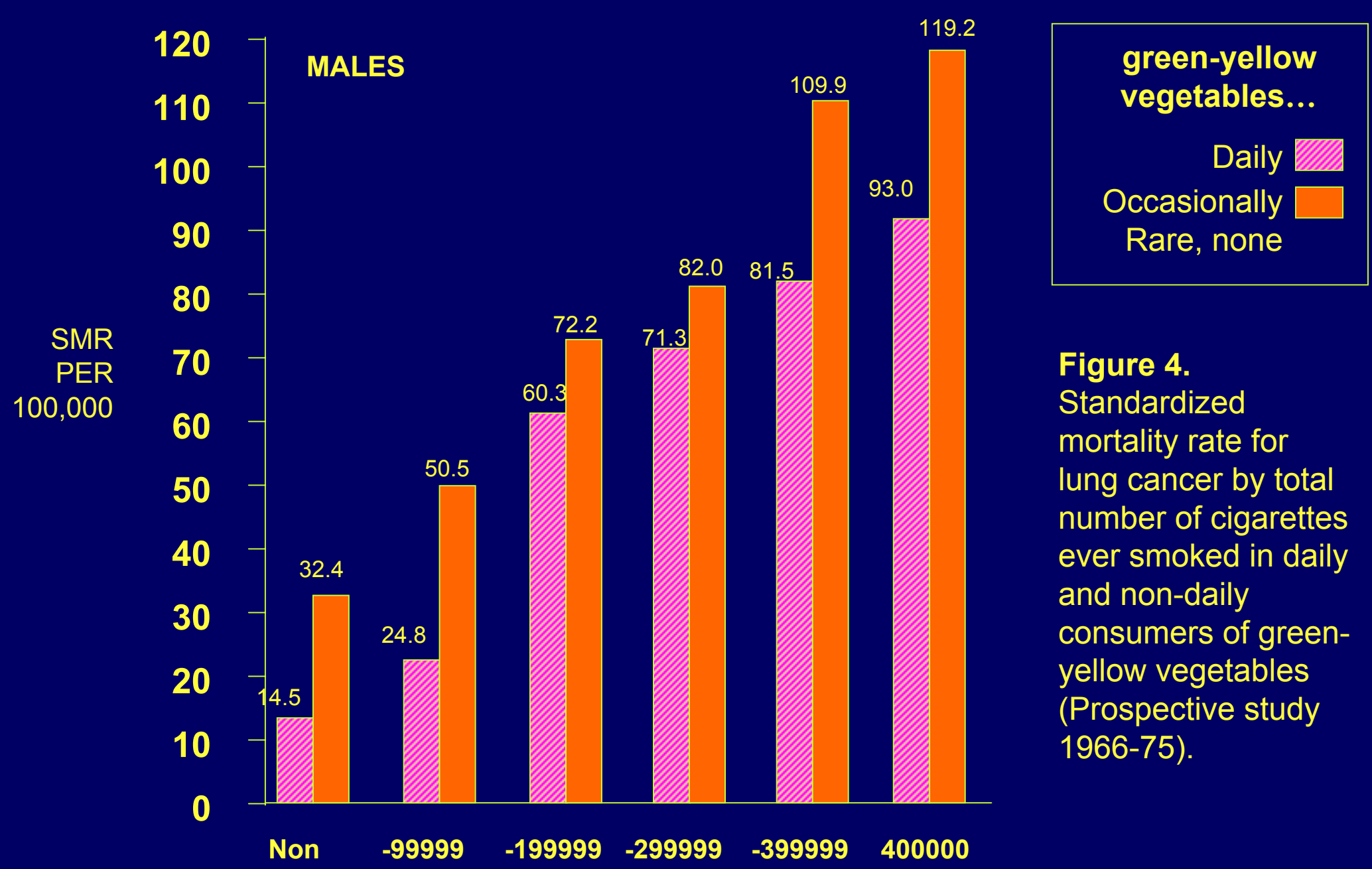


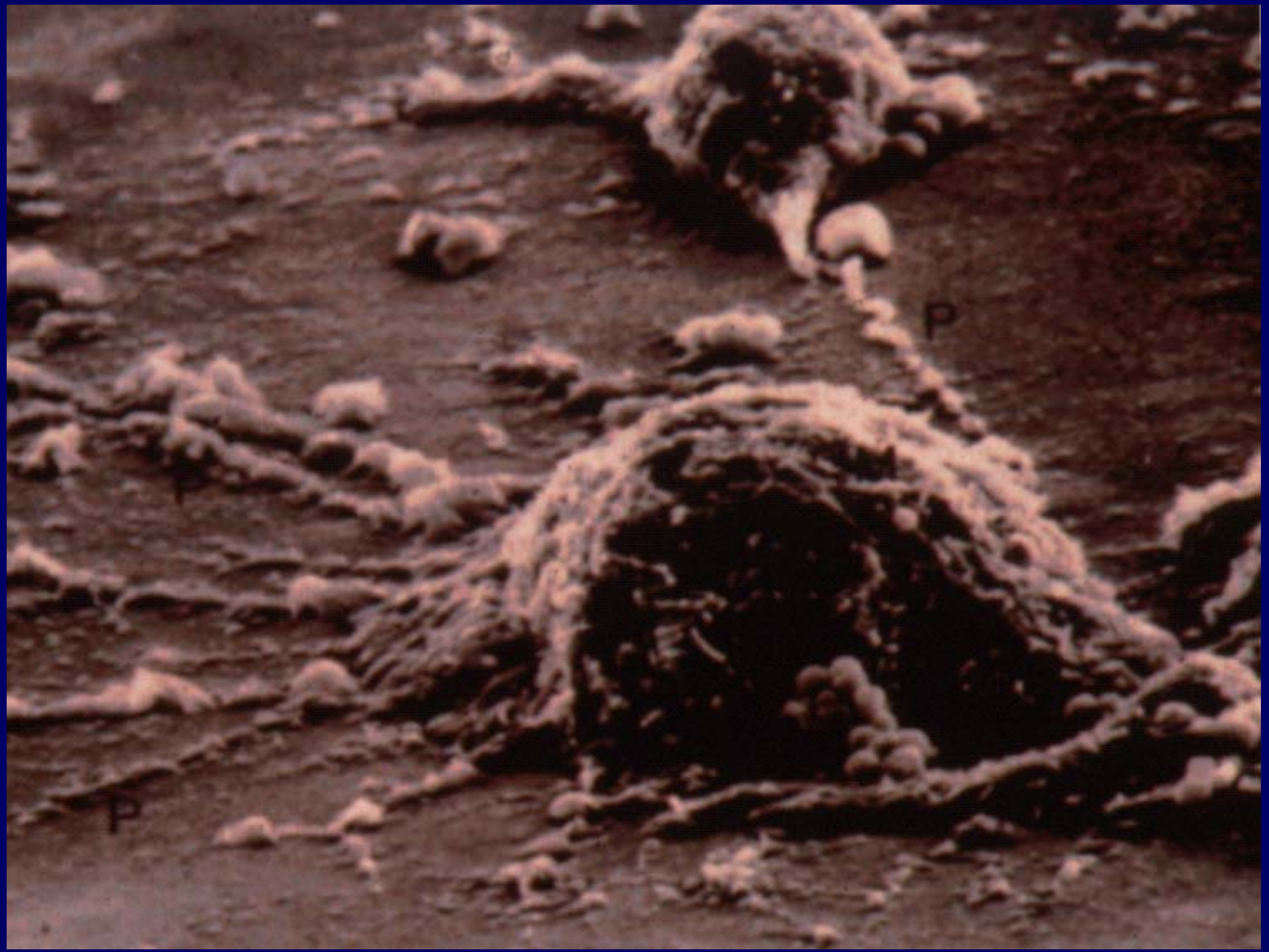
Figure 4. Standardized mortality rate for lung cancer by total number of cigarettes ever smoked in daily and non-daily consumers of green-yellow vegetables (Prospective study 1966-75).

T. Hirayama. *Nutrition and Cancer* **1**: 67 -81 (1979).

Fruits and Vegetables Protect Against Cancer

(Block, Patterson and Subar, *Nutr. Canc.,* **18**: 1-29, 1992)

Cancer Site	Fraction of Studies Showing a Protective Effect (p=0.05)	Relative Risk (Median)
Epithelial		
Lung	24/25	2.2
Oral	9/9	2.0
Larynx	4/4	2.3
Esophagus	15/16	2.0
Stomach	17/19	2.5
Pancreas	9/11	2.8
Cervix	7/8	2.0
Bladder	3/5	2.1
Colorectal	20/35	1.9
Miscellaneous	6/8	-
Hormone-Dependent		
Breast	8/14	1.3
Ovary/Endometrium	3/4	1.8
Prostate	4/14	1.3

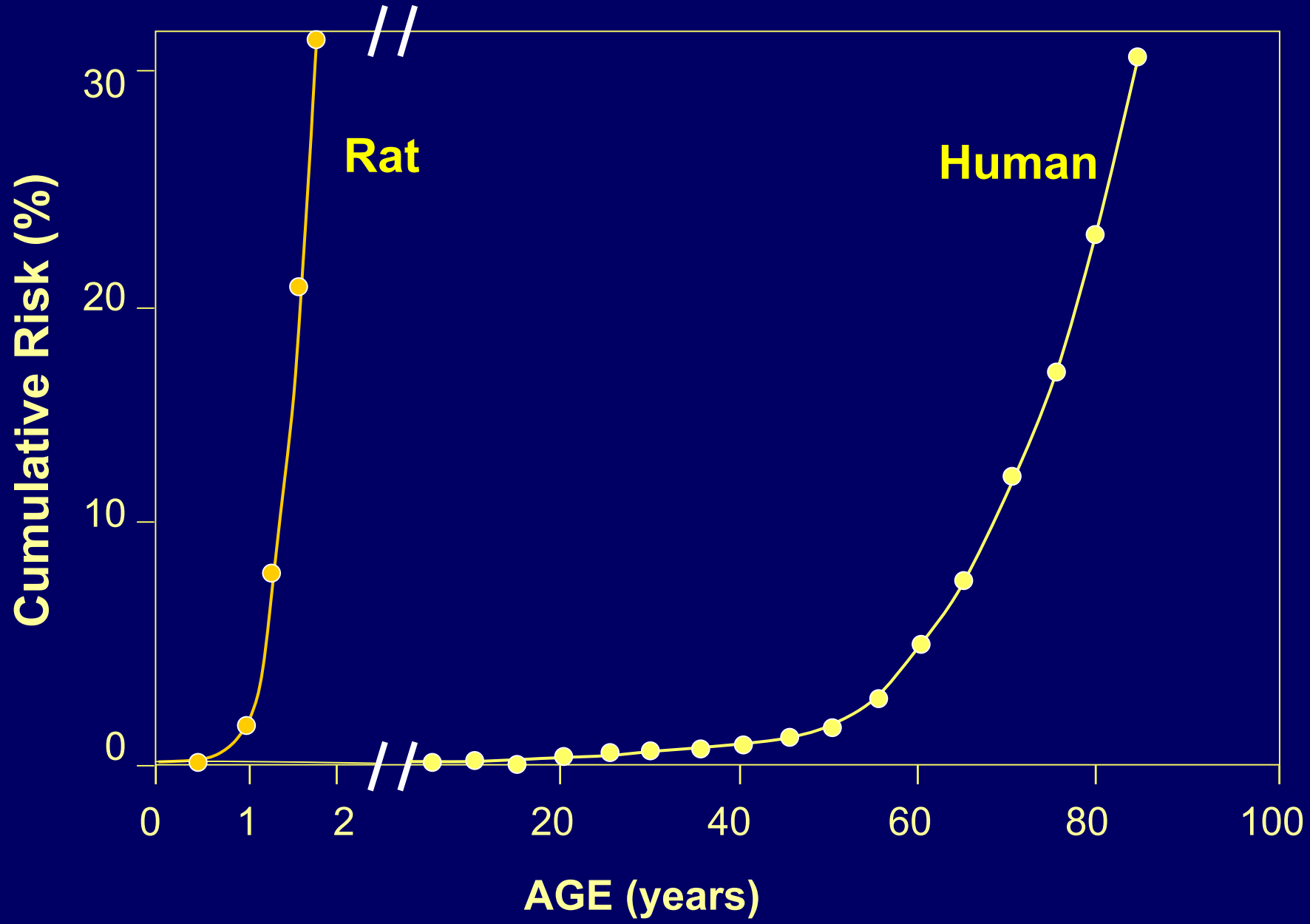

P
P

Oxidants from Phagocytic Cells

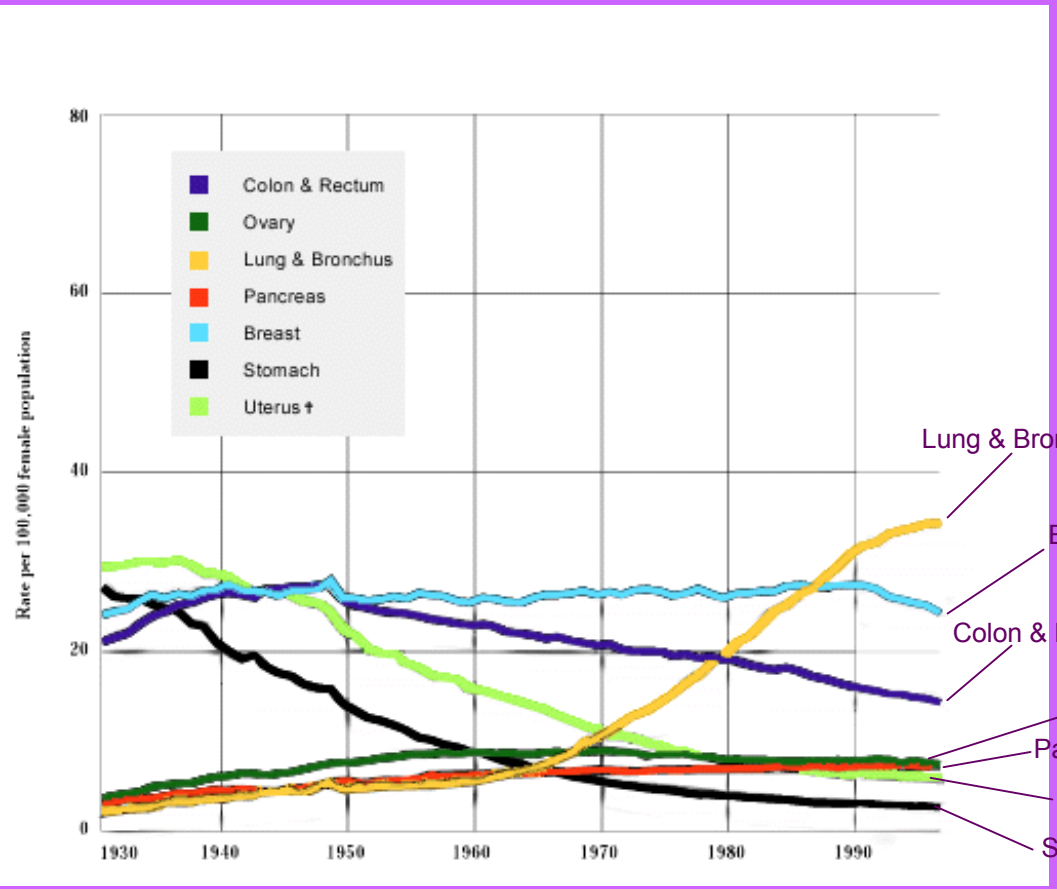
H_2O_2

OCl^-

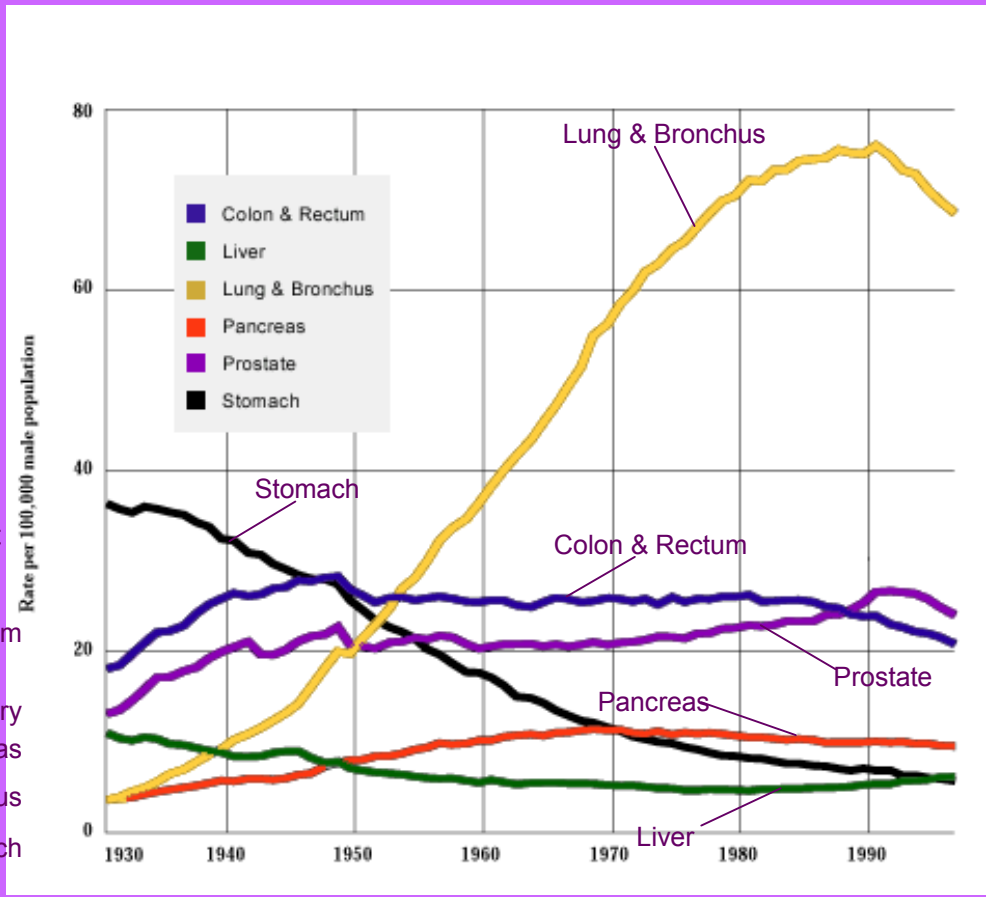
Cumulative Net Risk of Death from Cancer for Rat and Human



Age-Adjusted Cancer Death Rates by Site, U.S. 1930-1996



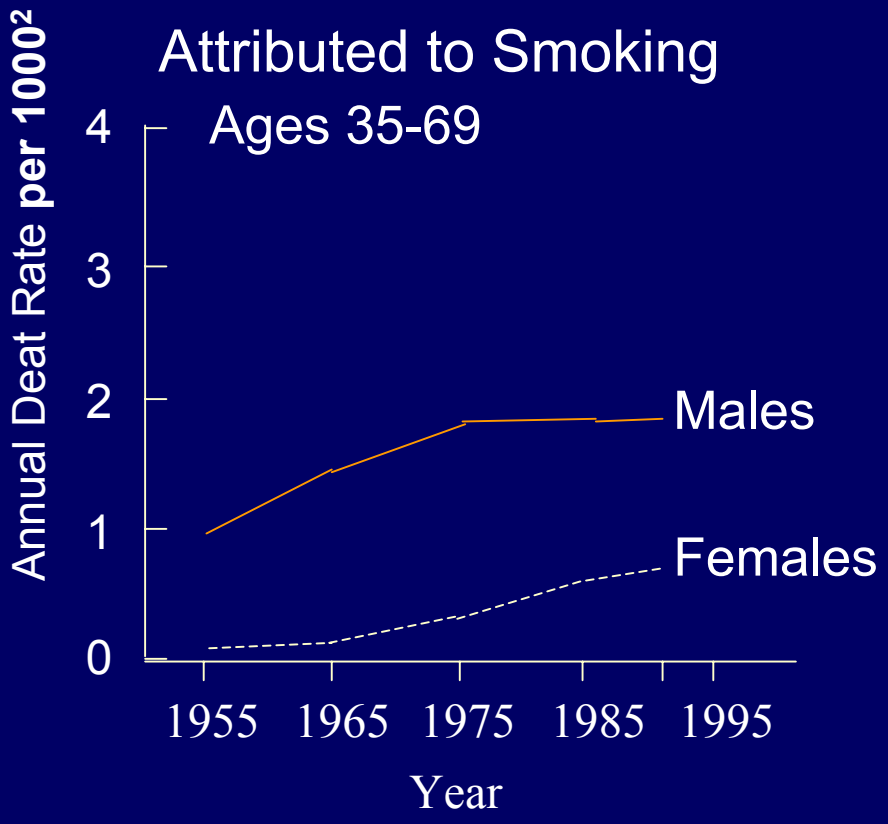
Women

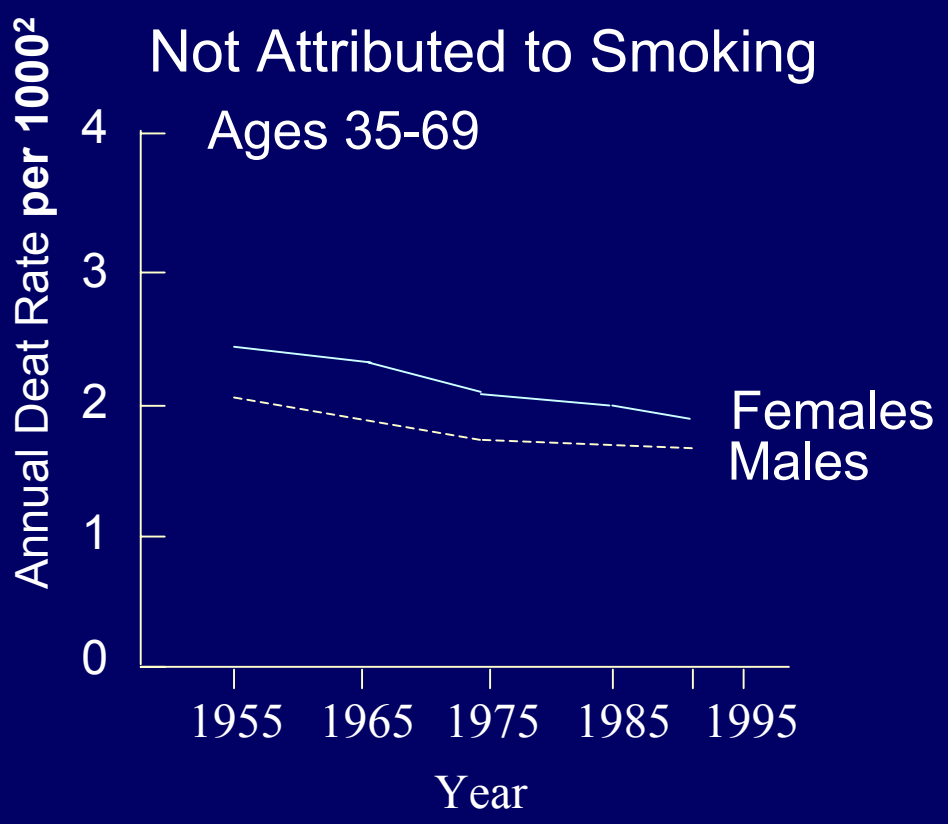


Men

Source: US Mortality Public Use Data Tapes 1960-1996, US Mortality Volumes 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 1999. **American Cancer Society, *Surveillance Research***

Total Cancer Mortality in the United States, 1955-1990

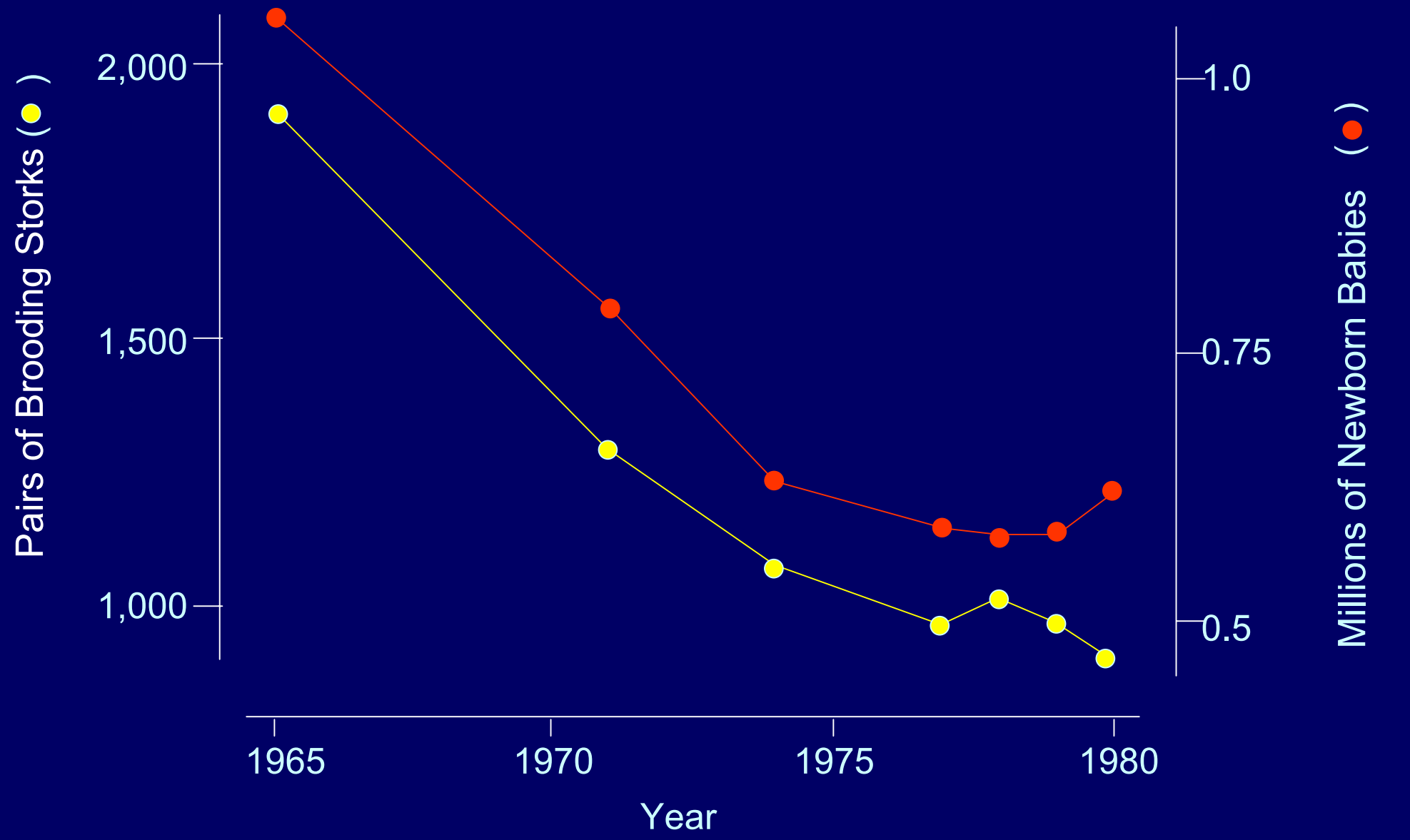


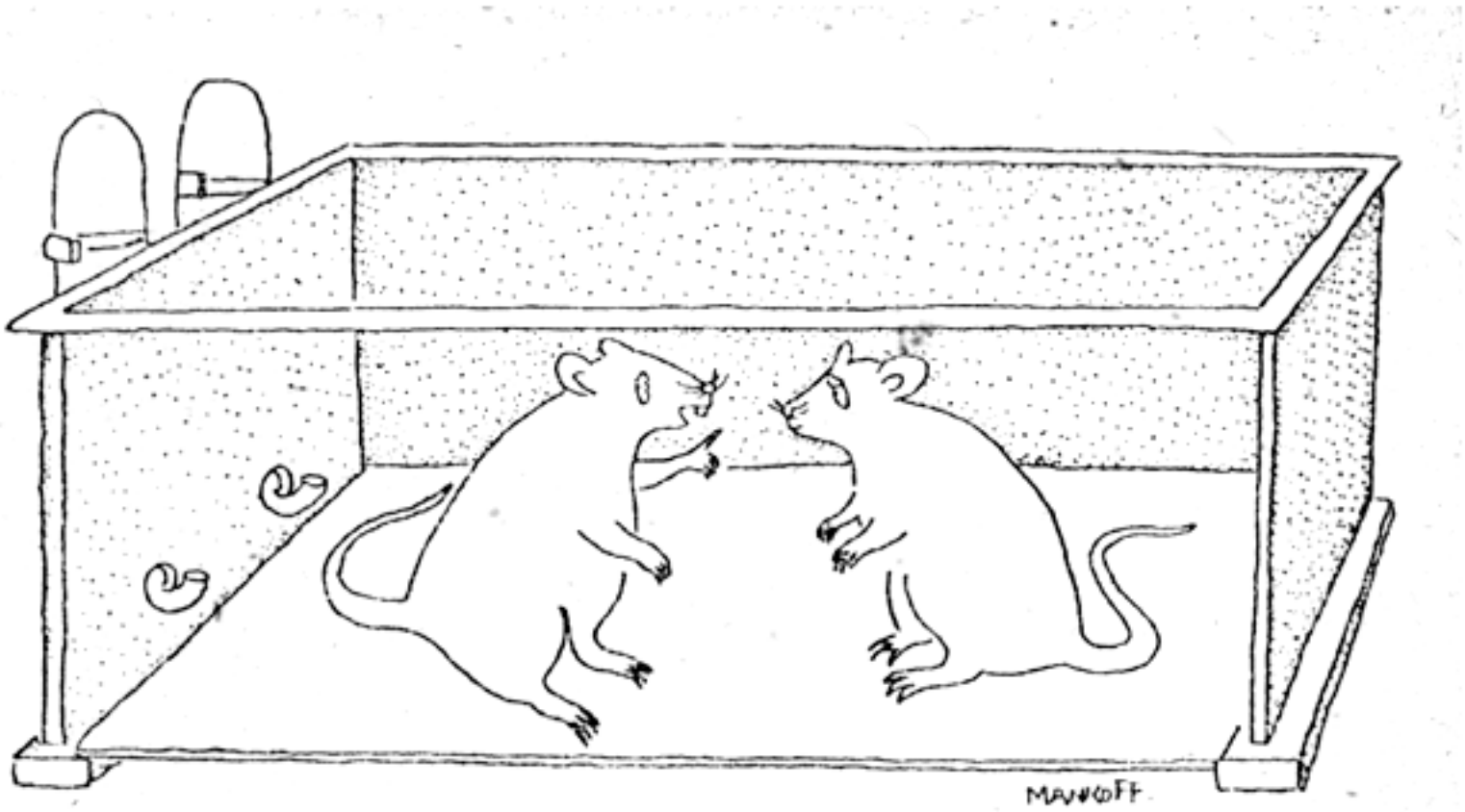


* Mean of seven age-specific rates, ages 35-69; annual death rate/1000.
Source: R. Peto, A.D. Lopez, J. Boreham,. M.Thun, and C. Heath, Jr., *Mortality from Smoking in Developed Countries*. 1950-2000 (Oxford: Oxford University Press, 1994)

“For the first time in the history of the world, every human being is now subjected to contact with dangerous chemicals, from the moment of conception until death.”

Rachel Carson
Silent Spring, 1962


Pairs of Brooding Storks ( )
2,000
1,500
1,000
1.0
0.75
0.5
Millions of Newborn Babies ( )
1965
1970
1975
1980
Year



"MY MAIN FEAR USED TO BE CATS - NOW IT'S CARCINOGENS."

Proportion of Chemicals Evaluated as Carcinogenic

TESTED IN BOTH RATS AND MICE[a]	330/559	59%
Naturally occurring chemicals	73/127	57%
Synthetic chemicals	257/432	59%
TESTED IN RATS AND/OR MICE[a]		
Carcinogenic Potency Database	668/1275	52%
Natural pesticides	35/64	55%
Mold toxins	14/23	61%
Chemicals in roasted coffee	19/28	68%
INNES NEGATIVES CHEMICALS RETESTED[a]	16/34	47%
PDR DRUGS WITH REPORTED CANCER TESTS[b]	117/241	49%
FDA DATABASE OF DRUG SUBMISSION[c]	125/282	44%

[a] From the Carcinogenic Potency Database (1997)

[b] Davies and Munro (1995)

[c] Contrera et al (1997), 140 drugs are in both the FDA and PDR databases

Dose-response data from animal cancer tests are usually limited to high doses and few points, and do not provide sufficient information to estimate risk at exposure levels 740,000 times below the MTD.

- **Data are available only for the MTD and 1/2 the MTD, both high doses.**

- **Data are available for only 3 points: 2 doses and a control.**

- **When tested for consistency of the dose-response with 3 different curve shapes (linear, square root, and quadratic) 2/3 of the statistically significant curves are consistent with all 3 models and 83% are consistent with at least 2 models.**

49 NATURAL PESTICIDES (AND METABOLITES) IN CABBAGE

GLUCOSINOLATES

2-propenyl glucosinolate (sinigrin)*
3-methyl-thio-propyl glucosinolate
3-methyl-sulfinyl-propyl glucosinolate
3-butenyl glucosinolate
2-hydroxy-3bnutenyl glucosinolate
4-methyl-thio-butyl-glucosinolate
4-methyl-sulfinyl-butyl-glucosinolate
4-methylsulfonyl-butyl-glucosinolate
Benzyl glucosinolate
Propyl glucosinolate
Butyl glucosinolate

INDOLE GLUCOSINOLATES AND RELATED INDOLES

2-indolyl-methyl glucosinolate (glucobrassicin)
1-methoxy-3-indolylmethyl (neoglucobrassicin)

3-indole-3-carbinol (IC)*

3-indole-3-acetonitrile*

3,3'-diindolylmethane*

ISOTHIOCYANATES AND GOITRIN

allyl isothiocyanate*
3-methyl-thio-propyl isothiocyanate
3-methyl-sulfinyl-propyl isothiocyanate
3-butenyl isothiocyanate
5-vinyloxazolidine-2-thione (goitrin)
4-methylthiobutyl isothiocyanate
4-methylsulfonylbutyl isothiocyanate
4-pentenyl isothiocyanate
Benzyl isothiocyanate
Pheylethyl isothiocyanate

ALCOHOLS

Menthol
Neomenthol
Isomenthol

KETONES

Carvone*

CYANIDES

1-cyano-2,3-epithiopropane
1-cyane-3,4-epithiobutane
1-cyano-3,4-epithiopentane
Threo-1-cyano-2-hydroxy-3,4 epithiobutane
Erythro-1-cyano-2-hydroxy-3,4 epithiobutane
2-phenylpropionitrile
Allyl cyanide*
1-cyano-2-hydroxy-3-butene
1-cyano-3-methylsulfinylpropane
1-cyano4-mehtylsulfinylbutane

PHENOLS AND TANNINS

2-methoxyphenol
3-caffoylquinic acid (chlorgenic aci

4-caffoylquinic acid*
5-caffoylquinic acid

(nechlorogenic acid)*
4-p-coumaroylquinic acid
5-p-coumaroylquinic acid
5-feruloylquinic acid

Plant Food	Rodent Carcinogen	Concentration (ppm)
Parsley	5- and 8-methoxypsoralen	14
Parsnip, cooked	"	32
Celery	"	.8
Celery, new cultivar	"	6.2
Celery, stressed	"	25
Mushroom, commercial	*p*-hydrazinobenzoate	11
Mushroom, commercial	glutamyl-*p*-hydrazinobenzoate	42
Cabbage	sinigrin (allylisothiocyanate)	35-590
Radish	"	11
Cauliflower	"	12-66
Brussels sprouts	"	110-1,560
Mustard (brown)	"	16,000-72,000
Horseradish	"	4,500
Orange juice	limonene	31
Mango	"	40
Pepper, black	"	8,000
Basil	estragole	3,800
Fennel	"	3,000
Nutmeg	safrole	3,000
Mace	"	10,000
Pepper, black	"	100
Sesame seeds (heated oil)	sesamol	75
Basil	benzyl acetate	82
Jasmine tea	"	230
Honey	"	15

PESTICIDE RESIDUES

1) US Consumption
FDA Estimate = 0.09 mg/day
- 0.04 mg known **non-carcinogens**
- 0.05 mg potential **carcinogens**

~105 chemicals in ppb range

NATURAL PESTICIDE RESIDUES

1) US Consumption
Ames Estimate = ~1500 mg/day
∴ 99.99% of pesticides are natural

~5000 chemicals at 1000 ppb or more

2) 52 assayed in animal cancer tests: 27 are **carcinogenic**

3) 72 tested for **clastogenicity**: 35 (48%) positive in all tests

Of synthetic chemicals tested (951) 53% were **clastogenic**

Comparison of average exposures to natural and synthetic pesticides.

HERP (%)	Average daily human exposure	Human dose of rodent carcinogen
0.1	Coffee (from 13.3 g) (3 cups)	Caffeic acid, 23.9 mg
0.04	Lettuce (14.9 g) (1/67th head)	Caffeic acid, 7.90 mg
0.03	Safrole in spices	Safrole, 1.2 mg
0.03	Orange juice (138 ml) (4/5th glass)	d-Limonene, 4.28 mg
0.03	pepper, black (446 mg)	d-Limonene, 3.57 mg
0.02	Mushroom (2.55 g)(1/6th)	Mix of hydrazines, etc.
0.02	Apple (32.0g) (1/7th)	Caffeic acid, 3.40 mg
0.01	Celery, (21.6g) (2/5th stalk)	Caffeic acid, 2.33 mg
0.006	Coffee (from 13.3 g) (3 cups)	catechol, 1.33 mg
0.004	potato (54.9 g; peeled) (1/4th)	caffeic acid, 867 μg
0.003	nutmeg (27.4 mg)	d-Limonene, 466 μg
0.003	carrot (12.1 g) [1/10th]	Caffeic acid, 624 μg
0.002	**DDT: daily dietary average**	**[DDT, 13.8 μg (before 1972 ban)]**
0.002	**apple juice (6 oz.;177 ml)**	**[UDMH, 5.89 μg (from Alar, 1988)]**
0.001	Plum (1.86 g)(1.25th)	Caffeic acid, 257 μg
0.001	Pear (3.29 g) (9/100th)	Caffeic acid, 240 μg
0.0009	Brown mustard (68.4 mg)	Allyl isothiocyanate, 62.9 μg
0.0008	**(DDE: daily dietary average)**	**[DDE, 6.91 μg (before 1972 ban)]**
0.0006	Celery (21.6 g) [2/5th stalk]	8-Methoxypsoralen, 13.2 μg
0.0006	Mushroom (2.55g) [1/6th]	Glutamyl-p-hydrazinobenzoate, 107 μg
0.0004	**EDB: Daily dietary average**	**[EDB, 420 ng (before 1984 ban)]**

Comparison of average exposures to natural and synthetic pesticides (continued).

HERP (%)	Average daily human exposure	Human dose of rodent carcinogen
0.0003	Carbaryl: daily dietary avg.	Carbaryl, 2.6μg (1990)
0.0002	Toxaphene: daily dietary avg.	Toxaphene, 595 ng (1990)
0.0002	Apple, 1 whole (230 g)	[UDMH, 598 ng (from Alar, 1988)]
0.0001	Mango (522 mg) (1/500th)	d-Limonene, 20.9 μg
0.00009	Mushroom (2.55 mg) (1/6th)	p-Hydrazinobenzoate, 28 μg
0.00008	DDE/DDT: daily dietary avg.	DDE, 659 ng (1990)
0.00007	Parsnip (54 mg) (1/3300th)	8-Methoxypsoralen, 1.57 μg
0.00005	Parsley, fresh (324 mg)	8-Methoxypsoralen, 1.17 μg
0.00002	Dicofol: daily dietary avg.	Dicofol, 544 ng (1990)
0.00001	Cocoa (3.34g) (4/5th serving)	α-Methylbenzyl alcohol, 4.3 μg
0.000001	Lindane: daily dietary avg.	Lindane, 32 ng (1990)
0.0000004	PCNB: daily dietary avg.	PCNB (Quintozene), 19.2 ng (1990)
0.0000001	Chlorobenzilate: daily dietary avg.	Chlorobenzilate, 6.4 ng (1989)
<0.00000001	Chlorothalonil: daily dietary avg.	Chlorothalonil, <6.4 ng (1990)
0.000000008	Folpet: daily dietary avg.	Folpet, 12.8 ng (1990)
0.000000006	Captan: daily dietary avg.	Captan 11.5 ng (1990)

Carcinogenicity status of volatile chemicals in tomato

Positive: N=17	Acetaldehyde, benzaldehyde, benzene, benzyl acetate, chloroform, 1,4-dioxane, ethanol, ethylbenzene, formaldehyde, furfuryl alcohol, limonene, naphthalene, pyridine, styrene, toluene, 1,2,4-trimethylbenzene, xylene
Negative: N=8	acrolein, allyl alcohol,benzoic acid, biphenyl, carvone, citronellyl acetate, eugenol, phenol
Yet to test:	365 volatile chemicals

Carcinogenicity Status of Natural Pesticides Tested in Rodents

Carcinogens: N=37

Acetaldehyde methylformylhydrazone, allyl isothiocyanate, arecoline.HCL, benzaldehyde, benzyl acetate, caffeic acid, capsaicin, catechol, clivorine, coumarin, crotonaldehyde, 3,4-dihydrocoumarin, estragole, ethyl acrylate, N2- γ -glutamyl-p-hydrazinobenzoic acid.HCL, hydroquinone, 1-hydroxyanthraquinone, lasiocarpine, d-limonene, 3-methoxycatechol, *8*-methoxypsoralen, N-methyl-N-formylhydrazone, 4-methylcatechol, methylhydrazine, monocrotaline, pentanal methylformylhydrazone, petasitenine, quercetin, reserpine, safrole, safrole, senkirkine, sesamol, symphytine

Noncarcinogens: N=34

Atropine, benzyl alcohol, benzylixothiocyanate, benzyl thiocyanate, biphenyl, d-carvone, codeine, deserpidne, disodium glycirrhysinate, ephedrine sulphate, epigallocatechin, eucalyptol, eugenol, gallic acid, geranyl acetate, β-N-[γ-/(+)-glutamyl]-4-hydroxymethylphenylhydrazine, glycyrrhetirric acid, p-hydrazino-benzoic acid, isosafrole, kaempferol, *dl*-menthol, nicotine, norharman, phenethyl, isothiocyanate, pilocarpine, piperidine, protocatechaic acid, rotenone, rutin sulfate, sodium benzotae, tannic acid, 1-trans-δ^9-tetrahydrocannabinol, turmeric oleoresin, xinblastine

These rodent carcinogens occur in: absinthe, allspice, anise, apple, apricot, banana, basil, beer, Broccoli, Brussels sprouts, cabbage, cantaloupe, caraway, cardamom, carrot, cauliflower, celery, cherries. Chili pepper, chocolate, cinnamon, cloves, coffee, collard greens, comfrey herb tea, corn, coriander, currants, dill., eggplant, endive, fennel, garlic, grapefruit., grapes, guava, honey, honeydew, melon, horseradish, kale, lemon, lentils, lettuce, licorice, lime, mace, mango, marjoram, mint, mushrooms, mustard, nutmeg,m onion, orange, paprika, parsley, parsnip, peach, pear, peas, black pepper, pineapple, plum, potato,radish, raspberries, rhubarb, rosemary, rutabaga, sage, savory, sesame seeds, soybean, star anise, tarragon, tea thyme, tomato, turmeric, and turnip.

Ranking possible carcinogenic hazards (HERP) from natural and synthetic chemicals: Part 1

HERP (%)	Daily human exposure	Human dose of rodent carcinogen
140	EDB: workers; daily intake (high exposure)	Ethylene dibromide, 150 mg
17	Clofibrate (average daily dose)	Clofibrate, 2g
16	Phenobarbital, 1 sleeping pill	Phenobarbital, 60 mg
[14]	Isoniazid pill (prophylactic dose)	Isoniazid, 300 mg
6.2	Comfrey-pepsin tablets, 9 daily	**Comfrey root, 2.7g**
[5.6]	Metronidazole (therapeutic dose)	Metronidazole, 2g
4.7	**Wine (250 ml)**	**Ethyl alcohol, 30 ml ***
4.0b	Formaldehyde: Workers' average daily intake	Formaldehyde, 6.1 mg
2.8	**Beer (12 ounces; 54 ml)**	**Ethyl alcohol, 18 ml**
1.4b	Mobile home air (14 hour/day)	Formaldehyde, 2.2 mg
1.3	Comfrey-pepsin tablets, 9 daily	**Symphytine, 1.8 mg**
0.4b	Conventional home air (14 hours/day)	Formaldehyde, 598 µg
[0.3]	Phenacetin pill (average dose)	Phenacetin, 300 mg
0.3	**Lettuce, 1/8 head (125 g)**	**Caffeic acid, 66.3 mg**

*** Natural chemicals in the diet are in bold**

TCDD (Dioxin) Compared With Alcohol

TERATOGENICITY

in mice 1 μg TCDD = 15g alcohol (1 beer)

6 fg/kg/day TCDD (EPA reference" dose)
= 1/3,000,000 beer/day
= 1 beer/8000 years

CARCINOGENICTY

in rats: 1 μg TCDD+ 300 g alcohol

6 fg/kg/day TCDD (EPA reference" dose)
= 1/150,000 beer/day
= 1 beer/345 years
U.S. average is one beer (drink)/day

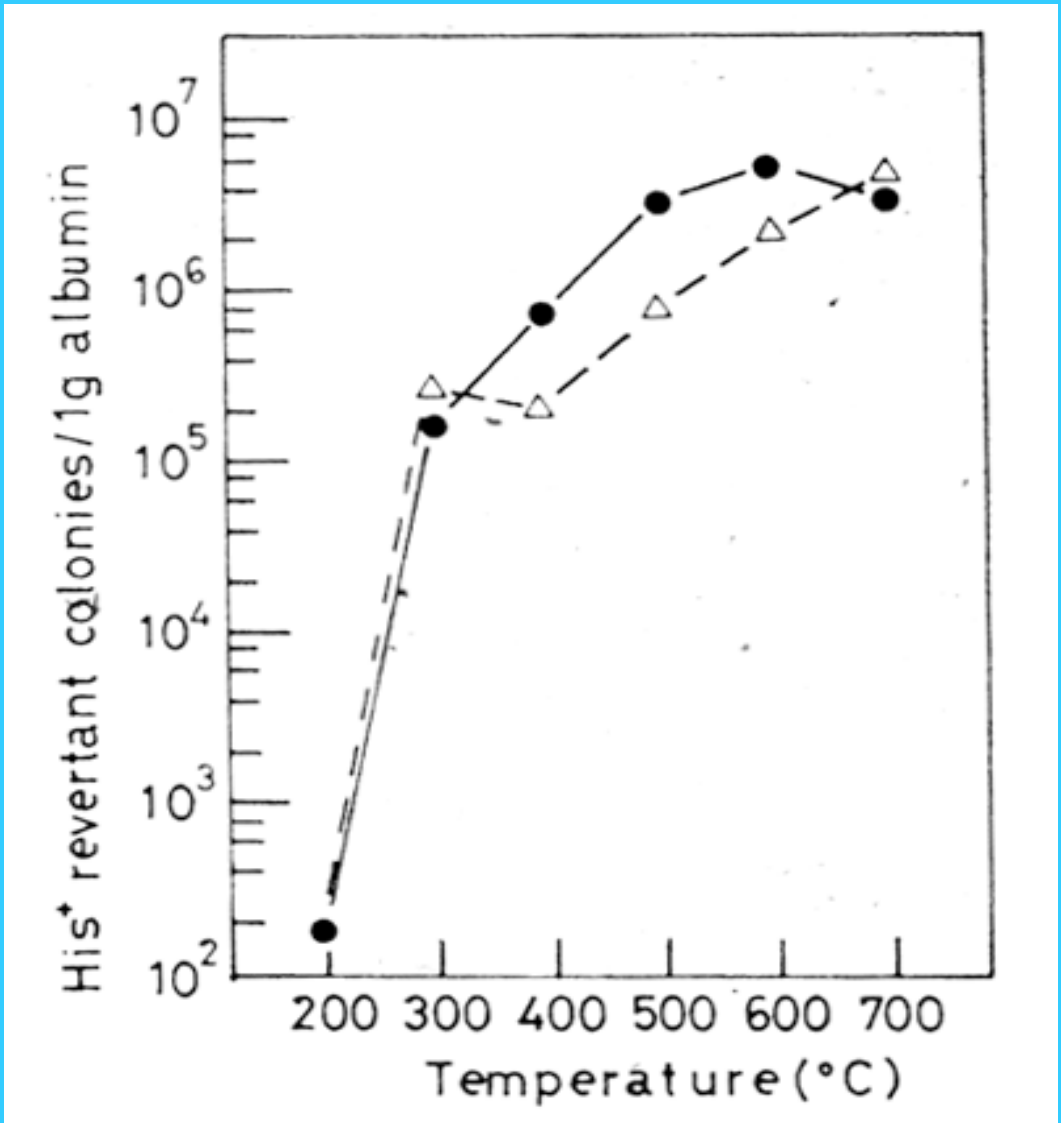
TCDD (Dioxin) Compared to Broccoli

CARCINOGENICITY

- Indole carbinol in broccoli, cabbage, and Brussels sprouts. Indole carbinol dimer (ICZ) is formed in the stomach and has the same properties as TCDD (Bjeldanes; PNAS)

- ICZ binds 1/27 as well as TCDD to Ah receptor.

- 1 portion of broccoli = more of a hazard than EPA "reference" dose of TCDD (Bjeldanes).



Mutagenic Activity (Number of His^+ Revertant Colonies) of Albumin Pyrolyzed at Different temperature Under N_2 or Air Atmosphere

Yoshida, Matsumoto, & Nishigata, *Agric. Biol. Chem*. **44**:253 (***1980***)

CARCINOGENICITY STATUS OF NATURAL CHEMICALS IN COFFEE

Carcinogens	Acetaldehyde, Benzaldehyde, Benzene, Benzofuran, Benzo(a)Pyrene, Caffeic Acid, Catechol, 1,2,5,6-Dibenzanthracene, Ethanol, Ethylbenzene, Formaldehyde, Furan, Furfural, Hydrogen Peroxide, Hydroquinone, Limonene, Styrene, and Toluene
Noncarcinogens	Biphenyl, Eugenol, Phenol, Piperidine, and Acrolein
Yet to be Tested	~ 1,000 chemicals

Vehicular Pollution

Means of Transport	Pollutant	Emissions (grams per mile)
Horses	Waste, solid	640
	Waste, liquid	300
Automobiles	Hydrocarbons	0.25
	CO	4.7
	NO_x	0.4

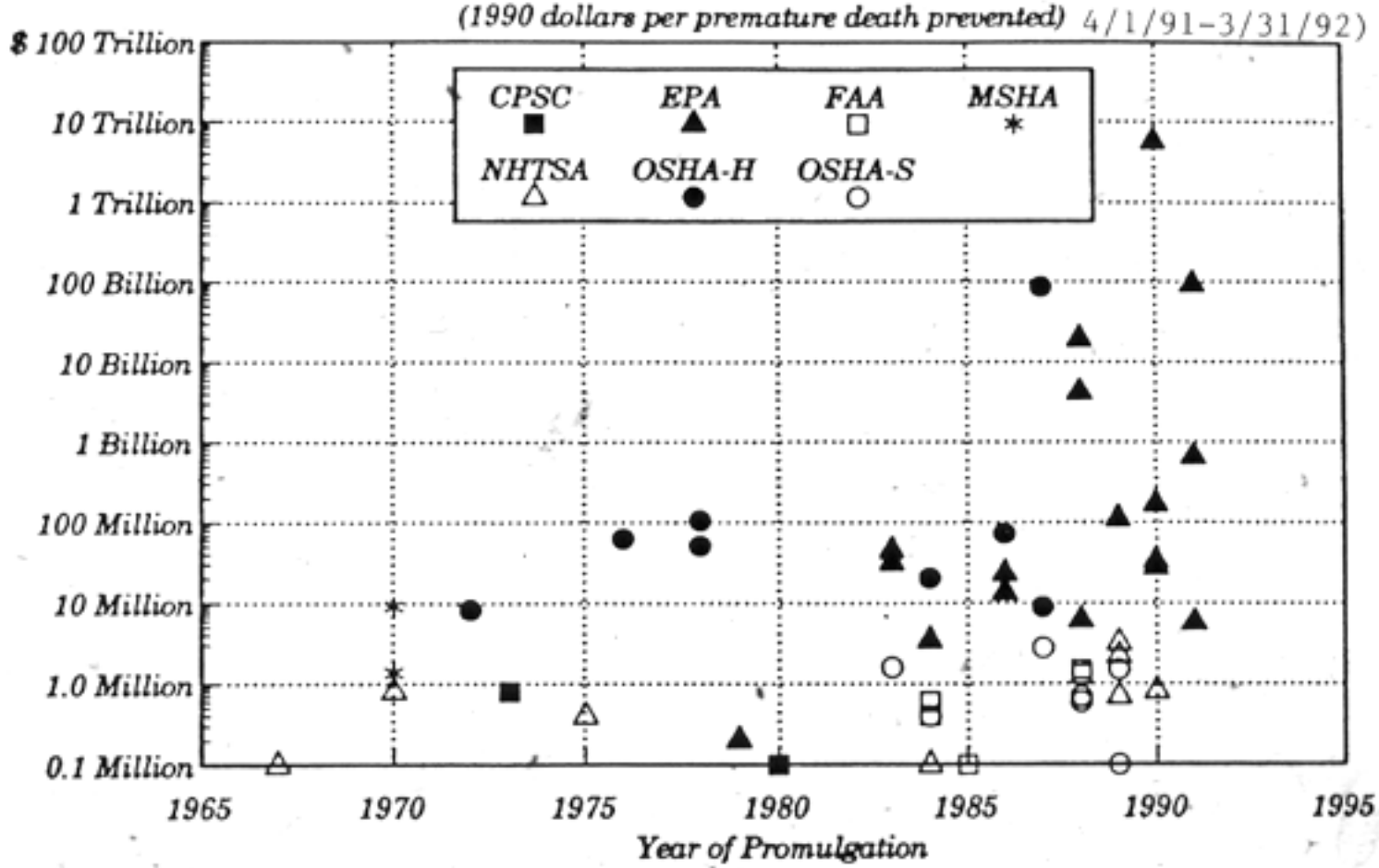
J.H. Ausubel in: "*Technology and Environment*", National Academy of Engineering, **1989**.

Overview of aims and achievements of toxicology.

	Illusion	***Reality***
Aim	Prevent human diseases from chemicals	Provide living for: Contract laboratories Civil Servants Lawyers Statisticians Consultants Conference organizers
Achievements	Public reassured that chemicals are properly tested for carcinogenic activity	Public worried to 'death' (or indifference) by: Politicians Sensational press statements

Figure 2. Cost-Effectiveness of Selected Federal Regulations by Year of Promulgation by Agency

(From: O.M.B.: Regulatory Program of the U.S. Gov't. 4/1/91-3/31/92)



Relax, I’ve come for your toaster