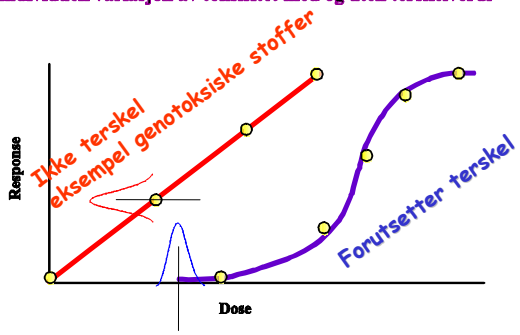
# BIO4530 Ekstrapolerings metoder

## Med vekt på kreftfremkallende stoffer

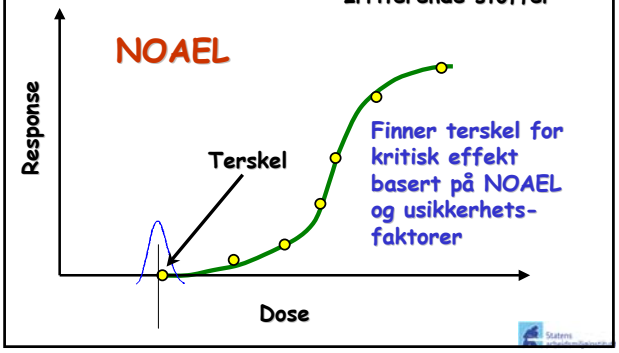
Steinar Øvrebø

**Individuell variasjon av toksisitet med og uten terskelverdi**

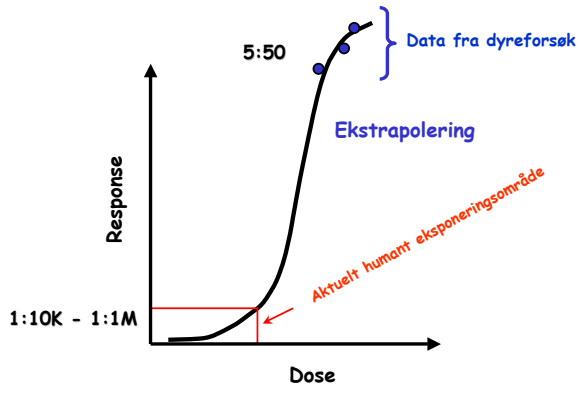



**Stoffer som en antar effekten har/viser en terskel**

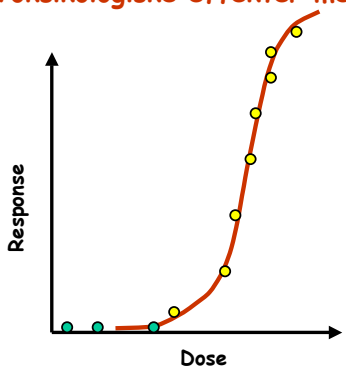
- Ikke genotoksiske karsinogener
- Organ skadende stoffer
- Irriterende stoffer



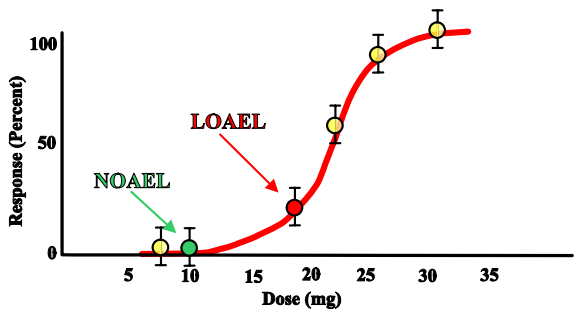

**Datagrunnlag og aktuell eksponering**

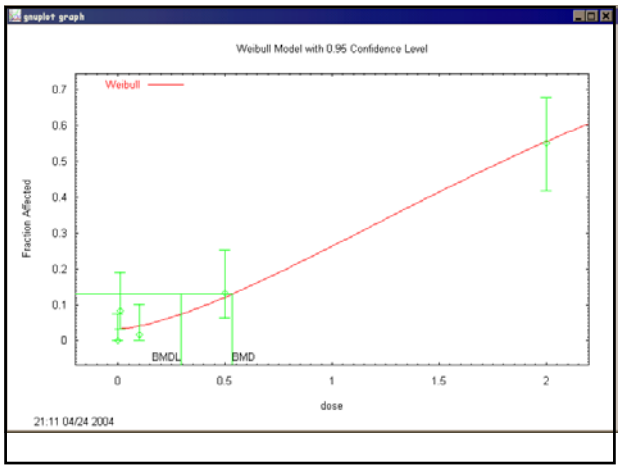



**Interpolering/kurvetilpassing**
**Toksikologiske effekter med terskel**

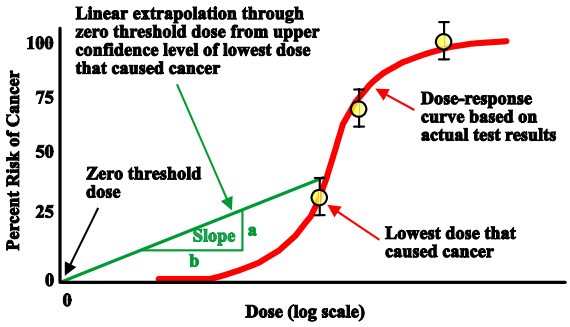



**NOAEL and LOAEL**

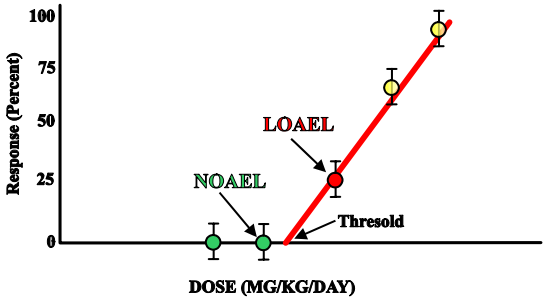





## Cancer Risk Assessment

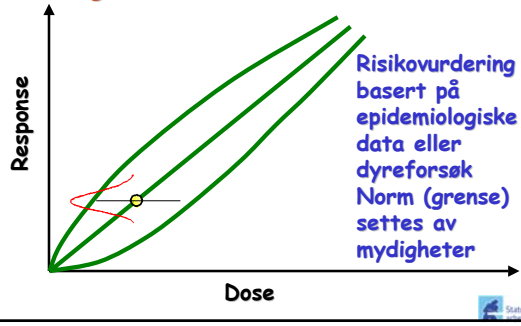



## Non-carcinogenic Risk Assessment




## Stoffer som en antar ikke har/viser 'terskel toksikologi'

Gentoksiske karsinogener
Mutagene stoffer
Sensibiliserende stoffer
Reproduksjonstoksiske stoffer



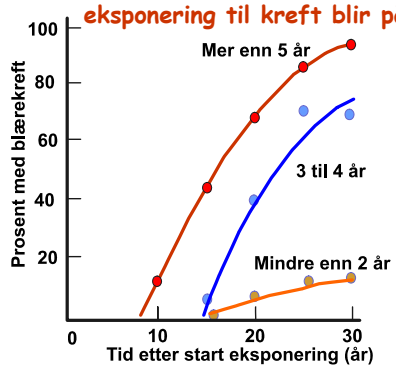

Risikovurdering basert på epidemiologiske data eller dyreforsøk
Norm (grense) settes av mydigheter

## Insidens av kreft i ulike celltyper

- Kreft i eksterne epitel (eksempler hud, tykktarm, mage og cervix)……..…..56%
- Kreft i indre epitel (eksempler bryst, prostata, egg, blære og pankreas……..36%
- Kreft i støtte vev og bloddannende organer (sarkom og leukemi)……..8%

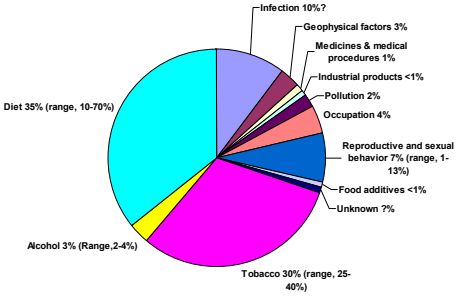
Kilde Cairns og J. Clemmesen Acta. Path. Microbiolo. Scand. Suppl. 175 (1964), 209(1969) og 247(1974)

## Latenstid - Tida det tar frå fyrste eksponering til kreft blir påvist




Tid for forekomst av blærekreft blant 78 menn eksponert for naftylamin

# Fordeling av kreftdødsfall etter miljøfaktorer (Doll and Peto - 1981)




# Variasjon av kreftinsidens mellom ulike land

**Variation in Incidence of Common Cancers**

| TYPE OF CANCER | REGION OF HIGHEST INCIDENCE | RISK UP TO AGE 75 (PERCENT) | RANGE OF VARIATION[a] | REGION OF LOWEST INCIDENCE |
|---|---|---|---|---|
| | | | | *Men* |
| Skin | Queensland | Over 20 | Over 200 | Bombay |
| Esophagus | Northeast Iran | 20 | 300 | Nigeria |
| Lung | Great Britain | 11 | 35 | Nigeria |
| Stomach | Japan | 11 | 25 | Uganda |
| Liver | Mozambique | 8 | 70 | Norway |
| Prostate | United States (blacks) | 7 | 30 | Japan |
| Colon | Connecticut | 3 | 10 | Nigeria |
| Mouth | India | Over 2 | Over15 | Denmark |
| Rectum | Denmark | 2 | 20 | Nigeria |
| Bladder | Connecticut | 2 | 4 | Japan |
| Nasopharynx | Singapore (Chinese) | 2 | 2 | Great Britain |
| | | *Woman* | | |
| Cervix | Colombia | 10 | 15 | Israel (Jews) |
| Breast | Connecticut | 7 | 15 | Uganda |
| Uterus | California | 3 | 30 | Japan |
| Ovary | Denmark | 2 | 60 | Japan |

[a]The highest incidence observed divided by the lowest incidence observed

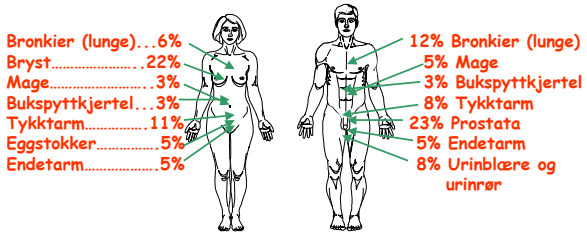
**Variation Between Countries in the Incidence of Some Common Cancers**

| Site of Origin of Cancer | High-Incidence Population | | Low-Incidence Population | |
|---|---|---|---|---|
| | Location | Incidence* | Location | Incidence* |
| Lung | USA (New Orleans, blacks) | 110 | India (Madras) | 5.8 |
| Breast | Hawaii (Hawaiians) | 94 | Israel (non-Jews) | 14.0 |
| Prostate | USA (Atlanta, blacks) | 91 | China (Tianjin) | 1.3 |
| Uterine cervix | Brazil (Recife) | 83 | Israel (non-Jews) | 3.0 |
| Stomach | Japan (Nagasaki) | 82 | Kuwait (Kuwaitis) | 3.7 |
| Liver | China (Shanghai) | 44 | Canada (Nova Scotia) | 0.7 |
| Colon | USA (Connecticut, whites) | 34 | India (Madras) | 1.8 |
| Melanoma | Australia (Queensland) | 31 | Japan (Osaka) | 0.2 |
| Nasopharynx | Hong Kong | 30 | UK (southwestern) | 0.3 |
| Esophagus | France (Calvados) | 30 | Romania (urban Cluj) | 1.1 |
| Bladder | Switzerland (Basel) | 28 | India (Nagpur) | 1.7 |
| Uterus | USA (San Francisco Bay Area, whites) | 26 | India (Nagpur) | 1.2 |
| Ovary | New Zealand (Polynesian Islanders) | 26 | Kuwait (Kuwaitis) | 3.3 |
| Rectum | Israel (European and USA born) | 23 | Kuwait (Kuwaitis) | 3.0 |
| Larynx | Brazil (São Paulo) | 18 | Japan (rural Miyagi) | 2.1 |
| Pancreas | USA (Los Angeles, Koreans) | 16 | India (Poona) | 1.5 |
| Lip | Canada (Newfoundland) | 15 | Japan (Osaka) | 0.1 |
| Kidney | Canada (NWT and Yukon) | 15 | India (Poona) | 0.7 |
| Oral cavity | France (Bas-Rhin) | 14 | India (Poona) | 0.4 |
| Leukemia | Canada (Ontario) | 12 | India (Nagpur) | 2.2 |
| Testis | Switzerland (urban Vaud) | 10 | China (Tianjin) | 0.6 |

*Incidence = number of new cases per year per 100,000 population, adjusted for a standardized population age distribution (so as to eliminate effects due merely to differences of population age distribution). Figures for cancers of breast, uterine cervix, uterus, and ovary are for women; other figures are for men.

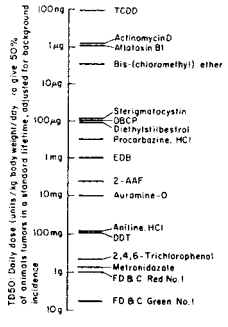
Adapted from V.T. DeVita, S. Hellman, and S.A. Rosenberg (eds.), Cancer: Principles and Practice of Oncology, 4th ed. Philadelphia: Lippincott, 1993; based on data from C. Muir et al., Cancer Incidence in Five Continents, Vol. 5. Lyon: International Agency for Research on Cancer, 1987.

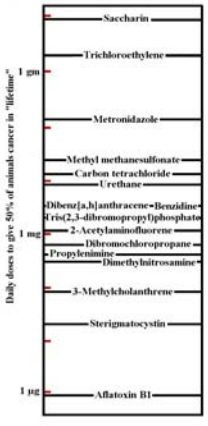
# Krefttilfeller i Norge




Nye tilfeller av kreft i Norge 1993
fra Kreftregisteret

**FIGURE 5.** Range of carcinogenic potency in male rats. (Reproduced from Gold *et al.*[50] with permission from the National Institute of Environmental Health Sciences.)



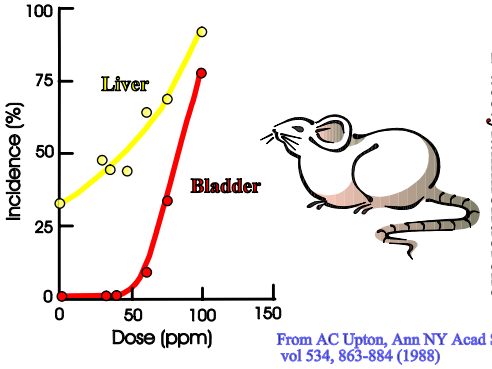




**Hvor farlige er kreftfremkallende stoffer? Eller hva er risikoen ved eksponering for et kreftfremkallende stoff?**

## Grunner til å ekstrapolere mot 0

- Unicellulær og monoklonal origin av kreft
  Evidens X linket glukose-6-fosfat dehydrogenase som markør
- Initiering, promotion og progresjon
- Cytotoksisitet
- Hvilken eksperimentell evidens har vi for ekstrapoleringern mot 0

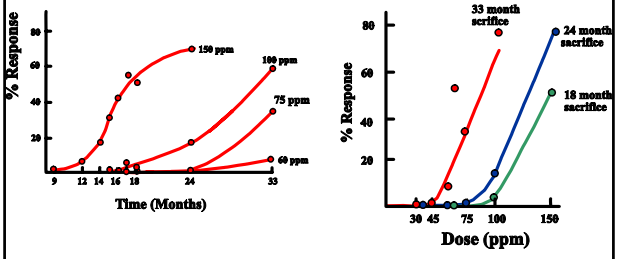
## Cumulative incidence of neoplasms in female BALB/c exposed to 2-acetylaminofluorene



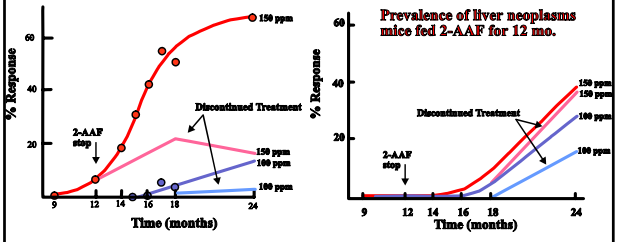

From AC Upton, Ann NY Acad Sci vol 534, 863-884 (1988)

from

## Bladder neoplasms in female mice 2-acethylaminofluorene




## Prevalence of bladder neoplasm mice fed 2-AAF for 12 mo.



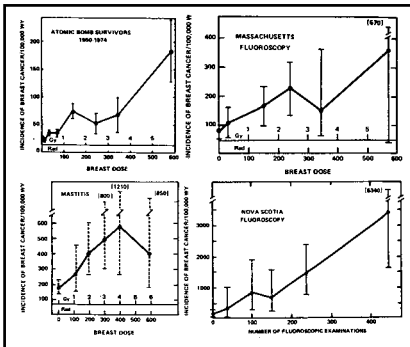
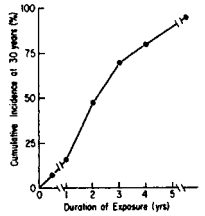




**FIGURE 1.** Incidence of cancer of the female breast as a function of dose in A-bomb survivors, in women treated with X-rays for acute postpartum mastitis, and in women subjected to multiple fluoroscopic examinations of the chest during treatment of pulmonary tuberculosis with artificial pneumothorax. (Reproduced from Boice *et al.*[34] with permission from the Radiological Society of North America.)

from AC Upton, Ann NY Acad Sci vol 534 (1988)863-884

**FIGURE 3.** Cumulative incidence of tumors of the urinary bladder, at 30 years after start of exposure in 78 distillers of 2-naphthylamine and benzidine, in relation to duration of occupational exposure. (Reproduced from Saffiotti[37] [based on data from Williams[38]] with permission from the International Agency for Research on Cancer.)




from AC Upton, Ann NY Acad Sci vol 534 (1988)863-884

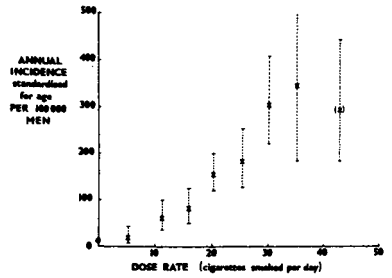



**FIGURE 2.** Incidence of lung cancer in regular smokers of cigarettes in relation to the number of cigarettes smoked per day. (Reproduced from Doll[35] with permission.)

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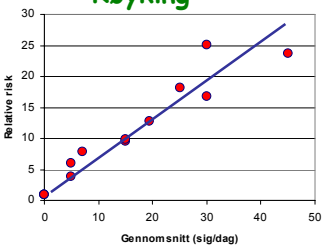
## Relativ risk - lungekreft ved røyking 3 studier

Doll & Peto 1976, Rogot & Murray 1980 og Lund & ZeinerHenriksen 1981




**Koksverksarbeidere der mange røyker**

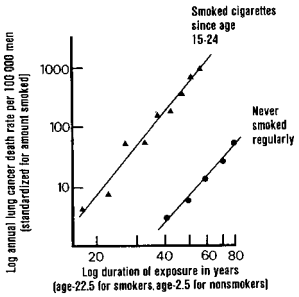
| Follow up year | Obs | RR |
|---|---|---|
| 7 | 3 | - |
| 12 | 11 | 2,69 |
| 17 | 32 | 4,01 |
| 22 | 40 | 2,81 |
| 25 | 50 | 2,49 |

Data fra IARC momographs vol 38 Tobacco smoking

CK Redmond Env Health Persp 52 1983 67-73

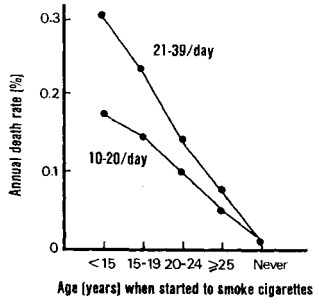


**Fig. 8. Background and excess risks: lung cancer death rates among nonsmokers in relation to age (lower line) and among regular cigarette smokers, in relation to approximate years of smoking (upper line)[a]**




[a]From Doll (1971) and Peto and Doll (1984)

**Fig. 9. Relationship between age of starting regular cigarette smoking in early adult life and lung cancer death rates at age 55-64 (mean, 60) for US men. Data presented separately for heavy and for moderate smokers[a]**




[a]From Doll and Peto (1981)

## EXPERIMENTAL DOSE-EFFECT DATA

### *Carcinogenesis in Laboratory Animals*

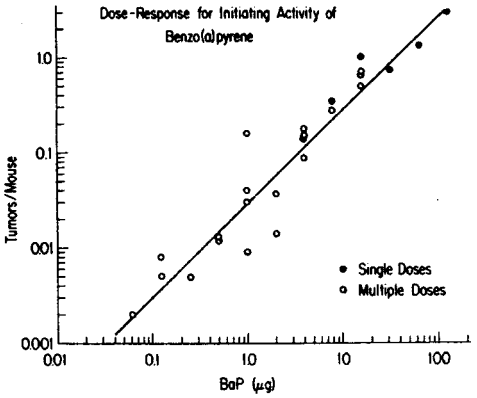
The neoplasms induced experimentally in animals of different species vary widely in dose–incidence relationships. Although neoplasms of virtually every

**TABLE 1.** Age-Standardized Lung Cancer Death Rates for Cigarette Smoking, Occupational Exposure to Asbestos Dust, or Both

| Group | Exposure to Asbestos? | History of Cigarette Smoking? | Death Rate | Mortality Difference | Mortality Ratio |
|---|---|---|---|---|---|
| Control | No | No | 11.3 | 0.0 | 1.00 |
| Asbestos workers | Yes | No | 58.4 | +47.1 | 5.17 |
| Control | No | Yes | 122.6 | +111.3 | 10.85 |
| Asbestos workers | Yes | Yes | 601.6 | +590.3 | 53.24 |

NOTE: Age-standardized lung cancer death rates are rates per 100,000 man-years standardized for age on the distribution of the man-years of all the asbestos workers. Number of lung cancer deaths based on death certificate information. (Adapted from Selikoff.[40])

from AC Upton, Ann NY Acad Sci vol 534 (1988)863-884




from AC Upton, Ann NY Acad Sci vol 534 (1988)863-884

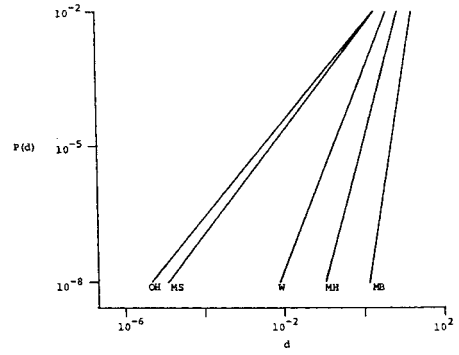



**FIGURE 11.** Estimated risk of liver cancer, P(d), in relation to dose of aflatoxin, d, as determined with different dose–incidence models. The models for the different curves are as follows: OH, one-hit model; MS, multistage model; W, Weibull model; MH, multihit model; MB, Mantel–Bryan (log-probit model). (Reproduced from Krewski and Van Ryzin[104] with permission from the Elsevier/North-Holland Publishing Company.)

from AC Upton, Ann NY Acad Sci vol 534 (1988)863-884

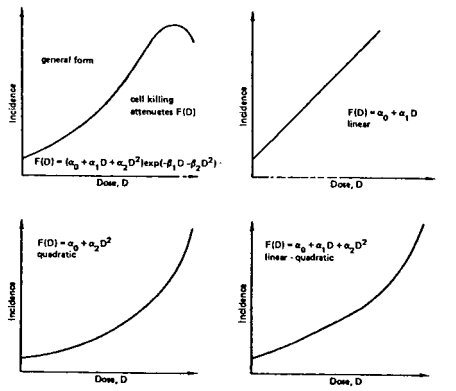
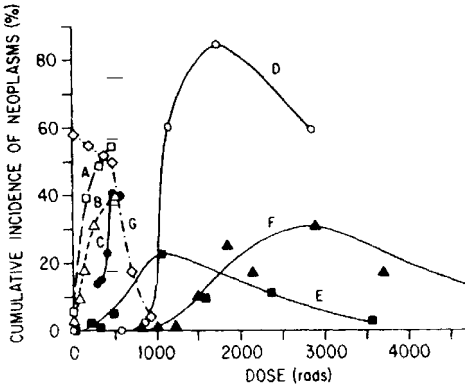



**FIGURE 10.** Dose–response curves for four different mathematical models relating cancer incidence to radiation dose. (Reproduced from Reference 28 with permission from the National Academy Press.)

from AC Upton, Ann NY Acad Sci vol 534 (1988)863-884

## Dose-incidence curves for different neoplasms in animals exposed to external radiation

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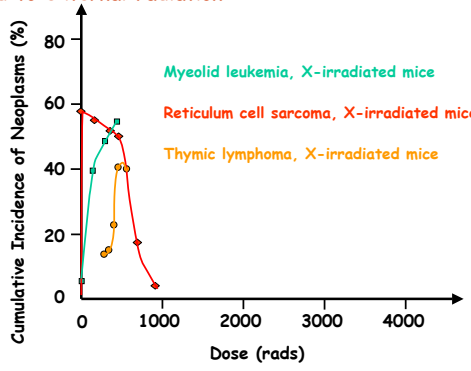


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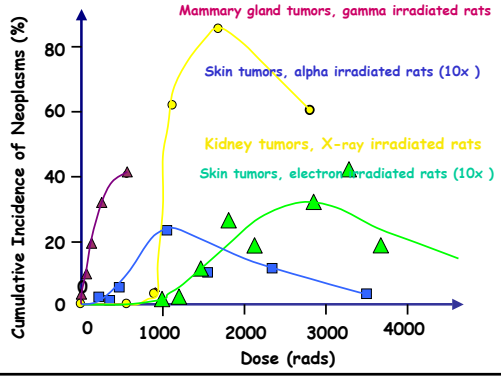
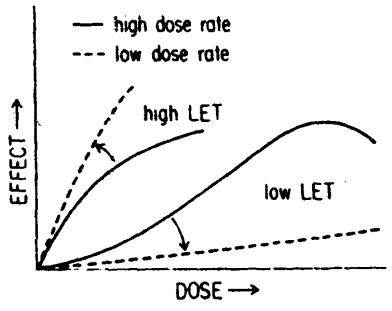



from AC Upton, Ann NY Acad Sci vol 534 (1988)863-884

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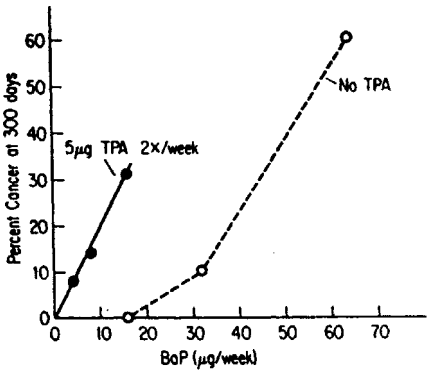



from AC Upton, Ann NY Acad Sci vol 534 (1988)863-884

## Matematiske modeller basert på biologisk teori

Tolerance distrubution models
- Log-normal (probit)
- Log-logistic (logit)
- Weibull

Mechanistic models
- One-hit
- Multi-hit
- Multi-stage

Linear-quadratic-expoential model

Time-to-response model (log-normal)

Modelerer for:
1) Best mulig kurvetilpassing
2) Biologisk modell utgangspunktet

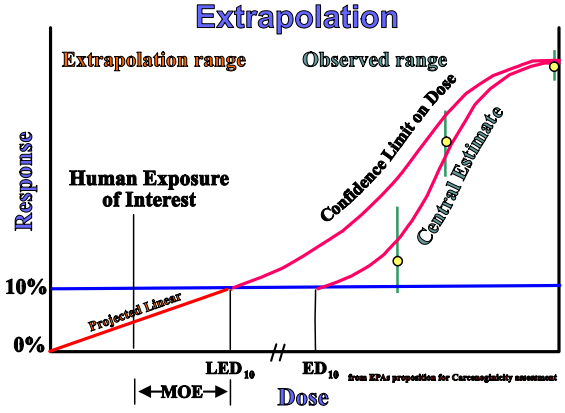
## Tolerance distrubution models

Forutsetter at hvert individ i gruppen har sin unike toleranse for det toksiske stoff. Under denne grense har stoffet ikke effekt. Ta ikke med intra-artsvariasjon i databasen

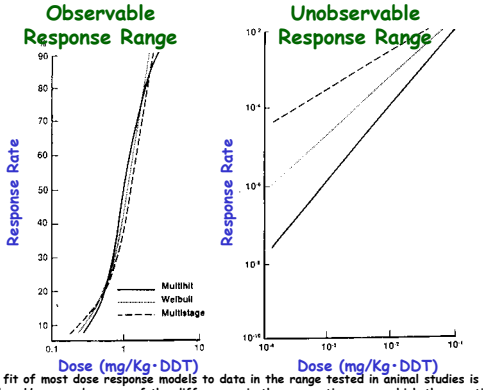
## Mechanistic Models

Disse modellen antar at responsen dannes som følge av at en reseptor er utsatt for et bestemt antall treff (reseptoren kan være DNA). I multistage så undergår en celle et bestemt antall endringstrinn (eng. stage)

## Extrapolation




## Extrapolation to low doses variations between 3 models




The fit of most dose response models to data in the range tested in animal studies is generally similar. However, because of the differences in the assumptions upon which the equations are based, the risk estimates at low doses can vary dramatically between the different models.

## Low dose extrapolation

| | Response | |
|---|---|---|
| Dose(mg/kgxday) | San Fransisco | New York |
| 0 | 0/50 | 0/50 |
| 3 | 2/50 | 1/50 |
| 10 | 10/50 | 10/50 |

| | Risk estimates | |
|---|---|---|
| Dose (mg/kgxday) | San Fransisco | New York |
| 3 | 0.04 | 0.02 |
| 1 | 0.01 | 0.002 |
| 0.1 | 1/1,000 | 3/100,000 |
| 0.01 | 1/10,000 | 1/2000,000 |

Multistage modell benyttet

| Model | Predicted Risk |
|---|---|
| Linear | Highest |
| One-hit | |
| Multistage | |
| Weibull | |
| Moolgakar-Knudson-Venzon | |
| Multihit | |
| Logit | |
| Probit | Lowest |

Dose Response Assessment

## Cancer Risk Assessment

- Human Carcinogen
- Probable Human Carcinogen B1
- Probable Human Carcinogen B2
- Possible Human Carcinogen
- Not Classifiable as to Human Carcinogenicity
- No Evidence of Carcinogenicity in Humans

**Chlordane - concentration in drinking water causing lifetime risk of cancer death in a million persons**

| | |
|---|---|
| Probit model | 50 µg/L |
| Multi-hit model | 2 µg/L |
| Linearized multistage model | 0.07 µg/L |
| One Hit Model | 0.03 µg/L |

**TABLE 2.** Estimated Human Risks from Ingestion of 0.12 G/Day of Saccharin

| Method of High- to Low-Dose Extrapolation | Lifetime Cases per Million Exposed | Cases per 50 Million per Year |
|---|---|---|
| *Rat dose adjusted to human dose by surface area rule* | | |
| Single-hit model | 1,200 | 840 |
| Multistage model (with quadratic term) | 5 | 3.5 |
| Multihit model | 0.001 | 0.0007 |
| Mantel–Bryan probit model | 450 | 315 |
| *Rat dose adjusted to human dose by mg/kg/day equivalence* | | |
| Single-hit model | 210 | 147 |
| Multihit model | 0.001 | 0.0007 |
| Mantel–Bryan probit model | 21 | 14.7 |
| *Rat dose adjusted to human dose by mg/kg/ lifetime equivalence* | | |
| Single-hit model | 5,200 | 3,640 |
| Multihit model | 0.001 | 0.0007 |
| Mantel–Bryan probit model | 4,200 | 2,940 |

NOTE: Adapted from Reference 105. from AC Upton, Ann NY Acad Sci vol 534 (1988)863-884

## Modeller for ekstrapolering kreftrisioko for bruk til beregning av human kreftrisiko fra dyreforsøk

**Linear model**
**P(d)=q(1) positive (slope factor)**

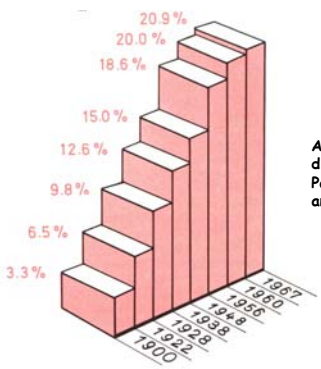
**One-Hit**
**P(d)=a-exp(-b·d)**

**Multistage**
**P(d)=1-exp{-[q(0) + q(1)d**2+ ...+q(k)d**k]}**

**Weibull**
**P(d)=1-exp[-b(d**m)]**

**Logit model**
**P(d)=1/[1 + exp-(a + b·logd)]**

**Probit model**
**P(d)=0.4{integral from minus infinity to[log(d - u)]/s of [exp-(y**2)/2]dy}**

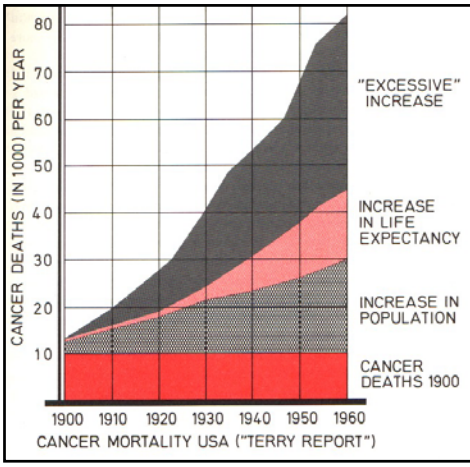



CANCER STAIRCASE: INCREASE IN CANCER MORTALITY

Antall lungekrefttilfeller diagonisert ved Heidelberg Pathology Departmentved de angitte tidsperiodene

| Periode | Antall tilfeller |
|---|---|
| 1841-1875 | 2 |
| 1876-1900 | 14 |
| 1901-1925 | 48 |
| 1926-1950 | 289 |
| 1951-1963 | 589 |

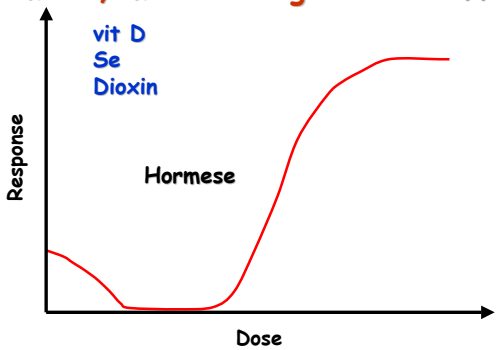
Kreftstatistikk fra Tyskland




CANCER MORTALITY USA ("TERRY REPORT")

Terry report forklarer mye av økningen

# Vitaminer, mineraler og andre stoffer?




*Scientific foundations of hormesis. Part 2. Maturation, strengths, limitations, and possible applications in toxicology, pharmacology, and epidemiology. Rozman KK, Doull J. Crit Rev Toxicol. 2003;33(3-4):451-62*

People have believed since antiquity that tiny doses of toxicants can be healthful. Now hormesis, a concept once discredited in scientific circles, is making a surprising comeback

## Sipping From a Poisoned Chalice

Dioxin and its chemical cousins are among the most deadly compounds on Earth. Spike a rat's water with 10 parts per billion—the equivalent of 7 teaspoons of dioxin dissolved in an Olympic-sized swimming pool—and there's a 50/50 chance that the rat will die of liver cancer. Yet even tinier concentrations of dioxins fed to rats inhibit tumors. The seemingly paradoxical findings have some scientists suggesting what would have been unthinkable not long ago: testing modified dioxins as an anticancer agent in humans.

Dioxin is a poster chemical of a bold campaign to rehabilitate the old saw that poisons or radioactivity at low doses are good for you. The concept, known as hormesis, has been kicking around for decades but until recently had been considered a marginal effect tainted by an unfortunate association with homeopathy. The improbable return of hormesis from the scientific wilderness, however, has riven the toxicology community.

A flurry of new findings and a re-examination of old ones have thrust hormesis into the limelight. Many drugs, vitamins, and essential minerals exhibit hormesis, as does alcohol: Moderate drinking lowers risk of heart disease, whereas higher levels are associated with higher risks of heart and liver disease. Calorie restriction, the sole indisputable means of extending an animal's life span, may also be a form of hormesis, proponents say. The lack of calories stresses an organism, firing up responses such as DNA repair enzymes and accelerates radiation punish the body at even the smallest of doses. If hormesis is as pervasive as its backers suggest, it could mean that regulations for many chemicals, from arsenic in drinking water to polychlorinated biphenyls at Superfund sites, are too stringent. "It would fundamentally change the whole risk-assessment paradigm," says Edward Calabrese, a toxicologist at the University of

**Crusader.** Edward Calabrese has spent 13 years urging toxicologi sts to reexamine the concept of hormesis "has been taken over by rhetoric," says William Farland, risk assessment chief at the U.S. Environmental Protection Agency (EPA). It's too soon, he says, to conclude that the benefits of low-level exposures outweigh the risks. Moreover, a recent wave of studies has found that some hormonelike toxicants known as endocrine disrupters may be more harmful at small doses than they are at larger ones. The declaration that low-dose effects are often healthy "is where Ed [Calabrese] falls off the edge of the earth," charges Frederick vom Saal, a reproductive biologist at the University of Missouri, Columbia.

One challenge is to pin down the mechanisms governing low-dose effects. Industry may well see it in their interests to pony up significant funds for such research. But what it will take to get regulators to buy into the concept is another question, says Joseph Rodricks, a risk assessment expert at Environ Corp. in Arlington, Virginia. Hormesis, he says, "is going to be a hard sell."

**The dose makes the poison?**

Hormesis was first described in 1888 by a German pharmacologist, Hugo Schulz, who observed that small doses of poisons seemed to stimulate the growth of yeast. Schulz also drew on animal studies of drugs at low doses



## CORRECTIONS AND CLARIFICATIONS

**News Focus:** "A healthful dab of radiation?" by J. Kaiser (17 Oct., p. 378). Sheldon Wolff did not win a Nobel prize. Also, a recent analysis challenges earlier claims that atomic bomb survivors exposed to low radiation doses are living longer than controls: www.rerf.or.jp/eigo/update/spring2002.pdf.



**Table 1.** Life expectancy by radiation dose[a]

| Dose range (Gy) | Mean dose (Gy) | No. of people | No. of deaths | Relative risk | Median age at death |
|---|---|---|---|---|---|
| 0 (<0.005)[b] | 0.0 | 34,064 | 16,775 | 1.000 | 81.082 |
| 0.005– | 0.06 | 40,403 | 19,641 | 1.002 | 81.025 |
| 0.250– | 0.36 | 4,899 | 2,548 | 1.031 | 80.435 |
| 0.500– | 0.61 | 2,427 | 1,296 | 1.085 | 80.068 |
| 0.750– | 0.86 | 1,360 | 693 | 1.120 | 80.312 |
| 1.000– | 1.22 | 1,527 | 802 | 1.138 | 79.769 |
| 1.500– | 1.90 | 1,160 | 619 | 1.259 | 77.994 |
| 2.500+ | 3.04 | 732 | 411 | 1.580 | 75.860 |
| Unknown | — | 7,097 | 3,151 | 1.031 | 80.945 |

[a]See also Figure 2.

[b]The dosimetry system assigns a dose estimate of zero to all persons whose calculated dose estimate would be less than 0.005 Gy free-in-air kerma.

**Figure1.** Survival curves for selected dose groups. Survival was estimated with adjustment for city, gender, and year of birth—all centered at their mean values—using Cox regression.

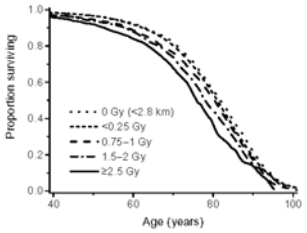
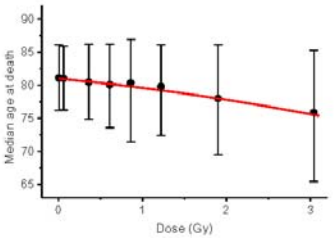
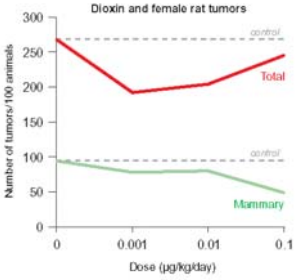
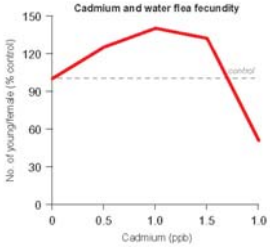



**Figure2.** Longevity as a function of radiation dose. The curve was estimated using a weighted least squares regression fit to the estimated median life expectancies of Table 1, using within-stratum mean doses as the independent variable and numbers of persons as the weights. The line represents the equation: median age at death = 81 – 1.2 × dose – 0.2 × dose$^2$

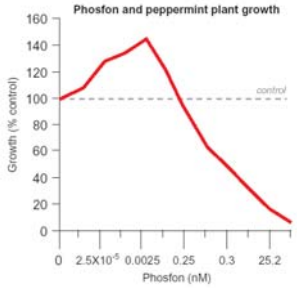





**The puzzle of hormesis.** Low doses of phosfon, a herbicide, caused plants to grow better (*below*); small amounts of dioxin, a carcinogen, reduced tumors in rats (*left*); and a little cadmium, ☹ toxic metal, caused water fleas to produce more young (*above*). The effects were reversed at higher doses.



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