Historisk perspektiv over regulatorisk toksikologi - introduksjon til kurset

BIO4530 Regulatorisk toksikologi

Steinar Øvrebø

Temaliste for forelesningen

Regulatorisk toksikologi eller risikovurdering?
Litt gammel historie fra 1800 tallet -->
Haber's lov
Yrkeseksponeringsgrenser historie
Kildekritikk
NAS 1983 The red book
Vitenskapelig grunnlag for Usf?
A Bradford Hill og R Doll
Thalidomide og Bophal og Chernobyl
Akseptabel risiko

Skillet mellom risikovurdering og regulatorisk toksikologi
Risk assessment & Risk management

Cassarett & Doull's Toxicology
Tidsskrifter
- Regulatory Toxicology Pharmacology
- Risk analysis

Norsk tradisjon? Finnes noen?
Internasjonal bruk?
Hva skal vi velge?

Engelsk - Norsk

Risk assesment = risikovurdering
- Hazard identification = 'fare' identifisering, identifisere stoffets iboende egenskaper
- Dose response assessment = dose-respons vurderinger
- Exposure assessment = Eksponeringsvudering

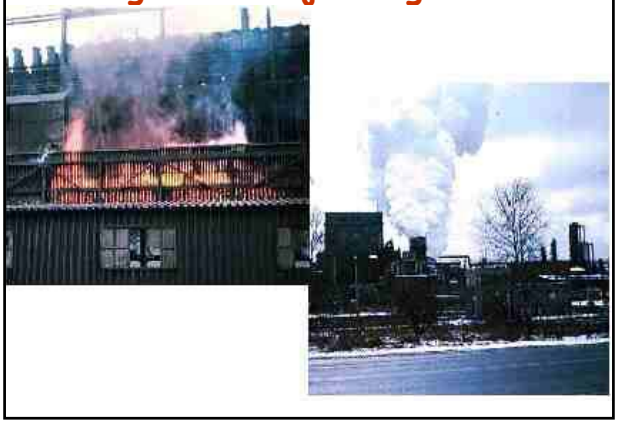
---Fag---

Risk characterization = risikokarakterisering

Risk mangement = risikohåndtering
risikoforvaltning
- Determination of acceptable risk level = Fastsettelse av akseptabelt risikonivå

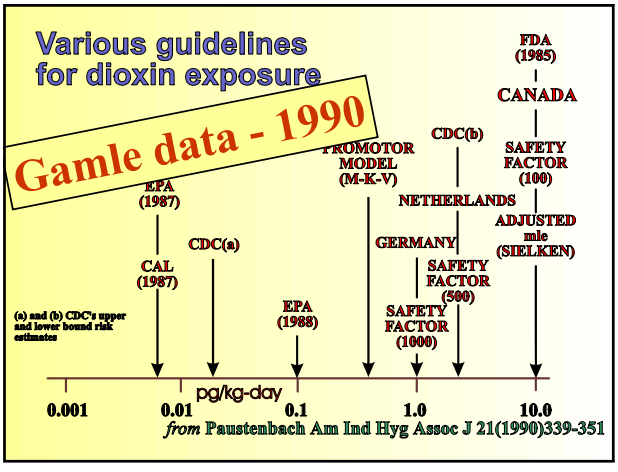
-Politikk-

Ytre og indre miljø henger sammen



Various guidelines for dioxin exposure

Gamle data - 1990



Worldwide occupational exposure limits (OEL) for formaldehyde in 1994

Country/agency	OEL (ppm)	Type of guideline
NIOSH	0.1	C (15 min)
World Health Organization (WHO)	0.24	TWA
ACGIH (1991)	0.3	C
Denmark	0.3	C
Germany	0.4	STEL
USSR (former)	0.4	TWA
Germany	0.5	TWA
U.S. Occupational Safety and Health Administration (OSHA, 1992)Hungary, Yugoslavia	0.75	TWA
Finland, Norway, Sweden	0.8	TWA
ACGIH (1990), AIHA, Australia, Austria, Germany, Italy, the Netherlands, Switzerland/OSHA	1.0	C
Brazil, Chile	1.0	TWA
Bulgaria	1.6	STEL
Australia, Belgium, India, Japan, the Netherlands, Venezuela	0.8	STEL
ACGIH (1990), AIHA, Argentina, France, the Netherlands, OSHA, United Kingdom	2.0	C
Hungary	2.0	STEL
Czech Republic, Poland	1.6	STEL
Argentina, Mexico, United Kingdom	1.6	TWA
People's Republic of China	2.0	TWA
Australia	2.5	TWA
Rumania	3.0	STEL
Czech Republic	3.2	C
Indonesia	4.1	C
Egypt, Republic of China	5.0	C
	5.0	TWA

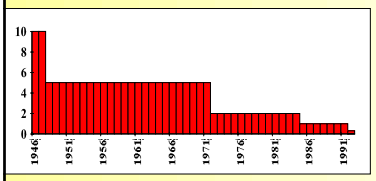
Note. All limits were obtained from one of the following publications: WHO (1977), Cook (1986), AIHA (1990), ACGIH (1989, 1992). C, ceiling value (maximum instantaneous concentration). STEL, short-term exposure limit (15 min; up to 4 times per day). TWA, time-weighted average (8 h/d).

from: **D. Paustenbach J Toxicol Env Health 50 (1997) 217-263**

Changes in the ACGIH TLV for formaldehyde and the rationale (1946-1992)

Year	Concentration (ppm)	Guideline	Rationale
1946-1947	10	MAC-TWA	Prevent skin and mucous membrane irritation
1948-1962	5	TLV[a]-TWA	Protective of respiratory injury
1963-1971	5	TLV-Ceiling	Protective of respiratory injury
1972-1984	2	TLV-Ceiling	Protective of eye irritation, mucous membrane irritation, disturbed sleep
1985	1	TLV-TWA	Prevent eye and nose irritation
1985	2	TLV-STEL	Minimize cancer hazard
1992	0.3	Ceiling	Eliminate eye and upper respiratory tract irritation; de minimis cancer risk

Note. MAC, maximum allowable concentration; TWA, time-weighted average; STEL, short-term exposure limit; Ceiling, maximum instantaneous concentration. [a] *MACS become TLVs during this time period.*



from: **D. Paustenbach J Toxicol En Health 50 (1997) 217-263**

Historie arbeidsmiljø

- The first proposals for occupational exposure limits were published by Karl Bernhard Lehmann in 1886. He recommended adherence to "maximum tolerable concentrations in the workplace"
- These recommendations were based on field studies, model exposures of volunteers and animal experiments.

D.Henschler the conceft of occupational exposure limits The Science oftheTotal Environment, 101 (1991)9-16

Historie arbeidsmiljø

These early efforts were fortified, from 1919 on at the University of Wurzburg, by a collaboration of K. B. Lemann with Ferdinand Flury. He introduced some basic dose-response-principles, derived from animal exposure studies with phosgene. With this compound, a hyperbolic relationship was found and expressed by the equation

cxt=W=const.

which later was called Haber's Law.

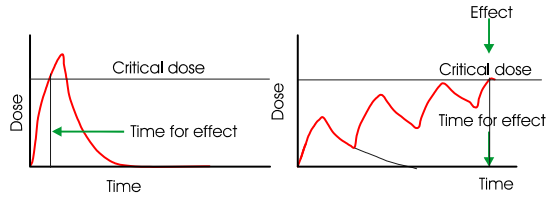
Haber laws

cxt = W = const.
(c - e) x t = W = const.
e = faktor for eliminering (av effekt)

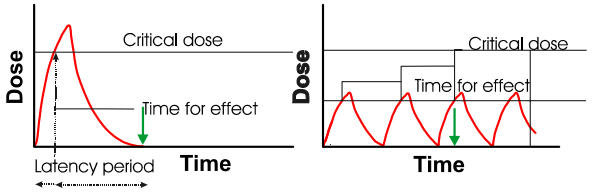
- < 24 timer
- Subakutt 1 måned og mindre
- Subkronisk 1 - 3 måneder
- Kronisk, mer enn 3 måneder

The use of Haber's Law in standard setting and risk assessment, David W. Gaylor, Toxicology volume 149, Issue 1 , 14 August 2000, 17 - 19

Dose - Effect -Time (1)



Dose - Effect -Time (2)



Historie arbeidsmiljø - USA (1)

According to Warren Cook [ACGIH, 1981], the first of the exposure limits for an air contaminant was established for carbon monoxide, in the last century by Max Gruber. As a result of exposing 12 rabbits, 2 hens, and himself to known concentrations of carbon monoxide, Gruber concluded, as published in volume one of "Archive fur Hygiene," that the limit should not be more than 500 parts per million.

In 1921, B.J. Newman and collaborators reporting on lead poisoning in the pottery trades proposed a maximum concentration for exposure to lead that was based on the data of animal experiments, corroborated by their own findings in workers: ". . . . About two milligrams, or 0.002 gram (per 10 cubic meters of air) of lead we regard as the lowest daily dose which inhaled as fume or dust in the air may in the course of years set up chronic plumbism."

from Jeffrey M. Paull,The Origin and Basis of Threshold Limit Values, American Journal of Industrial Medidne 5:227-238 (1984)

Historie arbeidsmiljø - USA (2)

In a 1924 study on mercury poisoning, J.A. Turner concluded that:
"an atmosphere containing as small a quantity as 0.02 milligram of mercury per cubic foot of air results in signs and symptoms of poisoning."

In 1926, L. Greenburg reported the results of a classic occupational study of chronic benzene poisoning; and A.E. Russell and colleagues in 1929 related the health of workers to siliceous dust in the granite industry.

from Jeffrey M. Paull,The Origin and Basis of Threshold Limit Values, American Journal of Industrial Medidne 5:227-238 (1984)

Amerikansk historie - viktig begrep terskel tankegangen

About 50 years ago (40 årene), toxicologists began to study the problem of establishing limits on exposures to hazardous substances that would protect human health. The early efforts began in the 1940s in connection with concerns about occupational exposures to chemicals and about residues of pesticides in foods. Toxicologists were guided by the principle that all substances could become harmful under some conditions of exposure - when the so-called threshold dose was exceeded-but that human health could be protected as long as those exposure conditions were avoided. Threshold doses were recognized to vary widely among among chemicals, but as long as human exposures were limited to sub threshold doses, no injury to health would be expected. The threshold hypothesis thus involved rejection of the simplistic view that the world is divided into toxic and nontoxic substances and acceptance of the principle that, for all chemicals…..

Science and Judgment in risk assessment / Committee on Risk Assessment of Hazardous Air Pollutants, Board on Environmental Studies and Toxicology, Commission on LifeSciences, National Research Council, National Academy Press. Washington, D.C. 1994

Om gifter

Paracelcius på 1500 tallet - alle stoff er gifter, det er dosen som bestemmer effekten

Age of Enlightenment
All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy
Paracelsus

Kildekritikk

- Nasjonale hensyn?
- Oversatt litteratur
- I oversiktsartikler skal forfatteren ha sett og lest alle refererte artikler
- Sovjetiske undersøkelser utført på svekkede dyr
- Ulike oppslagsverk har ulik praksis
- RTECS tar med det meste av data med lave verdier
- Andre selekterer mer

Red Book (1)

NATIONAL RESEARCH COUNCILIS THE PRINCIPAL OPERATING AGENCY OF THE NATIONAL ACADEMY OF SCIENCES AND THE NATIONAL ACADEMY OF ENGINEERING TO SERVE GOVERNMENT AND OTHER ORGANIZATIONS

Arthur Hull Hayes, Jr., M.D.
Commissioner of Food and Drugs
Food and Drug Administration .

I. THE NATURE OF RISK ASSESSMENT
II. INFERENCE GUIDELINES FOR RISK ASSESSMENT
III. ORGANIZATIONAL ARRANGEMENTS FOR RISK ASSESSMENT
IV. RECOMMENDATIONS

fra NATIONAL RESEARCH COUNCILIS 1983

Red Book (2)

- **Hazard identification:** The determination of whether a particular chemical is or is not causally linked to particular health effects.
- **Dose-response assessment:** The determination of the relation between the magnitude of exposure and the probability of occurrence of the health effects in question.
- **Exposure assessment:** The determination of the extent of human exposure before or after application of regulatory controls.
- **Risk characterization:** The description of the nature and often the magnitude of human risk including attendant uncertainty.

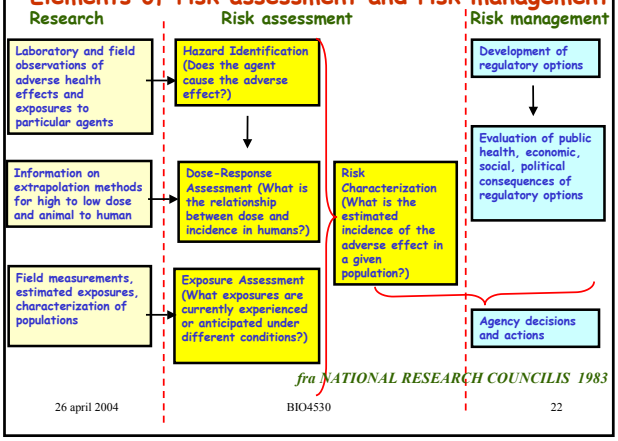
fra NATIONAL RESEARCH COUNCILIS 1983

Red Book (3)

(A) We recommend that regulatory agencies take steps to establish and maintain a clear conceptual distinction between assessment of risks and consideration of risk management alternatives; that is, the scientific findings and policy judgments embodied in risk assessments should be explicitly distinguished from the political, economic, and technical considerations that influence the design and choice of regulatory strategies.
(B) We recommend that uniform inference guidelines be developed for the use of federal regulatory agencies in the risk assessment process.
(C) We recommend to the Congress that a Board on Risk Assessment Methods be established to perform the following functions:.....

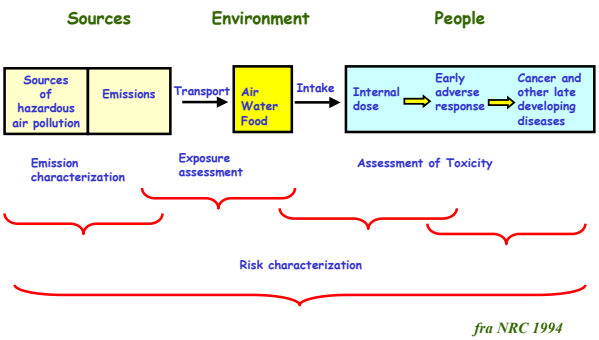
fra NATIONAL RESEARCH COUNCILIS 1983

Elements of risk assessment and risk management



fra NATIONAL RESEARCH COUNCILIS 1983

Risk assessment and risk Characterization



fra NRC 1994

Ekstrapolering

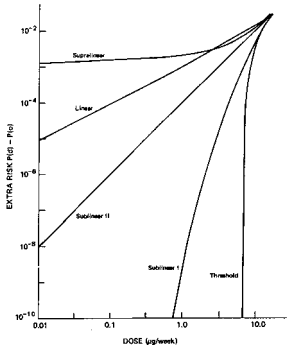


FIGURE I-2 Results of alternative extrapolation models for the same experimental data. NOTE: Dose-response functions were developed (Crump, in press) for data from a benzopyrene carcinogenesis experiment with mice conducted by Lee and O'Neill (1971).

fra NATIONAL RESEARCH COUNCILIS 1983

Recommendations

RECOMMENDATION 1

Regulatory agencies should take steps to establish and maintain a clear conceptual distinction between assessment of risks and the consideration of risk management alternatives; that is, the scientific findings and policy judgments embodied in risk assessments should be explicitly distinguished from the political, economic, and technical considerations that influence the design and choice of regulatory strategies.

RECOMMENDATION 2

Before an agency decides whether a substance should or should not be regulated as a health hazard, a detailed and comprehensive written risk assessment should be prepared and made publicly accessible. This written assessment should clearly distinguish between the scientific basis and the policy basis for the agency's conclusions.

2 av 10 anbefalinger fra NATIONAL RESEARCH COUNCILIS 1983

Vitenskapelig grunnlag for usikkerhetsfaktorer (1)

Usikkerhetsfaktorer er del av en 'metode', men finnes det data som støtter størrelsen på UF?

1954 Margin of safety: A.J. Leman and O.G. Fitzhugh, 100-fold margin of safety, Assoc. Food Drug Off. US Bull 18 (1954) 33-35

'Undersøkelsen' dreier seg om mattilsetning og henviser til dyreforsøk.
Eksempel 1: Menneske tolererer 1 ppm fluor i dietten, rotte kan ta 10 ppm
Eksempel 2: Subakutt toksisitet for arsenikk. Menneske intorelanse ved 30 ppm i dietten, hunder 127 ppm.
Flere momenter taes med

fra A.J. Leman and O.G. Fitzhugh, 100-fold margin of safety, Assoc. Food Drug Off. US Bull 18 (1954)33-35

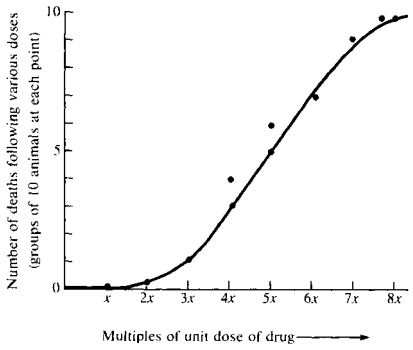
Vitenskapelig grunnlag for usikkerhetsfaktorer (2)

C. S. Weil and D. D. McCollister,Safety evaluation of chemicals. Relationship between short- and long-term feeding studies in designing an effective toxicity test Agric Food Chem 11 (1963) 486 - 491

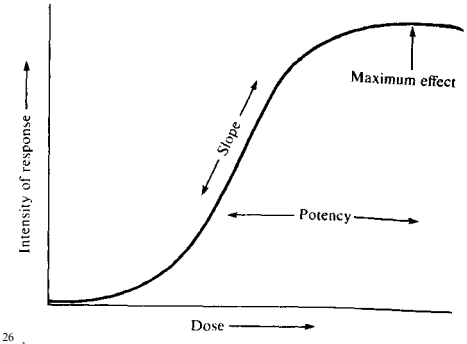
CARROL S. WEIL, Statistics vs Safety Factors and Scientific Judgment in the Evaluation of Safety for Man, Toxicology and Applied Pharmacology 21, 454-463 (1972)

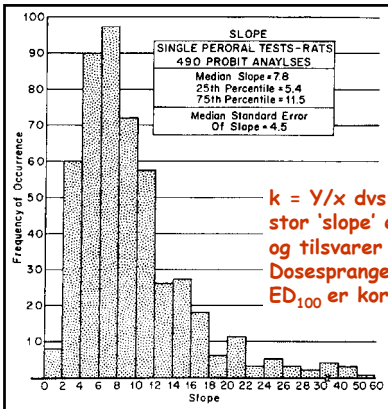
MICHAEL L. DOURSON AND JERRY F. STARA Regulatory History and Experimental Support of Uncertainty (Safety) Factors, Regulatory Toxicology and Pharmacology 3, 224-238 (1983)

Grunnbegreper - dose respons



Grunnbegreper - dose effekt





k = Y/x dvs at stor k eller stor 'slope' er en bratt kurve, og tilsvarer lav variasjon. Dosespranget fra ED_0 til ED_{100} er kort.

FIG. 1. Slopes calculated from 490 single po dose tests in rats.

Carrol S. Weil Statistics Vs Safety Factors and Scientific Judgment in the Evaluation of Safety for Man Toxicology And Applied Pharmacolocy 21, 454-463 (1972)

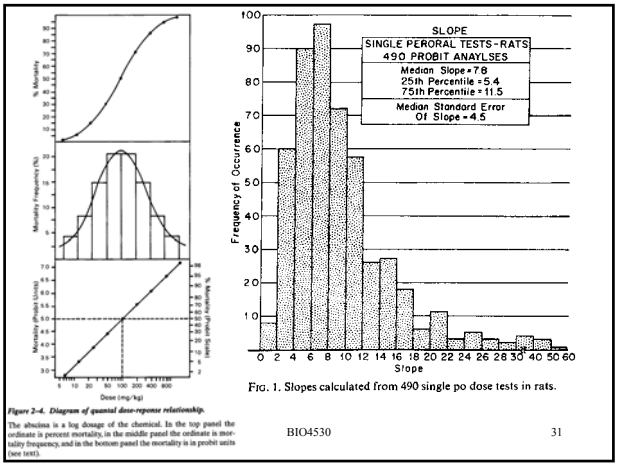
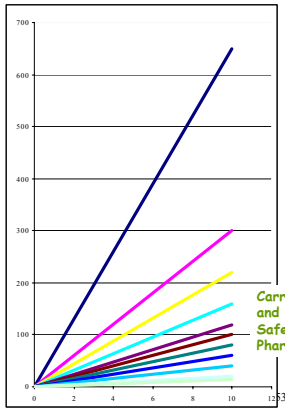


FIG. 1. Slopes calculated from 490 single po dose tests in rats.

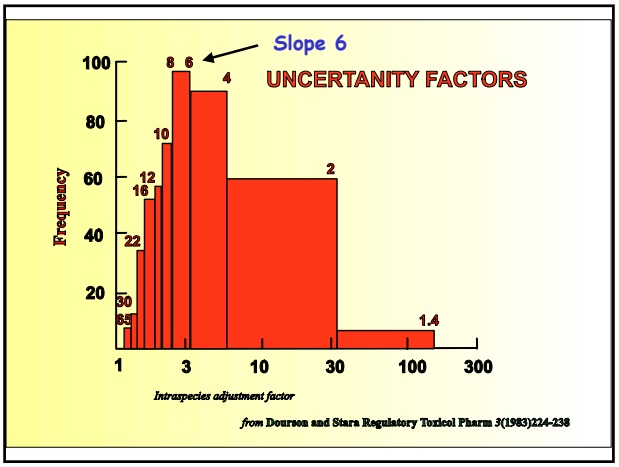
Figure 2–4. Diagram of quantal dose-reponse relationship.

The abscissa is a log dosage of the chemical. In the top panel the ordinate is percent mortality, in the middle panel the ordinate is mortality frequency, and in the bottom panel the mortality is in probit units (see text).

Vinkelkoeffisienter fra Weil sine data



Carrol S. Weil Statistics Vs Safety Factors and Scientific Judgment in the Evaluation of Safety for Man Toxicology And Applied Pharmacology 21, 454-463 (1972)



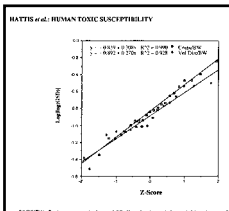


FIGURE 2. Log-normal plots of 23 C_{max}/body weight and 16 volume of distribution/body weight interindividual variability observations.

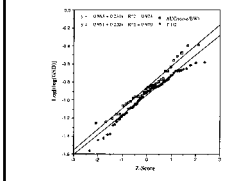
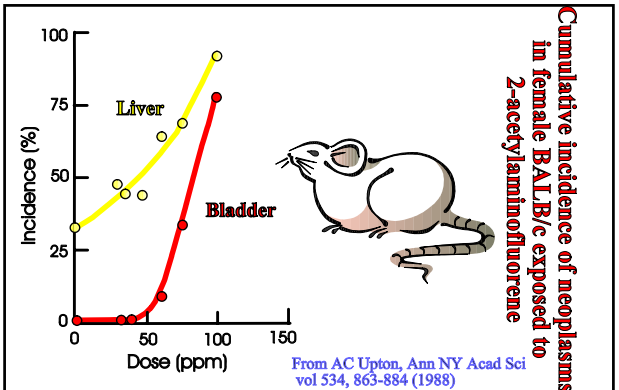


FIGURE 3. Log-normal plots of 34 AUC/body weight and 70 Tl/2 or clearance/body weight interindividual variability observations.

Alternativ metode til å samle data for bruk av UF?



Årsakssammenheng
Association and cause

Bradford Hill - are an association likely to be causal?

In the 1960s, Bradford Hill himself proposed a set of criteria which would allow epidemiologists to judge whether an association was likely to be causal
The fact that the association between cigarette smoking and lung cancer meets each of these criteria provides powerful evidence that indeed smoking causes cancer:

- The association is strong: the risk of a smoker dying of lung cancer is 25 times that of a non-smoker;
- The association is graded: the more you smoke, the greater the risk of cancer;

Årsakssammenheng
Association and cause

- The association stands independent of confounding variables, such as class, gender, race, occupation,
- The association is consistent: it has been observed in different types of study, in different study populations;
- The association is reversible: if you stop smoking, your risk of cancer declines;
- The association is plausible: cigarette smoke is known to contain substances that cause cancer (carcinogens).

Bradford-Hill A -"The Environment and Disease: Association or Causation?" Proc. Royal Soc. Med. 58:295 (1966)
Bradford-Hill, A. "The Environment and Disease: Association or Causation?" President's Address. Proc Royal Soc Med. 9:295-300 (1965)

Akseptabel risiko

EPA decided that it would base its regulatory decisions largely on quantitative risk assessment. The agency adopted a general policy that a lifetime cancer risk of one in 10,000 for the most exposed might constitute acceptable risk and that the margin of safety should reduce the risk for the greatest possible number of persons to an individual lifetime risk no higher than one in 1 million (10^{-6}).

from Science and judgment in risk assessment / Committee on Risk Assessment of Hazardous Air Pollutants, Board on EnvironmeStudies and Toxicology, Commission on Life Sciences, National Research Council, National Academy Press. Washington, D.C. 1994,

Akseptabel risiko

Acceptable risk acceptable when:
- it falls below an arbitrary defined probability
- it falls below some level that is already tolerated
- it falls below an arbitrary defined attributable fraction of total disease burden in the community
- the cost of reducing the risk would exceed the costs saved etc

In the UK, for example, the Health and Safety Executive (HSE) adopted the following levels of risk, in terms of the probability of dying in any one year:
- 1 in 1000 as the 'just about tolerable risk' for any substantial category of workers for any large part of a working life
- 1 in 10,000 as the 'maximum tolerable risk' for members of the public from any single non-nuclear plant.
- 1 in 100,000 as the 'maximum tolerable risk' for members of the public from any new nuclear power station.

from Acceptable risk Paul R. Hunter and Lorna Fewtrell © 2001 World Health Organization (WHO). Water Quality: Guidelmes, Standards and Health. Edited by Lorna Fewtrell and Jamie Bartram. Published by IWA Publishing, London, UK. ISBN: 1900222280

Akseptabel risiko

Examples of factors that lead to inequality of health risk in relation to water borne disease
- Age
- Pre-existing disease
- Genetic
- Gender/pregnancy
- Behavior
- Socio-economic
- Geography

from Science and judgment in risk assessment / Committee on Risk Assessment of Hazardous Air Pollutants, Board on EnvironmeStudies and Toxicology, Commission on Life Sciences, National Research Council, National Academy Press. Washington, D.C. 1994,

Historein lærer oss?

- Thalidomid ukjent effekt og manglende risikovurderingsmetoder i tilsynene. Har hatt stor betydning for senere tankegang
- Bophal - Lite kjent stoff blant toksikologene
- Chernobyl - kjent risiko, men overraskelser kom. I Norge betydning for risikohåndtering

Thalidomid utvikling og bruk

- Utviklet i Tyskland i 1950 årene, først syntetisert i 1953
- Viste ingen "effekter i dyreforsøk", men viste seg å være beroligende og ble derfor benyttet som sovemiddel og også mot kvalme hos gravide
- I dag sett som prototypen på teratogent stoff
- Første tilfelle av missdannelser rapportert på et vitenskapelig møte i 1959
- Sammenhengen mellom thalidomid og misdannelser ble påvist av Lenz i Tyskland og McBride i Australia i slutten av 1961
- Universitetsklinikk i Hamburg ingen Phocomelia påvist mellom 1940 og 1959; 1 tilfelle i 1959; 30 i 1960 og 154 i 1961.

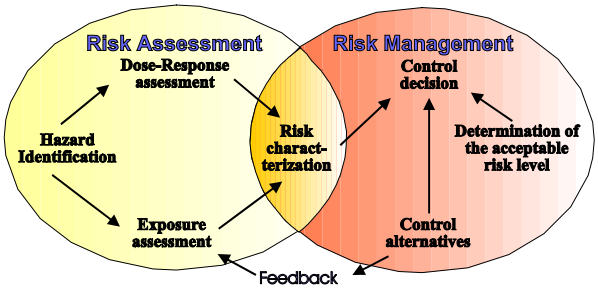
Fakta i thalidomid saken

- Thalidomid ble ikke testet for teratogene effekter i dyr før det ble brakt på markedet
- Det var utviklet test metoder for teratogen effekt på dyr. Men disse testene var utviklet på akademiske- og forskningsinstitutter og testene var lite kjent blant de som "regulerte" legemiddel-markedet

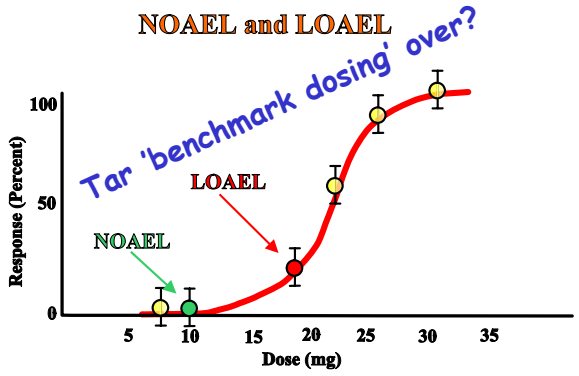
Reklame i bladet Motor april 2002

Risk Assessment and Risk Management

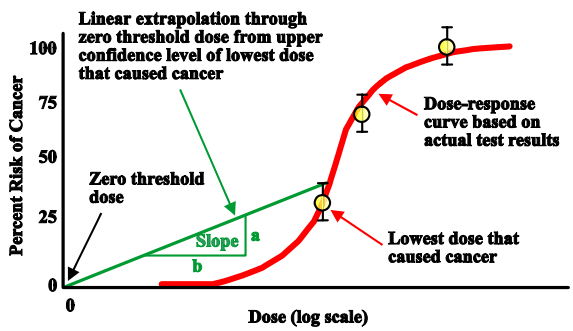
NAS, US 1983



NOAEL and LOAEL



Cancer Risk Assessment



Oppsummering

- Eg mener at risk assessment (risikovurdering) er det beste systemet, men systemet ikke ufeilbarlig, derfor vil eg være kritisk.
- Den beste måten å forbedre systemet er å fult ut forstå kritikken mot systemet.

Kursmål

1) Lære handverket risikovurdering (alle 3 + 1)
2) Kjenne til risikohåndterings metoder i Norge og internasjonalt
3) Kjenne svakhetene med systemene - vær kritisk
4) Erkjenne at data om et stoffs effekt er vårt viktigste grunnlag for risikovurdering (garbage in --> garbage out)