Risikovurdering: Karsinogenitet

kl 15.15 – 16.00 tirsdag 27 april

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CLASSIFICATION OF CARCINOGENS IN EU

- **Category 1.** ***Substances known to be carcinogenic to man.*** ***There is sufficient evidence to establish a causal association between human exposure to a substance and the development of cancer.***
- **Category 2.** ***Substances which should be regarded as if they were carcinogenic to man.*** ***There is sufficient evidence to provide a strong presumption that human exposure to a substance may result in the development of cancer, generally on the basis of: - Appropriate long-term animal studies, - other relevant information***

CLASSIFICATION OF CARCINOGENS IN EU'cont

- **Category 3.** ***Substances which cause concern for man owing to possible carcinogenic effect,*** ***but in respect of which the available information is not adequate for making a satisfactory assessment. There is some evidence from appropriate animal studies, but this is insufficient to place the substance in Category 2.***

CLASSIFICATION OF CARCINOGENS IN EU'cont

- Category 3 actually comprises 2 sub-categories:
- (a) substances which are well investigated but for which the evidence of a tumour-inducing effect is insufficient for classification in Category 2. Additional experiments would not be expected to yield further relevant information with respect to classification;

  (b) substances which are insufficiently investigated. The available date are inadequate, but they raise concern for man. This classification is provisional; further experiments are necessary before a final decision can be made.

CLASSIFICATION OF CARCINOGENS IN EU'cont

- -Categories 1 and 2:

  T; R45 **May cause cancer**

  However for substances and preparations which present a carcinogenic risk only when inhaled, for example, as dust, vapour or fumes, (other routes of exposure e.g. by swallowing or in contact with skin do not present any carcinogenic risk), the following symbol and specific risk phrase should be used:

  T; R49 **May cause cancer by inhalation**

-Category 3:

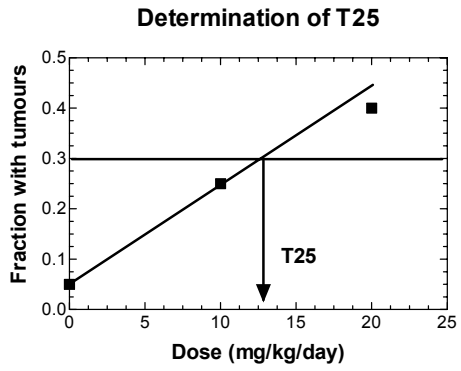
Xn; R40 **Limited evidence of a carcinogenic effect**

CLASSIFICATION OF CARCINOGENS IN EU'cont

- Commission Working Group on the Classification and Labelling of Dangerous Substances
- Commission Group of Specialised Experts in the field of Carcinogenicity, Mutagenicity and Reprotoxicity
- Adoption

WHY POTENCY GRADING?

- The amount of a carcinogen needed to induce tumours varies by a factor of more than 10^8.
- The EU criteria for classification are based on the strength of scientific evidence that the substance causes cancer. No specific considerations are given to the carcinogenic potency of the substance.



Dybing et al, Pharmacol Toxicol 80: 272, 1997

POTENCY GRADING

- **Carcinogens of high potency:** T25 value < 1 mg/kg bw/day
- **Carcinogens of medium potency:** 1 mg/kg bw/day < T25 value < 100 mg/kg bw/day
- **Carcinogens of low potency:** T25 value > 100 mg/kg bw/day.

http://europa.eu.int/comm/environment/dansub/potency.pdf

ELEMENTS THAT MAY MODIFY THE PRELIMINARY POTENCY EVALUATION

- **Dose-response relationships**
- **Site/species/strain/gender activity**
- **Mechanisms including genotoxicity**
- **Mechanistic relevance to humans**
- **Toxicokinetics**
- **Other elements relevant to potency evaluation**

Table 3: Proposed scheme for subdividing carcinogens in three potency classes

EU CATEGORY POTENCY GROUP	1	2	3
CARCINOGENS OF HIGH POTENCY	(7)[a] 0.01%	(7)[a] 0.01%	0.1%
CARCINOGENS OF MEDIUM POTENCY	0.1%	0.1%	1.0%
CARCINOGENS OF LOW POTENCY	-[b]	1.0%	1-5%[c]

Risk Assessment in EU

- Technical Meetings on Existing Chemicals
  Risk Assessment Reports
- Scientific Committee on Toxicity, Ecotoxicity and the Environment

RISK ASSESSMENT

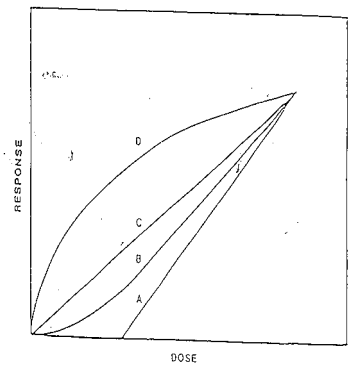
- Workers
- Consumers
- Man via the environment

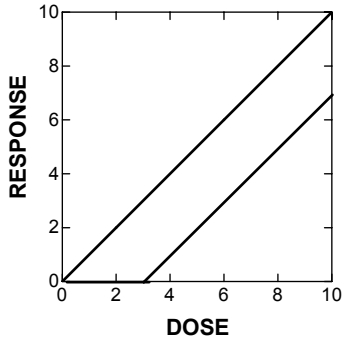
The risk characterisation ends often with one of the following conclusion

i. There is need for further information and/or testing.

ii. *There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied already.*

iii. *There is a need for limiting the risk; risk reduction measures which are already being applied shall be taken into account.*





RISK CHARACTERIZATION

- Threshold effects
  - Margin Of Safety (MOS)
  - MOS = N(L)OAEL/Estimated exposure
- Non-Threshold effects
  - Lifetime cancer risk

LIFETIME CANCER RISK

LIFETIME CANCER RISK =

$$\frac{\text{Number of death per year} \times \text{Living age}}{\text{Number exposed}}$$

NUMBER OF DEATH PER YEAR =

$$\frac{\text{Lifetime cancer risk} \times \text{Number exposed}}{\text{Living age}}$$

TOLERABLE RISK

negligible risk or acceptable risk taking into account sosio-economic benefits

- MOS = 10, 100, 1000
  Uncertainty, intra- and interspecies variation, nature and severity of effect
- LIFETIME CANCER RISK = 10^{-3}, 10^{-4}, 10^{-5}, 10^{-6}
  10^{-3}; Industry, 100.000 workers, 1-2 deaths/y; Total: 300 deaths/y
  10^{-5}; Country, 10 millions, 1-2 deaths/y; Total: 30.000 deaths/y

METHODS FOR QUANTITATIVE CANCER RISK CHARACTERISATION

- Linearised Multistage (LMS)
- LED10
- T25
- Weibull
- Mantel-Bryan
- Log-Normal

QUANTITATIVE RISK ASSESSMENT

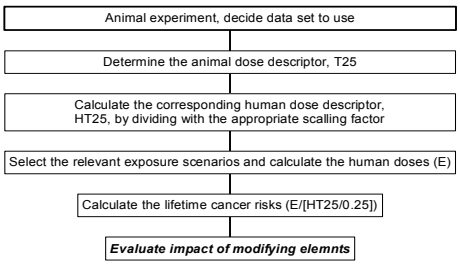
- Determine an animal dose descriptor
- Calculate human dose descriptor
- Determine risk by linear extrapolation

DOSE DESCRIPTORS

- TD50
- LED10
- TD0.05
- T25

http://europa.eu.int/comm/environment/dansub/potency.pdf

RISK CHARACTERISATION USING THE T25 METHOD



Sanner et al, Pharmacol Toxicol 88: 331, 2001

Modifying elements

- *Data-sets available*
- *Epidemiological studies*
- *Dose-response relationships*
- *Site/species/strain/gender activity*
- *Mechanistic relevance to humans*
- *Toxicokinetics*

$HT25 = T25/(w_h/w_a)^{0.25}$

Experimental animal	Sex	Weight (g)	$W^{0.25}$-values Assuming human body weigth 70 kg
Mouse	Male	30	7.0
	Female	25	7.3
Rat	Male	500	3.4
	Female	350	3.8
Hamster	Male	125	4.9
	Female	110	5.0

Determination of T25 and HT25 for benzo(a)pyrene

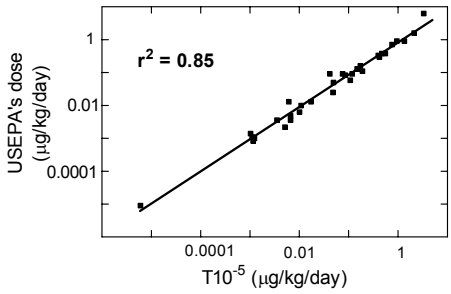
Oral administration

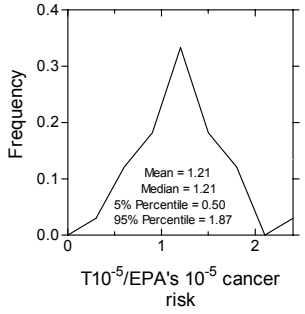
- ***Sprague Dawley rats***, forestomach tumours (Brune et al, 1981)
  T25 = 0.38 mg/kg/day (HT = 0.11 mg/kg/d)
- ***Wistar rats***, forestomach papilloma or carcinoma in male rats (Krose et al, 2001)
  T25 = 2.15 mg/kg/day (HT25 = 0.63 mg/kg/d
- ***B6C3F1 mice***, forestomach papilloma or carcinoma in female mice (Culp et al, 1998)
  T25 = 0.65 mg/kg/day (HT25 = 0.09 mg/kg/d)

Inhalation

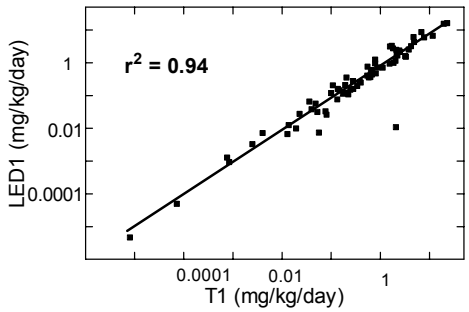
- ***Hamsters,*** respiratory tract male hamsters (Thyssen et al, 1981)
  T25 = 1.09 mg/kg/day HT25 = 0.22 mg/kg/d)

COMPARATION OF THE LMS AND T25 METHODS





COMPARATION OF THE LED10 AND T25 METHODS



RATIO BETWEEN T1 AND LED1

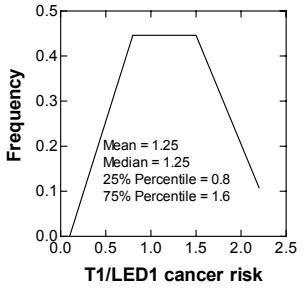
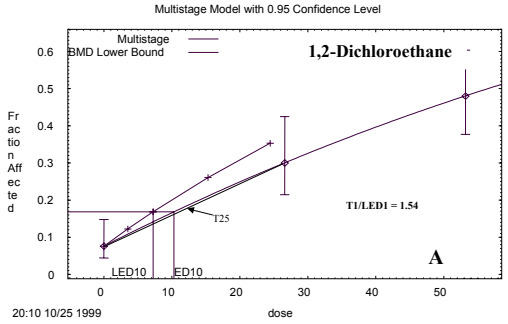
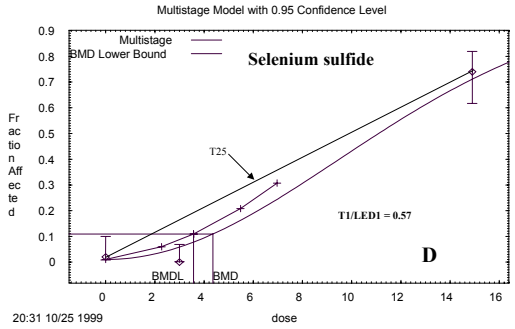
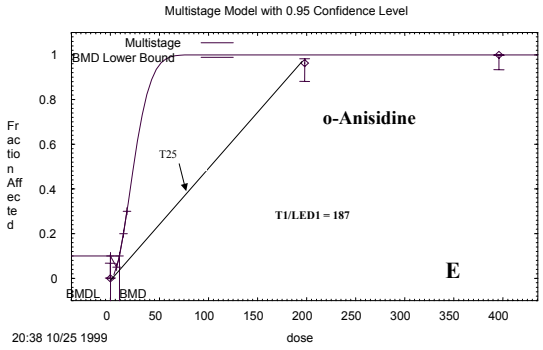


Fig. 6.

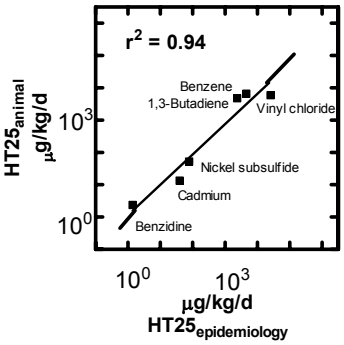






USEPA SUBSTANCES CLASSIFIED AS HUMAN OR LIKELY HUMAN CARCINOGENS (IRIS)

IRIS risk estimation based on		Animal data not suited for risk estimation
Epidemiology (animal data available)	Animal data	
Benzene	Acrylamide	Arcenic
Benzidine	Bis(chloromethyl)ether	Asbestos
1,3-Budadiene	Bromate	Beryllium
Cadmium	Chlordane	Chloromethylmethylether
Nickel subsulfide	Chloroform	Chromium
Vinyl chloride	Dichloroacetic acid	Coke oven emmision
	1,3-Dichloropropene	Creosote
	Formaldehyde	Diesel engine exhaust
	Quinoline	Nickel refinery dust



CONCLUSIONS

- The T25-method is fast and easy
- The T25-method is transparent
- The results with the T25-method, the LMS- method and the LED10 do all give very similar results
- Good correlation with epidemiological methods