Risikoevaluering med dataprogrammer - BMDS, ToxTools

BIO4530 Regulatorisk toksikologi

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I. Course Introduction

Course Objective

After completing this course you should:

1. Understand Benchmark Dose methods and terminology used by EPA;
2. Understand the purpose and capabilities of EPA's Benchmark Dose Software (BMDS);
3. Be able to use BMDS to perform Benchmark Software (BMDS) dose assessments of dichotomous, nested dichotomous and continuous data.

B. History

1. 1995 - EPA initiated the development of BMDS
2. 1999 - Public Review of Version 1.1b
3. 1999 - Quality Assurance Testing of Version 1.2
4. 2000 - Public Release of Version 1.2
5. 2000 - Development of Draft Benchmark Dose Technical Guidance Document
6. 2001 - Release of Version 1.3
7. 2002 - Release of Version 1.3.1

C. What's Coming?

1. 2002 - Final BMD Technical Guidance Document
2. 2003 - Categorical Regression Model
3. 2004 - Neurotoxicity Models
4. 2004 - Improved Continuous Models (e.g., Hybrid Option)
5. 2005 - Time-to-Tumor Cancer Model
6. 2006 - Tools for the Analysis of Human Data

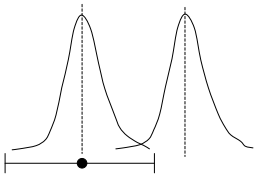
http://www.epa.gov/NCEA/bmds_training/introduction/introo.htm

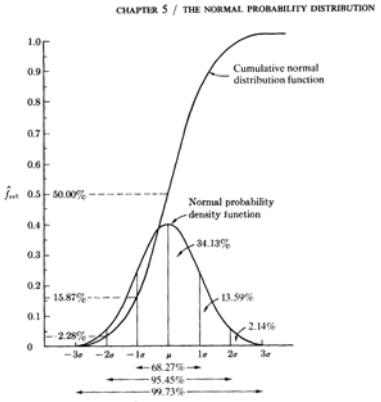
Benchmark Dose
Benchmark Dose lower confidence limits

BMD
BMDLs

BMD og BMC
BMDS

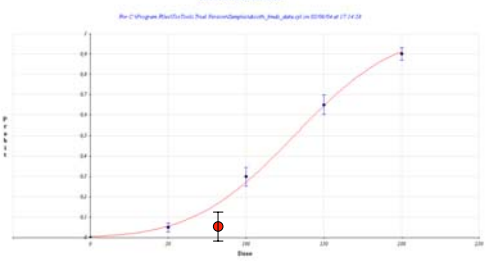
dose og concentration
BMD software





POD - Point of departure
Extrapolation from POD to low health relevant exposure levels

BMD vs NOAEL/LOAEL



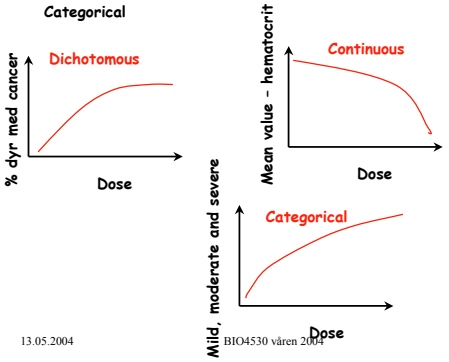
Benchmark Dose erstatter NOAEL/LOAEL for terskel toksikologi

Cancer: EPA vil også bruke BMD for kreftevaluering i fremtiden

BMD har vært benyttet istedenfor NOAEL/LOAEL
EPA – However, it is likely that there will continue to be endpoints that are not amenable to modeling and for which a NOAEL/LOAEL approach must be used there

All studies that show a graded Monotonic response with dose likely to will be useful for BMD analysis, and the minimum data set for calculating a BMD should at least show a significant dose-related trend in the selected-endpoint

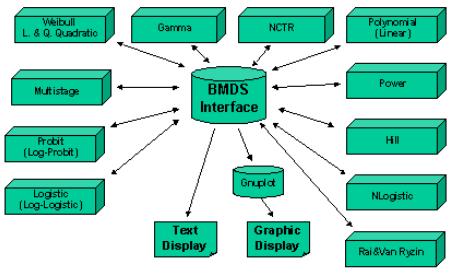
Three types of Endpoint data:
Dichotomous
Continuous
Categorical



Are the data appropriate for BMD analysis?

a) There must be at least a statistically or biologically significant dose-related trend in the selected endpoint
b) Not the same response in all non-control doses. The BMD may be just below the first dose , or orders of magnitude lower. Limitation with Weibull when maximum response is less than 100%. And goodness of fit provides no help in selecting among the possibilities.
c) Quantal data (dichotomous). Selection of BMR. An excess risk of 10% is the default BMR since the 10% response is at or near the limit of sensitivity in most cancer bioassay and in some non-cancer bioassays as well. With greater sensitivity lower BMR. Reproductive and development studies 5%, Epidemiology 1%,
d) Continuous data ….equal to a change in the mean response equal to one control standard deviation from the control mean should also be presented for comparison purposes

Overview - Program Structure



http://www.epa.gov/NCEA/bmds_training/software/overp.htm

Excess risk

'additional risk'
r(d) = P(d) – P(0)

'multiplicative risk'
r(d) = (P(d) – P(0))/ 1 – P(0)

BMD Computation

The BMD is computed as a function of the parameters of the model, which must heve already been estimated. The BMDs for dichotomous models are expressed as the dose that would give an (estimated) increase in incidence of x% above the control incidence (where *x* is usually in the range of 1 to 10; just what value to use is a policy decision, and should be based on the Benchmark Dose Guidance). This increase in incidence is referred to here as ``BMR'', for benchmark response. Note that, although we use the word ``response'' here, we are really talking about an increase of the incidence over the control incidence.

Two formulations for computing the excess over background are in common use, the extra risk model and the additional risk model. In the extra risk model,

$$BMR = \frac{p(BMD;\gamma,\alpha,\beta,\ldots) - p(0;\gamma,\alpha,\beta,\ldots)}{1 - p(0;\gamma,\alpha,\beta,\ldots)},$$

while in the additional risk model,

$$BMR = p(BMD;\gamma,\alpha,\beta,\ldots) - p(0;\gamma,\alpha,\beta,\ldots).$$

The equation appropriate to the risk type formulation that the user requests is solved to get the BMD for a specific model and data set. Details of this computation are included in the descriptions of the individual models.

Quantal Quadratic Model
The form of the probability function is:
P[response] = background + (1-background)*[1-EXP(-slope*dose^2)]

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-178.191			
Fitted model	-182.868	9.3412	4	0.05283
Reduced model	-332.032	307.682	4	<.0001

AIC: 367.736

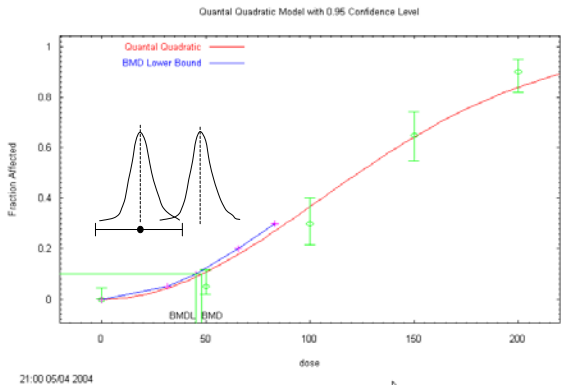
Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	100	0
50.0000	0.1080	10.796	5	100	-1.868
100.0000	0.3668	36.680	30	100	-1.386
150.0000	0.6423	64.235	65	100	0.1596
200.0000	0.8393	83.925	90	100	1.654

Chi-square = 8.17 DF = 4 P-value = 0.0855

Benchmark Dose Computation

Specified effect = 0.1
Risk Type = Added risk
Confidence level = 0.95
BMD = 48.0167
BMDL = 45.0612



Gamma multihit

The form of the probability function is:

P[response]= background+(1-background)*CumGamma[slope*dose,power],

where CumGamma(.) is the cummulative Gamma distribution function

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-178.191			
Fitted model	-178.803	1.22478	3	0.7471
Reduced model	-332.032	307.682	4	<.0001

AIC: 361.607

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	100	0
50.0000	0.0379	3.793	5	100	0.6318
100.0000	0.3208	32.083	30	100	-0.4463
150.0000	0.6711	67.109	65	100	-0.4488
200.0000	0.8784	87.843	90	100	0.6599

Chi-square = 1.24 DF = 3 P-value = 0.7446

Benchmark Dose Computation

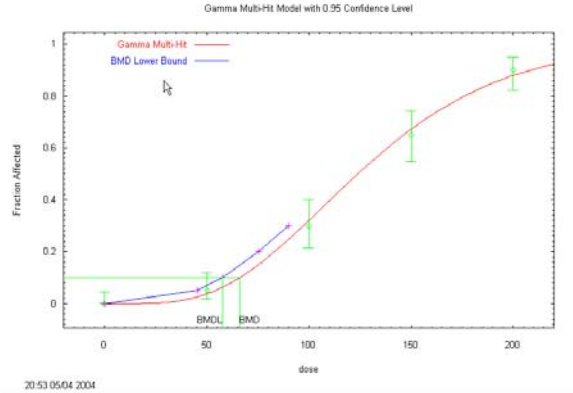
Specified effect = 0.1

Risk Type = Added risk

Confidence level = 0.95

BMD = 66.0372

BMDL = 57.6299



Quantal Linear Model

The form of the probability function is:

P[response] = background + (1-background)*[1-EXP(-slope*dose)]

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-178.191			
Fitted model	-210.797	65.212	4	2.3216817e-013
Reduced model	-332.032	307.682	4	<.0001

AIC: 423.594

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	100	0
50.0000	0.2577	25.768	5	100	-4.749
100.0000	0.4490	44.896	30	100	-2.995
150.0000	0.5910	59.095	65	100	1.201
200.0000	0.6964	69.636	90	100	4.429

Chi-square = 52.57 DF = 4 P-value = 0.0000

Benchmark Dose Computation

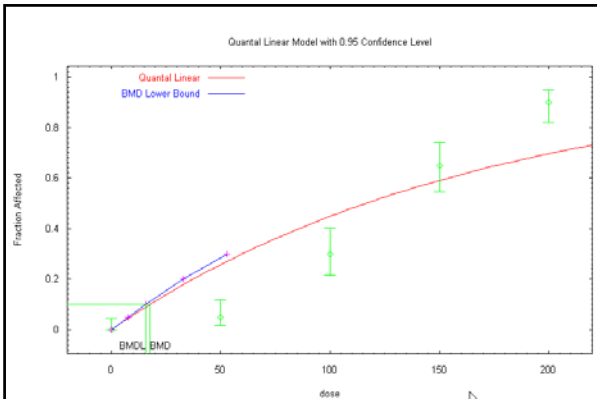
Specified effect = 0.1

Risk Type = Added risk

Confidence level = 0.95

BMD = 17.6795

BMDL = 15.6453



Weibull Model

The form of the probability function is:

P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-178.191			
Fitted model	-178.2	0.0178304	3	0.9994
Reduced model	-332.032	307.682	4	<.0001

AIC: 360.4

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	100	0
50.0000	0.0519	5.194	5	100	-0.08722
100.0000	0.2957	29.570	30	100	0.09426
150.0000	0.6517	65.168	65	100	-0.03532
200.0000	0.9002	90.015	90	100	-0.005098

Chi-square = 0.02 DF = 3 P-value = 0.9994

Benchmark Dose Computation

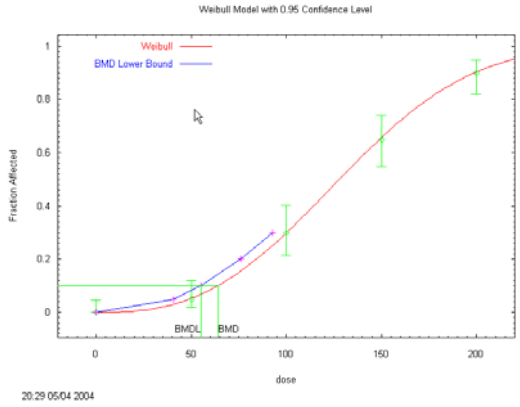
Specified effect = 0.1

Risk Type = Added risk

Confidence level = 0.95

BMD = 64.2417

BMDL = 55.2141



Basic Information

Data File	C:\Programfiler\ToxTools Trial Version\Samples\Devtox.cyl
Model(s)	*Death* *Weight* *Malformation*
Dose Variable	*Dose*
Dose Transformation	*<None>*
Cluster Variable	*ID*
Repeat Variable	*<None>*
Correlation Type	*Exchangeable*

Summary Information

Dose	Liters	No. Individuals	Percent Dead	No. Live	Percent Malformed	Fetal Weight Mean	Fetal Weight Std Dev
0	28	398	4.77%	379	1.32%	3.4031	0.3789
0.5	28	382	6.54%	357	6.08%	3.3028	0.3714
1	29	369	6.50%	345	24.93%	2.9038	0.3629
2	27	363	20.94%	287	68.64%	2.4754	0.4568

Fetal Death Model (Based on 1512 individuals in 112 clusters)

Model

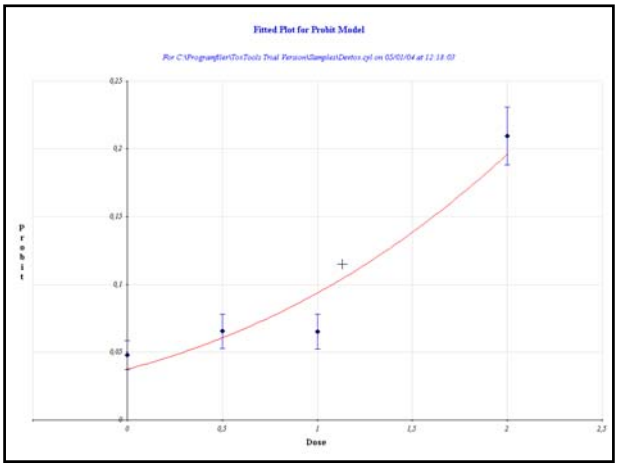
P(Death = 1) ~F(Predictor)
Predictor = %Intercept + Dose
F(x) = Φ(x)

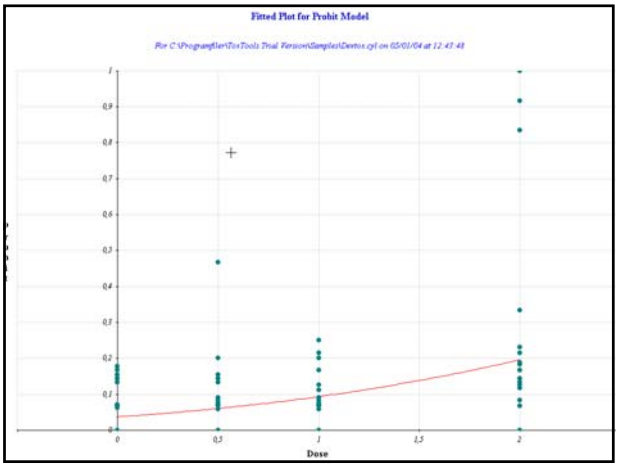
Parameter Estimates

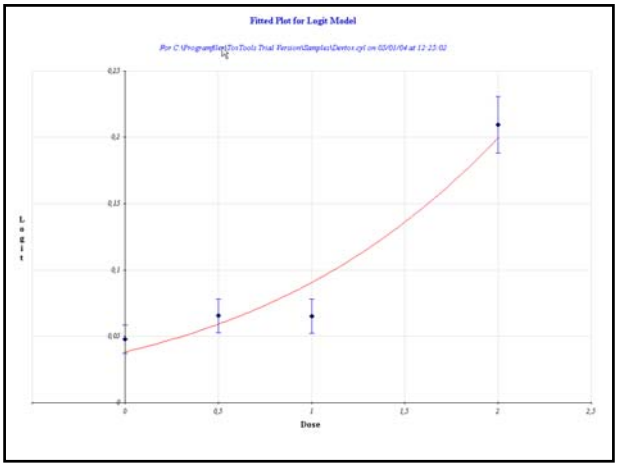
Parameter	Estimate	Std Err	z value	p-value
%Intercept	-1.7811	0.1186	-15.0189	< 0.0001
Dose	0.4625	0.1240	3.7290	0.0002
Loglikelihood	-446.5057			
Working Correlation	0.1360			
Scale Estimate	1.0354			

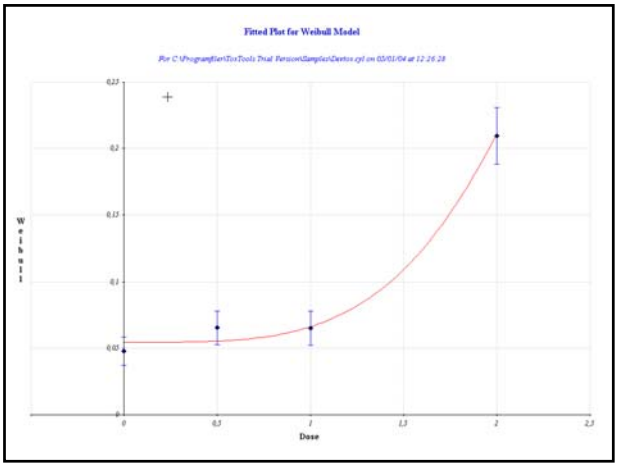
Covariance Matrix

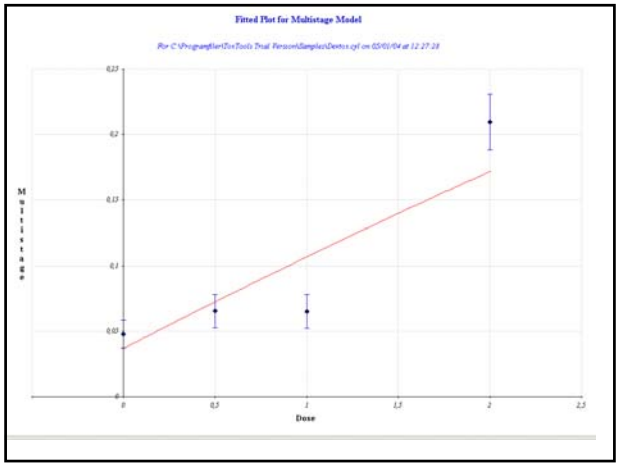
Parameter	%Intercept	Dose
%Intercept	0.0141	-0.0117
Dose	-0.0117	0.0154










Fitted Plot for Multistage Model
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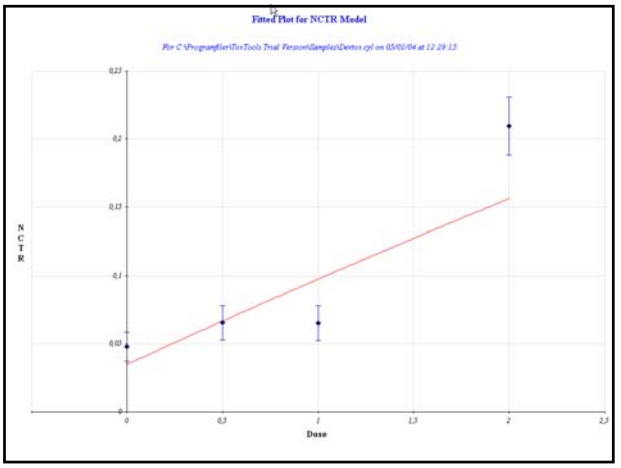
Multistage
Dose


Fitted Plot for NCTR Model
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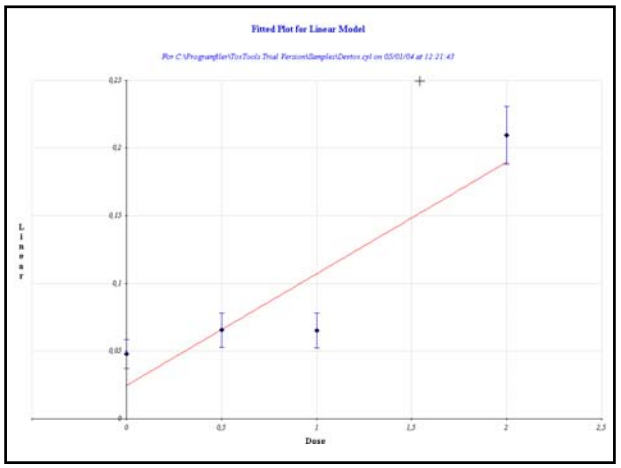
NCTR
Dose


Fitted Plot for Linear Model
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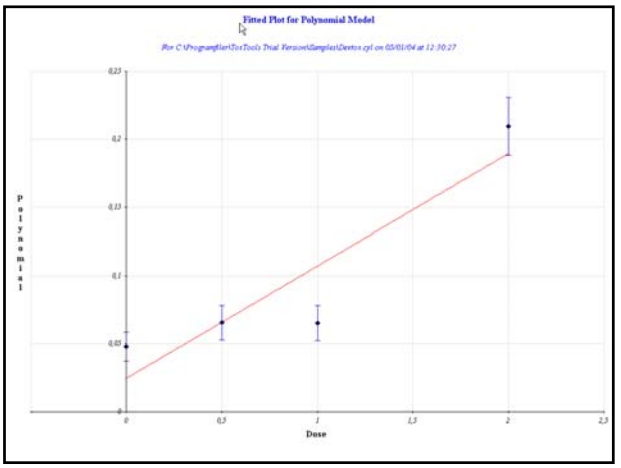
Linear
Dose


Fitted Plot for Polynomial Model
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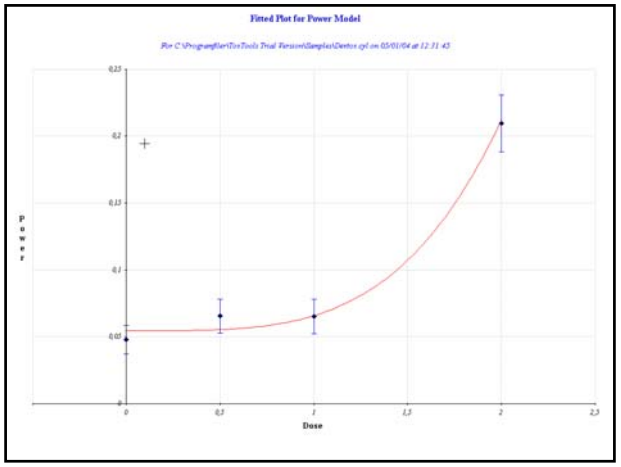
Polynomial
Dose


Fitted Plot for Power Model
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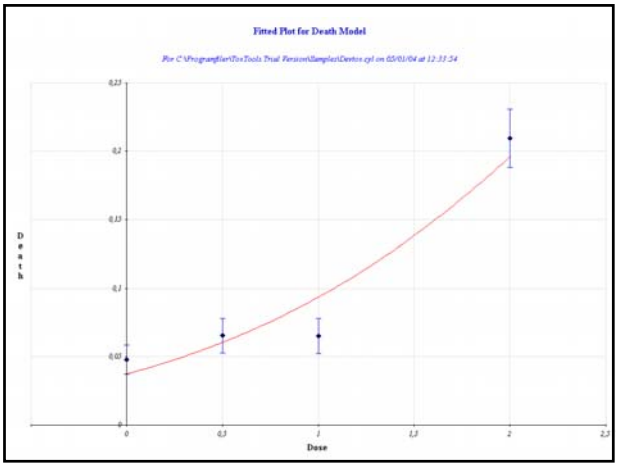
Power
Dose


Fitted Plot for Death Model
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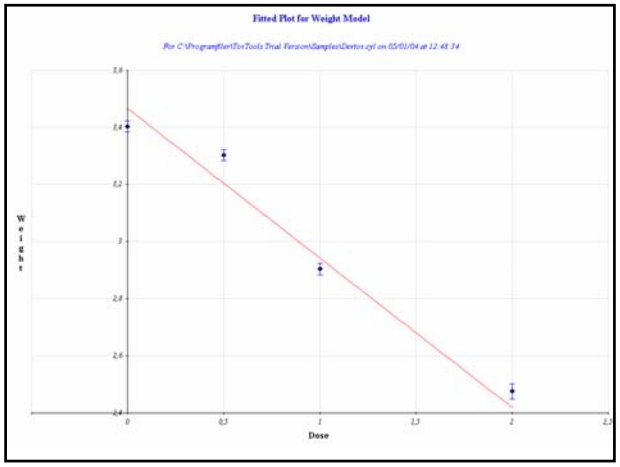
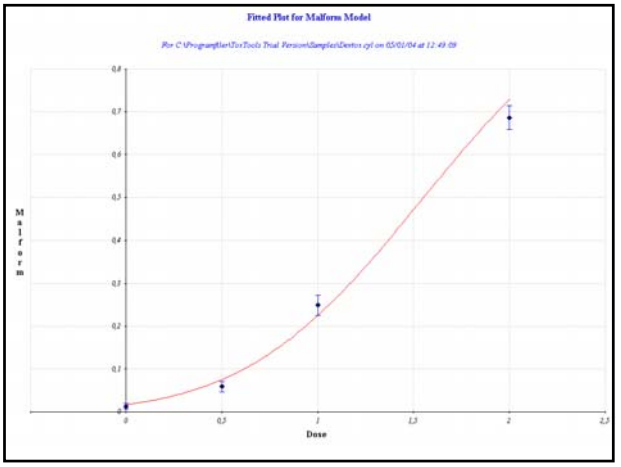
Death
Dose





Basic Information

Data File	C:\Program Files\ToxTools Trial Version\Samples\Oral.cyl
Model Run	Probit
Dose Variable	Dose
Dose Transformation	<None>
Cluster Variable	<None>
Repeat Variable	<None>
Correlation Type	Independent

Summary Information

Dose	No. Individuals	Percent Response
0	28	14.29%
1	29	13.79%
10	29	20.69%
100	32	25.00%

Probit Model (Based on 118 individuals)

Model

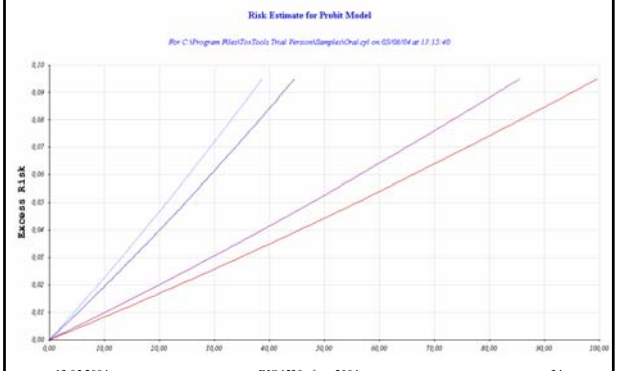
$P(Resp. = 1) = F(Predictor)$

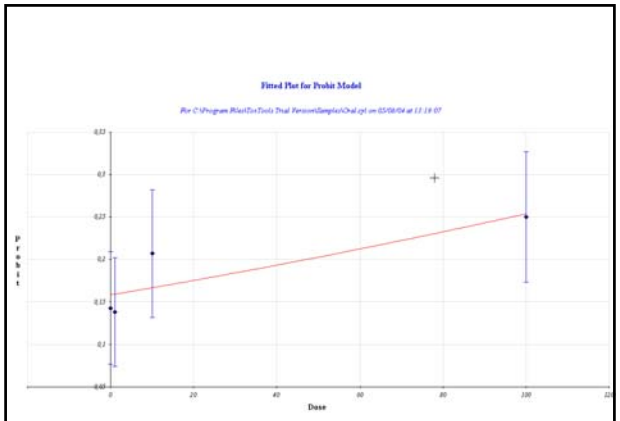
$Predictor = \%Intercept + Dose$

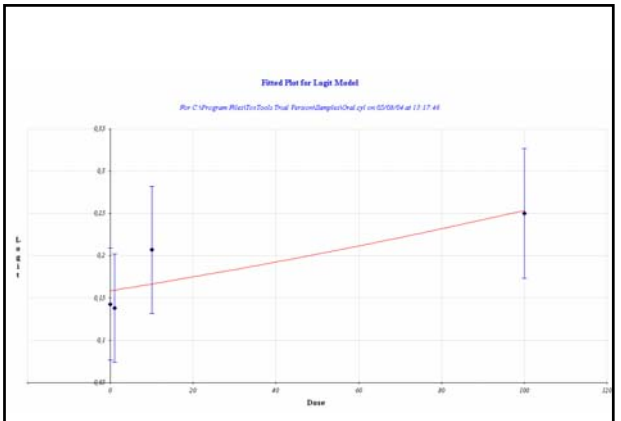
$F(x) = \Phi(x)$

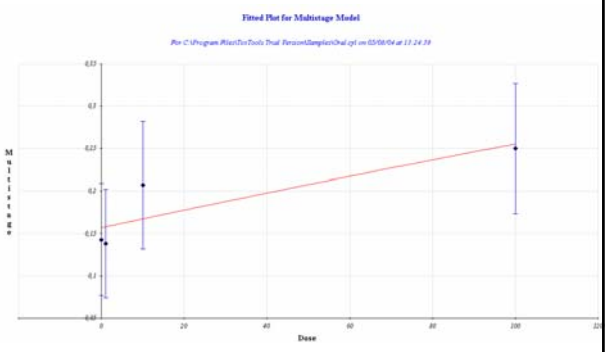
Parameter Estimates

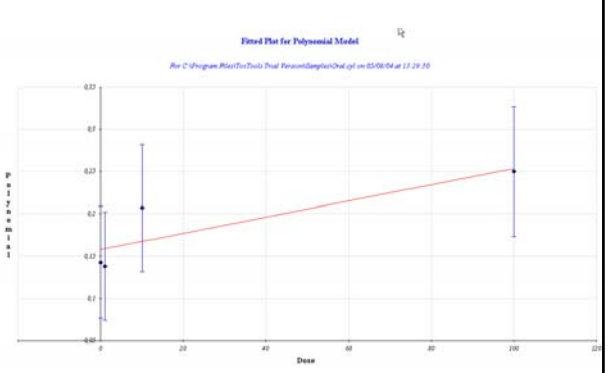
Parameter	Estimate	Std Err	z-value	p-value
%Intercept	-1.0013	0.1686	-5.9422	< 0.0001
Dose	0.0034	0.0030	1.1276	0.2595
Loglikelihood	-56.1343			

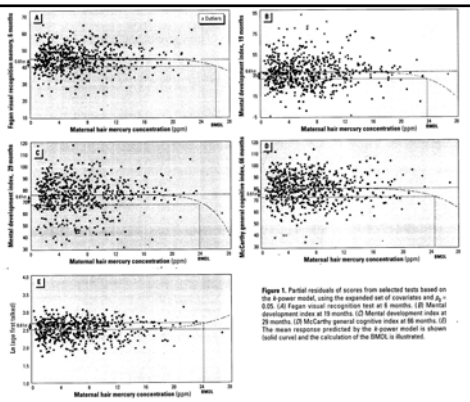












Environmental Health Perspectives • Volum

Benchmark Comparisons for Methylmercury Obtained from the Seychelles Child Development Study,K. S. Crump *et al.* Environment Health Perspectives, 108 (2000) 257-263

Children's Health • Crump et al

Table 3. Values of BMRC corresponding to certain values for p_2 and BMR.

p_2	BMR	BMRC
0.01	0.05	0.77
0.01	0.1	1.1
0.05	0.05	0.38
0.05	0.1	0.61

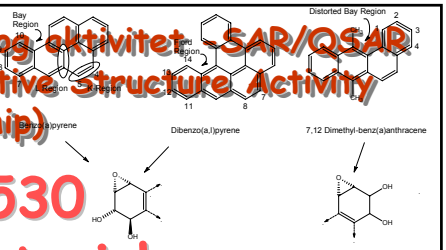
Table 4. Summary of BMDLs (parts per million mercury in maternal hair) by BMD analysis method.

Type of data	Definition of abnormal	Covariates	Model	No.	Average	Range
Continuous	χ^2	None	Weibu	12	26.8	25.3–29.0
			Logistic	12	26.7	25.3–29.1
			4-Power	12	26.1	24.7–27.8
	p^b	None	Weibull	12	25.0	23.1–27.2
			Log stic	12	25.0	23.0–27.3
			4-Power	12	24.4	20.0–26.1
		Reduced	Weibull	12	25.4	23.5–30.1
			Logistic	12	25.4	23.3–30.3
			4-Power	12	24.5	19.4–26.8
		Expanded	Weibul	12	24.8	23.4–27.2
			Logistic	12	25.7	23.2–27.7
			4-Power	12	24.3	23.2–26.3
Quantal		None	Weibu	12	21.6	15.8–23.7

[a]Abnormal defined as a response > 2 SDs in adverse direction from mean response of entire cohort. [b]Abnormal defined so that 5% of the responses are abnormal (p_0 = 0.05).

Benchmark Comparisons for Methylmercury Obtained from the Seychelles Child Development Study,K. S. Crump *et al.* Environment Health Perspectives, 108 (2000) 257-263

Struktur og aktivitet – SAR/QSAR (Quantitative Structure Activity Relationship)



BIO4530 Regulatorisk Toksikologi

Steinar Øvrebø

Hvorfor teste med QSAR/SAR?

- Prisen for å teste et stoff i et karsinogenisitets bioassay med gnager er 7 – 14 millioner NOK og det tar fra 3 til 5 år

- Prisen for å komme fram til første trinn i markedsføringen av legemidler svært høy. Og syntese og aktivitets testing av mulige legemidler er svært kostbart

- QSAR som en metode isteden for dyreforsøk, er også ønskelig fra et dyreetisk perspektiv

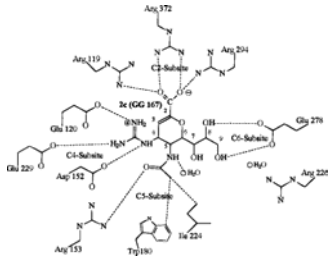
Quantitative Structure Activity Relationship (QSAR)

- Metode til å forutsi toksisiteten til et stoff
- Metode til å anslå farmakologiske egenskaper av et stoff
- Adsorption, distribution, metabolism and elimination (ADME)

SAR og QSAR

- Structure activity relationaship er basert på at strukturen til en forbindelse er related (henger sammen med - står i forhold til) forbindelsen sin struktur
- SAR har vært benyttet i farmasøytisk industri for forutsi reseptor binding
- Eksempel influensamedisin, Relenza
- QSAR - basert på LD_{50} fra over 2000 stoffer kunne forutsi LD_{50} innenfor en faktor på 8 den 'virkelige' for 95% av forbindelsene

Depiction of interaction of Relenza (GG 167) in the neuraminidase binding site



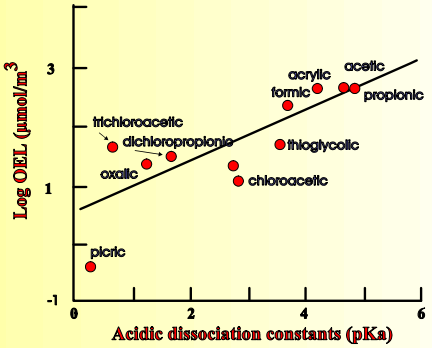
Når er det aktuelt å benytte QSAR

- QSAR brukes til forutsi toksisiteten når det ikke finnes eksperimentelle- eller observasjonsdata om stoffets toksisitet
- Spesielt aktuelt når det er behov for vurdering etter en ulykke
- Også ved vurdering av toksistiteten når eksponeringen er svært lav

Faktorer med betydning for biologisk aktivitet

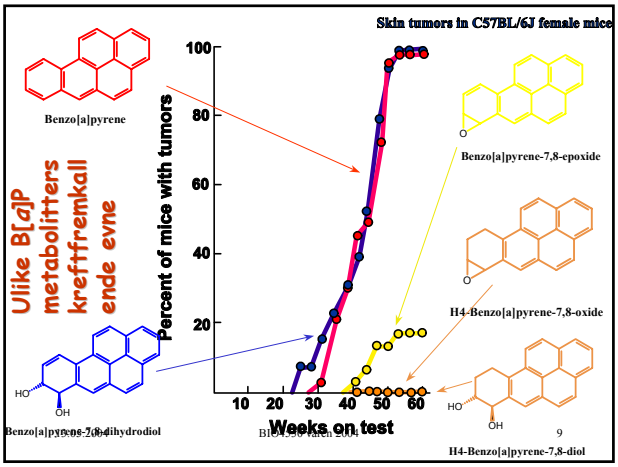
- Struktur
- Løselighet
- Stabilitet
- pH følsomhet
- Elektrofilisitet
- Flyktighet
- Kjemisk reaktivitet

Correlation of occupational exposure limits with equilibrium dissociation constants of organic acids



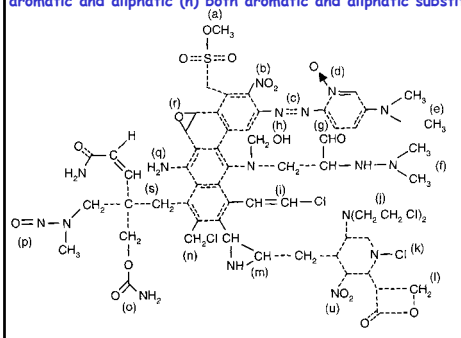
from Paustenbach in Patty´s Industrial Hygiene and Toxicology, Third Edition, Volume 3, Part A

Ulike B[a]P metabolitters kreftfremkall ende evne



(a) alkyl esters (b) aromatic nitro (c) aromatic azo groups (d) aromatic ring *N*-oxides (e) aromatic mono- and dialkylamino (i) alkyl hydrazines (g)alkyl aldehydes, (h) N-methylol derivatives (i) monohaloalkenes (j) a large family of N and S mustards (k) N-chloramines (l) propiolactones and propiosultones (m) aromatic and aliphatic (n) both aromatic and aliphatic substituted

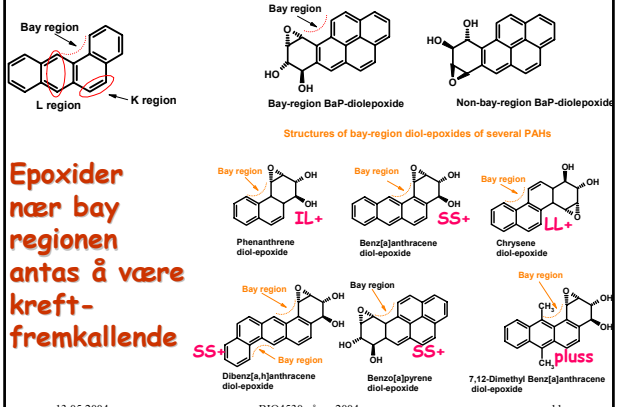
Mutagenicity



(t)
Halogenated methanes $C(X)_4$
X=H, F, Cl, Br, I
in any combination

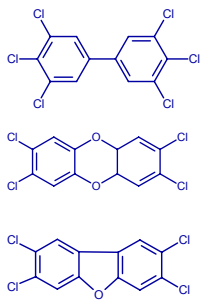
Potential structural alerts for mutagenicity.

Bay, I and K region of PAH compounds



Epoxider nær bay regionen antas å være kreft-fremkallende

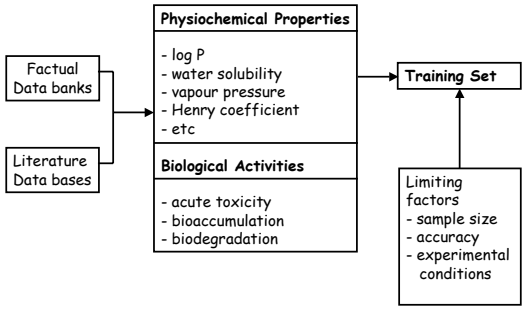
TEF - Toxicological Equivalence Factor

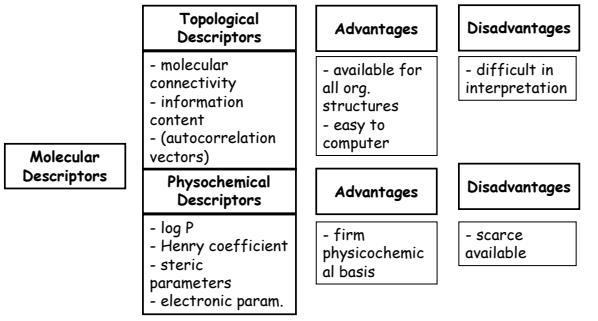


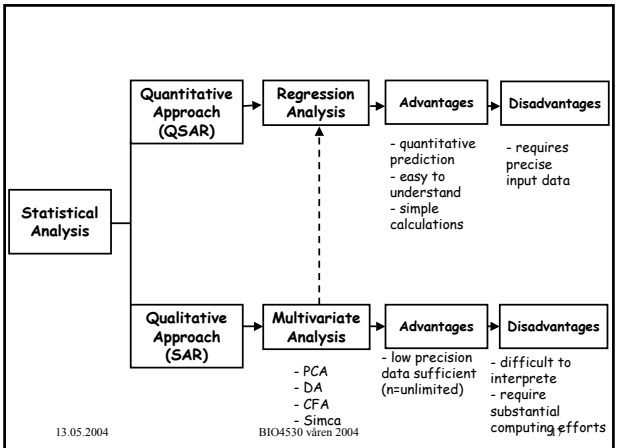
TEF for PAH

PAH-forbindelse	Nisbet og LaGoy, 1992	Thorslund og Farrer, 1991	US EPA (1984)[1]	Larsen og Larsen, 1998	OEHHA, 1994
Naftalen	0,001	ND	0		
Acenaftylen	0,001	ND	0		
Acenaften	0,001	ND	0		
Fluoren	0,001	ND	0		
Fenantren	0,001	ND	0	0,0005	
Antracen	0,01	ND	0	0,0005	
Fluoranten	0,001	ND	0	0,05	
Pyren	0,001	ND	0	0,001	
Benz[c]fenantren				0,023	
Benzo[a]antracen	0,1	0,145	1	0,005	0,1
Krysen	0,01	0,0044	1	0,03	0,01
Benzo[a]pyren	1	1	1	1	1
Benzo[e]pyren				0,002	
Dibenzo[a,h]antrazen	1	1,11	1	1,1	
Antantren				0,3	
Benzo[ghi]perylen	0,01	0,021	1	0,02	
Benzo[b]fluoranten	0,1	0,12	1	0,1	0,1
Benzo[j]fluoranten	0,1	0,12	1	0,05	0,1
Benzo[k]fluoranten	0,1	0,052	1	0,02	0,1
Cyclopenta[cd]pyrene				0,02	
Dibenz[a,h]acridin					0,1
Dibenz[a,j]acridin					0,1
7H-Dibenzo[c,g]carbazol					1,0
Dibenzo[a,e]pyren				0,2	1,0
Dibenzo[a,h]pyren				1	10
Dibenzo[a,i]pyren				0,1	10
Dibenzo[a,l]pyren				1	10
Indeno[1,2,3-c,d]pyren	0,1	0,278	1	0,1	0,1
5-Methylkrysen					1,0
6-Nitrokrysen					10
1-Nitropyren					0,1
4-Nitropyren					0,1
2-Nitrofluoren					0,01

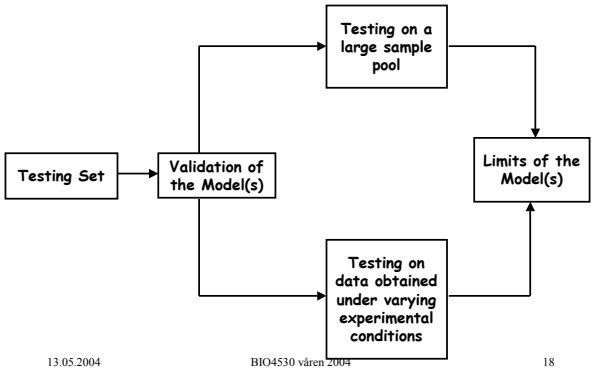
Basic Concepts and Aims of QSAR-Studies W. Karcher
QUANTITATIVE STRUCTURE/ACTIVITY RELATIONSHIPS (QSAR) IN TOXICOIOCY
Pavia, May 24-25, 1991
Edited by T. Coccini, L Glannonl, W. Karcher, L. Manzo, R. Rol
JOINT RESEARCH CENTRE COMMISSION OF THE EUROPEAN COMMUNITIES







Validation through testing set



Accuracy range of QSAR/SAR predictions

Estimated properties or activities	Prediction level	Accuracy
1. Physicochemical properties	quantitative	+/-25-50%
2. Bioconcentration Factor, Toxicity	quantitative	order of magnitude
3. Mutagenicity/Carcinogenicity	qualitative	variable

Table II Identification and molecular descriptor (log P) of the training set and comparison of experimental and calculated toxicities

Compound	CAS Bo.	LC 50 96h mg/l	log P	Toxicities Observation (log1/C)	Toxicities Calcuid. (log1/C)	Residuals
1 Dicrotophos	141-66-2	6.300	-0.260	1.576	1.482	0.094
2 Dimethoate	60-51-5	6.200	-0.197	1.568	1.500	0.068
3 Fenthion	55-38-9	0.550	3.432	2.704	2.547	0.157
4 Parathion	56-38-2	0.864	2.609	2.528	2.309	0.219
5 Carbaryl	63-25-2	1.950	2.408	2.014	2.251	-0.237
6 Disulfoton	298-04-4	1.850	2.671	2.171	2.327	-0.156
7 Bensulide	741-58-2	0.720	3.007	2.742	2.424	0.318
8 Methiocarb	2032-65-7	0.750	2.938	2.478	2.404	0.074
9 Methomyl	16752-77-5	1.600	1.434	2.006	1.970	0.036
10 Parathionmethyl	298-00-0	3.700	1.887	1.852	2.101	-0.249
11 Ovex	80-33-1	0.623	3.699	2.687	2.624	0.063
12 Picloram	1918-02-1	4.000	1.116	1.781	1.893	-0.112
13 Ronnell	299-84-3	0.550	4.054	2.767	2.726	0.041
14 Piperonylbutoxide	51-03-6	1.900	3.506	2.251	2.568	-0.317

Observert og beregnet 14 prøver

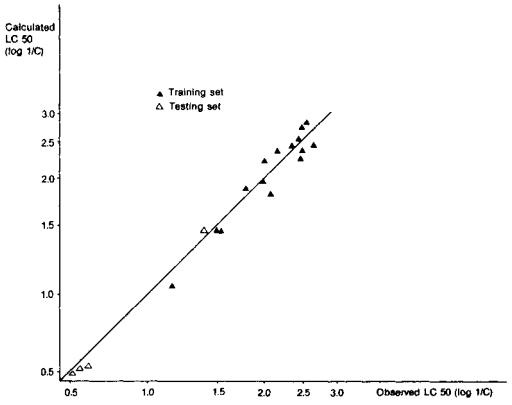


Fig. 6: Plot observed versus calculated LC 50 values.

Begynnelsen av QSAR

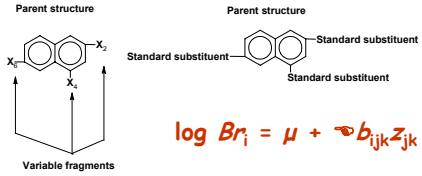
Biologisk aktivitet er en funksjon av kjemisk struktur
Crum-Brown Fraser i 1868

$\Phi = f(C)$

Moderne QSAR startet i 1964 med publikasjoner av:
Hansch og Fujita
og
Free og Wilson

Free-Wilson Analysis

Original Free-Wilson Analysis Fujita-Ban variant of Free-Wilson Analysis



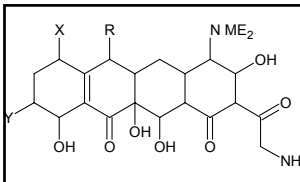
$$\log Br_i = \mu + \sum b_{ijk} z_{jk}$$

Br_i =Biological response of the ith molecule

μ =activity contribution of the parent structure

z_{jk}=activity contribution of the jth substituent in the kth position of substitution

b_{ijk}=indicates the occurence of of substitutents in each compound
=1 for compounds i, if the jth substitution in the kth position of substitution occurs in this compound



R = H, Me

X = NO_2, CL, Br

Y = NO_2, NH_2, CH_3CONH

Free-Wilson

Free-Wilson Matrix for the Compounds in Figure

	b_{ijk}								
i	*R*-H	*R*-Me	*X*-NO_2	*X*-Cl	*X*-Br	*Y*-NO_2	*Y*-NH_2	YMeCONH	log 1/C
1	1	0	1	0	0	1	0	0	1.78
2	1	0	0	1	0	1	0	0	1.32
3	1	0	0	0	1	1	0	0	1.18
4	1	0	0	1	0	0	1	0	2.72
5	1	0	0	0	1	0	1	0	2.51
6	1	0	1	0	0	0	1	0	2.44
7	0	1	1	0	0	0	1	0	2.20
8	0	1	1	0	0	0	0	1	1.18
9	0	1	0	0	1	0	1	0	2.15
10	0	1	0	0	1	0	0	1	1.88

Beregninger

En benytter regresjonsanalyse - problemet ikke løsbart

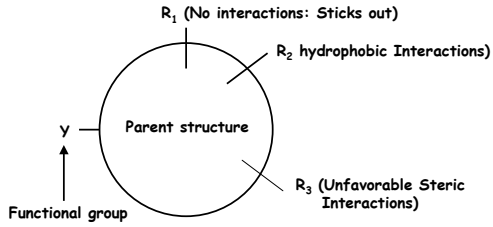
1) Introduction of so-called symmetry conditions (Free-Wilson analysis)
2) Fujita-Ban variant of Free-Wilson analysis. Den benyttes i dag.

μ	=1.40
[R-H]	= 0 (per definition)
[R-Me]	= - 0.36
[X-NO_2]	= 0 (per definition)
[X-Cl]	= 0.06
[X-Br]	= 0.03
[Y-NO_2]	= 0 (per definition)
[Y-NH_2]	= 1.13
[Y-MeCONH]	= 0.48

Hansch analysis

$\log Br = a_h x_h + a_e x_e + a_s x_s$ +constant
h - hydrophobic, e - electronix and s - steric hinderance

$\log Br = a_h x_h + a_e x_e + a_s x_s - a_1(\log P)^2 + a_2 \log P$ +constant



MUTACENICITY OF AROMATIC AND HETEROAROMATIC NITRO COMPOUNDS

188 aromatic and heteroaromatic nitro compounds, tested for mutagenicity in *Salmonella typhimurium* TA98, were taken from the literature and the E_{LUMO} (energy of lower unoccupied molecular orbital) values were calculated by AM1 method. Treating the electronic effects of molecules, the authors did not use the Hammett-Taft a constant but the quantum chemical properties, expressed by E_{LUMO}, that allow greater flexibility in the choice of substances.

The model developed was:

$\log TA98 = 0.65(\pm0.16) \log P - 2.90(\pm0.59) \log(\beta 10^{\log P} + 1) - 1.38(\pm0.25)E_{LUMO} + 1.88(\pm0.39)/I_1 - 2.89(\pm0.81)I_a - 4.15(\pm0.58)$

$n = 188$, $r = 0.900$, $s = 0.886$, $\log P_0 = 4.93$, $\log \beta = 5.48$, and $F_{1,181} = 48.6$

where:

- TA98 is the mutagenic activity (in revertants/nmol) produced by the mutagen.
- E_{LUMO} is the energy of the lowest unoccupied molecular orbital.
- I_1 is an indicator variable, set equal to 1 for compounds with three or more fused rings and to 0 when two or less rings are present.
- I_a is set equal to 1 for five substances of the set that are much less active than expected.
- Figures in parentheses are for construction of the 95% confidence limits.
- n is the number of the data points.
- r is the correlation coefficient.
- s is the standard deviation.
- F is the statistical test for the significance of each term.

Carcinogenic Potency Database (CPDB)

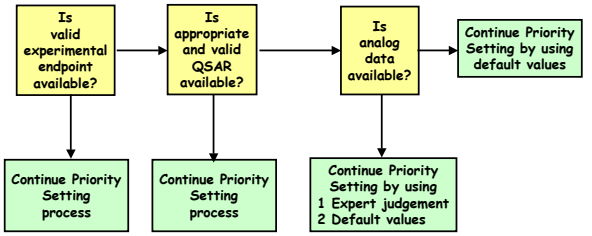
DATABASE - The database primarily used in this study is derived from the Carcinogenic Potency Database (CPDB) created by Gold and her associates.

For chemicals judged to be carcinogenic, a potency value (i.e., TD_{50}) is estimated. The TD_{50} is the dose in the assay that is estimated to result in 50% of the animals being tumor-free at the end of the standard lifespan (the TD_{50} accounts for the spontaneous cancers). In CPDB, a carcinogen is defined as a chemical that causes cancers in either rats or mice, or both.

A noncarcinogen is defined as a chemical that causes no cancers in either mice or rats. The TD_{50} values reported in Gold et al. in mg/kg/day were converted to mmol/kg/day. For the purpose of the present SAR analyses, chemicals with TD_{50} values in excess of 32 mmol/kg/day are considered noncarcinogens. Chemicals with TD_{50} values between 8 and 32 mmol/kg/day are marginal carcinogens, and chemicals with TD_{50} values less than 8 mmol/kg/day are considered carcinogens. To facilitate SAR analyses, the TD_{50} values were converted into SAR units:

SAR unit = 18.328 log (1/TDso) + 46.55

Based upon that relationship, less than 20 SAR units indicate noncarcinogenicity, 20 to 29 units indicate marginal carcinogenicity, and >30 units are associated with carcinogenicity.



Use of QSARs in priority setting