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Benchmark Dose Modeling – Modeling Time

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Models Covered in This Course

- Currently there are two models included in BMDS that can incorporate time in the modeling scheme
 - The toxicodiffusion model is used for time-course or repeated response data where a particular effect has been measured at multiple time-points
 - The ten Berge concentration × time (C × T) model is primarily used in the context of acute inhalation studies where groups of animals are exposed to multiple concentrations of a chemical for varying durations of exposure.
- Currently, there is a cancer model that incorporates time that is covered in the Cancer Training Module
 - This model, the Multistage-Weibull time-to-tumor model, is run outside of BMDS program but is available from the BMDS website: <u>http://epa.gov/ncea/bmds/dwnldu.html#msw</u>



Repeated Response Data – The Toxicodiffusion Model

Repeated Response Data

• Repeated response measures, or time-course data, can be used to characterize toxicity responses that vary according to dose and time

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- Neurotoxicity tests, such as functional observational batteries (FOBs), often generate repeated response data
- Repeated response data is different from concentration × time (C × t) data
 - C × t data involves animals exposed to a chemical at a particular dose for a certain duration of time
 - Repeated measure data involves animals exposed to a chemical once and where responses are measured at multiple time points before, during, or following that exposure

Traditional Analysis of Time-Course Data

- Historically, analysis of FOB or other repeated-response data has been conducted using Analysis of Variance (ANOVA) methods
 - ANOVA is effective at detecting dose- and time-related changes in responses
 - However, they cannot describe the magnitude or underlying shape of the doseresponse curve along the recorded time-course
- In order to describe the dose-response characteristics, one option would be to model independent time points separately, but this type of analysis is unsatisfactory for 3 reason:
 - It would be limited to the experimental time points
 - The time trend of the dose-effects would not be fully utilized
 - It might not reflect the magnitude of toxic effects at the most sensitive time point
- For these reasons Zhu et al. (2005a,b) developed the toxicodiffusion model

Toxicodiffusion Model Form

The equation for the toxicodiffusion model is given as:

 $\eta(d,t) = A(t) + f(d,t), \text{ where } f(d,t) = \frac{(B * t * d * exp(-k * t))}{(1 + C * t * d * exp(-k * t))}$

- When first order kinetics are applicable, the parameter k can be interpreted as the elimination coefficient
- A(t) represents the time-course that is predicted in the absence of exposure
 - Constant: $A(t) = A_0$

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- Linear: $A(t) = A_0 + A_1 t$
- 2nd degree polynomial: $A(t) = A_0 + A_1t + A_2t^2$
- The toxicodiffusion model is particularly well-suited for describing dose-timeresponse relationships of transient dose effects
 - f(d,t) starts at a value of 0 when t = 0, increases with time and reaches peak effect $\left(\frac{Bd}{Cd+k*e}\right)$ at $t = \frac{1}{k}$, and eventually returns to 0 with sufficiently large time

Repeated Response Data

• For the purposes of modeling repeated response data in BMDS, the data must be structured as follows:

- The response variable measured on a continuous scale
- A single exposure (or exposure interval) and several (4-5) doses
- The time component is coded between 0 (beginning) and the maximum positive value (last time point for which data is available).
- The outcome is measured repeatedly over time on each study subject, and the time of observation is given. It is not necessary for each subject to have the same time points
- Individual animal data and multiple subjects per dose group are required
- Dose effects are observed at more than one dose level, and differences in dose effect are seen at some time points

Repeated Response Datafile Format

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Toxicodiffusion Model in BMDS

- Unlike other models in BMDS, the toxicodiffusion model requires that users install the R Statistical software package (version 2.6.2 or higher)
- The toxicodiffusion model also is the only model in BMDS currently that uses the "hybrid approach" to calculate a BMD for continuous data based on dichotomized risk, requiring two user-selected parameters:
 - The benchmark response (BMR) expressed as either added or extra risk (e.g., 10% extra risk)
 - The background rate (i.e., probability) of an adverse response in the control group

The Hybrid Approach – Selecting the BMR

- As with dichotomous models, EPA recommends the use of extra risk as this accounts for the presence of background responses
- 10% extra risk would be expressed as:

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 $0.10 = \left[P(BMD_{\gamma}, t) - P(0, t) \right] / (1 - P(0, t)]$

If P(0, t) = 0.01 (i.e., there is a 1% probability of adversity in the control group at time t), then

 $P(BMD_{\gamma}, t) = (0.10 * [1 - P(0, t)]) + P(0, t) = (0.1 * 0.99) + 0.01 = 0.109$

 Therefore, we are interested in the dose that results in 10.9% of subjects exhibiting an adverse response

The Hybrid Approach – Selecting the Background Rate

- Next, the background rate of adverse response in the control group must be selected, in this example, we've chosen 1%
- AT EACH TESTING TIME POINT, the model calculates the cut-off values in the control group distribution that correspond to the background rate



The Hybrid Approach – Selecting the Background Rate

 Given a BMR of 10% extra risk AND a background rate of 1% for adverse responses in the control group the model will calculate the dose that corresponds to a shift in the mean that results in 10.9% of the animals falling beyond the control group cut-off values

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Toxicodiffusion Model – Calculating the BMD

• In order to profile the BMD (i.e., $BMD_{\gamma}(t)$) with respect to time, a sequence of points $\{t\}$ is chosen and the corresponding $\{BMD_{\gamma}(t)\}$ values are calculated

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- Given that response rates may vary over time, there may be multiple values of {BMD_γ(t)} that yield responses equal to the BMR at multiple time points {t}
- Therefore, the reported BMD is the minimum of these multiple doses,
 i.e., BMD_y(t*) = min_t {BMD_y(t)}

Toxicodiffusion Model – Calculating the BMD



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Toxicodiffusion Model – Calculating the BMD



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Toxicodiffusion Model – Calculating the BMDL

 The toxicodiffusion model uses bootstrap resampling of residuals and random effect coefficients to calculate the BMDL

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- The residuals and random effect coefficients were originally estimated during the original fitting of the model to the data
- The model repeats the sampling procedure a user-specified number of times, with each re-sampled residual resulting in a new estimate of model parameters, and thus, a new BMD
- This procedure produces a number of BMDs equal to the number of sampling repeats
 - The percentiles across this sampling of bootstrapped BMDs can be used to calculate the BMDL
 - The 5th percentile of a sampled set of BMDs would be reported as the 95% lower bound on the BMD, i.e., the BMDL

Toxicodiffusion Model – Calculating the BMDL

 Because the BMDL calculation uses random re-sampling, the BMDLs calculated from repeated modeling runs will differ slightly for the same dataset.

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 One way to control this difference is to increase the number of bootstrap iterations, this will decrease the range of calculated BMDLs





Running The Toxicodiffusion Model in BMDS

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A0 Default B0 Default C0 Default C0 Default Study Name ToxicoDiffusion Bo Data File: C:\Users\adavis10\B Out File Name: C:\Users\adavis10\B Save Save As		Chemical Name Exposure Type Species Name Condor RUN ip.dax Show reGrip_Setting.out Set To Optimize Initial Param. Values Close	Run	
A0 Default B0 Default C0 Default C0 Default C1 Default C2 Default C3 Default C4 Default		Chemical Name Exposure Type Species Name Condor RUN ip.dax Show reGrip_Setting.out Set To Optimize Initial Param. Values Close	Run	

\$EPA

Toxicodiffusion Model – Other Assignments

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Animal ID	[D •	Adverse Definition	Background Rate 🔻	^
Dose	dose 🔻	Adverse Level	0.05	
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		Use Two Sided Cl?		
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# of Time Points	100			Ŧ
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Parameters Options	Values			
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Parameters Options A0 Default B0 Default C0 Default	Values -99999 -9999 -9999 -9999 -9999 -9999 -9999 -9999 -9999 -9999 -9999 -9999 -9999 -9999 -	Chemical Name Exposure Type Species Name		
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Parameters Options A0 Default B0 Default C0 Default C0 Default Study Name ToxicoDiffusion Boo Data File: C:\Users\adavis10\BM Out File Name: C:\Users\adavis10\BM Save Save As ToxicoDiffusion_beta->Rptd_Resp_Measures	Values -9999 -9999 -9999 -9999 -9999 - -	Chemical Name Exposure Type Species Name Condor UN Odax Show eGrip_Setting.out Set To Optimize Initial Param. Values Close	Run	

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Toxicodiffusion Model – Results

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Analysis of ToxicoDiffusion Bootstrap BMDS MODEL RUN STUDY DESCRIPTION Dose Levels: 0 0.75 1.5 3 6 Test Times: 0 2 24 168 Exposure Time: 0 Sample Size: 198	^
DOSE-RESPONSE MODELING A+B*dose*time*exp(-K*time)/(1+C*dose*time*exp(-K*time))	
AIC BIC logLik -99.76988 -80.04027 55.88494	E
Random effects: Formula: A ~ 1 ID A Residual StdDev: 0.08384292 0.16723250	
Fixed effects: Value Std.Error DF t-value p-value A 1.02558328 0.021766397 145 47.117732 8.499645e-90 B.dose -0.01373109 0.006012917 145 -2.283599 2.384794e-02 C.dose 0.02673254 0.017756512 145 1.505507 1.343692e-01 K 0.01991699 0.002467258 145 8.072523 2.409297e-13	
Correlation: A B.dose C.dose K	
A 1.0000000 -0.4672524 0.3598873 0.0548682 B.dose -0.4672524 1.0000000 -0.9504070 -0.5524777 C.dose 0.3598873 -0.9504070 1.0000000 0.4633031 K 0.0548682 -0.5524777 0.4633031 1.0000000	
Standardized Within-Group Residuals: Min Q1 Med Q3 Max	
-2.66913962 -0.50714699 -0.03634028 0.72698913 2.44610785	T
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Sepa

Toxicodiffusion Model – Results

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Correlation:	*
A B.dose C.dose K	
B.dose -0.4672524 1.0000000 -0.9504070 -0.5524777	
C.dose 0.3598873 -0.9504070 1.0000000 0.4633031	
K 0.0548682 -0.5524777 0.4633031 1.0000000	
Standardized Within-Group Residuals:	
Min Q1 Med Q3 Max	
-2.66913962 -0.50714699 -0.03634028 0.72698913 2.44610785	
Initial Values: 1.018812 -0.03783458 0.0835662 0.01713397	
Possible Initial Values	
A0 B0 C0 K0	-
1 1.018812 -0.037834581 0.08356620 0.01713397	
2 1.018812 -0.021291539 0.06687200 0.02608923	
4 1.018812 -0.006326717 -0.06284446 0.02118212	
5 1.018812 -0.013809128 0.04031584 0.01921920	
6 1.018812 -0.017260204 0.02533835 0.02041540	
SENCHMARK DOSE ESTIMATION	
Risk Type: extra	
Spontaneous Risk Level: 5 %	E
Area of Adverse Effects: Lowertail	
BMR Level: 5 %	
BOOTSTRAP ESTIMATION OF BMDL	
Bootstrap Replications: 100	
Minimum BMD: 0.259562	
At Test Time: 50.4	
BMDL: 0.178158	*
	.::
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 Observed trajectory – displays each subject's responses by connecting the observed responses across time

SEPA

 Useful for determining the trajectory of the control group and how exposure changes the trajectory over time



33

 Fitted trajectory – displays each subject's fitted responses by connecting the observed responses across time

EPA

 Useful for determining whether the predicted responses show trajectories resembling the observed trends



• Pooled residuals across all dose groups

S FP

- Allows the user to check for randomness with respect to the level of response
- The presence of any trend (decreasing, increasing, curved) indicates the inappropriateness of the model



Standardized Residuals vs. Fitted values of fore.grip

Pooled residuals within dose groups

SEPA

- Allows the user to check for randomness with respect to the level of response
- The presence of any trend (decreasing, increasing, curved) indicates the inappropriateness of the model



Bootstrap graph – shows the time-profile of the resampled BMDs

- Dark black line original fit to the data
- Light grey lines resampled BMDs

SEPA

Dark dashed black line – chosen percentile of the resampled BMDs (i.e., BMDL)



BMD Time-Profile Based on fore.grip (extra Risk at 5 % BMR Level)

time Dashed lines(s) is 95 % Confidence Band(s)
Toxicodiffusion Model – Assessing Fit Across Models

 In this example, the observed trajectory in the control group appears to decrease over time.

EPA

- Therefore, a constant background rate (i.e., $A(t) = A_0$) may not be suitable, and the linear background rate (i.e., $A(t) = A_0 + A_1 t$) may be more appropriate
- The AIC and BIC values to assess whether the addition of an extra parameter improves model fit.

$A(t) = A_0$	$A(t) = A_0 + A_1 t$
BMDS 2.2 [Build: 12/08/2011] - [C:/BMDS220/Data/TETacForeGrip.out]	🎡 BMDS 2.2 [Build: 12/08/2011] - [C:/BMDS220/Data/TETacForeGrip.out]
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File Edit Preferences	File Edit Preferences
Analysis of ToxicoDiffusion Bootstrap BMDS MODEL RUN STUDY DESCRIPTION Dose Levels: 0 0.75 1.5 3 6 Test Times: 0 2 24 168 Exposure Time: 0 Sample Size: 198	Analysis of ToxicoDiffusion Bootstrap BMDS MODEL RUN STUDY DESCRIPTION Dose Levels: 0 0.75 1.5 3 6 Test Times: 0 2 24 168 Exposure Time: 0 Sample Size: 198
DOSE-RESPONSE MODELING A+B*dose*time*exp(-K*time)/(1+C*dose*time*exp(-K*time))	DOSE-RESPONSE MODELING A0+A1*time+B*dose*time*exp(-K*time)/(1+C*dose*time*exp(-K*time))
AIC BIC logLik -99.76988 -80.04027 55.88494	AIC BIC logLik -98.80104 -75.78317 56.40052



Toxicodiffusion Modeling Exercise

Toxicodiffusion Modeling Exercise

• Open hind_grip_A0.dax

EPA

- Model Type: Rptd_Resp_Measures
- Model Name: Toxicodiffusion_beta

Parameterize the option files as follows and run model:

- Fill in Column Assignments as appropriate
- Time Scale Axis = Log
- Exposure time = 0
- Background degree = 0
- BMR = 5% Extra risk
- Adverse Direction = Lowertail
- Adverse Definition = Background Rate
- Adverse Level = 5%
- Bootstrap Iterations = 1000



SEPA

Standardized Residuals vs. Fitted values of Hind_Grip 0.4 0.6 0.8 1.0 0.4 0.6 0.8 1.0 0 0.75 1.5 3 6 о 0 3 0 3 0 ο 0 0 0 N 0 0 0 2 0 0 00 о Standardized residuals 0 0 Standardized Residuals 0 \cap 0 0 00 0 <u>_</u> \cap 0 ο 0 00 0 0 00 1 0 0 0 o യുദ 0 00 0 °°0 8 O 0 0 0 0 0 ο 0 0 ത ο C 0 0 0 ° ° ₀ - 0° 0 0 • • 0 0 C о 0 Ο 0 0 0 **0** 0 0 ο °~ 80 ം രം о 0 0 0 0 0 0 0 00 6 00 C °o <u>ه</u>ر °°, о 0⁰ 0 ٥₀ 0 ο 0 0 ത 0 $\overline{}$ 0 0 00 0 00 ο 9 8 -1 0 0 ο ο Ъ° ο 0 0 0 ο 0 ο 0 0 0 0 о 00 ο о 2 0 0 0 -2 о 0 0 0.9 0.4 0.5 0.6 0.7 0.8 1.0 0.4 0.6 0.8 1.0 0.4 0.6 0.8 1.0 0.4 0.6 0.8 1.0 Fitted values Fitted values

\$EPA

Standardized Residuals vs. Fitted Values of Hind_Grip by Dose



\$EPA

Dashed lines(s) is 95 % Confidence Band(s)

BMDS Summary Table

	Toxicodiffusion (A=0)	Toxicodiffusion (A=1)
AIC	-120.495	
BIC	-100.7351	
C.dose	0.5935487	
К	0.0343045	
BMD	0.028027	
Test-time	28.56	
BMDL	0.018353	

€PA

Toxicodiffusion Modeling Exercise – Results

• Open hind_grip_Al.dax

- Model Type: Rptd_Resp_Measures
- Model Name: Toxicodiffusion_beta

• Parameterize the option files as follows and run model:

- Fill in Column Assignments as appropriate
- Time Scale Axis = Log
- Exposure time = 0
- Background degree = I (must change from default)
- BMR = 5% Extra risk
- Adverse Direction = Lowertail
- Adverse Definition = Background Rate
- Adverse Level = 5%
- Bootstrap Iterations = 1000



SEPA

Standardized Residuals vs. Fitted values of Hind_Grip 0.4 0.6 0.8 1.0 0.4 0.6 0.8 1.0 0 0.75 1.5 3 6 0 0 З 0 3 0 0 ο 0 0 N Ο 0 0 2 0 00 ο Standardized residuals 8 Standardized Residuals 0 00 0 0 0 0 ~ O 0 о 0 0 0 0 0 C 00 0 1 0 o 0⁰ 0 0 0 0 ۵ 0 0 0 0 O 0 0 0 0 0 ത 0 80 0 ൟഀ൦ 0 ° 0 0 00 00 0 0 о °°°° о 0 0 0 0 0 о ° 0 °°°°° 80 ō 0 0 о ο 00 0 6 0 о 0 0 o R 00 080 00 ୍ପଞ୍ଚ o о 0 ୁ କୃତ୍ତି 8 00 ο °0 0 0 0 О 0 0 0 $\overline{\mathbf{T}}$ 6 0 a Or o 0 0 0 00 8 00 8 0 0 о -1 ο °0 ° S 0 0 0 0 0 ο 0 0 o 0 00 0 ο 0 Ο Ņ 0 0 ο 0 -2 0 о 0 0.4 0.5 0.6 0.7 0.8 0.9 1.0 0.4 0.6 0.8 1.0 0.4 0.6 0.8 1.0 0.4 0.6 0.8 1.0 Fitted values Fitted values

SEPA

Standardized Residuals vs. Fitted Values of Hind_Grip by Dose

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⇔EPA

BMDS Summary Table

	Toxicodiffusion (A=0)	Toxicodiffusion (A=1)
AIC	-120.495	-118.6422
BIC	-100.7351	-95.58902
C.dose	0.5935487	0.6153080
К	0.0343045	0.0355523
BMD	0.028027	0.028045
Test-time	28.56	28.56
BMDL	0.018353	0.017513

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Concentration × Time (C × T) Data – The ten Berge Model

Concentration × Time (C × T) Modeling – Haber's Law

- C × T modeling has primarily been done in the context of acute inhalation exposures
- In these instances, both exposure concentration and duration of exposure are important for estimating responses
- Haber's Law

EPA

- $C \times t = k$
- Originally formulated in the early 1900s by Fritz Haber in the context of researching the effects of exposure to chemical warfare agents
- Assumes equivalency any two combinations of exposure concentration and duration that have equal products $(C_1t_1 = C_2t_2)$

Concentration × Time (C × T) Modeling – Haber's Law

 Haber himself recognized that the simplified form of his equation was an approximation and only useful under certain conditions

EPA

- Haber's law does not take into account rates of detoxification, fractional absorption, differences in physiological parameters (e.g., ventilation rate, body weight) of exposed subjects
- In certain cases, (e.g., when duration of exposure approaches the half-life of the chemical in the body) more sophisticated mathematical models are necessary
- However, due to its simplicity, Haber's Law extensively used toxicological doseresponse research
- However, multiple, alternative approaches have been recommended to more accurately describe the relationship between concentration, duration, and response

- ten Berge et al. (1986) investigated the ability of Haber's Law to describe mortality due to acute inhalation exposures
 - Haber's Law was expressed as $Y = b_0 + b_1 \ln(c) + b_2 \ln(t)$

EPA

 Assuming Haber's Law adequately describes the mortality response, the values of b₁ and b₂ should be roughly equivalent

TABLE 1

€PA

TABLE 2

Regression coefficients of the concentration-time mortality response relationships of several irritant chemicals for different species according to eqn. (1)

Regression	coefficients	of th	e concentration-tin	ne mortality	response	relationship	of
several syst	emically acti	ng che	micals for different s	pecies accord	ding to eqr	1. (1)	

Chemical .	Species, sex	Regressi coefficie	on nts		Chemical	Species, sex	Regression	on ints
		<i>b</i> ₀	<i>b</i> ₁	b 2			b ₀	b ₁
Ammonia [2]	male + female rats	-47.9	4.65	2.30	Hydrogen cyanide [14]	goat	-27.3	4,50
Ammonia [2]	male rats	-76.2	7.17	3.71	Hydrogen cyanide [14]	monkey	-6.87	1.57
Ammonia [2]	female rats	-62.6	5.91	2.76	Hydrogen cyanide [14]	rabbit	-15.6	3,22
Ammonia [3, 4]	mouse	-54.5	5.95	2.89	Hydrogen cyanide [14]	rat	-3.27	1.15
					Hydrogen cyanide [14]	eat	-8.26	2.09
HCl gas [5]	rat	-47.7	4.06	4.90	Hydrogen cyanide [14]	dog	-1.30	1.02
HCl aerosol [5]	rat	-29.1	2.77	2.68				
HCl gas [5]	mouse	-10.5	1.40	1.16	Hydrogen sulphide [15]	cat + rabbit	-42.6	5.13
HCl aerosol [5]	mouse	-22.8	2.51	2.21				_
					Methyl t-butyl ether [16]	mouse	-25.1	3.98
Chlorine pentafluoride [6]	rat	-29.3	3,92	2.10				
Chlorine pentafluoride [6]	mouse	-15.5	2.42	1.57	Methylenechlorobromide [17]	male rats	-45.0	3.56
Chlorine pentafluoride [6]	dog	-20.8	2.79	1.95	Methylenechlorobromide [17]	female rats	-49,1	3,86
Chlorine pentafluoride [6]	monkey	-17.6	2.87	0.696	Ethylenedibromide [18]	rat	-32.5	3.12
Nitrogen dioxide [7]	rat	-15.2	3.09	0.885	Tetreshiers the laws [10]			0.04
Nitrogen dioxide [7]	guinea pig	-10,5	2,63	0.537	Tetrachioroethylene [19]	rat	-39.1	3.34
Nitrogen dioxide [7]	rabbit	-5,43	1.52	0.352	Trichlereethylene [20]	not.	_0 26	0.769
Nitrogen dioxide [7]	dog	-38.7	6.48	1.97	Inchloroethylene [20]	rat	-0.00	0.700
Nitrogen dioxide [7]	mouse	-85.6	6.43	1.76	Carbon tetrachloride [21]	rat	-39.4	3.46
Chlorine [8]	mouse	-23.2	3.82	1.10	Acrylonitrile [22]	rat	-42,1	3.83
Perfluoroisobutylene [9]	rat	-14.9	2.87	2.36	Acrylonitrile [23]	rat	-165	15.2
Crotonaldehyde [10]	rat	-15.6	2,00	1.72	en e	······································		
Hydrogen fluoride [11]	rabbits + guinea pigs	7.35	1.38	0.71				
Telestres (10)			0.050	0.714				
Ethylene imine [12]	guinea pig	-19.5	2,25	2.58				
Bromine [8]	mouse.	-24.7	3.13	1.44				
Dibutylhexamethylenediamine [13]	rat	-11.7	1.33	1.29				

 b_2

2.02

0.835

0.744

0.701

0.741

0.327

2.36

2.02

2.26

2.34

2.69

1.65

0.909

1.22

3,74

11.4

- Given the failure of Haber's Law to adequately describe the mortality responses, ten Berge suggested an mathematical re-formulation of the relationship between concentration and duration
 - ten Berge's equation: $C^n \times t = k$

EPA

- Formulated by rearranging $Y = b_0 + b_1 \ln(c) + b_2 \ln(t)$ to $Y = b_0 + b_2 \ln(c^n t)$, where $n = b_1/b_2$
- ten Berge demonstrated that $c^n t$ predicted mortality response quite well
- The value of n indicates which variable influences responses to a greater degree
 - n > 1, response is concentration-dependent
 - n < 1, response is time-dependent
- ten Berge further extended Haber's Law to situations where concentration varies during the exposure period: $\int [c(t)]^n dt$

TABLE 4

⇔EPA

Value of the exponent n for several gases and vapours, of which the probit Y of the mortality response in relation to exposure concentration c and exposure period t can be predicted by eqn. (3).

Gas or vapour	Exponent n	95% confidence limits
Local irritants	· · · · · · · · · · · · · · · · · · ·	····
NH ₃	2.0	(1.6, 2.4)
HCI	1.0	(0.7, 1.3)
ClF ₅	2.0	(1.4, 2.6)
NO ₂	3.5	(2.7, 4.3)
Cl ₂	3.5	(2.5, 4.4)
Perfluoroisobutylene	1.2	(1.1, 1.4)
Crotonaldehyde	1.2	(1.1, 1.3)
HF	2.0	(1.2, 2.8)
Ethylene imine	1.1	(0.8, 1.3)
Br ₂	2.2	(2.0, 2.4)
Dibutylhexamethylenediamine	1.0	(0.6, 1.4)
Systemic action		
HCN	2.7	(1.8, 3.7)
H_2S	2.2	(1.6, 2.7)
Methyl t-butyl ether	2.0	(1.0, 2.9)
CH ₂ ClBr	1.6	(1.4, 1.8)
$C_2 \tilde{H}_4 Br_2$	1.2	(1.1, 1.2)
$C_2 Cl_4$	2,0	(1.4, 2.6)
C ₂ HCl ₃	0.8	(0.3, 1.4)
CCla	2.8	(1.9, 3.7)
Acrylonitrile	1.1	(1.0, 1.2)

ten Berge Modeling in BMDS

- The ten Berge model was originally coded in Visual Basic by the study authors, and has been implemented in BMDS in the C language
 - The general form of the equation is: $z = b_0 + b_1 f_c(c) + b_2 f_t(t) + b_3 f_x(x) + b_4 r_4(c, t, x) + \cdots$

EPA

- b_0 , b_1 ... are model parameters estimated via maximum likelihood methods
- c = concentration, t = time, x = some other explanatory variable
- $f_i(u)$ =some transformation on the explanatory variable: identity, u; logarithmic, $\ln(u)$; or reciprocal, $\frac{1}{u}$
- $r_j(c, t, x) =$ interactions (products) of the $f_c(c), f_t(t), f_x(x)$ terms
 - Number of product terms is limited to 2 currently
 - Inclusion of product terms may lead to difficulties in model interpretability

ten Berge Modeling in BMDS

• For most modeling applications, the model formulation of most interest only incorporates c and t parameters that have been logarithmically transformed:

 $z = b_0 + b_1 \ln(c) + b_2 \ln(t)$

SEPA

• Rearrangement by log rules leads to the model form

 $z = b_0 + b_2 \ln(c^n t)$, where $n = b_1/b_2$

Formatting Data for ten Berge Model

• Can create datasets within BMDS, or import them from other spreadsheet applications

Data needs to be in the following format:

- The first columns must be the main effect columns (i.e., concentration and time), in any order **BUT** they must appear first
- The final columns in the dataset should # Subjects and Incidence IN THAT ORDER
- Other explanatory variables (e.g., body weight, age) can appear in any order between the main effect columns and the # Subjects/Incidence columns

• Datasets needs at a minimum:

- Total number of exposed subjects
- Number of affected subjects
- 2 explanatory variables

EPA



Running The ten Berge Model in BMDS

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Dataset Structure

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3	50	20	235	10	0			
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6	50	50	227	10	1			
7	50	60	238	10	2			
8	300	5	240	10	0			
9	300	10	234	10	1			
10	300	20	239	10	1			
11	300	30	238	10	3			
12	300	40	233	10	2			
13	300	50	238	10	2			
14	300	60	214	10	4			
15	600	5	221	10	1			
16	600	10	232	10	1			
17	600	20	233	10	2			
18	600	30	223	10	4			
19	600	40	229	10	3			
20	600	50	229	10	2			
21	600	60	219	10	4			
22	1200	5	229	10	2			
23	1200	10	214	10	3			
24	1200	20	214	10	3			
25	1200	30	220	10	5			
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Select "Conc × Time" for Model Type

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	Continuous E Dichotomous		BodyWeight	Exposed	Dead	Col6	Col7	-
1	Dichotomous_A	Iternative 5	222	10	()		
2	Rptd_Resp_Mea	sures 10	217	10	1	I		
3	Conc_x_Time	20	235	10	()		
4	50	30	226	10	2	2		=
5	50	40	225	10	1	I		
6	50	50	227	10	1			
7	50	60	238	10	2	2		
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9	300	10	234	10	1	I		
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11	300	30	238	10	3	3		
12	300	40	233	10	2	2		
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6	50	50	227	10	1			
7	50	60	238	10	2			
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9	300	10	234	10	1			
10	300	20	239	10	1			
11	300	30	238	10	3			
12	300	40	233	10	2			
13	300	50	238	10	2			
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ten Berge Model – Column Assignments

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ten Berge Model – Variable Transformations

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ten Berge Model – Including Variables as Main Effects

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ten Berge Model – Product Terms

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Choose Model Calculations of Interest

• The ten Berge model is able to perform the following three calculations, providing the user with estimates and confidence intervals:

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- A value for one explanatory variable, given a percent response and specified values for the other explanatory variables
- The percent response given specified values for all of the explanatory variables
- The ratio between the regression coefficients of two explanatory variables (i.e., the value of n, when concentration and time are included as main effects and logarithmically transformed)

ten Berge Model – Calculations of Interest

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ten Berge Model – Results



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ten Berge Model - Results



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ten Berge Model – Results

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Selection of observations from number 1 through 42	
Transformation of input parameters	
Time min is transformed logarithically!	
BodyWeight is not transformed at all!	
Probit link used without background response correction!	
Variable 1 = Transformed Exposure ppm	
Variable 2 = Transformed Time_min	
Chi-Square = 30.53	
Degrees of Freedom = 39	
B0 = 1.024e-001 Student t for B0 = 0.20	
B1 = 4.490e-001 Student t for B1 = 8.15	
B2 = 4.704e-001 Student t for B2 = 5.35	
variance B00 = 2.640e-001	
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ten Berge Model – Results

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on response - 0.0000001 percent	
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The prediction of the model is sufficient. Use for estimation of the 95% confidence limits the Standard Normal Deviate	
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R010 - 0.991002	
Confidence limits 0.566673 1.342530	*
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ten Berge Model – Results

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No correction for variances required!	
Estimation of ratio between regression coefficients Ratio between regression coefficients	=
Exposure_ppm and Time_min	
Deviate Corresponding to Confidence Level of Interest = 1.960000	
Ratio = 0.954602	
Confidence limits	
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ten Berge Model – Plots



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ten Berge Model – Plots

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ten Berge Model – Plots

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ten Berge Modeling Exercise

ten Berge Modeling Exercise

 Open tenBerge_exercise.dax

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- Open option file (Model Type: Conc_x_Time; Model Name: tenBerge, Proceed)
- Parameterize the option file as shown

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ten Berge Modeling Results – Dose for a Given Response

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	Dose for Given	<pre>variance B00 = 3.001e-001 covariance B01 = -2.927e-002 covariance B02 = -3.194e-002 variance B11 = 3.992e-003 covariance B12 = 9.625e-004 variance B22 = 7.897e-003</pre>	~
	Response	Probability of correct model (p-value) is 0.954560 The prediction of the model is sufficient. Use for estimation of the 95% confidence limits the Standard Normal Deviate	
Response %	60%	No correction for variances required! Estimation of Exposure_ppm Response = 60.000000 percent Time_min = 30.000000	
Time	30 minutes	Estimated Exposure_ppm 60.000000 percent = 1.650e+003 Deviate Corresponding to Confidence Level of Interest = 1.960000 Lower limit Exposure_ppm 60.000000 percent = 1.240e+003 Upper limit Exposure_ppm 60.000000 percent = 2.417e+003	
p-value	0.95456	Probability of correct model (p-value) is 0.954560 The prediction of the model is sufficient. Use for estimation of the 95% confidence limits the Standard Normal Deviate	
Dose	1650 ppm	No correction for variances required! Estimation of response Exposure_ppm = 2000.000000	
Lower CI	1240 ppm	Response = 7.55+001 percent Deviate Corresponding to Confidence Level of Interest = 1.960000 LL-response = 6.69+001 percent UL-response = 8.27e+001 percent	E
Upper CI	2417 ррт	Probability of correct model (p-value) is 0.954560 The prediction of the model is sufficient. Use for estimation of the 95% confidence limits the Standard Normal Deviate	
		No correction for variances required! Estimation of ratio between regression coefficients	-
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ten Berge Modeling Results – Dose for a Given Response Plot



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ten Berge Modeling Results – Response for Given Variables

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Exposure	2000	Lower limit Exposure_ppm 60.000000 percent = 1.240e+003 Upper limit Exposure_ppm 60.000000 percent = 2.417e+003	
_,,p		Probability of correct model (p-value) is 0.954560 The prediction of the model is sufficient. Use for estimation of the 95% confidence limits the Standard Normal Deviate	
Time	60 minutes	No correction for variances required!	
p-value	0.95456	Estimation of response Exposure_ppm = 2000.000000 Time_min = 60.000000 Response = 7.55e+001 percent Deviate Corresponding to Confidence Level of Interest = 1.960000	
Response	75.5%	LL-response = 6.69e+001 percent UL-response = 8.27e+001 percent Probability of correct model (p-value) is 0.954560	
Lower Cl	66.9%	The prediction of the model is sufficient. Use for estimation of the 95% confidence limits the Standard Normal Deviate No correction for variances required!	
Upper Cl	82.7%	Estimation of ratio between regression coefficients Ratio between regression coefficients Exposure_ppm and Time_min Deviate Corresponding to Confidence Level of Interest = 1.960000	E
		Ratio = 1.154502 Confidence limits 0.699105 1.609898	
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ten Berge Modeling Results – Response for Given Variables Plot



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ten Berge Modeling Results – Response for Given Variables Plot



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ten Berge Modeling Results – Ratio Between Regression Coefficients

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	Ratio	The prediction of the model is sufficient. Use for estimation of the 95% confidence limits the Standard Normal Deviate	^
	Between Regression Coefficients	Estimation of Exposure_ppm Response = 60.000000 percent Time_min = 30.000000 Estimated Exposure_ppm 60.000000 percent = 1.650e+003 Deviate Corresponding to Confidence Level of Interest = 1.960000 Lower limit Exposure_ppm 60.000000 percent = 1.240e+003 Upper limit Exposure_ppm 60.000000 percent = 2.417e+003	
Ratio	1.154	Probability of correct model (p-value) is 0.954560 The prediction of the model is sufficient. Use for estimation of the 95% confidence limits the Standard Normal Deviate No correction for variances required!	
Lower CI	0.699	Estimation of response Exposure_ppm = 2000.000000 Time_min = 60.000000 Response = 7.55e+001 percent	
Upper CI	1.609	Deviate Corresponding to Confidence Level of Interest = 1.960000 LL-response = 6.69e+001 percent UL-response = 8.27e+001 percent	
		Probability of correct model (p-value) is 0.954560 The prediction of the model is sufficient. Use for estimation of the 95% confidence limits the Standard Normal Deviate No correction for variances required!	Π
		Ratio = 1.154502 Confidence limits 0.692105 1.69298	E
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