A.1. SUBCHRONIC ANIMAL TOXICOLOGY STUDIES FOR 1,2,3-TMB

Table A-1. Characteristics and quantitative results for Korsak and Rydzyński (1996)

Study Design					
Species	**Sex**	**N**	**Exposure route**	**Concentration range**	**Exposure duration**
IMP: Wistar	M	10/dose	Inhalation	25-250 ppm (123-1230 mg/m^3)	3 months (6h/day, 5 days/week)

Additional Study details

- Animals were exposed to either 1,2,3-, 1,2,4-, or 1,3,5-TMB in a dynamic inhalation chamber (1.3 m^3 volume) with 16 air changes/hour.
- Mean initial body weights were 250-300 grams; rats were housed in wire mesh stainless steel cages, with food and water provided *ad libitum.*
- Animals were randomized and assigned to the experimental groups.
- Rotarod and hot plate tests were conducted to measure effects on neuromuscular activity and pain sensitivity respectively.
- Rotarod performance was tested immediately after termination of exposure.
- Normal neuromuscular function was indicated by the rats' ability to remain on a rod rotating at 12 rpm for 2 minutes.
- Hot-plate behavior was tested immediately after termination of exposure.
- Latency of 60 seconds was considered as 100% inhibition of pain sensitivity.
- Authors also investigated the effects of exposure to 1,2,3-, 1,2,4- and 1,3,5- TMB on rotarod test performance and pain-sensing response two weeks after the termination of exposure.

Observation	**Latency of the Paw-Lick Response, sec**	
	1,2,4-TMB	**1,2,3-TMB**
Control	15.4±5.8	9.7±2.1
25 ppm (123 mg/m^3)	18.2±5.7	11.8±3.8*
100 ppm (492 mg/m^3)	27.6±3.2**	16.3±6.3***
250 ppm(1230 mg/m^3)	30.1±7.9**	17.3±3.4**
250 ppm (1230 mg/m^3) two weeks after termination of exposure	17.3±3.9	11.0±2.4
Health Effect at LOAEL	**NOAEL**	**LOAEL**
Decreased pain sensitivity	Control for 1,2,3-TMB 25 ppm for 1,2,4-TMB	25 ppm for 1,2,3-TMB 100 ppm for 1,2,4-TMB

Comments: Although rotarod data are useful in providing a qualitative description of neuromuscular impairment following 1,2,4-TMB or 1,2,3-TMB exposure, in comparison to effects on pain sensitivity, the data are not considered as robust regarding suitability for derivation of reference values. Namely, data are presented as dichotomized values instead of a continuous measurement of latency.

*, ** statistically significant from controls at p ≤ 0.05 and p≤0.01, respectively

*** Level of significance not reported in Table 1 from Korsak and Rydzyński (1996), however the results of an ad-

hoc t-test (performed by EPA) indicated significance at $p < 0.01$

Table A-2. Characteristics and quantitative results for Korsak et al. (2000b)

Study Design					
Species	**Sex**	**N**	**Exposure route**	**Concentration range**	**Exposure duration**
IMP: Wistar	M & F	10/dose, 20 in 1230mg/m^3 group	Inhalation	0, 123, 492, 1230 mg/m^3	90 days (6h/day, 5 d/ week)

Additional Study details

- Animals were exposed to 1,2,3-TMB in a dynamic inhalation chamber (1.3 m^3 volume) with 16 air changes/hour.
- Mean initial body weights were 290±25 g for males and 215±13 g for females; rats were housed in polypropylene cages with wire-mesh covers (5 animals/cage), with food and water provided *ad libitum.*
- Animals were randomized and assigned to the experimental groups.
- Hematological parameters were evaluated prior to exposure and 1 week prior to termination of exposure, and for the 1230 mg/m^3 exposure group, also evaluated two weeks after termination of exposure; blood clinical chemistry parameters were evaluated 18 hours after termination of exposure (animals were deprived of food for 24 hours)
- Necropsy was performed on all animals.
- Pulmonary effects were graded using an arbitrary scale: 0 = normal status, 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

Observation	**Exposure Concentration (mg/m^3)**			
	0	**123**	**492**	**1230**
	Body and Organ weights (mean ± SD)			
	Males			
Terminal Body weight (g)	390±35	408±50	404±33	413±46
Absolute organ weight (g)				
Lungs	1.90±0.22	1.86±0.26	1.99±0.37	1.88±0.34
Liver	8.28±0.97	8.83± 1.40	9.05±0.99	9.54± 1.50
Spleen	0.71±0.06	0.12±0.10	0.82±0.11	0.79±0.20
Kidney	2.34±0.27	2.29±0.23	2.48±0.25	2.50±0.25
Adrenals	0.059±0.012	0.061 ±0.016	0.061 ± 0.013	0.061 ±0.012
Testes	3.78±0.44	3.69±0.24	3.71 ±0.36	3.91 ±0.12
Heart	1.04±0.13	0.98 ±0.11	1.08±0.13	1.15 ±0.19
Relative organ weight (g)				
Lungs	0.510±0.071	0.479±0.026	0.504±0.082	0.468 ± 0.073
Liver	2.208 ±0.163	2.271 ±0.129	2.287±0.115	2.414 ±0.214*
Spleen	0.190±0.019	0.187 ± 0.015	0.207 ±0.021	0.203 ± 0.058
Kidney	0.623 ±0.049	0.594 ± 0.029	0.629 ± 0.033	0.637 ±0.060

Adrenals	0.016 ±0.003	0.016±0.003	0.015 ±0.003	0.016 ± 0.003
Testes	1.014±0.087	0.961 ±0.091	0.941 ±0.063	1.002±0.106
Heart	0.277 ±0.027	0.252±0.018	0.274±0.032	0.284±0.026
	Females			
Terminal Body weight (g)	268±18	262±21	263±14	259±23
Absolute organ weight (g)				
Lungs	1.62±0.15	1.55±0.33	1.47 ±0.18	1.51±0.16
Liver	6.05±0.42	5.85±0.47	5.94±0.51	6.05±0.44
Spleen	0.63±0.05	0.61±0.10	0.57±0.05*	0.56±0.06*
Kidney	1.58±0.16	1.53±0.12	1.54±0.10	1.62±0.16
Adrenals	0.080±0.014	0.082±0.010	0.083 ±0.011	0.075 ± 0.015
Ovaries	0.12±0.03	0.12±0.03	0.13±0.02	0.14±0.04
Heart	0.74±0.05	0.71±0.50	0.75±0.06	0.73±0.08
Relative organ weight (g)				
Lungs	0.651 ±0.053	0.637 ±0.122	0.604 ± 0.049	0.639±0.076
Liver	2.434 ±0.143	2.400 ± 0.088	2.448±0.190	2.555 ± 0.214
Spleen	0.257 ± 0.027	0.249 ± 0.032	0.234±0.019	0.237±0.022
Kidney	0.639±0.076	0.628 ± 0.024	0.638 ±0.032	0.686 ± 0.058
Adrenals	0.032 ± 0.005	0.034 ± 0.004	0.034±0.005	0.032±0.008
Ovaries	0.051±0.014	0.050±0.014	0.056 ±0.006	0.060±0.018
Heart	0.298±0.016	0.291 ± 0.012	0.309 ± 0.024	0.307 ± 0.026

Observation	**Exposure Concentration (mg/m³)**					
	0	**123**	**492**	**1230**	**1230[a]**	**Trend test[b]**
	Hematological parameters (mean ± SD)					
Hematocrit (%) Males	46.4± 1.6	45.8±2.6	45.7±1.3	45.5±2.1	43.5±26	0.1615
Hematocrit (%) Females	42.7±2.2	45.0±2.4	41.8 ± 1.6	41.5±24	41.7±20	0.0198
Hemoglobin (g/dL) Males	16.4± 1.0	17.6± 1.6	17.6±0.8	15.0± 1.2	ND	0.0688
Hemoglobin (g/dL) Females	13.9±0.7	15.1 ± 1.0*	14.6±0.6	14.7±0.9	ND	0.0748
RBCs (× 10^3/mm^3)[c] Males	9.49±2.03	10.25±1.29	10.11 ±1.27	8.05 ± 1.38*	8.6±1.5	0.0011
RBCs (× 10^3/mm^3)[c] Females	8.03± 1.11	8.73± 1.24	7.79±1.57	7.27 ± 1.32	6.6± 1.8	0.0185
WBCs (× 10^3/mm^3)[d] Males	10.09±2.23	9.38±3.29	7.71±3.45	9.03±275	6.3±4.6	0.1661
WBCs (× 10^3/mm^3)[d] Females	10.71 ±4.28	9.54±2.37	13.02±3.07	13.01 ±4.53	62±2.5	0.0189
Rod neutrophil (%) Males	0.8± 1.0	1.0± 1.1	0.4±0.5	0.5±0.6	5.2±3.0	0.1878
Rod neutrophil (%) Females	0.4±0.8	0.6±0.6	1.1 ± 1.4	0.4±0.8	1.8±22	0.4711
Segmented neutrophil (%) Males	24.8±4.5	25.4±5.8	20.7±5.8	17.7±8.3*	27.5±9.2	0.0032
Segmented neutrophil	23.1 ±6.1	19.7±3.4	16.4±4.2*	11.9± 7.1**	19.6±8.3	0.0000

(%)Females						
Eosinophil (%) Males	1.3± 1.4	0.8±1.0	0.8±1.1	0.6±0.8	0.6±0.6	0.1439
Eosinophil (%) Females	1.4± 1.0	0.6±0.6	0.7±0.8	0.8±0.9	0.7±0.8	0.2778
Lymphocyte (%) Males	71.2±5.0	71.6±6.8	75.4±4.7	79.3±78.0 **	63.7 ± 11.3	0.0015
Lymphocyte (%) Females	73.2±7.9	77.5±4.9	80.4±5.1	84.0±78.0 **	75.7±9.9	0.0003
Monocyte (%) Males	1.9± 1.6	1.3 ± 1.4	2.3±20	1.6±22	3.1 ±3.7	0.3014
Monocyte (%) Females	2.0±2.0	1.6± 1.6	1.1±1.3	2.1 ± 1.7	1.3± 1.8	0.2426
Lymphoblast (%) Males	0.0±0.0	0.0±0.0	0.2±0.6	0.2±0.6	0.0±0.0	0.2911
Lymphoblast (%) Females	0.0±0.0	0.0±0.0	0.1±0.3	0.3±0.7	0.0±0.0	0.1403
Myelocyte (%) Males	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.5000
Myelocyte (%) Females	0.0±0.0	0.0±0.0	0.0±0.0	0.5 ±0.2	0.0±0.0	0.3963
Erythroblast (%) Males	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.5000
Erythroblast (%) Females	0.0±0.0	0.0±0.0	0.0±0.0	0.1 ±0.3	0.0±0.0	0.2995
Reticulocyte (%) Males	2.8±1.3	2.1 ± 1.7	3.8±2.1	4.5 ± 1.8*	6.9±3.1**	0.0017
Reticulocyte (%) Females	2.6±0.9	4.6±2.5*	5.2±0.50	4.4±3.0	6.8±3.5	0.0459
Platelet (× 10^3/mm^3) Males	262±51	266±70	257 ±81	242±76	277±80	0.1708
Platelet (× 10^3/mm^3) Females	224±68	290±70	249±53	204±44	258±45	0.0329
Clotting time (sec) Males	29.7±8.6	23.0±10.0	37.9±9.9	29.2±15.6	21.7±5.4	0.4650
Clotting time (sec) Females	27.2±2.8	25.0±9.4	23.8±9.5	25.1 ± 12.1	25.9±8.0	0.3479
Observation	**Exposure Concentration (mg/m^3)**					
	0	**123**	**492**	**1230**		**Trend test[b]**
	Clinical Chemistry Parameters (mean ± SD)					
AST (U/dL)[e] Males	107.8±14.2	102.9±15.1	103.6±14.5	119.6±27.3		0.2223
AST (U/dL)[e] Females	96.1 ±9.4	96.9±9.9	117.1±23.9	104.6± 15.7		0.2118
ALT (U/dL)[f] Males	41.3±2.0	40.7±3.1	41.5±5.5	45.5±5.6		0.0637
ALT (U/dL)[f] Females	39.7±3.5	39.5±6.4	36.2±3.3	30.5±9.9**		0.1844
ALP (U/dL)[g] Males	70.5±15.2	70.6±11.7	66.5± 10.8	63.7±15.7		0.1518
ALP (U/dL)[g] Females	21.5±2.7	25.8±8.4	31.1±8.6*	30.5±9.9*		0.1740
SDH (U/dL)[h] Males	1.6±0.7	2.3± 1.3	2.5±0.9	2.7±0.7*		0.0083
SDH (U/dL)[h] Females	1.7±0.7	1.9±0.9	1.5±0.7	1.8± 1.0		0.0637
GGT (µU/ml)[i] Males	0.77±0.66	0.77±0.97	0.40±0.51	0.50±0.75		0.4700
GGT (µU/ml)[i] Females	0.55±0.72	0.44± 1.01	0.66± 1.11	0.30±0.48		0.2821
Bilirubin (mg/dL) Males	0.600±0.516	0.600±0.516	0.800±0.422	0.625±0.518		0.2594
Bilirubin (mg/dL) Females	0.911 ±0.348	1.161 ±0.469	0.930±0.463	0.976±0.421		0.3092

Total cholesterol (mg/dL) Males	63.1 ± 10.1	62.2±11.6	64.5±16.2	65.0±9.1	0.0920
Total cholesterol (mg/dL) Females	60.1 ±12.2	62.4±15.3	62.3±7.7	64.4±14.1	0.4775
Glucose (mg/dL) Males	95.5±13.1	110.8±14.7	100.2±15.2	114.5±20.6	0.0876
Glucose (mg/dL) Females	115.9±8.5	121.0±17.5	109.2±5.8	109.8±10.8	0.4838
Total protein (g) Males	7.84±0.13	8.02±0.50	7.76±0.27	8.04±0.59	0.3242
Total protein (g) Females	8.24±1.24	8.36±1.14	8.65±0.84	8.62±0.96	0.4036
Albumin (g) Males	3.15±0.73	3.15 ±1.33	3.08±1.30	2.95±1.12	0.2279
Albumin (g) Females	3.22±1.28	3.17 ±1.03	2.58±1.28	3.60±1.17	0.2408
Creatinine (mg/dL) Males	41.24±8.94	41.35 ± 11.28	40.79 ± 9.30	43.61± 13.10	0.3982
Creatinine (mg/dL) Females	62.54±10.66	61.60±7.07	67.11 ± 10.86	59.71 ± 7.51	0.1641
Urea (mg/dL) Males	38.7±4.5	38.1±9.1	36.9±4.1	41.7 ± 7.5	0.1145
Urea (mg/dL) Females	42.0±5.5	43.5±4.4	40.0±4.3	39.0±29	0.4718
Calcium (mg/dL) Males	10.6±0.6	10.7 ±0.8	10.8±0.7	10.9±0.5	0.2449
Calcium (mg/dL) Females	11.1 ±0.8	11.7 ±0.3	11.8 ±0.2	11.8±0.7	0.3011
Phosphorus (mg/dL) Males	8.60±0.95	8.26±0.60	9.19±0.88	9.41±0.55	0.1580
Phosphorus (mg/dL) Females	6.56±0.70	6.25±1.17	6.41± 1.02	7.18± 1.09	0.4050
Sodium (mmol/L) Males	143.9±2.1	144.1 ± 1.5	143.9±25	144.8±24	0.4950
Sodium (mmol/L) Females	144.0±1.5	143.8±1.3	142.7± 1.3	143.8± 1.4	0.3628
Potassium (mmol/L) Males	4.70±0.35	4.45±0.28	4.75±0.37	4.97±0.56	0.2907
Potassium (mmol/L) Females	4.52±0.41	4.51 ±0.43	4.28±0.41	4.37±0.34	0.4108
Chloride (mmol/L) Males	107.3±2.3	107.7 ±4.3	106.8± 1.8	106.5 ± 1.9	0.4353
Chloride (mmol/L) Females	108.1 ±3.2	108.1±1.5	107.1± 1.3	107.2±23	0.0601

Observation	**Exposure Concentration (mg/m³) [Dose group ID]**					
	0 [1]	**123 [2]**	**492 [3]**	**1230 [4]**	**Comparison to Controls[c]**	**Trend test[b]**
Proliferation of peribronchial lymphatic tissue (0-3)[j] Males	2.0[d] (23.4)[e]	1.2 (11.5)	1.8 (22.0)	2.0 (23.5)	1-2*	0.2
Proliferation of peribronchial lymphatic tissue (0-3)[j] Females	24(22.8)	1.3 (12.1)	1.5 (16.4)	L3 (22.3)	1-2**; 1-3	0.2
Formation of lymphoepithelium in bronchii (0-3) Males	1.5 (23.9)	0.9 (14.9)	1.0 (16.0)	1.5 (25.7)	1-3*; 1-4**	0.3

Formation of lymphoepithelium in bronchii (0-3) Females	1.8 (27.9)	0.7 (11.1)	1.1 (16.9)	1.5 (23.8)		0.3
Goblet Cells (0-3) Males	1.8 (18.6)	1.5 (14.5)	2.5 (28.5)	1.8 (18.2)		0.18
Goblet Cells (0-3) Females	1.3 (11.9)	1.6 (16.9)	2.0 (23.1)	2.4 (28.4)	1-3*; 1-4**	0.001
Interstitial lymphocytic infiltration (0-3) Males	0.4 (18.0)	0.1 (14.1)	0.4 (18.0)	1.5 (31.0)	1-4*	0.006
Interstitial lymphocytic infiltration (0-3) Females	1.2 (23.7)	0.6 (15.3)	0.8 (17.9)	1.1 (22.9)		0.4
Alveolar macrophages (0-3) Males	0.9 (17.9)	0.9 (17.9)	1.2 (22.6)	1.2 (21.7)		0.15
Alveolar macrophages (0-3) Females	1.5 (26.1)	1.1 (21.1)	0.5 (17.8)	0.7 (14.8)		0.01
Bronchitis and broncho-pneumonia (0-4) Males	0.5 (20.1)	0.2 (16.6)	0.8 (23.8)	0.7 (19.5)		0.3
Bronchitis and broncho-pneumonia (0-4) Females	0.2 (17.6)	0.4 (22.5)	0.2 (17.5)	0.6 (21.8)		0.3
Cumulative score of all individual Males	7.1 (19.8)	4.8 (11.2)	7.7 (24.2)	8.7 (25.8)		0.01
Cumulative score of all individual Females	8.4 (24.9)	5.7 (13.5)	6.5 (16.8)	8.2 (24.6)	1-2*	0.4
Health Effect at LOAEL	**NOAEL**			**LOAEL**		
Pulmonary lesions	492 mg/m^3			1230 mg/m^3		
Comments: The observed inflammatory lesions are coherent with observations of increased inflammatory cell populations in bronchoalveolar lavage fluid due to 1,2,4-TMB exposure in Korsak et al. (1997). The authors did not report the incidences of pulmonary lesions, but rather the results of the Kruskall-Wallis test. This makes it difficult to interpret the dose-response relationship and limits analysis of these endpoints to the NOAEL/LOAEL method rather than a BMD modeling method.						

[a] Responses measured 14 days after termination of exposure

[b] p-value reported from Jonckheere's trend test

[c] Reports the results of pair-wise statistical significance of exposure groups compared to controls (i.e., 1-3 would indicate that the 492 mg/m^3 was statistically significantly different from controls)

[d] Mean

[e] Results presented as ranges of the Kruskal-Willis test

*, ** statistically significant from controls at $p \leq 0.05$ and $p \leq 0.01$, respectively

1

APPENDIX B. DOSE-RESPONSE MODELING FOR THE DERIVATION OF REFERENCE VALUES FOR EFFECTS OTHER THAN CANCER

B.1. BENCHMARK DOSE MODELING SUMMARY

Table B-1. Model predictions (constant variance) for increased latency to pawlick in male Wistar rats, 1,2,3-TMB. (Korsak and Rydzyński, 1996)

Model[a]	Goodness-of-fit		BMD_{1SD} (mg/m^3)	$BMDL_{1SD}$ (mg/m^3)	Basis for Model Selection
	p-value	AIC			
Exponential 2 Exponential 3	0.005704	262.2082	700.938	566.333	No model selected as Test 2 *p*-value was < 0.1.
Exponential 4	0.5461	254.2393	192.288	107.132	
Exponential 5[b]	N/A	255.8749	201.187	111.315	
Hill[b]	N/A	255.874906	185.863	110.398	
Linear Polynomial 2° Polynomial 3° Power	0.01728	259.991214	577.555	442.59	

[a] Constant variance case presented (Test 2 *p*-value = 0.0.0001146). This *p*-value indicates that a constant variance model does not adequately describe the observed variances. BMDS recommends using a non-homogenous variance model.
[b] *p*-value not reported due to estimated model parameters = dose groups

1

Table B-2. Model predictions (modeled variance) for increased latency to pawlick in male Wistar rats, 1,2,3-TMB. (Korsak and Rydzyński, 1996)

Model[a]	Goodness-of-fit		BMD_{1SD} (mg/m^3)	$BMDL_{1SD}$ (mg/m^3)	Basis for Model Selection
	p-value	AIC			
Exponential 2 Exponential 3	<0.0001	259.5324	496.844	329.318	No model selected as Test 3 *p*-value was < 0.1.
Exponential 4	0.301	241.4193	86.2091	46.7265	
Exponential 5[b]	N/A	242.5858	113.028	51.9836	
Hill[b]	N/A	265.438765	334.7333	Not calculated	

Linear **Polynomial 2°** **Polynomial 3°[c]** **Power**	0.0003247	254.414778	319.651	195.989	

[a] Modeled variance case presented (Test 3 *p*-value = 0.07076). This *p*-value indicates that a modeled variance model does not adequately describe the observed variances.
[b] *p*-value not reported due to estimated model parameters = dose groups
[c]The 3rd degree polynomial model failed to converge.

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Table B-3. Model predictions (modeled variance, high dose dropped) for increased latency to pawlick in male Wistar rats, 1,2,3-TMB. (Korsak and Rydzyński, 1996)

Model[a]	Goodness-of-fit		BMD_{1SD} (mg/m³)	$BMDL_{1SD}$ (mg/m³)	Basis for Model Selection
	p-value	AIC			
Exponential 2 **Exponential 3**	0.07449	203.2651	192.144	131.627	Of the models that provided an adequate fit and valid BMDL estimate, the linear model was selected based on the lowest AIC (BMDLs differed by less than 3-fold).
Exponential 4[b]	N/A	202.0839	104.546	52.5736	
Linear **Polynomial 2°** **Polynomial 3°** **Power**	**0.2016**	**201.714812**	**152.065**	**97.1911**	

[a] Modeled variance case presented (Test 3 *p*-value = 0.5008). Selected model in bold; scaled residuals for selected model for concentrations 0, 123, and 492 mg/m³ were -0.102, 0.319, and -0.354, respectively.
[b] A goodness-of-fit p-value was not calculated for the Exponential 4 model (due to estimated model parameters = dose groups); however, inspection of scaled residuals and visual fit indicated appropriate model fit.

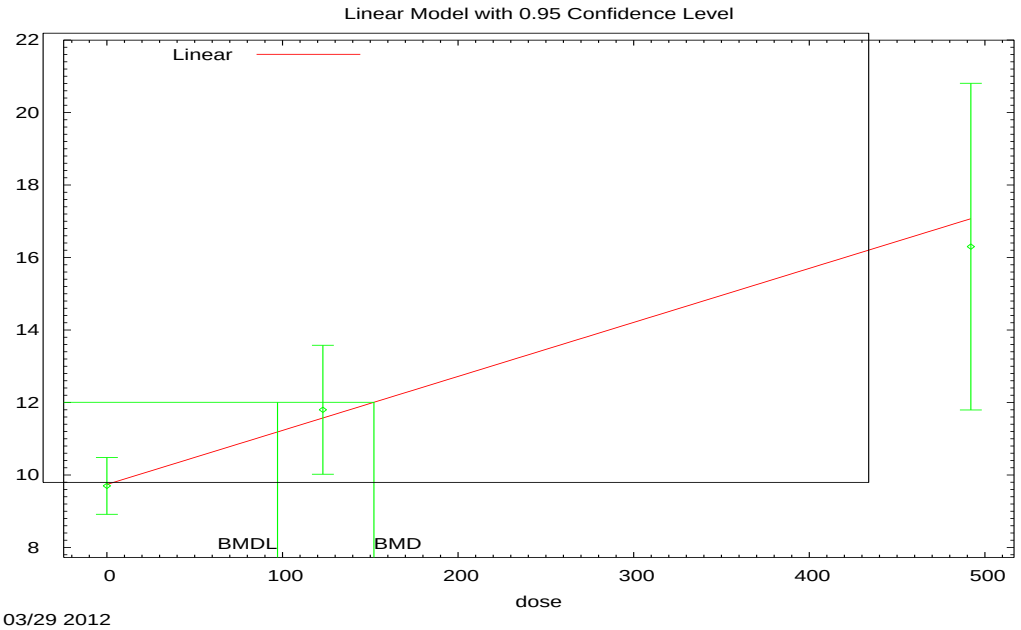

Figure B-1. Plot of mean response by dose (mg/m³ 1,2,3-TMB) for increased latency to pawlick in male Wistar rats, with fitted curve for Linear model (BMR = 1 SD, modeled variance, high dose dropped). (Korsak et al., 2000b)

Table B-4. Model predictions (constant variance) for decreased segmented neutrophils in male Wistar rats, 1,2,3-TMB. (Korsak et al., 2000b)

Model[a]	Goodness-of-fit		BMD_{1SD} (mg/m^3)	$BMDL_{1SD}$ (mg/m^3)	Basis for Model Selection
	p-value	AIC			
Exponential 2 Exponential 3	**0.7155**	**189.1052**	**915.77**	**534.809**	Of the models that provided an adequate fit and valid BMDL estimate, the Exponential 2 model was selected based on the lowest AIC (BMDLs differed by less than 3-fold).
Exponential 4	0.4482	191.0108	814.879	261.734	
Exponential 5[b]	N/A	192.4867	547.805	137.551	
Hill[b]	N/A	192.486705	564.348	Not calculated	
Linear Polynomial 2° Polynomial 3° Power	0.6711	189.233222	979.089	632.777	

[a] Constant variance case presented (Test 2 *p*-value = 0.2692). Selected model in bold; scaled residuals for selected model for concentrations 0, 123, 492 and 1230 mg/m^3 were -0.242, 0.5701, -0.4994, 0.176, respectively.

[b] A goodness-of-fit p-value was not calculated for the Exponential 5 or Hill models, inspection of scaled residuals indicated appropriate model fit; however, inspection of visual fit indicated uncertain dose-response characteristics, and therefore, these models were excluded from consideration.

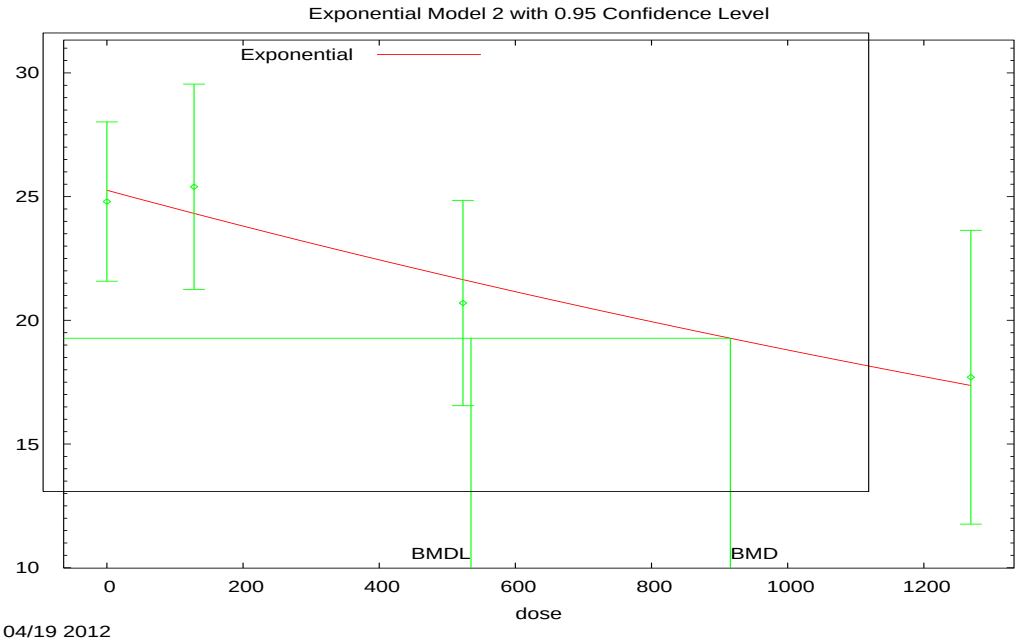

Figure B-2. Plot of mean response by dose (mg/m^3 1,2,3-TMB) for decreased segmented neutrophils in male Wistar rats, with fitted curve for Exponential 2 model (BMR = 1 SD, constant variance). (Korsak et al., 2000b)

Table B-5. Model predictions (constant variance) for decreased segmented neutrophils in female Wistar rats, 1,2,3-TMB. (Korsak et al., 2000b)

Model[a]	Goodness-of-fit		BMD_{1SD} (mg/m³)	$BMDL_{1SD}$ (mg/m³)	Basis for Model Selection
	p-value	AIC			
Exponential 2 Exponential 3	0.6401	177.6514	517.048	334.805	Of the models that provided an adequate fit and valid BMDL estimate, the Hill model was selected based on the lowest BMDL (BMDLs differed by more than 3-fold).
Exponential 4 Exponential 5	0.5208	179.1714	365.397	134.354	
Hill	**0.5692**	**179.083138**	**337.442**	**99.2111**	
Linear Polynomial 2° Polynomial 3° Power	0.4533	178.341743	645.521	465.309	

[a] Constant variance case presented (Test 2 *p*-value = 0.09252). Although this *p*-value is less than 0.10, it indicates a marginal fit at the 95% confidence level, and therefore a constant variance is determined to adequately fit the observed variance data. Selected model in bold; scaled residuals for selected model for concentrations 0, 128, 523, and 1269 mg/m³ were 0.209, -0.412, 0.312, and -0.108, respectively.

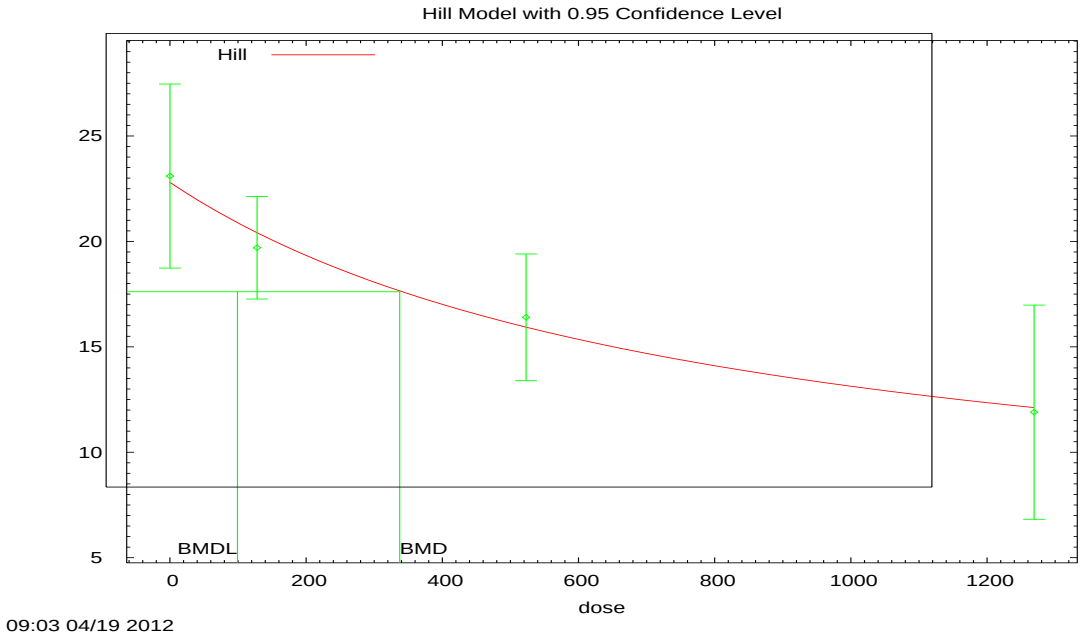

Figure B-3. Plot of mean response by dose (mg/m³ 1,2,3-TMB) for decreased segmented neutrophils in female Wistar rats, with fitted curve for Hill model (BMR = 1 SD, constant variance). (Korsak et al., 2000b)

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Table B-6. Model predictions (constant variance) for increased reticulocytes in male Wistar rats, 1,2,3-TMB. (Korsak et al., 2000b)

Model[a]	Goodness-of-fit		BMD_{1SD} (mg/m³)	$BMDL_{1SD}$ (mg/m³)	Basis for Model Selection
	p-value	AIC			
Exponential 2 Exponential 3	0.2733	89.08418	1112.25	806.744	Of the models that provided an adequate fit and valid BMDL estimate, the Linear model was selected based on the lowest AIC (BMDLs differed by less than 3-fold).
Exponential 4	0.1397	90.67033	900.404	308.017	
Exponential 5[b]	N/A	91.37006	540.186	140.925	
Hill	N/A	91.370061	554.848	Not calculated	
Linear Polynomial 2° Polynomial 3° Power	**0.3105**	**88.828645**	**1025.1**	**652.898**	

[a] Constant variance case presented (Test 2 *p*-value = 0.5223). Selected model in bold; scaled residuals for selected model for concentrations 0, 128, 523 and 1269 mg/m³ were 0.555, -1.14, 0.793, and -0.212, respectively.

[b] A goodness-of-fit p-value was not calculated for the Exponential 5 model, inspection of scaled residuals indicated appropriate model fit; however, inspection of visual fit indicated uncertain dose-response characteristics, and therefore, these models were excluded from consideration.

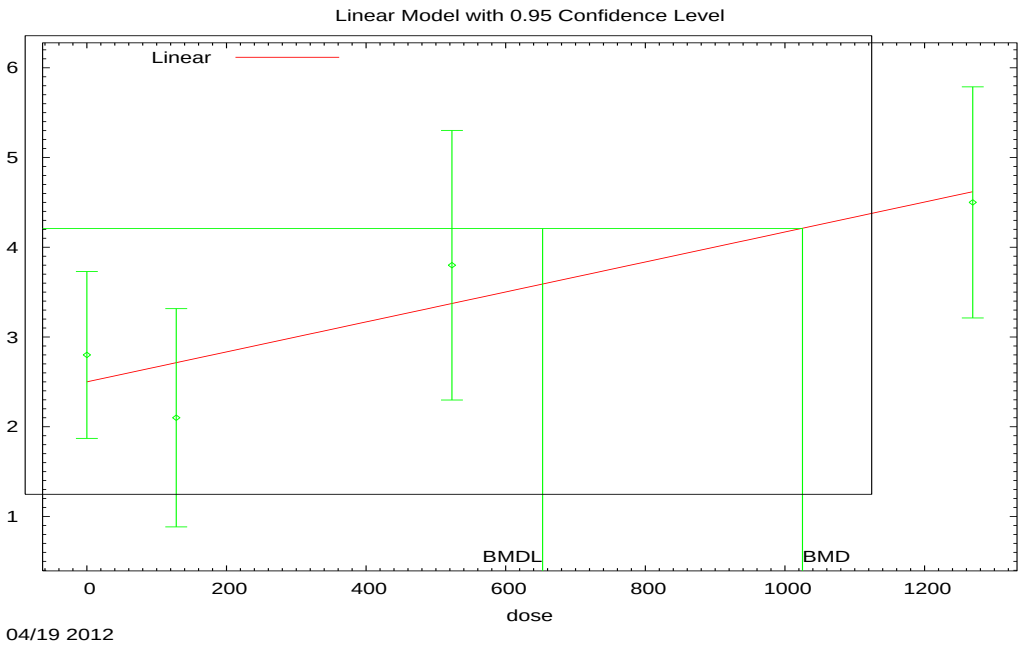

Figure B-4. Plot of mean response by dose (mg/m³ 1,2,3-TMB) for increased reticulocytes in male Wistar rats, with fitted curve for Linear model (BMR = 1 SD, constant variance). (Korsak et al., 2000b)

REFERENCES FOR APPENDICES[1]

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[1] Multiple references published in the same year by the same author(s) have been assigned a letter (e.g., 1986a, 1986b) in Volume 1 of the Toxicological Review, based on which publication's title comes first alphabetically. Those same letters have been retained for the appendices.