

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 | | | | | |
| <ul style="list-style-type: none"> Animals were exposed to either 1,2,3-, 1,2,4-, or 1,3,5-TMB in a dynamic inhalation chamber (1.3 m³ 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 <i>ad libitum</i>. 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 | |
| <p>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.</p> | | | | | |

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

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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 | | | | | |
| <ul style="list-style-type: none"> Animals were exposed to 1,2,3-TMB in a dynamic inhalation chamber (1.3 m³ 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 <i>ad libitum</i>. 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/m³ 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/m³) | | | | |
| | 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 | |

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| 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 |

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| (%)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/m³) | | | | | Trend test^b |
| | 0 | 123 | 492 | 1230 | | |
| | 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±0.51 6 | 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 | |

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| 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 |

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| 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 Kruskal-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/m³ was statistically significantly different from controls)

^d Mean

^e Results presented as ranges of the Kruskal-Willis test

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

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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 = 0.0001146). 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

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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 | |

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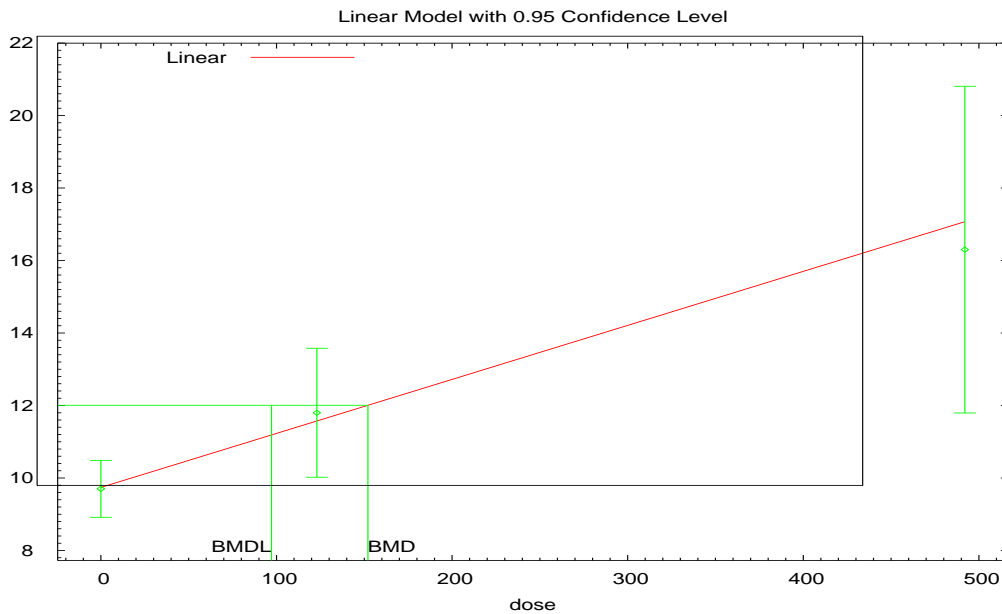
Table B-3. Model predictions (modeled variance, high dose dropped) for increased latency to pawlick in male Wistar rats, 1,2,3-TMB. ([Korsak and Rydzyński, 1996](#))

| Model ^a | Goodness-of-fit | | BMD _{1SD} (mg/m ³) | BMDL _{1SD} (mg/m ³) | 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^o Polynomial 3^o 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.

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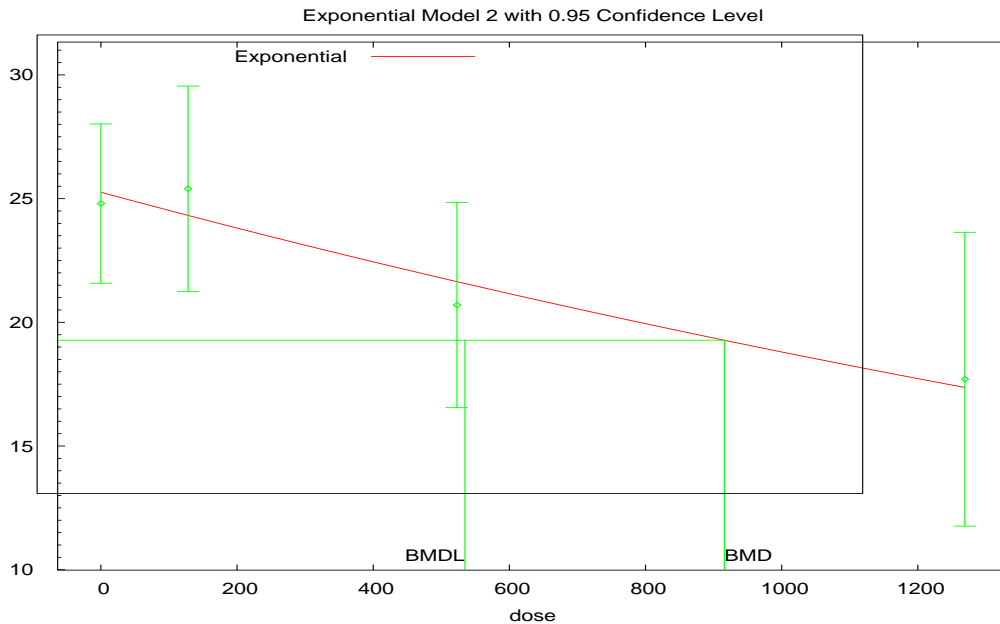
Figure B-1. Plot of mean response by dose (mg/m³ 1,2,3-TMB) for increased latency to pawlick in male Wistar rats, with fitted curve for Linear model (BMR = 1 SD, modeled variance, high dose dropped). ([Korsak et al., 2000b](#))

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^o Polynomial 3^o 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/m³ 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.



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Figure B-2. Plot of mean response by dose (mg/m³ 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/m ³) | BMDL _{1SD} (mg/m ³) | 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.

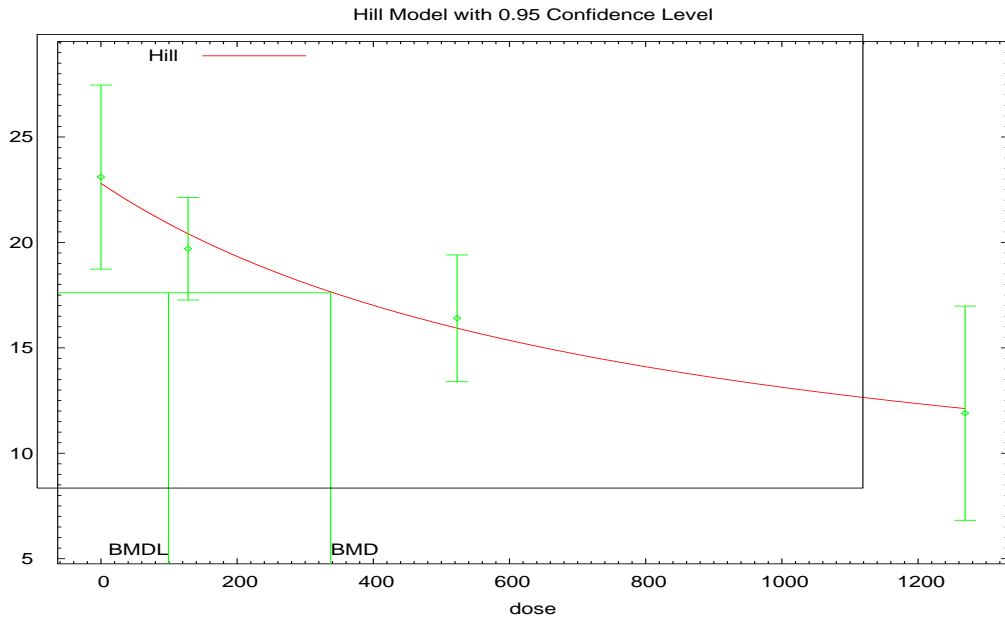


Figure B-3. Plot of mean response by dose (mg/m³ 1,2,3-TMB) for decreased segmented neutrophils in female Wistar rats, with fitted curve for Hill model (BMR = 1 SD, constant variance). (Korsak et al., 2000b)

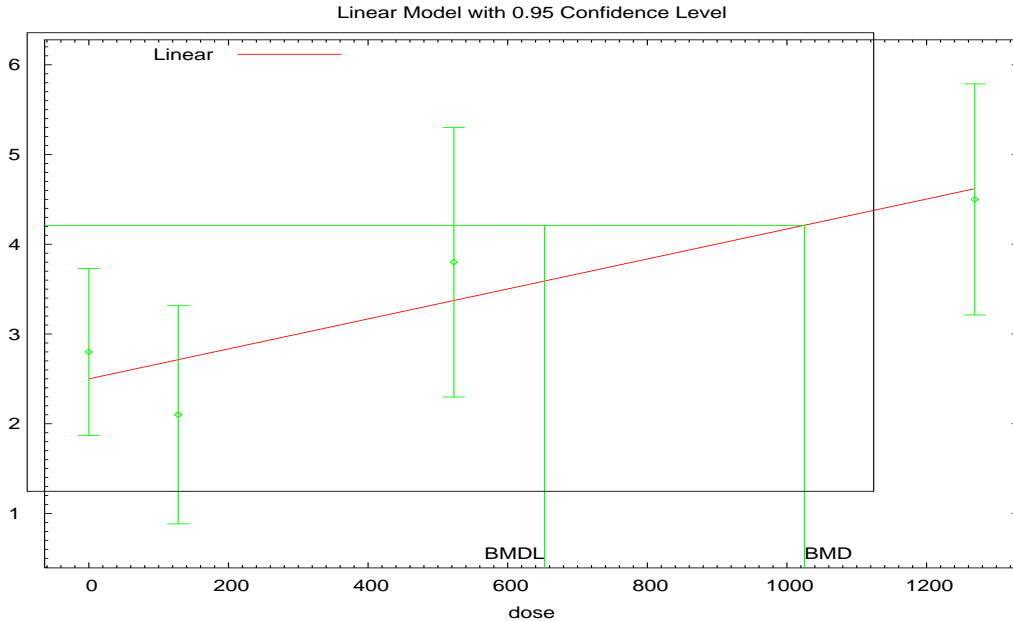
Table B-6. Model predictions (constant variance) for increased reticulocytes in male Wistar rats, 1,2,3-TMB. (Korsak et al., 2000b)

| Model ^a | Goodness-of-fit | | BMD _{1SD} (mg/m ³) | BMDL _{1SD} (mg/m ³) | 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.

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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 APPENDICES¹

- 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.