

Health Consultation

Sulfolane

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Introduction and Background

The Alaska Department of Health and Social Services requested that the ATSDR Division of Toxicology and Environmental Medicine review the chemical-specific health consultation for sulfolane issued in February 2010 (ATSDR 2010). Sulfolane has been detected in groundwater under the city of North Pole, Alaska. A completed exposure pathway connects sulfolane to North Pole residents through private and community wells. Alaska previously requested that ATSDR develop a public health action level for sulfolane in drinking water, as well as describe potential health effects of sulfolane exposure. The public health action level is a non-regulatory level set to identify whether human exposure needs further evaluation. ToxStrategies, a contractor for the site's potentially responsible party, provided an additional toxicological study of sulfolane and expressed concern about the methodology ATSDR employed in setting the action level for sulfolane (ToxStrategies 2010). ToxStrategies presented several alternative screening values, all derived with Benchmark Dose (BMD) methodology. ToxStrategies criticized ATSDR for not having done an independent dose-response analysis of the key study and for using semi-quantitative methods to derive its public health action level (ToxStrategies 2010). Additionally, ToxStrategies contended that there was no need to use child-specific intake factors to derive an action level (ToxStrategies 2010). ATSDR, as a matter of policy, will re-examine its decisions in the event that compelling new evidence or reasoning is presented.

BMD methods use nonlinear curve fitting software to fit a dose-response curve to the toxicological testing data. A point of departure, usually the 10% response rate (BMD_{10}) for dichotomous data or the 1 standard deviation (BMD_{1SD}) change in a continuous variable, is established. The methodology then calculates a lower statistical confidence on this BMD, referred to as the lower confidence limit of the benchmark dose (BMDL). ATSDR derived its 2010 sulfolane action level using a reported no observed adverse effect level (NOAEL) and dividing by uncertainty factors (UF). The BMD approach has several advantages over the NOAEL approach used by ATSDR (Crump 1984). Nevertheless, BMD methods require decisions such as appropriate model selection and restrictions on model parameters; these decisions can radically affect the BMDL reported. To be responsive to Alaska Department of Health and Social Services, ATSDR initially utilized the NOAEL/UF approach in its 2010 health consultation because default BMD models did not appear to adequately fit the data. Therefore, in light of these issues, this document reviews:

1. Does the new information warrant revision to the ATSDR recommendations for the site public health action level?
2. Do the data support the use of child-specific and infant-specific consumption and body weights in the public health action level of sulfolane?
3. What is the appropriate point of departure for setting a provisional health guidance value dose for sulfolane?

This document focuses on the above issues. Additional background information regarding what is known about toxicity of sulfolane is contained in the 2010 health consultation (ATSDR 2010).

Summary of Previous Health Consultation

Sulfolane is an industrial solvent used in liquid-liquid and liquid-vapor extraction of compounds such as aromatic hydrocarbons from petroleum (Brown et al. 1966; Andersen 1976; HSDB 2006). Sulfolane has also been reportedly used in fractionalization of wood tars, a component of hydraulic fluid, textile finishing, and as a curing agent in epoxy resins (HSDB 2006). Sulfolane is completely miscible in water, acetone, glycerol and many oils (Brown et al. 1966). Sulfolane has an odor threshold in water between 1.79 and 10.6 milligrams per liter (mg/L) (Zhu 1987 et al.). Sulfolane mixes well in water, is not very volatile, is not highly viscous, and is highly polar.

Sulfolane is acutely toxic at relatively high doses (over 200 milligrams per kilogram (mg/kg)) in several species tested (ATSDR 2010). While sulfolane's acute toxicity has been characterized in a number of species, only a limited number of studies examine longer-term exposure (Table 1). Of the available intermediate duration studies, Zhu et al. (1987) has been identified as the key study, with effects noted in hepatic and lymphoreticular systems of rats (90 days) and guinea pigs (90 days and 6 months). The study author identified an oral NOAEL for guinea pigs as 0.25 mg/kg/day. In its February 2010 health consultation, ATSDR applied an uncertainty factor of 100 to the NOAEL of 0.25 mg/kg/day (10 for extrapolation from animals to humans, 10 to account for human variability), resulting in a health guidance value dose of 0.0025 mg/kg/day (2.5 micrograms/kilogram/day ($\mu\text{g}/\text{kg}/\text{day}$)). Using standard water consumption assumptions (ATSDR 2005), this sulfolane dose would equate to the following action levels:

- 25 parts-per-billion¹ (ppb) for infant populations (assumes 1 liter water per day at 10 kg bodyweight)
- 40 ppb for child populations (assumes 1 liter water per day at 16 kg bodyweight)
- 87.5 ppb for adult populations (assumes 2 liters water per day at 70 kg bodyweight)

Utilizing BMD methods, and after consultation with members of the ATSDR Minimal Risk Level Committee, ATSDR now recommends:

- 20 ppb for infant populations (Assumes 1 liter water per day at 10 kg bodyweight)
- 32 ppb for child populations (Assumes 1 liter water per day at 16 kg bodyweight)
- 70 ppb for adult populations (Assumes 2 liters water per day at 70 kg bodyweight)

Discussion

BMDS analysis of Available Intermediate Duration Studies

An ad hoc committee of ATSDR's Minimal Risk Level (MRL) workgroup convened to review and discuss the February 2010 Health Consultation of sulfolane, and to review the information and issues raised by ToxStrategies in its August 2010 sulfolane assessment. These recommendations were further reviewed with toxicologists—including experts in Benchmark Dose Modeling—at the U.S. Environmental Protection Agency (USEPA), The U.S. Food and Drug Administration, and the National Institute for Occupational Safety and Health. For the derivation of a health guidance sulfolane value, ATSDR considered three intermediate exposure

¹ 1 part-per-billion of sulfolane is equivalent to 1 microgram of sulfolane per liter of water

duration studies² (Table 2). ATSDR has been unable to locate chronic studies on sulfolane. ATSDR used U.S.EPA's Benchmark Dose Modeling System (BMDS) version 2.12 to establish BMDLs for each of the studies and their health effects (Appendix B) (USEPA 2010a).

Zhu et al. 1987

The Zhu et al. study (Table 3), reports an intermediate-duration oral study of guinea pigs (Zhu et al. 1987). The manner and schedule of oral administration is not specified. This introduces some uncertainty in the dosing. If the animals were gavaged on a less-than 7 day per week schedule for the study duration, the average dose could be potentially less than the administered dose. Zhu et al.'s purported purpose was to derive a cumulative toxicity value for sulfolane in drinking water. The authors specifically report a chronic threshold dose of 2.5 mg/kg and a NOAEL of 0.25 mg/kg, suggesting that these values were averaged over the study's duration. ATSDR assumes the chronic dose was accurately reported.

For the Zhu et al. study, ATSDR considered the following toxic end points: shrinkage of the white pulp of the spleen at 3 months and 6 months, and fatty degeneration of the liver at 6 months. The study noted changes in blood chemistry and cell counts in the bone marrow, but the lack of reporting of parameter variability details prevent a full dose-response analysis. ATSDR does not use severe health effects to establish a point of departure. Thus, severe fatty degeneration of the liver was not modeled. The liver and spleen effects, however, showed a significant trend (using the Cochran-Armitage test for trend). Compared with controls, Fisher's Exact test p-values decreased with dose in the 3-month spleen data and in the 6-month liver and spleen data. P-values were below the standard statistical-significance threshold (less than 5% chance of no difference, $p < 0.05$) at 250 mg/kg/day. Borderline statistical significance ($p = 0.054$) occurred at 25 mg/kg/day. Multiple comparison adjustment (e.g., Holm's correction) was not used because Fisher's Exact Test will fail to reject the null hypothesis at a rate far less than it nominally reports (Armitage et al. 2002; Lin and Yang 2009).

For fatty liver degeneration effects in the Zhu et al. study, ATSDR considered the primary and alternative models in the BMDS. ATSDR utilized the BMDS models with restrictions on parameters—as recommended in the BMDS system—and also without restrictions. While several of the primary models passed the X^2 criterion of $p > 0.1$ (Appendix B, Table B-1), boundary restrictions constrained all of the primary models' parameters. The literature has discussed some statistical issues and concerns that arise when a model parameter hits a boundary restriction (Kopylev and Fox 2009) with respect to derivation of BMDLs. This is illustrated by the magnitude of the changes observed in BMDL's and goodness-of-fit measures, when the restrictions are removed from the models. The purpose of parameter boundary restrictions are to prevent the occurrence of unrealistic model predictions. For example, the restriction on slope in the log-logistic model prevents an unrealistically high dose-response rate at very low doses. Accurate assessment of the dose response data is critical for ATSDR's public health assessment process (cf. ATSDR Public Health Assessment Guidance Manual, chapter 8) (ATSDR 2005). Thus, ATSDR considered alternative models in BMDS, with USEPA recommended restrictions on the parameters. Of the alternatives, the restricted dichotomous Hill model provided superior fits to the Zhu et al. fatty liver dose-response data than did the restricted log-logistic model. In

² ATSDR considers intermediate exposure to be from 2 weeks to 1 year.

fact, the dichotomous Hill model is similar to the log-logistic model, and two of the four ATSDR external reviewers recommended it. The restricted dichotomous Hill model predicted the BMDL for the liver effect seen in Zhu et al. as 2.4 mg/kg/day.

Likewise, in evaluating the 6-month spleen data, the restricted dichotomous Hill model best described the dose response data, as measured by higher X^2 , lower Akaike information criterion (AIC), and lower residuals (Appendix B, Table B-2). While passing the X^2 criterion, parameter boundaries constrained the primary models. The restricted dichotomous Hill model predicted a BMDL for sulfolane of 1.5 mg/kg/day.

For the 3-month spleen dichotomous data, ATSDR considered all the primary and alternative models with and without recommended restrictions on model parameters (Appendix B, Table B-3). The dichotomous Hill model, Zhu et al. better fit the data than other restricted models, and predicted a BMDL at 1.5 mg/kg/day.

Huntingdon Life Sciences 2001

Huntingdon Life Sciences (HLS) (2001) conducted a detailed 90-day study of male and female rats exposed to sulfolane in their drinking water *ad libitum*. This administration mode may be more relevant to water contamination than is oral gavage, because in a gavage study the animals typically receive a bolus dose of the contaminant on a daily basis, whereas with a drinking water study the animals would receive their dose gradually as they drink water. While good laboratory practices (GLP) governed this study, the study is not available in the open, peer-reviewed literature.

Only 10 rats per sex per dose group were exposed. At the time of ATSDR's original health consultation, this study was unavailable to the agency for review, although summaries were available (CCME 2006). ToxStrategies obtained a copy of this study and later provided it to ATSDR. In the study, HLS researchers conducted a comprehensive battery of observations (weight, food/water intake, reflexes, and behavior), examined 13 major organ systems (adrenals, brain, femur, heart, ileum, kidneys, liver, lungs, mammary area, spinal cord, stomach, thyroid, and uterus), and performed hematological examination and chemical analysis of the blood. The only reported significant effect relevant to human health was a reduction of white blood cell and lymphocyte counts in female rats (NOAEL=2.9 mg/kg/day). The HLS study does increase the data available for development of a health-based guidance value. However, the rats in the HLS study did not suffer from fatty degeneration of the liver or from effects on the spleen, even at doses as high as 191 mg/kg/day. This suggests rats are not the most sensitive species.

Furthermore, Zhu et al. (1987) studied rats concurrently with guinea pigs, and concluded that the guinea pig appeared to be the species more sensitive to sulfolane's effects. In the absence of adequate human data, ATSDR will normally select the most sensitive animals and endpoints for derivation of health guidance values. Nevertheless, others have recommended the HLS study for deriving health guidance values. The Canadian Council of Ministers of the Environment (CCME) calculated a tolerable daily intake for sulfolane based on the HLS NOAEL of 2.9 mg/kg/day in female rats (CCME 2006). CCME used uncertainty factors of 10 for human to animal extrapolation, 10 for human variability, and 3 for extrapolation to chronic exposures, as well as other database uncertainties. Thus, CCME applied a total uncertainty factor of 300 for a tolerable daily intake of 0.0097 mg/kg/day (9.7 µg/kg/day). Using default Canadian drinking

water guidance, CCME derived a sulfolane drinking water guidance value of 0.09 mg/l (90 µg/l or ppb) for adult receptors drinking 1.5 liters of water per day.

In contrast, ToxStrategies used benchmark dose modeling to fit a linear model of the log-transformed dose ($\ln(\text{dose}+1)$) to the reduced total white blood cell and lymphocyte data (ToxStrategies 2010). As these measures were continuous measurements, the benchmark response dose represents a 1 standard deviation reduction in laboratory historical female rat white blood cell counts. ATSDR repeated this analysis using BMDS, but also considering concurrent and historical controls.³ BMD models for the reduction in monocytes, basophils, and large unstained cells did not meet statistical tests for fit, nor did they produce a valid answer (i.e., $\text{BMDL} < 0$). ToxStrategies arrived at a “Reference Dose” of 0.01 mg/kg/day (Table 4) by selecting the linear model based on parsimony and applying a $\frac{3}{4}$ power body weight scaling and standard uncertainty factors.

Results of ATSDR’s modeling of the HLS data (with and without substitution of historical control data) are shown in Appendix B, Tables B-4 through B-7. Because the polynomial and the power models resulted in models identical to the linear model, these results are not presented. Following USEPA guidance on model selection, when the BMDLs differ by a factor greater than three, the lowest BMDL is recommended (USEPA 2000). When the BMDLs are within a factor of three, the lowest AIC is chosen. Or, if multiple values have the same AIC, then an average is recommended (USEPA 2000). Parsimony does not provide much guidance on model selection because the linear and exponential regressions are equally parsimonious as applied to the log-transformed HLS data. Algebraic reduction of the linear model results in an equation with a logarithm function:

$$Y[\text{dose}] = \text{beta}_0 + \text{beta}_1 * (\ln(1 + \text{dose}))$$

the exponential (M2) model reduces to:

$$Y[\text{dose}] = a \times (\text{dose} + 1)^{-b}$$

the exponential (M4) model reduces to:

$$Y[\text{dose}] = a \times c \times (c - 1) \times (\text{dose} + 1)^{-b}$$

In terms of functions and number of variables, the M2 and the linear models are equally complex. In considering the exponential equation, exponential submodel M2 and M4 resulted in identical curves (in this case $c=0$). The difference in BMDL is a result of submodel M4 having an additional parameter. In the regressions, as the BMDS searched for a $\text{BMDL}_{1\text{SD}}$, this additional parameter increased the likelihood of the $\text{BMDL}_{1\text{SD}}$.

The BMDL is dependent on model-selection as well as controls. Unfortunately the statistical indicators (AIC, X^2) do not provide a clear indication as to which model is preferable for any of the endpoints. ATSDR selected the lowest BMDL values to evaluate whether the HLS data had a higher BMDL than did the Zhu et al. guinea pig data. Regardless of the model selected however, the BMDLs from the HLS 2001 are higher than those in the Zhu et al. study. The lowest BMDL

³ ATSDR noted that the WBC standard deviation of the highest dose group in the female rats is 1.019. ToxStrategies modeled the standard deviation as 1.109 (cf ToxStrategies 2010 p 53). ATSDR also noted also that some animal blood samples were clotted and not readable, resulting in fewer than 10 blood samples in some dose groups.

would have been the exponential M4 lymphocyte-reduction model. If concurrent controls were used, and if historical controls were used in the BMDS, this model would have resulted in a BMDL of 4.12 or 4.38, based on the lowest AIC for this effect.

Japanese Ministry of Health 1999

A 2004 Organization for Economic Cooperation (OECD) report (OECD 2004) contained a reproduction/developmental toxicity sulfolane screening test study. The Japanese Ministry of Health (MHW 1999) conducted the study, which OECD peer-reviewed. Rats were dosed at 0, 60, 200, or 700 mg/kg/day of sulfolane by gavage for 41 to 50 days from 14 days before mating to day 3 of lactation. Some mortality occurred in the high-dose group. During the pre-mating period, a decrease in body weight gain and food consumption occurred for both males and females at a dose of 700 mg/kg/day. The number of estrus cycles also decreased in the 700 mg/kg/day group. In the 700 mg/kg/day group, four dams lost all their pups during the lactation period. Birth index, live index, number of pups alive on days 1 and 4 of lactation, viability index, and body weights of pups of both sexes on days 0 and 4 of lactation all decreased at this dose. In addition, the number of stillbirths increased. In the 200 mg/kg/day group, delivery and birth index also decreased. The NOAEL for reproductive and developmental toxicity was 60 mg/kg/day. However, at 60 mg/kg/day, no treatment-related observations were recorded in the external appearance, general conditions and necropsy findings in offspring.

The BMDS successfully fit BMDL_{1SD} models to both the birth index and the number of live pups. BMDL_{1SD} for the live pups on day 4 was 160 mg/kg/day (exponential model M3) and for birth index, the BMDL established was 120 mg/kg/day (exponential model M3). Results are shown in Tables B-8 and B-9 in Appendix B. As discussed in ATSDR's original health consultation, developmental effects occur at relatively high sulfolane doses (half of the lethal dose) and probably are not sensitive endpoints for basing a provisional health guidance value.

Selection of Study and Endpoint

ATSDR has selected the Zhu et al. study for the derivation of the provisional health guidance value. It has the advantage of having been conducted for the longest period of time (twice the duration of the HLS study). Another key advantage of the Zhu et al. study is that it is available in the peer-reviewed literature, although in Chinese.

ATSDR received criticism (ToxStrategies 2010) for selecting the Zhu et al. study because:

1. The Zhu et al. study lacked standard deviations of the bone marrow and hepatic enzymes, preventing independent verification and analysis of cell counts in the blood and bone marrow and hepatic enzyme levels in the blood.
2. Zhu et al. did not provide incidence or standard deviation data for the 90-day rat and guinea pig study.
3. ATSDR was unclear regarding the endpoint from which it derived its public health action level.

In response, ATSDR notes that despite the HLS study's extensive pathological examinations, no changes to the liver or spleen were noted (HLS 2001; ToxStrategies 2010). Zhu et al. also studied rats over 90 days together with guinea pigs, and noted that with respect to sulfolane, guinea pigs were the more sensitive species. While Zhu et al. contains acknowledged

uncertainties, the lack of some parameters does not automatically invalidate other data on which the study relies. Using BMD analysis, the most sensitive departure point is a BMDL for dispersion of the white pulp of the spleen at 1.5 mg/kg/day in the guinea pig.

ATSDR Derivation of Action Level using Zhu et al. 1987

Use of BMD methodology outlined above would alter ATSDR's recommended public health action levels (Table 5). Using the 1.5 mg/kg/day BMDL (dispersion of the spleen's white pulp), we recommend a total uncertainty factor of 1000 (10 for animal to human extrapolation, 10 for variability in human sensitivity, and 10 for extrapolation of an intermediate dose to a chronic dose), resulting in a sulfolane action level of 0.002 mg/kg/day. The additional uncertainty factor for intermediate to chronic exposure, as compared with ATSDR's 2010 Health Consultation, is added to account for the longer duration of exposure apparently occurring at this site.

Child-Specific Intake Factors

ATSDR's use of child-specific intake factors for health guidance values is outlined in the Public Health Assessment Guidance Manual (ATSDR 2005) and is established policy at the agency. ToxStrategies cites the USEPA Region III Risk Based Concentration (RBC) intake and bodyweight factors as a justification for using adult body weight (70 kilograms) and water intake (2 liters per day) (ToxStrategies 2010). ATSDR's public health action levels were based on body weights specific for age categories (infant = 10 kg, child = 16 kg, and adult = 70 kg) and intake factors (child/infant = 1 liter per day, adult = 2 liters per day).

The RBC purpose and the ATSDR screening value purpose, while similar, are not identical. The RBC's tables stated purposes are (USEPA 2010b):

- Prioritizing multiple sites or operable units or areas of concern within a facility or exposure units
- Setting risk-based detection limits for contaminants of potential concern (COPCs)
- Focusing future site investigation and risk assessment efforts (e.g., selecting COPCs for the baseline risk assessment)
- Identifying contamination that may warrant cleanup
- Identifying sites, or portions of sites, that warrant no further action or investigation
- Initial cleanup goals when site-specific data are lacking

The ATSDR action level is specifically designed to support screening of environmental data using the process outlined in the ATSDR Public Health Guidance Manual (PHAGM). This is distinct from the purposes outlined above for the RBCs (ATSDR 2005). Simply put, an action level is intended to serve only as a screening tool to help decide whether to evaluate more closely exposures to a substance found at a site (ATSDR 2005). Exceeding the recommended action level supports the need for additional assessment of site conditions. Some of the elements that assessment might include activities outlined in Chapter 8 of the PHAGM. That is, at the location where the action levels are exceeded, the assessment might include a review of the specific demographics of the population exposed. ATSDR requires consideration of children's health issues at all sites (PHAGM 8.5.3). Given the developmental effects reported in OECD (2004),

the use of child and infant-specific intake factors is a prudent way to ensure protection for these sensitive populations.

Uncertainties

As mentioned in the discussion of the Zhu et al. study, the exact mode of administration for sulfolane is not known. Depending on the dosing schedule, the mode of administration could affect the dose value calculation. However, that said, the authors report the values used as “chronic values,” and the study was clearly directed towards deriving drinking water toxicity values. Thus, the reported doses were in all likelihood accurately reported. The alternative Huntingdon Life Science study is not available in the open peer-reviewed literature. Zhu et al., in side-by-side comparison of 90-day studies of both guinea pigs and rats, found guinea pigs to be the more sensitive species (Zhu et al. 1987). Not surprisingly, the HLS data in a 90-day study failed to find histopathological changes in rat livers. This was consistent with Zhu et al.’s findings. ATSDR’s dose-response analysis, using USEPA’s BMDS, looked at both the Zhu et al. data and the HLS data. ATSDR found the lowest benchmarks with the Zhu et al. guinea pig data.

In addition to drinking water, Alaska health officials are considering and evaluating other exposure routes. The Alaska Department of Health and Social Services reported that sulfolane was detected in relatively low concentrations in a small sample of garden produce that was watered with well water containing sulfolane (ADHSS 2011). Additional exposure pathways may be present through inhalation of water vapor containing sulfolane during showering, bathing, and dishwashing. However, because sulfolane has a relatively low vapor pressure, ATSDR did not address this pathway in its 2010 consultation. ATSDR understands, however, that USEPA is in the process of developing a Provisional Peer Review Toxicity inhalation value for sulfolane (State of Alaska 2011).

This health consultation does not consider exposure to additional chemicals in the environment. This introduces a slight uncertainty because the presence of other chemicals can sometimes amplify a given chemical’s toxicity (ATSDR 2005; Chou 2002). Examining multiple chemical exposures in the context of Public Health Assessments/Consultations is addressed in ATSDR’s *Guidance Manual for the Assessment of Joint Action of Chemical Mixtures* and in ATSDR’s *Public Health Assessment Guidance Manual* (ATSDR 2001; ATSDR 2005).

Recommended Public Health Action Levels

Using the provisional health guidance value of 0.002 mg/kg/day, ATSDR recommends the following environmental public health action levels for chronic (greater than 1-year) sulfolane exposure:

- 20 ppb for infant populations (assumes 1 liter water per day at 10 kg bodyweight)
- 32 ppb for child populations (assumes 1 liter water per day at 16 kg bodyweight)
- 70 ppb for adult populations (assumes 2 liters water per day at 70 kg bodyweight)

Conclusions

- The Zhu et al. (1987) study of sulfolane represents the longest period of exposure studied in the most sensitive animal. Using this study, ATSDR's BMDS analysis showed the lowest BMDL endpoints (shrinkage of the spleen's white pulp).
- For deriving a point of departure, the alternative dichotomous Hill model's (restricted slope) lowest BMDL using the Zhu et al. data is 1.5 mg/kg/day.
- To support the intended use in the context of public health assessment, child and infant factors are appropriate. Other contexts might require different exposure factors to derive an appropriate screening value, but for public health assessments ATSDR is mandated to consider children's health issues.
- A total uncertainty factor of 1000 is recommended (10 for animal to human extrapolation, 10 for variability in human sensitivity, and 10 for extrapolation of a intermediate duration dose to a chronic dose), resulting in an action level of 0.002 mg/kg/day. This computes to a similar, 2010 action level—as ATSDR previously recommended—of 0.0025 mg/kg/day.

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A peer review panel was assembled for this health consultation. The panel consisted of the following members:

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2. Matthew Wheeler, M.S. Statistician, Risk Evaluation Branch Education and Information Division NIOSH/CDC – Cincinnati, OH
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Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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Appendix A – Tables

Table 1: Intermediate Duration Studies of Sulfolane

Species	Effect	Route	Value	Source
Rat	NOAEL* – Respiratory	Inhalation 23 hrs/day 5 days/week 90 days	20 mg/m ³	(Andersen et al. 1977)
	LOAEL [†] – Inflamed hemorrhagic lungs	Inhalation 23 hrs/day 5 days/week 90 days	159 mg/m ³	(Andersen et al. 1977)
	LOAEL – Chronic inflammation	Inhalation 8 hrs/day 5 days/week 27 days	495 mg/m ³	(Andersen et al. 1977)
	NOAEL	Oral (drinking water) 90 days	2.9 mg/kg/day	(HLS 2001)
	LOAEL – decreased lymphocyte, white blood cells, monocytes, and large unstained cell counts in females	Oral (drinking water) 90 days	10.6 mg/kg/day	(HLS 2001)
	NOAEL	Oral, 90 days	167 mg/kg/day	(Zhu et al. 1987)
	LOAEL – Decreased ascorbic acid in adrenal glands	Oral, 90 days	500 mg/kg/day	(Zhu et al. 1987)
	LOAEL – decreased birth index and number of pups (day 0 and 4 of lactation)	Oral 49 days (males) 41-50 days (females)	200 mg/kg/day	(JMH 1999/OECD 2004)
	NOAEL – Reproductive Developmental	Oral 49 days (males) 41-50 days (females)	60 mg/kg/day	(JMH 1999/OECD 2004)
	Monkey	LOAEL – Death	Inhalation 8 hrs/day 5 days/week 27 days	495 mg/m ³
Dog	NOAEL – Respiratory	Inhalation 23 hrs/day 5 days/week 90 DAYS	20 mg/m ³	(Andersen et al. 1977)
	LOAEL – Inflamed hemorrhagic lungs	Inhalation 23 hrs/day 5 days/week 90 DAYS	159 mg/m ³	(Andersen et al. 1977)

Guinea Pig	LOAEL - Hepatic Effects Changes in Serum ALP Changes in White Blood Cell count	Oral (6 months)	2.5 mg/kg/day	(Zhu et al. 1987)
	NOAEL (reported by author)	Oral (6 months)	0.25 mg/kg/day [‡]	(Zhu et al. 1987)

*NOAEL: No Observed Adverse Effect Level

†LOAEL: No Observed Adverse Effect Level

‡ Author reported NOAEL as 0.25 mg/kg/day but statistical analysis showed NOAEL to probably be at the 2.5 mg/kg/day level.

Table 2 – Studies Considered in Provisional Health Guidance Value

Study	Animal	Period of Study	Doses (mg/kg/day)	Route	Critical Effects
Zhu et al. 1987	Guinea Pig	6 months, 3 months	0,0.25,2.5,25,250	Oral	Fatty degeneration of the liver, Dispersion of the white pulp of the spleen, , reported changes in AST and ALT
Huntingdon Life Sciences 2001	Rat	90 days	0, 2.9, 10.6, 42, 191.1	Oral (drinking water)	White blood cell counts decreased, Lymphocytes decreased in females at 10.6, 42, and 191.1 mg/kg/day
JMH 1999/OECD 2004	Rat	49 days (males) 41-50 days (females)	60, 200, 700 mg/kg/day	Oral (gavage)	Birth index, decreased number of pups alive at day 0 and day 4

Table 3 – Zhu et al. toxicity data (Guinea Pig)

Oral Dose (mg/kg/day)	Spleen (3-month)	Spleen (6-month)	Fatty Liver (6-month)	Severe Fatty Liver (6-month)	Bone Marrow Count
0	0/14	0/25	0/25	0/25	16.43 × 10 ⁴ /mm ³
0.25	0/14	0/22	0/22	0/22	n.d.
2.5	1/14	2/26	2/26	1/26	10.99 × 10 ⁴ /mm ³
25	2/14	2/25	4/25 (p=0.054) *	2/25	12.25 × 10 ⁴ /mm ³
250	6/14 (p=0.008) *	7/22 (p=0.0027) *	7/22 (p=0.0027) *	5/22 (p=0.017) *	10.56 × 10 ⁴ /mm ³
Cochran-Armitage Trend (p-value)	2.04x10 ⁻⁴	2.04x10 ⁻⁴	1.22x10 ⁻⁴	7.09x10 ⁻⁴	NA
* Significant by Pair-wise Fisher Exact test vs. control (p≤0.05)					

Table 4 – ToxStrategies RfD for HLS 2001 Reduction in White Blood Cells in Rats

Point of Departure (mg/kg/day)	Dose Scaling Factor	Human Equivalent Dose (mg/kg/day)	Uncertainty Factors					RfD dose
			A	H	S	D	Total	
15.1	4.08	3.7	3	3	10	3	270(300)*	0.012 (0.01)*

A: Animal to human extrapolation

H: Human variability uncertainty factor

S: Extrapolation from intermediate duration to chronic exposure

D: Database uncertainties

* Value rounded to 1 significant figure

Table 5 – ATSDR provisional Health Guidance Level (p-HGV) for Sulfolane based on Zhu et al. 1987

<i>Source</i>	<i>Point of Departure (mg/kg/day)</i>	<i>Uncertainty Factors</i>					<i>p-HGV (dose)</i>
		A	H	S	D	Total	
Zhu et al. – Spleen	1.5	10	10	10	_	1000	0.002

A: Animal to human extrapolation
H: Human variability uncertainty factor
S: Extrapolation from intermediate duration to chronic exposure
D: Database uncertainties

Appendix B – Benchmark Dose System Output Summary

Table B-1: Zhu et al. 1987: Liver

Summary Table of BMDS modeling results

Liver (Zhu et al. 1987)						
Model	Degrees of Freedom	X² p-Value	AIC	BMD (mg/kg-d)	BMDL (mg/kg-d)	Notes
Gamma	3.00	0.15	74.00	62.78	34.84	power bound hit (power = 1)
gamma, unrestricted	3.00	0.84	68.94	10.41	1.09	unrestricted (power = 0.385)
log-logistic	3.00	0.17	73.47	48.51	22.63	slope bound hit (slope = 1)
log-logistic, unrestricted	3.00	0.87	68.75	9.45	1.21	unrestricted (slope = 0.462)
log-probit, unrestricted	3.00	0.90	68.49	8.56	1.33	unrestricted (slope = 0.252)
multistage, 4-degree	3.00	0.15	74.00	62.78	34.84	final $\beta = 0$
Weibull	3.00	0.15	74.00	62.78	34.84	power bound hit (power = 1)
Weibull, unrestricted	3.00	0.86	68.84	9.92	1.15	unrestricted (power= 0.343)
quantal linear	3.00	0.15	74.00	62.78	34.84	
dichotomous Hill^a	3.00	0.84	68.58	5.88	2.40	slope bound hit (slope = 1)
dichotomous Hill, unrestricted	2.00	0.75	70.41	6.94	1.34	
log-Probit, background dose, unrestricted	3.00	0.90	68.49	8.56	1.33	
Weibull, unrestricted	3.00	0.86	68.84	9.92	1.15	

^a Best-fitting model, BMDS output presented in this appendix

Output for selected model: dichotomous Hill

Zhu et al. 1987: Liver

=====

Dichotomous Hill Model. (Version: 1.2; Date: 12/11/2009)

ATSDR Health Consultation – Sulfolane

Input Data File: C:/USEPA/BMDS212/Data/1A_Zhu_1987_Liver_DichHill_dich_hill_liver.(d)
Gnuplot Plotting File:
C:/USEPA/BMDS212/Data/1A_Zhu_1987_Liver_DichHill_dich_hill_liver.plt
Tue Feb 08 13:54:53 2011

=====
[add_notes_here]
~~~~~

The form of the probability function is:

$$P[\text{response}] = v * g + (v - v * g) / [1 + \text{EXP}(-\text{intercept} - \text{slope} * \text{Log}(\text{dose}))]$$

where:  $0 \leq g < 1$ ,  $0 < v \leq 1$

v is the maximum probability of response predicted by the model,

and v\*g is the background estimate of that probability.

Dependent variable = y  
Independent variable = dose  
Slope parameter is restricted as slope >= 1

Total number of observations = 5  
Total number of records with missing values = 0  
Maximum number of iterations = 250  
Relative Function Convergence has been set to: 1e-008  
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values  
v = -9999  
g = -9999  
intercept = -5.81209  
slope = 1

Asymptotic Correlation Matrix of Parameter Estimates

( \*\*\* The model parameter(s) -g -slope  
have been estimated at a boundary point, or have been specified by the user,  
and do not appear in the correlation matrix )

|           | v     | intercept |
|-----------|-------|-----------|
| v         | 1     | -0.74     |
| intercept | -0.74 | 1         |

Parameter Estimates

| Variable  | Estimate | Std. Err. | 95.0% Wald Confidence Interval |                   |
|-----------|----------|-----------|--------------------------------|-------------------|
|           |          |           | Lower Conf. Limit              | Upper Conf. Limit |
| v         | 0.303254 | 0.108989  | 0.0896387                      | 0.516869          |
| g         | 0        | NA        |                                |                   |
| intercept | -2.47993 | 1.15449   | -4.7427                        | -0.217172         |
| slope     | 1        | NA        |                                |                   |

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Analysis of Deviance Table

ATSDR Health Consultation – Sulfolane

| Model         | Log(likelihood) | # Param's | Deviance | Test d.f. | P-value   |
|---------------|-----------------|-----------|----------|-----------|-----------|
| Full model    | -31.8035        | 5         |          |           |           |
| Fitted model  | -32.2879        | 2         | 0.96878  | 3         | 0.8088    |
| Reduced model | -41.162         | 1         | 18.717   | 4         | 0.0008932 |

AIC: 68.5757

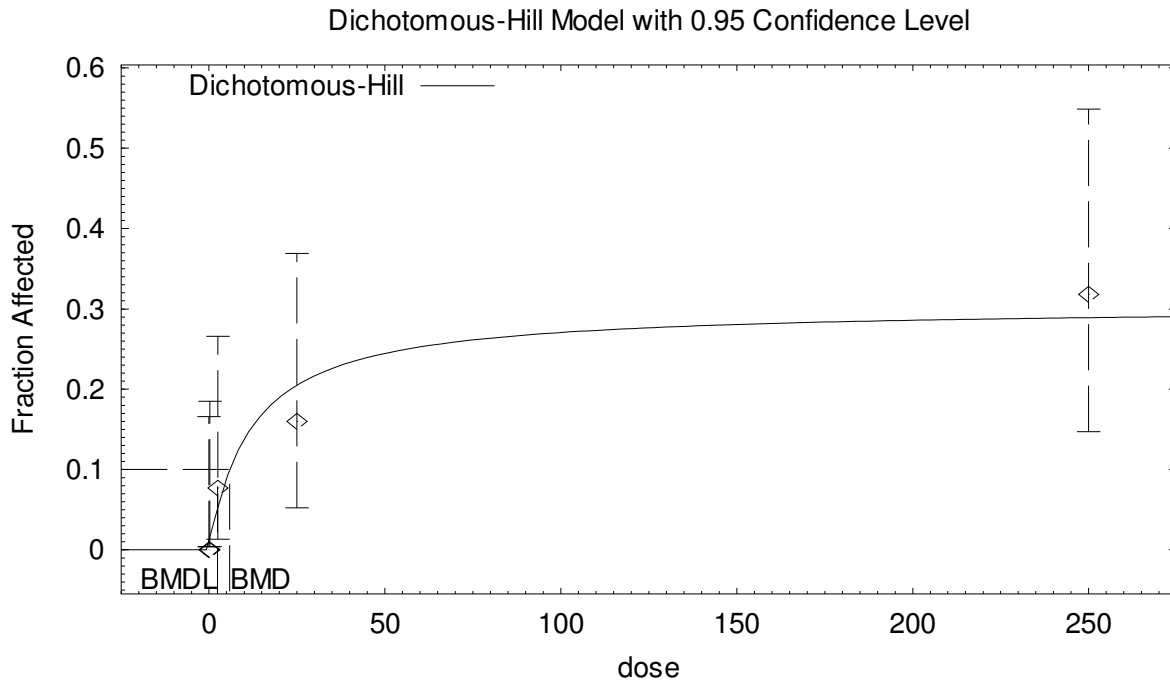
| Goodness of Fit |            |          |          |                 |
|-----------------|------------|----------|----------|-----------------|
| Dose            | Est._Prob. | Expected | Observed | Scaled Residual |
| 0.0000          | 0.0000     | 0.000    | 0.000    | 0.000           |
| 0.2500          | 0.0062     | 0.137    | 0.000    | -0.371          |
| 2.5000          | 0.0525     | 1.365    | 2.000    | 0.558           |
| 25.0000         | 0.2052     | 5.131    | 4.000    | -0.560          |
| 250.0000        | 0.2894     | 6.367    | 7.000    | 0.297           |

Chi^2 = 0.85      d.f. = 3      P-value = 0.8371

Benchmark Dose Computation

Specified effect = 0.1  
 Risk Type = Extra risk  
 Confidence level = 0.95  
 BMD = 5.87467

Warning: BMDL computation is at best imprecise for these data  
 BMDL = 2.39471



Zhu et al. 1987: Liver

**Table B-2: Zhu et al. 1987: Spleen (3 months)***Summary Table of BMDS modeling results*

| <b>Spleen (3 month) (Zhu et al. 1987)</b> |                           |                              |            |                      |                       |                                         |
|-------------------------------------------|---------------------------|------------------------------|------------|----------------------|-----------------------|-----------------------------------------|
| <b>Model</b>                              | <b>Degrees of Freedom</b> | <b>X<sup>2</sup> p-Value</b> | <b>AIC</b> | <b>BMD (mg/kg-d)</b> | <b>BMDL (mg/kg-d)</b> | <b>Notes</b>                            |
| Gamma                                     | 3.00                      | 0.52                         | 44.47      | 43.29                | 23.61                 | power bound hit (power = 1)             |
| gamma, unrestricted                       | 3.00                      | 0.94                         | 42.40      | 11.53                | 0.88                  | unrestricted (power = 0.492)            |
| Logistic                                  | 3.00                      | 0.37                         | 45.87      | 109.80               | 75.41                 | negative intercept (intercept = -2.996) |
| log-logistic                              | 3.00                      | 0.56                         | 44.03      | 31.26                | 13.20                 | slope bound hit (slope = 1)             |
| log-logistic, unrestricted                | 3.00                      | 0.94                         | 42.36      | 10.30                | 1.00                  | unrestricted (slope = 0.596)            |
| log-probit                                | 3.00                      | 0.30                         | 46.26      | 85.33                | 45.24                 | slope bound hit (slope = 1)             |
| log-probit, unrestricted                  | 3.00                      | 0.94                         | 42.30      | 8.87                 | 1.05                  | unrestricted (slope = 0.323)            |
| multistage, 4-degree                      | 3.00                      | 0.52                         | 44.47      | 43.29                | 23.61                 | final $\beta = 0$                       |
| Probit                                    | 3.00                      | 0.38                         | 45.76      | 99.65                | 68.31                 | negative intercept (intercept = -1.684) |
| Weibull                                   | 3.00                      | 0.52                         | 44.47      | 43.29                | 23.61                 | power bound hit (power = 1)             |
| Weibull, unrestricted                     | 3.00                      | 0.94                         | 42.38      | 10.95                | 2.38                  | unrestricted (power = )                 |
| quantal linear                            | 3.00                      | 0.52                         | 44.47      | 43.29                | 23.61                 |                                         |
| <b>dichotomous Hill<sup>a</sup></b>       | 3.00                      | 0.79                         | 42.74      | 9.42                 | 1.47                  |                                         |
| dichotomous Hill, unrestricted slope      | 2.00                      | 0.81                         | 44.36      | 10.16                | 1.00                  |                                         |
| log-Probit, background dose               | 3.00                      | 0.49                         | 44.94      | 54.38                | 29.20                 |                                         |
| log-Probit, background dose, unrestricted | 3.00                      | 0.94                         | 42.30      | 8.87                 | 1.05                  |                                         |
| multistage, background dose               | 2.00                      | 0.32                         | 46.47      | 43.29                | 23.61                 |                                         |
| probit, background response, unrestricted | 2.00                      | 0.22                         | 47.76      | 99.65                | 68.31                 |                                         |

<sup>a</sup> Best-fitting model, BMDS output presented in this appendix



*Output for selected model: dichotomous Hill*

Zhu et al. 1987: Spleen (3 months)

```
=====
      Dichotomous Hill Model. (Version: 1.2; Date: 12/11/2009)
      Input Data File:
C:/USEPA/BMDS212/Data/2A_Zhu_1987_Spleen_3_DichHill_dich_hill_spleen3.(d)
      Gnuplot Plotting File:
C:/USEPA/BMDS212/Data/2A_Zhu_1987_Spleen_3_DichHill_dich_hill_spleen3.plt
                                          Tue Feb 08 13:56:46 2011
=====
```

[add\_notes\_here]

The form of the probability function is:

$$P[\text{response}] = v * g + (v - v * g) / [1 + \text{EXP}(-\text{intercept} - \text{slope} * \text{Log}(\text{dose}))]$$

where:  $0 \leq g < 1$ ,  $0 < v \leq 1$

v is the maximum probability of response predicted by the model,

and  $v * g$  is the background estimate of that probability.

Dependent variable = y  
 Independent variable = dose  
 Slope parameter is restricted as slope  $\geq 1$

Total number of observations = 5  
 Total number of records with missing values = 0  
 Maximum number of iterations = 250  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008

```
Default Initial Parameter Values
      v =          -9999
      g =          -9999
      intercept =  -5.63082
      slope =           1
```

Asymptotic Correlation Matrix of Parameter Estimates

( \*\*\* The model parameter(s) -g -slope  
 have been estimated at a boundary point, or have been specified by the user,  
 and do not appear in the correlation matrix )

|           | v     | intercept |
|-----------|-------|-----------|
| v         | 1     | -0.79     |
| intercept | -0.79 | 1         |

Parameter Estimates

| Variable | Estimate | Std. Err. | 95.0% Wald Confidence Interval |                   |
|----------|----------|-----------|--------------------------------|-------------------|
|          |          |           | Lower Conf. Limit              | Upper Conf. Limit |
| v        | 0.469041 | 0.205517  | 0.0662347                      | 0.871846          |

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|           |         |         |          |          |
|-----------|---------|---------|----------|----------|
| g         | 0       | NA      |          |          |
| intercept | -3.5483 | 1.25897 | -6.01583 | -1.08077 |
| slope     | 1       | NA      |          |          |

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Analysis of Deviance Table

| Model         | Log(likelihood) | # Param's | Deviance | Test d.f. | P-value  |
|---------------|-----------------|-----------|----------|-----------|----------|
| Full model    | -18.9048        | 5         |          |           |          |
| Fitted model  | -19.3684        | 2         | 0.927139 | 3         | 0.8189   |
| Reduced model | -26.8563        | 1         | 15.9031  | 4         | 0.003152 |

AIC: 42.7367

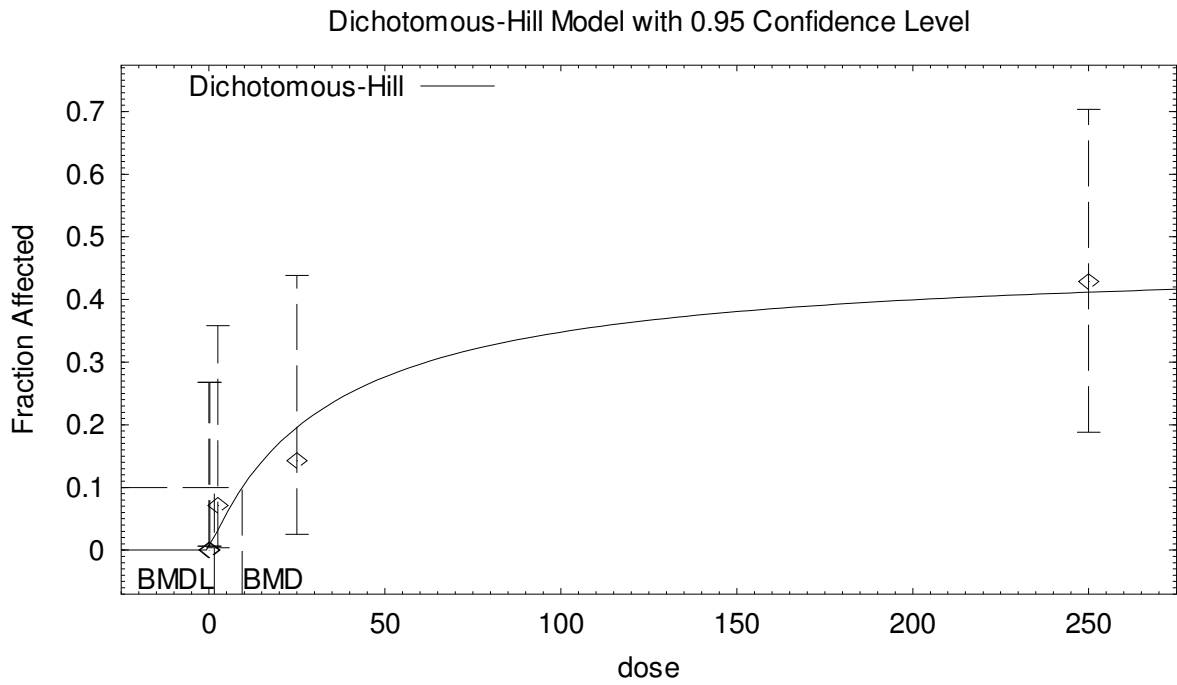
Goodness of Fit

| Dose     | Est._Prob. | Expected | Observed | Size | Scaled Residual |
|----------|------------|----------|----------|------|-----------------|
| 0.0000   | 0.0000     | 0.000    | 0.000    | 14   | 0.000           |
| 0.2500   | 0.0033     | 0.047    | 0.000    | 14   | -0.217          |
| 2.5000   | 0.0315     | 0.441    | 1.000    | 14   | 0.856           |
| 25.0000  | 0.1962     | 2.747    | 2.000    | 14   | -0.503          |
| 250.0000 | 0.4118     | 5.765    | 6.000    | 14   | 0.128           |

Chi^2 = 1.05      d.f. = 3      P-value = 0.7893

Benchmark Dose Computation

Specified effect = 0.1  
 Risk Type = Extra risk  
 Confidence level = 0.95  
 BMD = 9.41743  
 BMDL = 1.46712



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Zhu et al. 1987: Spleen (3 months)

**Table B-3: Zhu et al. 1987: Spleen (6 months)***Summary Table of BMDs modeling results*

| <b>Spleen (6 month) (Zhu et al. 1987)</b>   |                           |                              |            |                      |                       |                                          |
|---------------------------------------------|---------------------------|------------------------------|------------|----------------------|-----------------------|------------------------------------------|
| <b>Model</b>                                | <b>Degrees of Freedom</b> | <b>X<sup>2</sup> p-Value</b> | <b>AIC</b> | <b>BMD (mg/kg-d)</b> | <b>BMDL (mg/kg-d)</b> | <b>Notes</b>                             |
| gamma                                       | 3.00                      | 0.33                         | 63.62      | 69.11                | 38.53                 | power bound hit (power = 1)              |
| gamma, unrestricted                         | 3.00                      | 0.69                         | 61.22      | 18.73                | 2.89                  | unrestricted (power = 0.44)              |
| logistic                                    | 3.00                      | 0.32                         | 64.46      | 137.80               | 101.60                | negative intercept (intercept = - 3.258) |
| log-logistic                                | 3.00                      | 0.33                         | 63.47      | 58.85                | 28.26                 | slope bound hit (slope = 1)              |
| log-logistic, unrestricted                  | 3.00                      | 0.67                         | 61.28      | 16.71                | 2.77                  | unrestricted (slope = 0.503)             |
| log-probit                                  | 3.00                      | 0.28                         | 64.84      | 118.90               | 72.46                 | slope bound hit (slope = 1)              |
| log-probit, unrestricted                    | 3.00                      | 0.66                         | 61.30      | 14.10                | 2.61                  | unrestricted (slope = 0.259)             |
| multistage, 4-degree                        | 3.00                      | 0.33                         | 63.62      | 69.11                | 38.53                 | final $\beta = 0$                        |
| probit                                      | 3.00                      | 0.33                         | 64.38      | 127.40               | 92.09                 | negative intercept (intercept = - 1.797) |
| Weibull                                     | 3.00                      | 0.33                         | 63.62      | 69.11                | 38.53                 | power bound hit (power = 1)              |
| quantal linear                              | 3.00                      | 0.33                         | 63.62      | 69.11                | 38.53                 |                                          |
| <b>dichotomous Hill<sup>a</sup></b>         | 3.00                      | 0.35                         | 62.64      | 10.70                | 1.47                  |                                          |
| dichotomous Hill, unrestricted              | 3.00                      | 0.67                         | 61.28      | 16.71                | 2.75                  |                                          |
| logistic, background response, unrestricted | 3.00                      | 0.32                         | 64.46      | 137.80               | 101.60                |                                          |
| log-Probit, background dose                 | 3.00                      | 0.34                         | 63.93      | 84.24                | 48.76                 |                                          |
| log-Probit, background dose, unrestricted   | 3.00                      | 0.66                         | 61.30      | 14.10                | 2.61                  |                                          |
| multistage, background dose                 | 3.00                      | 0.33                         | 63.62      | 69.11                | 38.53                 |                                          |
| Weibull, unrestricted                       | 3.00                      | 0.68                         | 61.24      | 17.77                | 2.84                  | unrestricted (power = 0.861)             |

<sup>a</sup> Best-fitting model, BMDS output presented in this appendix

*Output for selected model: dichotomous Hill*

Zhu et al. 1987: Spleen (6 months)

```
=====
      Dichotomous Hill Model. (Version: 1.2; Date: 12/11/2009)
      Input Data File:
C:/USEPA/BMDS212/Data/2B_Zhu_1987_Spleen_6_DichHill_dich_hill_spleen6.(d)
      Gnuplot Plotting File:
C:/USEPA/BMDS212/Data/2B_Zhu_1987_Spleen_6_DichHill_dich_hill_spleen6.plt
                                          Tue Feb 08 13:58:31 2011
=====
```

[add\_notes\_here]

The form of the probability function is:

$$P[\text{response}] = v * g + (v - v * g) / [1 + \text{EXP}(-\text{intercept} - \text{slope} * \text{Log}(\text{dose}))]$$

where:  $0 \leq g < 1$ ,  $0 < v \leq 1$

v is the maximum probability of response predicted by the model,  
and  $v * g$  is the background estimate of that probability.

Dependent variable = y  
Independent variable = dose  
Slope parameter is restricted as slope  $\geq 1$

Total number of observations = 5  
Total number of records with missing values = 0  
Maximum number of iterations = 250  
Relative Function Convergence has been set to: 1e-008  
Parameter Convergence has been set to: 1e-008

```
Default Initial Parameter Values
      v =          -9999
      g =          -9999
      intercept =  -6.10214
      slope =           1
```

Asymptotic Correlation Matrix of Parameter Estimates

( \*\*\* The model parameter(s) -g -slope  
have been estimated at a boundary point, or have been specified by the user,  
and do not appear in the correlation matrix )

|           | v     | intercept |
|-----------|-------|-----------|
| v         | 1     | -0.84     |
| intercept | -0.84 | 1         |

Parameter Estimates

95.0% Wald Confidence Interval

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| Variable  | Estimate | Std. Err. | Lower Conf. Limit | Upper Conf. Limit |
|-----------|----------|-----------|-------------------|-------------------|
| v         | 0.299454 | 0.147519  |                   | 0.588585          |
| g         | 0        | NA        |                   |                   |
| intercept | -3.06102 | 1.51231   | -6.0251           | -0.0969394        |
| slope     | 1        | NA        |                   |                   |

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

### Analysis of Deviance Table

| Model         | Log(likelihood) | # Param's | Deviance | Test d.f. | P-value  |
|---------------|-----------------|-----------|----------|-----------|----------|
| Full model    | -27.781         | 5         |          |           |          |
| Fitted model  | -29.3188        | 2         | 3.07571  | 3         | 0.3801   |
| Reduced model | -36.7652        | 1         | 17.9685  | 4         | 0.001252 |

AIC: 62.6376

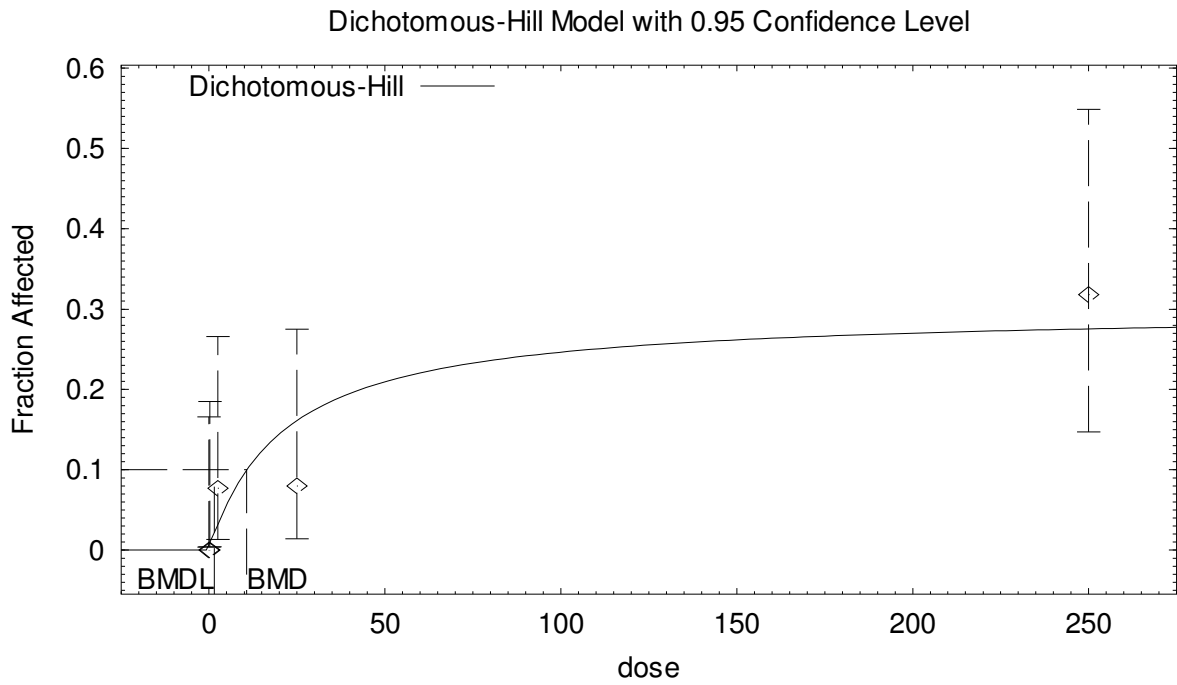
### Goodness of Fit

| Dose     | Est._Prob. | Expected | Observed | Size | Scaled Residual |
|----------|------------|----------|----------|------|-----------------|
| 0.0000   | 0.0000     | 0.000    | 0.000    | 25   | 0.000           |
| 0.2500   | 0.0035     | 0.076    | 0.000    | 22   | -0.277          |
| 2.5000   | 0.0314     | 0.816    | 2.000    | 26   | 1.331           |
| 25.0000  | 0.1615     | 4.038    | 2.000    | 25   | -1.108          |
| 250.0000 | 0.2759     | 6.070    | 7.000    | 22   | 0.444           |

Chi<sup>2</sup> = 3.27      d.f. = 3      P-value = 0.3514

### Benchmark Dose Computation

Specified effect = 0.1  
 Risk Type = Extra risk  
 Confidence level = 0.95  
 BMD = 10.7039  
 BMDL = 1.4671



Zhu et al. 1987: Spleen (6 months)

**Table B-4: HLS 2001: White Blood Cells ((historical control)**

| Model Predictions for Reduction in White Blood Cells (Historical Controls) |                                      |                                              |                      |                                       |                |                                        |                 |             |
|----------------------------------------------------------------------------|--------------------------------------|----------------------------------------------|----------------------|---------------------------------------|----------------|----------------------------------------|-----------------|-------------|
| Model                                                                      | Homogeneity Variance <i>p</i> -value | Goodness of fit <i>p</i> -value <sup>b</sup> | AIC for fitted model | BMD <sub>1sd</sub> ln(dose+1) mg/kg-d | BMD1sd mg/kg-d | BMDL <sub>1sd</sub> ln(dose+1) mg/kg-d | BMDL1sd mg/kg-d | Notes       |
| Exponential (M4) (nonconstant variance) <sup>a</sup>                       | 0.017                                | 0.161                                        | 111.58               | 3.91                                  | 48.88          | 1.88                                   | 5.54            | Lowest BMDL |
| Exponential (M2) (nonconstant variance)                                    | 0.017                                | 0.161                                        | 111.58               | 3.91                                  | 48.88          | 2.28                                   | 8.78            |             |
| <b>Linear (nonconstant variance)</b>                                       | <b>0.017</b>                         | <b>0.161</b>                                 | <b>111.58</b>        | <b>4.31</b>                           | 73.13          | <b>2.84</b>                            | 16.12           |             |

<sup>a</sup> Best-fitting model, BMDS output presented in this appendix

<sup>b</sup> Values <0.10 fail to meet conventional goodness-of-fit criteria

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL lower confidence limit (95%) on the benchmark dose

*Output for selected model: exponential (M4)*

HLS 2001: White Blood Cells

```

=====
Exponential Model. (Version: 1.7; Date: 12/10/2009)
Input Data File: C:/USEPA/BMDS212/Test/HLS_2001_WBC_Exp_BMR2. (d)
Gnuplot Plotting File:
Sun Feb 13 21:14:37 2011
=====

```

```

HLS 2001
~~~~~

```

```

The form of the response function by Model:
Model 2: Y[dose] = a * exp(sign * b * dose)
Model 3: Y[dose] = a * exp(sign * (b * dose)^d)
Model 4: Y[dose] = a * [c-(c-1) * exp(-b * dose)]
Model 5: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

```

Note: Y[dose] is the median response for exposure = dose;  
 sign = +1 for increasing trend in data;  
 sign = -1 for decreasing trend.

Model 2 is nested within Models 3 and 4.



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---

Model 3 is nested within Model 5.  
 Model 4 is nested within Model 5.

Dependent variable = WBC  
 Independent variable = alt\_dose  
 Data are assumed to be distributed: normally  
 Variance Model:  $\exp(\ln\alpha + \rho * \ln(Y[\text{dose}]))$   
 The variance is to be modeled as  $\text{Var}(i) = \exp(\ln\alpha + \log(\text{mean}(i)) * \rho)$

Total number of dose groups = 5  
 Total number of records with missing values = 0  
 Maximum number of iterations = 250  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

### Initial Parameter Values

| Variable | Model 4  |
|----------|----------|
| lnalpha  | -4.88402 |
| rho      | 3.34041  |
| a        | 8.3685   |
| b        | 0.140286 |
| c        | 0.108502 |
| d        | 1        |

### Parameter Estimates

| Variable | Model 4  |
|----------|----------|
| lnalpha  | -4.84106 |
| rho      | 3.31339  |
| a        | 8.10018  |
| b        | 0.110604 |
| c        | 0        |
| d        | 1        |

### Table of Stats From Input Data

| Dose  | N  | Obs Mean | Obs Std Dev |
|-------|----|----------|-------------|
| 0     | 10 | 7.97     | 2.626       |
| 1.361 | 10 | 7.63     | 2.653       |
| 2.451 | 9  | 5.41     | 1.392       |
| 3.761 | 9  | 5.53     | 1.756       |
| 5.258 | 10 | 4.54     | 1.019       |

### Estimated Values of Interest

| Dose  | Est Mean | Est Std | Scaled Residual |
|-------|----------|---------|-----------------|
| 0     | 8.1      | 2.844   | -0.1448         |
| 1.361 | 6.968    | 2.216   | 0.9444          |
| 2.451 | 6.177    | 1.815   | -1.268          |
| 3.761 | 5.343    | 1.427   | 0.392           |
| 5.258 | 4.528    | 1.085   | 0.03437         |

Other models for which likelihoods are calculated:

Model A1:  $Y_{ij} = \mu(i) + e(ij)$

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$$\text{Var}\{e(ij)\} = \text{Sigma}^2$$

Model A2:  $Y_{ij} = \text{Mu}(i) + e(ij)$   
 $\text{Var}\{e(ij)\} = \text{Sigma}(i)^2$

Model A3:  $Y_{ij} = \text{Mu}(i) + e(ij)$   
 $\text{Var}\{e(ij)\} = \exp(\text{lalpha} + \log(\text{mean}(i)) * \text{rho})$

Model R:  $Y_{ij} = \text{Mu} + e(i)$   
 $\text{Var}\{e(ij)\} = \text{Sigma}^2$

Likelihoods of Interest

| Model | Log(likelihood) | DF | AIC      |
|-------|-----------------|----|----------|
| A1    | -55.03553       | 6  | 122.0711 |
| A2    | -49.00331       | 10 | 118.0066 |
| A3    | -49.2142        | 7  | 112.4284 |
| R     | -64.89649       | 2  | 133.793  |
| 4     | -51.79076       | 4  | 111.5815 |

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)  
 Test 2: Are Variances Homogeneous? (A2 vs. A1)  
 Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

| Test    | -2*log(Likelihood Ratio) | D. F. | p-value   |
|---------|--------------------------|-------|-----------|
| Test 1  | 31.79                    | 8     | 0.0001017 |
| Test 2  | 12.06                    | 4     | 0.01688   |
| Test 3  | 0.4218                   | 3     | 0.9357    |
| Test 6a | 5.153                    | 3     | 0.1609    |

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data.

Benchmark Dose Computations:

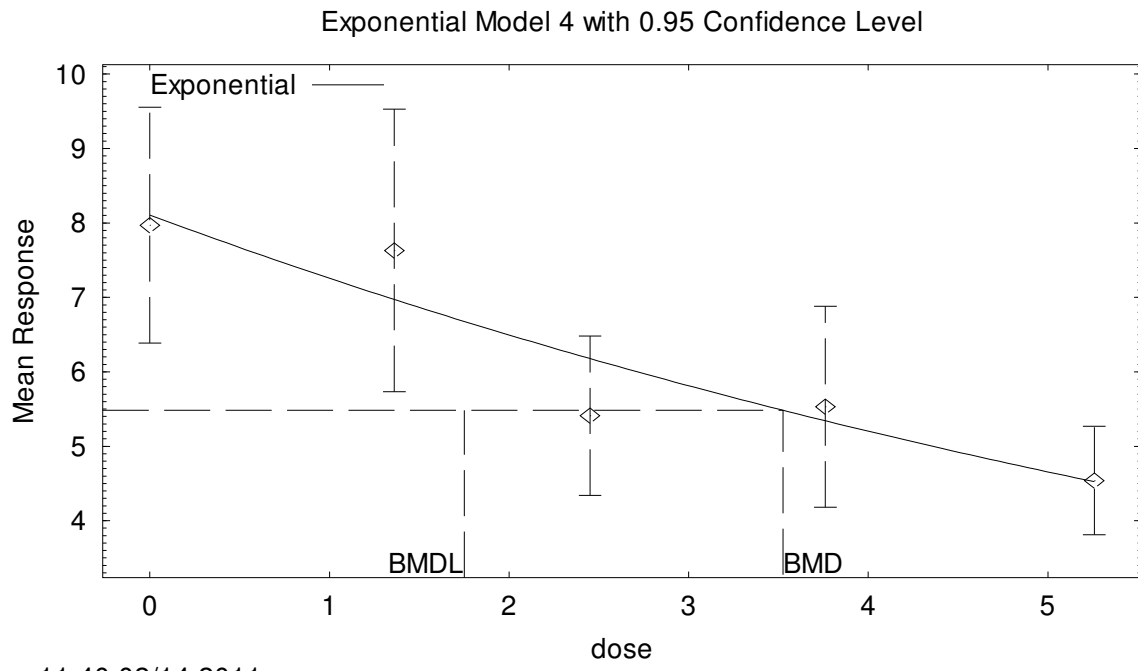
Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 3.90954

BMDL = 1.87853



HLS 2001: White Blood Cells (historical controls)

**Table B-5 of BMDS modeling results (concurrent control)**

| Model Predictions for Reduction in White Blood Cells (Concurrent Control) |                                      |                                              |                      |                                       |                |                                        |                 |                   |
|---------------------------------------------------------------------------|--------------------------------------|----------------------------------------------|----------------------|---------------------------------------|----------------|----------------------------------------|-----------------|-------------------|
| Model                                                                     | Homogeneity Variance <i>p</i> -value | Goodness of fit <i>p</i> -value <sup>b</sup> | AIC for fitted model | BMD <sub>1sd</sub> ln(dose+1) mg/kg-d | BMD1sd mg/kg-d | BMDL <sub>1sd</sub> ln(dose+1) mg/kg-d | BMDL1sd mg/kg-d | Notes             |
| Exponential (M4) (nonconstant variance) <sup>a</sup>                      | 0.036                                | 0.130                                        | 109.18               | 3.53                                  | 32.96          | 1.75                                   | 4.75            | Lowest BMDL       |
| Exponential (M2) (nonconstant variance)                                   | 0.036                                | 0.130                                        | 109.18               | 3.53                                  | 32.96          | 2.08                                   | 6.99            |                   |
| <b>Linear (nonconstant variance)</b>                                      | <b>0.036</b>                         | <b>0.136</b>                                 | <b>109.06</b>        | <b>3.96</b>                           | 51.23          | <b>2.61</b>                            | 12.66           | <b>Lowest AIC</b> |

<sup>a</sup> Best-fitting model, BMDS output presented in this appendix

<sup>b</sup> Values <0.10 fail to meet conventional goodness-of-fit criteria

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL lower confidence limit (95%) on the benchmark dose

*Output for model presented: exponential (M4)*

HLS 2001: WBC (Concurrent Control)

```

=====
Exponential Model. (Version: 1.7; Date: 12/10/2009)
Input Data File: C:/USEPA/BMDS212/Test/HLS_2001_WBC_con_Exp_BMR2. (d)
Gnuplot Plotting File:
Sun Feb 13 21:29:06 2011
=====

```

HLS 2001

```

The form of the response function by Model:
Model 2: Y[dose] = a * exp{sign * b * dose}
Model 3: Y[dose] = a * exp{sign * (b * dose)^d}
Model 4: Y[dose] = a * [c-(c-1) * exp{-b * dose}]
Model 5: Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

```

Note: Y[dose] is the median response for exposure = dose;  
 sign = +1 for increasing trend in data;  
 sign = -1 for decreasing trend.

Model 2 is nested within Models 3 and 4.  
 Model 3 is nested within Model 5.

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---

Model 4 is nested within Model 5.

Dependent variable = WBC  
Independent variable = alt\_dose  
Data are assumed to be distributed: normally  
Variance Model:  $\exp(\ln\alpha + \rho * \ln(Y[\text{dose}]))$   
The variance is to be modeled as  $\text{Var}(i) = \exp(\ln\alpha + \log(\text{mean}(i)) * \rho)$

Total number of dose groups = 5  
Total number of records with missing values = 0  
Maximum number of iterations = 250  
Relative Function Convergence has been set to: 1e-008  
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

### Initial Parameter Values

| Variable | Model 4   |
|----------|-----------|
| lnalpha  | -4.23146  |
| rho      | 2.9407    |
| a        | 8.3685    |
| b        | 0.129448  |
| c        | 0.0542511 |
| d        | 1         |

### Parameter Estimates

| Variable | Model 4  |
|----------|----------|
| lnalpha  | -4.16406 |
| rho      | 2.91156  |
| a        | 8.10768  |
| b        | 0.110916 |
| c        | 0        |
| d        | 1        |

### Table of Stats From Input Data

| Dose  | N  | Obs Mean | Obs Std Dev |
|-------|----|----------|-------------|
| 0     | 10 | 7.97     | 2.213       |
| 1.361 | 10 | 7.63     | 2.653       |
| 2.451 | 9  | 5.41     | 1.392       |
| 3.761 | 9  | 5.53     | 1.756       |
| 5.258 | 10 | 4.54     | 1.019       |

### Estimated Values of Interest

| Dose  | Est Mean | Est Std | Scaled Residual |
|-------|----------|---------|-----------------|
| 0     | 8.108    | 2.624   | -0.1659         |
| 1.361 | 6.972    | 2.106   | 0.9884          |
| 2.451 | 6.178    | 1.766   | -1.304          |
| 3.761 | 5.342    | 1.43    | 0.3942          |
| 5.258 | 4.525    | 1.123   | 0.0423          |

Other models for which likelihoods are calculated:

Model A1:  $Y_{ij} = \mu(i) + e(ij)$   
 $\text{Var}\{e(ij)\} = \sigma^2$

Model A2:  $Y_{ij} = \mu(i) + e(ij)$   
 $\text{Var}\{e(ij)\} = \sigma(i)^2$

Model A3:  $Y_{ij} = \mu(i) + e(ij)$   
 $\text{Var}\{e(ij)\} = \exp(\lambda \ln \mu(i) + \log(\text{mean}(i)) * \rho)$

Model R:  $Y_{ij} = \mu + e(i)$   
 $\text{Var}\{e(ij)\} = \sigma^2$

| Likelihoods of Interest |                 |    |          |
|-------------------------|-----------------|----|----------|
| Model                   | Log(likelihood) | DF | AIC      |
| A1                      | -52.43142       | 6  | 116.8628 |
| A2                      | -47.29218       | 10 | 114.5844 |
| A3                      | -47.75877       | 7  | 109.5175 |
| R                       | -63.20171       | 2  | 130.4034 |
| 4                       | -50.58752       | 4  | 109.175  |

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)  
 Test 2: Are Variances Homogeneous? (A2 vs. A1)  
 Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

| Test    | -2*log(Likelihood Ratio) | D. F. | p-value   |
|---------|--------------------------|-------|-----------|
| Test 1  | 31.82                    | 8     | 0.0001004 |
| Test 2  | 10.28                    | 4     | 0.03599   |
| Test 3  | 0.9332                   | 3     | 0.8174    |
| Test 6a | 5.658                    | 3     | 0.1295    |

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data.

Benchmark Dose Computations:

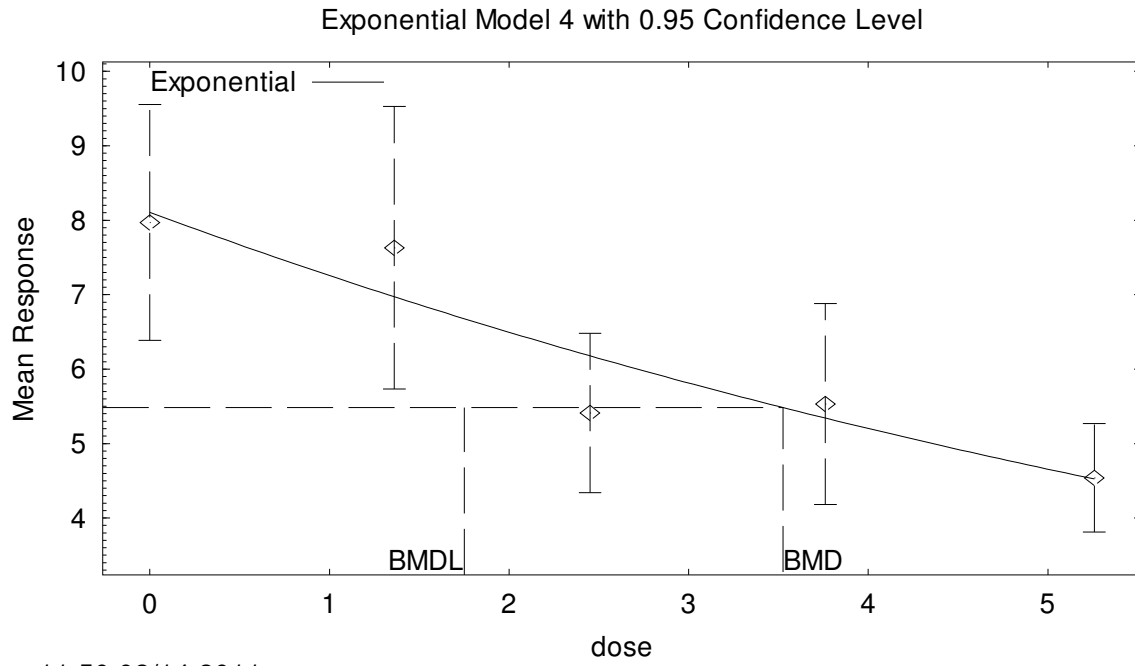
Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 3.52527

BMDL = 1.7499



11:50 02/14 2011

HLS 2001: WBC (Concurrent Control)

**Table B-6: HLS 2001: Lymphocytes (historical control)**

| Model Predictions for Reduction in Lymphocytes (Historical Control) |                                      |                                              |                      |                                       |                            |                                        |                             |                           |
|---------------------------------------------------------------------|--------------------------------------|----------------------------------------------|----------------------|---------------------------------------|----------------------------|----------------------------------------|-----------------------------|---------------------------|
| Model                                                               | Homogeneity Variance <i>p</i> -value | Goodness of fit <i>p</i> -value <sup>b</sup> | AIC for fitted model | BMD <sub>1sd</sub> ln(dose+1) mg/kg-d | BMD <sub>1sd</sub> mg/kg-d | BMDL <sub>1sd</sub> ln(dose+1) mg/kg-d | BMDL <sub>1sd</sub> mg/kg-d | Notes                     |
| Exponential (M4) (nonconstant variance) <sup>a</sup>                | 0.023                                | 0.168                                        | 102.46               | 3.86                                  | 46.46                      | 1.68                                   | 4.38                        | Lowest AIC<br>Lowest BMDL |
| Exponential (M2) (nonconstant variance)                             | 0.023                                | 0.168                                        | 102.46               | 3.86                                  | 46.46                      | 2.19                                   | 7.96                        | Lowest AIC                |
| Linear (nonconstant variance)                                       | 0.023                                | 0.158                                        | 102.61               | 4.34                                  | 75.55                      | 2.83                                   | 15.90                       |                           |

<sup>a</sup> Best-fitting model, BMDS output presented in this appendix

<sup>b</sup> Values <0.10 fail to meet conventional goodness-of-fit criteria

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL lower confidence limit (95%) on the benchmark dose

*Output for selected model: exponential (M4)*

HLS 2001: Lymphocytes (Historical Control)

```
=====
Exponential Model. (Version: 1.7; Date: 12/10/2009)
Input Data File: C:/USEPA/BMDS212/Test/HLS_2001_Lymphocytes_Exp_BMR2.(d)
Gnuplot Plotting File:
 Mon Feb 14 10:49:36 2011
=====
```

HLS 2001

~~~~~

The form of the response function by Model:

```
Model 2: Y[dose] = a * exp{sign * b * dose}
Model 3: Y[dose] = a * exp{sign * (b * dose)^d}
Model 4: Y[dose] = a * [c-(c-1) * exp{-b * dose}]
Model 5: Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
```

Note: Y[dose] is the median response for exposure = dose;  
 sign = +1 for increasing trend in data;  
 sign = -1 for decreasing trend.



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Model 2 is nested within Models 3 and 4.  
 Model 3 is nested within Model 5.  
 Model 4 is nested within Model 5.

Dependent variable = Lymph  
 Independent variable = alt\_dose  
 Data are assumed to be distributed: normally  
 Variance Model:  $\exp(\ln\alpha + \rho * \ln(Y[\text{dose}]))$   
 The variance is to be modeled as  $\text{Var}(i) = \exp(\ln\alpha + \log(\text{mean}(i)) * \rho)$

Total number of dose groups = 5  
 Total number of records with missing values = 0  
 Maximum number of iterations = 250  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

| Variable | Model 4  |
|----------|----------|
| lnalpha  | -3.80574 |
| rho      | 2.92924  |
| a        | 7.329    |
| b        | 0.208881 |
| c        | 0.254469 |
| d        | 1        |

Parameter Estimates

| Variable | Model 4  |
|----------|----------|
| lnalpha  | -3.90323 |
| rho      | 2.98476  |
| a        | 6.9219   |
| b        | 0.118982 |
| c        | 0        |
| d        | 1        |

Table of Stats From Input Data

| Dose  | N  | Obs Mean | Obs Std Dev |
|-------|----|----------|-------------|
| 0     | 10 | 6.98     | 2.29        |
| 1.361 | 10 | 6.36     | 2.452       |
| 2.451 | 9  | 4.39     | 1.308       |
| 3.761 | 9  | 4.63     | 1.564       |
| 5.258 | 10 | 3.73     | 0.941       |

Estimated Values of Interest

| Dose  | Est Mean | Est Std | Scaled Residual |
|-------|----------|---------|-----------------|
| 0     | 6.922    | 2.549   | 0.07208         |
| 1.361 | 5.887    | 2.002   | 0.7471          |
| 2.451 | 5.171    | 1.649   | -1.42           |
| 3.761 | 4.425    | 1.307   | 0.4715          |
| 5.258 | 3.703    | 1.002   | 0.08592         |

Other models for which likelihoods are calculated:

Model A1:  $Y_{ij} = \mu(i) + e(ij)$   
 $\text{Var}\{e(ij)\} = \sigma^2$

Model A2:  $Y_{ij} = \mu(i) + e(ij)$   
 $\text{Var}\{e(ij)\} = \sigma(i)^2$

Model A3:  $Y_{ij} = \mu(i) + e(ij)$   
 $\text{Var}\{e(ij)\} = \exp(\alpha + \log(\mu(i)) * \rho)$

Model R:  $Y_{ij} = \mu + e(i)$   
 $\text{Var}\{e(ij)\} = \sigma^2$

| Likelihoods of Interest |                 |    |          |
|-------------------------|-----------------|----|----------|
| Model                   | Log(likelihood) | DF | AIC      |
| A1                      | -50.12088       | 6  | 112.2418 |
| A2                      | -44.44769       | 10 | 108.8954 |
| A3                      | -44.70446       | 7  | 103.4089 |
| R                       | -60.31932       | 2  | 124.6386 |
| 4                       | -47.2319        | 4  | 102.4638 |

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

- Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
- Test 2: Are Variances Homogeneous? (A2 vs. A1)
- Test 3: Are variances adequately modeled? (A2 vs. A3)
- Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

| Test    | -2*log(Likelihood Ratio) | D. F. | p-value   |
|---------|--------------------------|-------|-----------|
| Test 1  | 31.74                    | 8     | 0.0001035 |
| Test 2  | 11.35                    | 4     | 0.02294   |
| Test 3  | 0.5135                   | 3     | 0.9159    |
| Test 6a | 5.055                    | 3     | 0.1678    |

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data.

Benchmark Dose Computations:

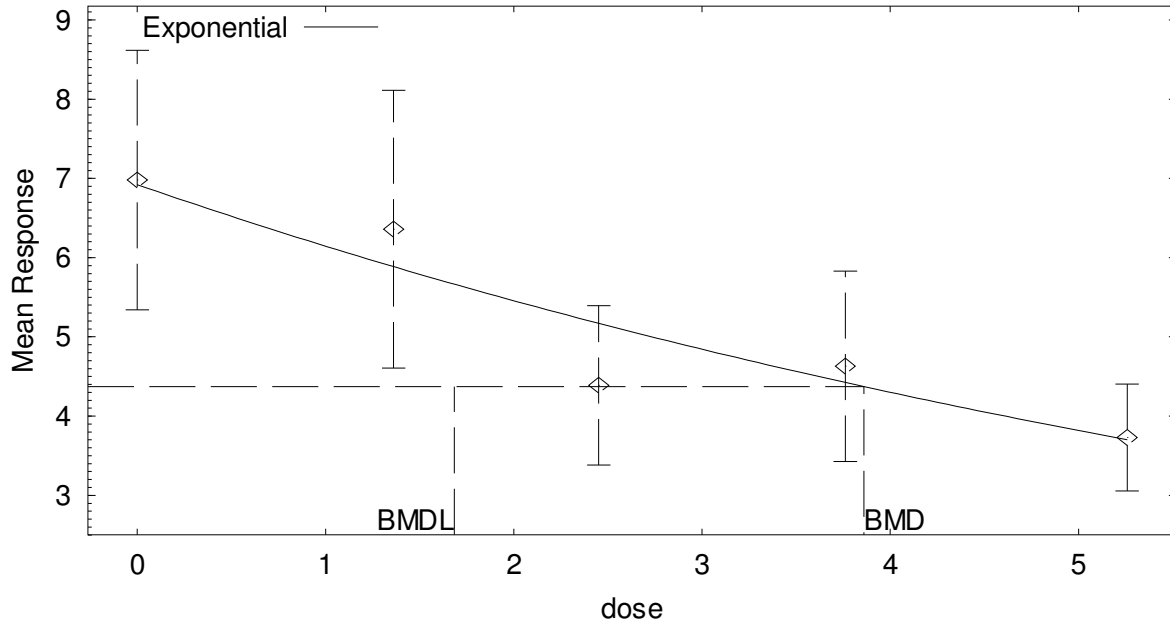
Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 3.85985  
BMDL = 1.68317

Exponential Model 4 with 0.95 Confidence Level



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HLS 2001: Lymphocytes

HLS 2001: Lymphocytes (Concurrent Control)

**TableB-7 of BMDS modeling results (Concurrent Control)**

| Model Predictions for Reduction in Lymphocytes (Concurrent Control)    |                                             |                                                     |                            |                                             |                               |                                              |                                |                                           |
|------------------------------------------------------------------------|---------------------------------------------|-----------------------------------------------------|----------------------------|---------------------------------------------|-------------------------------|----------------------------------------------|--------------------------------|-------------------------------------------|
| Model                                                                  | Homogeneity<br>Variance <i>p</i> -<br>value | Goodness<br>of fit <i>p</i> -<br>value <sup>b</sup> | AIC for<br>fitted<br>model | BMD <sub>1sd</sub><br>ln(dose+1)<br>mg/kg-d | BMD <sub>1sd</sub><br>mg/kg-d | BMDL <sub>1sd</sub><br>ln(dose+1)<br>mg/kg-d | BMDL <sub>1sd</sub><br>mg/kg-d | Notes                                     |
| <b>Exponential<br/>(M4)<br/>(nonconstant<br/>variance)<sup>a</sup></b> | <b>0.031</b>                                | <b>0.158</b>                                        | <b>101.55</b>              | <b>3.70</b>                                 | 39.47                         | <b>1.63</b>                                  | 4.12                           | <b>Lowest<br/>AIC<br/>Lowest<br/>BMDL</b> |
| <b>Exponential<br/>(M2)<br/>(nonconstant<br/>variance)</b>             | <b>0.031</b>                                | <b>0.158</b>                                        | <b>101.55</b>              | <b>3.70</b>                                 | 39.47                         | <b>2.11</b>                                  | 7.26                           | <b>Lowest<br/>AIC</b>                     |
| Linear<br>(nonconstant<br>variance)                                    | 0.031                                       | 0.151                                               | 101.65                     | 4.20                                        | 65.48                         | 2.74                                         | 14.45                          |                                           |

<sup>a</sup> Best-fitting model, BMDS output presented in this appendix

<sup>b</sup> Values <0.10 fail to meet conventional goodness-of-fit criteria

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL lower confidence limit (95%) on the benchmark dose

```

=====
Exponential Model. (Version: 1.7; Date: 12/10/2009)
Input Data File: C:/USEPA/BMDS212/Test/HLS_2001_Lymphocytes_con_Exp_BMR2.(d)
Gnuplot Plotting File:
 Mon Feb 14 11:04:45 2011
=====

```

HLS 2001

```

The form of the response function by Model:
Model 2: Y[dose] = a * exp{sign * b * dose}
Model 3: Y[dose] = a * exp{sign * (b * dose)^d}
Model 4: Y[dose] = a * [c-(c-1) * exp{-b * dose}]
Model 5: Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

```

Note: Y[dose] is the median response for exposure = dose;  
 sign = +1 for increasing trend in data;  
 sign = -1 for decreasing trend.

Model 2 is nested within Models 3 and 4.  
 Model 3 is nested within Model 5.  
 Model 4 is nested within Model 5.

Dependent variable = Lymph  
 Independent variable = alt\_dose

## ATSDR Health Consultation – Sulfolane

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Data are assumed to be distributed: normally  
 Variance Model:  $\exp(\ln\alpha + \rho * \ln(Y[\text{dose}]))$   
 The variance is to be modeled as  $\text{Var}(i) = \exp(\ln\alpha + \log(\text{mean}(i)) * \rho)$

Total number of dose groups = 5  
 Total number of records with missing values = 0  
 Maximum number of iterations = 250  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

### Initial Parameter Values

| Variable | Model 4  |
|----------|----------|
| lnalpha  | -3.58873 |
| rho      | 2.77965  |
| a        | 7.329    |
| b        | 0.208881 |
| c        | 0.254469 |
| d        | 1        |

### Parameter Estimates

| Variable | Model 4  |
|----------|----------|
| lnalpha  | -3.68366 |
| rho      | 2.8384   |
| a        | 6.92764  |
| b        | 0.119266 |
| c        | 0        |
| d        | 1        |

### Table of Stats From Input Data

| Dose  | N  | Obs Mean | Obs Std Dev |
|-------|----|----------|-------------|
| 0     | 10 | 6.98     | 2.146       |
| 1.361 | 10 | 6.36     | 2.452       |
| 2.451 | 9  | 4.39     | 1.308       |
| 3.761 | 9  | 4.63     | 1.564       |
| 5.258 | 10 | 3.73     | 0.941       |

### Estimated Values of Interest

| Dose  | Est Mean | Est Std | Scaled Residual |
|-------|----------|---------|-----------------|
| 0     | 6.928    | 2.472   | 0.06698         |
| 1.361 | 5.89     | 1.963   | 0.7575          |
| 2.451 | 5.172    | 1.633   | -1.436          |
| 3.761 | 4.424    | 1.308   | 0.4736          |
| 5.258 | 3.7      | 1.015   | 0.09245         |

Other models for which likelihoods are calculated:

Model A1:  $Y_{ij} = \mu(i) + e(ij)$   
 $\text{Var}\{e(ij)\} = \sigma^2$

Model A2:  $Y_{ij} = \mu(i) + e(ij)$   
 $\text{Var}\{e(ij)\} = \sigma(i)^2$

Model A3:  $Y_{ij} = \mu(i) + e(ij)$

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$$\text{Var}\{e(ij)\} = \exp(\text{lalpha} + \log(\text{mean}(i)) * \text{rho})$$

Model R:  $Y_{ij} = \mu + e(i)$   
 $\text{Var}\{e(ij)\} = \text{Sigma}^2$

### Likelihoods of Interest

| Model | Log(likelihood) | DF | AIC      |
|-------|-----------------|----|----------|
| A1    | -49.13278       | 6  | 110.2656 |
| A2    | -43.79823       | 10 | 107.5965 |
| A3    | -44.17752       | 7  | 102.355  |
| R     | -59.6779        | 2  | 123.3558 |
| 4     | -46.77582       | 4  | 101.5516 |

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

### Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)

Test 2: Are Variances Homogeneous? (A2 vs. A1)

Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

### Tests of Interest

| Test    | -2*log(Likelihood Ratio) | D. F. | p-value   |
|---------|--------------------------|-------|-----------|
| Test 1  | 31.76                    | 8     | 0.0001029 |
| Test 2  | 10.67                    | 4     | 0.03055   |
| Test 3  | 0.7586                   | 3     | 0.8593    |
| Test 6a | 5.197                    | 3     | 0.158     |

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data.

### Benchmark Dose Computations:

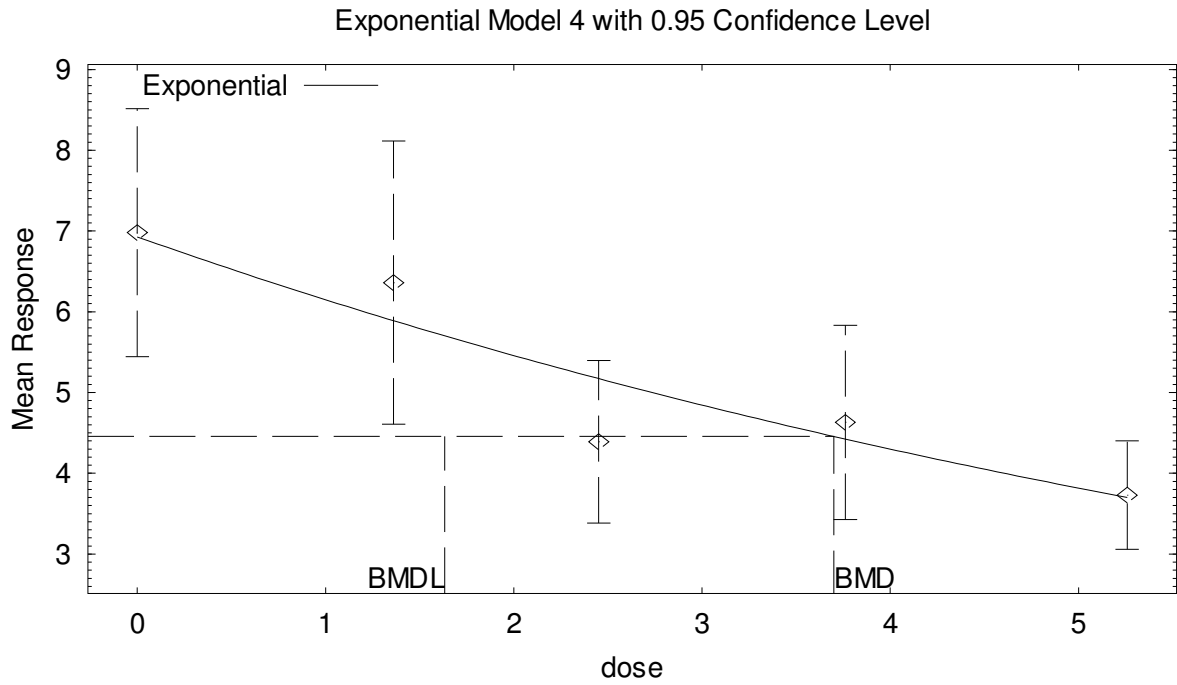
Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 3.70068

BMDL = 1.6333



HLS 2001: Lymphocytes (Concurrent Control)

**Table B-8:OECD 2004: Live Pups Day 4**

*Summary Table of BMDS modeling results*

| Survival (OECD 2004)          |                    |                        |        |               |                |            |
|-------------------------------|--------------------|------------------------|--------|---------------|----------------|------------|
| Model <sup>a</sup>            | Degrees of Freedom | X <sup>2</sup> p-Value | AIC    | BMD (mg/kg-d) | BMDL (mg/kg-d) | Notes      |
| exponential (M3) <sup>b</sup> | 1.00               | 0.71                   | 114.86 | 239.40        | 161.20         | Lowest AIC |
| polynomial, 3-degree          | 1.00               | 0.62                   | 114.97 | 255.80        | 146.50         |            |
| power                         | 1.00               | 0.66                   | 114.92 | 248.20        | 153.10         |            |

<sup>a</sup> Non-constant variance model selected ( $p = <0.0001$ )

<sup>b</sup> Best-fitting model, BMDS output presented in this appendix

*Output for selected model: exponential (M3)*

**OECD 2004: Live Pups Day 4**

```

=====
Exponential Model. (Version: 1.7; Date: 12/10/2009)
Input Data File: C:/USEPA/BMDS212/Data/OECD 2004_pups_alive_day4_Exp_birth.(d)
Gnuplot Plotting File:
 Tue Feb 08 14:03:40 2011
=====

OECD 2004
~~~~~

The form of the response function by Model:
Model 2:   Y[dose] = a * exp{sign * b * dose}
Model 3:   Y[dose] = a * exp{sign * (b * dose)^d}
Model 4:   Y[dose] = a * [c-(c-1) * exp{-b * dose}]
Model 5:   Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

Note: Y[dose] is the median response for exposure = dose;
      sign = +1 for increasing trend in data;
      sign = -1 for decreasing trend.

Model 2 is nested within Models 3 and 4.
Model 3 is nested within Model 5.
Model 4 is nested within Model 5.

Dependent variable = Obs_Mean
Independent variable = dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
    
```



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Total number of records with missing values = 0  
 Maximum number of iterations = 250  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

### Initial Parameter Values

| Variable | Model 3     |
|----------|-------------|
| lnalpha  | 5.99242     |
| rho      | -1.86471    |
| a        | 3.58254     |
| b        | -8.246e-007 |
| c        | 0           |
| d        | 2           |

### Parameter Estimates

| Variable | Model 3    |
|----------|------------|
| lnalpha  | 5.58675    |
| rho      | -1.7118    |
| a        | 14.902     |
| b        | 0.00163543 |
| c        | 0          |
| d        | 2.30684    |

### Table of Stats From Input Data

| Dose | N  | Obs Mean | Obs Std Dev |
|------|----|----------|-------------|
| 0    | 11 | 14.8     | 1.8         |
| 60   | 12 | 15       | 1.9         |
| 200  | 10 | 13.7     | 1.3         |
| 700  | 9  | 4        | 5.6         |

### Estimated Values of Interest

| Dose | Est Mean | Est Std | Scaled Residual |
|------|----------|---------|-----------------|
| 0    | 14.9     | 1.618   | -0.2091         |
| 60   | 14.83    | 1.625   | 0.3587          |
| 200  | 13.81    | 1.727   | -0.2059         |
| 700  | 3.802    | 5.209   | 0.1143          |

Other models for which likelihoods are calculated:

- Model A1:  $Y_{ij} = \mu(i) + e(ij)$   
 $\text{Var}\{e(ij)\} = \sigma^2$
- Model A2:  $Y_{ij} = \mu(i) + e(ij)$   
 $\text{Var}\{e(ij)\} = \sigma(i)^2$
- Model A3:  $Y_{ij} = \mu(i) + e(ij)$   
 $\text{Var}\{e(ij)\} = \exp(\ln\alpha + \log(\text{mean}(i)) * \rho)$
- Model R:  $Y_{ij} = \mu + e(i)$   
 $\text{Var}\{e(ij)\} = \sigma^2$

Likelihoods of Interest

| Model | Log(likelihood) | DF | AIC      |
|-------|-----------------|----|----------|
| A1    | -64.80532       | 5  | 139.6106 |
| A2    | -51.19334       | 8  | 118.3867 |
| A3    | -52.36184       | 6  | 116.7237 |
| R     | -90.21303       | 2  | 184.4261 |
| 3     | -52.43031       | 5  | 114.8606 |

Additive constant for all log-likelihoods = -38.6. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)

Test 2: Are Variances Homogeneous? (A2 vs. A1)

Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 5a: Does Model 3 fit the data? (A3 vs 3)

Tests of Interest

| Test    | -2*log(Likelihood Ratio) | D. F. | p-value  |
|---------|--------------------------|-------|----------|
| Test 1  | 78.04                    | 6     | < 0.0001 |
| Test 2  | 27.22                    | 3     | < 0.0001 |
| Test 3  | 2.337                    | 2     | 0.3108   |
| Test 5a | 0.1369                   | 1     | 0.7113   |

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 5a is greater than .1. Model 3 seems to adequately describe the data.

Benchmark Dose Computations:

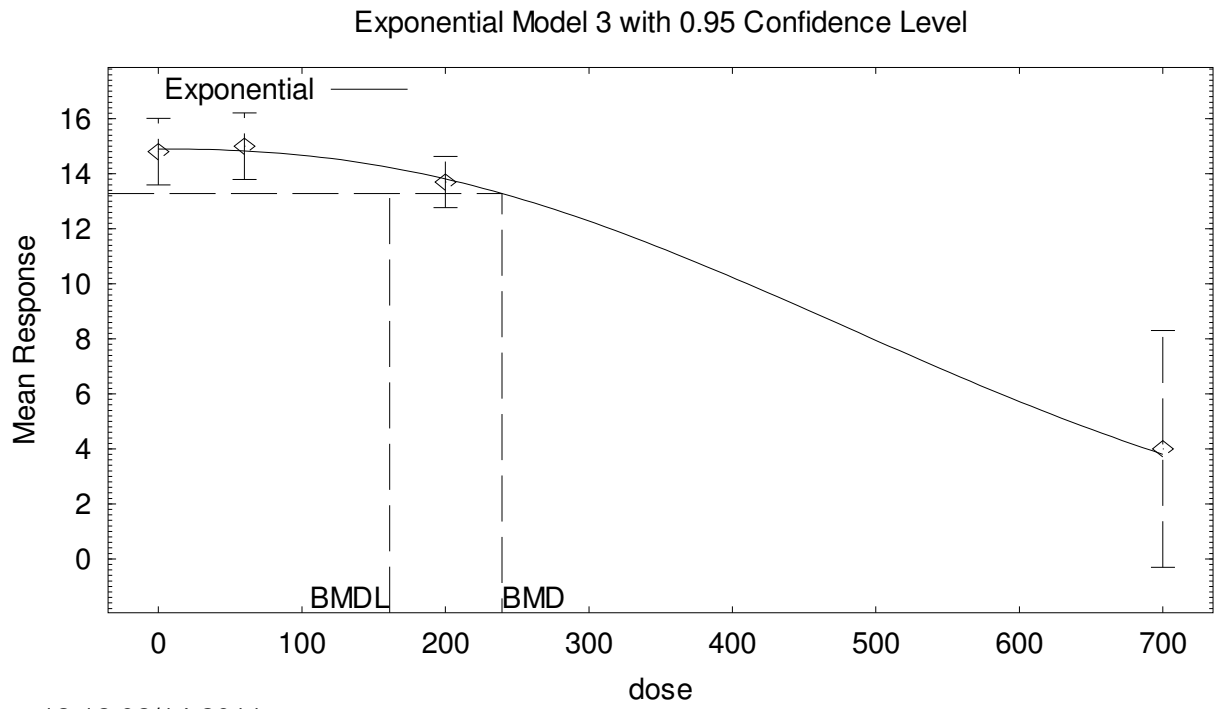
Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 239.373

BMDL = 161.176



OECD 2004: Live Pups Day 4

**Table B-9: OECD 2004: Birth index**

*Summary Table of BMDS modeling results*

| <b>Birth Index (OECD 2004)</b> |                           |                              |            |                      |                       |              |
|--------------------------------|---------------------------|------------------------------|------------|----------------------|-----------------------|--------------|
| <b>Model<sup>a</sup></b>       | <b>Degrees of Freedom</b> | <b>X<sup>2</sup> p-Value</b> | <b>AIC</b> | <b>BMD (mg/kg-d)</b> | <b>BMDL (mg/kg-d)</b> | <b>Notes</b> |
| exponential (M2)               | 2.00                      | 0.18                         | 229.80     | 137.70               | 88.48                 |              |
| exponential (M3) <sup>b</sup>  | 1.00                      | 0.58                         | 228.70     | 214.90               | 119.70                | Lowest AIC   |
| linear                         | 2.00                      | 0.28                         | 228.97     | 142.60               | 95.69                 |              |
| polynomial, 3-degree           | 1.00                      | 0.46                         | 228.95     | 219.90               | 113.70                |              |
| power                          | 1.00                      | 0.55                         | 228.76     | 216.70               | 117.40                |              |

<sup>a</sup> Non-constant variance model selected ( $p = <0.0001$ )

<sup>b</sup> Best-fitting model, BMDS output presented in this appendix

*Output for selected model: exponential (M3)*

OECD 2004: Birth index

```

=====
Exponential Model. (Version: 1.7; Date: 12/10/2009)
Input Data File: C:/USEPA/BMDS212/Data/OECD 2004_birth_index_Exp_birth.(d)
Gnuplot Plotting File:
                                     Tue Feb 08 14:04:30 2011
=====

OECD 2004
~~~~~

The form of the response function by Model:
Model 2: Y[dose] = a * exp{sign * b * dose}
Model 3: Y[dose] = a * exp{sign * (b * dose)^d}
Model 4: Y[dose] = a * [c-(c-1) * exp{-b * dose}]
Model 5: Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

Note: Y[dose] is the median response for exposure = dose;
 sign = +1 for increasing trend in data;
 sign = -1 for decreasing trend.

 Model 2 is nested within Models 3 and 4.
 Model 3 is nested within Model 5.
 Model 4 is nested within Model 5.

Dependent variable = Obs_Mean

```

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Independent variable = dose  
 Data are assumed to be distributed: normally  
 Variance Model:  $\exp(\ln\alpha + \rho * \ln(Y[\text{dose}]))$   
 The variance is to be modeled as  $\text{Var}(i) = \exp(\ln\alpha + \log(\text{mean}(i)) * \rho)$

Total number of dose groups = 4  
 Total number of records with missing values = 0  
 Maximum number of iterations = 250  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

### Initial Parameter Values

| Variable | Model 3     |
|----------|-------------|
| lnalpha  | 52.9161     |
| rho      | -10.8897    |
| a        | 80.128      |
| b        | 0.000438051 |
| c        | 0           |
| d        | 1           |

### Parameter Estimates

| Variable | Model 3     |
|----------|-------------|
| lnalpha  | 46.0602     |
| rho      | -9.38104    |
| a        | 96.135      |
| b        | 0.000708097 |
| c        | 0           |
| d        | 1.5534      |

### Table of Stats From Input Data

| Dose | N  | Obs Mean | Obs Std Dev |
|------|----|----------|-------------|
| 0    | 11 | 96.3     | 6.5         |
| 60   | 12 | 95.8     | 4.8         |
| 200  | 10 | 90.5     | 5.1         |
| 700  | 10 | 71.6     | 26.2        |

### Estimated Values of Interest

| Dose | Est Mean | Est Std | Scaled Residual |
|------|----------|---------|-----------------|
| 0    | 96.13    | 5.025   | 0.1089          |
| 60   | 95.43    | 5.202   | 0.2488          |
| 200  | 91.63    | 6.294   | -0.5669         |
| 700  | 68.69    | 24.31   | 0.3783          |

Other models for which likelihoods are calculated:

Model A1:  $Y_{ij} = \mu(i) + e(ij)$   
 $\text{Var}\{e(ij)\} = \sigma^2$

Model A2:  $Y_{ij} = \mu(i) + e(ij)$   
 $\text{Var}\{e(ij)\} = \sigma(i)^2$

Model A3:  $Y_{ij} = \mu(i) + e(ij)$   
 $\text{Var}\{e(ij)\} = \exp(\ln\alpha + \log(\text{mean}(i)) * \rho)$

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Model R:  $Y_{ij} = \mu + e(i)$   
 $\text{Var}\{e(ij)\} = \sigma^2$

| Likelihoods of Interest |                 |    |          |
|-------------------------|-----------------|----|----------|
| Model                   | Log(likelihood) | DF | AIC      |
| A1                      | -131.2566       | 5  | 272.5131 |
| A2                      | -107.7633       | 8  | 231.5267 |
| A3                      | -109.2007       | 6  | 230.4013 |
| R                       | -141.2441       | 2  | 286.4883 |
| 3                       | -109.3519       | 5  | 228.7037 |

Additive constant for all log-likelihoods = -39.51. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

### Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)

Test 2: Are Variances Homogeneous? (A2 vs. A1)

Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 5a: Does Model 3 fit the data? (A3 vs 3)

### Tests of Interest

| Test    | -2*log(Likelihood Ratio) | D. F. | p-value  |
|---------|--------------------------|-------|----------|
| Test 1  | 66.96                    | 6     | < 0.0001 |
| Test 2  | 46.99                    | 3     | < 0.0001 |
| Test 3  | 2.875                    | 2     | 0.2376   |
| Test 5a | 0.3024                   | 1     | 0.5824   |

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 5a is greater than .1. Model 3 seems to adequately describe the data.

### Benchmark Dose Computations:

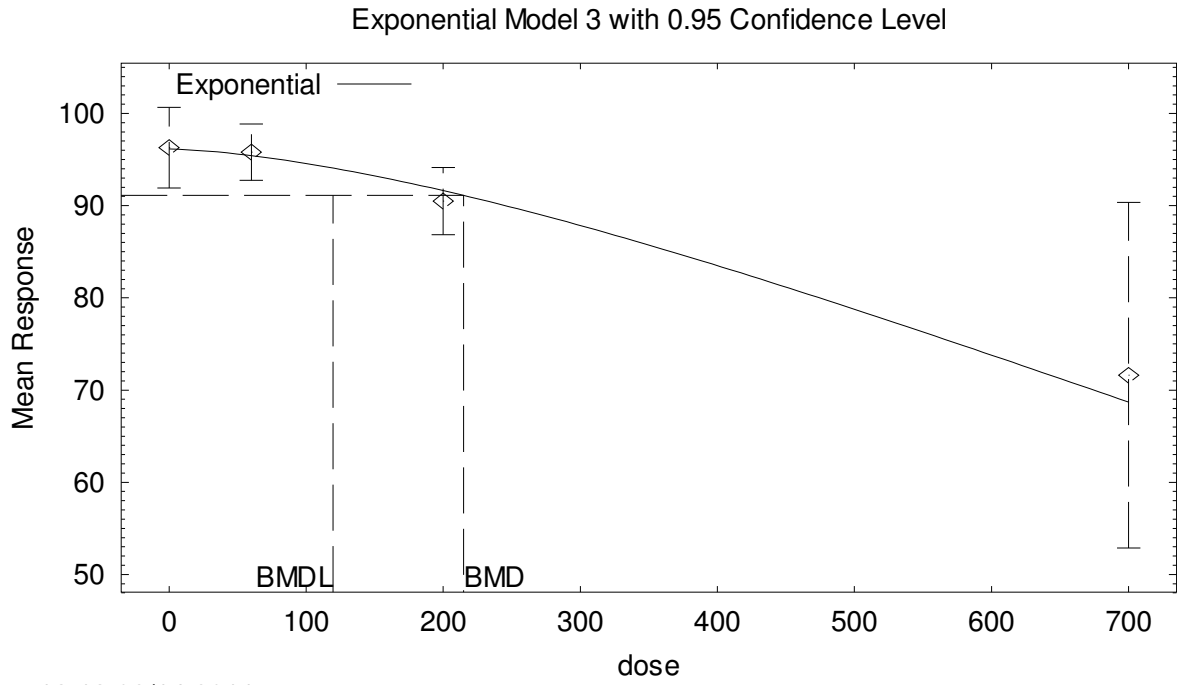
Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 214.899

BMDL = 119.71



13:13 02/14 2011

OECD 2004: Birth index