Provisional Peer-Reviewed Toxicity Values for

Thiodiglycol
(CASRN 111-48-8)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

COMMONLY USED ABBREVIATIONS

BMD	Benchmark Dose
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
LOAEL$_{ADJ}$	LOAEL adjusted to continuous exposure duration
LOAEL$_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
NOAEL$_{ADJ}$	NOAEL adjusted to continuous exposure duration
NOAEL$_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
RfC	inhalation reference concentration
RfD	oral reference dose
UF	uncertainty factor

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR THIODIGLYCOL (CASRN 111-48-8)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (U.S. EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1. U.S. EPA's Integrated Risk Information System (IRIS).

2. Provisional Peer-Reviewed Toxicity Values (PPRTV) used in U.S. EPA's Superfund Program.

3. Other (peer-reviewed) toxicity values, including:

   ‣ Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   ‣ California Environmental Protection Agency (CalEPA) values and
   ‣ U.S. EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in U.S. EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the U.S. EPA IRIS Program. All provisional toxicity values receive internal review by two U.S. EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a five-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV manuscripts conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and RCRA program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV manuscript and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

Thiodiglycol is used as a chemical intermediate, as a solvent in coloring processes in the textile industry, as a solvent in preparations for coloring paper, and as a softener in special rubbers (OECD/SIDS, 2004). The empirical formula for thiodiglycol is $C_4H_{10}O_2S$.
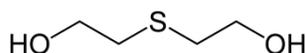
The U.S. Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS; U.S. EPA, 2007) does not list a chronic reference dose (RfD), chronic reference concentration (RfC), or cancer assessment for thiodiglycol. Subchronic or chronic RfDs or RfCs or a cancer assessment for thiodiglycol are not listed in the Health Effects Assessment Summary Tables (HEAST; U.S. EPA, 1997) or the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006). The Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991, 1994) does not include thiodiglycol. No standards for occupational exposure to thiodiglycol have been established by the American Conference of Governmental Industrial Hygienists (ACGIH, 2007), the National Institute of Occupational Safety and Health (NIOSH, 2007), or the Occupational Safety and Health Administration (OSHA, 2007). The Agency for Toxic Substances and Disease Registry (ATSDR, 2007), the International Agency for Research on Cancer (IARC, 2007), and the World Health Organization (WHO, 2007) have not published toxicological reviews on thiodiglycol.

Literature searches for studies relevant to the derivation of provisional toxicity values for thiodiglycol (CASRN 111-48-8) were conducted in MEDLINE, TOXLINE special, and DART/ETIC (1960's-July 2007); BIOSIS (August 2000-July 2007); TSCATS/TSCATS 2, CCRIS, GENETOX, HSDB, and RTECS (not date limited); and Current Contents (March 2007-September 2007). An updated literature search (September 2007-November 2008) was conducted using PubMed.

REVIEW OF PERTINENT DATA

Human Studies
No studies investigating the effects of subchronic or chronic oral or inhalation exposure to thiodiglycol in humans were identified.

Animal Studies
Oral Exposure
Information regarding the toxicity of thiodiglycol published in the open literature is limited to a developmental toxicity study in rats (Houpt et al., 2007) and a 90-day study of metabolic enzymes from rat liver (Vodela et al., 1999). Summaries of a limited number of subchronic and developmental studies are also available in the Screening Information Data Set on thiodiglycol prepared by the Organization for Economic Cooperation and Development (OECD/SIDS, 2004). Information from these summaries and from Houpt et al. (2007) and Vodela et al. (1999) is presented below.

Short-term and Subchronic Studies—Reddy et al. (2005) summarized a 14-day study conducted by Angerhofer et al. (1998). In this study, groups of Sprague-Dawley rats (6/sex/dose level) were administered 0, 157, 313, 625, 1250, 2500, 5000, or 9999 mg/kg-day thiodiglycol (≥99.9% pure) by gavage neat (no solvent was used) 5 days per week for 2 weeks. During the 14-day study, food consumption, body weights, and clinical signs were recorded. At the end of the 14-day period, rats were euthanized using CO_2 and blood samples were collected for hematology and clinical chemistry. The study authors performed gross necropsies, and various organs were removed at necropsy for weighing; however, they did not perform histopathology on any tissues. The high dose of 9999 mg/kg-day resulted in death in 4 out of 6 male rats and 5 out of 6 female rats, respectively, within 1 to 3 days, of dosing. Clinical signs observed were lethargy followed by death. At the end of study, decreased body weights were observed in the surviving male and female rats in the high dose group. The only reported organ weight changes are increased kidney weights in both males and females in the 5000 and 9999 mg/kg-day groups. In males, the kidney:body weight ratio in the 5000 and 9999 mg/kg-day dose groups and kidney:brain weight ratio in the 9999 mg/kg-day group were both significantly higher than in controls. In females, these kidney:body and kidney:brain weight ratios were higher but not significant in the ≥2500 mg/kg-day dose groups. There were no biologically relevant changes in hematological or other clinical parameters between treated and control groups. This study identifies a NOAEL and LOAEL of 2500 (average daily dose of 1786 mg/kg-day) and 5000 mg/kg-day (average daily dose of 3571 mg/kg-day), respectively, based on increased kidney weight in both males and females.

Groups of Wistar rats (5/sex/dose level) were administered 0 (vehicle) or 1000 mg/kg thiodiglycol (≥98.4% pure) by gavage in distilled water once per day for 28 days (BASF AG, 1993, as reported in OECD/SIDS, 2004); the study followed Organization for Economic Cooperation and Development (OECD) guideline 407 (OECD, 1995). Endpoints evaluated include the following: clinical signs and mortality (twice daily), and body weight and food consumption (once per week). On day 31, the animals were sacrificed and blood was collected for comprehensive hematology and clinical chemistry testing. All major tissues and organs were subjected to gross and microscopic examination. There were no compound-related adverse clinical signs or deaths during the study. The only effects reported in treated males consist of significant decreases in red blood cell (RBC) counts, hemoglobin levels, and hematocrit levels. OECD/Screening Information Data Set (SIDS) (2004) states that these alterations were considered incidental because they were within the normal historical range for the laboratory and the values in control males were unusually high. Treated males also showed a significant decrease in blood bilirubin and albumin concentrations, which were also within the normal range. Gross and microscopic evaluation of organs and tissues did not reveal any correlated alterations. This study identifies a NOAEL of 1000 mg/kg-day.

OECD/SIDS (2004) and Reddy et al. (2005) summarized a 90-day study conducted by Angerhofer et al. (1998). In this study, groups of Sprague-Dawley rats (10/sex/dose level) were administered 0, 50, 500, or 5000 mg/kg-day thiodiglycol (≥99.9% pure) by gavage neat 5 days per week for 91-92 days. Controls were sham-treated with an empty gavage needle; methods were comparable to OECD guideline 408 (OECD, 1998). Endpoints evaluated include the following: clinical signs and mortality (daily); body weight and food consumption (days -3, -1, 0, 1, 3, and 7, and then weekly); ophthalmology (control and high-dose before study began and several days before termination); urinalysis (all rats towards the end of the study); and hematology, clinical chemistry, and organ weights (at termination). All major tissues were subjected to gross and microscopic examination. No significant alterations were reported on ophthalmology, hematology, and clinical chemistry tests. Body weights of high-dose males and females appear significantly reduced throughout the study relative to controls, although food consumption was not significantly affected by treatment. Final body weight was reduced 12 and 14% in the high-dose females and males, respectively, relative to the controls. Absolute and relative kidney weights were significantly increased in high-dose males and females. Also, in the high-dose groups, the relative weights of the liver, brain, and testes (in males) and adrenals (in females) were significantly elevated. The increases in the relative weight of these organs were probably secondary to the reduced body weight. Urinalysis including microscopic examination revealed the following effects in the high-dose groups: increased urine volume (males and females), decreased urine pH (males and females), increase in specific gravity (males), reduction in triple phosphate (males; crystals per microscopic field), and granular casts (females). There were no treatment-related gross or microscopic alterations in the tissues examined. At the lower doses, the only significant effect reported was a reduction in urine pH in females from the 500 mg/kg-day group, and OECD/SIDS summary (2004) states that this reduction is considered as adaptive rather than an adverse effect. Based on the reduced body

weight and alterations in kidney weight, accompanied by changes in urinalysis parameters, this study identifies a NOAEL and LOAEL of 500 (average daily dose of 357 mg/kg-day[1]) and 5000 mg/kg-day (average daily dose of 3571 mg/kg-day), respectively.

Vodela et al. (1999) performed analyses of liver enzyme activity in livers from the rats tested by Angerhofer et al. (1998). At the end of the study, livers were removed and processed for determination of mixed-function oxidase (MFO) and cytosolic glutathione antioxidant system (GAS) activities. Treatment with thiodiglycol resulted in the following significant biochemical changes in male rats: an increase in CYP2B1/B2 activity (5000 mg/kg-day), a decrease in cytochrome b5 activity (500 and 5000 mg/kg-day), a decrease in reduced glutathione (500 and 5000 mg/kg-day), a decrease in GSH transferase activity (≥50 mg/kg-day), and a decrease in GSH peroxidase activity (500 mg/kg-day). No significant changes occurred in female rats. Given the limited scope of the endpoints evaluated in this study, defining a NOAEL and LOAEL would not be appropriate.

Reproduction/Developmental Studies—The reproductive organs have been examined in previously mentioned short-term and subchronic studies. No significant alterations in the weight or in gross or microscopic appearance of the reproductive organs from male and female Wistar rats exposed to 1000 mg/kg-day thiodiglycol were reported in the 28-day oral gavage study summarized above (OECD/SIDS, 2004). Also, except for an increase in the relative weight of the testis in male Sprague-Dawley rats treated with 5000 mg/kg-day, similar negative results were reported in the 90-day study summarized above (OECD/SIDS, 2004). The effect in the testes was likely due to a decrease in body weight experienced by the male rats throughout the study because no significant effects were seen with the mean absolute organ weight, and no changes in histopathology were reported.

A limit-test study, in accordance with OECD guideline 414 (OECD, 2001), was conducted in Wistar rats (BASF AG, 1995a, as reported in OECD/SIDS, 2004). Groups of pregnant rats (24/dose level) were administered 0 or 1000 mg/kg-day thiodiglycol (≥98.4% pure) by gavage in distilled water on gestation days (GD) 6 to 15. Sacrifices were conducted on GD 20. There were no maternal effects as assessed by clinical signs, body weight gain, and food consumption (both monitored 10 times throughout pregnancy) and pathological alterations at necropsy. In addition, no treatment-related effects were noted regarding uterine weight, mean number of *corpora lutea*, live and dead fetuses, implantations, early and late resorptions, or in conception rate, and pre- and post-implantation losses. Morphological evaluation of the fetuses revealed a significant increase in dumbbell ossifications of thoracic vertebral bodies in the treated group relative to controls (12% vs. 5.2%). OECD/SIDS summary (2004) states that this variation was outside the historical control rate for the laboratory (0.0-8.8%). There were also increases in skeletal variations, such as rudimentary cervical ribs (7.1% vs. 1.2%) and a general increase in total variations (52.9% affected fetuses/litter vs. 38.6% in controls). It appears that the 1000 mg/kg-day dose level can be considered a maternal NOAEL and a developmental LOAEL in this study.

---

[1] Average daily dose = daily dose × days of treatment/week ÷ 7

Due to the effects observed in the limit test, a second study was performed with additional dose groups (BASF AG, 1995b, as reported in OECD/SIDS, 2004). Groups of pregnant Wistar rats (25/dose level) were administered 0, 100, 400, or 1000 mg/kg thiodiglycol (≥98.4% pure) by gavage in distilled water on gestation days 6 to 15. Endpoints examined are the same as in the limit-test study summarized above. The only significant maternal effect is a 32% lower body weight in high-dose dams, relative to controls, on GD 8. The OECD/SIDS summary (2004) states that, according to the investigators, the effect was transient and marginal but, possibly, treatment-related. Food consumption was not significantly affected by treatment with thiodiglycol at any point during the study. As observed in the limit-test study, the incidence of dumbbell ossifications of thoracic vertebral bodies in the high-dose group was increased relative to the controls (6.3% vs. 3.6%), although the difference was not statistically significant. The OECD/SIDS summary (2004) states that this type of variation is considered to be of toxicological significance because it was observed at the same dose level as in the limit-test study and the incidence in both studies was higher than in historical controls. There were other effects: uneven sex distribution (more females in the mid dose group), decreased placental weights of male fetuses in the mid dose group, increased incidence of fetuses with soft tissue malformations per litter in the mid dose group, and number of affected/litter with accessory 14th rib in the high dose group. These effects are statistically significant, but they are not considered toxicologically relevant because there was no dose-dependency and/or were within historical control values or were not observed in the limit test. In this study, it appears that the dose level of 400 mg/kg-day is a developmental NOAEL and 1000 mg/kg-day is a developmental LOAEL. The transient decrease in maternal weight gain on GD 8, although significant, is not reported at the same dose level in the limit test study; therefore, it seems appropriate to consider the 1000 mg/kg-day dose level a maternal NOAEL.

Developmental effects have also been studied in Sprague-Dawley rats. Houpt et al. (2007) administered 0, 430, 1290, or 3870 mg/kg-day neat thiodiglycol (99.9% pure) by gavage to groups of pregnant Sprague-Dawley rats (25/dose level) from Gestation Day 5 to Day 19. Sacrifices were conducted on day 20 of gestation. Controls were sham-treated with an empty gavage needle. The uterus was weighed and examined for number and location of implantations, resorptions, and dead fetuses and live fetuses. The number of *corpora lutea* was also recorded. In addition, the litters were examined for soft tissue and skeletal alterations. Maternal toxicity was limited to high-dose dams and consisted of a reduction in body weight gain and food consumption during certain periods of gestation. Final adjusted maternal weight in high-dose females is 10.4% lower than in controls. Fetuses born to these dams had an increased incidence of variations (soft tissue and skeletal combined) compared with controls, but the differences do not achieve statistical significance (28.9% vs. 23.4% in controls). In addition, fetal weights in the high-dose group are significantly lower than controls (2.92 g average fetal body weight vs. 3.60 g in controls). However, the litter size is also significantly increased in the high-dose group compared to the control (15.2 vs. 13.0), indicating a possible litter size effect on the fetal weight. Treatment with thiodiglycol has no significant effect on the incidence of fetal anomalies. Based on the changes in maternal and fetal body weights at 3870 mg/kg-day, Houpt et al. (2007) considered the dose level of 1290 mg/kg-day a maternal and developmental NOAEL and the dose level of 3870 mg/kg-day a maternal and developmental LOAEL.

Inhalation Exposure

No subchronic, chronic, developmental, or reproduction studies on inhaled thiodiglycol in animals were identified.

Other Studies
Acute Studies

Smyth et al. (1941) reported that the 14-day LD_{50} for a single dose of thiodiglycol in male Wistar rats (10/dose level) was 6610 mg/kg (95% CI 6100-7160); under the same conditions, the LD_{50} in groups of male and female guinea pigs was 3960 mg/kg (95% CI 3440-4560). Smyth et al. (1941) noted that fatal or near-fatal doses produced no narcosis but, rather, varying degrees of "sluggish depressed functioning." In a study in male and female Sprague-Dawley rats (1/sex/dose level) given oral gavage doses of up to 9900 mg/kg body weight neat thiodiglycol ($\geq$95% pure), no toxic effects or deaths occurred in females (OECD/SIDS, 2004). The male rat administered 9900 mg/kg thiodiglycol was slightly lethargic starting 1 hour post-dosing but recovered within 4 hours; no other effects were noted. Exposure of 12 rats (neither sex nor strain were identified) to a saturated atmosphere of thiodiglycol for 8 hours caused irritation of the mucous membranes 1 hour after exposure started, but it caused no mortality (OECD/SIDS, 2004). Thiodiglycol is not irritating to the skin of rabbits, but it is slightly irritating to the rabbit eye (OECD/SIDS, 2004). Using a scale from 1 to 10 (with 10 representing the most irritating), Carpenter and Smyth (1946) placed thiodiglycol in grade 2 for eye irritation in rabbits.

Genotoxicity Studies

The information regarding the genotoxicity of thiodiglycol is limited to a few *in vitro* assays and one study *in vivo*; OECD/SIDS (2004) and Reddy et al. (2005) summarized the results from these assays. The limited data available suggest that thiodiglycol is not mutagenic, but it may be clastogenic under certain conditions. Thiodiglycol was negative in reverse mutation assays in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and in *Escherichia coli* WP2uvrA conducted with or without metabolic activation at doses up to 5000 µg/plate (BASF AG, 1989; Stankowski, 2001). There is no evidence of cytotoxicity in these assays except for a slight decrease in revertants in the TA100 strain in the presence of metabolic activation at $\geq$2500 µg/plate in one of the studies (BASF AG, 1989). Thiodiglycol was also not mutagenic in mouse lymphoma cells at concentrations up to 5 mg/ml in the presence or absence of metabolic activation (Clark and Donner, 1998). In a study in CHO cells incubated with thiodiglycol at concentrations between 1 and 5 mg/ml, thiodiglycol increased the incidences of chromosome and chromatid breaks and chromatid type rearrangements (Tice et al., 1997). The effects were significant at 5 mg/ml without metabolic activation and at $\geq$4 mg/ml with metabolic activation. Cell density was not affected, but the mitotic index was significantly decreased at $\geq$1 mg/ml. In the single *in vivo* study (micronucleus assay) available, groups of male ICR mice (6/dose level) were gavaged once with 0, 500, 1000, or 2000 mg/kg thiodiglycol in deionized water and sacrificed 24 hours later (Erexson, 2001). Positive controls were gavaged with cyclophosphamide. No signs of toxicity were observed during the observation period. Thiodiglycol did not induce micronuclei in the bone marrow.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC
RfDs FOR THIODIGLYCOL

Studies evaluating subchronic or chronic oral exposure of humans to thiodiglycol were not located. OECD/SIDS (2004) and Reddy et al. (2005) summarized two unpublished studies: one by BASF AG and a second by the U.S. Army Center for Health Promotion and Preventive Medicine (CHPPM). Because the key studies are unpublished, no values are presented here. However, information is available for this chemical which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix and develops a "Screening Value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of Screening Values should be directed to the Superfund Health Risk Technical Support Center.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC
INHALATION p-RfC VALUES FOR THIODIGLYCOL

No studies investigating the effects of subchronic or chronic inhalation exposure to thiodiglycol in humans or animals were identified. The lack of suitable data precludes derivation of subchronic and chronic p-RfCs for thiodiglycol.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR THIODIGLYCOL

Weight-of-Evidence Descriptor
Studies evaluating the carcinogenic potential of oral or inhalation exposure to thiodiglycol in humans were not identified in the available literature. Cancer bioassays for thiodiglycol have not been conducted in animals by either oral or inhalation exposure. Limited genotoxicity data suggest that thiodiglycol is not mutagenic, but, rather, that it could be clastogenic under certain conditions. Under the 2005 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), we classify thiodiglycol as "*Inadequate Information is Available to Assess Carcinogenic Potential.*"

Quantitative Estimates of Carcinogenic Risk
The lack of suitable data precludes the derivation of quantitative estimates of cancer risk for thiodiglycol.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2007. Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. Cincinnati, OH.

Angerhofer, R.A., M.W. Michie and G.J. Leach. 1998. Subchronic oral toxicity of thiodiglycol in rats. U.S. Army Center for Health Promotion and Preventative Medicine, Aberdeen Proving Ground, MD. Report Number 6415-38-97-05-01. (Cited in OECD/SIDS, 2004 and Reddy et al., 2005).

ATSDR (Agency for Toxic Substances and Disease Registry). 2007. Toxicological Profile Information Sheet. Online. http://www.atsdr.cdc.gov/toxprofiles/index.asp.

BASF AG. 1989. Data on the study of Glyezin A in the Ames test. Department of Toxicology, unpublished report. Project No. 40M1018/884405. (Cited in OECD/SIDS, 2004).

BASF AG. 1993. Oral toxicity of Glyecine A in rats after administration by gavage for 4 weeks. Department of Toxicology, unpublished report. Project No. 21C0811/89094. (Cited in OECD/SIDS, 2004).

BASF AG. 1995a. Study of prenatal toxicity of Glyecin A in Wistar rats after oral administration. Department of Toxicology, unpublished report. Project No. 80R0811/89096. (Cited in OECD/SIDS, 2004).

BASF AG. 1995b. 2nd study of the prenatal toxicity of Glyecin A in Wistar rats after oral administration. Department of Toxicology, unpublished report. Project No. 30R0811/89118. (Cited in OECD/SIDS, 2004).

Carpenter, C.P. and H.F. Smyth. 1946. Chemical burns of the rabbit cornea. Am. J. Ophthalmol. 29: 1363-1372.

Clark, S.L. and M.E. Donner. 1998. Mouse lymphoma mammalian mutagenesis assay. Integrated Laboratory System, Durham, NC for U.S. Army Center for Health Promotion and Preventative Medicine, Aberdeen Proving Ground, MD. Project No. A083-001. (Cited in OECD/SIDS, 2004 and Reddy et al., 2005).

Erexson, L.G. 2001. In vivo mouse micronucleus assay with 2,2'-thiodiethanol. Covance Laboratories, Vienna, VA for U.S. Army Center for Health Promotion and Preventative Medicine, Aberdeen Proving Ground, MD. Covance Study No. 22283-0-455OECD. (Cited in OECD/SIDS, 2004 and Reddy et al., 2005).

Houpt, J.T., L.C. Crouse, R.A. Angerhofer et al. 2007. Developmental toxicity of thiodiglycol in Sprague-Dawley rats. Int. J. Toxicol. 26: 365-371.

IARC (International Agency for Research on Cancer). 2007. Search IARC Monographs. Online. http://monographs.iarc.fr/.

NIOSH (National Institute for Occupational Safety and Health). 2007. NIOSH Pocket Guide to Chemical Hazards. Online. http://www.cdc.gov/niosh/npg/.

OECD (Organization for Economic Cooperation and Development) 1995. OECD guideline (407) for testing of chemicals: Repeated dose 28-day oral toxicity study in rodents. Online. http://www.oecd.org/chemicalsafety/risk-assessment/1948386.pdf.

OECD. 1998. OECD guideline (408) for testing of chemicals: Repeated dose 90-day oral toxicity study in rodents. Online. http://www.oecd-ilibrary.org/environment/test-no-408-repeated-dose-90-day-oral-toxicity-study-in-rodents_9789264070707-en.

OECD. 2001. OECD guideline (414) for testing of chemicals: Prenatal Developmental Toxicity Study. Online. http://iccvam.niehs.nih.gov/SuppDocs/FedDocs/OECD/OECD_GL414.pdf.

OECD/SIDS (Organization for Economic Cooperation and Development/Screening Information Data Set). 2004. Thiodiglycol. Screening Information Data Set (SIDS) of OECD High Production Volume Chemicals Programme. Online. http://www.inchem.org/documents/sids/sids/111488.pdf.

OSHA (Occupational Safety and Health Administration). 2007. OSHA Standard 1910.1000 TableZ-1. Part Z, Toxic and Hazardous Substances. Online. https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=standards&p_id=9992.

Reddy, G., M.A. Major and G.J. Leach. 2005. Toxicity assessment of thiodiglycol. Int. J. Toxicol. 24: 435-442.

Smyth, H.F., Jr., J. Seaton and L. Fischer. 1941. The single dose toxicity of some glycols and derivatives. J. Ind. Hyg. Toxicol. 23: 259-268.

Stankowski, L.F. 2001. *Salmonella - Escherichia coli* mammalian microsome reverse mutation assay with confirmatory assay with 2,2'-thiodiethanol. Covance Laboratories, Vienna, VA for U.S. Army Center for Health Promotion and Preventative Medicine, Aberdeen Proving Ground, MD. Covance Study No. 22283-0-409OECD. (Cited in OECD/SIDS, 2004 and Reddy et al., 2005).

Tice, R.R., M. Donner, A. Udumundi and M. Vasquez. 1997. Integrated Laboratory System, Durham, NC for U.S. Army Center for Health Promotion and Preventative Medicine, Aberdeen Proving Ground, MD. Project No. A083-002. (Cited in OECD/SIDS, 2004 and Reddy et al., 2005).

U.S. EPA. 1991. Chemical Assessments and Related Activities. Office of Health and Environmental Assessment, Washington, DC. April.

U.S. EPA. 1994. Chemical Assessments and Related Activities. Office of Health and Environmental Assessment, Washington, DC. December.

U.S. EPA. 1997. Health Effects Assessment Summary Tables. FY-1997 Update. Prepared by the Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC. EPA/540/R-97/036. NTIS PB 97-921199.

U.S. EPA. 2005. Guidelines for Cancer Risk Assessment. Risk Assessment Forum, Washington, DC. EPA/630/P-03/001F. Online. http://www.epa.gov/raf/.

U.S. EPA. 2006. 2006 Edition of the Drinking Water Standards and Health Advisories. Office of Water, Washington, DC. Summer, 2006. EPA/822/R-06/013. Online. http://water.epa.gov/drink/standards/hascience.cfm.

U.S. EPA. 2007. Integrated Risk Information System (IRIS). Online. Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Online. http://www.epa.gov/iris/.

Vodela, J.K., R.A. Angerhofer, M.W. Michie et al. 1999. Effects of subchronic oral exposure of thiodiglycol on hepatic mixed-function oxidase and cytosolic glutathione antioxidant system in rats. Environ. Nutr. Interact. 3:207-216.

WHO (World Health Organization). 2007. Online Catalogs for the Environmental Criteria Series. Online. http://www.who.int/dsa/cat98/zehc.htm.

APPENDIX A. DERIVATION OF SCREENING
VALUES FOR THIODIGLYCOL

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional toxicity values for thiodiglycol. However, information is available for this chemical which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix and develops a "Screening Value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of Screening Values should be directed to the Superfund Health Risk Technical Support Center.

Studies evaluating subchronic or chronic oral exposure of humans to thiodiglycol were not located. OECD/SIDS (2004) and Reddy et al. (2005) summarized two unpublished studies: one by BASF AG and a second by the U.S. Army Center for Health Promotion and Preventive Medicine (CHPPM). These studies include both 28-day and 90-day standard toxicity studies in rats and two developmental (gestational exposure) studies in rats. In addition, another developmental study in rats (Houpt et al., 2007) and an analysis of liver metabolic enzymes from the 90-day rat study (Vodela et al., 1999) conducted by researchers associated with U.S. Army CHPPM were published in the open literature. Although efforts to obtain the unpublished material were unsuccessful, OECE/SIDS (2004) provided most of the necessary information for identification of the critical effects. Based on the summaries available in OECD/SIDS (2004), the unpublished studies appear to have been well conducted, following standardized protocols. In general, thiodiglycol showed little toxicity at the dose levels tested.

In the 90-day study, Sprague-Dawley rats dosed with 5000 mg/kg-day thiodiglycol had significantly reduced body weight without a significant reduction in food consumption. Significant alterations in kidney weight and urinalysis parameters were also reported at this dose level. The apparent NOAEL was 500 (average daily dose of 357) mg/kg-day. In the 28-day study, the only dose level tested, 1000 mg/kg-day, was an apparent NOAEL for clinical signs, weight gain, hematology, clinical chemistry, and pathology.

In the developmental studies summarized by OECD/SIDS (2004), fetuses from Wistar rats exposed to 1000 mg/kg-day thiodiglycol on GDs 6-15, a dose level that did not induce maternal toxicity, had a significantly increased incidence of dumbbell ossifications of thoracic vertebral bodies; no such effect was reported at 400 mg/kg-day. In Sprague-Dawley rats treated on GDs 5-19, a dose level of 1290 mg/kg-day thiodiglycol was a maternal and developmental NOAEL, whereas 3870 mg/kg-day reduced maternal weight gain and fetal weight and increased the incidence of variations (Houpt et al., 2007).

Both the 90-day toxicity study (Reddy et al., 2005) and the developmental toxicity study in Wistar rats (BASF AG, 1995b) provide comparable NOAELs (357 mg/kg-day and 400 mg/kg-day, respectively). Among all the changes observed in the 90-day study, a body weight change more than 10% is commonly considered an adverse effect. In contrast, the organ weight changes, such as kidney weight, were observed without pathological changes. Therefore, it is not clear whether these organ weight changes should be considered adverse. Detailed data from the developmental study (BASF AG, 1995b) suitable for BMD modeling are not available; therefore, those data are not modeled. Thus, only the body weight data in the 90-day toxicity study (Reddy et al., 2005) have been modeled with U.S. EPA Benchmark Dose software (BMDS) to estimate benchmark dose (BMD) and its lower confidence limit (BMDL). Appendix B summarizes the detailed BMD modeling procedure and results. The estimated BMDLs for body weight changes in male and female rats are 215 mg/kg-day and 2681 mg/kg-day. The lower BMDL of 215 mg/kg-day is lower than the NOAEL of 400 mg/kg-day from the developmental toxicity study in Wistar rats (BASF AG, 1995b). Therefore, the BMDL of 215 mg/kg-day is used as the appropriate point of departure to estimate screening RfDs.

The **subchronic screening p-RfD of 0.7 mg/kg-day** for thiodiglycol, based on the BMDL of 215 mg/k-day in 90-day rat study (Reddy et al., 2005; OECD/SIDS, 2004), is derived as follows:

$$
\begin{aligned}
\textbf{Subchronic Screening p-RfD} \quad &= \quad \text{BMDL} \div \text{UF} \\
&= \quad 215 \text{ mg/kg-day} \div 300 \\
&= \quad \textbf{0.7 mg/kg-day or } 7 \times 10^{-1} \textbf{ mg/kg-day}
\end{aligned}
$$

The uncertainty factor (UF) of 300 is composed of the following:

- A default UF of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response in humans.
- A default UF of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between rats and humans.
- A default UF of 3 is applied for database insufficiencies. Although the database included a 90-day study, and two developmental studies, all these studies were conducted in rats. The database does not include a reproductive study or a developmental study in a second animal species.

Confidence in the critical study is medium because the original study report is not available for review; however, the study was conducted following OECD test guidelines, and the study summary is available from an OECD assessment document (2004). Confidence in the database is medium due to lack of a reproductive study and a developmental study in a second animal species. However, the current database does provide study duration up to 90 days, and it includes two developmental studies in rats. The overall confidence in the subchronic screening p-RfD is medium.

Chronic toxicity studies for oral exposure to thiodiglycol are not available. Therefore, the chronic screening p-RfD is based on the BMDL of 215 mg/kg-day estimated for the 90-day rat study used for deriving subchronic p-RfD. The **chronic screening p-RfD of 0.07 mg/kg-day or 7×10^{-02} mg/kg-day** for thiodiglycol is derived as follows:

$$
\begin{aligned}
\textbf{Chronic screening p-RfD} \quad &= \quad \text{BMDL} \div \text{UF} \\
&= \quad 215 \text{ mg/kg-day} \div 3000 \\
&= \quad \textbf{0.07 mg/kg-day or } \mathbf{7 \times 10^{-02}} \textbf{ mg/kg-day}
\end{aligned}
$$

The composite UF of 3000 is composed of the same UFs applied for chronic screening p-RfD plus one extra UF for using a BMDL from a less than chronic exposure duration study:

- A UF of 10 is applied to account for less than chronic exposure duration; duration of the critical study was only 90 days. This UF accounts for the possibility that more severe responses might occur if experimental animals were exposed to thiodiglycol for their lifetime.

Confidence in the critical study is medium because the original study report is not available for review; however, the study was conducted following OECD test guidelines, and the study summary is available from an OECD assessment document (2004). Confidence in the database is low due to lack of chronic studies, a reproductive study, and a developmental study in a second animal species. However, the current database does provide study duration up to 90 days, and it includes two developmental studies in rats. The overall confidence in the chronic screening p-RfD is low to medium.

APPENDIX B. DETAILS OF BMD ANALYSIS FOR THIODIGLYCOL

The Benchmark Dose (BMD) model fitting procedure for continuous data is as follows. The BMD modeling was conducted with the U.S. EPA's BMD software (BMDS version 1.4.1). For the body weight changes, the original data were modeled with all the continuous models available within the software. An adequate fit based on the goodness-of-fit *p*-value ($p > 0.1$), scaled residual at the range of benchmark response (BMR), and visual inspection of the model fit. In addition to the three criteria for judging the adequate model fit, whether the variance needed to be modeled, and if so, how it was modeled also determined final use of the model results. If a homogenous variance model was recommended based on statistics (Test 2) provided from the BMD model runs, the final BMD results would be estimated from a homogenous variance model. If the test for homogenous variance (Test 2) was negative ($p < 0.1$), the model would be run again while applying the power model integrated into the BMDS to account for nonhomogenous variance (known as nonhomogenous model). If the nonhomogenous variance model did not provide an adequate fit to the variance data (Test 3, *p*-value less than 0.1), the data set would be considered unsuitable for BMD modeling. Among all the models providing adequate data fit, we will select the lowest BMDL if the BMDLs estimated from different models varied >3 fold, otherwise, we would consider the BMDL from the model with the lowest Akaike's Information Criterion (AIC) appropriate for the data set.

Following the above procedure, continuous-variable models in the U.S. EPA BMDS were fit to the data shown in Table B-1 for decreased body weight in male and female rats (Reddy et al., 2005). Tables B-2 and B-3 summarize the BMD modeling results for the data.

Table B-1. Body Weight in Sprague-Dawley Rats Exposed to Oral Thiodiglycol for 90 Days[a]				
	Exposure Group (mg/kg-day)			
Parameter	**0**	**50**	**500**	**5000**
Males				
Body Weight (g)	588 ± 67.8[b]	566 ± 65.6	562 ± 53.6	506 ± 57.1[c]
Sample Size	8	10	9	10
Females				
Body Weight (g)	338 ± 39.3	336 ± 36.2	339 ± 32.6	298 ± 17.9[c]
Sample Size	9	10	10	8

[a]Reddy et al., 2005
[b]Means ± SD
[c]Significantly different from control ($p \leq 0.05$)

Table B-2. Model Predictions for Changes in Body Weight (g) in Male Rats Exposed to Oral Thiodiglycol for 90 Days[a]

Model	Goodness-of-fit *p*-value	Scaled residual at control	AIC for fitted model	BMD_{1sd} (mg/kg-day)	$BMDL_{1sd}$ (mg/kg-day)
Restricted Models					
Linear	0.7057	0.684	343.8	4193	2761
Polynomial	0.7057	0.684	343.8	4193	2761
Power	0.7057	0.684	343.8	4193	2761
Hill	**0.4627**	**0.504**	**345.6**	**2971**	**301**

[a]Reddy et al., 2005

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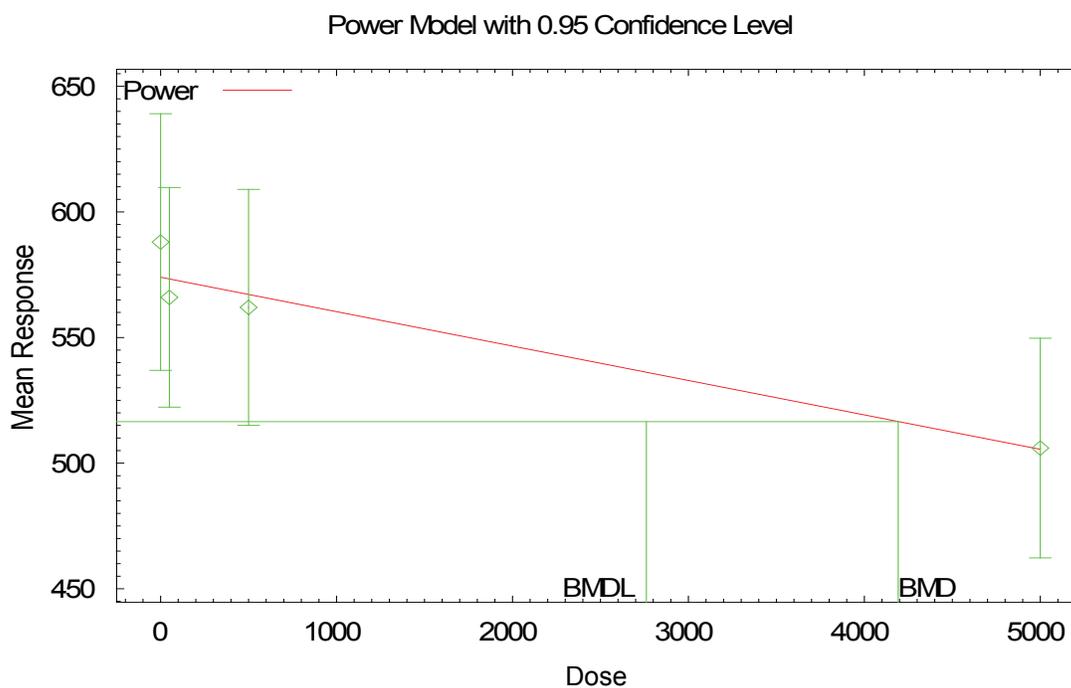

Power Model with 0.95 Confidence Level

11:27 09/09 2008

Figure B-1. Power model for body weight in male rats.

Hill Model with 0.95 Confidence Level
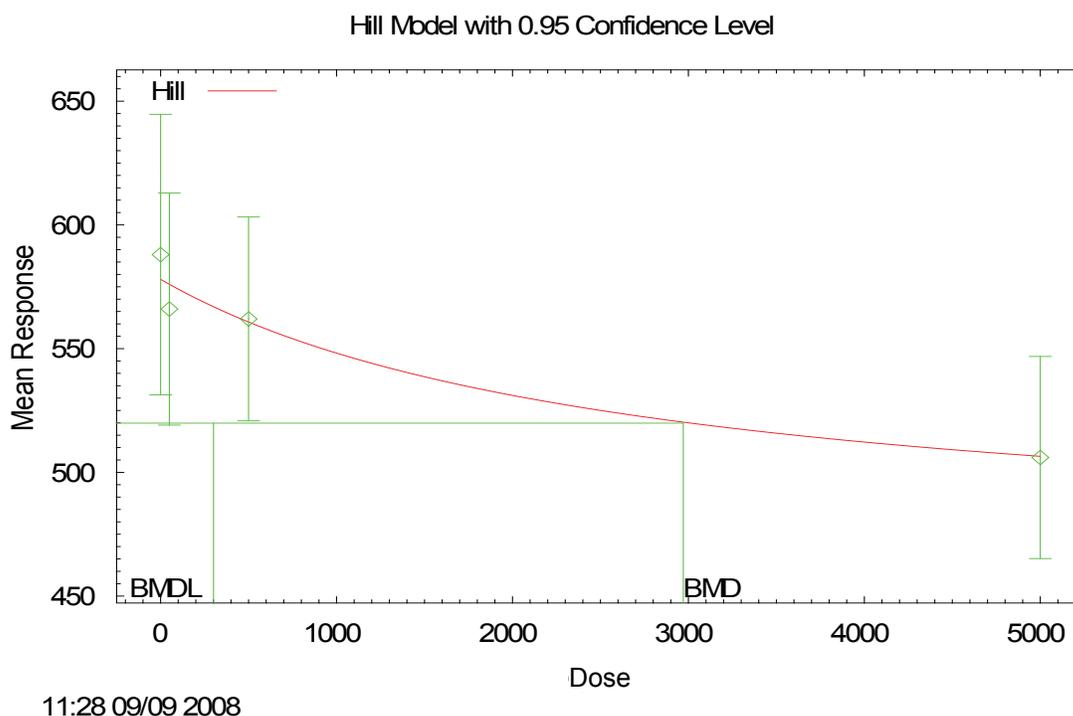
11:28 09/09 2008

Figure B-2. Hill model for body weight in male rats.

For body weight data in male rats, we fitted the variance data adequately by the homogenous variance ($p = 0.8873$); therefore, we ran all the models with a homogenous variance setting. Based on the goodness-of-fit p values (see Table B-2), all the available models provided adequate fit to the mean response ($p > 0.1$). Among all these models, the Hill model provides an estimate for the control mean closest to the original data as evident by the smallest scaled residual (see Table B-2), and Figures B-1 and B-2. In addition, the estimated BMDL from this model is more than 3-fold lower than those estimated from the rest of models. Thus, we consider a BMD of 2971 mg/kg-day and a BMDL of 301 mg/kg-day to be the best estimates for the body weight changes in male rats in this study. The corresponding average daily doses are 2122 and 215 mg/kg-day, respectively.

Table B-3. Model Predictions for Changes in Body Weight (g) in Female Rats Exposed to Oral Thiodiglycol for 90 Days[a]					
Model	**Goodness-of-fit *p*-value**	**Scaled residual at control**	**AIC for fitted model**	**BMD_{1sd} (mg/kg-day)**	**$BMDL_{1sd}$ (mg/kg-day)**
Restricted Models					
Linear	0.8832	-0.102	297.8	4176	2764
Polynomial	0.9706	0.0204	297.6	4608	3753
Power	0.8268	0.0332	299.6	4892	2800
Hill	N/A	0.0332	301.6	4935	failed

[a]Reddy et al., 2005
AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

For body weight data in female rats, we fitted the variance data adequately by the homogenous variance ($p = 0.1675$); therefore, we ran all the models with a homogenous variance setting (see Table B-3 and Figure B-3). Based on the goodness-of-fit *p* values, only the Linear, Polynomial and Power models provide adequate fit to the mean response ($p > 0.1$), while the Hill model fails to calculate a goodness-of-fit p value due to an over-parameterization. The estimated BMDLs from the three adequate models are within a 3-fold range (see Table B-3) with the lowest AIC of 297.6 obtained from the Polynomial model; therefore, we select the BMDL of 3753 mg/kg-day as the best estimate for this dataset. The corresponding average daily dose, using the average BMDL, is 2681 mg/kg-day.
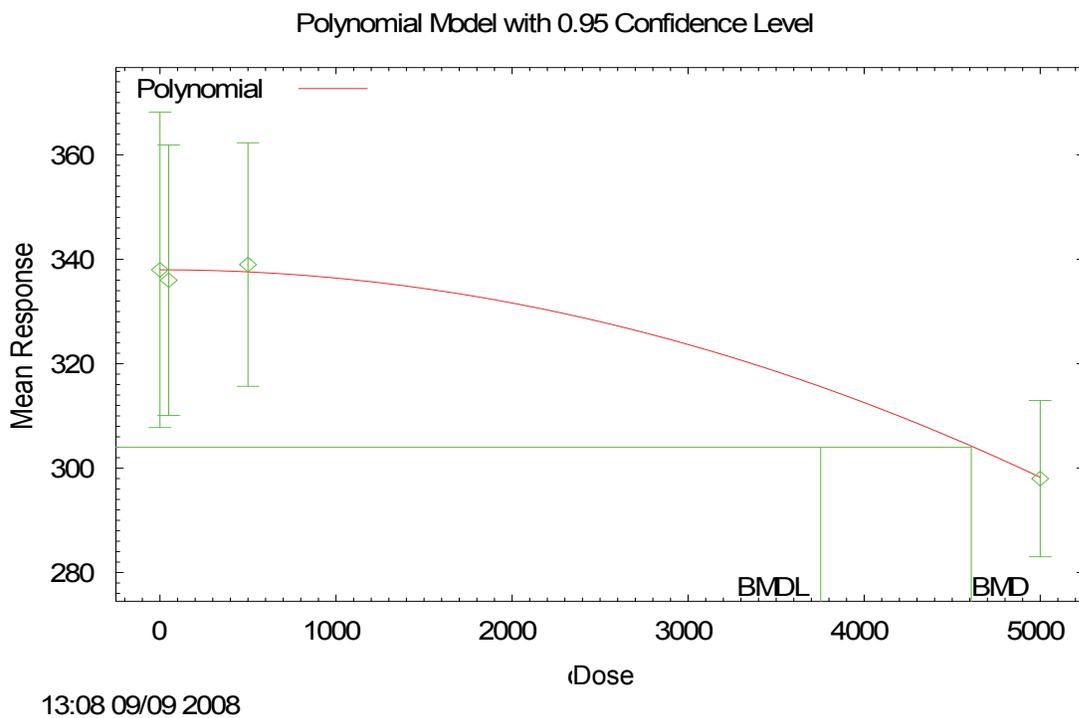
Figure B-3. Polynomial model for body weight in female rats.