Development Support Document
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1,3-Butadiene

CAS Registry Number: 106-99-0

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TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

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Chapter 1 Summary Tables and Figure

Table 1 provides a summary of health- and welfare-based values based on an acute and chronic evaluation of 1,3-butadiene (BD). Chapters 3 and 4 of the Development Support Document (DSD) provide information on the development of the acute and chronic values, respectively. Table 2 provides summary information on BD's physical/chemical data.

Table 1. Health- and Welfare-Based Values

Short-Term ESL for Air Permit Reviews: 240 µg/m^3 (110 ppb)		
Short-Term Values	**Values**	**Notes**
Acute ReV	800 µg/m^3 (360 ppb)	**Critical Effect:** Maternal toxicity; reduction in weight gain in pregnant CD-1 mice
^{acute}ESL [1 h]	240 µg/m^3 (110 ppb)	
^{acute}ESL$_{odor}$ [1 h]	510 µg/m^3 (230 ppb) [1]	50% detection threshold, mild aromatic odor
^{acute}ESL$_{veg}$	---	Concentrations producing vegetative effects were significantly above other ESLs
Long-Term ESL for Air Permit Reviews: 10 µg/m^3 (4.5 ppb)		
Long-Term Values	**Values**	**Notes**
Chronic ReV	33 µg/m^3 (15 ppb) [1]	**Critical Effect:** Reproductive toxicity: ovarian atrophy in B6C3F1 mice
^{chronic}ESL$_{nonlinear(nc)}$	10 µg/m^3 (4.5 ppb)	
^{chronic}ESL$_{linear(c)}$	62 µg/m^3 (28 ppb) [2]	**Cancer Endpoint:** Leukemia in occupational exposure study of styrene-butadiene synthetic rubber production workers
^{chronic}ESL$_{veg}$	---	No data found

[1] Screening value for air monitoring data.
[2] Based on unit risk factor (URF) = 0.00016/mg/m^3 (0.00036/ppm)

Abbreviations used: ppb, parts per billion; µg/m^3, micrograms per cubic meter; h, hour; ESL, Effects Screening Levels; ReV, Reference Value; ^{acute}ESL, acute health-based ESL; ^{acute}ESL$_{odor}$, acute odor-based ESL; ^{acute}ESL$_{veg}$, acute vegetation-based ESL; ^{chronic}ESL $_{linear(c)}$, chronic health-based ESL for linear dose-response cancer effect; ^{chronic}ESL$_{nonlinear(nc)}$, chronic health-based ESL for nonlinear dose-response noncancer effects; and ^{chronic}ESL$_{veg}$, chronic vegetation-based ESL

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Table 2. Chemical and Physical Data

Parameter	Value	Reference
Molecular Formula	C_4H_6 or H_2C:CHHC:CH_2	Lewis 1993
Chemical Structure		ChemIDplus Lite
Molecular Weight	54.1	TRRP 2006
Physical State	gas/organic	TRRP 2006
Color	colorless	Lewis 1993
Odor	mild aromatic odor	ACGIH 2001
CAS Registry Number	106-99-0	TRRP 2006
Synonyms	vinylethylene; erythrene; bivinyl; divinyl; biethylene; pyrrolylene; a,g-butadiene	Lewis 1993 NTP 1993
Solubility in water	735 mg/L	TRRP 2006
Log K_{ow}	2.03	TRRP 2006
Vapor Pressure	2,100 mm Hg at 20^0 C	TRRP 2006
Vapor Density (air = 1)	1.87	Lewis 1992
Density (water = 1)	0.6211 (liquid at 20^0 C)	Lewis 1993
Melting Point	-113°C	Lewis 1992
Boiling Point	-4.41 ° C	Lewis 1993
Conversion Factors	1 µg/m^3 = 0.45 ppb @ 25°C 1 ppb = 2.21 µg/m^3	NTP 1993

2

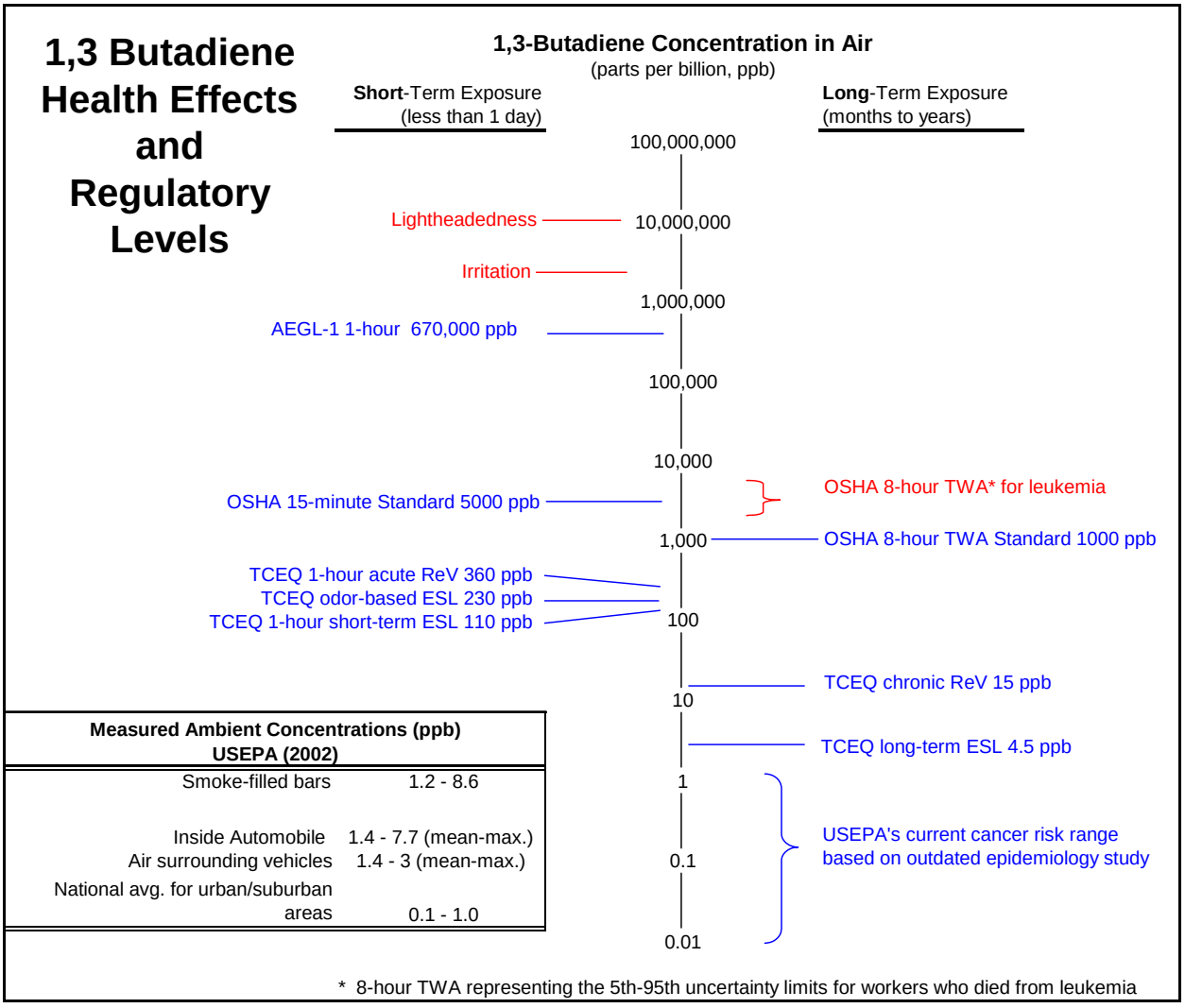

Figure 1. BD Health Effects and Regulatory Levels. This figure compares BD's acute toxicity values (acute ReV, odor-based ESL, and health-based, short-term ESL) and chronic toxicity values (chronic ReV and long-term ESL) found in Table 1 to USEPA's current acceptable cancer risk range based on an outdated epidemiology study, OSHA's occupational values, and the AEGL-1 value.

Abbreviations used: BD, 1,3-butadiene; TCEQ, Texas Commission on Environmental Quality; TWA, Time-Weighted Average; ESL, Effects Screening Level; ReV, Reference Value; OSHA, Occupational Safety and Health Administration; USEPA, United State Environmental Protection Agency; and AEGL-1, Acute Exposure Guideline Levels-1.

Chapter 2 Major Sources or Uses

BD is used as an intermediate in the production of polymers, elastomers, and other chemicals. Its major uses are in the manufacture of styrene-butadiene rubber (SBR) (synthetic rubber) and thermoplastic resins. Elastomers of BD are used in the manufacture of tires, footwear, sponges, hoses and piping, luggage, packaging, and a variety of other molded products. In addition, BD is used as an intermediate to produce a variety of industrial chemicals, including the fungicides captan and captfol. The primary way that BD is released into the environment is via emissions from gasoline- and diesel-powered vehicles and equipment. Lesser releases occur from the combustion of other fossil fuels and biomass. Minor releases occur in production processes, tobacco smoke, gasoline vapors, and vapors from the burning of plastics as well as rubber (Miller 1978; USEPA 2002). United States Environmental Protection Agency's (USEPA) (2001) National-Scale Air Toxics Assessment of emissions from the 1996 National Toxics Inventory indicates that statewide BD emissions from mobile sources (onroad and nonroad) accounted for approximately 54% of the National Toxics Inventory BD emissions in Texas, with major facility sources and area/other sources (e.g., smaller facilities) comprising the remainder of 46%.

Chapter 3 Acute Evaluation

3.1 Health-Based Acute ReV and ^{acute}ESL

3.1.1 Physical/Chemical Properties and Key Studies

3.1.1.1 Physical/Chemical Properties

BD is a highly volatile, colorless gas with a mildly aromatic odor. The main chemical and physical properties of BD are summarized in Table 2. It is soluble in ethanol, diethyl ether, and organic solvents, and only slightly soluble in water.

3.1.1.2 Key Studies

This section is based on USEPA (2002) and AEGL (2005). Both of these sources state "The acute toxicity of BD is of low order." (USEPA 2002; AEGL 2005). A review of the scientific literature since 2002 indicates that a subchronic inhalation study in rats conducted by the American Chemistry Council (ACC 2003) is a new study that was not considered by USEPA (2002). Therefore, this study is discussed in Section 3.1.1.2.2. Animal data show BD is a potential reproductive/developmental hazard to humans. Since the reproductive/developmental effects of BD in rats and mice are among the effects observed at the lowest exposure levels following acute inhalation exposure, the following sections focus on these health effects. Chapter 5 of *Health Assessment of 1,3-Butadiene* (USEPA 2002) provides a detailed discussion on potential reproductive/developmental effects in humans and animals, and AEGL (2005) discusses other types of acute toxicity data.

3.1.1.2.1 Human Studies

Mice are more susceptible to BD-induced reproductive/developmental effects than rats, whereas reproductive/developmental effects in humans after exposure to BD have never been observed (Albertini et al. 2007; USEPA 2002).

The health effects observed in humans occur at high concentrations and include the following: odor perception (ACGIH 2001; Ruth 1986; and Nagata 2003); slight smarting of the eyes and difficulty in focusing (Carpenter et al. 1944); and tingling sensation and dryness of the nose and throat (Larionov et al. 1934) (Table 3). A poorly reported study conducted by Ripp (1967) in human volunteers reported effects of olfactory perception at 4.0 milligram per cubic meter (mg/m^3) (1.8 parts per million (ppm)) and sensitivity of the eye to light at 3.9 mg/m^3 (1.7 ppm). There were no effects on the occurrence of an electrocortical conditioned reflex at 3 mg/m^3 (1.4 ppm).

Table 3. Acute Effects of BD in Humans

Study	Concentration (Exposure Duration)	Subjective Symptoms	Differences Observed
Carpenter et al. 1944 2 males 1-h lunch break Nominal Concentrations	2,000 ppm [1] (7 hour (h))	Slight smarting of the eyes; difficulty in focusing	Results of tapping test and steadiness test – no differences
	4,000 ppm (6 h)	Slight smarting of the eyes; difficulty in focusing	
	8,000 ppm (8 h)	No subjective complaints [2]	
Larionov et al. (1934) No details on number of subjects and gender	1% (10,000 ppm) 5 minute (min)	Tingling sensation and dryness of the nose and throat.	Slight increase in pulse rate. No effects on blood pressure or respiration

[1] Difficulty in focusing was the basis of the AEGL-1 value. The 1-h AEGL-1 value of 670 ppm = 2,000 ppm divided by an intraspecies uncertainty factor of 3.

[2] No subjective complaints because of slight anxiety of subjects concerning the possibility of an explosion.

3.1.1.2.2 Animal Studies

3.1.1.2.2.1 Reproductive/Developmental Toxicity in Rats

In 1982, Hackett et al. (International Institute of Synthetic Rubber Producers (IISRP) 1982) conducted a reproductive/developmental study that included exposure of pregnant rats at 0, 200, 1,000, and 8,000 ppm 6 hours/day (h/day) on gestation day (GD) 6-15 and then sacrifice on GD 20. The most sensitive endpoints were a significant decrease in maternal body weight gain on GD 6-9 and extragestational weight gain (lowest observed adverse effect level (LOAEL) of 1,000 ppm and no observed adverse effect level (NOAEL) of 200 ppm for both endpoints). Minor skeletal defects were found to be significantly elevated at the lowest concentration, and the percentage of fetuses with major skeletal defects was significantly elevated at 1,000 ppm and above. The incidence of marked-to-severe wavy ribs and the total number of abnormal ossifications and irregular ossification of the ribs were elevated at 8,000 ppm.

In 1987, Hackett et al. (1987a) repeated the IISRP (1982) study at slightly lower concentrations to confirm the 1982 findings in rats and to compare the effects of similar BD exposures in mice (Hackett et

al. 1987b). The results of the Hackett et al. (1987b) study in mice are discussed in the next section. Pregnant rats (Hackett et al. 1987a) were exposed for 10-days via inhalation to 0, 40, 200, and 1,000 ppm on GD 6-15 for 6 h/day (Hackett et al. 1987a). For rats, the most sensitive short-term endpoints were decreases in maternal body weight gain on GD 6-11 and decreases in extragestational weight gain (LOAEL of 1,000 ppm and NOAEL of 200 ppm for both endpoints). Effects from BD exposure for fetal measures were not observed (i.e., no developmental toxicity was observed).

In 2003, a subchronic reproductive/developmental study in rats sponsored by the American Chemistry Council was conducted by WIL Research Laboratories, Inc (ACC 2003). Since this study was not available for USEPA's BD assessment (USEPA 2002), the major findings of the study are discussed below. The study was conducted using the following guidelines:

- USEPA TSCA Good Laboratory Practice Standards;
- The protocol met or exceeded applicable regulations of the Organisation for Economic Cooperation and Development (OECD) Guideline for Testing of Chemicals, Guideline 421, Reproduction/Development Toxicity Screening Test (July 27, 1995); and
- Office of Prevention, Pesticides & Toxic Substances (USEPA) 870.3550 (July 2000) requirements.

This study was conducted to provide information on the potential adverse effects of BD on male and female reproduction within the scope of a screening study. Assessments of gonadal function, mating behavior, conception, gestation, parturition, lactation of the F_0 generation, and the development of F_1 offspring from conception through weaning and post-weaning exposure were included. Three groups of F_0 animals, each consisting of 12 male and 12 female Crl:CD®(Sprague-Dawley) IGS BR rats, were exposed to 300, 1,500, and 6,000 ppm BD via whole-body inhalation exposure 6 h/day for 14 days prior to the breeding period and continuing throughout the gestation and lactation periods. A control group was exposed to clean, filtered air on a comparable regimen. For F_0 dams, the daily inhalation exposures were suspended on GD 21 through lactation day 4, to avoid any confounding effects of exposure on nesting or nursing behavior. Exposures were resumed for these dams on lactation day 5. The F_1 generation pups were potentially exposed to the BD *in utero,* and through nursing during lactation until weaning. Beginning on postnatal day (PND) 21, one male and one female from each litter were exposed for seven consecutive days to the same concentration of the BD concentration as its dam. Beginning on PND 28, one previously unexposed male and one previously unexposed female per litter were exposed for seven consecutive days to the same BD concentration as its dam.

Under the conditions of the current study, there were no adverse BD-related effects on any parameter measured in either the F_0 or F_1 animals at the exposure level of 300 ppm. Adverse BD-related effects were noted at 1,500 and 6,000 ppm and consisted of persistent reductions in body weight parameters in F_0 and F_1 males and females and transient reductions in food consumption (week 0-1) for F_0 males and females.

Adverse BD-related effects noted exclusively at 6,000 ppm consisted of clinical observations indicative of chromodacryorrhea, chromorhinorrhea, and salivation in F_0 males and females as well as infrequent occurrences of dried red material in the perioral and perinasal regions of four exposed F_1 pups (three males and one female).

Based on the results of this study, an exposure level of 300 ppm was considered to be the NOAEL in rats for F_0 parental systemic toxicity and for systemic toxicity for F_1 animals following post-weaning 6-h daily

exposures (PND 21-27 or PND 28-34). The NOAEL for effects on gonadal function, mating behavior, conception, gestation, parturition, lactation of the F_0 generation, and the development of F_1 offspring from conception through weaning was considered to be 6,000 ppm.

The findings of this subchronic reproductive/developmental study showed effects of reduction in body weight parameters as the most sensitive endpoint in male and female rats with a NOAEL of 300 ppm. Developmental effects were not observed. This study is included in the acute toxicity section because it is a well-conducted, high-quality study with a NOAEL of 300 ppm, which is slightly higher than the NOAEL of 200 ppm determined in previous rat studies (IISRP 1982; Hackett et al. 1987a).

3.1.1.2.2.2 Reproductive/Developmental Toxicity in Mice

Hackett et al. (1987b) exposed pregnant mice for 10 days via inhalation at 0, 40, 200, and 1,000 ppm on GD 6-15 for 6 h/day. Maternal toxicity manifested as reduced body weight gain (GD 11-16) and extragestational weight gain was observed at 200 and 1,000 ppm. Total body weight at GD 18 was decreased at 1,000 ppm. Therefore, the NOAEL for maternal toxicity was 40 ppm. Hackett et al. (1987b) reported the most sensitive short-term developmental endpoint was decreased fetal weight in male mice at 40 ppm. BD caused reduced fetal body weight and increased frequency of skeletal variations at 200 and 1,000 ppm which are concentrations corresponding to maternal toxicity expressed as reduced body weight. Major malformations in the mouse fetus were not detected although the potential for altered development was indicated by a dose-related increase in supernumerary ribs and reduced ossifications, particularly of the sternebrae.

Hackett et al. (1987b) reported that statistical differences were observed at the lowest exposure concentration of 40 ppm for male fetal body weight. Therefore, a NOAEL was not identified for this effect. However, Hackett et al. (1987b) conducted analyses of variance (ANOVA) on the average pup weight followed-up by Student's t-tests comparing the average pup weight for different treatment groups. Their pairwise comparisons using Student's t-test did not adjust significance levels for the number of multiple tests. In addition, their analyses did not adjust for well-known important covariate effects such as litter size. Christian (1996) noted that the apparent significant decrease in male fetal weight in the 40 ppm group was the result of the statistical analysis used, which was considered to be inappropriate.

Data reported by Hackett et al. (1987b) were reanalyzed by Green (2003). The Green (2003) reanalysis was based on analysis of covariance (ANCOVA) on the average pup weight adjusted for covariates and used the Dunnett-Hsu test to compare the mean weights for each of the exposed groups to the mean weight for the control group. Application of the statistical analysis indicates that the 40 ppm exposure concentration is a NOAEL in this study. Other previously analyzed endpoints were also analyzed by more appropriate methodology (Green 2003). In each instance, the NOAEL was at least as high as previously reported. For a few endpoints, a higher NOAEL was found. The overall NOAEL for this study is 40 ppm, based on the fetal weights.

In order to assess the Green (2003) reanalysis, Sielken et al. (Appendix 1) conducted a review of the Hackett et al. (1987b) study and the Green (2003) reanalysis, concentrating on male fetal body weight. The Sielken et al. review (Appendix 1) indicates that Green's (2003) conclusions are reasonable and based on standard statistical analyses practices that were overlooked by Hackett et al. (1987b). Green used the Dunnett-Hsu test to compare the mean weights for each of the exposed groups to the mean weight for the control group after both were adjusted for the effects of the covariates. This is the specific

situation for which the Dunnett-Hsu test was designed. In addition to reviewing the statistical methodology used in the Hackett et al. (1987b) and Green (2003) studies, Sielken et al. (Appendix 1) re-analyzed the fetal weight data to confirm the numerical results obtained by Green (2003) and performed a sensitivity analysis with respect to the effects of covariates, and determined the outcome of the more powerful statistical analyses where the individual pup weights were analyzed and the dams were treated as random effects. These analyses support the finding that the NOAEL based on fetal weight for this study is 40 ppm (Sielken et al. (Appendix 1)).

Table 4 is similar to Table 5-6 in USEPA (2002) but only contains parameters that were significantly different from controls. There were no statistical differences in number of pregnant dams, litters with live fetuses, implantations per dam, resorptions per litter, dead fetuses per litter, fetuses per number of litters examined, or sex ratio (% males) between treated mice and control mice (data not shown). The highlighted cells in Table 4 have been corrected based on the Hackett et al. (1987b) study reanalyses by Green (2003) and Sielken et al. (Appendix 1). The appropriate LOAEL for early resorptions is 1,000 ppm (not 200 ppm as reported by Hackett et al. (1987b)) and the LOAEL for decreases in male fetal body weight is 200 ppm (not 40 ppm). Decreases in male fetal body weight occur at the same concentrations as decreases in maternal weight gain (Table 6).

Table 5 is similar to Table 5-7 in USEPA (2002) but only contains parameters that were significantly different from controls. There were no results contrary to those of the Hackett et al. (1987b) after the reanalysis by Green (2003). The only fetal effects noted were slight, significant increases in minor skeletal abnormalities at 200 and/or 1,000 ppm, indicative of growth retardation. These effects occurred at the same concentrations as decreases in maternal weight gain (Table 6).

Table 4. Developmental Toxicity in CD-1 Mice Exposed to BD by Inhalation [a]

Parameters	Concentration (ppm)			
	0	40	200	1,000
Early resorptions	1.00 ± 0.23	0.58 ± 0.21	0.43 ± 0.13 [c, g]	0.75 ± 0.16
Fetal body weight (g)	1.34 ± 0.03 [b]	1.28 ± 0.01	1.13 ± 0.02 [c]	1.04 ± 0.03 [c]
Females	1.30 ± 0.03 [b]	1.25 ± 0.01	1.10 ± 0.02 [c]	1.06 ± 0.02 [c, f]
Males	1.38 ± 0.03 [b]	1.31 ± 0.02 [c, d]	1.13 ± 0.02 [c]	1.06 ± 0.02 [c]
Placental weight (mg)	86.8 ± 2.99 [b]	85.4 ± 2.29	78.6 ± 3.24 [c]	72.6 ± 1.88 [c]
Females	83.1 ± 3.03 [b]	80.9 ± 2.46	74.7 ± 3.52 [c]	70.1 ± 2.33 [c]
Males	89.3 ± 3.03 [b, e]	89.5 ± 2.27	80.1 ± 2.35 [c]	74.5 ± 1.81 [c]

[a] All values mean ± standard error from USEPA (2002)
[b] $p \leq 0.05$, significant linear trend
[c] $p \leq 0.05$, pairwise comparison with corresponding control parameter based on Hackett et al. (1987b)
[d] $p > 0.05$ based on Green (2003) and Sielken et al. reanalyses(Appendix 1)
[e] 89.3 $\pm$ 3.05 (Hackett et al. 1987b)
[f] 1.02 $\pm$ 0.02 (Hackett et al. 1987b)
[g] $p \geq 0.05$ based on Green (2003)
Source: USEPA (2002)

Table 5. Variations in CD-1 Mice Exposed to BD by Inhalation

Parameters	Concentration (ppm)			
	0	40	200	1,000
Variations: Abnormal sternebrae [a, b]	0.6 ± 0.9	0.4 ± 0.7	0.4 ± 0.8	0.8 ± 1.3 [c]
Variations: Supernumerary ribs [a, b]	1.7 ± 2.3	1.6 ± 2.1	6.0 ± 3.6 [c]	9.9 ± 3.0 [c]
Reduced ossification (all sites) [a]	1.7 ± 1.7	1.2 ± 1.5	2.7 ± 2.7	3.9 ± 2.6 [c]
Sternebrae	31/13	20/9	57/16 [d]	76/19 [d]

[a] Mean percentage per litter (mean ± SD)
[b] $p \leq 0.05$, significant linear trend, orthogonal contrast test
[c] $p \leq 0.05$, Tukey's test
[d] $p \leq 0.05$, Fisher exact test (fetal incidence)
Source: USEPA (2002)

Table 6. Maternal Toxicity in Pregnant CD-1 Mice Exposed to BD by Inhalation [a]

Parameters	Concentration (ppm)			
	0	40	200	1,000
Whole-body weight (g)				
Day 0	28.4 ± 0.25	28.3 ± 0.32	28.3 ± 0.32	28.4 ± 0.32
Day 18	54.9 ± 1.21 [b]	55.4 ± 1.09	52.5 ± 1.01	50.8 ± 0.86 [c, f]
Body weight gain (g)				
Days 0-6	2.7 ± 0.3	3.0 ± 0.3	2.5 ± 0.2	2.3 ± 0.2
Days 6-11	5.5 ± 0.4	5.8 ± 0.3	5.6 ± 0.3	4.8 ± 0.3
Days 11-16	13.3 ± 0.6 [b]	12.7 ± 0.4	11.4 ± 0.5 [c]	10.6 ± 0.4 [c]
Days 16-18	5.5 ± 0.3 [b]	5.7 ± 0.3	4.7 ± 0.4	4.8 ± 0.3
Gravid uterine weight (g)	19.3 ± 1.00 [b]	20.3 ± 0.80	18.0 ± 0.87	16.8 ± 0.67 [c, g]
Extragestational weight (g) [d]	35.5 ± 0.48 [b]	35.1 ± 0.44	34.5 ± 0.46	34.1 ± 0.36 [c]
Extragestational weight gain (g) [e]	7.60 ± 0.48 [b]	6.99 ± 0.38	6.20 ± 0.38 [c]	5.91 ± 0.28 [c]

[a] All values mean ± standard error from USEPA (2002)
[b] $p \leq 0.05$, significant linear trend
[c] $p \leq 0.05$, pairwise comparison with corresponding control parameter
[d] Body weight on GD 18 minus gravid uterine weight
[e] Extragestational weight minus body weight on GD 0
[f] 50.8 ± 0.87 (Hackett et al. 1987b)
[g] 16.7 ± 0.67 (Hackett et al. 1987b)
Source: USEPA (2002)

Table 6 is similar to Table 5-5 in USEPA (2002), but only lists data on maternal weight loss measures which are the main parameters that were significantly different from controls. There were no results contrary to those of Hackett et al. (1987b) based on the reanalysis of Green (2003). Table 6 indicates that there was a statistical reduction in extragestational weight gain (i.e., maternal weight minus gravid uterine weight) and weight gain (GD 11-16) at 200 ppm. A statistical decrease in gravid uterine weight did not occur at 200 ppm but did occur at 1,000 ppm. These results suggest that BD produces maternal toxicity but little or no intrauterine effects at 200 ppm. For mice and rats, body weight changes and changes in body weight gain in pregnant dams with no change in gravid uterine weight usually indicate maternal toxicity as discussed by Pohl et al. (1998):

> "Changes in maternal body weight corrected for gravid uterine weight at sacrifice may indicate whether the effect is primarily maternal or fetal. For example, there may be a significant reduction in weight gain and in gravid uterine weight throughout gestation but no change in corrected maternal weight gain, which would generally indicate an intrauterine effect. Conversely, a change in corrected weight gain and no change in gravid uterine weight generally suggest maternal toxicity and little or no intrauterine effect."

Therefore, if a point of departure (POD) for maternal toxicity is determined using the endpoints of "extragestational weight gain" and "weight gain at GD 11-16," then potential effects on the developing fetus (i.e., reduction in fetal weight, minor skeletal abnormalities) would be prevented (Tables 5 and 6). Reduction in maternal body weight gain was an effect that was consistently observed in studies in rats, although at much higher concentrations (IISRP 1982; Hackett et al. 1987a; and ACC 2003).

3.1.2 Mode-of-Action (MOA) Analysis

It is generally agreed that BD produces toxicity when it is metabolized to its reactive metabolites after animals are exposed to BD. However, there is a difference in the metabolism amongst species. The basis of the species differences between rats and mice may be related to the greater production of toxic intermediates and a lower capacity for detoxification of these intermediates, although uptake of BD via inhalation exposure appears to be faster in mice compared to rats and humans (USEPA 2002).

The following chemical terminology, similar to the terminology in USEPA (2002), is used in the DSD. Figure 2 (below) is Figure 5 from USEPA (2002):

- 1,2-Epoxy-3-butene (EB). EB is also used for epoxybutene, 1,3-butadiene monoepoxide, 1,3-butadiene monoxide, 1,2-epoxybutene-3, vinyl oxirane, and 3,4-epoxy-1-butene;

- 1,2:3,4-Diepoxybutane (DEB). DEB is also used for diepoxybutane, butadiene diepoxide, and butadiene bisoxide;

- 3-Butene-1,2-diol (butene-diol). Butene-diol is also used for 1,2-dihydroxybut-3-ene; and

- 1,2-Dihydroxy-3,4-epoxybutane (EBD). EBD is also used for epoxybutanediol, 3,4-epoxybutanediol, 3,4-epoxybutane-1,2-diol, and 3,4-epoxy-1,2-butanediol.

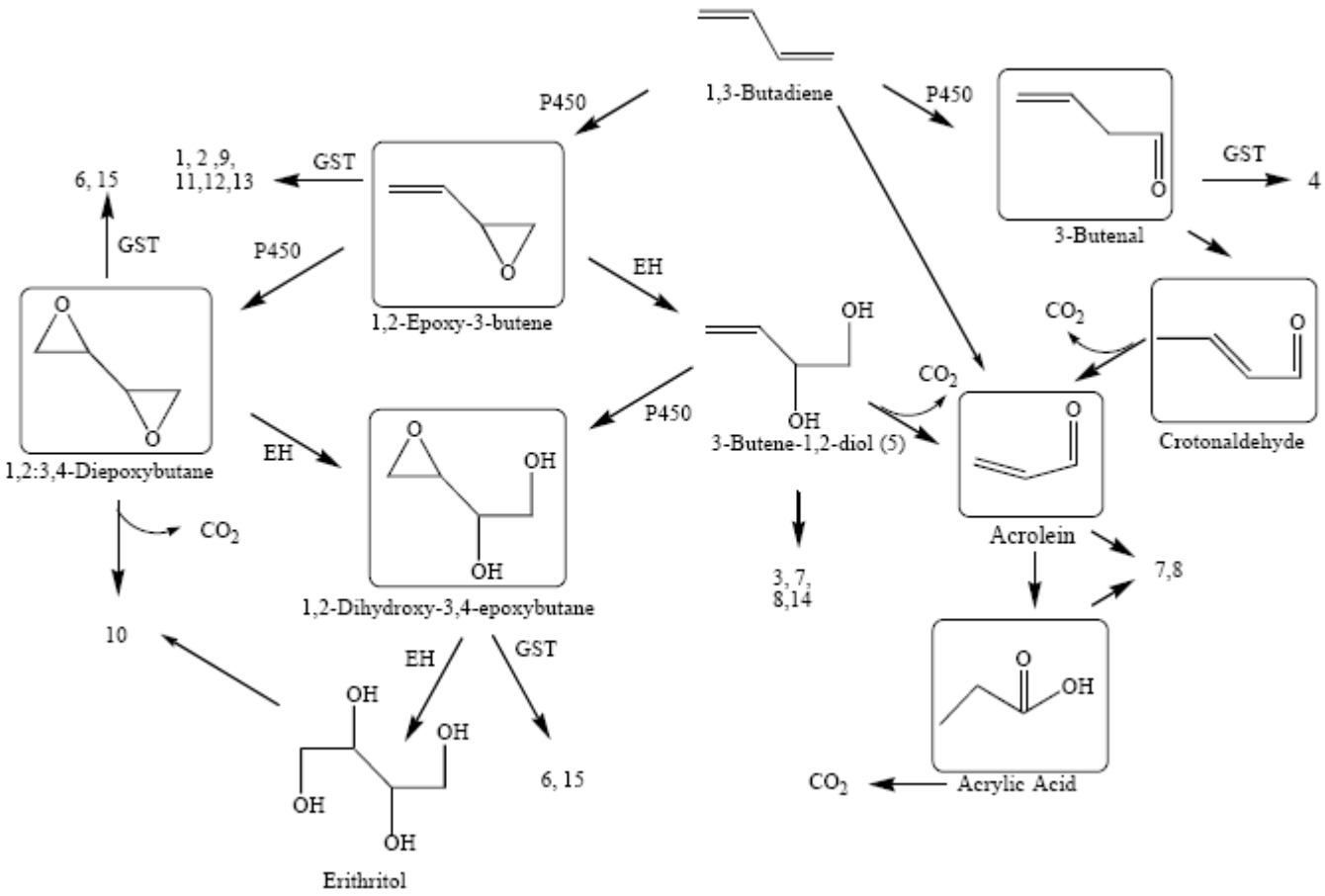

Figure 2. Schematic of BD Metabolism (Figure 3-1 from USEPA (2002))
P450 stands for cytochrome P450, EH stands for epoxide hydrolase, GST stands for glutathione transferase, and GSH stands for glutathione. The reactive metabolites are shown inside boxes. The urinary metabolites are numbered and listed in Table 3-1 of USEPA (2002).

The general metabolic scheme of BD, which has been reviewed by Himmelstein et al. (1997), is shown in Figure 2. BD is first metabolized to 1,2-epoxy-3-butene (EB), a process that is primarily associated with CYP 2E1, but can also be accomplished by additional isoforms including CYP 2A6 and 4B1. This electrophilic metabolite can be detoxified by conjugation with glutathione and subsequent excretion in the urine as M2. It can also undergo hydrolysis by epoxide hydrolase (EH) to form 3-butene-1,2-diol (butene-diol). Butene-diol can also be conjugated with glutathione and subsequently excreted in the urine as M1. It can be further oxidized by cytochrome P450 to the 1,2-dihydroxy-3,4-epoxybutane (EBD). An alternative pathway for the metabolism of EB is oxidation to the 1,2:3,4-diepoxybutane (DEB) which can be further hydrolyzed to EBD or conjugated by glutathione and excreted as M3. This series of epoxidation and detoxication steps generates three electrophilic metabolites: EB, DEB, and EBD.

Cochrane and Skopek (1994) have shown that DEB is 100 times more mutagenic than EB and 200 times more mutagenic than EBD. Kligerman and Yu (2007) used an in vitro system of lymphocytes treated with EB or DEB and measured sister chromatid exchange and chromosome aberrations. DEB-induced damage for both sister chromatid exchange and chromosome aberrations were persistent in G_0 cells and DEB was much more genotoxic than EB. EB did not induce sister chromatid exchange in lymphocytes unless actively cycling cells were treated. The extent to which DEB is produced and reaches target tissues will play a role in the toxicity. The ability of EB to reach actively dividing or repair deficient cells will also somewhat contribute to toxicity (Kligerman and Yu 2007). Mice form more DEB than rats or humans whereas EBD is more readily formed in humans than in rats (Slikker et al. 2004; Swenberg et al. 2007).

Human genetic polymorphisms are likely to affect individual susceptibility to BD and its metabolites. Activation rates in humans exhibit a high degree of variability and appear to span the range of activation rates between mice and rats, so humans may be as sensitive as mice. Several genes appear to be important in the BD metabolic pathway. Inherent susceptibilities have been shown for both EB and DEB (Weincke and Kelsey 1993), which may be due to glutathione S-transferase theta (GSTT1) status. Also, glutathione S-transferase GSTM1 appears to be an important detoxifying factor for EB, so that GSTM1 null individuals would be expected to have greater effects following formation of EB. Unfortunately, no data have been published on the effects of GST polymorphisms of EBD. Genetic polymorphisms have also been identified for EH and CYP 2E1 that would be expected to affect susceptibility to BD and its metabolites. The role of these proteins in the toxicokinetics of numerous chemicals is reasonably well known. Three *in vitro* studies (Csanády et al. 1992; Seaton et al. 1995; and Duescher and Elfarra 1994) using rodent and human tissue samples have demonstrated that CYP 2E1 plays a role in the oxidation of both BD and EB. Polymorphisms that reduce EH activity may increase susceptibility to BD-induced effects. Likewise, rapid CYP 2E1 metabolizers may potentially be at greater risk.

The specific mode-of-action (MOA) for the reproductive/developmental effects produced by BD is unknown. Uptake of BD in mice is faster than rats and may account for the increased susceptibility of mice compared to rats. However, the basis of the species differences between rats and mice may be related to the greater production of toxic intermediates and a lower capacity for detoxification of these intermediates (USEPA 2002). Conjugation with GSH is an important detoxification route. Himmelstein et al. (1997) points out that GSH depletion occurs at longer exposure duration or at higher concentrations leading to higher body burdens of EB and DEB (Himmelstein et al. 1997). Based on the above information and consistent with USEPA (2002), the reproductive/developmental effects in mice are considered to have a threshold (i.e., a nonlinear MOA) and to be concentration and duration dependent.

3.1.3 Dose Metric

In the reproductive/developmental studies selected as key studies, data on the exposure concentration of the parent chemical are available. Since the MOA of the toxic response is not fully understood and data on other more appropriate dose metrics are not available (e.g. blood concentration of parent chemical, area under blood concentration curve of parent chemical, or putative metabolite concentrations in blood or target tissue), the exposure concentration of the parent chemical was used as the default dose metric.

3.1.4 Points of Departure (PODs) for Key Studies

The LOAEL for maternal toxicity in rats (1,500 ppm) reported from a subchronic study conducted by the American Chemistry Council (ACC 2003) is more than seven times the LOAEL for maternal toxicity observed in mice (200 ppm), so maternal toxicity in rats will not be considered. Decreases in extragestational weight gain and body weight gain (GD 11-16) from the Hackett et al. (1987b) study were modeled because they had the lowest NOAEL and LOAEL (40 and 200 ppm, respectively) (Table 7).

Table 7. Relevant Endpoints of Maternal Toxicity

Parameters	Concentration (ppm) [a]			
	0	**40**	**200**	**1,000**
No. litters	18	19	21	20
Body weight gain (g) Days 11-16	13.3 ± 0.6 [b] (2.55 SD)	12.7 ± 0.4 (1.74 SD)	11.4 ± 0.5 [c] (2.29 SD)	10.6 ± 0.4 [c] (1.79 SD)
% decrease from controls	---	4.5%	14.3	20.3%
Extragestational weight gain (g)	7.60 ± 0.48 [b] (2.04 SD)	6.99 ± 0.38 (1.66 SD)	6.20 ± 0.38 [c] (1.74 SD)	5.91 ± 0.28 [c] (1.25 SD)
% decrease from controls	---	8.0%	18.4%	22.2%

[a] All values mean ± standard error from USEPA (2002). Standard deviation (SD) equals the standard error times the square root of n (no. litters)
[b] $p \leq 0.05$, significant linear trend
[c] $p \leq 0.05$, pairwise comparison with corresponding control parameter

Decreases in maternal weight gain on GD 11-16 and decreases in extragestational weight gain were modeled with Benchmark Dose Modeling (BMDS) Software (Version 1.4.1) using both the continuous polynomial model (using three doses and four doses) and the Hill model. Both models provided an adequate statistical fit to the data (Appendix 2). The polynomial model was fit with unrestricted parameters and is not monotone. Adequacy of fit to the Hill model and the three-dose polynomial model were determined by visual inspection of the data plot. The three-dose continuous polynomial model and the Hill model provided a better fit of the data than the four-dose continuous polynomial model based on visual inspection and residual evaluation. Therefore, only the results from these models were considered for selection of the POD. The three- and four-dose linear model (data not shown), and the three- and four-dose power model (data not shown) provided an adequate statistical fit to both maternal weight gain (GD 11-16) and decreases in extragestational weight gain, but did not fit the data as well based on visual inspection and residual evaluation.

The 95% lower confidence limit on the concentration corresponding to the benchmark response of a 5% reduction in weight gain ($BMCL_{05}$) was considered a NOAEL (Table 8). Calculated values at a BMR of 10% and 1 SD are provided in Table 8 as well as modeling results for the polynomial model using four

doses for comparison purposes. Appendix 2 provides modeling output files for modeling results of a 5% reduction in extragestational weight gain and maternal weight gain (GD 11-16) for all models in Table 8.

Reduction in extragestational weight gain was a more sensitive endpoint than reduction in maternal weight gain (GD 11-16) (Table 8). For reduction in extragestational weight gain, the three-dose polynomial $BMCL_{05}$ was 8.909 ppm and the Hill $BMCL_{05}$ was 2.811 ppm, which is within a factor of three. The three-dose polynomial model and the Hill model had similar Akaike's information criterion (AIC) values (132 and 165, respectively). According to guidance in USEPA (2000), the average $BMCL_{05}$ of the modeling results should be used ((8.909 ppm + 2.811 ppm)/2 = 5.860 ppm). Therefore, 5.860 ppm was chosen as the POD for reduction in extragestational weight gain.

For reduction in maternal weight gain (GD 11-16), the three-dose polynomial $BMCL_{05}$ was 13.95 ppm and the Hill $BMCL_{05}$ was 10.31 ppm, which is within a factor of three. The three-dose polynomial model and the Hill model had similar AIC values (155 and 201, respectively). According to guidance in USEPA (2000), the average $BMCL_{05}$ of the modeling results should be used ((13.95 ppm + 10.31 ppm)/2 = 12.13 ppm). Therefore, the average $BMCL_{05}$ of 12.13 ppm was chosen as the POD for reduction in maternal weight gain (GD 11-16).

3.1.5 Dosimetric Adjustments

The USEPA closely examined the physiologically-based toxicokinetic (PBTK) models for BD to determine if additional modeling could reduce uncertainties in the interspecies scaling between mice and humans for ovarian atrophy and other endpoints (USEPA, 2002, Chapter 9). USEPA stated that despite advances in the models over the past decade, the current models are inadequate for this purpose. For example, the PBTK models do not yet accurately describe the distribution of the major metabolites in various compartments, they do not yet include the reportedly important epoxydiol metabolites, and they have not been adequately validated. Recently, Filser et al. (2007) measured and evaluated the BD-dependent blood burden of the following metabolites: EB, DEB, EBD and butene-diol (refer to Figure 2) in rats and mice. Smith et al. (2001) investigated genetic and dietary factors affecting human metabolism of BD. Human volunteers were exposed to 2 ppm BD for a 20-min exposure with a 40-min washout period. Smith et al. (2001) fitted a three-compartment PBTK model to investigate BD uptake and estimate model parameters. Brochot et al. (2007) conducted a global sensitivity analysis for a proposed PBTK model. However, relevant parameters and a validated PBTK model for extrapolation from animals to humans is still lacking. Therefore, default duration exposure and dosimetric adjustments from animal-to human exposure were used.

1
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Table 8. BMC Modeling of Reduction in Maternal Weight Gain				
Response	**Model**	**Cutoff**	**BMC (ppm)**	**BMCL (ppm)**
Reduction in maternal weight gain (GD 11-16)	Polynomial AIC = 199 4 Doses Poor fit	5% reduction	64.01	41.00
		10% reduction	135.8	85.19
		1 SD	230.0	133.5
	Polynomial AIC = 155 3 Doses	5% reduction	44.83	13.95
		10% reduction	103.9	29.82
		1 SD	- - -	- - -
	Hill AIC = 201	5% reduction	44.49	10.31
		10% reduction	103.8	28.09
		1 SD	245.9	- - -
Decrease in extragestational weight gain	Polynomial AIC = 164 doses Poor fit	5% reduction	50.31	31.23
		10% reduction	105.46	64.34
		1 SD	272.5	146.0
	Polynomial AIC = 132 3 doses	5% reduction	23.61	8.909
		10% reduction	51.93	18.57
		1 SD	- - -	- - -
	Hill AIC = 165	5% reduction	23.69	2.811
		10% reduction	53.35	8.174
		1 SD	599.4	---

3
4

3.1.5.1 Default Exposure Duration Adjustments

The POD of 5.860 ppm based on 6 h/day for 10 days (Hackett et al. 1987b) for reduction in extragestational weight gain and 12.13 ppm for reduction in maternal weight gain (GD 11-16) were used. The 6-h exposure duration (C_1) was adjusted to a POD_{ADJ} of 1-h exposure duration (C_2) using Haber's Rule with n = 3 where both concentration and duration play a role in toxicity:

Reduction in extragestational weight gain

$$POD_{ADJ} = C_2 = [(C_1)^3 \times (T_1 / T_2)]^{1/3}$$
$$= [(5.860 \text{ ppm})^3 \times (6 \text{ h}/1 \text{ h})]^{1/3}$$
$$= 10.65 \text{ ppm}$$

Reduction in maternal weight gain (GD 11-16)

$$POD_{ADJ} = C_2 = [(C_1)^3 \times (T_1 / T_2)]^{1/3}$$
$$= [(12.13 \text{ ppm})^3 \times (6 \text{ h}/1 \text{ h})]^{1/3}$$
$$= 22.04 \text{ ppm}$$

3.1.5.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

BD is only slightly soluble in water and is moderately soluble in blood (USEPA 2002). It is readily absorbed from the air into the blood through the lungs. The health effects it produces at lower concentrations are mainly remote effects, so dosimetric adjustments were performed as a Category 3 gas which is consistent with USEPA (2002) and based on guidance in USEPA (1994). For Category 3 gases, the default dosimetric adjustment from animal-to-human exposure is conducted using the following equation:

$$POD_{HEC} = POD_{ADJ} \times [(H_{b/g})_A / (H_{b/g})_H]$$

where:

$H_{b/g}$ = ratio of the blood:gas partition coefficient
A = animal
H = human

For BD, the blood:gas partition coefficients for mice range from 1.2 to 3.0 with a mean of 1.67 (Appendix 3 of USEPA 2005a) and for humans 1.22 $\pm$ 0.30 (mean $\pm$ SD) (Brochot et al. 2007). When $(H_{b/g})_A / (H_{b/g})_H$, > 1, a default value of 1 is used for $(H_{b/g})_A / (H_{b/g})_H$, the regional gas dose ratio (RGDR) (USEPA 1994).

Reduction in extragestational weight gain

$POD_{HEC} = POD_{ADJ} \times RGDR = 10.65 \text{ ppm} \times 1 = 10.65 \text{ ppm}$

Reduction in maternal weight gain (GD 11-16)

$POD_{HEC} = POD_{ADJ} \times RGDR = 22.04 \text{ ppm} \times 1 = 22.04 \text{ ppm}$

3.1.6 Adjustments of the POD_{HEC} and Critical Effect

3.1.6.1 Uncertainty Factors (UFs)

The MOA by which BD produces maternal toxicity is not understood (Section 3.1.2), so the default for noncarcinogenic effects is to determine a POD and apply UFs to derive a ReV (i.e., assume a nonlinear MOA). The following UFs were applied to the POD_{HEC} of 10.65 ppm and 22.04 ppm: 10 for intraspecies variability (UF_H), 3 for extrapolation from animals to humans (UF_A), 1 for extrapolation from a LOAEL-to-NOAEL (UF_L), and 1 for database uncertainly (UF_D), a total UF = 30:

Reduction in extragestational weight gain
acute ReV = POD_{HEC} / (UF_H x UF_A x UF_L x UF_D) = 10.65 ppm / (10 x 3 x 1 x 1) = 0.3550 ppm

Reduction in maternal weight gain (GD 11-16)
acute ReV = POD_{HEC} / (UF_H x UF_A x UF_L x UF_D) = 22.04 ppm / (10 x 3 x 1 x 1) = 0.7347 ppm

A full UF_H of 10 was used to account for intraspecies variability because there is experimental evidence that indicates that BD-sensitive human subpopulations may exist due to metabolic genetic polymorphisms (USEPA 2002). A UF_A of 3 was used for extrapolation from animals to humans because default dosimetric adjustments from animal-to-human exposure were conducted which accounts for toxicokinetic differences but not toxicodynamic differences. This approach is conservative, since existing studies indicate that mice are relatively sensitive laboratory animals in regards to the reproductive effects of BD (e.g., relatively high respiratory rates, greater production of toxic intermediates, and a lower capacity for detoxification of these intermediates (USEPA 2002)). A UF_L of 1 was used because BMC modeling was performed to determine a POD based on the $BMCL_{05}$ and the BMR was set at a response level considered to be a NOAEL (i.e., 5% decrease in weight gain). A database UF_D of 1 was used because the overall acute toxicological database for BD meets the minimum database requirements used to derive an acute ReV (TCEQ 2006) (i.e., acute inhalation studies in humans, two inhalation bioassays in different species investigating a wide range of endpoints and two prenatal developmental toxicity studies in different species (USEPA 2002; AEGL 2005)). Both the quality of the studies and the confidence in the acute database is high.

3.1.6.2 Critical Effect

The critical effect is a 5% reduction in extragestational weight gain for pregnant CD-1 mice exposed to BD (Hackett et al. 1987b) because it has the lowest POD_{HEC} and the lowest acute ReV of 0.3550 ppm. In addition, reduction in body weight was the health effect observed at the lowest BD concentrations in studies conducted in both mice and rats.

3.1.7 Health-Based Acute ReV and ^{acute}ESL

The acute ReV value in Section 3.1.6.2 for extragestational weight gain was rounded to the least number of significant figures for a measured value at the end of all calculations. Rounding to two significant figures, the 1-h acute ReV is 360 ppb (800 µg/m^3). The rounded acute ReV was then used to calculate the ^{acute}ESL. At the target hazard quotient of 0.3, the ^{acute}ESL is 110 ppb (240 µg/m^3) (Table 9). This acute ReV and ^{acute}ESL are conservative since pregnant mice exposed to BD develop maternal toxicity much easier than similarly exposed rats do, available scientific information suggests mice are more sensitive than humans, and reproductive/developmental effects have never been observed in humans.

Table 9. Derivation of the Acute ReV and ^{acute}ESL	
Study	Hackett et al. 1987b
Study population	CD-1 mice (18-21 pregnant mice per dose group)
Study quality	high
Exposure Methods	10-day exposures via inhalation at 0, 40, 200, and 1,000 ppm on gestation days (GD) 6-15 for 6 h/day
Critical Effects	Reduction in extragestational weight gain; maternal toxicity
POD	5.86 ppm (average $BMCL_{05}$)
Exposure Duration	6 h
Extrapolation to 1 h	Haber's Law with n = 3
POD_{ADJ} (1 h)	10.65 ppm
POD_{HEC}	10.65 ppm (gas with systemic effects, based on default RGDR = 1.0)
Total uncertainty factors (UFs)	30
Interspecies UF	3
Intraspecies UF	10
LOAEL UF	1
Incomplete Database UF	1
Database Quality	high
acute ReV [1 hr] (HQ = 1)	**800 µg/m^3 (360 ppb)**
^{acute}ESL [1 h] (HQ = 0.3)	**240 µg/m^3 (110 ppb)**

3.2. Welfare-Based Acute ESLs

3.2.1 Odor Perception

ACGIH (2001) reports BD has a mildly aromatic odor with recognition occurring at 1 to 1.6 ppm. Ruth (1986) states the 50% odor detection threshold is 352 µg/m^3 (160 ppb) and the 100% recognition threshold is 2,860 µg/m^3 (1,300 ppb). The 50% odor detection threshold for BD determined by the triangular odor bag method was 230 ppb (Nagata 2003). Both Ruth (1986) and Nagata (2003) are listed as sources of information for odor thresholds in Appendix B of the ESL Guidelines (TCEQ 2006). However, only the Nagata (2003) study meets the criteria for acceptable odor threshold measurement techniques developed by the American Industrial Hygiene Association (TCEQ 2006). Therefore, the $^{acute}ESL_{odor}$ is 230 ppb (510 µg/m^3). Since odor is a concentration-dependent effect, the same 1-h $^{acute}ESL_{odor}$ is assigned to all averaging times.

3.2.2 Vegetation Effects

BD concentrations that produce vegetative effects, such as abscission and inhibition of growth, are orders of magnitude higher than concentrations of ethylene, propylene, and acetylene that produce similar effects

(USDHEW 1970). Since concentrations producing vegetative effects (approximately > 10,000 ppm) are significantly above other health- and odor-based concentrations, an $^{acute}ESL_{veg}$ was not developed for BD.

3.3. Short-Term ESL and Values for Air Monitoring Evaluation

The acute evaluation resulted in the derivation of the following values:

- Acute ReV = 800 µg/m^3 (360 ppb)
- $^{acute}ESL$ = 240 µg/m^3 (110 ppb)
- $^{acute}ESL_{odor}$ = 510 µg/m^3 (230 ppb)

The short-term ESL for air permit evaluations is the health-based $^{acute}ESL$ of 240 µg/m^3 (110 ppb) as it is lower than the $^{acute}ESL_{odor}$ (Table 1). For the evaluation of ambient air monitoring data, the $^{acute}ESL_{odor}$ of 510 µg/m^3 (230 ppb) is lower than the acute ReV of 800 µg/m^3 (360 ppb) (Table 1), although both values will be used for the evaluation of air data (Table 1).

3.4 Derivation of Acute ReV versus USEPA's Acute Reference Concentration (RfC)

USEPA (2002) derived an acute RfC of 3.2 µg/m^3 (7 ppb) representative for a 24-h exposure duration based on developmental toxicity (decreased male fetal body weight at 40 ppm was inappropriately assumed to be the LOAEL). A value of 2.9 ppm for a 24-h POD_{HEC} is reported in Table 10-25 of USEPA. USEPA applied UFs of 3 for interspecies variability, 10 for intraspecies variability, 4 for effect level extrapolation factor (to decrease risk to below the benchmark response level; analogous conceptually to the LOAEL-to-NOAEL UF) and 3 for incomplete database because a neurodevelopmental toxicity study has not been completed (total UF = 400) (Table 10).

The acute ReV for a 1-h exposure duration is based on maternal toxicity (5% reduction in extragestational weight gain). The adjusted 1-hr POD_{HEC} is 10.65 ppm. A UF of 3 was applied for interspecies extrapolation and 10 for intraspecies variability (total UF = 30). The Toxicology Section (TS) did not apply an effect level extrapolation factor analogous to a LOAEL-to-NOAEL UF since numerous investigators have demonstrated or recommended that the $BMCL_{05}$ is analogous to the NOAEL and should be treated as such (Barnes et al. 1995; Fowles et al. 1999; Filipsson et al. 2003). An acute database UF was not applied because the acute database for BD is adequate (i.e., meets the minimum database used to derive an acute Rev (TCEQ (2006)). Table 10 compares the derivation of the 1-h acute ReV and $^{acute}ESL$ to USEPA's 24-h acute RfC (USEPA 2002).

Table 10. Acute ReV Compared to USEPA's Acute RfC						
POD_{HEC}	Inter-species	Intra-species	Effect Level Extrapolation Factor	Incomplete Database	Total UF	Acute Reference Value
TCEQ 10.65 ppm [1 h] [1] Maternal toxicity (5% reduction in extragestational weight gain)	3	10	---	---	30	acute ReV [1 h] 360 ppb ^{acute}ESL [1 h] 110 ppb
USEPA 2.9 ppm [24 h] [2] Fetal toxicity (5% reduction in fetal body weight)	3	10	4	3	400	acute RfC [24 h] 7 ppb

[1] The unadjusted 6-h $BMCL_{05}$ for a 5% reduction in maternal extragestational weight gain was 5.860 ppm
[2] The unadjusted 6-h $BMCL_{05}$ for a 5% reduction in decreased fetal body weight was 11.6 ppm

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

4.1.1 Physical/Chemical Properties and Key Studies

Refer to Section 3.1.1.1 for a discussion of physical/chemical properties.

This section is based on USEPA (2002). Chapter 5 of USEPA (2002) discusses the chronic reproductive/developmental effects of BD. Animal data indicate that BD is a potential reproductive hazard because reproductive effects are observed at the lowest concentrations tested in animals. Chapter 6 of USEPA (2002) discusses other subchronic and chronic health effects observed in animals exposed to BD. Few adverse noncarcinogencic effects have been observed other than reproductive and developmental effects, except for hematological effects in mice exposed to higher concentrations and increases in organ weights in rats (USEPA 2002, Chapter 6). A review of the scientific literature since 2002 did not reveal any other chronic inhalation studies that could be used instead of the 2-year chronic bioassays conducted by the National Toxicology Program (NTP 1993) which are summarized in the following sections but discussed in detail in USEPA (2002).

4.1.1.1 Human Studies

Albertini et al. (2007) conducted a molecular epidemiological study of BD-exposed Czech workers to compare female to male responses. The focus of the study was to collect data on urine concentrations of BD metabolites and blood concentrations of BD-metabolite hemoglobin adducts. However, questionnaire responses for female-specific adverse health questions in control and exposed females were obtained. There were 26 female control workers and 23 female BD-exposed workers. The years spent in the

company were 17.6 ± 9.3 years for control and 19.4 ± 9.9 years for exposed females (mean ± S.D.). Multiple external exposure measurements were obtained (10 full 8-h shift measures by personal monitoring per worker) over a 4-month period before biological samples were collected. Mean 8-h time-weighted average (TWA) exposure levels were 0.008 mg/m^3 (0.0035 ppm) for controls and 0.397 mg/m^3 (0.180 ppm) for exposed but with individual single 8-h TWA values up to 9.793 mg/m^3 (4.45 ppm) in the exposed group. Analysis of questionnaire responses for female-specific adverse health questions showed no significant differences between controls and exposed for miscarriages, still births, ectopic pregnancies, molar pregnancies, low birth weight (<2,500 g) babies, or pre-term births, based on information collected on all pregnancies.

4.1.1.2 Animal Studies

The most sensitive reproductive effects observed in 2-year chronic exposure studies were ovarian atrophy in female mice and testicular atrophy in male mice (NTP 1993). Testicular atrophy was primarily a high-exposure effect so this section focuses on ovarian atrophy. In this bioassay, groups of 70 female B6C3F1 mice were exposed by inhalation 6 h/day, 5 days/week to 0, 6.25, 20, 62.5, or 200 ppm BD for up to 103 weeks and groups of 90 female mice were exposed to 625 ppm. An interim evaluation of ovarian atrophy was conducted at 9 months on ten mice per group and also at 15 months. Significant concentration-related decreases in survival were seen in female mice exposed to concentrations ≥ 20 ppm, primarily due to the development of malignant neoplasms. Statistically significant increases in the incidence of ovarian atrophy were observed in all exposure groups following lifetime exposures. The LOAEL for ovarian atrophy was observed at the lowest exposure level (6.25 ppm, 6 h/day, 5 days/week, for 2 years). Uterine atrophy was also observed in the highest exposure groups; however, this is likely to be a secondary effect of ovarian atrophy. Similarly exposed rats did not develop adverse reproductive effects, thus providing further evidence that rats are less sensitive to the effects of BD than mice.

4.1.2 MOA Analysis

Refer to Section 3.1.2 for a discussion of BD metabolism. There is strong evidence that ovarian atrophy is mediated by the diepoxide metabolite, DEB, the most reactive of BD metabolites (Doerr et al. 1995, 1996; USEPA 2002). There are marked species differences in effects seen between rats which do not exhibit BD-induced ovarian atrophy, and mice which do exhibit BD-induced ovarian atrophy Doerr et al. (1995, 1996) evaluated the ovarian effects of the metabolites of BD in mice and rats and also examined 4-vinylcyclohexene, a structurally similar compound. Doerr et al. (1995, 1996) showed that the diepoxide of BD or 4-vinylcyclohexene is required for ovarian toxicity to occur in the rat. EB was ovotoxic to mice but not rats. Thus, the resistance of the rat to ovarian toxicity of BD is likely due to the decreased ability of the rat to produce DEB. Filser et al. (2007) was unable to detect DEB in venous blood of male Sprague-Dawley rats (detection limit 0.01 µmol/l) when they were exposed to 1,200 ppm for 6-8 hr, whereas DEB was detected in B6C3F1 mice at 3.2 µmol/l at 1,280 ppm BD. Humans are similar to rats in that they do not readily produce the diepoxide metabolite.

Swenberg et al. (2007) compared results in Czech Republic occupationally-exposed workers to results in mice and rats for a N,N-(2,3-dihydroxy-1,4-butadiyl) valine (pry-Val) hemoglobin adduct specific for DEB at similar BD concentrations (Table 11). The pry-Val adduct was not detected in human females or males, while female mice were 78 times more likely than human females to produce DEB as evaluated with pry-Val adducts (Table 11). Pry-Val adducts for human females were based on the limit of quantitation (LOQ) because pry-Val adducts were not detected (Swenberg et al. 2007). At the 2007

Society of Toxicology meeting, Georgieva et al. (2007) presented results using a more sensitive analytical method to measure pry-Val adducts. Pry-Val adducts were detected at low concentrations in Czech Republic workers, although there was not a clear dose-response relationship between pry-Val adducts and BD concentrations which may indicate pry-Val adducts are formed from other unknown sources.

Table 11. DEB-Specific pyr-Val Hb Adduct in Mouse, Rat, and Human from Swenberg et al. (2007)

Concentration	1 ppm BD 6 h/day 4 weeks (4.0 ppm-weeks)		1 ppm BD 6 h/day 4 weeks (4.0 ppm-weeks)		Mean 0.18 ppm for 4 months (3.1 ppm-weeks)	Mean 0.37 ppm for 4 months (6.3 ppm-weeks)
Species	Female mice	Male mice	Female rat	Male rat	Female human	Male human
Pyr-VAL Hb adducts (pmol/g in 50 mg globin)	23.5 ± 3.1 female mice have 78 times more pyr-Val adducts than female humans	30.8 ± 4.6 male mice have 103 times more pyr-Val adducts than male humans	0.7 ± 0.1	0.9 ± 0.03	< 0.3 (LOQ)	< 0.3 (LOQ)

4.1.3 Dose Metric

For ovarian atrophy, data on the exposure concentration of the parent chemical are available whereas data on more appropriate dose metrics, such as the monoepoxide or diepoxide metabolites in blood or target tissue, are not available. As discussed previously in Section 3.1.5, a validated PBTK model for extrapolation from animals to humans is still lacking. Therefore, the exposure concentration of the parent chemical was used as the default dose metric.

4.1.4 PODs for Key Studies and Critical Effect

Using benchmark concentration dose modeling and a Weibull time-to-response model, USEPA (2002) calculated a BMC_{10} of 1.05 ppm and $BMCL_{10}$ of 0.88 ppm based on the 1993 NTP 2-year inhalation bioassay, including interim sacrifice data. In calculating the BMC_{10} and $BMCL_{10}$, lesion severity was not taken into account, and the 625 ppm group was excluded because of high early mortality. In addition, ovarian atrophy was modeled to reflect extra risks only until age 50, because BD-induced ovarian atrophy is believed to result from follicular failure, and after menopause, follicles would no longer be available.

The PODs for all prenatal deaths (dominant lethal effect) ($BMCL_{05}$ = 10 ppm) and for testicular atrophy ($BMCL_{10}$ = 16 ppm) were also determined by USEPA (2002) and were significantly higher than the $BMCL_{10}$ of 0.88 ppm. Therefore, ovarian atrophy was selected as the critical effect (USEPA 2002).

Sielken et al. (Appendix 3) repeated the BMC modeling performed by USEPA using the same procedures described above and calculated the BMC_{05} and $BMCL_{05}$ as well as the BMC_{10} and $BMCL_{10}$ (Appendix 3). The $BMCL_{05}$ has generally been considered a NOAEL (Barnes et al. 1995; Fowles et al. 1999; Filipsson et al. 2003) whereas the $BMCL_{10}$ may be analogous to a NOAEL or LOAEL. The BMC_{10} and $BMCL_{10}$

calculated by Sielken et al. (Appendix 3) were 1.15 ppm and 0.881 ppm, respectively, which agreed with the BMC_{10} of 1.05 ppm and $BMCL_{10}$ of 0.88 ppm calculated by USEPA (2002).

USEPA (2002) analyzed ovarian atrophy data excluding the highest dose group and also including all the data. Traditionally, EPA drops the highest dose group when the model does not fit the data well due to some biological phenomenon or when quantal data are fit with a quantal model and there is high mortality in the highest dose group. The ovarian atrophy data, however, were modeled with a time-to-response model (i.e., a model that accounts for the time of death) as opposed to a quantal model which do not account for time of death. Furthermore, the model fit to the data that excluded the highest dose group was not better than the model fit to the data that included the highest dose group as shown by Sielken et al. (Appendix 3). However, USEPA (2002) excluded the highest dose group because of early mortality. The BMC_{05} and $BMCL_{05}$ were 0.560 ppm and 0.429 ppm, respectively, excluding the highest dose and 0.607 ppm and 0.462 ppm, respectively, including the highest dose. Since a time-to-response model was used, the TS used the $BMCL_{05}$ modeling result of 0.462 ppm that uses all the data as the POD.

Because the Weibull time-to-response model in these analyses is linear in dose, the BMC_{05} and $BMCL_{05}$ values are approximately half the corresponding BMC_{10} and $BMCL_{10}$ values. The values of BMC_{05} and $BMCL_{05}$ can be used if the dose-response relationship below the lowest experimental dose is believed to be the linear Weibull time-to-response model fit to the data. The assumption of linearity below the lowest experimental dose is usually conservative and, therefore, health protective. However, the motivation behind the benchmark dose methodology is to identify the POD (BMC_{05} and $BMCL_{05}$) to be within the range of the experimental data (the range of the non-zero doses in the experimental data) and to be a dose whose risk can be reasonably reliably estimated without undue sensitivity to the dose-response model selected or the model estimation. Here, the BMC_{05} and $BMCL_{05}$ are below the range of the experimental data and, hence, introduce an additional element of uncertainty into the POD. However, the $BMCL_{05}$ for ovarian atrophy was used as the POD because the TS preferentially uses a benchmark response level of 5% for more severe effects such as ovarian atrophy, and the $BMCL_{05}$ is considered to be a NOAEL (TCEQ 2006).

4.1.5 Dosimetric Adjustments

Based on the summary of information in Section 3.1.5 and the detailed discussion in USEPA (2002, Chapter 9), default duration exposure and dosimetric adjustments from animal-to-human exposure were used.

4.1.5.1 Default Exposure Duration Adjustments

The $BMCL_{05}$ = 0.462 ppm for ovarian atrophy (Appendix 3) represents exposure concentrations that were already adjusted from discontinuous to continuous exposures.

4.1.5.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

BD is only slightly soluble in water and is moderately soluble in blood (USEPA 2002). It is readily absorbed from the air into the blood through the lungs. The health effects it produces at lower concentrations are mainly remote effects, so dosimetric adjustments were performed as a Category 3 gas which is consistent with USEPA (2002) and based on guidance in USEPA (1994). For Category 3 gases,

the default dosimetric adjustment from animal-to-human exposure is conducted using the following formula:

$$POD_{HEC} = POD_{ADJ} \times [(H_{b/g})_A / (H_{b/g})_H]$$

where:

$H_{b/g}$ = ratio of the blood:gas partition coefficient
A = animal
H = human

For BD, the blood:gas partition coefficients for mice range from 1.2 to 3.0 with a mean of 1.67 (Appendix 3 of USEPA 2005a) and for humans 1.22 $\pm$ 0.30 (mean $\pm$ SD) (Brochot et al. 2007). When $(H_{b/g})_A / (H_{b/g})_H$, > 1, a default value of 1 is used for $(H_{b/g})_A / (H_{b/g})_H$, the regional gas dose ratio (RGDR) (USEPA 1994).

$$POD_{HEC} = POD_{ADJ} \times RGDR = 0.462 \text{ ppm} \times 1 = 0.462 \text{ ppm}$$

4.1.6 Adjustments of the POD_{HEC}

The MOA by which BD produces ovarian atrophy is metabolism of the parent compound to DEB (Section 4.1.2), which is considered a threshold, nonlinear MOA. Therefore, a POD was determined and UFs applied to derive a ReV. The following UFs were applied to the POD_{HEC} of 0.462 ppm: 10 for intraspecies variability (UF_H), 1 for extrapolation from animals to humans (UF_A), 1 for extrapolation from a LOAEL-to-NOAEL (UF_L), 1 for extrapolation from a subchronic to chronic study (UF_{Sub}), and 3 for database uncertainly (UF_D), a total UF = 30:

$$\text{Chronic ReV} = POD_{HEC} / (UF_H \times UF_A \times UF_L \times UF_{Sub} \times UF_D)$$
$$= 0.462 \text{ ppm} / (10 \times 1 \times 1 \times 1 \times 3)$$
$$= 0.0154 \text{ ppm}$$

A full UF_H of 10 was used to account for intraspecies variability because there is experimental evidence to indicate that BD-sensitive human subpopulations may exist due to metabolic genetic polymorphisms (USEPA 2002).

The UF_A is composed of a toxicokinetic and toxicodynamic component. A toxicokinetic UF_A of 1 was used for extrapolation from animal to human because default dosimetric adjustments from animal-to-human exposure were conducted (Section 4.1.5.2). A toxicodynamic UF_A of 1 was used because humans produce much lower levels of DEB than mice as demonstrated by experimental data on DEB-specific pyr-Val adducts (Section 4.1.2). DEB is the BD metabolite responsible for ovarian atrophy (Section 4.1.2; USEPA 2002). Although these experimental data are not sufficient to develop a chemical-specific adjustment factor (CSAF) for BD, it would support an interspecies UF substantially less than 1. At the present time, procedures for developing a CSAF based on Hb adducts or for decreasing the UF to a value less than one based on other considerations are not available.

A UF_L of 1 was used because BMC modeling was performed to determine a POD based on the $BMCL_{05}$ (TCEQ 2006). A UF_{Sub} of 1 was used because the study was a chronic study. The toxicological database for BD is extensive. However, a UF_D of 3 was applied because of the absence of multigenerational

reproductive studies (USEPA 2002). Both the quality of the studies and the confidence in the chronic database is high.

4.1.7 Health-Based Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

The chronic ReV value based on ovarian atrophy was rounded to the least number of significant figures for a measured value at the end of all calculations. Rounding to two significant figures, the chronic ReV is 15 ppb (33 µg/m^3). The rounded chronic ReV was then used to calculate the $^{chronic}ESL_{nonlinear(nc)}$. At the target hazard quotient of 0.3, the $^{chronic}ESL_{nonlinear(nc)}$ is 4.5 ppb (10 µg/m^3) (Table 12).

Table 12. Derivation of the Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

Study	2-year bioassays (NTP 1993)
Study Population	70 female B6C3F1 mice; 90 female mice
Study Quality	high
Exposure Method	103 week exposures via inhalation at 0, 6.25, 20, 62.5, or 200 ppm; 90 female mice exposed to 625 ppm
Critical Effects	ovarian atrophy in female mice
POD (original animal study)	Not available. BMD modeling was conducted on data already adjusted from discontinuous to continuous exposure
Exposure Duration	6 hs/day, 5 days/week, for 2 years
Extrapolation to continuous exposure (POD_{ADJ})	0.462 ppm ($BMCL_{05}$)
POD_{HEC}	0.462 ppm (gas with systemic effects, based on default RGDR = 1.0)
Total UFs	30
Interspecies UF	1
Intraspecies UF	10
LOAEL UF	1
Subchronic to chronic UF	1
Incomplete Database UF	3
Database Quality	high
Chronic ReV (HQ = 1)	**33 µg/m^3 (15 ppb)**
$^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3)	**10 µg/m^3 (4.5 ppb)**

4.1.8 Derivation of Chronic ReV versus USEPA's Chronic RfC

Table 13 provides a comparison of the derivation of the chronic ReV of 33 µg/m^3 (15 ppb) versus the chronic RfC of 2 µg/m^3 (0.9 ppb) (USEPA 2002). USEPA (2002) applied a toxicodynamic UF_A of 3 but the TS applied a toxicodynamic UF_A of 1 for reasons explained in Sections 4.1.2 and 4.1.6. Based on experimental data and the MOA of BD, a UF_A of 1 is conservative and a $UF_A < 1$ may be justified. USEPA applied an effect level extrapolation factor to the $BMCL_{10}$ because USEPA considered it a significant response level. In contrast, the TS used a $BMCL_{05}$, which is considered to be a NOAEL, so a UF_L was not applied.

Table 13. Comparison of Chronic ReV and Chronic RfC

Chronic Toxicity Value	POD_{HEC}	UF_H	UF_A	UF_L or Effect Level Extrapolation Factor	UF_{Sub}	UF_D	Total UFs	Chronic Toxicity Value
ReV based on ovarian atrophy	462 ppb $BMCL_{05}$ including highest dose	10	1	1 UF_L	1	3	30	15 ppb
RfC based on ovarian atrophy	880 ppb $BMCL_{10}$ excluding highest dose	10	3	10 Effect Level extrapolation Factor	1	3	1,000	0.88 ppb

4.2 Carcinogenic Potential

4.2.1 Carcinogenic Weight-of-Evidence and MOA

USEPA has classified BD as known to be carcinogenic to humans by inhalation (DHHS 2000; USEPA 2002) based on the following findings:

- Increased lymphohematopoietic cancers in workers occupationally exposed via inhalation to BD based on epidemiologic studies (leukemias in polymer workers and non-Hodgkin's lymphoma in monomer workers);
- BD causes a variety of tumors in mice and rats by inhalation in various studies;
- Demonstration that BD is metabolized into genotoxic metabolites by experimental animals and humans.

Table 14 provides information on the carcinogenic weight-of-evidence provided by other organizations. Although the MOA by which BD produces tumors is unknown, scientific evidence suggests that carcinogenic effects are mediated by genotoxic metabolites of BD (i.e., EB, DEB, and EBD, Section 3.1.2 and Figure 2). A detailed review of the weight-of-evidence, carcinogenic hazard assessment, and MOA analysis for lifetime exposure potential is included in USEPA (2002). Preston (2007) recently reviewed

the evidence that BD works through a mutagenic MOA and concluded: "For butadiene, the MoA is DNA-reactivity and subsequent mutagenicity and so following the EPA's cancer guidelines, a linear extrapolation is used from the POD, unless additional data support a non-linear extrapolation." Therefore, an inhalation unit risk factor (URF) and $^{chronic}ESL_{linear(c)}$ (i.e., air concentration at 1 in 100,000 excess cancer risk) was developed for BD.

Table 14. Carcinogenic Weight-of-Evidence

International Agency for Research on Cancer 2007	Group 1, Carcinogenic to humans
National Institute for Occupational Safety and Health 1997	Potential occupational carcinogen
Occupational Safety and Health Administration 1996	"Potential occupational carcinogen" There is strong evidence that workplace exposure to BD poses an increased risk of death from cancers of the lymphohematopoietic system.
ACGIH 2001	A2, Suspected Human Carcinogen
USEPA 2002; DHHS 2000	Carcinogenic to humans by inhalation

4.2.2 Epidemiological Studies and Exposure Estimates

Chapter 7 of USEPA (2002) discusses the epidemiologic studies of carcinogenicity for BD and Chapter 10 discusses the dose-response assessment of the preferred occupational epidemiological study conducted by researchers at the University of Alabama at Birmingham (UAB) (Delzell et.al. 1995; 1996). Numerous epidemiology studies were reviewed, but USEPA (2002) concluded the UAB exposure estimates provided the best published set of data to evaluate human cancer risk from BD exposure. USEPA published an inhalation URF of $3.0 \times 10^{-5}/(\mu g/m^3)$ or 0.08/ppm based on leukemia mortality data from the UAB occupational epidemiological study (Delzell et.al. 1995; 1996).

Delzell et al. (1995, 1996) investigated a cohort of synthetic rubber production workers exposed to BD in a retrospective cohort mortality study. The investigators developed a job exposure matrix (JEM) for BD, styrene, and benzene based on industrial hygiene data, which contained estimates of the average daily exposure (in ppm based on the 8-h TWA) and the number of annual peaks (defined as > 100 ppm for BD and >50 ppm for styrene) for each area and job code for each study year. The investigators were then able to estimate cumulative exposures (ppm-years) and number of peak exposures (peak years) for each individual worker by linking the JEM with the study subjects' work histories.

Recently, the UAB epidemiology study of leukemia was updated (Sathiakumar et al. 2005; Graff et al. 2005; HEI 2006; Cheng et al. 2007) as well as the BD occupational exposure estimates for the occupational cohort (Macaluso et al. 2004). In addition, Sathiakumar et al. (2007) assessed the validity of the BD exposure estimates. These new, updated studies were used by the TS to update the USEPA (2002) assessment. A review of the scientific literature indicated there were no other epidemiology studies (e.g., Alder et al. 2006) that would be appropriate to evaluate human cancer risk from BD exposure.

Subjects included in the updated study were 16,579 men classified as having worked (for at least one year before 1 January 1992) at any of six synthetic rubber plants located in Texas (two plants), Louisiana (two plants), Kentucky (one plant) and Canada (one plant). Of the 16,579 subjects in the updated study, 488 subjects were excluded because they dropped out of follow-up at ages younger than the youngest leukemia decedent (age 33 years) (Cheng et al. 2007). Thus, results of leukemia analyses were based on 16,091 subjects and 485,732 person-years of observation. The updated study provided seven more years of follow-up (through 1998), a larger number of decedents, and a total of 81 deaths with leukemia as the primary or contributing cause. The association of BD exposure to lymphoid and myeloid neoplasms was investigated. BD-exposure estimates were also updated, and quantitative estimates of each subject's exposure to butadiene, styrene and dimethyldithiocarbamate (DMDTC) were calculated. DMDTC is an immune system depressant (Irons and Pyatt 1998; Irons et al. 2001).

4.2.3 Dose-Response Assessment

4.2.3.1 Beta coefficient (β) and Standard Error Based on Observed Data

Cheng et al. (2007) investigated the dose-response relationship between BD and leukemia rate ratios using an exponential Cox regression analysis. Cumulative exposure to BD in ppm-years, cumulative number of exposures to >100 ppm BD (referred to as peaks), and average intensity (ppm) of exposure to BD were considered as BD exposure dose metrics. The term "peak" is used by the UAB group to refer to the cumulative number of exposures to >100 ppm BD. These exposures were frequently of short duration (several seconds to several minutes). However, the term "peak" or "peak exposures" is misleading and will not be used in this assessment. Instead, the more descriptive term "number of high-intensity tasks" (i.e., number of HITs) was used.

Whereas Cheng et al. (2007) used the exponential Cox regression analysis, Sielken et al. (2007) used a linear Poisson regression analysis to investigate the relationship between BD and leukemia rate ratios. Cheng et al. (2007) and Sielken et al. (2007) calculated betas (β) (maximum likelihood estimates (MLEs)) and standard errors (SE) from the updated UAB epidemiological study and updated exposure estimates (Table 15). The TS used these values to calculate 95% upper confidence limit (UCL) values, URFs and corresponding air concentrations at 1 in 100,000 excess cancer risk (Table 16). The data needed to conduct a detailed MOA analysis were not available, so the use of a biologically-based model was not possible. Rather, standard models such as the linear Poisson regression, a conservative linear default model, and exponential Cox regression hazard proportional models were selected. The dose metric was cumulative BD parts per million years (ppm-years), a dose metric commonly used for epidemiological studies. Three other BD exposure indices were evaluated by Cheng et al. (2007): (1) continuous, time-dependent BD exposure indices ppm-years); (2) the total number of exposures to BD concentrations >100 ppm (number of HITs) and (3) average intensity of BD. All three BD exposure indices were positively associated with leukemia.

Table 15. Values of Maximum Likelihood Estimate (MLE) of Beta (β), Standard Error (SE), and 95% Upper Confidence Limit (UCL) on β [a]

Covariates	Model	Source	β (MLE)	Standard Error (SE)	β (95% UCL) [b]
Age	Cox regression ppm-years continuous [c]	Cheng et al. (2007)	2.9E-04	1.0E-04	4.545E-04
	Cox regression ppm-years mean-scored deciles [d]	Cheng et al. (2007)	7.5E-04	2.2E-04	1.112E-03
	Poisson regression ppm-years mean-scored deciles [d]	Sielken et al. (2007)	1.68E-03	8.21E-04	3.031E-03
Age & Number of HITs > 100 ppm	Cox regression ppm-years continuous [c], # of HITs continuous [e]	Cheng et al. (2007)	2.5E-04	1.2E-04 [g]	4.474E-04
	Cox regression ppm-years continuous [c], # of HITs categorical [f]	Sielken et al. (Appendix 4)	2.0E-04	1.3E-04	4.138E-04
	Cox regression ppm-years mean-scored deciles [d], # of HITs categorical [f]	Sielken et al. (Appendix 4)	2.8E-04	2.4E-04	6.748E-04
	Poisson regression ppm-years mean-scored deciles [d], # of HITs categorical [f]	Sielken et al. (2007)	1.89E-04	3.6E-04	7.812E-04
Age & Other Covariates [h]	Cox regression ppm-years continuous [c]	Cheng et al. (2007)	3.0E-04	1.4E-04	5.303E-04
	Cox regression ppm-years mean-scored deciles [d]	Cheng et al. (2007)	5.8E-04	2.7E-04	1.024E-03

[a] units are in ppm-years and based on occupational exposure concentrations
[b] β (95% UCL) = β(MLE) + (1.645 x SE)
[c] ppm-years is included as a continuous variable (untransformed) in a parametric model of the effect of ppm-years
[d] ppm-years is included as a categorical variable (based on mean-scored deciles, untransformed) in a parametric model of the effect of ppm-years
[e] number of HITs > 100 ppm is included as a continuous variable (untransformed) in a parametric model of the effect of the number of HITS > 100 ppm
[f] number of HITs > 100 ppm is included as a categorical variable (based on quintiles) in a nonparametric model of the effect of the number of HITs > 100 ppm
[g] back calculated from the corresponding p-value in Cheng et al. (2007)
[h] other covariates are year of birth, race, DMDTC, years since hire and plant

Table 15 shows results from the BD dose-response relationship conducted by Cheng et al. (2007) using exponential Cox regression procedures adjusted either for age as a covariate, age + number of HITs > 100 ppm, or adjusted for other covariates (age, year of birth, race, plant, years since hire and DMDTC). Cox regression procedures permit estimation of the dose-response relationship throughout the exposure range and also potentially provide optimal control of confounding by age (in these Cox regressions age is the index variable and implicitly a covariate). Cheng et al. (2007) results support the presence of a relationship between high cumulative exposure and leukemia and high intensity of exposure and leukemia. Dose-response modeling was conducted with continuous, untransformed data and mean-scored deciles of BD exposure. The impact of exposure estimate errors/misclassification may be somewhat alleviated by the use of mean-scored deciles of BD exposure (Cheng et al. 2007). Sielken et al. (Appendix 4) provided β (MLE) and SE values not included in the Cheng et al. (2007) analyses: (1) Cox regression, mean-scored deciles, when evaluating age + number of HITs as covariates and (2) Cox regression, ppm-years continuous, number of HITs categorical, when evaluating age + number of HITs as covariates.

The UAB group recommended the estimate of the dose-response relationship that is based on the continuous, untransformed form of BD ppm-years, age as the covariate, and the full range of exposure data (2.9E-04 (β), 1.0E-04 (S.E.)). However, due to the high potential for distortion of the dose-response relationship as a result of exposure misclassification, Cheng et al. (2007) also recommended that an uncertainty analyses be incorporated into any risk assessment that uses these data.

Beta estimates were also calculated by Cheng et al. (2007) for unlagged and lagged BD exposure but these β estimates were not used by the TS because lagging BD exposure had little impact on the dose-response relationship between leukemia and BD ppm-years. The association of BD exposure with leukemia, lymphoid neoplasms and myeloid neoplasms was examined. Lymphoid neoplasms were associated with ppm-years and myeloid neoplasms were associated with number of HITs in models that controlled only for age but not after adjusting for multiple covariates (age, year of birth, race, plant, years since hire and DMDTC). These potency estimates were not used by the TS because evidence of an association between BD and all lymphoid neoplasm or all myeloid neoplasms was not persuasive (Cheng et al. 2007).

Sielken et al. (2007) used a linear Poisson regression model to examine the dose-response relationships adjusted either for age as a categorical covariate and age + number of HITs as covariates (Table 15). Sielken et al. (2007) found that if the exposure dosimetric is cumulative ppm-years, the performance of the predictor for leukemia rate ratio is statistically significantly improved if the categorical covariates age + number of HITs are included in the Poisson regression model. If covariates other than age + number of HITs are included, the model fit using cumulative ppm-years was not significantly improved except for styrene. However, if styrene was included as a covariate, the slope was negative, so styrene was not included as a covariate. Although Sielken et al. (2007) performed this statistical analysis for covariates using the Poisson regression model, his findings are generally applicable for the Cox regression model.

4.2.3.2 Dosimetric Adjustments

Occupational concentrations were converted into environmental concentrations for the general population using the following equation:

$Concentration_{HEC} = Concentration_{OC} \times (VE_{ho}/VE_h) \times (days\ per\ year_{oc}/days\ per\ year_{res})$

where: VE_{ho} = occupational ventilation rate for an 8-h day (10 m^3/day)
VE_h = non-occupational ventilation rate for a 24-h day (20 m^3/day)
$days\ per\ year_{oc}$ = occupational exposure frequency (240 days)
$days\ per\ year_{res}$ = residential exposure frequency (365 days)

RG-442 ESL Guidelines (TCEQ 2006) recommends using the ratio "5 days per week/7 days per week" to adjust occupational exposure concentrations to concentrations relevant to the general population, but it is standard practice in USEPA epidemiological cancer risk assessments to use the ratio "240 days/365 days," which is slightly more conservative. The value of 240 days per year = 52 weeks x 5 days per week = 260 days per year minus approximately 10 holidays (Christmas, New Year's, Independence Day, etc.) and minus approximately 2 weeks vacation or sick days.

4.2.3.3 Extrapolation to Lower Exposures

4.2.3.3.1 URFs and Air Concentrations at 1 in 100,000 Excess Cancer Risk

Table 16 shows estimates of air concentrations at 1 in 100,000 excess cancer risk (10^{-5}-risk air concentrations) based on βs (column three) and 95% UCLs (column five) using the exponential Cox Regression and linear Poisson regression models. Air concentrations were solved iteratively with life-table analyses using the BEIR IV approach (NRC 1988). Air concentrations based on extra risk were calculated as opposed to added risk. The following mortality and survival rates were used to calculate air concentrations based on a lifetime exposure of 70 years, the default used by TCEQ for exposure analysis:

- US mortality rates for 2000-2003 for all leukemia (Surveillance, Epidemiology, and End Results database (SEER 2006)) (Appendix 5)
- US survival rates for 2000 (Arias 2002) (Appendix 5).

Columns four and six provide URFs calculated using the linear extrapolation default approach (USEPA 2005a; TCEQ 2006). Risk estimates are obtained by first calculating a POD_{HEC} at the low end of the range of observations using appropriate models, and then extrapolating to zero by means of a straight line (linear extrapolation default). The air concentration at 0.1% excess risk level (i.e., 1 in 1,000 excess cancer risk) is chosen for determining the POD because it is within the observable response range of leukemia deaths. The URFs in units of ppm^{-1} at the POD_{HEC} (when the POD_{HEC} was set to either the effective concentration (EC) or the 95% UCL lowest effective concentration (LEC)) was calculated as follows:

$$URF = 0.001/EC_{001}$$
$$URF = 0.001/LEC_{001}$$

Columns four and six also provide 10^{-5}-risk air concentrations based on the corresponding URFs. Air concentrations calculated using the corresponding URFs are more conservative than air concentrations calculated based on the Cox regression model, because this model is an exponential model. As a health-protective policy decision, 10^{-5}-risk air concentrations calculated with a URF based on the default linear approach was adopted and all subsequent discussions will refer to the URF (MLE) or URF (95%UCL) and their corresponding 10^{-5}-risk air concentration values.

Table 16. URFs and Air Concentrations Corresponding to 1 in 100,000 Extra Leukemia Risk

Covariates	Model type of data	β (MLE) Air Concentration 1 in 100,000 excess cancer risk using model	EC_{001} URF (MLE) [a] Air Concentration 1 in 100,000 excess cancer risk using URF	β (95% UCL) Air Concentration 1 in 100,000 excess cancer risk using model	LEC_{001} URF (95% UCL) [b] Air Concentration 1 in 100,000 excess cancer risk using URF
Age	Cox regression [h] ppm-years continuous [c]	80.42 ppb	1.490E-04/ppm 67.14 ppb	51.31 ppb	2.334E-04/ppm 42.84 ppb
	Cox regression [h] ppm-years mean-scored deciles [d]	31.09 ppb	3.852E-04/ppm 25.96 ppb	20.97 ppb	5.712E-04/ppm 17.51 ppb
	Poisson regression [i] ppm-years mean-scored deciles [d]	13.91 ppb	7.184E-04/ppm 13.92 ppb	7.713 ppb	1.296E-03/ppm 7.715 ppb
Age & Number of HITs > 100 ppm	Cox regression [h] ppm-years continuous [c], # of HITs continuous [e]	93.28 ppb	1.284E-04/ppm 77.88 ppb	52.13 ppb	2.298E-04/ppm 43.52 ppb
	Cox regression [j] ppm-years continuous [c], # of HITs categorical [f]	116.6 ppb	1.027E-04/ppm 97.35 ppb	56.36 ppb	2.125E-04/ppm 47.05 ppb
	Cox regression [j] ppm-years mean-scored deciles [d], # of HITs categorical [f]	83.29 ppb	1.438E-04/ppm 69.53 ppb	34.56 ppb	3.466E-04/ppm 28.85 ppb
	Poisson regression [i] ppm-years mean-scored deciles [d], # of HITs categorical [f]	123.7 ppb	8.083E-05/ppm 123.7 ppb	29.92 ppb	3.341E-04/ppm 29.93 ppb
Age & Other Covariates [g]	Cox regression [h] ppm-years continuous [c]	77.74 ppb	1.541E-04/ppm 64.90 ppb	43.98 ppb	2.724E-04/ppm 36.71 ppb
	Cox regression [h] ppm-years mean-scored deciles [d]	40.21 ppb	2.979E-04/ppm 33.57 ppb	22.78 ppb	5.260E-04/ppm 19.01 ppb

[a] URF = $0.001/EC_{001}$
[b] URF = $0.001/LEC_{001}$
[c] ppm-years is included as a continuous variable (untransformed) in a parametric model of the effect of ppm-years
[d] ppm-years is included as a categorical variable (based on mean-scored deciles, untransformed) in a parametric model of the effect of ppm-years
[e] number of HITs > 100 ppm is included as a continuous variable (untransformed) in a parametric model of the effect of the number of HITs > 100 ppm
[f] number of HITs > 100 ppm is included as a categorical variable (based on quintiles) in a nonparametric model of the effect of the number of HITs > 100 ppm
[g] Other covariates are year of birth, race, DMDTC, years since hire and plant
[h] Cheng et al. (2007)
[i] Sielken et al. (2007)
[j] Sielken et al. (Appendix 4)

4.2.3.3.2 Age as a Covariate

Models that only include age as a non-exposure covariate have the advantage of model parsimony (i.e., the model includes as few variables as necessary to explain the relationship when there is not sufficient biological knowledge to justify the inclusion or exclusion of a variable). When age is included as a covariate (Table 17), the 10^{-5}-risk air concentrations using the Poisson regression model were the most conservative: 13.92 ppb (MLE) and 7.715 ppb (95% UCL). However, as stated previously, Cox regression models provide optimal control of confounding by age, so estimates from the Cox regression model are preferred over estimates using the Poisson regression model. Using the Cox regression model, the 10^{-5}-risk air concentrations for mean-scored deciles (25.96 ppb MLE and 17.51 ppb 95% UCL) were more conservative than continuous, untransformed data (67.14 ppb MLE and 42.84 ppb 95% UCL). The 10^{-5}-risk air concentration estimates based on mean-scored deciles are preferred because the impact of exposure estimate errors/misclassification may be somewhat alleviated by the use of categorical deciles of BD exposure (Cheng et al. 2007).

Table 17. Age as a Covariate

Model type of data	EC_{001} URF (MLE) [a] Air Concentration 1 in 100,000 excess cancer risk using URF	LEC_{001} URF (95% UCL) [b] Air Concentration 1 in 100,000 excess cancer risk using URF
Cox regression Cheng et al. (2007) ppm-years continuous [c]	1.490E-04/ppm 67.14 ppb	2.334E-04/ppm 42.84 ppb
Cox regression Cheng et al. (2007) ppm-years mean-scored deciles [d]	3.852E-04/ppm 25.96 ppb	5.712E-04/ppm 17.51 ppb
Poisson regression Sielken et al. (2007) ppm-years mean-scored deciles [d]	7.184E-04/ppm 13.92 ppb	1.296E-03/ppm 7.715 ppb

[a] URF = $0.001/EC_{001}$
[b] URF = $0.001/LEC_{001}$
[c] ppm-years is included as a continuous variable (untransformed) in a parametric model of the effect of ppm-years
[d] ppm-years is included as a categorical variable (based on mean-scored deciles, untransformed) in a parametric model of the effect of ppm-years

4.2.3.3.3 Age + Number of HITs as Covariates

The USEPA Science Advisory Board (USEPA 1998) recommended that consideration of peak exposures to BD (i.e., number of BD HITs > 100 ppm) be evaluated during its review of the draft health risk assessment of BD (USEPA 1998b). Sielken et al. (2007) demonstrated that when the categorical covariates of age + number of HITs are included in the Poisson regression model, the model's ability to predict the leukemia rate ratio was statistically improved. The cumulative number of HITs may better explain the increased leukemia mortality observed in the BD worker cohort.

If age + number of HITs are included as covariates, the 10^{-5}-risk air concentrations using URFs (MLE) range from 69.53 to 123.7 ppb (Table 18), less than a factor of two. The most conservative 10^{-5}-risk air concentration that is obtained using the URF (MLE) is calculated with the Cox regression model, mean-scored deciles. The 10^{-5}-risk air concentrations using URFs (95% UCL) range from 28.85 to 47.05 ppb, less than a factor of two. The most conservative 10^{-5}-risk air concentration of 28.85 ppb is obtained using the URF (95% UCL) calculated from the Cox regression model, mean-scored deciles, although the 10^{-5}-risk air concentration of 29.93 ppb from the Poisson regression, mean-scored deciles, is essentially identical. The use of mean-scored deciles for both the Cox regression and the Poisson regression tend to minimize the effects of exposure misclassification and address concerns about exposure estimates and are preferred. For predicting risk relevant to the general population, the estimates that account for age + number of BD HITs > 100 ppm as covariates are the most relevant because it is highly unlikely that the general population will ever be exposed to peak exposures of BD HITs > 100 ppm.

Table 18. Age + Number of BD HITs > 100 ppm as Covariates

Model **type of data**	**EC_{001}** **URF (MLE) [a]** **Air Concentration** **1 in 100,000 excess cancer risk using URF**	**LEC_{001}** **URF (95% UCL) [b]** **Air Concentration** **1 in 100,000 excess cancer risk using URF**
Cox regression Cheng et al. (2007) ppm-years continuous [c] # of HITs continuous [e]	1.284E-04/ppm 77.88 ppb	2.298E-04/ppm 43.52 ppb
Cox regression Sielken et al. (Appendix 4) ppm-years continuous [c] # of HITs categorical [f]	1.027E-04/ppm 97.35 ppb	2.125E-04/ppm 47.05 ppb
Cox regression Sielken et al. (Appendix 4) ppm-years mean-scored deciles [d] # of HITs categorical [f]	1.438E-04/ppm 69.53 ppb	3.466E-04/ppm 28.85 ppb
Poisson regression Sielken et al. (2007) ppm-years mean-scored deciles [d] # of HITs categorical[f]	8.083E-05/ppm 123.7 ppb	3.341E-04/ppm 29.93 ppb

[a] URF = $0.001/EC_{001}$
[b] URF = $0.001/LEC_{001}$
[c] ppm-years is included as a continuous variable (untransformed) in a parametric model of the effect of ppm-years
[d] ppm-years is included as a categorical variable (based on mean-scored deciles, untransformed) in a parametric model of the effect of ppm-years
[e] number of HITs > 100 ppm is included as a continuous variable (untransformed) in a parametric model of the effect of the number of HITs > 100 ppm
[f] number of HITs > 100 ppm is included as a categorical variable (based on quintiles) in a nonparametric model of the effect of the number of HITs > 100 ppm

4.2.3.3.4 Other Covariates

Cheng et al. (2007) fit models that adjusted for age, year of birth, race, DMDTC, years since hire and plant. Except for the exposure covariate DMDTC, an immune system depressant (Irons and Pyatt 1998; Irons et al. 2001), these covariates are the ones typically evaluated in epidemiology dose-response models. Sielken et al. (2007) included statistically-based covariates and determined that if covariates other than age + number of HITs were included, the model fit using cumulative ppm-years was not significantly improved except for the covariate, styrene. Therefore, URF (MLE) and URF (95% UCL) from models that adjusted for age, year of birth, race, DMDTC, years since hire and plant were not considered as potency factors by the TS, although these values are provided in Tables 15 and 16 for comparison purposes.

4.2.4 Potency Estimate Selected to Represent Excess Leukemia Mortality Risk

The cancer potency estimates and 10^{-5}-risk air concentrations using URFs (MLE) in Table 16 range from 7.184E-04/ppm (13.92 ppb) to 8.083E-05/ppm (123.7 ppb). The cancer potency estimates and 10^{-5}-risk air concentrations using URFs (95% UCL) in Table 16 range from 1.296E-03/ppm (7.715 ppb) to 2.125E-04/ppm (47.05 ppb). Of the various estimates presented in Table 16, the potency estimate of 3.466E-04/ppm (10^{-5}-risk air concentrations of 28.85 ppb) from the Cox regression model, mean-scored deciles, age + number of BD HITs as covariates, based on the URF (95% UCL) and a linear default approach is selected to represent the excess leukemia mortality risk from the occupational data. However, refer to Sections 4.2.4.1 and 4.2.4.2 for additional adjustments to the URF (95% UCL) and 10^{-5}-risk air concentrations.

A linear default was used to extrapolate to lower concentrations and the URF (95% UCL) was preferred to account for the following uncertainties:

- Uncertainty of calculating potency estimates for BD from mortality data, not incidence data (i.e., to protect against developing leukemia) (Section 4.2.5.1)
- Uncertainty of calculating potency estimates for the general population when the SBR cohort was comprised primarily of males (Section 4.2.5.2)

The URFs (MLE) based on mean-scored deciles were preferred because the impact of exposure estimate errors/misclassification may be somewhat alleviated by the use of categorical deciles of BD exposure (Section 4.2.5.3). The Cox regression model was preferred because it potentially provides optimal control of confounding by age. While the cancer potency estimate from the Poisson regression (mean-scored deciles, age + number of BD HITs) of 3.341E-04/ppm (10^{-5}-risk air concentrations of 29.93 ppb) is similar to the values from the Cox regression, it is slightly less conservative.

The models that use age + number of BD HITs > 100 ppm as covariates are preferred because once age is in the model, inclusion of number of BD HITs results in a significant improvement in the fit (likelihood). In addition, the general population is not expected to be exposed to BD concentrations greater than 100 ppm, so adjusting for BD HITs > 100 ppm as a covariate produces cancer potency estimates more relevant to BD exposures experienced by the general population. Slikker et al. (2004) provides a discussion of the role of dose-dependent transitions in mechanisms of toxicity for BD as well as several other chemicals. Exposure to BD at high concentrations may result in a change from the hydrolytic pathways that are normally used by humans to form EBD to the formation of the more toxic metabolite, DEB (i.e., metabolic enzymes may be saturated). In addition, protective enzymes and other protective

cellular constituents may be depleted which could result in mechanisms of toxic tissue injury that are not relevant at exposures significantly less than 100 ppm. In a study conducted by Albertini et al. (2001), a clear NOAEL for biomarkers of effect (hypoxanthine-guanine phosphoribosyltransferase (HPRT) mutations and chromosome aberrations) at mean BD exposure concentrations of 0.800 ppm was reported in a study of workers in the Czech Republic (see Section 4.5 for additional information).

4.2.4.1 Evaluating Susceptibility from Early-Life Exposures

USEPA (2005b) provides default, age-dependent adjustment factors (ADAFs) to account for potential increased susceptibility in children due to early-life exposure when a chemical has been identified as acting through a mutagenic MOA for carcinogenesis and the cancer assessment did not include exposures at an early age (generally before age 16). This is the case for the epidemiological leukemia data utilized in this evaluation. BD is currently identified by USEPA as having a mutagenic MOA. USEPA (2005b) states:

> "The following adjustments represent a practical approach that reflects the results of the preceding analysis, which concluded that cancer risks generally are higher from early-life exposure than from similar exposure durations later in life:
>
> - For exposures before 2 years of age (i.e., spanning a 2-year time interval from the first day of birth up until a child's second birthday), a 10-fold adjustment.
>
> - For exposures between 2 and <16 years of age (i.e., spanning a 14-year time interval from a child's second birthday up until their sixteenth birthday), a 3-fold adjustment
>
> - For exposures after turning 16 years of age, no adjustment."

The ADAF is an adjustment to the slope factor (as opposed to an adjustment to the dose metric). The ADAF is to be applied on an age-specific basis. That is, the ADAFs are applied to each relevant year in a life and the risks for all years summed to get the lifetime risk, as opposed to calculating a lifetime excess risk without ADAFs and then multiplying this calculated value by a constant ADAF.

When the dose metric is cumulative exposure and when using a life-table analysis BEIR IV approach (NRC 1988), an implementation consistent with USEPA guidelines is to calculate the excess risk in each year using the age-specific dose (cumulative dose) for that year and multiply the slope by the age-specific ADAF for that year (age). This is consistent with USEPA's guidelines from the point of view of both excess risk being calculated using age-specific exposures and ADAFs being age-specific modifiers of the slope (potency). That is, the excess risk in year "i" is calculated with the β or 95% UCL multiplied by ADAF(i). Refer to Appendix 6 *Calculating Excess Risk with Age-Dependent Adjustment Factors using a Life-Table Analysis*.

The TS calculated potency factors both with and without ADAFs. When the ADAFs are not applied, the selected potency estimate is 3.466E-04/ppm. When the ADAFs are incorporated into the life-table analyses using the BEIR IV approach (NRC 1988), the selected potency estimate is 3.505E-04/ppm.

4.2.4.2 Relevance of Estimated Risks to the Texas General Population

There is uncertainty about whether potency estimates are representative of the mortality risks that might be associated with environmental BD exposures in Texas because potency estimates were developed based on the leukemia mortality experience of predominantly male workers in the styrene-butadiene rubber industry, total US rates of mortality from leukemia and total US survival rates (Appendix 5). In order to address this uncertainty, Texas-specific mortality rates for 1999-2003 for all leukemia and Texas-specific survival rates for 2003 were kindly provided by the Texas Department of State Health Services, Cancer Epidemiology and Surveillance Branch, Texas Cancer Registry. There were minor differences in calculated air concentrations when Texas versus US all leukemia mortality rates and survival rates were used because the Texas-specific rates are very similar to US rates (Appendix 5). The selected potency estimate is 3.505E-04/ppm using US rates of mortality from leukemia and total US survival rates when ADAFS are incorporated (Section 4.2.4.1) and is 3.622E-04/ppm using Texas-specific mortality rates for 1999-2003 for all leukemia and Texas-specific survival rates for 2003 when ADAFS are incorporated.

The adjusted URF of 3.622E-04/ppm using Texas-specific rates is used because, in addition to being slightly more conservative, the residents of Texas are the target population of this DSD. It becomes 3.6E-04/ppm when the URF is rounded to the least number of significant figures for a measured value at the end of all calculations. The $^{chronic}ESL_{linear(c)}$ or air concentration at 1 in 100,000 excess cancer risk is 28 ppb (62 $\mu g/m^3$).

4.2.5 Uncertainty Analysis

4.2.5.1 Use of Mortality Rates to Predict Incidence

The URF (95% UCL) was used instead of the URF (MLE) to account for the uncertainty of calculating a potency estimate for BD from mortality data, not incidence data (i.e., to protect against developing leukemia). This is consistent with guidance in TCEQ (2006) and USEPA (2005a). In addition, a linear default was used to extrapolate to lower concentrations, which is a conservative procedure.

USEPA (2002) used leukemia incidence rates instead of mortality rates to calculate air concentrations based on a life-table analyses using the BEIR IV approach (NRC 1988) in an attempt to account for the uncertainty that potency estimates were based on mortality and not incidence. The BEIR IV methodology for calculating excess risk is mathematically correct when the specified response is mortality and leukemia mortality rates are used but not when the specified response is mortality and leukemia incidence rates are used as was done by USEPA (2002). This error is demonstrated in Appendix 7 *Issues in Quantitative Epidemiology: Calculating Excess Risk When Specified Response is Mortality versus Incidence*. Appendix 7 also shows that if the specified response is incidence, then the BEIR IV methodology for mortality cannot be used. Teta et al. (2004) investigated the validity and implications of using a mortality-based leukemia relative rate model with background leukemia incidence rates, rather than mortality rates. They concluded that a biased estimate of excess lifetime risk will result, and the direction of the bias will vary by potency and the type of leukemia being modeled. Therefore, the TS did not use leukemia incidence rates to account for the uncertainty of calculating potency estimates for BD from mortality data.

4.2.5.2 Adjustments for Other Potentially Sensitive Subpopulations

Leukemia mortality was evaluated based on male workers employed at North American plants that manufactured SBR. It is unknown whether workers with genetic polymorphisms as discussed in Section 3.1.2 (i.e., genes that regulate the metabolism of BD to mutagenic intermediates and genes that regulate the detoxification of those metabolites) were represented in the cohort. Populations with certain lifestyle choices may be more sensitive to health effects caused by BD. Children may also be more sensitive to mutagenic carcinogens (Section 4.2.4.1).

Since the UAB cohort was comprised primarily of males, a linear default was used to extrapolate to lower concentrations, and the URF (95% UCL) was used instead of the URF (MLE) to account for the uncertainty of calculating potency estimates for the general population. Studies in which animals were exposed to high BD concentrations suggest that female animals may be more sensitive than male animals for cancer effects after exposure to BD (USEPA 2002). Initial studies conducted in humans by Albertini et al. (2007) indicate that except for lower production of both urine BD metabolites in females, no female-male differences in response to low BD exposures were detected (mean 8-h TWA exposure levels were 0.180 ppm for BD-exposed female workers and 0.370 ppm for BD-exposed male workers as discussed in Section 4.5).

The UAB group has analyzed mortality results for 4,863 female workers employed in the SBR industry from 1943 to 2002 (Sathiakumar and Delzell 2007a, b). Preliminary results indicate that standard mortality rates (SMRs) for lung and bladder cancer were elevated in female workers. Both excesses were concentrated among ever-hourly employees and among ever-hourly employees with 20+ years since hire, but neigher cancer displayed a pattern of increasing SMRs with increasing duration of employment. For lung cancer, analyses of cumulative exposure indices were conducted. Results for lung cancer indicated a moderately positive association with each agent, without exposure-response. The SMRs for leukemia, non-Hodgkin lymphoma or other forms of lymphohematopoietic cancers, breast cancer and ovarian cancer were not elevated (Sathiakumar and Delzell 2007b). For lung and bladder cancer, the absence of any tread of increasing SMRs with increasing duration of employment, the lack of any exposure-response trend for cumulative exposure to BD, styrene or DMDTC and the absence of positive results in studies of male employees indicate that these occupational exposures may not have been responsible for the observed excesses of lung and bladder cancers among women in the industry (Sathiakumar and Delzell 2007b).

4.2.5.3 Effect of Occupational Exposure Misclassification

One of the limitations of most epidemiological studies is potential exposure misclassification. Health Canada (2000) and USEPA (2002) expressed concerns about the validity of exposure estimates from the Delzell (1995, 1996) study. In the updated exposure estimates, Macaluso et al. (2004) used a more in-depth job, task, and exposure classification for the cohort, and exposure estimates were developed using exposure modeling, historical exposure data, and plant equipment analysis. Recently, Sathiakumar et al. (2007) assessed the validity of the BD exposure estimates by measuring the differences and correlations between calendar year- and job-specific estimates and measurements of BD concentrations at the Canadian Sarnia plant (a latex operation), one plant included in the UAB cohort. BD measurements from the late 1970s onward were available. Before 1984, estimated concentrations were lower than measured concentrations, whereas after 1984 an opposite pattern was observed. This pattern reversal does not

suggest that exposure values before and after 1984 balance out because exposure estimates before 1984 were the larger exposures (in absolute value) and contributed more to the estimation of the slopes in the dose-response models. Increasing the larger exposure estimates will tend to decrease the estimated slopes and increase the estimated doses (ppb) corresponding to specified risk levels.

At lower concentrations, there was reasonably good agreement between measured versus estimated BD exposures; whereas at higher exposures, the estimates tended to be less than the measured values. On average, estimates were about 10% lower than measurements. The Cox regression analysis using mean-scored deciles was used to calculate the URF (95% UCL) to account for concerns about potential exposure misclassification and exposure estimates and as a health-protective policy decision.

4.2.5.4 Estimated Risks from Occupational Worker

There is uncertainty regarding the extrapolation of risks from occupational workers exposed to high BD concentrations and to BD HITs > 100 ppm to risks for the general population who are exposed to much lower BD concentrations and not exposed to BD HITs > 100 ppm. There are no reliable data linking BD exposures at low concentrations typical for the general population to increased mortality from any cause in Texas (Grant et al. 2007). The inclusion of age and number of HITs > 100 ppm BD as covariates in the Cox regression modeling may result in cancer potency estimates that are more relevant to BD exposures experienced by the general population. Figure 3 shows the 5^{th}, 50^{th}, and 95^{th} percentiles of the distribution of the cumulative number of BD HITs > 100 ppm in the UAB cohort study indicating SBR workers were frequently exposed to BD HITs > 100 ppm. In contrast, air monitoring data in Texas do not indicate the general population is exposed to BD HITs > 100 ppm. For example, Figure 4 provides 40-min BD concentrations (ppbv) at a monitoring site at Milby Park (2005 – present) which is located predominantly downwind of nearby major industrial sources of BD emissions. There were only four times in a two-year period that the concentration of BD exceeded 0.2 ppm and the maximum peak BD concentration was 1.6 ppm. Maximum 40-min BD concentration data from 25 other ambient air monitoring sites in Texas indicate peak concentrations have not approached 1.6 ppm; in fact, maximum concentrations are less than 0.15 ppm. Other exposure studies indicate that the general population is exposed to concentrations of BD much lower than occupational workers (USEPA 2002, Gordon et al. 1999; Sapkota and Buckley 2003; Sapkota et al. 2005; Grant et al. 2007).

4.2.5.5 Dose-Response Modeling

The use of the linear Poisson regression and exponential Cox regression models introduces uncertainty in the dose-response analyses since the MOA of BD is not sufficiently understood to use a more appropriate biologically-based model. These models are commonly used to investigate dose-response relationships derived from occupational cohort epidemiologic studies based on mortality. Both β and upper 95% UCL estimates were reported in order to provide information on the residual uncertainty in the relative risk estimates. Generally, there was less than a factor of two difference between 10^{-5}-risk air concentrations calculated with URFs (MLE) versus URFs (95% UCL) except for a four-fold difference for Poisson regression, mean-scored deciles, age + number of HITs as covariates (Table 16).

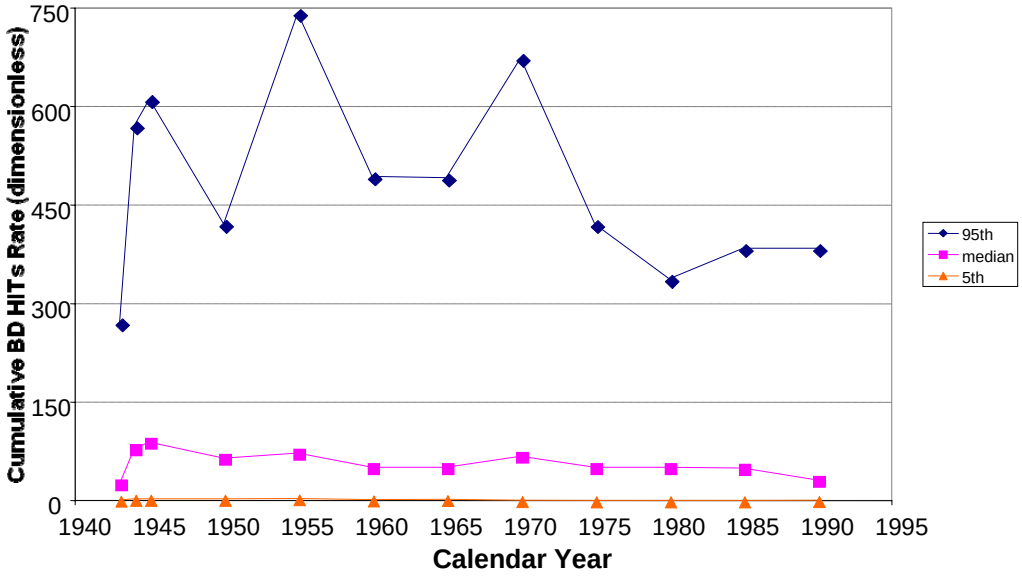

Figure 3. Distribution of BD HITs > 100 ppm among BD-Exposed Workers in a Calendar Year. The cumulative number of BD HITs rate (dimensionless) versus calendar year is shown for the 5th, 50th, and 95th percentiles of the distribution among BD-exposed workers included in the UAB cohort study.

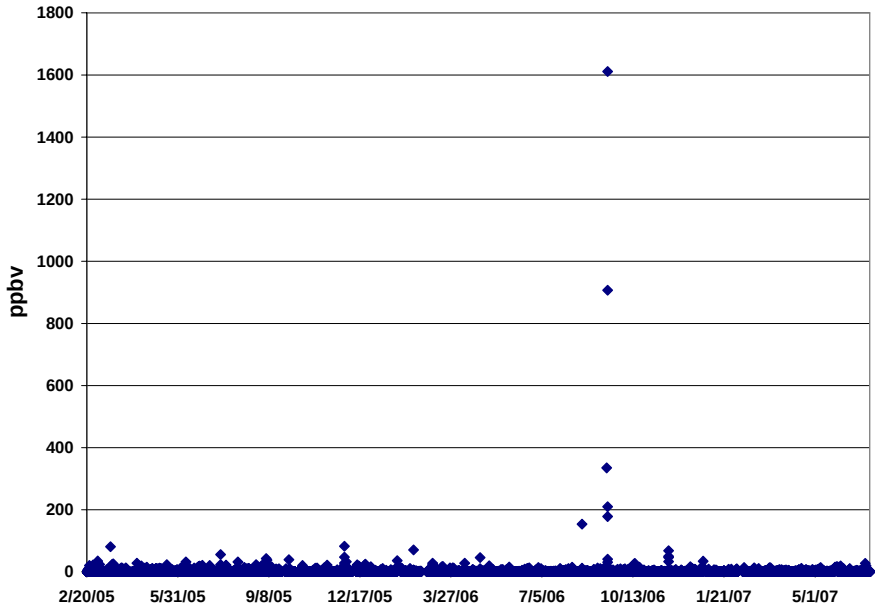

Figure 4. Forty-Minute BD Concentrations (ppbv) at Milby Park (2005 – present). Milby Park is located predominantly downwind of nearby major industrial sources of BD emissions (Grant et al. 2007). Forty-minute auto gas chromatography data.

4.2.6 Comparison of TCEQ's URF to USEPA's URF

USEPA published an inhalation URF of 0.08/ppm which was last reviewed in 2002. The URF is based on a Health Canada analysis of data from Delzell et al. (1995, 1996) using a linear relative rate model and was calculated for up to 85 years. Relative risks were evaluated with leukemia incidence rates, which is not mathematically correct as demonstrated in Appendix 7. Using the LEC_{01} (i.e., the 95% lower confidence limit of the exposure concentration associated with a 1% increased risk) of 0.254 ppm as the POD and a linear extrapolation to zero yields a URF of 0.04/ppm. An adjustment factor of 2 was applied to the URF to yield a final URF of 0.08/ppm. This adjustment was applied to reflect evidence from studies in mice which suggest that extrapolating leukemia risks from a male-only occupational cohort may underestimate the cancer risks for the general public.

The TCEQ derived an inhalation URF of 0.00036/ppm based on the most current exposure estimates and updated epidemiological study conducted by the UAB group (Macaluso et al. 2004; Sathiakumar et al. 2005; Graff et al. 2005; HEI 2006). Relative risks were evaluated with Texas-specific leukemia mortality rates and survival rates and were calculated for up to 70 years. The URF is based on the 95% UCL estimate derived with a exponential Cox regression model, age + number of HITs > 100 ppm as covariates, and mean-scored deciles (Cheng et al. 2007). Using the LEC_{001} (i.e., the 95% lower confidence limit of the exposure concentration associated with a 0.1% increased risk) as the POD, a linear extrapolation to zero, and adjusting for the increased susceptibility of children using a life-table approach (Appendix 6) yields a URF of 0.00036/ppm.

4.3. Welfare-Based Chronic ESL

No data were found regarding long-term vegetative effects.

4.4 Long-Term ESL and Values for Air Monitoring Evaluation

The chronic evaluation resulted in the derivation of the following values:

- Chronic ReV = 33 µg/m^3 (15 ppb)
- $^{chronic}ESL_{nonlinear(nc)}$ = 10 µg/m^3 (4.5 ppb)
- URF = 3.6E-04/ppm (1.6E-04/mg/m^3)
- $^{chronic}ESL_{linear(c)}$ = 62 µg/m^3 (28 ppb)

The long-term ESL for air permit reviews is the $^{chronic}ESL_{nonlinear(nc)}$ of 10 µg/m^3 (4.5 ppb) based on ovarian atrophy because it is lower than the $^{chronic}ESL_{linear(c)}$ of 62 µg/m^3 (28 ppb) (Table 1). For evaluation of long-term ambient air monitoring data, the chronic ReV of 33 µg/m^3 (15 ppb) based on ovarian atrophy is lower than the $^{chronic}ESL_{linear(c)}$ of 62 µg/m^3 (28 ppb), although both values will be used for the evaluation of air data as well as the URF of 3.6E-04/ppm (1.6E-04/mg/m^3).

4.5 Other Relevant Information

The proceedings of the International Symposium on Evaluation of Butadiene and Chloroprene Health Risks, held in Charleston, South Carolina on September 20-22, 2005 have recently been published, and the findings and results from many of these articles have been cited in the Development Support

Document (DSD). Refer to Himmelstein et al. (2007), which provides an excellent summary the main findings of the symposium. A summary of the molecular epidemiology findings from Albertini et al. (2007) as summarized by Himmelstein et al. (2007) is reproduced here because of the significance of their findings. The references, which are in numerical format in the journal, have been supplemented with the author(s) names and year of publication.

> "1.1.3. Molecular epidemiology
>
> Albertini [9 *(Albertini et al. 2001)]* reported that the initial study of workers in the Czech Republic demonstrated a clear no-observed-adverse-effect level (NOAEL) for biomarkers of effect (hypoxanthine-guanine phosphoribosyltransferase (HPRT) mutations and chromosome aberrations) at mean BD exposure concentrations of 0.800 ppm.
>
> This NOAEL reflects the maximum average exposure level experienced by these workers and was based on extensive external exposure assessments and a comprehensive series of biomarker responses, which included urine metabolites (M1 and M2) and hemoglobin adducts of epoxybutene and EBD (N-[2-dihydroxy-3-butenyl]valine = HB-Val and N- [2,3,4-trihydroxybutyl]valine = THB-Val, respectively), HPRT mutations, sister-chromatid-exchange frequencies and chromosomal aberrations determined by traditional methods and chromosome painting (fluorescence in situ hybridization). Both the urine metabolite and hemoglobin adduct concentrations proved to be excellent biomarkers of exposure. A second study of Czech workers was conducted at this same facility to compare biomarker responses in female and male employees [10 *(Albertini et al. 2007)*]. Mean BD exposure concentrations were lower in this second study than in the first, being 0.180 ppm and 0.370 ppm for females and males, respectively. Again, there were no BD-associated elevations of HPRT mutation or chromosome aberration frequencies above background in either sex. Similarly, there was no difference between genders in the pattern of BD detoxification, as evidenced by urinary M1 and M2 levels. Females, however, appeared to absorb less BD per unit of exposure, as reflected by urine metabolite concentrations. Concentrations of the N,N-(2,3-dihydroxy-1,4-butadiyl)valine (pyr-Val) hemoglobin adduct, which is specific for the highly genotoxic 1,2:3,4-diepoxybutane (DEB) metabolite of BD, were measured in this second study and found to be below the level of quantification for all workers. Later presentations by Swenberg [11 *(Swenberg et al. 2007)*] and Boysen [12 (*Boysen et al. 2007)*] in this Symposium described extensive studies of pyr-Val concentrations in BD exposed rodents that, coupled with the results of this Czech worker study, indicate that DEB production in humans is below levels produced in mice or rats exposed to as little as 1.0 ppm BD by inhalation."

Chapter 5. References

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Appendix 1. Statistical Analyses of Developmental Endpoints

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The analyses performed by Hackett et al. (1987) did have some important statistical flaws that needed to be corrected. The statistical analyses reported by Green (2003) are valid and correct the flaws of Hackett et al. analyses. We have focused on the analyses of fetal body weights. The NOAEL based on the fetal weights for this study is 40 ppm.

Hackett et al. (1987) conducted analyses of variance (ANOVA) on the average pup weight followed up by Student's t-tests comparing the average pup weight for different treatment groups. Their pairwise comparisons using Student's t-test do not adjust significance levels that occur for the number of multiple tests. In addition, their analyses did not adjust for well-known important covariate effects such as litter size. Hackett et al. analyses were based on dam's average pup weights instead of analyzing the individual pup weights and treating the dam as a random effect, which would result in a more powerful statistical test.

The Green (2003) reanalysis was based on analysis of covariance (ANCOVA) on the average pup weight and adjusting for covariates. In this context, Green used the Dunnett-Hsu test to compare the mean weights for each of the exposed groups to the mean weight for the control group after both are adjusted for the effects of the covariates. This is the specific situation for which the Dunnett-Hsu test was designed. Furthermore, the Dunnett-Hsu test is the appropriate test to use here to determine a NOAEL. Green considered the p-values in the Dunnett-Hsu test to draw his conclusions of significant effects. Green's discussion in A. Evaluation of Earlier Methods and B. Method of Re-Analysis is appropriate.

Green's analyses were based on dam's average pup weights instead of analyzing the individual pup weights and treating the dam as a random effect, which would result in a more powerful statistical test. The statistical conclusions reached by Green (2003) hold even when the more powerful statistical analyses where the individual pup weights are analyzed and the dams are treated as random effects.

Thus, the Green (2003) conclusions are reasonable and based on standard statistical analyses practices that were overlooked by Hackett et al. (2003). The NOAEL based on the fetal weights for this study is 40 ppm.

Statistical Analyses Performed by Sielken & Associates

In addition to reviewing the methodology used in Hackett et al. (1987) and Green (2003), Sielken & Associates re-analyzed the fetal weight data. This was to confirm the numerical results obtained by Green, do a sensitivity analysis with respect to the effects of covariates, and determine the outcome of the more powerful statistical analyses where the individual pup weights are analyzed and the dams are treated as random effects. These analyses support the finding that the NOAEL based on the fetal weights for this study is 40 ppm.

Table 1 contains an overview of the results in Tables 2 to 10 which contain the detailed analyses. The raw data used are given in Table 11. The statistical analyses were done in SAS Ver. 9. In the overview in Table 1, all comparisons to control were based on Dunnett-Hsu tests and were one-sided tests for a decrease in fetal weight compared to control. The outcomes of the more powerful statistical analyses where the individual pup weights are analyzed and the dams are treated as random effects were comparable to the outcomes obtained with the Green ANCOVA model. The results for 1 Covariate (Litter Size) are highlighted since this covariate was always statistically significant at the 5% significance level – the 2nd Covariate (% Males in Litter) was significant for the Males Only analyses.

Table 1. Overview of Statistical Analyses of Fetal Weight Data: The results for 1 Covariate (Litter Size) are highlighted since this covariate was always statistically significant at the 5% significance level – the 2nd Covariate (% Males in Litter) was significant for the Males Only analyses

Table #	Model: Mixed Model: (1) Based on Mean Data (2) Based on Individual Data and Dam as Random Effect	Sex	# of Covariates	Covariates (1) Litter Size (2) % Males in Litter	p-value in Dunnett-Hsu one-sided comparison to control		
					dose=40	200	1,000
2	(1)	M&F	2	(1) & (2)	0.1354	<0.0001	<0.0001
2	(2)	M&F	2	(1) & (2)	0.1383	<0.0001	<0.0001
3	(1)	M&F	1	(1)	0.1120	<0.0001	<0.0001
3	(2)	M&F	1	(1)	0.1184	<0.0001	<0.0001
4	(1)	M&F	0	None	0.0832	<0.0001	<0.0001
4	(2)	M&F	0	None	0.0849	<0.0001	<0.0001
5	(1)	F	2	(1) & (2)	0.2091	<0.0001	<0.0001
5	(2)	F	2	(1) & (2)	0.2373	<0.0001	<0.0001
6	(1)	F	1	(1)	0.1919	<0.0001	<0.0001
6	(2)	F	1	(1)	0.2298	<0.0001	<0.0001
7	(1)	F	0	None	0.1427	<0.0001	<0.0001
7	(2)	F	0	None	0.1854	<0.0001	<0.0001
8	(1)	M	2	(1) & (2)	0.0687	<0.0001	<0.0001
8	(2)	M	2	(1) & (2)	0.0795	<0.0001	<0.0001
9	(1)	M	1	(1)	0.0603	<0.0001	<0.0001
9	(2)	M	1	(1)	0.0695	<0.0001	<0.0001
10	(1)	M	0	None	0.0408	<0.0001	<0.0001
10	(2)	M	0	None	0.0479	<0.0001	<0.0001

Table 2.

Males & Females Combined

Litter Size & %Males as Covariates

Mixed Model Based on Mean Data

Data Set WORK.MEANDATA

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
dose	3	72	50.29	<.0001
PercMales	1	72	3.54	0.0640
LitterSize	1	72	19.10	<.0001

Least Squares Means

Effect	dose	Estimate	Standard Error	DF	t Value	Pr > |t|
dose	0	1.3348	0.02034	72	65.63	<.0001
dose	40	1.2898	0.01984	72	65.02	<.0001
dose	200	1.1243	0.01879	72	59.83	<.0001
dose	1000	1.0378	0.01926	72	53.88	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > |t|	Adjustment	Adj P
dose	40	0	-0.04497	0.02849	72	-1.58	0.1188	Dunnett-Hsu	0.2701
dose	200	0	-0.2104	0.02767	72	-7.60	<.0001	Dunnett-Hsu	<.0001
dose	1000	0	-0.2969	0.02801	72	-10.60	<.0001	Dunnett-Hsu	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > t	Adjustment	Adj P
dose	0	40	0.04497	0.02849	72	1.58	0.0594	Dunnett-Hsu	0.1354
dose	0	200	0.2104	0.02767	72	7.60	<.0001	Dunnett-Hsu	<.0001
dose	0	1000	0.2969	0.02801	72	10.60	<.0001	Dunnett-Hsu	<.0001

Mixed Model Based on Individual Data and Dam as Random Effect

Data Set WORK.ANDATA

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
dose	3	69.3	52.75	<.0001
PercMales	1	72.9	4.17	0.0448
LitterSize	1	83.5	14.69	0.0002

Least Squares Means

Effect	dose	Estimate	Standard Error	DF	t Value	Pr > |t|
dose	0	1.3265	0.02009	69.5	66.04	<.0001
dose	40	1.2829	0.01930	68.6	66.47	<.0001
dose	200	1.1145	0.01847	69	60.34	<.0001
dose	1000	1.0306	0.01886	68.9	54.64	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > |t|	Adjustment	Adj P
dose	40	0	-0.04357	0.02782	69.1	-1.57	0.1218	Dunnett-Hsu	0.2759
dose	200	0	-0.2120	0.02714	70	-7.81	<.0001	Dunnett-Hsu	<.0001
dose	1000	0	-0.2959	0.02739	69.5	-10.81	<.0001	Dunnett-Hsu	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > t	Adjustment	Adj P
dose	0	40	0.04357	0.02782	69.1	1.57	0.0609	Dunnett-Hsu	0.1383
dose	0	200	0.2120	0.02714	70	7.81	<.0001	Dunnett-Hsu	<.0001
dose	0	1000	0.2959	0.02739	69.5	10.81	<.0001	Dunnett-Hsu	<.0001

Table 3.

Males & Females Combined
LitterSize as Covariate (%Males not included as a covariate)
Mixed Model Based on Mean Data

Data Set WORK.MEANDATA

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
dose	3	73	48.14	<.0001
LitterSize	1	73	16.36	0.0001

Least Squares Means

Effect	dose	Estimate	Standard Error	DF	t Value	Pr > |t|
dose	0	1.3358	0.02068	73	64.60	<.0001
dose	40	1.2871	0.02013	73	63.95	<.0001
dose	200	1.1249	0.01911	73	58.85	<.0001
dose	1000	1.0388	0.01959	73	53.03	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > |t|	Adjustment	Adj P
dose	40	0	-0.04870	0.02891	73	-1.68	0.0963	Dunnett-Hsu	0.2237
dose	200	0	-0.2109	0.02815	73	-7.49	<.0001	Dunnett-Hsu	<.0001
dose	1000	0	-0.2971	0.02849	73	-10.43	<.0001	Dunnett-Hsu	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > t	Adjustment	Adj P
dose	0	40	0.04870	0.02891	73	1.68	0.0482	Dunnett-Hsu	0.1120
dose	0	200	0.2109	0.02815	73	7.49	<.0001	Dunnett-Hsu	<.0001
dose	0	1000	0.2971	0.02849	73	10.43	<.0001	Dunnett-Hsu	<.0001

Mixed Model Based on Individual Data and Dam as Random Effect

Data Set WORK.ANDATA

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
dose	3	71	49.56	<.0001
LitterSize	1	86.7	12.60	0.0006

Least Squares Means

Effect	dose	Estimate	Standard Error	DF	t Value	Pr > |t|
dose	0	1.3274	0.02058	71.3	64.50	<.0001
dose	40	1.2803	0.01974	70.4	64.86	<.0001
dose	200	1.1162	0.01892	70.7	59.01	<.0001
dose	1000	1.0318	0.01932	70.7	53.40	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > |t|	Adjustment	Adj P
dose	40	0	-0.04706	0.02846	71	-1.65	0.1026	Dunnett-Hsu	0.2365
dose	200	0	-0.2112	0.02781	71.7	-7.60	<.0001	Dunnett-Hsu	<.0001
dose	1000	0	-0.2956	0.02807	71.2	-10.53	<.0001	Dunnett-Hsu	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > t	Adjustment	Adj P
dose	0	40	0.04706	0.02846	71	1.65	0.0513	Dunnett-Hsu	0.1184
dose	0	200	0.2112	0.02781	71.7	7.60	<.0001	Dunnett-Hsu	<.0001
dose	0	1000	0.2956	0.02807	71.2	10.53	<.0001	Dunnett-Hsu	<.0001

Table 4.

Males & Females Combined
No Covariates
Model Based on Mean Data

Data Set WORK.MEANDATA

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
dose	3	74	40.30	<.0001

Least Squares Means

Effect	dose	Estimate	Standard Error	DF	t Value	Pr > |t|
dose	0	1.3407	0.02269	74	59.10	<.0001
dose	40	1.2824	0.02208	74	58.08	<.0001
dose	200	1.1259	0.02100	74	53.60	<.0001
dose	1000	1.0379	0.02152	74	48.22	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > |t|	Adjustment	Adj P
dose	40	0	-0.05832	0.03166	74	-1.84	0.0695	Dunnett	0.1664
dose	200	0	-0.2148	0.03092	74	-6.95	<.0001	Dunnett	<.0001
dose	1000	0	-0.3028	0.03127	74	-9.68	<.0001	Dunnett	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > t	Adjustment	Adj P
dose	0	40	0.05832	0.03166	74	1.84	0.0347	Dunnett	0.0832
dose	0	200	0.2148	0.03092	74	6.95	<.0001	Dunnett	<.0001
dose	0	1000	0.3028	0.03127	74	9.68	<.0001	Dunnett	<.0001

Mixed Model Based on Individual Data and Dam as Random Effect

Data Set WORK.ANDATA

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
dose	3	68.5	44.45	<.0001

Least Squares Means

Effect	dose	Estimate	Standard Error	DF	t Value	Pr > |t|
dose	0	1.3377	0.02163	69.1	61.84	<.0001
dose	40	1.2825	0.02095	67.9	61.23	<.0001
dose	200	1.1217	0.02001	68.7	56.04	<.0001
dose	1000	1.0377	0.02044	68.2	50.78	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > |t|	Adjustment	Adj P
dose	40	0	-0.05520	0.03011	68.5	-1.83	0.0711	Dunnett	0.1696
dose	200	0	-0.2160	0.02947	68.9	-7.33	<.0001	Dunnett	<.0001
dose	1000	0	-0.3001	0.02976	68.6	-10.08	<.0001	Dunnett	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > t	Adjustment	Adj P
dose	0	40	0.05520	0.03011	68.5	1.83	0.0355	Dunnett	0.0849
dose	0	200	0.2160	0.02947	68.9	7.33	<.0001	Dunnett	<.0001
dose	0	1000	0.3001	0.02976	68.6	10.08	<.0001	Dunnett	<.0001

Table 5.

Females Only

LitterSize & %Males as Covariates

Mixed Model Based on Mean Data

Data Set WORK.MEANDATABYSEX

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
dose	3	72	45.71	<.0001
PercMales	1	72	0.47	0.4936
LitterSize	1	72	13.89	0.0004

Least Squares Means

Effect	dose	Estimate	Standard Error	DF	t Value	Pr > |t|
dose	0	1.2949	0.02020	72	64.09	<.0001
dose	40	1.2579	0.01971	72	63.83	<.0001
dose	200	1.0991	0.01867	72	58.87	<.0001
dose	1000	1.0155	0.01913	72	53.07	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > |t|	Adjustment	Adj P
dose	40	0	-0.03706	0.02830	72	-1.31	0.1945	Dunnett-Hsu	0.4148
dose	200	0	-0.1958	0.02749	72	-7.12	<.0001	Dunnett-Hsu	<.0001
dose	1000	0	-0.2794	0.02783	72	-10.04	<.0001	Dunnett-Hsu	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > t	Adjustment	Adj P
dose	0	40	0.03706	0.02830	72	1.31	0.0973	Dunnett-Hsu	0.2091
dose	0	200	0.1958	0.02749	72	7.12	<.0001	Dunnett-Hsu	<.0001
dose	0	1000	0.2794	0.02783	72	10.04	<.0001	Dunnett-Hsu	<.0001

Mixed Model Based on Individual Data and Dam as Random Effect

Data Set WORK.ANDATA

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
dose	3	67.9	48.10	<.0001
PercMales	1	77.9	0.65	0.4228
LitterSize	1	85.2	10.64	0.0016

Least Squares Means

Effect	dose	Estimate	Standard Error	DF	t Value	Pr > |t|
dose	0	1.2850	0.02019	67.3	63.66	<.0001
dose	40	1.2514	0.01897	65.2	65.97	<.0001
dose	200	1.0881	0.01853	67.3	58.72	<.0001
dose	1000	1.0063	0.01889	66.8	53.27	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > |t|	Adjustment	Adj P
dose	40	0	-0.03367	0.02761	67.1	-1.22	0.2269	Dunnett-Hsu	0.4692
dose	200	0	-0.1969	0.02714	69.4	-7.26	<.0001	Dunnett-Hsu	<.0001
dose	1000	0	-0.2788	0.02738	68.9	-10.18	<.0001	Dunnett-Hsu	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > t	Adjustment	Adj P
dose	0	40	0.03367	0.02761	67.1	1.22	0.1134	Dunnett-Hsu	0.2373
dose	0	200	0.1969	0.02714	69.4	7.26	<.0001	Dunnett-Hsu	<.0001
dose	0	1000	0.2788	0.02738	68.9	10.18	<.0001	Dunnett-Hsu	<.0001

Table 6.

Females Only

LitterSize as Covariate (%Males not included as a covariate)

Mixed Model Based on Mean Data

Data Set WORK.MEANDATABYSEX

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
dose	3	73	45.91	<.0001
LitterSize	1	73	13.51	0.0004

Least Squares Means

Effect	dose	Estimate	Standard Error	DF	t Value	Pr > |t|
dose	0	1.2953	0.02012	73	64.37	<.0001
dose	40	1.2569	0.01959	73	64.17	<.0001
dose	200	1.0993	0.01860	73	59.10	<.0001
dose	1000	1.0159	0.01906	73	53.30	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > |t|	Adjustment	Adj P
dose	40	0	-0.03841	0.02813	73	-1.37	0.1763	Dunnett-Hsu	0.3813
dose	200	0	-0.1960	0.02739	73	-7.15	<.0001	Dunnett-Hsu	<.0001
dose	1000	0	-0.2795	0.02773	73	-10.08	<.0001	Dunnett-Hsu	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > t	Adjustment	Adj P
dose	0	40	0.03841	0.02813	73	1.37	0.0881	Dunnett-Hsu	0.1919
dose	0	200	0.1960	0.02739	73	7.15	<.0001	Dunnett-Hsu	<.0001
dose	0	1000	0.2795	0.02773	73	10.08	<.0001	Dunnett-Hsu	<.0001

Mixed Model Based on Individual Data and Dam as Random Effect

Data Set WORK.ANDATA

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
dose	3	69.2	47.97	<.0001
LitterSize	1	87.8	10.11	0.0020

Least Squares Means

Effect	dose	Estimate	Standard Error	DF	t Value	Pr > |t|
dose	0	1.2864	0.02010	70	63.99	<.0001
dose	40	1.2522	0.01893	66.9	66.15	<.0001
dose	200	1.0904	0.01830	69.3	59.58	<.0001
dose	1000	1.0084	0.01869	69.2	53.96	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > |t|	Adjustment	Adj P
dose	40	0	-0.03424	0.02758	68.7	-1.24	0.2186	Dunnett-Hsu	0.4550
dose	200	0	-0.1960	0.02709	70.5	-7.23	<.0001	Dunnett-Hsu	<.0001
dose	1000	0	-0.2780	0.02734	70.1	-10.17	<.0001	Dunnett-Hsu	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > t	Adjustment	Adj P
dose	0	40	0.03424	0.02758	68.7	1.24	0.1093	Dunnett-Hsu	0.2298
dose	0	200	0.1960	0.02709	70.5	7.23	<.0001	Dunnett-Hsu	<.0001
dose	0	1000	0.2780	0.02734	70.1	10.17	<.0001	Dunnett-Hsu	<.0001

Table 7.

Females Only
No Covariates
Model Based on Mean Data

Data Set WORK.MEANDATABYSEX

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
dose	3	74	39.62	<.0001

Least Squares Means

Effect	dose	Estimate	Standard Error	DF	t Value	Pr > |t|
dose	0	1.2996	0.02172	74	59.83	<.0001
dose	40	1.2527	0.02114	74	59.25	<.0001
dose	200	1.1001	0.02011	74	54.71	<.0001
dose	1000	1.0151	0.02061	74	49.26	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > |t|	Adjustment	Adj P
dose	40	0	-0.04692	0.03031	74	-1.55	0.1259	Dunnett	0.2846
dose	200	0	-0.1995	0.02960	74	-6.74	<.0001	Dunnett	<.0001
dose	1000	0	-0.2846	0.02994	74	-9.50	<.0001	Dunnett	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > t	Adjustment	Adj P
dose	0	40	0.04692	0.03031	74	1.55	0.0630	Dunnett	0.1427
dose	0	200	0.1995	0.02960	74	6.74	<.0001	Dunnett	<.0001
dose	0	1000	0.2846	0.02994	74	9.50	<.0001	Dunnett	<.0001

Mixed Model Based on Individual Data and Dam as Random Effect

Data Set WORK.ANDATA

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
dose	3	67.1	43.81	<.0001

Least Squares Means

Effect	dose	Estimate	Standard Error	DF	t Value	Pr > |t|
dose	0	1.2935	0.02092	68.7	61.84	<.0001
dose	40	1.2536	0.01982	64.9	63.24	<.0001
dose	200	1.0947	0.01911	67.7	57.28	<.0001
dose	1000	1.0130	0.01951	67.2	51.92	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > |t|	Adjustment	Adj P
dose	40	0	-0.03992	0.02882	66.9	-1.39	0.1706	Dunnett	0.3688
dose	200	0	-0.1988	0.02833	68.3	-7.02	<.0001	Dunnett	<.0001
dose	1000	0	-0.2805	0.02860	68	-9.81	<.0001	Dunnett	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > t	Adjustment	Adj P
dose	0	40	0.03992	0.02882	66.9	1.39	0.0853	Dunnett	0.1854
dose	0	200	0.1988	0.02833	68.3	7.02	<.0001	Dunnett	<.0001
dose	0	1000	0.2805	0.02860	68	9.81	<.0001	Dunnett	<.0001

Table 8.

Males Only

LitterSize & %Males as Covariates

Mixed Model Based on Mean Data

Data Set WORK.MEANDATABYSEX

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
dose	3	71	51.81	<.0001
PercMales	1	71	6.19	0.0152
LitterSize	1	71	5.31	0.0241

Least Squares Means

Effect	dose	Estimate	Standard Error	DF	t Value	Pr > |t|
dose	0	1.3704	0.02113	71	64.86	<.0001
dose	40	1.3131	0.02053	71	63.95	<.0001
dose	200	1.1321	0.02011	71	56.30	<.0001
dose	1000	1.0582	0.01993	71	53.09	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > |t|	Adjustment	Adj P
dose	40	0	-0.05724	0.02950	71	-1.94	0.0563	Dunnett-Hsu	0.1372
dose	200	0	-0.2382	0.02934	71	-8.12	<.0001	Dunnett-Hsu	<.0001
dose	1000	0	-0.3122	0.02901	71	-10.76	<.0001	Dunnett-Hsu	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > t	Adjustment	Adj P
dose	0	40	0.05724	0.02950	71	1.94	0.0282	Dunnett-Hsu	0.0687
dose	0	200	0.2382	0.02934	71	8.12	<.0001	Dunnett-Hsu	<.0001
dose	0	1000	0.3122	0.02901	71	10.76	<.0001	Dunnett-Hsu	<.0001

Mixed Model Based on Individual Data and Dam as Random Effect

Data Set WORK.ANDATA

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
dose	3	69.5	52.24	<.0001
PercMales	1	73	5.56	0.0210
LitterSize	1	74.4	4.65	0.0343

Least Squares Means

Effect	dose	Estimate	Standard Error	DF	t Value	Pr > |t|
dose	0	1.3704	0.02132	69.9	64.28	<.0001
dose	40	1.3158	0.02065	69.2	63.73	<.0001
dose	200	1.1346	0.01953	67.4	58.09	<.0001
dose	1000	1.0607	0.01992	69.1	53.25	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > |t|	Adjustment	Adj P
dose	40	0	-0.05466	0.02928	70.7	-1.87	0.0661	Dunnett-Hsu	0.1588
dose	200	0	-0.2359	0.02892	68.9	-8.16	<.0001	Dunnett-Hsu	<.0001
dose	1000	0	-0.3098	0.02879	70.6	-10.76	<.0001	Dunnett-Hsu	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > t	Adjustment	Adj P
dose	0	40	0.05466	0.02928	70.7	1.87	0.0330	Dunnett-Hsu	0.0795
dose	0	200	0.2359	0.02892	68.9	8.16	<.0001	Dunnett-Hsu	<.0001
dose	0	1000	0.3098	0.02879	70.6	10.76	<.0001	Dunnett-Hsu	<.0001

Table 9.

Males Only

LitterSize as Covariate (%Males not included as a covariate)

Mixed Model Based on Mean Data

Data Set WORK.MEANDATABYSEX

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
dose	3	72	47.18	<.0001
LitterSize	1	72	5.88	0.0178

Least Squares Means

Effect	dose	Estimate	Standard Error	DF	t Value	Pr > |t|
dose	0	1.3697	0.02188	72	62.61	<.0001
dose	40	1.3086	0.02118	72	61.79	<.0001
dose	200	1.1368	0.02073	72	54.84	<.0001
dose	1000	1.0583	0.02064	72	51.28	<.0001

Differences of Least Squares Means

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > |t|	Adjustment	Adj P
dose	40	0	-0.06107	0.03050	72	-2.00	0.0490	Dunnett-Hsu	0.1206
dose	200	0	-0.2329	0.03029	72	-7.69	<.0001	Dunnett-Hsu	<.0001
dose	1000	0	-0.3114	0.03003	72	-10.37	<.0001	Dunnett-Hsu	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > t	Adjustment	Adj P
dose	0	40	0.06107	0.03050	72	2.00	0.0245	Dunnett-Hsu	0.0603
dose	0	200	0.2329	0.03029	72	7.69	<.0001	Dunnett-Hsu	<.0001
dose	0	1000	0.3114	0.03003	72	10.37	<.0001	Dunnett-Hsu	<.0001

Mixed Model Based on Individual Data and Dam as Random Effect

Data Set WORK.ANDATA

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
dose	3	69.6	48.38	<.0001
LitterSize	1	74.2	5.26	0.0246

Least Squares Means

Effect	dose	Estimate	Standard Error	DF	t Value	Pr > |t|
dose	0	1.3647	0.02176	70.3	62.71	<.0001
dose	40	1.3066	0.02084	70.2	62.69	<.0001
dose	200	1.1334	0.02007	67.5	56.47	<.0001
dose	1000	1.0560	0.02037	69.6	51.84	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > |t|	Adjustment	Adj P
dose	40	0	-0.05810	0.03005	70.6	-1.93	0.0572	Dunnett-Hsu	0.1389
dose	200	0	-0.2312	0.02965	69	-7.80	<.0001	Dunnett-Hsu	<.0001
dose	1000	0	-0.3087	0.02958	70.5	-10.44	<.0001	Dunnett-Hsu	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > t	Adjustment	Adj P
dose	0	40	0.05810	0.03005	70.6	1.93	0.0286	Dunnett-Hsu	0.0695
dose	0	200	0.2312	0.02965	69	7.80	<.0001	Dunnett-Hsu	<.0001
dose	0	1000	0.3087	0.02958	70.5	10.44	<.0001	Dunnett-Hsu	<.0001

Table 10.

Males Only
No Covariates
Model Based on Mean Data

Data Set WORK.MEANDATABYSEX

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
dose	3	73	45.68	<.0001

Least Squares Means

Effect	dose	Estimate	Standard Error	DF	t Value	Pr > |t|
dose	0	1.3754	0.02246	73	61.23	<.0001
dose	40	1.3070	0.02186	73	59.78	<.0001
dose	200	1.1319	0.02131	73	53.12	<.0001
dose	1000	1.0596	0.02131	73	49.72	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > |t|	Adjustment	Adj P
dose	40	0	-0.06845	0.03135	73	-2.18	0.0322	Dunnett	0.0815
dose	200	0	-0.2435	0.03096	73	-7.86	<.0001	Dunnett	<.0001
dose	1000	0	-0.3158	0.03096	73	-10.20	<.0001	Dunnett	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > t	Adjustment	Adj P
dose	0	40	0.06845	0.03135	73	2.18	0.0161	Dunnett	0.0408
dose	0	200	0.2435	0.03096	73	7.86	<.0001	Dunnett	<.0001
dose	0	1000	0.3158	0.03096	73	10.20	<.0001	Dunnett	<.0001

Mixed Model Based on Individual Data and Dam as Random Effect

Data Set WORK.ANDATA

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
dose	3	69.9	47.22	<.0001

Least Squares Means

Effect	dose	Estimate	Standard Error	DF	t Value	Pr > |t|
dose	0	1.3729	0.02202	71.3	62.36	<.0001
dose	40	1.3081	0.02136	70.5	61.24	<.0001
dose	200	1.1326	0.02059	67.8	55.00	<.0001
dose	1000	1.0604	0.02080	70.2	50.98	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > |t|	Adjustment	Adj P
dose	40	0	-0.06478	0.03068	70.9	-2.11	0.0382	Dunnett	0.0957
dose	200	0	-0.2404	0.03015	69.6	-7.97	<.0001	Dunnett	<.0001
dose	1000	0	-0.3125	0.03029	70.8	-10.32	<.0001	Dunnett	<.0001

Effect	dose	dose	Estimate	Standard Error	DF	t Value	Pr > t	Adjustment	Adj P
dose	0	40	0.06478	0.03068	70.9	2.11	0.0191	Dunnett	0.0479
dose	0	200	0.2404	0.03015	69.6	7.97	<.0001	Dunnett	<.0001
dose	0	1000	0.3125	0.03029	70.8	10.32	<.0001	Dunnett	<.0001

Table 11. Fetal Weight Data

(These data are the same as provided by TCEQ except that a few errors in going from the Hackett et al. (1987) data sheets to the electronic copy have been corrected.)

Index	Dam	SITE	Status	FetalSex	dose	fetalwt
1	228	1	1	1	0	1.611
2	228	2	1	2	0	1.393
3	228	3	1	1	0	1.524
4	228	4	1	1	0	1.512
5	228	5	1	2	0	1.573
6	228	6	1	1	0	1.526
7	228	7	1	1	0	1.563
8	228	8	2		0	
9	228	9	1	2	0	1.311
10	228	10	1	1	0	1.55
11	256	1	1	1	0	1.406
12	256	2	1	2	0	1.277
13	256	3	1	2	0	1.272
14	256	4	1	1	0	1.22
15	256	5	2		0	
16	256	6	1	1	0	1.362
17	256	7	1	2	0	1.273
18	256	8	1	2	0	1.293
19	256	9	2		0	
20	256	10	1	1	0	1.336
21	256	11	1	1	0	1.312
22	256	12	1	1	0	1.316
23	270	1	1	2	0	1.433
24	270	2	1	1	0	1.763
25	270	3	2		0	
26	270	4	2		0	
27	270	5	1	1	0	1.613
28	270	6	2		0	
29	273	1	1	2	0	1.352
30	273	2	2		0	
31	273	3	1	2	0	1.215
32	273	4	1	2	0	1.181
33	273	5	1	1	0	1.425
34	273	6	1	2	0	1.204
35	273	7	1	2	0	1.183
36	273	8	1	1	0	1.106
37	273	9	1	2	0	1.372
38	273	10	1	1	0	1.37
39	273	11	1	1	0	1.379
40	273	12	1	2	0	1.355

41	273	13	1	2	0	0.664
42	273	14	1	1	0	1.436
43	304	1	1	2	0	1.189
44	304	2	1	1	0	1.165
45	304	3	1	2	0	1.14
46	304	4	1	1	0	1.172
47	304	5	1	1	0	1.289
48	304	6	1	2	0	1.179
49	304	7	1	1	0	1.098
50	304	8	1	1	0	1.105
51	304	9	1	2	0	1.231
52	304	10	1	2	0	1.183
53	304	11	1	1	0	1.349
54	304	12	1	1	0	1.118
55	320	1	1	1	0	1.322
56	320	2	1	2	0	1.132
57	320	3	1	2	0	1.281
58	320	4	1	1	0	1.354
59	320	5	1	1	0	1.383
60	320	6	1	1	0	1.338
61	320	7	1	2	0	1.016
62	320	8	1	2	0	1.273
63	320	9	1	2	0	1.39
64	320	10	1	2	0	1.249
65	320	11	1	1	0	1.444
66	320	12	1	2	0	1.31
67	320	13	1	2	0	1.381
68	321	1	1	2	0	1.294
69	321	2	1	1	0	1.299
70	321	3	1	2	0	1.342
71	321	4	1	2	0	1.294
72	321	5	1	1	0	1.308
73	321	6	1	1	0	1.336
74	321	7	1	1	0	1.285
75	321	8	1	2	0	1.153
76	321	9	1	2	0	1.151
77	321	10	1	1	0	1.3
78	321	11	1	1	0	1.459
79	321	12	1	1	0	1.477
80	321	13	1	2	0	1.259
81	321	14	1	1	0	1.276
82	321	15	1	2	0	1.184
83	341	1	1	1	0	1.493
84	341	2	1	1	0	1.492
85	341	3	1	1	0	1.469
86	341	4	1	2	0	1.379

87	341	5	1	1	0	1.429
88	341	6	1	2	0	1.361
89	341	7	1	2	0	1.269
90	341	8	1	1	0	1.429
91	341	9	1	2	0	1.381
92	341	10	1	1	0	1.404
93	341	11	1	2	0	1.311
94	341	12	1	2	0	1.403
95	341	13	1	1	0	1.426
96	351	1	1	2	0	1.285
97	351	2	1	2	0	1.18
98	351	3	1	1	0	1.18
99	351	4	1	1	0	1.148
100	351	5	1	2	0	1.117
101	351	6	1	1	0	1.234
102	351	7	1	2	0	1.128
103	351	8	1	2	0	1.218
104	351	9	1	2	0	1.169
105	351	10	1	1	0	0.932
106	351	11	1	2	0	1.214
107	351	12	2		0	
108	351	13	1	2	0	1.158
109	351	14	1	2	0	1.214
110	372	1	1	2	0	1.43
111	372	2	1	2	0	1.252
112	372	3	1	1	0	1.2
113	372	4	1	1	0	1.354
114	372	5	1	2	0	1.322
115	372	6	1	2	0	1.38
116	372	7	1	1	0	1.451
117	372	8	1	1	0	1.316
118	372	9	1	2	0	1.262
119	372	10	1	1	0	1.353
120	372	11	1	2	0	1.24
121	372	12	4		0	
122	372	13	1	2	0	1.305
123	372	14	1	1	0	1.41
124	378	1	1	1	0	1.338
125	378	2	1	1	0	1.402
126	378	3	1	1	0	1.464
127	378	4	1	1	0	1.46
128	378	5	1	2	0	1.348
129	378	6	2		0	
130	378	7	1	1	0	1.35
131	378	8	2		0	
132	378	9	1	1	0	1.346

133	378	10	1	1	0	1.398
134	378	11	1	1	0	1.4
135	378	12	1	1	0	1.347
136	378	13	1	1	0	1.332
137	378	14	1	1	0	1.245
138	380	1	1	2	0	1.337
139	380	2	1	1	0	1.36
140	380	3	2		0	
141	380	4	1	2	0	1.276
142	380	5	1	1	0	1.429
143	380	6	1	2	0	1.295
144	380	7	1	2	0	1.284
145	380	8	1	1	0	1.482
146	380	9	1	2	0	1.334
147	380	10	1	2	0	1.236
148	380	11	1	1	0	1.365
149	380	12	1	1	0	1.357
150	380	13	1	2	0	1.36
151	380	14	1	1	0	1.275
152	388	1	2		0	
153	388	2	1	1	0	1.511
154	388	3	1	2	0	1.37
155	388	4	1	1	0	1.459
156	388	5	1	2	0	1.428
157	388	6	1	2	0	1.345
158	388	7	1	2	0	1.441
159	388	8	1	2	0	1.376
160	388	9	1	1	0	1.279
161	388	10	1	2	0	1.419
162	391	1	1	2	0	1.206
163	391	2	1	1	0	1.341
164	391	3	1	2	0	1.362
165	391	4	1	1	0	1.482
166	391	5	1	2	0	1.46
167	391	6	1	1	0	1.281
168	391	7	1	1	0	1.179
169	391	8	2		0	
170	391	9	1	2	0	1.07
171	391	10	1	2	0	1.261
172	391	11	1	1	0	1.269
173	391	12	1	1	0	1.344
174	391	13	1	1	0	1.489
175	391	14	1	1	0	1.502
176	415	1	1	1	0	1.459
177	415	2	2		0	
178	415	3	2		0	

179	415	4	1	1	0	1.364
180	415	5	2		0	
181	415	6	1	2	0	1.288
182	415	7	1	1	0	1.226
183	415	8	1	2	0	1.332
184	415	9	1	2	0	1.137
185	415	10	1	1	0	1.333
186	415	11	1	1	0	1.217
187	415	12	1	1	0	1.456
188	418	1	1	2	0	1.154
189	418	2	1	2	0	1.281
190	418	3	1	2	0	1.383
191	418	4	1	1	0	1.354
192	418	5	1	2	0	1.318
193	418	6	1	2	0	0.957
194	418	7	1	2	0	1.311
195	418	8	1	2	0	1.3
196	418	9	1	1	0	1.37
197	418	10	1	1	0	1.296
198	418	11	1	2	0	1.218
199	418	12	2		0	
200	418	13	1	2	0	1.22
201	418	14	1	2	0	1.328
202	422	1	1	2	0	1.475
203	422	2	1	2	0	1.511
204	422	3	1	1	0	1.49
205	422	4	1	2	0	1.405
206	422	5	1	1	0	1.5
207	422	6	1	2	0	1.413
208	422	7	1	1	0	1.518
209	422	8	1	1	0	1.524
210	422	9	1	1	0	1.498
211	422	10	1	2	0	1.368
212	422	11	1	2	0	1.36
213	422	12	1	2	0	1.351
214	422	13	1	1	0	1.478
215	422	14	2		0	
216	422	15	1	1	0	1.497
217	444	1	1	2	0	1.343
218	444	2	1	2	0	1.347
219	444	3	1	1	0	1.372
220	444	4	1	2	0	1.311
221	444	5	1	1	0	1.357
222	444	6	1	2	0	1.259
223	444	7	1	1	0	1.35
224	444	8	1	2	0	1.275

225	444	9	1	1	0	1.31
226	444	10	1	1	0	1.138
227	444	11	1	2	0	1.278
228	444	12	1	1	0	1.444
229	444	13	1	2	0	1.304
230	444	14	1	2	0	1.332
231	242	1	1	1	40	1.47
232	242	2	2		40	
233	242	3	1	1	40	1.377
234	242	4	1	1	40	1.429
235	242	5	1	2	40	1.363
236	242	6	1	2	40	1.325
237	242	7	1	1	40	1.269
238	242	8	1	1	40	1.319
239	242	9	1	2	40	1.33
240	242	10	1	1	40	1.381
241	242	11	1	2	40	1.214
242	242	12	1	2	40	1.302
243	242	13	2		40	
244	246	1	1	2	40	1.422
245	246	2	1	2	40	1.394
246	246	3	1	2	40	1.237
247	246	4	1	1	40	1.329
248	246	5	1	2	40	1.372
249	246	6	1	2	40	0.94
250	246	7	1	2	40	1.287
251	246	8	1	1	40	1.356
252	246	9	1	2	40	1.29
253	246	10	1	2	40	1.304
254	246	11	1	1	40	1.168
255	263	1	1	2	40	1.308
256	263	2	1	1	40	1.313
257	263	3	1	2	40	1.373
258	263	4	1	2	40	1.275
259	263	5	1	2	40	1.378
260	263	6	1	2	40	1.295
261	263	7	1	2	40	1.301
262	263	8	1	1	40	1.267
263	263	9	2		40	
264	263	10	1	2	40	1.326
265	263	11	1	1	40	1.363
266	263	12	1	2	40	1.312
267	263	13	1	2	40	1.321
268	263	14	1	2	40	1.048
269	286	1	1	1	40	1.429
270	286	2	1	2	40	1.233

271	286	3	1	1	40	1.32
272	286	4	1	1	40	1.326
273	286	5	1	1	40	1.359
274	286	6	1	2	40	1.334
275	286	7	1	2	40	1.321
276	286	8	1	1	40	1.426
277	286	9	1	1	40	1.407
278	286	10	1	2	40	1.283
279	286	11	1	2	40	1.356
280	286	12	1	2	40	1.142
281	286	13	1	1	40	1.409
282	286	14	1	1	40	1.313
283	295	1	1	1	40	1.426
284	295	2	1	1	40	1.292
285	295	3	1	1	40	1.25
286	295	4	1	1	40	1.443
287	295	5	1	2	40	1.241
288	295	6	1	2	40	1.23
289	295	7	1	1	40	1.289
290	295	8	4		40	
291	295	9	1	1	40	1.376
292	295	10	1	1	40	1.287
293	295	11	1	2	40	1.157
294	295	12	1	2	40	1.291
295	295	13	1	1	40	1.349
296	295	14	1	2	40	1.264
297	302	1	1	1	40	1.133
298	302	2	1	1	40	1.14
299	302	3	1	2	40	1.065
300	302	4	1	1	40	1.193
301	302	5	1	2	40	1.079
302	302	6	1	1	40	1.108
303	302	7	4		40	
304	302	8	1	1	40	1.183
305	302	9	1	2	40	1.191
306	302	10	1	1	40	1.172
307	302	11	1	2	40	1.121
308	302	12	1	1	40	1.038
309	302	13	1	1	40	1.13
310	302	14	1	1	40	1.22
311	302	15	1	1	40	1.167
312	302	16	1	1	40	1.173
313	307	1	1	2	40	1.343
314	307	2	1	2	40	1.227
315	307	3	1	1	40	1.356
316	307	4	1	1	40	1.423

317	307	5	1	1	40	1.351
318	307	6	1	2	40	1.179
319	307	7	1	2	40	1.364
320	307	8	1	1	40	1.397
321	307	9	1	1	40	1.362
322	307	10	1	1	40	1.384
323	307	11	1	2	40	1.252
324	307	12	1	2	40	1.265
325	307	13	1	2	40	1.35
326	311	1	1	1	40	1.378
327	311	2	1	1	40	1.337
328	311	3	1	1	40	1.4
329	311	4	1	2	40	1.315
330	311	5	1	2	40	1.297
331	311	6	1	1	40	1.43
332	311	7	1	1	40	1.38
333	311	8	1	2	40	1.294
334	311	9	1	2	40	1.296
335	311	10	1	2	40	1.31
336	311	11	1	1	40	1.28
337	311	12	1	2	40	1.063
338	312	1	1	1	40	1.344
339	312	2	1	1	40	1.239
340	312	3	1	2	40	1.273
341	312	4	1	2	40	1.249
342	312	5	1	2	40	1.259
343	312	6	1	2	40	1.149
344	312	7	1	1	40	1.312
345	312	8	1	2	40	1.217
346	312	9	1	2	40	1.386
347	312	10	1	1	40	1.235
348	312	11	1	2	40	1.151
349	312	12	1	1	40	1.215
350	312	13	1	1	40	1.291
351	312	14	1	1	40	1.146
352	312	15	1	2	40	1.199
353	312	16	4		40	
354	312	17	1	1	40	1.305
355	314	1	1	1	40	1.405
356	314	2	1	2	40	1.184
357	314	3	1	1	40	1.184
358	314	4	1	1	40	1.424
359	314	5	1	2	40	1.3
360	314	6	1	1	40	1.313
361	314	7	1	1	40	1.416
362	314	8	1	1	40	1.437

363	314	9	1	2	40	1.288
364	314	10	2		40	
365	314	11	1	2	40	1.287
366	314	12	1	2	40	1.321
367	318	1	1	1	40	1.482
368	318	2	1	2	40	1.289
369	318	3	1	1	40	1.245
370	318	4	1	1	40	1.379
371	318	5	1	2	40	1.256
372	318	6	1	1	40	1.217
373	318	7	1	2	40	1.339
374	318	8	1	2	40	1.308
375	318	9	4		40	
376	318	10	1	2	40	1.205
377	318	11	1	1	40	1.49
378	318	12	1	2	40	1.284
379	318	13	1	1	40	1.321
380	346	1	1	2	40	1.092
381	346	2	2		40	
382	346	3	2		40	
383	346	4	2		40	
384	346	5	1	1	40	1.31
385	346	6	1	1	40	1.322
386	346	7	1	1	40	1.048
387	346	8	1	2	40	1.238
388	346	9	1	2	40	1.167
389	349	1	1	2	40	1.015
390	349	2	1	2	40	1.227
391	349	3	1	1	40	1.249
392	349	4	1	2	40	1.394
393	349	5	1	2	40	1.334
394	349	6	1	1	40	1.404
395	349	7	1	1	40	1.344
396	349	8	1	1	40	1.395
397	349	9	1	1	40	1.391
398	349	10	1	1	40	1.246
399	349	11	1	1	40	1.411
400	349	12	1	2	40	1.349
401	349	13	1	2	40	1.354
402	368	1	1	2	40	1.283
403	368	2	1	2	40	1.396
404	368	3	1	1	40	1.421
405	368	4	1	2	40	1.253
406	368	5	1	1	40	1.355
407	368	6	1	1	40	1.391
408	368	7	1	1	40	1.379

409	368	8	1	1	40	1.48
410	368	9	1	2	40	1.365
411	368	10	1	1	40	1.235
412	368	11	1	1	40	1.369
413	369	1	1	2	40	1.286
414	369	2	1	2	40	1.237
415	369	3	1	1	40	1.292
416	369	4	1	2	40	1.216
417	369	5	1	1	40	1.23
418	369	6	2		40	
419	369	7	1	1	40	1.276
420	369	8	1	1	40	1.127
421	369	9	1	2	40	1.345
422	369	10	2		40	
423	369	11	1	2	40	1.251
424	369	12	1	2	40	1.287
425	373	1	1	1	40	1.421
426	373	2	1	2	40	1.307
427	373	3	1	2	40	1.26
428	373	4	1	1	40	1.342
429	373	5	1	2	40	1.315
430	373	6	1	1	40	1.382
431	373	7	1	1	40	1.391
432	373	8	1	1	40	1.338
433	373	9	1	1	40	1.301
434	373	10	1	1	40	1.289
435	373	11	1	1	40	1.266
436	373	12	1	2	40	1.27
437	373	13	1	2	40	1.308
438	373	14	1	2	40	1.268
439	373	15	1	2	40	1.259
440	381	1	2		40	
441	381	2	1	1	40	1.401
442	381	3	1	2	40	1.243
443	381	4	1	2	40	1.077
444	381	5	1	1	40	1.278
445	381	6	1	1	40	1.283
446	381	7	1	1	40	1.289
447	381	8	1	1	40	1.399
448	381	9	1	2	40	1.238
449	381	10	1	1	40	1.234
450	381	11	1	1	40	1.344
451	381	12	1	2	40	1.41
452	381	13	1	2	40	1.39
453	381	14	1	2	40	0.902
454	381	15	1	2	40	1.37

455	390	1	1	2	40	1.277
456	390	2	1	1	40	1.338
457	390	3	1	2	40	1.25
458	390	4	1	2	40	1.211
459	390	5	1	2	40	1.215
460	390	6	1	2	40	1.058
461	390	7	1	2	40	1.082
462	390	8	1	2	40	1.078
463	390	9	1	2	40	1.085
464	390	10	1	1	40	1.009
465	390	11	1	1	40	1.187
466	390	12	1	2	40	1.351
467	390	13	1	2	40	1.303
468	390	14	1	2	40	1.298
469	433	1	1	1	40	1.314
470	433	2	1	1	40	1.225
471	433	3	1	2	40	1.115
472	433	4	1	1	40	1.141
473	433	5	1	2	40	1.202
474	433	6	1	2	40	1.214
475	433	7	1	1	40	1.23
476	433	8	1	1	40	1.194
477	433	9	1	1	40	1.293
478	433	10	1	1	40	1.358
479	433	11	1	2	40	1.168
480	433	12	2		40	
481	433	13	4		40	
482	433	14	1	2	40	1.239
483	433	15	1	2	40	1.252
484	251	1	1	2	200	1.124
485	251	2	1	1	200	1.228
486	251	3	1	1	200	1.142
487	251	4	1	1	200	1.183
488	251	5	1	1	200	1.08
489	251	6	1	1	200	1.19
490	251	7	1	1	200	1.061
491	251	8	1	2	200	1.127
492	251	9	1	2	200	1.064
493	251	10	1	1	200	1.123
494	251	11	1	2	200	1
495	251	12	1	2	200	1.068
496	251	13	1	2	200	0.984
497	258	1	1	1	200	1.198
498	258	2	1	2	200	1.122
499	258	3	1	1	200	1.141
500	258	4	1	1	200	1.157

501	258	5	1	1	200	1.146
502	258	6	2		200	
503	258	7	1	1	200	1.169
504	258	8	1	1	200	1.18
505	258	9	1	2	200	1.127
506	258	10	1	2	200	1.178
507	258	11	1	1	200	1.164
508	258	12	1	1	200	1.121
509	258	13	1	2	200	1.14
510	260	1	1	1	200	1.229
511	260	2	4		200	
512	260	3	1	1	200	1.255
513	260	4	1	2	200	1.224
514	260	5	1	1	200	1.137
515	260	6	2		200	
516	260	7	1	1	200	1.294
517	260	8	1	2	200	1.088
518	260	9	1	2	200	1.223
519	260	10	1	2	200	1.175
520	260	11	1	1	200	1.181
521	260	12	1	2	200	1.13
522	260	13	1	1	200	1.186
523	260	14	1	1	200	1.217
524	265	1	1	2	200	1.075
525	265	2	1	1	200	1.049
526	265	3	1	2	200	1.131
527	265	4	1	1	200	1.139
528	265	5	1	1	200	1.118
529	265	6	1	2	200	1.038
530	265	7	1	2	200	1.078
531	265	8	1	2	200	1.064
532	265	9	1	2	200	0.988
533	265	10	1	1	200	0.974
534	265	11	1	2	200	0.978
535	265	12	1	2	200	0.921
536	265	13	1	2	200	1.051
537	272	1	1	1	200	1.041
538	272	2	1	1	200	0.953
539	272	3	1	2	200	1.051
540	272	4	1	2	200	1.016
541	272	5	1	2	200	1.037
542	272	6	1	2	200	1.01
543	272	7	1	1	200	0.953
544	272	8	1	2	200	0.962
545	272	9	1	2	200	1.026
546	272	10	1	1	200	1.127

547	272	11	1	1	200	0.993
548	272	12	1	1	200	1.122
549	272	13	1	2	200	0.905
550	272	14	1	2	200	1.06
551	274	1	1	1	200	1.135
552	274	2	1	1	200	1.192
553	274	3	1	1	200	1.13
554	274	4	1	2	200	0.983
555	274	5	1	1	200	1.187
556	274	6	1	2	200	0.995
557	274	7	1	2	200	1.115
558	274	8	1	1	200	0.826
559	274	9	1	2	200	0.967
560	274	10	1	1	200	1.15
561	274	11	1	1	200	1.176
562	274	12	1	2	200	1.106
563	274	13	1	1	200	1.167
564	274	14	1	2	200	1.038
565	274	15	1	1	200	1.138
566	296	1	1	2	200	1.19
567	296	2	1	1	200	1.1
568	296	3	1	1	200	1.159
569	296	4	1	2	200	1.124
570	296	5	1	1	200	1.092
571	296	6	1	1	200	1.18
572	296	7	1	2	200	1.063
573	296	8	1	2	200	1.113
574	296	9	1	2	200	1.097
575	296	10	1	1	200	1.094
576	296	11	1	2	200	1.06
577	319	1	1	2	200	1.071
578	319	2	1	2	200	1.207
579	319	3	1	2	200	1.175
580	319	4	1	2	200	1.139
581	319	5	1	1	200	1.148
582	319	6	1	1	200	1.144
583	319	7	1	2	200	1.092
584	319	8	2		200	
585	319	9	1	2	200	0.951
586	319	10	1	1	200	1.182
587	319	11	1	1	200	1.146
588	319	12	1	1	200	1.186
589	319	13	1	2	200	0.973
590	319	14	1	1	200	1.073
591	319	15	1	1	200	1.121
592	328	1	2		200	

593	328	2	1	2	200	0.975
594	328	3	1	1	200	1.028
595	328	4	1	2	200	1.007
596	328	5	1	1	200	1.033
597	328	6	4		200	
598	328	7	1	1	200	1.1
599	328	8	1	2	200	0.906
600	328	9	1	1	200	0.843
601	328	10	4		200	
602	328	11	1	1	200	0.99
603	328	12	1	2	200	1.064
604	328	13	1	2	200	1.026
605	328	14	1	1	200	1.002
606	337	1	1	1	200	1.205
607	337	2	1	2	200	1.102
608	337	3	1	1	200	1.231
609	337	4	1	2	200	1.112
610	337	5	1	2	200	1.098
611	337	6	1	2	200	1.087
612	337	7	1	1	200	1.07
613	337	8	1	1	200	1.207
614	337	9	1	2	200	1.048
615	337	10	1	1	200	1.173
616	337	11	1	2	200	0.945
617	337	12	1	1	200	1.141
618	339	1	1	1	200	1.163
619	339	2	1	1	200	1.207
620	339	3	1	2	200	1.072
621	339	4	1	1	200	1.09
622	339	5	1	1	200	0.993
623	339	6	1	2	200	1.049
624	339	7	1	2	200	1.073
625	339	8	1	1	200	1.11
626	339	9	1	2	200	1.034
627	339	10	1	1	200	1.056
628	339	11	1	1	200	0.73
629	342	1	1	2	200	0.979
630	342	2	1	1	200	1.148
631	342	3	1	1	200	1.028
632	342	4	1	1	200	1.116
633	342	5	1	1	200	1.162
634	342	6	1	1	200	1.135
635	342	7	1	2	200	1.026
636	342	8	1	2	200	1.071
637	342	9	1	1	200	1.119
638	342	10	1	1	200	1.116

639	342	11	1	1	200	1.134
640	343	1	2		200	
641	343	2	1	2	200	1.097
642	343	3	1	2	200	1.118
643	343	4	1	1	200	1.052
644	343	5	1	1	200	1.133
645	343	6	1	2	200	1.087
646	343	7	1	2	200	0.981
647	343	8	1	1	200	1.049
648	343	9	1	1	200	1.077
649	343	10	1	2	200	1.036
650	343	11	1	2	200	1.159
651	343	12	1	2	200	0.94
652	343	13	1	1	200	1.101
653	343	14	1	2	200	1.057
654	348	1	1	2	200	1.257
655	348	2	1	2	200	1.162
656	348	3	1	1	200	1.255
657	348	4	1	2	200	1.181
658	348	5	1	2	200	1.154
659	348	6	1	1	200	1.161
660	348	7	1	2	200	1.167
661	348	8	1	2	200	1.177
662	348	9	1	2	200	1.142
663	348	10	1	1	200	1.186
664	348	11	1	1	200	1.107
665	348	12	1	2	200	1.149
666	348	13	1	1	200	1.242
667	348	14	1	1	200	1.209
668	353	1	1	1	200	1.198
669	353	2	4		200	
670	353	3	1	1	200	1.181
671	353	4	1	1	200	1.236
672	353	5	1	1	200	1.167
673	353	6	1	1	200	1.104
674	353	7	1	2	200	1.182
675	353	8	1	2	200	1.187
676	353	9	1	2	200	1.158
677	353	10	1	1	200	1.167
678	353	11	1	2	200	1.151
679	353	12	1	1	200	1.182
680	353	13	1	1	200	1.226
681	366	1	1	2	200	1.212
682	366	2	1	1	200	1.263
683	366	3	1	1	200	1.378
684	366	4	1	2	200	1.178

685	366	5	1	2	200	1.27
686	366	6	1	1	200	1.21
687	366	7	1	1	200	1.192
688	366	8	1	1	200	1.226
689	366	9	1	2	200	1.133
690	366	10	2		200	
691	366	11	1	1	200	1.232
692	366	12	1	1	200	1.144
693	366	13	2		200	
694	366	14	1	2	200	1.189
695	371	1	1	1	200	1.091
696	371	2	1	1	200	1.093
697	371	3	1	2	200	0.902
698	371	4	1	2	200	0.976
699	371	5	1	1	200	1.012
700	371	6	1	2	200	0.935
701	371	7	1	2	200	0.987
702	371	8	1	2	200	1.002
703	371	9	1	1	200	1.022
704	371	10	1	2	200	0.984
705	371	11	1	2	200	1.001
706	371	12	1	1	200	1.055
707	371	13	1	1	200	0.973
708	371	14	1	1	200	1.068
709	371	15	1	2	200	0.897
710	382	1	1	2	200	1.548
711	382	2	1	2	200	1.325
712	392	1	1	1	200	1.206
713	392	2	1	1	200	1.253
714	392	3	1	2	200	1.214
715	392	4	1	1	200	1.295
716	392	5	1	2	200	1.087
717	392	6	1	2	200	1.052
718	392	7	1	1	200	1.114
719	392	8	1	2	200	1.135
720	392	9	1	2	200	1.123
721	392	10	1	1	200	1.252
722	392	11	1	1	200	1.134
723	392	12	1	2	200	1.132
724	392	13	1	1	200	1.168
725	392	14	1	2	200	1.176
726	392	15	1	1	200	1.24
727	392	16	1	2	200	1.198
728	402	1	1	2	200	0.903
729	402	2	1	1	200	1.208
730	402	3	1	1	200	1.093

731	402	4	1	2	200	1.078
732	402	5	1	1	200	1.052
733	402	6	1	2	200	1.098
734	402	7	1	2	200	0.941
735	402	8	1	1	200	1.109
736	402	9	1	2	200	1.051
737	402	10	1	2	200	1.164
738	402	11	1	1	200	1.135
739	402	12	1	2	200	0.933
740	402	13	2		200	
741	402	14	1	2	200	1.061
742	402	15	1	1	200	1.071
743	402	16	1	1	200	1.072
744	420	1	1	1	200	1.294
745	420	2	1	1	200	1.289
746	420	3	2		200	
747	420	4	1	1	200	1.284
748	420	5	2		200	
749	420	6	1	2	200	1.16
750	420	7	1	1	200	1.144
751	420	8	1	1	200	1.263
752	420	9	1	1	200	1.239
753	420	10	1	1	200	1.13
754	420	11	1	2	200	1.143
755	420	12	1	1	200	1.192
756	420	13	1	1	200	1.306
757	231	1	2		1000	
758	231	2	1	1	1000	1.112
759	231	3	1	2	1000	0.932
760	231	4	1	2	1000	1.063
761	231	5	1	2	1000	1.026
762	231	6	1	2	1000	0.955
763	231	7	1	1	1000	1.051
764	231	8	1	2	1000	1.036
765	231	9	1	1	1000	1.038
766	231	10	1	1	1000	1.046
767	243	1	1	2	1000	0.982
768	243	2	1	2	1000	0.96
769	243	3	1	2	1000	1.016
770	243	4	1	1	1000	1.13
771	243	5	1	2	1000	0.949
772	243	6	1	2	1000	1.046
773	243	7	1	1	1000	1.003
774	243	8	1	1	1000	0.998
775	243	9	1	1	1000	1.001
776	243	10	1	2	1000	1.077

777	243	11	1	2	1000	1.028
778	243	12	1	2	1000	1.041
779	243	13	1	2	1000	1.018
780	243	14	1	1	1000	1.037
781	244	1	1	1	1000	0.934
782	244	2	1	2	1000	0.537
783	244	3	1	2	1000	0.862
784	244	4	1	2	1000	0.746
785	244	5	1	2	1000	0.889
786	244	6	1	1	1000	0.942
787	244	7	1	2	1000	0.948
788	244	8	1	1	1000	0.885
789	244	9	1	2	1000	1
790	244	10	1	1	1000	0.925
791	244	11	1	1	1000	1.08
792	244	12	2		1000	
793	255	1	1	2	1000	1.067
794	255	2	1	2	1000	1.13
795	255	3	1	1	1000	1.081
796	255	4	1	1	1000	1.073
797	255	5	1	1	1000	1.056
798	255	6	1	2	1000	1.034
799	255	7	1	1	1000	1.087
800	255	8	1	2	1000	1.078
801	255	9	1	2	1000	1.058
802	255	10	1	1	1000	1.087
803	255	11	1	1	1000	1.133
804	255	12	1	1	1000	1.131
805	264	1	1	1	1000	1.067
806	264	2	1	1	1000	0.901
807	264	3	1	2	1000	1.057
808	264	4	1	2	1000	0.98
809	264	5	1	2	1000	1.036
810	264	6	1	2	1000	0.856
811	264	7	1	2	1000	0.937
812	264	8	1	1	1000	0.95
813	264	9	1	2	1000	1.09
814	264	10	1	1	1000	1.162
815	264	11	1	2	1000	1.074
816	264	12	1	1	1000	1.004
817	264	13	1	1	1000	1.083
818	264	14	1	2	1000	1.001
819	276	1	1	1	1000	0.862
820	276	2	1	2	1000	0.93
821	276	3	1	2	1000	0.786
822	276	4	1	2	1000	0.783

823	276	5	4		1000	
824	276	6	1	2	1000	0.809
825	276	7	1	1	1000	0.737
826	276	8	1	1	1000	0.964
827	276	9	1	1	1000	1
828	276	10	1	1	1000	0.84
829	276	11	1	1	1000	0.85
830	276	12	1	1	1000	0.695
831	276	13	1	1	1000	0.934
832	276	14	1	2	1000	0.79
833	276	15	1	1	1000	0.915
834	294	1	1	1	1000	1.047
835	294	2	1	1	1000	1.164
836	294	3	1	1	1000	1.091
837	294	4	1	2	1000	0.917
838	294	5	1	1	1000	1.065
839	294	6	1	1	1000	1.059
840	294	7	1	2	1000	0.934
841	294	8	1	1	1000	1.042
842	294	9	1	2	1000	0.956
843	294	10	1	2	1000	1.029
844	294	11	1	1	1000	0.958
845	294	12	1	2	1000	0.894
846	294	13	1	2	1000	1.032
847	294	14	1	2	1000	0.951
848	294	15	1	2	1000	1.02
849	305	1	1	1	1000	1.197
850	305	2	1	1	1000	1.021
851	305	3	1	2	1000	1.031
852	305	4	1	2	1000	0.924
853	305	5	1	2	1000	1.106
854	305	6	1	1	1000	1.029
855	305	7	1	1	1000	1.127
856	305	8	1	1	1000	1.23
857	305	9	1	1	1000	1.054
858	305	10	1	2	1000	0.996
859	305	11	1	2	1000	0.952
860	305	12	1	1	1000	0.991
861	309	1	1	2	1000	1.045
862	309	2	1	2	1000	1.062
863	309	3	1	1	1000	1.165
864	309	4	1	1	1000	1.076
865	309	5	1	1	1000	1.106
866	309	6	1	2	1000	1.054
867	309	7	1	2	1000	1.097
868	309	8	1	2	1000	1.09

869	309	9	1	1	1000	1.086
870	309	10	1	1	1000	1.097
871	309	11	1	1	1000	1.153
872	309	12	1	2	1000	1.183
873	309	13	1	2	1000	1.019
874	309	14	1	1	1000	1.072
875	309	15	1	1	1000	1.017
876	309	16	1	1	1000	1.105
877	317	1	1	1	1000	1.046
878	317	2	1	1	1000	1.071
879	317	3	1	1	1000	
880	317	4	1	1	1000	1.055
881	317	5	1	1	1000	1.054
882	317	6	1	1	1000	1.08
883	317	7	1	2	1000	0.902
884	317	8	1	1	1000	0.806
885	317	9	1	2	1000	0.982
886	317	10	1	2	1000	1.034
887	317	11	1	1	1000	
888	317	12	1	1	1000	1.018
889	317	13	1	2	1000	1.031
890	317	14	1	1	1000	1.006
891	325	1	1	1	1000	1.076
892	325	2	2		1000	
893	325	3	1	2	1000	1.156
894	325	4	1	1	1000	1.128
895	325	5	1	2	1000	1.129
896	325	6	1	2	1000	1.082
897	325	7	1	2	1000	1.176
898	325	8	1	1	1000	1.037
899	325	9	1	1	1000	1.187
900	325	10	1	1	1000	1.08
901	325	11	1	1	1000	1.134
902	325	12	1	1	1000	1.068
903	325	13	1	1	1000	1.003
904	325	14	1	1	1000	0.935
905	325	15	1	2	1000	0.985
906	340	1	1	1	1000	1.071
907	340	2	1	1	1000	1.106
908	340	3	1	2	1000	1.078
909	340	4	1	1	1000	1.112
910	340	5	1	2	1000	1.045
911	340	6	1	1	1000	1.017
912	340	7	2		1000	
913	340	8	1	1	1000	1.09
914	340	9	2		1000	

915	340	10	1	2	1000	1.143
916	340	11	1	1	1000	1.138
917	340	12	1	2	1000	1.069
918	340	13	1	1	1000	1.056
919	365	1	1	1	1000	0.846
920	365	2	1	2	1000	0.829
921	365	3	1	2	1000	0.937
922	365	4	1	2	1000	0.688
923	365	5	1	2	1000	0.868
924	365	6	1	2	1000	0.57
925	365	7	1	1	1000	0.839
926	365	8	1	2	1000	0.945
927	365	9	1	1	1000	0.902
928	365	10	1	1	1000	0.818
929	365	11	2		1000	
930	374	1	2		1000	
931	374	2	1	2	1000	1.022
932	374	3	1	2	1000	1.048
933	374	4	1	1	1000	1.091
934	374	5	1	1	1000	1.048
935	374	6	1	1	1000	1.15
936	374	7	1	1	1000	1.201
937	374	8	1	1	1000	1.068
938	374	9	1	1	1000	1.092
939	374	10	1	1	1000	1.077
940	377	1	1	2	1000	1.189
941	377	2	1	1	1000	1.129
942	377	3	1	2	1000	1.049
943	377	4	1	2	1000	1.127
944	377	5	1	1	1000	0.985
945	377	6	2		1000	
946	377	7	1	1	1000	1.056
947	377	8	1	1	1000	1.248
948	377	9	1	1	1000	1.02
949	377	10	1	2	1000	1.188
950	377	11	1	2	1000	1.082
951	377	12	1	2	1000	1.025
952	377	13	1	2	1000	1.155
953	389	1	1	1	1000	1.087
954	389	2	1	2	1000	1.025
955	389	3	1	2	1000	1.074
956	389	4	1	2	1000	1.14
957	389	5	2		1000	
958	389	6	1	2	1000	1.015
959	389	7	1	2	1000	0.945
960	389	8	1	1	1000	1.191

961	389	9	1	1	1000	1.182
962	389	10	4		1000	
963	389	11	2		1000	
964	400	1	1	2	1000	1.276
965	400	2	1	2	1000	1.375
966	400	3	1	1	1000	1.341
967	400	4	1	1	1000	1.468
968	400	5	1	2	1000	1.349
969	400	6	2		1000	
970	400	7	1	1	1000	1.249
971	400	8	2		1000	
972	400	9	1	1	1000	1.358
973	400	10	1	1	1000	1.368
974	400	11	1	1	1000	1.415
975	400	12	1	2	1000	1.3
976	427	1	1	2	1000	1.119
977	427	2	1	1	1000	1.235
978	427	3	1	1	1000	1.222
979	427	4	1	1	1000	1.153
980	427	5	1	1	1000	1.078
981	427	6	1	2	1000	1.032
982	427	7	1	1	1000	0.975
983	427	8	1	1	1000	1.092
984	427	9	1	1	1000	1.217
985	427	10	1	2	1000	1.121
986	427	11	1	2	1000	1.105
987	427	12	1	1	1000	1.172
988	427	13	2		1000	
989	427	14	1	1	1000	1.188
990	428	1	1	2	1000	1.017
991	428	2	1	1	1000	0.965
992	428	3	1	2	1000	1.044
993	428	4	1	2	1000	0.993
994	428	5	1	2	1000	0.971
995	428	6	1	1	1000	1.011
996	428	7	1	2	1000	0.928
997	428	8	1	2	1000	0.956
998	428	9	2		1000	
999	428	10	1	2	1000	1.069
1000	428	11	1	2	1000	0.935
1001	428	12	1	2	1000	0.982
1002	445	1	1	1	1000	0.889
1003	445	2	4		1000	
1004	445	3	1	2	1000	0.926
1005	445	4	1	1	1000	1.105
1006	445	5	1	1	1000	1.058

1007	445	6	1	2	1000	
1008	445	7	1	2	1000	1.039
1009	445	8	1	1	1000	1.067
1010	445	9	1	2	1000	0.983
1011	445	10	1	1	1000	1.056
1012	445	11	1	2	1000	0.977
1013	445	12	1	2	1000	0.975
1014	445	13	1	2	1000	0.993
1015	445	14	2		1000	
1016	445	15	1	2	1000	1.021
1017	445	16	1	2	1000	0.53
1018	445	17	1	1	1000	1.03

Some 6's were 8's and have been corrected for fetalwt
Animal 445 Pup 14 had status 2 and FetalSex=2 in report,
it was changed to FetalSex missing

1
2

Appendix 2. BMC Modeling for Acute ReV

2.1 Extragestational Weight Gain

```
================================================================================
            Polynomial Model. (Version: 2.12;  Date: 02/20/2007)
            Input Data File: C:\BMDS\MATERNAL TOXICITY\EXTRAGESTATIONAL WEIGHT
GAIN FOUR DOSES.(d)
            Gnuplot Plotting File:  C:\BMDS\MATERNAL TOXICITY\EXTRAGESTATIONAL
WEIGHT GAIN FOUR DOSES.plt
                                                      Fri Jun 15 12:02:13 2007
 ================================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = MEAN
   Independent variable = dose
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   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



                Default Initial Parameter Values
                      alpha =      2.84578
                        rho =            0   Specified
                     beta_0 =      7.46597
                     beta_1 =  -0.00778544
                     beta_2 = 6.23087e-006


          Asymptotic Correlation Matrix of Parameter Estimates
```

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

	alpha	beta_0	beta_1	beta_2
alpha	1	-1.4e-009	-4.1e-010	1.7e-010
beta_0	-1.4e-009	1	-0.7	0.64
beta_1	-4.1e-010	-0.7	1	-0.99
beta_2	1.7e-010	0.64	-0.99	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	2.71186	0.434246	1.86076	3.56297
beta_0	7.46083	0.307655	6.85783	8.06382
beta_1	-0.00772578	0.00307077	-0.0137444	-0.00170717
beta_2	6.17626e-006	2.89958e-006	4.93184e-007	1.18593e-005

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	18	7.6	7.46	2.04	1.65	0.359
40	19	6.99	7.16	1.66	1.65	-0.454
200	21	6.2	6.16	1.74	1.65	0.104
1000	20	5.91	5.91	1.25	1.65	-0.00354

Model Descriptions for likelihoods calculated

Model A1: $Yij = Mu(i) + e(ij)$
$Var\{e(ij)\} = Sigma^2$

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

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that
were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-77.734504	5	165.469009
A2	-75.503795	8	167.007591
A3	-77.734504	5	165.469009
fitted	-77.907806	4	163.815611
R	-83.514230	2	171.028460

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.0209	6	0.01364
Test 2	4.46142	3	0.2158
Test 3	4.46142	3	0.2158
Test 4	0.346603	1	0.556

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 greater than .1. A homogeneous variance
model appears to be appropriate here

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

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

Benchmark Dose Computation

Specified effect = 0.05

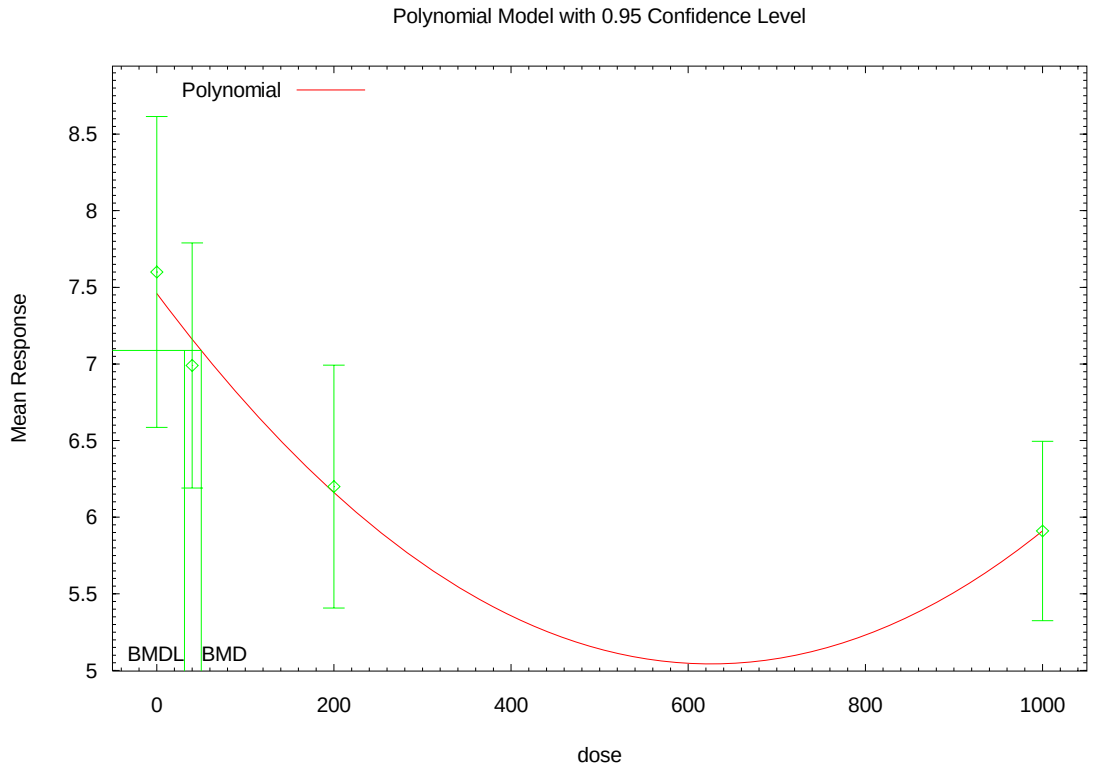
Risk Type = Relative risk

Confidence level = 0.95

BMD = 50.3086

BMDL = 31.2322

BMDL computation failed for one or more point on the BMDL curve. The BMDL curve will not be plotted



```
 1
 2   ================================================================================
 3              Hill Model. (Version: 2.12;  Date: 02/20/2007)
 4              Input Data File: C:\BMDS\ MATERNAL TOXICITY\EXTRAGESTATIONAL WEIGHT
 5   GAIN FOUR DOSES.(d)
 6              Gnuplot Plotting File:  C:\BMDS\ MATERNAL TOXICITY\EXTRAGESTATIONAL
 7   WEIGHT GAIN FOUR DOSES.plt
 8                                                        Fri Jun 15 12:47:56 2007
 9   ================================================================================
10
11   BMDS MODEL RUN
12   ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
13
14     The form of the response function is:
15
16     Y[dose] = intercept + v*dose^n/(k^n + dose^n)
17
18
19     Dependent variable = MEAN
20     Independent variable = dose
21     rho is set to 0
22     Power parameter restricted to be greater than 1
23     A constant variance model is fit
24
25     Total number of dose groups = 4
26     Total number of records with missing values = 0
27     Maximum number of iterations = 250
28     Relative Function Convergence has been set to: 1e-008
29     Parameter Convergence has been set to: 1e-008
30
31
32
33                  Default Initial Parameter Values
34                        alpha =      2.84578
35                          rho =            0   Specified
36                    intercept =          7.6
37                            v =        -1.69
38                            n =      1.31786
39                            k =      87.5949
40
41
42            Asymptotic Correlation Matrix of Parameter Estimates
43
44            ( *** The model parameter(s)  -rho
45                 have been estimated at a boundary point, or have been specified by the user,
46                 and do not appear in the correlation matrix )
47
```

	alpha	intercept	v	n	k
alpha	1	8.3e-010	1.9e-008	9.6e-009	-2.2e-008
intercept	8.3e-010	1	-0.59	-0.18	-0.38
v	1.9e-008	-0.59	1	0.7	-0.34
n	9.6e-009	-0.18	0.7	1	-0.4
k	-2.2e-008	-0.38	-0.34	-0.4	1

Parameter Estimates

		95.0% Wald Confidence Interval		
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
alpha	2.69984	0.43232	1.85251	3.54717
intercept	7.6	0.387287	6.84093	8.35907
v	-1.74522	0.695364	-3.1081	-0.382328
n	1.25583	1.43345	-1.55368	4.06534
k	65.593	66.7166	-65.1692	196.355

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	18	7.6	7.6	2.04	1.64	-5.18e-009
40	19	6.99	6.99	1.66	1.64	5.96e-008
200	21	6.2	6.2	1.74	1.64	1.8e-008
1000	20	5.91	5.91	1.25	1.64	-1.67e-007

Degrees of freedom for Test A3 vs fitted <= 0

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)

Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that
were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-77.734504	5	165.469009
A2	-75.503795	8	167.007591
A3	-77.734504	5	165.469009
fitted	-77.734504	5	165.469009
R	-83.514230	2	171.028460

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.0209	6	0.01364
Test 2	4.46142	3	0.2158
Test 3	4.46142	3	0.2158
Test 4	5.68434e-014	0	NA

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 greater than .1. A homogeneous variance
model appears to be appropriate here

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

NA - Degrees of freedom for Test 4 are less than or equal to 0. The Chi-Square test for fit is not valid

Benchmark Dose Computation

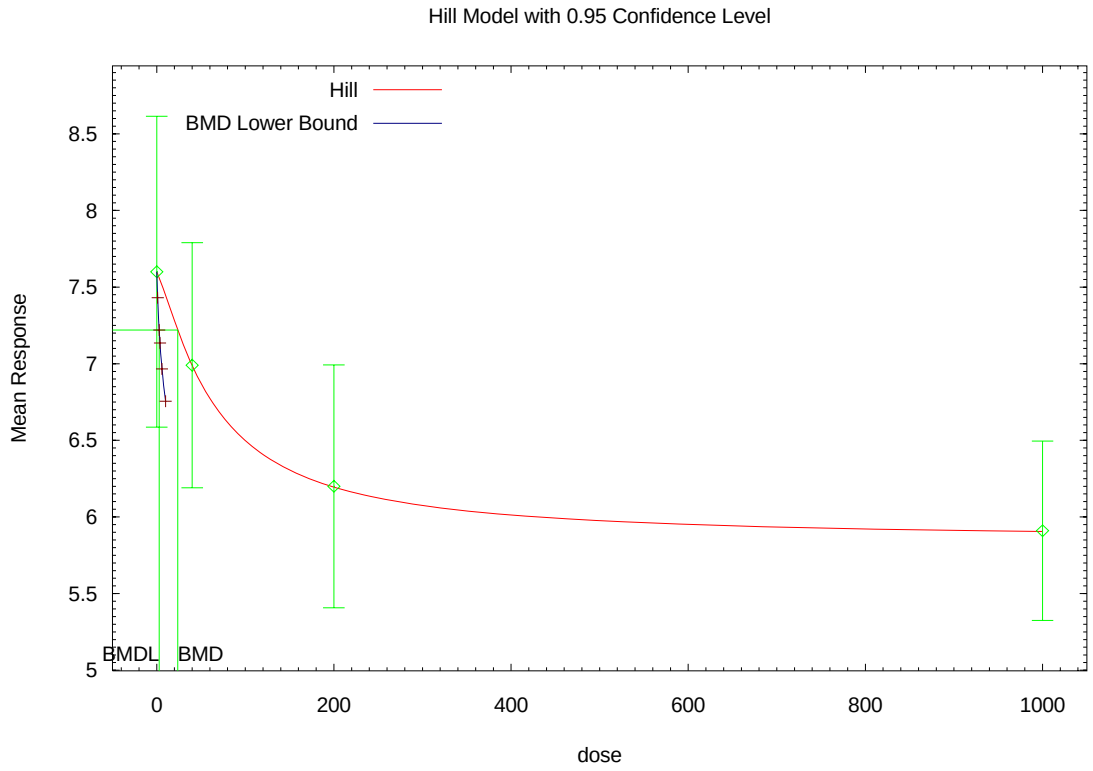
Specified effect = 0.05

Risk Type = Relative risk

Confidence level = 0.95

BMD = 23.6911

BMDL = 2.8111



12:47 06/15 2007

```
 1
 2   ================================================================
 3              Polynomial Model. (Version: 2.12;  Date: 02/20/2007)
 4              Input Data File: C:\BMDS\ MATERNAL TOXICITY\EXTRAGESTATIONAL WEIGHT
 5   GAIN THREE DOSES.(d)
 6              Gnuplot Plotting File:  C:\BMDS\ MATERNAL TOXICITY\EXTRAGESTATIONAL
 7   WEIGHT GAIN THREE DOSES.plt
 8                                                    Fri Jun 15 13:14:35 2007
 9   ================================================================
10
11   BMDS MODEL RUN
12   ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
13
14     The form of the response function is:
15
16     Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...
17
18
19     Dependent variable = MEAN
20     Independent variable = dose
21     rho is set to 0
22     Signs of the polynomial coefficients are not restricted
23     A constant variance model is fit
24
25     Total number of dose groups = 3
26     Total number of records with missing values = 0
27     Maximum number of iterations = 250
28     Relative Function Convergence has been set to: 1e-008
29     Parameter Convergence has been set to: 1e-008
30
31
32
33                 Default Initial Parameter Values
34                       alpha =      3.28909
35                         rho =            0   Specified
36                      beta_0 =          7.6
37                      beta_1 =   -0.0173125
38                      beta_2 = 5.15625e-005
39
40
41           Asymptotic Correlation Matrix of Parameter Estimates
42
43           ( *** The model parameter(s)  -rho
44                have been estimated at a boundary point, or have been specified by the user,
45                and do not appear in the correlation matrix )
46
47                  alpha       beta_0       beta_1       beta_2
```

alpha	1	-4.5e-008	9.1e-009	3.8e-009
beta_0	-4.5e-008	1	-0.7	0.63
beta_1	9.1e-009	-0.7	1	-0.99
beta_2	3.8e-009	0.63	-0.99	1

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
alpha	3.11897	0.579177	1.9838	4.25413
beta_0	7.6	0.416264	6.78414	8.41586
beta_1	-0.0173125	0.0177901	-0.0521805	0.0175555
beta_2	5.15625e-005	8.28263e-005	-0.000110774	0.000213899

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	18	7.6	7.6	2.04	1.77	2.42e-007
40	19	6.99	6.99	1.66	1.77	1.56e-007
200	21	6.2	6.2	1.74	1.77	-3.67e-007

Degrees of freedom for Test A3 vs fitted <= 0

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that

were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-61.987540	4	131.975080
A2	-61.553857	6	135.107715
A3	-61.987540	4	131.975080
fitted	-61.987540	4	131.975080
R	-64.921732	2	133.843464

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	6.73575	4	0.1505
Test 2	0.867366	2	0.6481
Test 3	0.867366	2	0.6481
Test 4	5.82645e-013	0	NA

The p-value for Test 1 is greater than .05. There may not be a
diffence between responses and/or variances among the dose levels
Modelling the data with a dose/response curve may not be appropriate

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

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

NA - Degrees of freedom for Test 4 are less than or equal to 0. The Chi-Square
test for fit is not valid

Benchmark Dose Computation

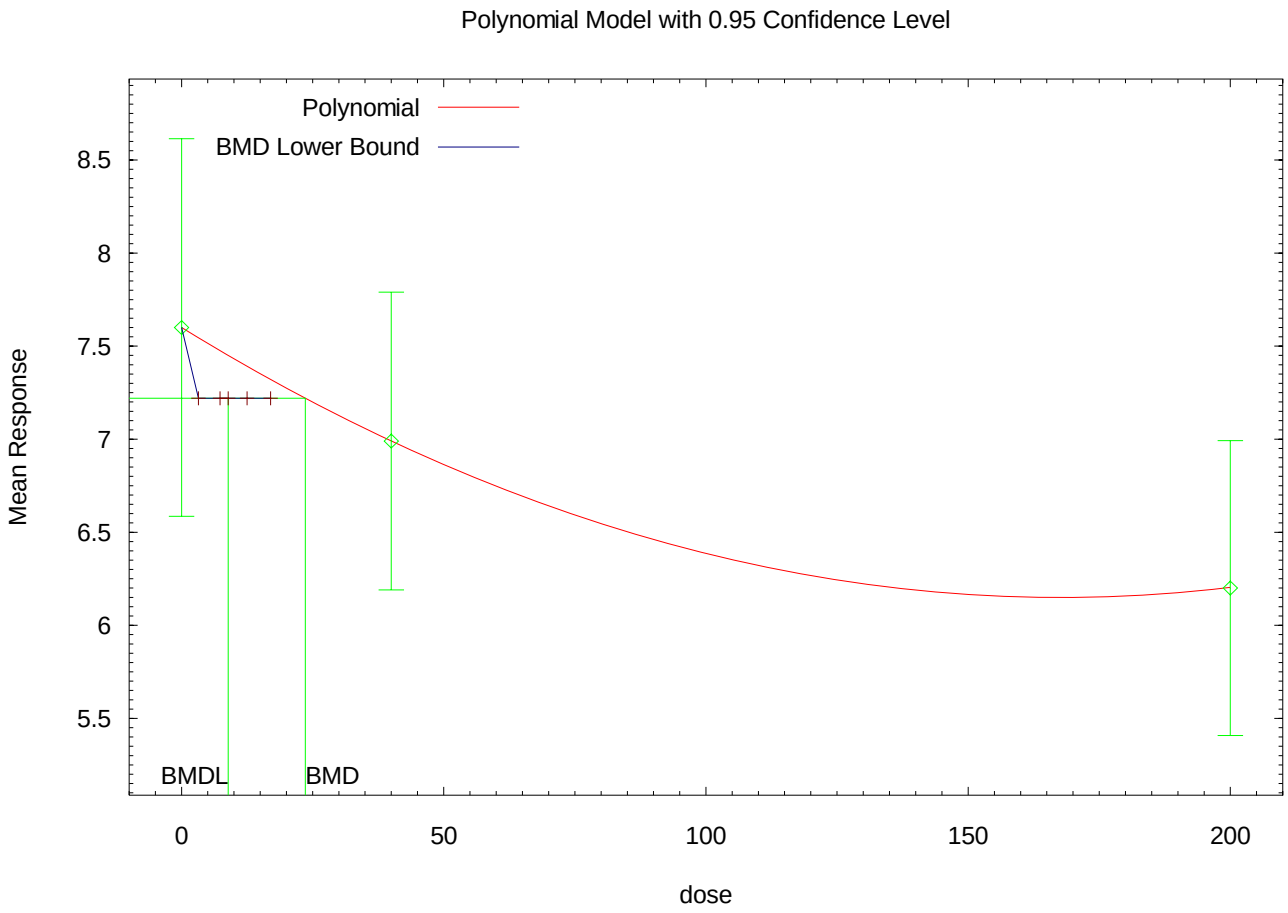
Specified effect = 0.05

Risk Type = Relative risk

Confidence level = 0.95

BMD = 23.6096

BMDL = 8.90895



13:14 06/15 2007

2.2 Body Weight Gain (GD 11-16)

```
 ================================================================================
            Polynomial Model. (Version: 2.12;  Date: 02/20/2007)
            Input Data File: C:\BMDS\MATERNAL TOXICITY\BODYWEIGHT GAIN GD11-16 FOUR
DOSES.(d)
            Gnuplot Plotting File:  C:\BMDS\ MATERNAL TOXICITY\BODYWEIGHT GAIN GD11-16
FOUR DOSES.plt
                                                        Fri Jun 15 10:27:22 2007
 ================================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

   Dependent variable = MEAN
   Independent variable = Dose
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   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

              Default Initial Parameter Values
                    alpha =      4.47026
                      rho =            0   Specified
                   beta_0 =      13.2228
                   beta_1 =   -0.0108878
                   beta_2 =  8.2658e-006


        Asymptotic Correlation Matrix of Parameter Estimates

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

              alpha       beta_0       beta_1       beta_2
```

alpha	1	-5.8e-010	-6.2e-009	6.3e-009
beta_0	-5.8e-010	1	-0.7	0.64
beta_1	-6.2e-009	-0.7	1	-0.99
beta_2	6.3e-009	0.64	-0.99	1

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
alpha	4.245	0.679745	2.91273	5.57728
beta_0	13.2198	0.384919	12.4654	13.9743
beta_1	-0.0108534	0.00384196	-0.0183835	-0.00332333
beta_2	8.23434e-006	3.62777e-006	1.12404e-006	1.53446e-005

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	18	13.3	13.2	2.55	2.06	0.165
40	19	12.7	12.8	1.74	2.06	-0.209
200	21	11.4	11.4	2.29	2.06	0.0478
1000	20	10.6	10.6	1.79	2.06	-0.00163

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that
were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-95.347306	5	200.694612
A2	-93.364104	8	202.728208
A3	-95.347306	5	200.694612
fitted	-95.383968	4	198.767936
R	-104.387527	2	212.775055

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	22.0468	6	0.001187
Test 2	3.9664	3	0.2651
Test 3	3.9664	3	0.2651
Test 4	0.073324	1	0.7866

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 greater than .1. A homogeneous variance
model appears to be appropriate here

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

The p-value for Test 4 is greater than .1. The model chosen seems
to adequately describe the data

Benchmark Dose Computation

Specified effect = 0.05

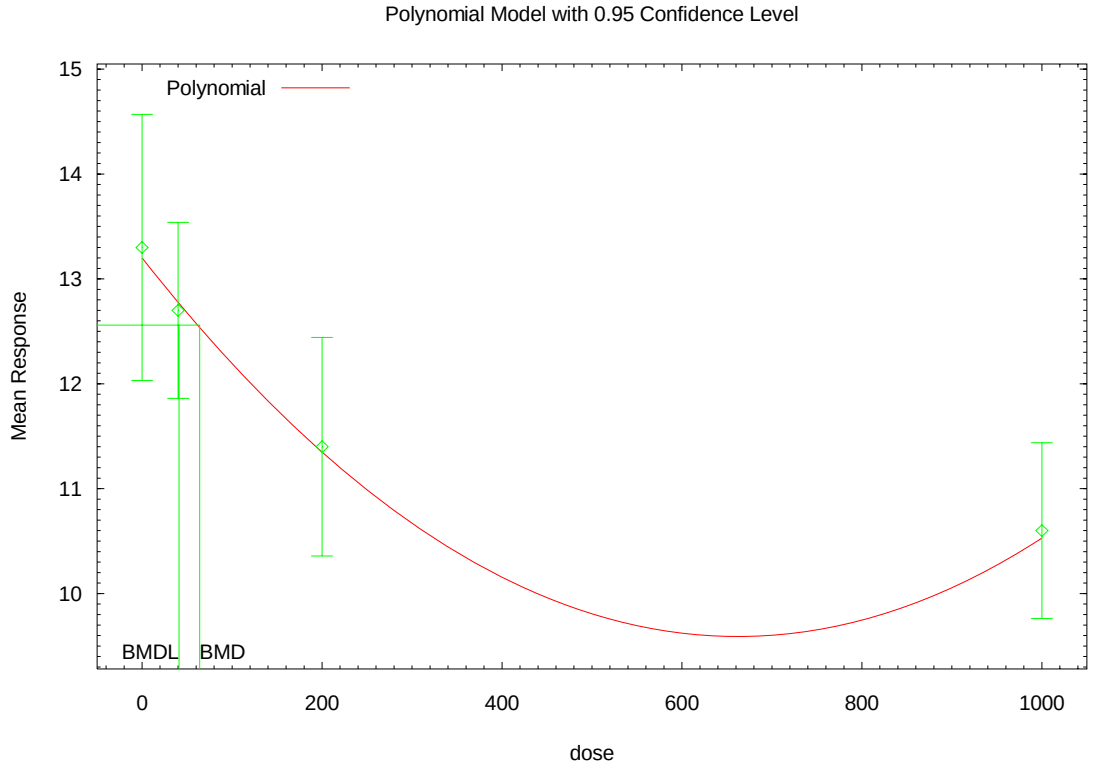
Risk Type = Relative risk

Confidence level = 0.95

BMD = 64.0102

BMDL = 40.9875

BMDL computation failed for one or more point on the BMDL curve.
The BMDL curve will not be plotted



10:27 06/15 2007

```
 1
 2
 3  ================================================================
 4            Hill Model. (Version: 2.12;  Date: 02/20/2007)
 5            Input Data File: C:\BMDS\MATERNAL TOXICITY\BODYWEIGHT GAIN GD11-16 FOUR
 6  DOSES.(d)
 7            Gnuplot Plotting File:  C:\BMDS\ MATERNAL TOXICITY\BODYWEIGHT GAIN GD11-16
 8  FOUR DOSES.plt
 9                                                  Fri Jun 15 10:38:57 2007
10  ================================================================
11
12  BMDS MODEL RUN
13  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
14
15    The form of the response function is:
16
17    Y[dose] = intercept + v*dose^n/(k^n + dose^n)
18
19
20    Dependent variable = MEAN
21    Independent variable = Dose
22    rho is set to 0
23    Power parameter restricted to be greater than 1
24    A constant variance model is fit
25
26    Total number of dose groups = 4
27    Total number of records with missing values = 0
28    Maximum number of iterations = 250
29    Relative Function Convergence has been set to: 1e-008
30    Parameter Convergence has been set to: 1e-008
31
32
33
34                 Default Initial Parameter Values
35                       alpha =     4.47026
36                         rho =           0   Specified
37                   intercept =        13.3
38                           v =        -2.7
39                           n =     1.57036
40                           k =     132.308
41
42
43            Asymptotic Correlation Matrix of Parameter Estimates
44
45            ( *** The model parameter(s)  -rho
46                 have been estimated at a boundary point, or have been specified by the user,
47                 and do not appear in the correlation matrix )
```

	alpha	intercept	v	n	k
alpha	1	4.2e-009	2.8e-008	9.6e-009	-3.2e-008
intercept	4.2e-009	1	-0.59	-0.38	-0.32
v	2.8e-008	-0.59	1	0.77	-0.44
n	9.6e-009	-0.38	0.77	1	-0.37
k	-3.2e-008	-0.32	-0.44	-0.37	1

Parameter Estimates

		95.0% Wald Confidence Interval		
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
alpha	4.24102	0.679106	2.90999	5.57204
intercept	13.3	0.485399	12.3486	14.2514
v	-2.89296	1.05232	-4.95547	-0.830463
n	1.2362	1.02244	-0.767751	3.24015
k	118.32	98.6055	-74.9435	311.583

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	18	13.3	13.3	2.55	2.06	-2.61e-008
40	19	12.7	12.7	1.74	2.06	3.18e-008
200	21	11.4	11.4	2.29	2.06	5e-008
1000	20	10.6	10.6	1.79	2.06	-2.63e-007

Degrees of freedom for Test A3 vs fitted <= 0

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that
were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-95.347306	5	200.694612
A2	-93.364104	8	202.728208
A3	-95.347306	5	200.694612
fitted	-95.347306	5	200.694612
R	-104.387527	2	212.775055

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	22.0468	6	0.001187
Test 2	3.9664	3	0.2651
Test 3	3.9664	3	0.2651
Test 4	2.84217e-013	0	NA

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 greater than .1. A homogeneous variance
model appears to be appropriate here

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

NA - Degrees of freedom for Test 4 are less than or equal to 0. The Chi-Square test for fit is not valid

Benchmark Dose Computation

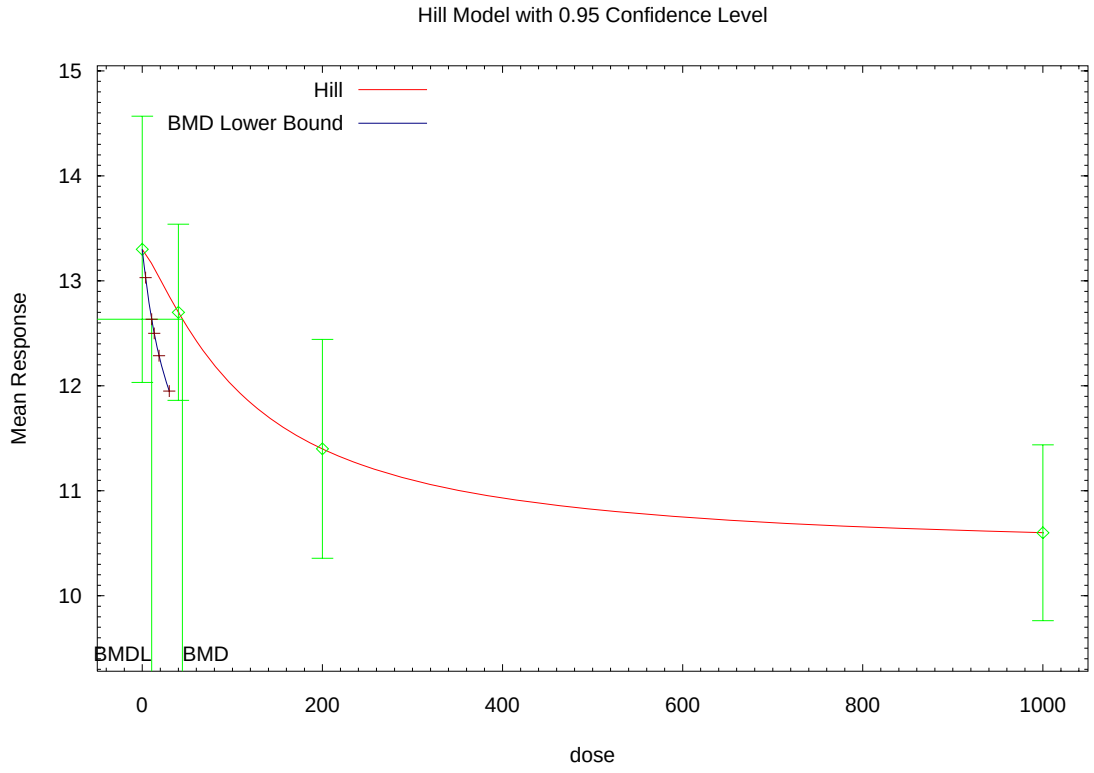
Specified effect = 0.05

Risk Type = Relative risk

Confidence level = 0.95

BMD = 44.4937

BMDL = 10.3097



```
 1
 2
 3   ================================================================
 4              Polynomial Model. (Version: 2.12;  Date: 02/20/2007)
 5              Input Data File: C:\BMDS\ MATERNAL TOXICITY\BODYWEIGHT GAIN GD11-16
 6   THREE DOSES.(d)
 7              Gnuplot Plotting File:  C:\BMDS\ MATERNAL TOXICITY\BODYWEIGHT GAIN GD11-16
 8   THREE DOSES.plt
 9                                                      Fri Jun 15 13:34:32 2007
10   ================================================================
11
12   BMDS MODEL RUN
13   ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
14
15     The form of the response function is:
16
17     Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...
18
19
20     Dependent variable = MEAN
21     Independent variable = Dose
22     rho is set to 0
23     Signs of the polynomial coefficients are not restricted
24     A constant variance model is fit
25
26     Total number of dose groups = 3
27     Total number of records with missing values = 0
28     Maximum number of iterations = 250
29     Relative Function Convergence has been set to: 1e-008
30     Parameter Convergence has been set to: 1e-008
31
32
33
34                  Default Initial Parameter Values
35                        alpha =      4.90766
36                          rho =            0   Specified
37                       beta_0 =         13.3
38                       beta_1 =    -0.016375
39                       beta_2 =  3.4375e-005
40
41
42             Asymptotic Correlation Matrix of Parameter Estimates
43
44             ( *** The model parameter(s)  -rho
45                  have been estimated at a boundary point, or have been specified by the user,
46                  and do not appear in the correlation matrix )
47
```

	alpha	beta_0	beta_1	beta_2
alpha	1	-4e-010	9.1e-011	1.8e-011
beta_0	-4e-010	1	-0.7	0.63
beta_1	9.1e-011	-0.7	1	-0.99
beta_2	1.8e-011	0.63	-0.99	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	4.65382	0.864192	2.96003	6.3476
beta_0	13.3	0.508474	12.3034	14.2966
beta_1	-0.016375	0.0217309	-0.0589669	0.0262169
beta_2	3.4375e-005	0.000101174	-0.000163922	0.000232672

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	18	13.3	13.3	2.55	2.16	2.16e-009
40	19	12.7	12.7	1.74	2.16	1.33e-009
200	21	11.4	11.4	2.29	2.16	-3.03e-009

Degrees of freedom for Test A3 vs fitted <= 0

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A3 uses any fixed variance parameters that
were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-73.592935	4	155.185871
A2	-72.232725	6	156.465449
A3	-73.592935	4	155.185871
fitted	-73.592935	4	155.185871
R	-77.344372	2	158.688744

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	10.2233	4	0.03683
Test 2	2.72042	2	0.2566
Test 3	2.72042	2	0.2566
Test 4	0	0	NA

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 greater than .1. A homogeneous variance
model appears to be appropriate here

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

NA - Degrees of freedom for Test 4 are less than or equal to 0. The Chi-Square

test for fit is not valid

Benchmark Dose Computation

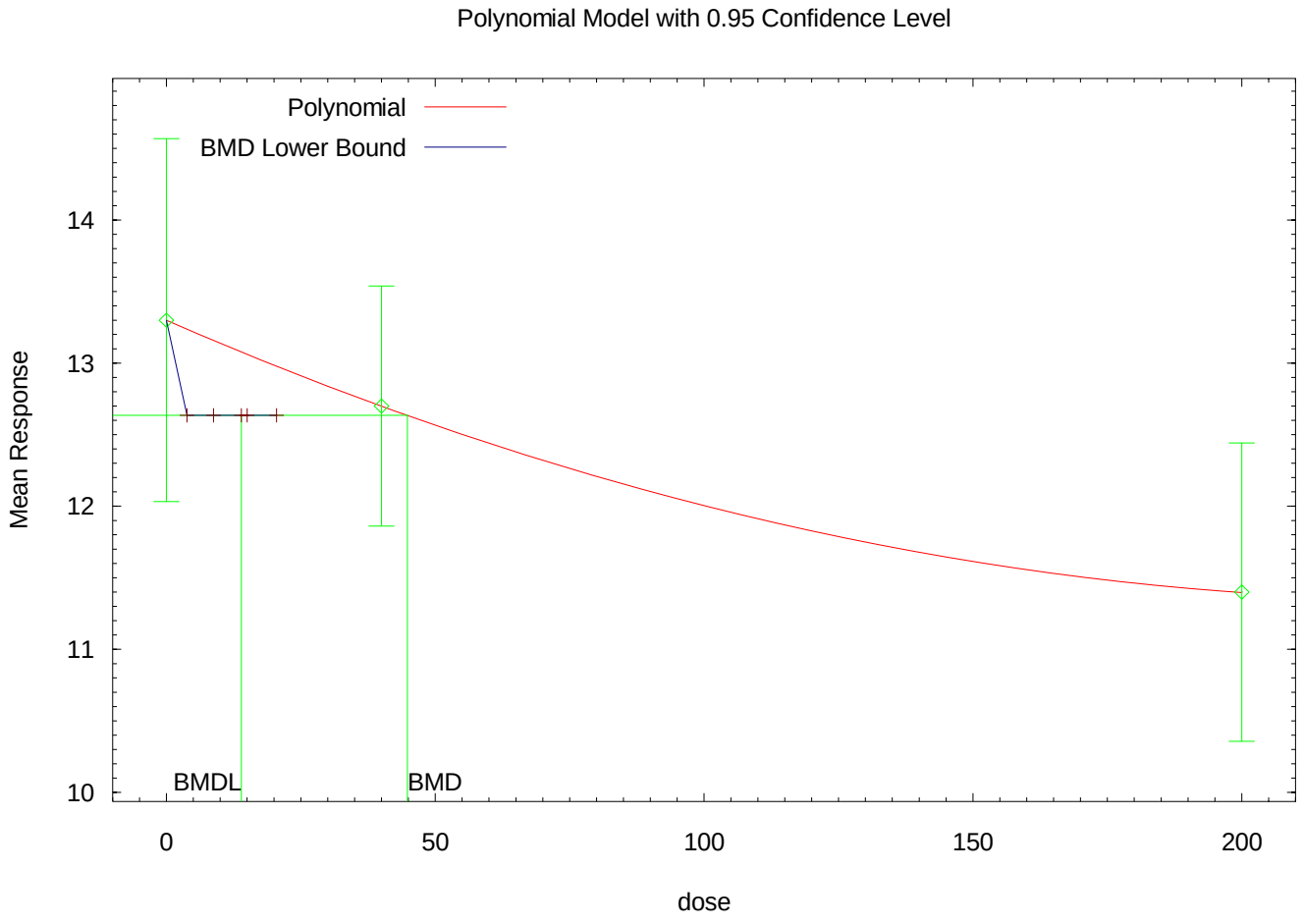
Specified effect = 0.05

Risk Type = Relative risk

Confidence level = 0.95

BMD = 44.8295

BMDL = 13.9502



13:34 06/15 2007

Appendix 3. Statistical Analyses of Reproductive Endpoints

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August 6, 2007

TCEQ Contract 582-7-81521

EPA's 2002 final risk assessment for BD (USEPA. 2002. Health Assessment of 1,3-Butadiene. EPA/600/P-98/001F) derived a reference concentration using the ovarian atrophy in female mice exposed to butadiene via inhalation. This animal study was conducted by the NTP in 1993 (NTP. 1993. Toxicology and carcinogenesis studies of 1,3-butadiene (CAS No. 106-99-0) in B6C3F1 mice (inhalation studies). Research Triangle Park, NC: National Toxicology Program, U.S. Public Health Service, U.S. Department of Health and Human Services. TR 434). EPA used a Weibull time-to-tumor dose-response model to fit the time-to-ovarian atrophy data and excluded the highest dose group because of excessive early mortality. The ECs and LECs for ovarian atrophy were calculated at an equivalent human age of 50 years "to reflect only the time before average age at menopause when follicles are no longer present and available for ovulation, because in the mouse studies of ovarian atrophy, the atrophy occurs as a result of follicular failure."

In the NTP 1993 critical study, female mice were exposed to 0, 6.25, 20, 62.5, 200, or 625 ppm BD for 6 hours/day, 5 days/week for two years (i.e., equivalent to 0, 1.12, 3.57, 11.2, 35.7, and 111.6 ppm BD of continuous exposure – for example, $6.25 \times (5/7) \times (6/24) = 1.12$). The air concentration 6.25 ppm was identified as a LOAEL for ovarian atrophy. The final 2002 EPA's risk assessment for BD reports several analyses of these data, including application of a log-logistic model, a quantal Weibull model, and a Weibull time-to-response model.

The final Weibull time-to-response model that EPA used is linear in dose with time raised to a power. EPA used TOX_RISK version 3.5 (Crump et al., ICF Kaiser International, Ruston, LA) for the model fitting and the estimation of the ECs and LECs. In February 2006, the Olefins Panel of the American Chemistry Council asked the Sapphire Group, Inc. to recalculate EPA's ECs and LECs for ovarian atrophy (Kirman, C. R. and M. L. Gargas. 2006. Benchmark Dose Analyses for Reproductive and Developmental Endpoints for 1,3-Butadiene, Submitted to Olefins Panel, American Chemistry Council, Arlington, VA, February 2006). The Sapphire Group, Inc.'s report included the time-to-response data for ovarian atrophy of the NTP 1993 study, and those data are reproduced here in Attachment A.

Sielken & Associates Consulting, Inc. reanalyzed the ovarian atrophy data using the Weibull time-to-response model and the data presented in Attachment A. The linear Weibull time-to-response model had the following form:

Probability of a response (ovarian atrophy) by week T at dose d =
$$1 - \exp \{ - [Q_0 + Q_1 \times d] \times T^Z \}.$$

Tables 1 and 2 list the results of the analyses when the highest exposure group is not included in the estimation of the model and when all exposure groups are included, respectively. The results labeled SA# were calculated using Sielken & Associates, Inc.'s GEN.T software package – however, Sielken & Associates verified that the parameter estimates are identical to those estimated with TOX_RISK version 3.5. The LEC_{10} values for the SA# analyses in the table were estimated using 99 simulated bootstrap data sets. The two analyses in addition to EPA's analyses included in Tables 1 and 2 are:

1) Analysis SA1 parallels the analysis performed by EPA. The small discrepancies between the SA1 and EPA analyses may be due to assumptions that EPA may have made and did not describe in their report.

2) Analysis SA2 uses a modified data set in which all animals that lived beyond age 521 days (74.3 weeks – which is equivalent to 50 years in a 70-year human lifetime -- (50/70) × 104 weeks) were excluded from the parameter estimation.

In Tables 1 and 2, the range of EC_{10} values derived by EPA, SA1, and SA2 analyses is 1.05 to 1.25 ppm whereas the range of the LEC_{10} values derived by EPA, SA1, and SA2 analyses is 0.768 to 0.958 ppm.

Table 1 and 2 also show the results for concentrations corresponding to an extra risk of 0.05. Because the Weibull time-to-tumor model in these analyses is linear in dose, the EC_{05} and LEC_{05} values are approximately half the corresponding EC_{10} and LEC_{10} values.

Table 1. Parameters (Q_0, Q_1, and Z) for Weibull time-to-response model for ovarian atrophy and corresponding human benchmark 1,3-butadiene exposure concentrations for extra risks of 0.1 and 0.05 at 50 years of age using different methods of calculation – **excluding** the highest dose group

Analysis	Q_0	Q_1	Z	EC_{10}	LEC_{10}	EC_{05}	LEC_{05}
EPA	4.86×10^{-6}	7.06×10^{-6}	2.21	1.05	0.878	n/a	n/a
SA1	6.96×10^{-6}	8.62×10^{-6}	2.15	1.15	0.881	0.560	0.429
SA2	6.76×10^{-23}	6.90×10^{-5}	1.66	1.18	0.768	0.573	0.374

Table 2. Parameters for Weibull time-to-response model for ovarian atrophy and corresponding human benchmark 1,3-butadiene exposure concentrations for extra risks of 0.1 and 0.05 at 50 years of age using different methods of calculation – **including** the highest dose group

Analysis	Q_0	Q_1	Z	EC_{10}	LEC_{10}	EC_{05}	LEC_{05}
EPA	9.01×10^{-6}	1.32×10^{-6}	2.58	1.13	0.958	n/a	n/a
SA1	1.68×10^{-6}	2.04×10^{-6}	2.47	1.25	0.949	0.607	0.462
SA2	3.61×10^{-25}	1.95×10^{-6}	2.49	1.17	0.812	0.569	0.396

The estimated values of EC_{10} and LEC_{10} are close to the lowest experimental dose (1.12 ppm) while the values of EC_{05} and LEC_{05} are approximately half way between the lowest experimental dose and zero. The values of EC_{05} and LEC_{05} can be used if the dose-response relationship below the lowest experimental dose is believed to be the linear Weibull time-to-response model fit to the data. The assumption of linearity below the lowest experimental dose is usually conservative and, therefore, health protective. However, the motivation behind the benchmark dose methodology is to identify the point of departure (EC or LEC) to be within the range of the experimental data (the range of the non-zero doses in the experimental data) and to be a dose whose risk can be reasonably reliably estimated without undue sensitivity to the dose-response model selected or the model estimation. Here, the EC_{05} and LEC_{05} in the SA1 and SA2 analyses are below the range of the experimental data and, hence, introduce an additional element of uncertainty into the point of departure.

The EPA and SA1 analyses include ovarian atrophy responses beyond the equivalent of age 50 years in humans. These older-age responses in mice may not be relevant to humans and may inappropriately impact the fitted dose-response model used to estimate the risk at age 50. SA2 eliminates all animals that lived beyond the equivalent of age 50. However, it is known that some of these animals did not have an observed response (ovarian atrophy) and this information is ignored/lost and not incorporated into the dose-response modeling as it should be. The fitted models for all the mice (analyses SA1) are very similar to the fitted models for only mice that died on or before week 74.3 (analyses SA2). This suggests that the older-age animals in the SA1 analyses are not distorting those analyses. Therefore, the results for analyses SA1 are preferable to the SA2 analyses because the SA1 analyses include more data (i.e., mice that lived past 74.3 weeks) and the inclusion of mice older than 74.3 weeks does not distort the fit of the model. In other words, the models fit to either all the mice (analyses SA1) or only to mice that died on or before week 74.3 are (analyses SA2) very similar but the confidence limits for analyses SA1 are more reliable because they are based on more animals.

The ovarian atrophy data were analyzed excluding the highest dose group (Table 1) and also including all the data (Table 2). The analyses that exclude the high dose were performed to parallel those analyses used by EPA. Traditionally, EPA drops the highest dose group when the model does not fit the data well due to some biological phenomenon or when quantal data are fit with a quantal model and there is high mortality in the highest dose group. The ovarian atrophy data, however, were modeled with a time-to-response model (i.e., a model that accounts for the time of death) as opposed to a quantal model which do not account for time of death. Furthermore, the model fit to the data that excluded the highest dose group was not better than the model fit to the data that included the highest dose group. Figure 1 shows the fit of analysis SA1 to the lower four dose groups and the control group while Figure 2 shows the fit of analysis SA1 to all dose groups and the control group.

In summary, the SA1 analysis in Table 2 that includes all the exposure groups and all animals in each exposure group is the most statistically sound analysis of the ovarian atrophy study because: 1) the model fit using all animals is similar to the model fit using only animals that died on or before 74.3 weeks of age, 2) the model fit using all dose groups is similar to the model fit to only the four lowest dose groups, and 3) using all the data results in more reliable maximum likelihood estimates and corresponding confidence limits.

Figure 1. Observed versus multistage-Weibull model predicted proportions of mice with ovarian atrophy when only the four lowest dose groups and the control group are used to fit the model

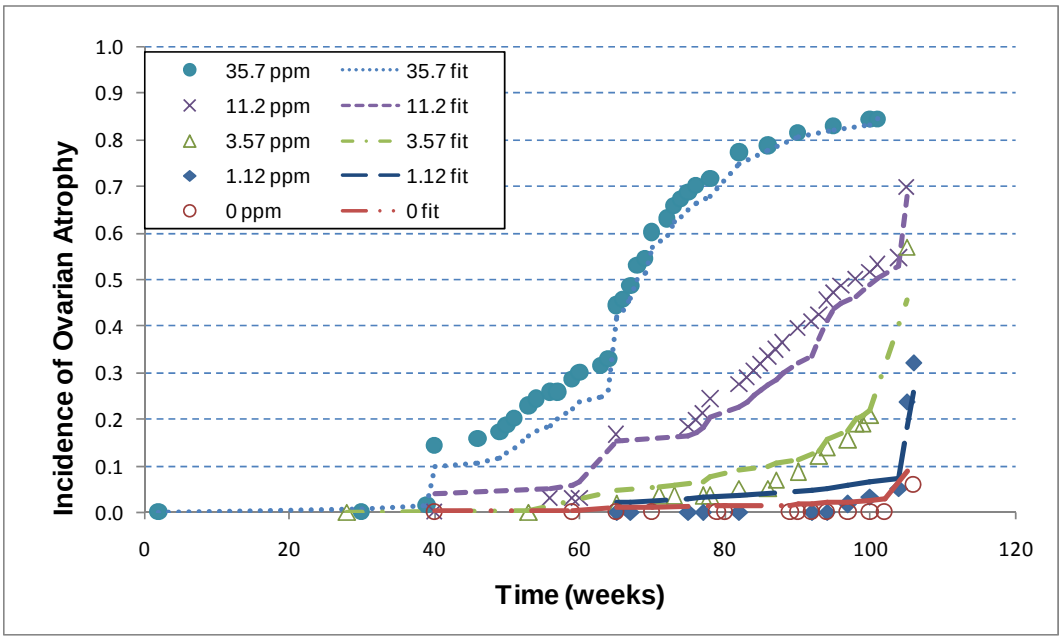
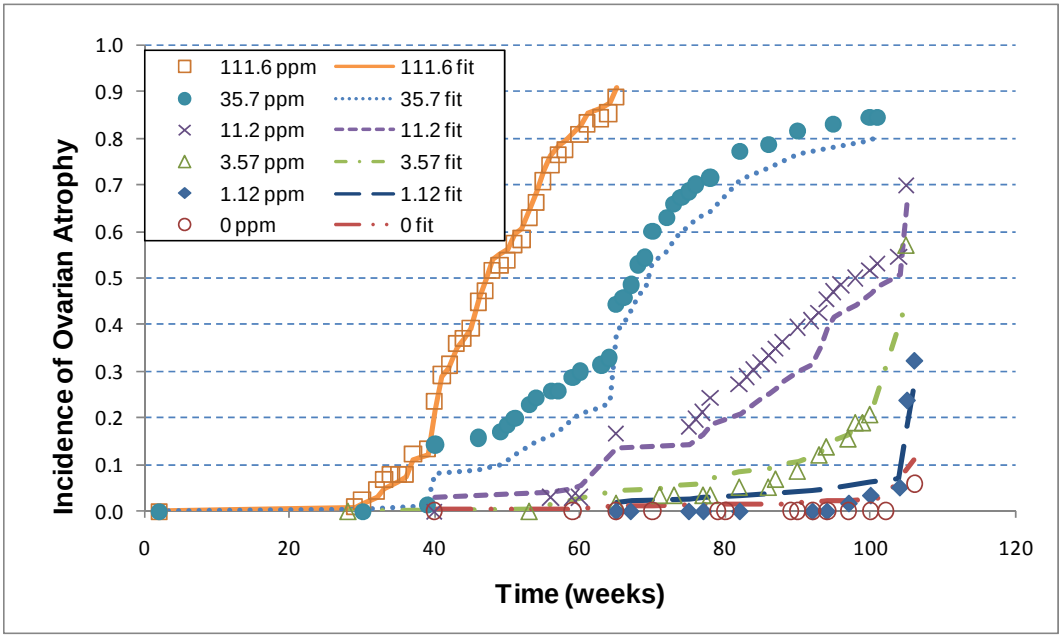


Figure 2. Observed versus multistage-Weibull model predicted proportions of mice with ovarian atrophy when all five dose groups and the control group are used to fit the model.



Attachment A

Time-to-response for ovarian atrophy as reported by the Sapphire Group, Inc. of the NTP 1993 study (NTP. 1993. Toxicology and carcinogenesis studies of 1,3-butadiene (CAS No. 106-99-0) in B6C3F1 mice (inhalation studies). Research Triangle Park, NC: National Toxicology Program, U.S. Public Health Service, U.S. Department of Health and Human Services. TR 434).

Concentration (ppm)	Responders	Non-Responders	n	Day	Week
0	0	10	10	280	40
0	0	1	1	413	59
0	0	10	10	455	65
0	0	1	1	490	70
0	0	1	1	553	79
0	0	1	1	560	80
0	0	1	1	623	89
0	0	1	1	630	90
0	0	1	1	644	92
0	0	1	1	658	94
0	0	1	1	679	97
0	0	1	1	700	100
0	0	3	3	714	102
0	4	32	36	742	106
6.25	0	10	10	455	65
6.25	0	1	1	469	67
6.25	0	2	2	525	75
6.25	0	1	1	539	77
6.25	0	1	1	574	82
6.25	0	3	3	644	92
6.25	0	1	1	658	94
6.25	1	0	1	679	97
6.25	1	1	2	700	100
6.25	1	0	1	728	104
6.25	11	10	21	735	105
6.25	5	10	15	742	106
20	0	1	1	196	28
20	0	1	1	371	53
20	1	9	10	455	65
20	1	0	1	497	71
20	0	1	1	511	73
20	0	1	1	539	77

20	0	2	2	546	78
20	1	1	2	574	82
20	0	1	1	602	86
20	1	0	1	609	87
20	1	0	1	630	90
20	2	0	2	651	93
20	1	2	3	658	94
20	1	1	2	679	97
20	2	1	3	686	98
20	0	1	1	693	99
20	1	0	1	700	100
20	21	3	24	735	105
62.5	0	10	10	280	40
62.5	2	0	2	392	56
62.5	0	1	1	413	59
62.5	0	1	1	420	60
62.5	9	1	10	455	65
62.5	1	0	1	525	75
62.5	1	0	1	532	76
62.5	1	0	1	539	77
62.5	2	0	2	546	78
62.5	2	0	2	574	82
62.5	1	0	1	581	83
62.5	1	0	1	588	84
62.5	1	0	1	595	85
62.5	1	0	1	602	86
62.5	1	0	1	609	87
62.5	1	0	1	616	88
62.5	2	0	2	630	90
62.5	1	0	1	644	92
62.5	1	2	3	651	93
62.5	2	1	3	658	94
62.5	1	1	2	665	95
62.5	1	0	1	672	96
62.5	1	0	1	686	98
62.5	1	1	2	700	100
62.5	1	0	1	707	101
62.5	1	1	2	728	104
62.5	10	1	11	735	105

200	0	1	1	14	2
200	0	1	1	210	30
200	1	0	1	2733*	390.4286
200	9	1	10	280	40
200	1	0	1	322	46
200	1	0	1	343	49
200	1	0	1	350	50
200	1	0	1	357	51
200	2	0	2	371	53
200	1	0	1	378	54
200	1	0	1	392	56
200	0	1	1	399	57
200	2	0	2	413	59
200	1	0	1	420	60
200	1	0	1	441	63
200	1	0	1	448	64
200	8	4	12	455	65
200	1	0	1	462	66
200	2	0	2	469	67
200	3	0	3	476	68
200	1	0	1	483	69
200	4	0	4	490	70
200	2	0	2	504	72
200	2	0	2	511	73
200	1	0	1	518	74
200	1	0	1	525	75
200	1	0	1	532	76
200	1	0	1	546	78
200	4	1	5	574	82
200	1	1	2	602	86
200	2	0	2	630	90
200	1	0	1	665	95
200	1	0	1	700	100
200	0	1	1	707	101
625	0	1	1	14	2
625	1	0	1	203	29
625	1	0	1	210	30
625	2	0	2	224	32
625	2	0	2	231	33

625	1	0	1	238	34
625	0	1	1	245	35
625	0	1	1	252	36
625	4	0	4	259	37
625	1	0	1	273	39
625	9	1	10	280	40
625	5	2	7	287	41
625	2	0	2	294	42
625	4	0	4	301	43
625	1	1	2	308	44
625	2	0	2	315	45
625	5	1	6	322	46
625	2	2	4	329	47
625	4	0	4	336	48
625	1	0	1	343	49
625	1	0	1	350	50
625	3	0	3	357	51
625	1	0	1	364	52
625	4	0	4	371	53
625	3	0	3	378	54
625	4	0	4	385	55
625	3	0	3	392	56
625	2	0	2	399	57
625	1	0	1	406	58
625	3	0	3	420	60
625	2	0	2	427	61
625	1	0	1	441	63
625	1	0	1	448	64
625	3	0	3	455	65

***2733 was replaced by 273 in our analyses**

Appendix 4. Cox Proportional Hazards Models Not Included in Cheng et al. (2007)

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Cheng et al. presented several analyses with the objective of showing different alternatives they thought could be relevant. For example, they restricted the analyses to include only cumulative ppm-years, average intensity or lagged cumulative ppm-years as the relevant doses. There is no evidence that any of these measures of dose is the relevant dose. They also fit models that adjusted for race, year of birth, race, years since hire, plant and number of high intensity tasks (HITs) and exposures to DMDTC. Cheng et al. did not give any biological reasons to include or exclude from the model. Ideally, the final model should adjust for effects that are biologically relevant to the outcome of study. However, there is not enough scientific knowledge to indicate what, if any, covariate effects should be included in a model of leukemia mortality with cumulative exposure to butadiene. The research closest to shedding some light on which covariates to include in the model is that published by Albertini et al. (2007), which seems to indicate that leukemia does not occur at low exposure to butadiene.

Although the decision of whether or not to adjust for a confounder should ideally be based on biological knowledge, Sielken et al. (2007) adjustment for confounders was determined using a statistically-based approach. The use of statistical methodology instead of biological arguments serves for the purpose of corroborating new biological evidence about possible confounders – specifically the role of the number of high intensity tasks in leukemia rate ratios. That is, the inclusion of the number of HITs as a covariate, although based on statistical arguments, was consistent with the biological findings of Albertini et al. (2007). In other words, not only was the number of HITs a plausible explanation of the increase in the number of leukemia deaths from a biological and mechanistic standpoint but also the statistical analysis of the data reached the same conclusion. Other attributes to see in model selection are issues like: consistency with biological expectations (i.e., the model should make biological sense), model parsimony (i.e., include as few variables as necessary to explain the relationship when there is no sufficient biological knowledge to justify the inclusion or exclusion of a variable), etc.

Cheng et al. (2007) presented a model that adjusts for age and the number of HITs (BD peaks). That is, $\beta = 2.5\times10{-}4$, $p = 0.03$ presented in Section 3.5 of the Cheng et al. (2007) paper. This results in a S.E. of $1.2\times10{-}4$. This model is close to the Poisson regression model in the Sielken et al. (2007) paper with the

exceptions that: 1) Sielken et al. adjusted for the number of HITs using a nonparametric relation based on quintiles whereas Cheng et al. adjusted for the number of HITs using a parametric linear relationship, 2) Cheng et al. models assume an exponential relationship between rate ratios and cumulative BD ppm-years whereas Sielken et al. uses a linear relationship, 3) Cheng et al. use Cox proportional hazards model and Sielken et al. use Poisson regression model, and 4) Cheng et al. use continuous cumulative BD ppm-years and Sielken et al. uses BD ppm-years mean-scored deciles.

Model	**Covariates**	**Parameter Estimate**		**URF[a] (ppm^{-1})** **Air Concentration for an excess risk of 1 in 100,000 (ppb)**	
		β (S.E.)	95% UCL	URF (MLE)	URF(95% UCL); 95% LCL on Conc.
Cox regression Cheng et al. (2007) ppm-years continuous[b], # of HITS continuous[c]	Age number of HITs > 100 ppm	2.5E-04 (1.2E-04)	4.474E-04	1.284E-04 77.88	2.298E-04 43.52
Cox regression ppm-years continuous[b], # of HITS categorical[d]	Age number of HITs > 100 ppm	2.0E-04 (1.3E-04)	4.138E-04	1.027E-04 97.35	2.125E-04 47.05
Cox regression ppm-years mean-scored deciles[e], # of HITS categorical[d]	Age number of HITs > 100 ppm	2.8E-04 (2.4E-04)	6.748E-04	1.438E-04 69.53	3.466E-04 28.85
Poisson regression (Sielken et al. (2007) ppm-years mean-scored deciles[e], # of HITS categorical[d]	Age number of HITs > 100 ppm	1.89E-04 (3.6E-04)	7.812E-04	8.083E-05 123.7	3.314E-04 29.93

[a] URF(MLE) = 0.001 / EC_{001} and URF(95% UCL) = 0.001 / LEC_{001}

[b] ppm-years is included as a continuous variable (untransformed) in a parametric model of the effect of ppm-years

[c] number of HITS > 100 ppm is included as a continuous variable (untransformed) in a parametric model of the effect of the number of HITS > 100 ppm

[d] number of HITS > 100 ppm is included as a categorical variable (based on quintiles) in a nonparametric model of the effect of the number of HITS > 100 ppm

[e] ppm-years is included as a categorical variable (based on mean-scored deciles, untransformed) in a parametric model of the effect of ppm-years

Despite all these differences, the models are close and converge to very similar results if some of the discrepancies are resolved. For example, if the Cox proportional hazards exponential model presented by Cheng et al. were non-parametrically adjusted for BD peaks, then the estimate of the coefficient for cumulative BD ppm-years would be $\beta = 0.00020$ (S.E.=0.00013), which is close to the parameter estimates reported in Sielken et al. (i.e., $\beta = 0.000189$, S.E.=0.00036) for the Poisson linear model. If, in addition to adjusting for the number of HITs nonparametrically, the Cox proportional hazards exponential model used BD ppm-years mean-scored deciles instead of continuous exposures, then the coefficient for cumulative BD ppm-years would be $\beta = 0.00028$ (S.E.=0.00024). This last model differs from Sielken et al. model only in that Sielken et al. used a Poisson regression model and a linear relationship as opposed to the Cox proportional hazards model and a log-linear relationship. The following table summarizes the results of the Cox proportional hazards model and the Sielken et al. Poisson regression model when adjusting for the number of HITs.

In the above discussion, a parametric model is a model that assumes a specified functional form (e.g., linear or log-linear), and a nonparametric model is a model that does not assume a specified functional form. This is analogous to the difference between regression which assumes a specified functional form (e.g., linear or polynomial) and hence is parametric and analysis of variance (ANOVA or AOV) which is nonparametric. Continuing with the analogy, if a treatment can be characterized by a number (e.g., concentration or amount), then in a regression analysis (say, a linear regression) the magnitudes of the different treatment values are important and a treatment with twice the magnitude has twice the effect. On the other hand, in an analysis of variance the different treatments are dealt with nonparametrically (say, as treatments A, B, C, etc.) and the magnitudes (numerical values) are ignored. Therefore, in an analysis of variance there is no functional relationship specified between the effects of the different treatments.

If a variable is said to be treated continuously, then each individual value of that variable is used – the values are not grouped and no representative values for the groups are used. On the other hand, if a variable is treated categorically, then the individual values of that variable are grouped and representative values for the groups replace the individual values in the analysis. Cumulative butadiene ppm-years and cumulative number of HITS > 100 ppm can both be treated either as continuous or categorical variables. Since the categorical (group) values for these variables are numerical, a categorical variable could be included in both parametric and nonparametric models.

In the table above, both the Cox and Poisson regressions assume a parametric model for the effect of cumulative butadiene ppm-years. The model for the effect of ppm-years is log-linear in Cox regression and is linear in Poisson regression. In Cox regression, ppm-years is treated as a continuous variable in the first two models and treated as a categorical variable in the third model. In the Poisson regression, ppm-years is treated as a categorical variable.

In the first model in the table above, the cumulative number of HITS > 100 ppm is treated as a continuous variable and treated parametrically. In the other three models, the cumulative number of HITS > 100 ppm is treated as a categorical variable and treated nonparametrically.

Albertini, R., Sram, R. J., Vacek, P. M., Lynch, J., Rossner, P., Nicklas, J. A., McDonald, J. D., Boysen, G., Georgieva, N., and Swenberg, J. A. (2007). Molecular epidemiological studies in 1,3-butadiene exposed Czech workers: Female-male comparisons. Chemico-Biological Interactions, Volume 166, Issues 1-3, 20 March 2007, Pages 63-77.

Appendix 5. Leukemia Mortality Rates and Survival Rates

US Total Population 2000-2003		Texas Statewide 1999-2003	
Total Leukemia Mortality Rates per 100,000 [1]		Total Leukemia Mortality Rates per 100,000 [2]	
	Rate		Rate
00 years	0.7	00 years	0.9
01-04 years	0.9	01-04 years	0.9
05-09 years	0.7	05-09 years	0.6
10-14 years	0.8	10-14 years	0.9
15-19 years	1.1	15-19 years	1.3
20-24 years	1.2	20-24 years	1.5
25-29 years	1.1	25-29 years	1.1
30-34 years	1.3	30-34 years	1.4
35-39 years	1.6	35-39 years	1.5
40-44 years	2.0	40-44 years	1.8
45-49 years	2.9	45-49 years	3.4
50-54 years	4.4	50-54 years	4.2
55-59 years	7.5	55-59 years	8.4
60-64 years	12.9	60-64 years	13.2
65-69 years	20.8	65-69 years	21.3
70-74 years	33.0	70-74 years	31.8
75-79 years	47.0	75-79 years	43.4
80-84 years	63.2	80-84 years	65.5
85+ years	81.5	85+ years	81.3

[1] Table XIII-8, Seer Cancer Statistics Review 2000-2003Surveillance, Epidemiology, and End Results database (SEER 2006))

[2] Texas-specific mortality rates for 1999-2003 for all leukemia and Texas-specific survival rates for 2003 were kindly provided by the Texas Department of State Health Services, Cancer Epidemiology and Surveillance Branch, Texas Cancer Registry.

2000 US All [1]		Total Texas Population 2003 [2]	
Age	**Survival**	**Life Tables**	
0	1	0	1
1	0.99307	1	0.99342
5	0.99177	5	0.99191
10	0.99095	10	0.99105
15	0.98992	15	0.99005
20	0.98654	20	0.98659
25	0.98181	25	0.9818
30	0.97696	30	0.9772
35	0.97132	35	0.97192
40	0.96349	40	0.9641
45	0.9521	45	0.95248
50	0.93522	50	0.93546
55	0.91113	55	0.91092
60	0.87498	60	0.87584
65	0.82131	65	0.82385
70	0.74561	70	0.75079
75	0.64244	75+	0.65073
80	0.51037		
85	0.34959		

[1] US survival rates for 2000 (Arias 2002)

[2] Texas-specific survival rates for 2003 were kindly provided by the Texas Department of State Health Services, Cancer Epidemiology and Surveillance Branch, Texas Cancer Registry.

Appendix 6. Calculating Excess Risk with Age-Dependent Adjustment Factors

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1. Background:

When calculating an excess risk, a general guiding principle is that the dose-response model, model parameter, dose metric, response, and population used in the excess risk calculation using the BEIR IV approach (NRC 1988) should be the same as the dose-response model, model parameter, dose metric, response, and population used in the dose-response modeling of the epidemiological study data.

If the population in the dose-response modeling has specific characteristics (e.g., gender, race, and geographic region), then the inference (the calculated excess risk) applies directly to that specified population. It only applies to a more general population under the assumption that the estimated model parameter and dose-response model apply to that population – this is an assumption, not a guarantee, and not something that is necessarily proven or implied by the study data.

2. Age-Dependent Adjustment Factor (ADAF): General

An ADAF is intended to be used when the epidemiological study data do not include exposures at an early age (generally before age 16). According to U.S. EPA (Barton, H., et al. Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens, EPA/360/R-03/003F, March 2005, Washington, D.C.), an ADAF is intended to address the "…potential for increased susceptibility to cancer from early-life exposure, relative to comparable exposure later in life…".

ADAFs are age-specific adjustments to the susceptibility (slope) in the dose-response model and are not adjustments to the dose metric itself.

If the epidemiological study data do not include exposures at an early age (e.g., before age 16) such as would generally be the case for occupational epidemiological studies, then ADAFs that are only different than 1 before age 16 do not impact the dose-response modeling and cannot reflect different susceptibilities at early ages relative to later ages. Thus, the fitted model parameter cannot directly reflect different susceptibilities at early ages relative to later ages. Therefore, it is reasonable to do an excess risk calculation using the dose metric and model parameter estimated from the epidemiological data – without

explicitly recomputing the model parameter based on the susceptibilities implied by the ADAFs – since the model parameter won't change anyway.

Although it is somewhat of an aside, it is important to note the treatment of "background doses" needs to be the same in the dose-response modeling and the excess risk calculation. Specifically, if for example, there is a general background exposure of X ppm per year to the chemical of interest, then the excess risk calculation should treat that X ppm per year in the same way as the dose-response model fitting. If the dose-response modeling was done with the dose metric including that X ppm per year, then the excess risk calculation should be done with the dose metric including that X ppm per year. If the dose-response modeling was done with the dose metric excluding that X ppm per year, then the excess risk calculation should be done with the dose metric excluding that X ppm per year. It would be invalid for the dose-response modeling to be done with the dose metric excluding that X ppm per year, and the excess risk calculation to be done with the dose metric including that X ppm per year – or vice versa.

3. Age-Dependent Adjustment Factor (ADAF): EPA Guidelines

EPA guidelines call for the default use of ADAFs be considered only when the chemicals mode of action is mutagenic.

EPA guidelines (pages 32-34) also include the following text:

> *The adjustments described below reflect the potential for early-life exposure to make a greater contribution to cancers appearing later in life. The 10-fold adjustment represents an approximation of the weighted geometric mean tumor incidence ratio from juvenile or adult exposures in the repeated dosing studies (see Table 8). This adjustment is applied for the first 2 years of life, when toxicokinetic and toxicodynamic differences between children and adults are greatest (Ginsberg et al., 2002; Renwick, 1998). Toxicokinetic differences from adults, which are greatest at birth, resolve by approximately 6 months to 1 year, while higher growth rates extend for longer periods. The 3-fold adjustment represents an intermediate level of adjustment that is applied after 2 years of age through <16 years of age. This upper age limit represents middle adolescence following the period of rapid developmental changes in puberty and the conclusion of growth in body height in NHANES data (Hattis et al., 2005). Efforts to map the approximate start of mouse and rat bioassays (i.e., 60 days) to equivalent ages in humans ranged from 10.6 to 15.1 years (Hattis et al., 2005). Data are not available to calculate a specific dose response adjustment factor for the 2 to <16-year age range, so EPA selected the 3-fold adjustment because it reflects a midpoint, i.e., approximately half the difference between 1 and 10 on a logarithmic scale ($10^{1/2}$), between the 10-fold adjustment for the first two years of life and no adjustment (i.e., 1-fold) for adult exposure. ...*
>
> *...the Supplemental Guidance emphasizes that chemical-specific data should be used in preference to these default adjustment factors whenever such data are available.*
>
> *The following adjustments represent a practical approach that reflects the results of the preceding analysis, which concluded that cancer risks generally are higher from early-life exposure than from similar exposure durations later in life:*

- For exposures before 2 years of age (i.e., spanning a 2-year time interval from the first day of birth up until a child's second birthday), a 10-fold adjustment.

- For exposures between 2 and <16 years of age (i.e., spanning a 14-year time interval from a child's second birthday up until their sixteenth birthday), a 3-fold adjustment

- For exposures after turning 16 years of age, no adjustment.

...This Supplemental Guidance focuses on carcinogens with a mutagenic mode of action.

...When data, including well established mode of action data, are available that allow specific evaluation of lifestage differences in toxicokinetics or toxicodynamics that would lead to lesser or greater susceptibility from early-life exposures to carcinogens, then those data should be used, as generally discussed in EPA's cancer guidelines (U.S. EPA, 2005), in preference to the default procedures described in this Supplemental Guidance.

*The 10-fold and 3-fold **adjustments in slope factor** are to be combined with age-specific exposure estimates when estimating cancer risks from early life exposure to carcinogens that act through a mutagenic mode of action. It is important to emphasize that these adjustments are combined with corresponding age-specific estimates of exposure to assess cancer risk. For example, for a 70-year lifetime, where there are data showing negligible exposure to children, the estimated cancer risk from childhood exposure would be also negligible and the lifetime cancer risk would be reduced to that resulting from the relevant number of years of adult exposure (in the absence of specific information, 55 years). Where there are data (measured or modeled) for childhood exposures, the age-group specific exposure values are used along with the corresponding **adjustments to the slope factor**. Where there are no relevant data or models for childhood exposures and only lifetime average exposure data are available, the lifetime exposure data are used with the **adjustments to the slope factor** for each age segment.*
(emphasis added)

There are several important points/clarifications in this last paragraph. The first is that the ADAF is an adjustment to the slope factor (as opposed to an adjustment to the dose metric). The second is that the ADAF is to be applied on an age-specific basis. That is, the ADAFs are applied to each year in a life and summed to get the lifetime risk, as opposed to calculating a lifetime excess risk without ADAFs and then multiplying this calculated value by a constant ADAF.

This second point is reinforced in the examples provided by EPA (Sections 6.1 and 6.2, pages 36 to 41). Although EPA's examples do not explicitly refer to cumulative doses, they do refer to age-dependent doses and cumulative doses are age-dependent doses.

4. Age-Dependent Adjustment Factor (ADAF): Recent Implementations by EPA and Others when the Dose Metric is Cumulative Exposure are Inconsistent with EPA Guidelines

In recent risk assessments (e.g., for ethylene oxide) **when the dose metric is cumulative exposure**, EPA has implemented the ADAF by calculating the excess risk by first calculating the excess risk without any ADAFs and then multiplying this excess risk by a weighted average of the age-specific ADAFs over the "lifetime" (i.e., the period over which the excess risk is calculated, 70, 78, or 85 years). Similarly, the

EPA has implemented the ADAF by calculating the point of departure (POD) by first calculating the POD without an ADAF and then dividing this POD by a weighted average of the age-specific ADAFs over the "lifetime".

In these recent risk assessments (e.g., for ethylene oxide) **when the dose metric is cumulative exposure**, EPA's method of incorporating an ADAF has been inconsistent with EPA's Guidelines, has not properly incorporated age-dependence, and is mathematically incorrect. There is no good scientific/mathematical reason for incorporating an ADAF in the manner in which EPA has attempted to do it. Others (including the first draft assessment of butadiene by NC SAB) have made the same mistake.

For inhalation exposure of a chemical with a mutagenic mode of action, EPA guidelines [Barton, H., et al. Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens. EPA/630/R-03/003F, March 2005] suggest that the increased risk caused by early-life exposure be determined through the use of three Age-Dependent Adjustment Factors (ADAFs):

(1) ADAF(age) = 10 for exposure before 2 years of age
(2) ADAF(age) = 3 for exposure between ages 2 and < 16 years of age
(3) ADAF(age) = 1 for exposure after turning 16 years of age.

Furthermore, **assuming that exposure to a mutagenic chemical via inhalation is constant over a 70-year lifetime**, EPA's proposed overall adjustment factor (ADAF) for early-life exposure is:

$$ADAF = \sum_i (ADAF(i) \times \text{Age Interval}) / 70 \text{ years}$$

$$= [\ (10 \times 2 \text{ years}) + (3 \times 13 \text{ years}) + (1 \times 55 \text{ years})\ ] / 70 \text{ years} = 1.63.$$

For a 78-year lifespan, the corresponding ADAF would be 1.56 because

$$[(10 \times 2 \text{ years}) + (3 \times 13 \text{ years}) + (1 \times 63 \text{ years})\ ] / 78 \text{ years} = 1.56.$$

For an 85-year lifespan, the corresponding ADAF would be 1.52 because

$$[(10 \times 2 \text{ years}) + (3 \times 13 \text{ years}) + (1 \times 70 \text{ years})\ ] / 85 \text{ years} = 1.52.$$

Then, the point of departure (POD) is "adjusted for early-life exposure" by dividing the unadjusted POD by ADAF, according to the EPA proposed method of adjustment.

This adjustment is consistent with EPA Guidelines provided that **exposure to a mutagenic chemical via inhalation is constant over the lifetime and the dose metric is the exposure concentration (as opposed to cumulative exposure).** Here, "lifetime" should be interpreted as the period over which the excess risk is calculated (e.g., 70, 78, or 85 years).

Specifically, in Example 2 (part a) in Section 6.1 of EPA Guidelines, the calculation of excess risk for 70 years exposure to a constant dose (0.0001 mg/kg-d) when the dose metric is exposure concentration (as opposed to cumulative exposure) is as follows:

a. To calculate lifetime risk for a population with average life expectancy of 70 years, sum the risk associated with each of the three relevant time periods:

- *Risk during the first 2 years of life (where the ADAF = 10);*
- *Risk for ages 2 through < 16 (ADAF = 3); and*
- *Risk for ages 16 until 70 years (ADAF = 1).*

Thus, risk equals the sum of:

- *Risk for birth through < 2 yr =*

(2 per mg/kg-d) x 10 (ADAF) x (0.0001 mg/kg-d) x 2yr/70yr = 0.6 x 10^{-4}

- *Risk for ages 2 through < 16 =*

(2 per mg/kg-d) x 3 (ADAF) x (0.0001 mg/kg-d) x (13yr/70yr) = 1.1 x 10^{-4}

- *Risk for ages 16 until 70 =*

(2 per mg/kg-d) x 1 (ADAF) x (0.0001 mg/kg-d) x (55yr/70yr) = 1.6 x 10-4

Risk = 0.6 x 10^{-4} + 1.1 x 10^{-4} + 1.6 x 10^{-4} = 3.3 x 10^{-4}

Here, **where the exposure is to a constant dose (0.0001 mg/kg-d) and the dose metric is exposure concentration (as opposed to cumulative exposure)**, the risk could be calculated as "risk without ADAFs" times a weighted average adjustment factor -- here,

$$\text{ADAF} = \sum_i (\text{ADAF}(i) \times \text{Age Interval}) / 70 \text{ years}$$

$$= [(10 \times 2 \text{ years}) + (3 \times 13 \text{ years}) + (1 \times 55 \text{ years})] / 70 \text{ years} = 1.63.$$

This works only when the age-specific risk per year (before ADAF) is a constant for all ages. Here, the lifetime risk (before ADAF) is

(2 per mg/kg-d) x (0.0001 mg/kg-d).

Here,

(2 per mg/kg-d) x (0.0001 mg/kg-d)

is a common term in each of the risks being summed, so it can be factored out and the calculation represented as

(2 per mg/kg-d) x (0.0001 mg/kg-d)
x [(10 × 2 years) + (3 ×13 years) + (1 x 55 years)] / 70 years

= (2 per mg/kg-d) x (0.0001 mg/kg-d) x 1.63.

= 0.000326 = 3.3 x 10^{-4}.

However, **the ADAFs do not factor out when the dose is not constant for each age in the age-specific calculation**. For example, in Example 2 (part b) in Section 6.1 of EPA Guidelines, the calculation is as follows:

> *b. If exposure varies with age, then such differences are also included. Now suppose the same example as immediately above, except that exposure for ages 1 through <12 was twice as high as exposure for all other ages. In this case, sum the risk associated with each of the five relevant time periods in which exposure rates and/or potencies (slope factors) vary:*
>
> *Risk equals the sum of:*
>
> • *Risk for birth through < 1 yr (1yr) =*
> *(2 per mg/kg-d) x 10 (ADAF) x 0.0001 mg/kg-d x 1yr/70yr = 0.3 x 10^{-4}*
>
> • *Risk for ages 1 through < 2 (1yr) =*
> *(2 per mg/kg-d) x 10 (ADAF) x 0.0002 mg/kg-d x 1yr/70 yr = 0.6 x 10^{-4}*
>
> • *Risk for ages 2 through < 12 (10yr) =*
> *(2 per mg/kg-d) x 3 (ADAF) x 0.0002 mg/kg-d x 10yr/70yr = 1.7 x 10^{-4}*
>
> • *Risk for ages 12 through < 16 (4yr) =*
> *(2 per mg/kg-d) x 3 (ADAF) x 0.0001 mg/kg-d x 4yr/70yr = 0.3 x 10^{-4}*
>
> • *Risk for ages 16 until 70 years (55yr) =*
> *(2 per mg/kg-d) x 1 (ADAF) x 0.0001 mg/kg-d x 55yr/70yr = 1.6 x 10^{-4}*
>
> *Risk = 0.3 x 10^{-4} + 0.6 x 10^{-4} + 1.7 x 10^{-4} + 0.3 x 10^{-4} + 1.6 x 10^{-4} = 4.5 x 10^{-4}*

Here, the dose x slope does not factor out of the above calculation – even though the slope is constant for all ages (namely, 2 per mg/kg-d) -- since the dose is 0.0002 mg/kg-d for ages between 1 and 12 and 0.0001 mg/kg-d for ages <1 and ages 12 and above. If one calculated the risk without ADAFs, namely,

> Risk equals the sum of:
>
> • Risk for birth through < 1 yr (1yr) =
> (2 per mg/kg-d) x 0.0001 mg/kg-d x 1yr/70yr = 2.9 x 10^{-6}
>
> • Risk for ages 1 through < 2 (1yr) =
> (2 per mg/kg-d) x 0.0002 mg/kg-d x 1yr/70 yr = 5.7 x 10^{-6}

- Risk for ages 2 through < 12 (10yr) =

(2 per mg/kg-d) x 0.0002 mg/kg-d x 10yr/70yr = 5.7×10^{-5}

- Risk for ages 12 through < 16 (4yr) =

(2 per mg/kg-d) x 0.0001 mg/kg-d x 4yr/70yr = 1.1×10^{-5}

- Risk for ages 16 until 70 years (55yr) =

(2 per mg/kg-d) x 0.0001 mg/kg-d x 55yr/70yr = 1.6×10^{-4}

Risk = $2.9 \times 10^{-6} + 5.7 \times 10^{-6} + 5.7 \times 10^{-5} + 1.1 \times 10^{-5} + 1.6 \times 10^{-4}$
= 2.4×10^{-4}

and then multiplied this sum by a weighted average adjustment factor -- here, ADAF = [(10 × 2 years) + (3 ×13 years) + (1 x 55 years)]/ 70 years = 1.63 – the result would be

$(2.4 \times 10^{-4}) \times 1.63 = 3.9 \times 10^{-4}$

and not 4.5×10^{-4}.

Except for the trivial case in which the exposure concentration is only non-zero in the first year, cumulative exposure changes from year to year and is not constant throughout the period included in the excess risk calculation. Hence, when dose is cumulative exposure, the ADAFs do not factor out of the excess risk calculation and the risk can NOT be calculated as "risk without ADAFs" times a weighted average adjustment factor.

5. Age-Dependent Adjustment Factor (ADAF): An Implementation When the Dose Metric is Cumulative Exposure That Is Consistent with EPA Guidelines

An implementation that is consistent with EPA guidelines when the dose metric is cumulative exposure would be to calculate the excess risk as in Example 2 (part b) in Section 6.1 of EPA Guidelines. That is, calculate the excess risk in each year using the age-specific dose (cumulative dose) for that year and multiplying the slope by the age-specific ADAF for that year (age). This would be consistent with EPA's Guidelines from the point of view of both the excess risk calculation being done using age-specific exposures and also the ADAFs being age-specific modifiers of the slope (potency). This implementation of the ADAF is NOT equivalent to computing the excess risk by first calculating the excess risk without any ADAFs and then multiplying this excess risk by a weighted average of the age-specific ADAFs over the lifetime.

APPENDIX 7. CALCULATING EXCESS RISK WHEN SPECIFIED RESPONSE IS MORTALITY VERSUS INCIDENCE

Issues in Quantitative Epidemiology
Calculating Excess Risk When Specified Response is Mortality
Vs When the Specified Response is Incidence

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The BEIR IV methodology for calculating excess risk is mathematically correct when the specified response is mortality; however, the BEIR IV methodology is mathematically incorrect when the specified response is incidence (not death).

The following slides are divided into two presentations. The first presentation provides a step-by-step derivation of the BEIR IV methodology when the specified response is mortality. This presentation directly parallels the same derivation in BEIR IV. The second presentation provides a step-by-step derivation that is "parallel" to that in the first presentation except that in the second presentation the specified response is incidence (not death). However, the steps and result are fundamentally different when the specified response is incidence (not death) than when the response is death.

The fact that the "result" (i.e., the mathematical formula for calculating excess risk) is different when the response is mortality than it is when the response is incidence, means that when the response is incidence (not death) the excess risk cannot be validly calculated using the formula (BEIR IV methodology) for death.

The First Presentation: Issues in Quantitative Epidemiology: Calculating Excess Risk: When Specified Response is Mortality

Calculating Excess Risk using Actuarial Method or Life Table Method. This way of calculating excess risks from a RR function is the implementation of the methodology described in "BEIR IV. Health Risks of Radon and Other Internally Deposited Alpha-Emitters. Committee on the Biological Effects of Ionizing Radiations. Board on Radiation Effects Research Commission of Life Sciences. National Research Council. National Academy Press, Washington, DC, 1988."

1

BEIR IV:

Derivation of Formulas:
(Using notation in BEIR report)

i = 1, 2, ..., T

i = index for the years for a person's life

year i is the year from the person's (i-1)-th birthday
to his (or her) i-th birthday

i=1 refers to the year from birth to the 1st birthday
i=1 = age 0
...
i=7 refers to the year from the 6-th birthday to the 7-th birthday
i=7 = age 6

2

BEIR IV: Derivation of Formulas:

i = 1, 2, ..., T

q(i) = probability of surviving year i
when all causes of death are acting
conditional on the person surviving through year i -1

q(7) = probability of reaching a person 's 7-th birthday
given that he reached his 6 -th birthday

$q(7) = P(\text{Death} \geq 7 \mid \text{Death} \geq 6)$

h(i)* = mortality rate due to all causes in year i
conditional on the person surviving through year i -1

$q(i) = \exp[- h(i)^*]$

1 - q(i) = probability of death in year i
conditional on the person surviving through year i -1

3

1

BEIR IV: Derivation of Formulas:

i = 1, 2, ..., T

q(i) = probability of surviving year i
when all causes of death are acting
conditional on the person surviving through year i-1

h(i)* = mortality rate due to all causes in year i
conditional on the person surviving through year i-1

q(i) = exp[- h(i)*]

1 - q(i) = probability of death in year i
conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) mortality rate in year i
conditional on the person not having the response
through year i-1

2

BEIR IV: Derivation of Formulas:

i = 1, 2, ..., T

q(i) = probability of surviving year i
when all causes of death are acting
conditional on the person surviving through year i-1

h(i)* = mortality rate due to all causes in year i
conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) mortality rate in year i
conditional on the person not having the response
through year i-1

S(1,i) = probability of surviving up to year i is the product of surviving each prior year:

$S(1,i) = q(1) \times q(2) \times ... \times q(i-1)$ with $S(1,1) = 1.0$.

$S(1,i) \times [\ 1 - q(i)\ ]$ = probability of surviving up to year i and then dying (from any cause) in year i

1

BEIR IV: Derivation of Formulas:

i = 1, 2, ..., T

q(i) = probability of surviving year i
when all causes of death are acting
conditional on the person surviving through year i-1

h(i)* = mortality rate due to all causes in year i
conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) mortality rate in year i
conditional on the person not having the response
through year i-1

S(1,i) = probability of surviving up to year i

S(1,i) × [1 - q(i)] = probability of surviving up to year i and
then dying (from any cause) in year i

h(i)/h(i)* = proportion of deaths in year i due to the response

[h(i)/h(i)*] × S(1,i) × [1 - q(i)] = probability of surviving i-1 years
and dying of response in year i

2

BEIR IV: Derivation of Formulas:

i = 1, 2, ..., T

q(i) = probability of surviving year i
when all causes of death are acting
conditional on the person surviving through year i-1

h(i)* = mortality rate due to all causes in year i
conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) mortality rate in year i
conditional on the person not having the response
through year i-1

S(1,i) = probability of surviving up to year i = q(1) × q(2) × ... × q(i -1)

S(1,i) × [1 - q(i)] = probability of surviving up to year i and
then dying (from any cause) in year i

h(i)/h(i)* = proportion of deaths in year i due to the response

[h(i)/h(i)*] × S(1,i) ×[1 - q(i)] = probability of surviving i-1 years
and dying of response in year i

$R_0 = \sum_{i=1,...,T} [h(i)/h(i)^*] \times S(1,i) \times [1 - q(i)]$
= probability of a response mortality in the first T years of life
(i.e., up to the T-th birthday, age T) at dose 0
(no exposure in addition to background exposure)

1

BEIR IV: Derivation of Formulas: Risk with exposure

i=1, 2, ..., T

q(i) = probability of surviving year i without exposure
when all causes of death are acting
conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) mortality rate in year i without exposure
conditional on the person not having the response through year i-1

h(i)* = mortality rate due to all causes in year i without exposure
conditional on the person surviving through year i-1

f(i) = proportional effect (multipler) in year i assuming a proportional hazards model for the effect of exposure of the form h(i) × f(i)
f(i) = [1 + e(i)] if the multiplier is a linear function

h(i) × f(i) = response (e.g., lung cancer) mortality rate in year i with exposure
conditional on the person not having the response through year i-1

h(i) × [f(i) - 1] = increase in response mortality rate in year due to exposure

2

BEIR IV: Derivation of Formulas: Risk with exposure

i=1, 2, ..., T

q(i) = probability of surviving year i without exposure
when all causes of death are acting
conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) mortality rate in year i without exposure
conditional on the person not having the response through year i-1

h(i)* = mortality rate due to all causes in year i without exposure
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f(i) = proportional effect (multipler) in year i assuming a proportional hazards model for the effect of exposure of the form h(i) × f(i)
f(i) = [1 + e(i)] if multiplier is a linear function

h(i) × f(i) = response (e.g., lung cancer) mortality rate in year i with exposure
conditional on the person not having the response through year i-1

h(i) × [f(i) - 1] = increase in response mortality rate in year due to exposure

h(i)* + h(i) × [f(i) - 1] = mortality rate due to all causes in year i with exposure
conditional on the person surviving through year i-1

1

BEIR IV: Derivation of Formulas: Risk with exposure

i=1, 2, ..., T

q(i) = probability of surviving year i without exposure
when all causes of death are acting
conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) mortality rate in year i without exposure
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conditional on the person surviving through year i-1

f(i) = proportional effect (multipler) in year i assuming a proportional hazards model for the effect of exposure of the form h(i) × f(i)
f(i) = [1 + e(i)] if multiplier is a linear function

h(i) × f(i) = response (e.g., lung cancer) mortality rate in year i with exposure
conditional on the person not having the response through year i-1

h(i) × [f(i) - 1] = increase in response mortality rate in year i due to exposure

h(i)* + h(i) × [f(i) - 1] = mortality rate due to all causes in year i with exposure
conditional on the person surviving through year i-1

$\exp \{ - h(i)^* - h(i) \times [f(i) - 1] \}$ = probability with exposure of surviving year i conditional on person surviving thru year i-1

$q(i) \times \exp \{ - h(i) \times [f(i) - 1] \}$ = probability with exposure of surviving year i conditional on person surviving thru year i-1

2

BEIR IV: Derivation of Formulas: Risk with exposure

q(i) = probability of surviving year i without exposure
when all causes of death are acting conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) mortality rate in year i without exposure
conditional on the person not having the response through year i-1

h(i)* = mortality rate due to all causes in year i without exposure
conditional on the person surviving through year i-1

f(i) = proportional effect (multipler) in year i assuming a proportional hazards model for the effect of exposure of the form h(i) × f(i); f(i) = [1 + e(i)] if multiplier is a linear function

h(i) × f(i) = response (e.g., lung cancer) mortality rate in year i with exposure
conditional on the person not having the response through year i-1

h(i) × [f(i) - 1] = increase in response mortality rate in year due to exposure

h(i)* + h(i) × [f(i) - 1] = mortality rate due to all causes in year i with exposure
conditional on the person surviving through year i-1

exp { - h(i)* - h(i) × [f(i) - 1] } = probability with exposure of surviving year i
conditional on person surviving thru year i-1

q(i) × exp { - h(i) × [f(i) - 1] } = probability with exposure of surviving year i
conditional on person surviving thru year i-1

$q(1) \times \exp \{ - h(1) \times [f(1) - 1] \} \times \ldots \times q(i-1) \times \exp \{ - h(i-1) \times [f(i-1) - 1] \}$
$= S(1,i) \times \exp (- \sum_{k=1,\ldots,i-1} \{ - h(k) \times [f(k) - 1] \})$
= probability of surviving up to year i with exposure

$S(1,i) \times \exp (- \sum_{k=1,\ldots,i-1} \{-h(k) \times [f(k) - 1] \}) \times (1 - q(i) \times \exp\{-h(i) \times [f(i) - 1] \})$
= probability with exposure of surviving up to year i
and then dying (from any cause) in year i

1

BEIR IV: Derivation of Formulas: Risk with exposure

q(i) = probability of surviving year i without exposure
when all causes of death are acting conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) mortality rate in year i without exposure
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h(i)* = mortality rate due to all causes in year i without exposure
conditional on the person surviving through year i-1

f(i) = proportional effect (multipler) in year i assuming a proportional hazards model for the effect of exposure of the form h(i) × f(i); f(i) = [1 + e(i)] if multiplier is a linear function

h(i) × f(i) = response (e.g., lung cancer) mortality rate in year i with exposure
conditional on the person not having the response through year i-1

h(i) × [f(i) - 1] = increase in response mortality rate in year due to exposure

h(i)* + h(i) × [f(i) - 1] = mortality rate due to all causes in year i with exposure
conditional on the person surviving through year i-1

exp { -h(i)* - h(i) × [f(i) - 1] } = probability with exposure of surviving year i
conditional on person surviving thru year i-1

q(i) × exp { - h(i) × [f(i) - 1] } = probability with exposure of surviving year i
conditional on person surviving thru year i-1

q(1) × exp { - h(1) × [f(1) - 1] } × ... × q(i -1) × exp { - h(i -1) × [f(i -1) - 1] }
= S(1,i) × exp (- $\sum_{k=1,...,i-1}$ { - h(k) × [f(k) - 1] })= probability of surviving up to year i with exposure

S(1,i) × exp (- $\sum_{k=1,...,i-1}$ {-h(k)×[f(k) - 1] }) × (1 - q(i)×exp{-h(i)×[f(i) - 1] })
= probability with exposure of surviving up to year i and then dying (from any cause) in year i
{ h(i) × f(i) } / { h(i)* + h(i) × [f(i) - 1] }
= proportion of deaths in year i due to the response with exposure
({h(i)×f(i)}/{h(i)*+h(i)×[f(i)-1]}) × S(1,i) × exp(- $\sum_{k=1,...,i-1}${-h(k)×[f(k)-1]}) × (1-q(i)×exp{-h(i)×[f(i)-1] })
= probability of surviving i-1 years and dying of response in year i with exposure

2

BEIR IV: Derivation of Formulas: Risk with exposure

({h(i)×f(i)}/{h(i)*+h(i)×[f(i)-1]})
× S(1,i) × exp(- $\sum_{k=1,...,i-1}${-h(k)×[f(k)-1]})
× (1-q(i)×exp{-h(i)×[f(i)-1] })
= probability of surviving i-1 years
and dying of response in year i with exposure

$R_{exposure} = \sum_{i=1,...,T}$
({h(i) × f(i)} / {h(i)* + h(i) × [f(i)-1] })
× S(1,i) × exp(- $\sum_{k=1,...,i-1}$ { -h(k) × [f(k)-1] })
× (1 - q(i) × exp { - h(i) × [f(i) - 1] })

= probability of a response mortality in the first T years of life (i.e., up to the T-th birthday, age T) with exposure
(with exposure in addition to the background exposure)

BEIR IV: Risks

$R_0 = \sum_{i=1,\ldots,T} [\, h(i)/h(i)^* \,] \times S(1,i) \times [1 - q(i)\,]$

= probability of a response mortality in the first T years of life (i.e., up to the T-th birthday, age T) at dose 0 (no exposure in addition to background exposure)

$R_{exposure} = \sum_{i=1,\ldots,T} (\{h(i) \times f(i)\} / \{h(i)^* + h(i) \times [\, f(i)-1 \,] \})$
$\times S(1,i) \times \exp(- \sum_{k=1,\ldots,i-1} \{ -h(k) \times [\, f(k)-1 \,] \})$
$\times (1 - q(i) \times \exp \{ - h(i) \times [\, f(i) - 1 \,] \})$

= probability of a response mortality in the first T years of life (i.e., up to the T-th birthday, age T) with exposure (with exposure in addition to the background exposure)

Added Risk = $R_{exposure} - R_0$

Extra Risk = $(R_{exposure} - R_0) / (1 - R_0)$

Excess Risk = either Added Risk or Extra Risk

The Second Presentation: 3.1 Issues in Quantitative Epidemiology: Calculating Excess Risk: When Specified Response is Incidence

Calculating Excess Risk using Actuarial Method or Life Table Method. The following derivation for the situation in which the specified response is incidence (not death) "parallels" the derivation in BEIR IV; however, the derivation and result are necessarily different for incidence than for mortality.

"BEIR IV. Health Risks of Radon and Other Internally Deposited Alpha-Emitters. Committee on the Biological Effects of Ionizing Radiations. Board on Radiation Effects Research Commission of Life Sciences. National Research Council. National Academy Press, Washington, DC, 1988."

1

Derivation of Formulas:
(Using notation in BEIR report)

i = 1, 2, ..., T

i = index for the years for a person's life

year i is the year from the person's (i-1)-th birthday
to his (or her) i-th birthday

i=1 refers to the year from birth to the 1st birthday
i=1 = age 0
...
i=7 refers to the year from the 6-th birthday to the 7-th birthday
i=7 = age 6

2

Derivation of Formulas:

i = 1, 2, ..., T

q(i) = probability of surviving year i
when all causes of death are acting
conditional on the person surviving through year i-1

q(7) = probability of reaching a person's 7-th birthday
given that he reached his 6-th birthday

$q(7) = P(\text{Death} \geq 7 \mid \text{Death} \geq 6)$

h(i)* = mortality rate due to all causes in year i
conditional on the person surviving through year i-1

q(i) = exp[- h(i)*] -- definition of hazard rate

1 - q(i) = probability of death in year i
conditional on the person surviving through year i-1

3

Derivation of Formulas:

i = 1, 2, ..., T

q(i) = probability of surviving year i
when all causes of death are acting
conditional on the person surviving through year i-1

h(i)* = mortality rate due to all causes in year i
conditional on the person surviving through year i-1

q(i) = exp[- h(i)*]

1 - q(i) = probability of death in year i
conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) incidence rate in year i
conditional on the person not having the response
through year i-1

Note that h(i) is NOT part of h(i)*,
because h(i) refers to incidence and h(i)* refers to death.

1

Derivation of Formulas:

i = 1, 2, ..., T

q(i) = probability of surviving year i
when all causes of death are acting
conditional on the person surviving through year i-1

h(i)* = mortality rate due to all causes in year i
conditional on the person surviving through year i-1

q(i) = exp[- h(i)*]

1 - q(i) = probability of death in year i
conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) incidence rate in year i
conditional on the person not having the response
through year i-1

qr(i) = exp[- h(i)] = probability of no response in year i
conditional on the person not responding through year i-1

1 -qr(i) = probability of response (incidence) in year i
conditional on the person not responding through year i-1

2

Derivation of Formulas:

i = 1, 2, ..., T

q(i) = probability of surviving year i
when all causes of death are acting
conditional on the person surviving through year i-1

h(i)* = mortality rate due to all causes in year i
conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) incidence rate in year i
conditional on the person not having the response
through year i-1

qr(i) =probability of no response (incidence) in year i
conditional on the person not responding through year i-1

S(1,i) = probability of surviving up to year i is the product of surviving each prior year:

$S(1,i) = q(1) \times q(2) \times ... \times q(i-1)$ with $S(1,1) = 1.0$.

SR(1,i) = probability of no response up to year i is the product of no response in each prior year:

$SR(1,i) = qr(1) \times qr(2) \times ... \times qr(i-1)$ with $SR(1,1) = 1.0$.

1

Derivation of Formulas:

i = 1, 2, ..., T

q(i) = probability of surviving year i when all causes of death are acting conditional on the person surviving through year i-1

h(i)* = mortality rate due to all causes in year i conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) incidence rate in year i conditional on the person not having the response through year i-1

qr(i) =probability of no response (incidence) in year i conditional on the person not responding through year i-1

S(1,i) = probability of surviving up to year i is the product of surviving each prior year:

$S(1,i) = q(1) \times q(2) \times ... \times q(i-1)$ with $S(1,1) = 1.0$.

SR(1,i) = probability of no response up to year i is the product of no response in each prior year:

$SR(1,i) = qr(1) \times qr(2) \times ... \times qr(i-1)$ with $SR(1,1) = 1.0$.

$S(1,i) \times SR(1,i) \times [1 - q(i) \times qr(i)]$ = probability of surviving to year i, not responding before year i, and then dying (from any cause) or having the response in year i

1

Derivation of Formulas:

i = 1, 2, ..., T

q(i) = probability of surviving year i when all causes of death are acting conditional on the person surviving through year i-1

h(i)* = mortality rate due to all causes in year i conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) incidence rate in year i conditional on the person not having the response through year i-1

qr(i) =probability of no response (incidence) in year i conditional on the person not responding through year i-1

S(1,i) = probability of surviving up to year i is the product of surviving each prior year:
S(1,i) = q(1) × q(2) × ... × q(i-1) with S(1,1) = 1.0.

SR(1,i) = probability of no response up to year i is the product of no response in each prior year:
SR(1,i) = qr(1) × qr(2) × ... × qr(i-1) with SR(1,1) = 1.0.

S(1,i) × SR(1,i) ×[1 - q(i) × qr(i)] = probability of surviving to year i, not responding before year i, and then dying (from any cause) or having the response in year i

A person is "observed" in year i if that person either dies in year i or has the specified response (incidence) in year i.

h(i)/ [h(i)* + h(i)] = proportion of observations (deaths plus incidences) in year i due to the response

{ h(i)/ [h(i)* + h(i)] } × S(1,i) × SR(1,i) × [1 - q(i) × qr(i)] = probability of surviving to year i, not responding before year i, and then having the response (incidence) in year i

2

Derivation of Formulas:

i = 1, 2, ..., T

q(i) = probability of surviving year i when all causes of death are acting conditional on the person surviving through year i-1

h(i)* = mortality rate due to all causes in year i conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) incidence rate in year i conditional on the person not having the response through year i-1

qr(i) =probability of no response (incidence) in year i conditional on the person not responding through year i-1

S(1,i) = probability of surviving up to year i is the product of surviving each prior year:
S(1,i) = q(1) × q(2) × ... × q(i-1) with S(1,1) = 1.0.

SR(1,i) = probability of no response up to year i is the product of no response in each prior year:
SR(1,i) = qr(1) × qr(2) × ... × qr(i-1) with SR(1,1) = 1.0.

S(1,i) × SR(1,i) ×[1 - q(i) × qr(i)] = probability of surviving to year i, not responding before year i, and then dying (from any cause) or having the response in year i

h(i)/ [h(i)* + h(i)] = proportion of observations (deaths plus incidences) in year i due to the response

{ h(i)/ [h(i)* + h(i)] } × S(1,i) × SR(1,i) × [1 - q(i) × qr(i)] = probability of surviving to year i, not responding before year i, and then having the response (incidence) in year i

$R_0 = \sum_{i=1,...,T} \{ h(i) / [h(i)^* + h(i)] \} \times S(1,i) \times SR(1,i) \times [1 - q(i) \times qr(i)]$
= probability of a response (incidence) in the first T years of life (i.e., up to the T-th birthday, age T) at dose 0 (no exposure in addition to background exposure)

3

Derivation of Formulas:

Background Risk of an Incidence:

$R_0 = \sum_{i=1,...,T} \{ h(i) / [h(i)^* + \mathbf{h(i)}] \} \times S(1,i) \times \mathbf{SR(1,i)} \times [1 - q(i) \times \mathbf{qr(i)}]$
= probability of a response (incidence) in the first T years of life
(i.e., up to the T-th birthday, age T) at dose 0
(no exposure in addition to background exposure)

Contrast with the form of the calculation for the
Background Risk of a Mortality
and that h(i) refers to mortality here and incidence above:

$R_0 = \sum_{i=1,...,T} [h(i) / h(i)^*] \times S(1,i) \times [1 - q(i)]$
= probability of a response mortality in the first T years of
life (i.e., up to the T-th birthday, age T) at dose 0
(no exposure in addition to background exposure)

1

Derivation of Formulas: Risk with exposure

i=1, 2, ..., T

q(i) = exp [- h(i)*] = probability of surviving year i without exposure
when all causes of death are acting
conditional on the person surviving through year i-1

h(i)* = mortality rate due to all causes in year i without exposure
conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) incidence rate in year i without exposure
conditional on the person not having the response through year i-1

qr(i) = exp [- h(i)] = probability of no response in year i without exposure
conditional on the person not responding through year i-1

f(i) = proportional effect (multipler) in year i assuming a proportional hazards
model for the effect of exposure of the form h(i) × f(i)
f(i) = [1 + e(i)] if the multiplier is a linear function

h(i) × f(i) = response (e.g., lung cancer) incidence rate in year i with exposure
conditional on the person not having the response
through year i-1

Derivation of Formulas: Risk with exposure

i=1, 2, ..., T

q(i) = exp [- h(i)*] = probability of surviving year i without exposure
when all causes of death are acting
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h(i)* = mortality rate due to all causes in year i without exposure
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h(i) = response (e.g., lung cancer) incidence rate in year i without exposure
conditional on the person not having the response through year i-1

qr(i) = exp [- h(i)] = probability of no response (incidence) in year i without exposure
conditional on the person not responding through year i-1

f(i) = proportional effect (multipler) in year i assuming a proportional hazards
model for the effect of exposure of the form h(i) × f(i)
f(i) = [1 + e(i)] if the multiplier is a linear function

h(i) × f(i) = response (e.g., lung cancer) incidence rate in year i with exposure
conditional on the person not having the response through year i-1

A person is "observed" in year i if that person either dies in year i
or has the specified response (incidence) in year i.

h(i)* + h(i) × f(i) = observation rate due to all causes in year i with exposure
conditional on the person not dying or having the response through year i-1

1

Derivation of Formulas: Risk with exposure

i=1, 2, ..., T

q(i) = = exp[- h(i)*] = probability of surviving year i without exposure
when all causes of death are acting
conditional on the person surviving through year i-1

h(i)* = mortality rate due to all causes in year i without exposure
conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) incidence rate in year i without exposure
conditional on the person not having the response through year i-1

qr(i) = exp[-h(i)] = probability of no response (incidence) in year i without exposure
conditional on the person not responding through year i-1

f(i) = proportional effect (multipler) in year i assuming a proportional hazards
model for the effect of exposure of the form h(i) × f(i)
f(i) = [1 + e(i)] if the multiplier is a linear function

h(i) × f(i) = response (e.g., lung cancer) incidence rate in year i with exposure
conditional on the person not having the response through year i-1

h(i)* + h(i) × f(i) = observation rate due to all causes in year i with exposure
conditional on the person not dying or having the response through year i-1

exp { - h(i)* - h(i) × f(i) } = q(i) × exp { - h(i) × f(i) }
= q(i) × exp{ - h(i) - h(i) × [f(i) - 1] } = q(i) × qr(i) × exp {- h(i) × [f(i)-1] }
probability with exposure of not dying and not
responding in year i conditional on not dying and not responding thru year i-1

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Derivation of Formulas: Risk with exposure

i=1, 2, ..., T

q(i) = = exp[- h(i)*] = probability of surviving year i without exposure when all causes of death are acting conditional on the person surviving through year i-1

h(i)* = mortality rate due to all causes in year i without exposure conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) incidence rate in year i without exposure conditional on the person not having the response through year i-1

qr(i) = exp[-h(i)] = probability of no response (incidence) in year i without exposure conditional on the person not responding through year i-1

S(1,i) = probability of surviving up to year i is the product of surviving each prior year: S(1,i) = q(1) × q(2) × ... × q(i-1) with S(1,1) = 1.0.

SR(1,i) = probability of no response up to year i is the product of no response in each prior year: SR(1,i) = qr(1) × qr(2) × ... × qr(i-1) with SR(1,1) = 1.0.

q(i) × qr(i) × exp {- h(i) × [f(i)-1] } = probability with exposure of not dying and not responding in year i conditional on not dying and not responding thru year i-1

$q(1)\times qr(1)\times\exp\{-h(1)\times[\,f(1)-1\,]\,\}\times\ldots\times q(i-1)\times qr(i-1)\times\exp\{-h(i-1)\times[\,f(i-1)-1\,]\,\}$

$= S(1,i)\times SR(1,i)\times\exp\left(-\sum_{k=1,\ldots,i-1}\{-h(k)\times[\,f(k)-1\,]\,\}\right)$

= probability with exposure of not dying and not responding up to year i

$S(1,i)\times SR(1,i)\times\exp(-\sum_{k=1,\ldots,i-1}\{-h(k)\times[f(k)-1]\})\times[1-q(i)\times qr(i)\times\exp\{-h(i)\times[\,f(i)-1]\}]$

= probability with exposure of not dying and not responding up to year i and then dying (from any cause) or having the response in year i

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Derivation of Formulas: Risk with exposure

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q(i) = = exp[- h(i)*] = probability of surviving year i without exposure when all causes of death are acting conditional on the person surviving through year i-1

h(i)* = mortality rate due to all causes in year i without exposure conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) incidence rate in year i without exposure conditional on the person not having the response through year i-1

qr(i) = exp[-h(i)] = probability of no response (incidence) in year i without exposure conditional on the person not responding through year i-1

S(1,i) = probability of surviving up to year i is the product of surviving each prior year: S(1,i) = q(1) × q(2) × ... × q(i-1) with S(1,1) = 1.0.

SR(1,i) = probability of no response up to year i is the product of no response in each prior year: SR(1,i) = qr(1) × qr(2) × ... × qr(i-1) with SR(1,1) = 1.0.

q(i) × qr(i) × exp {- h(i) × [f(i)-1] } = probability with exposure of not dying and not responding in year i conditional on not dying and not responding thru year i-1

$S(1,i)\times SR(1,i)\times\exp(-\sum k=1,\ldots,i-1\{-h(k)\times[\,f(k)-1\,]\,\})\times[1-q(i)\times qr(i)\times\exp\{-h(i)\times[\,f(i)-1]\}]$
= probability with exposure of not dying and not responding up to year i and then dying (from any cause) or having the response in year i

$\{\,h(i)\times f(i)\,\}/\{\,h(i)^*+h(i)\times f(i)\,\}$ = proportion of observations (deaths plus incidences) in year i due to the response with exposure

$(\{h(i)\times f(i)\}/\{h(i)^*+h(i)\times f(i)\})\times S(1,i)\times SR(1,i)\times\exp(-\sum_{k=1,\ldots,i-1}\{-h(k)\times[f(k)-1]\})\times[1-q(i)\times qr(i)\times\exp\{-h(i)\times[\,f(i)-1]\}]$ = probability with exposure of not dying and not responding up to year i and then having the response in year i

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Derivation of Formulas: Risk with exposure

$$(\{ h(i) \times f(i) \} / \{ h(i)^* + h(i) \times f(i) \})$$
$$\times S(1,i) \times SR(1,i) \times \exp(- \sum_{k=1,\ldots,i-1} \{-h(k) \times [f(k)-1]\})$$
$$\times [1 - q(i) \times qr(i) \times \exp \{ -h(i) \times [f(i)-1] \}]$$

= probability of not dying and not responding in i-1 years and then having the response in year i with exposure

$$R_{exposure} = \sum_{i=1,\ldots,T}$$
$$(\{h(i) \times f(i)\} / \{ h(i)^* + h(i) \times f(i) \})$$
$$\times S(1,i) \times SR(1,i) \times \exp(- \sum_{k=1,\ldots,i-1} \{ -h(k) \times [f(k)-1] \})$$
$$\times [1 - q(i) \times qr(i) \times \exp \{ -h(i) \times [f(i)-1] \}]$$

= probability of a response (incidence) in the first T years of life (i.e., up to the T-th birthday, age T) with exposure (with exposure in addition to the background exposure)

Derivation of Formulas:

Risk of an Incidence with exposure:

$$R_{exposure} = \sum_{i=1,\ldots,T}$$
$$(\{h(i) \times f(i)\} / \{ h(i)^* + h(i) \times \mathbf{f(i)} \})$$
$$\times S(1,i) \times \mathbf{SR(1,i)} \times \exp(- \sum_{k=1,\ldots,i-1} \{ -h(k) \times [f(k)-1] \})$$
$$\times [1 - q(i) \times \mathbf{qr(i)} \times \exp \{ -h(i) \times [f(i)-1] \}])$$

Contrast with the form of the calculation for the Risk of a Mortality with exposure and that h(i) refers to mortality here and incidence above:

$$R_{exposure} = \sum_{i=1,\ldots,T} (\{h(i) \times f(i)\} / \{h(i)^* + h(i) \times [f(i)-1] \})$$
$$\times S(1,i) \times \exp(- \sum_{k=1,\ldots,i-1} \{ -h(k) \times [f(k)-1] \})$$
$$\times (1 - q(i) \times \exp \{ - h(i) \times [f(i) - 1] \})$$

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Risks

$R_0 = \sum_{i=1,\ldots,T} \{ h(i) / [h(i)^* + h(i)] \} \times S(1,i) \times SR(1,i) \times [1 - q(i) \times qr(i)]$
= probability of a response (incidence) in the first T years of life (i.e., up to the T-th birthday, age T)
at dose 0 (no exposure in addition to background exposure)

$R_{exposure} = \sum_{i=1,\ldots,T}$

$(\{h(i) \times f(i)\} / \{ h(i)^* + h(i) \times f(i) \})$
$\times S(1,i) \times SR(1,i) \times \exp(- \sum_{k=1,\ldots,i-1} \{ -h(k) \times [f(k)-1] \})$
$\times [1 - q(i) \times qr(i) \times \exp \{ -h(i) \times [f(i)-1] \}]$

= probability of a response (incidence) in the first T years of life (i.e., up to the T-th birthday, age T) with exposure
(with exposure in addition to the background exposure)

Added Risk = $R_{exposure} - R_0$

Extra Risk = $(R_{exposure} - R_0) / (1 - R_0)$

Excess Risk = either Added Risk or Extra Risk

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