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Provisional Peer-Reviewed Toxicity Values for

n-Butylbenzene
(CASRN 104-51-8)

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COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMD	benchmark dose
BMCL	benchmark concentration lower bound 95% confidence interval
BMDL	benchmark dose lower bound 95% confidence interval
HEC	human equivalent concentration
HED	human equivalent dose
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
POD	point of departure
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
UF	uncertainty factor
UF_A	animal-to-human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete-to-complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
WOE	weight of evidence

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR *n*-BUTYLBENZENE (CASRN 104-51-8)

BACKGROUND

HISTORY

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

1) EPA's Integrated Risk Information System (IRIS).
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in EPA's Superfund Program.
3) Other (peer-reviewed) toxicity values, including
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

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

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

DISCLAIMERS

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

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

QUESTIONS REGARDING PPRTVS

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

INTRODUCTION

No RfD, RfC, or carcinogenicity assessment for *n*-butylbenzene is available on IRIS (U.S. EPA, 2008), in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006), or in the HEAST (U.S. EPA, 1997). The only document on the CARA list (U.S. EPA, 1991, 1994) that includes information about *n*-butylbenzene is a Drinking Water Health Advisory for *n*-Butylbenzene (U.S. EPA, 1987); it concluded that data were inadequate for derivation of health advisory levels. ATSDR (2008) has not produced a Toxicological Profile for *n*-butylbenzene, and no Environmental Health Criteria Document is available (WHO, 2008). The American Conference of Governmental Industrial Hygienists (ACGIH, 2007), the Occupational Safety and Health Administration (OSHA, 2008), and the National Institute for Occupational Safety and Health (NIOSH, 2008) have not established occupational health standards for *n*-butylbenzene. The carcinogenicity of *n*-butylbenzene has not been assessed by IARC (2008) or NTP (2005, 2008).

Literature searches were conducted from the 1960s through December 2009 for studies relevant to the derivation of provisional toxicity values for *n*-butylbenzene. Databases searched include MEDLINE, TOXLINE (Special), BIOSIS, TSCATS1/TSCATS 2, CCRIS, DART/ETIC, GENETOX, HSDB, RTECS, and Current Contents. A review by Henderson (2001) was also consulted for relevant information.

REVIEW OF PERTINENT DATA

HUMAN STUDIES

No relevant human studies were located.

ANIMAL STUDIES

In a two-generation reproductive summary report (Yamasaki et al., 2005) in SD rats for nine chemicals, *n*-butylbenzene was administered orally by gavage at dose levels of 0, 30, 100, or 300 mg/kg-day. The study authors found no effects on the endocrine system and no reproductive effects in the F0 and F1 parents or F1 and F2 offspring for the study of *n*-butylbenzene. The study was primarily designed for detecting endocrine-mediated influence by *n*-butylbenzene and other eight chemicals; the study authors conducted no further histopathology or clinical chemistry on the rats exposed to *n*-butylbenzene at any dose level. The highest tested dose in this study, 300 mg/kg-day, is considered a NOAEL in this PPRTV document.

In a preliminary study, *n*-butylbenzene (98% purity) was administered by gavage to Crj:CD (SD) IGS rats (6/sex/dose) at doses of 0, 30, 100, 300, or 1000 mg/kg-day every day for 4 weeks prior to mating, and throughout gestation and lactation (Izumi et al., 2005). Methods for the preliminary study are not further described. Body-weight gain was inhibited in parental rats treated with 1000 mg/kg-day, and the study authors evaluated the liver, kidney, and adrenal weights in males treated with 300 or 1000 mg/kg-day (no further details reported; data not shown). The study authors reported that there were no effects on the fertility of the parental animals, but there was a decreased viability of offspring at Postnatal Day (PND) 4 among F1 rats in the 1000-mg/kg-day group; body-weight gain was also inhibited among F1 offspring in this treatment group (no further details reported; data not shown).

Based on the results of this study, *n*-butylbenzene was administered by gavage (in olive oil; volume adjusted to 5 ml/kg) to Crj:CD (SD) IGS rats (24/sex/dose) at doses of 0, 30, 100, or 300 mg/kg-day, every day for over two generations (Izumi et al., 2005). F0 males and females were exposed for 10 weeks prior to mating and during the mating period (up to 2 weeks). F0 males were exposed for an additional 4–6 weeks after mating, while F0 females were exposed throughout gestation and lactation (to Day 21); both sexes were exposed for a total of 14–16 weeks. F1 males were exposed for approximately 18 weeks, and F1 females were exposed for 19–21 weeks; exposures included the 10 weeks prior to mating (starting at weaning at 3 weeks of age), the mating period, and, in females, gestation and lactation (to Day 21). Animals were observed daily for clinical signs and mortality. Body weight and food consumption were measured weekly for males, and weekly for females prior to conception. For females, body weight was also measured on Gestational Days (GDs) 0, 7, 14, and 20, and PNDs 0, 4, 7, 14, and 21. Food consumption was measured on GDs 1, 7, 14 and 20, and on PNDs 1, 4, 7, 14, and 21. Fertility was assessed in parental animals by measurement of estrous count, estrous interval, number of pregnancies, number of confirmed copulations, number of viable offspring, implantations, gestation length, and litter size. The timing of sexual maturation was assessed in offspring by examining them for vaginal opening (females) or preputial separation (males) every day until completion of the process. Sperm counts and motility were determined for 10 males per dose. Hormone levels, including estradiol, testosterone, follicle stimulating hormone (FSH), and luteinizing hormone (LH) were assessed in six males (different group than those in whom sperm variables were assessed) and six females from each dose.

The following variables were assessed for each litter: number of each sex, number of live offspring, and number of live offspring on PNDs 4 and 21 (Izumi et al., 2005). Offspring were assessed daily for clinical signs. Each litter was culled to four males and four females, where

possible, on PND 4. The following developmental milestones were assessed for each individual within a litter to detect potential effects related to endocrine disruption: pinna detachment from PND 4 to completion; incisor eruption from PND 10 to completion; eyelid separation from PND 15 to completion; righting reflex from PND 5 to completion; visual placing reflex from PND 16 to completion and Preyer's reflex from PND 28 to completion. Organ weights were assessed for all major organs in parental animals. The weights of brain, thymus, spleen, testes, epididymides, ovaries, and uterus were measured in F1 and F2 weanlings. All parental animals, offspring that died during lactation or were culled and weanlings that were not selected as parental animals were necropsied. The following tissues from all F0 and F1 adult animals from the control and high-dose groups were examined microscopically: pituitary gland, thyroid and parathyroid glands, liver, kidneys, adrenal glands, testes, epididymides, seminal vesicles, coagulating glands, prostate, ovaries, oviduct, uterus, uterine cervix, vagina, mammary glands, and any macroscopically identified abnormal tissue. Based on changes observed in the high-dose group, liver, kidneys, ovaries, oviduct, uterus, uterine cervix, and vagina were also examined microscopically for the 30- and 100-mg/kg-day dose groups. The pituitary glands, testes, epididymides, prostate, seminal vesicles, and coagulating glands were examined in the noncopulating and infertile copulating males in the 30-and 100-mg/kg-day dose groups and in five fertile animals from the control group.

No treatment-related mortality was observed in parental animals, although one high-dose F0 female and one control F1 female died during the study due to spontaneous leukemia and gavage error, respectively (Izumi et al., 2005). Excessive salivation was observed immediately after *n*-butylbenzene administration in parental rats (primarily the males) from both generations in the 100- and 300-mg/kg-day treatment groups. No other clinical signs were observed. According to the study authors, body weight and food consumption were not affected by treatment, and there were no treatment-related effects on any indicator of fertility[1] in either parental sex and in any generation (but, in the F0 dams, there was a tendency for reduced number of implantations at 300 mg/kg/day and a prolonged estrus interval at 100 and 300 mg/kg/day but not statistically significant [$p < 0.05$]), and no treatment-related effects on hormone levels of parental animals. No treatment-related effects were observed upon gross necropsy of parental animals. Statistically significant increases (12–19% at $p < 0.05$) in absolute and relative liver weight were seen in parental F0 males at ≥100 mg/kg-day (liver histopathological changes were observed at 300 mg/kg-day, but not at 100 mg/kg-day), F0 females at ≥30 mg/kg-day, and F1 males and females at 300 mg/kg-day (no histopathological change was observed in the liver of the female animals). Absolute and relative kidney weights were statistically significantly increased (7–21% at $p < 0.05$) in parental male (with histopathological changes) and female rats (with no histopathological change) of both generations at 300 mg/kg-day. In addition, a histopathological change accompanied by statistically increased relative kidney weights (7% at $p < 0.05$) at 100 mg/kg-day was observed in F1 parent males only. As discussed by Izumi et al. (2005), the observed pattern of kidney changes is consistent with male-rat-specific alpha$_{2u}$-globulin-associated nephropathy—a condition that is not relevant to humans, but an analysis of the mode of action has not been conducted in this assessment. Therefore, this effect is considered relevant to humans. Incidence data for liver and kidney histopathological effects are presented in Table 1. There was also a statistically significant increase (13% at $p < 0.05$) in absolute and relative adrenal glands weights in high-dose F1 parental females (but not F1 males

[1] Estrous count, estrous interval, copulations, numbers mating, number of pregnant females, gestation length, numbers of implantations, litter size, etc.

or F0 males or females). There were no histopathological findings in adrenal glands of parental animals of either generation. There were no other significant treatment-related effects on organ weights, including reproductive organs, in F0 or F1 parental animals.

Table 1. Incidence of Histopathological Findings of Interest in Parental Male Rats via Oral Exposure to *n*-Butylbenzene

	Mean Dose (mg/kg-day)			
Generation/Sex/Target/Lesion	**0**	**30**	**100**	**300**
F0 Males				
Liver, Hypertrophy, hepatocytes	0/24	0/24	0/24	5/24[a]
Kidney, hyaline droplets, proximal tubules	0/24	0/24	1/24	11/24[b]
Kidney, basophilic tubules	0/24	0/24	0/24	5/24[a]
F1 Males				
Liver, Hypertrophy, hepatocytes	0/19	0/19	0/21	6/19[b]
Kidney, hyaline droplets, proximal tubules	0/19	1/19	5/21[a]	12/19[a]
Kidney, basophilic tubules	0/19	0/19	1/21	5/19[a]

[a]Significantly different from controls ($p < 0.05$).
[b]Significantly different from controls ($p < 0.01$).

Source: Izumi et al. (2005).

In summary, for parental animals several effects were observed (increased liver, kidney, and adrenal weights, hyaline droplets in proximal tubules, and hepatocellular hypertrophy) at 300 mg/kg-day. Statistically significant increases in liver weight were seen in parental F0 males at ≥100 mg/kg-day (liver histopathological changes were observed at 300 mg/kg-day, but not at 100 mg/kg-day), F0 females at ≥30 mg/kg-day, and F1 males and females at 300 mg/kg-day (no histopathological change was observed in the liver of the female animals). Absolute and relative kidney weights were statistically significantly increased in parental male (with histopathological changes) and female rats (with no histopathological change) of both F0 and F1 generations at 300 mg/kg-day. A histopathological change accompanied by statistically increased relative kidney weights (7%) at 100 mg/kg-day was observed in F1 parent males only. There was also a statistically significant increase in absolute and relative adrenal glands weights in F1 parental females (but not F1 males or F0 males or females) at 300 mg/kg-day that was not accompanied by histopathological changes. The LOAEL for parental animals is identified as 300 mg/kg-day based on hepatocellular hypertrophy, and increases in liver, kidney, and adrenal weights.

There were no treatment-related effects on any measure of growth or development in F1 or F2 offspring, other than slight increases in absolute and/or relative thymus weight in some groups exposed to 300 mg/kg-day (Izumi et al., 2005). Thymus and body-weight data are shown in Table 2. The magnitude of the observed increases ranged from 10–27%, but the standard deviations around the control means were large (15–32%), so, that in each case, the observed increase was within 1 standard deviation of the control mean. There were no consistent changes in other organ weights in the F1 or F2 pups (liver and kidney weights not reported).

Table 2. Body and Thymus Weights in Rats Treated with *n*-Butylbenzene

Parameter	Dose (mg/kg-day)							
	0		30		100		300	
	Males	Females	Males	Females	Males	Females	Males	Females
F0 parents								
Number of rats	24	19	24	19	24	21	24	19
Body weight (g)	636.7 ± 72.9[a]	322.8 ± 24.7	627.6 ± 51.2	331.3 ± 23.7	635.09 ± 70.2	328.4 ± 17.9	623.4 ± 60.8	321.4 ± 22.6
Liver weight								
Absolute (g)	21.35 ± 3.71	13.30 ± 1.62	21.53 ± 2.54	15.09 ± 1.50[b]	22.78 ± 3.04	15.11 ± 1.64[b]	25.02 ± 3.42[b]	15.20 ± 1.70[b]
Relative (%)	3.34 ± 0.28	4.13 ± 0.47	3.43 ± 0.21	4.56 ± 0.33[c]	3.58 ± 0.18	4.61 ± 0.50[b]	4.00 ± 0.27[b]	4.74 ± 0.54[b]
Thymus weight								
Absolute (g)	0.27 ± 0.08	0.21 ± 0.06	0.26 ± 0.08	0.22 ± 0.05	0.27 ± 0.09	0.21 ± 0.07	0.25 ± 0.07	0.22 ± 0.07
Relative (%)	0.04 ± 0.01	0.07 ± 0.02	0.04 ± 0.01	0.06 ± 0.02	0.04 ± 0.01	0.06 ± 0.02	0.04 ± 0.01	0.07 ± 0.02
F1 parents								
Number of rats	19	12	19	11	21	12	19	13
Body weight (g)	680.4 ± 99.7	328.9 ± 21.9	698.4 ± 45.1	329.2 ± 20.7	668.0 ± 61.3	323.4 ± 33.6	653.3 ± 75.5	325.4 ± 20.3
Liver weight								
Absolute (g)	24.05 ± 5.57	15.15 ± 1.75	25.08 ± 2.95	15.03 ± 1.44	24.15 ± 2.75	14.90 ± 1.52	26.82 ± 4.14	17.02 ± 2.26[c]
Relative (%)	3.51 ± 0.34	4.62 ± 0.52	3.58 ± 0.25	4.57 ± 0.37	3.62 ± 0.24	4.62 ± 0.39	4.09 ± 0.28[b]	5.22 ± 0.48[b]
Thymus weight								
Absolute (g)	0.29 ± 0.08	0.22 ± 0.07	0.29 ± 0.07	0.22 ± 0.07	0.30 ± 0.08	0.22 ± 0.07	0.28 ± 0.12	0.21 ± 0.06
Relative (%)	0.04 ± 0.01	0.07 ± 0.02	0.04 ± 0.01	0.07 ± 0.02	0.04 ± 0.01	0.07 ± 0.02	0.04 ± 0.02	0.06 ± 0.02
F1 offspring								
Number of rats	19	19	19	19	21	21	17	17
Body weight (g)	61.4 ± 6.6	57.6 ± 10.8	61.5 ± 6.0	59.9 ± 5.0	59.1 ± 6.1	57.3 ± 5.9	65.3 ± 7.6	64.0 ± 6.0
Thymus weight								
Absolute (g)	0.22 ± 0.07	0.23 ± 0.07	0.24 ± 0.04	0.24 ± 0.04	0.21 ± 0.04	0.21 ± 0.05	0.28 ± 0.04[c]	0.28 ± 0.06[c]
Relative (%)	0.36 ± 0.07	0.40 ± 0.08	0.39 ± 0.05	0.40 ± 0.06	0.35 ± 0.05	0.37 ± 0.07	0.43 ± 0.05[b]	0.44 ± 0.08

Table 2. Body and Thymus Weights in Rats Treated with *n*-Butylbenzene

Parameter	Dose (mg/kg-day)							
	0		30		100		300	
	Males	Females	Males	Females	Males	Females	Males	Females
F2 offspring								
Number of rats	12	12	11	11	12	12	13	13
Body weight (g)	71.4 ± 6.2	68.3 ± 5.8	71.9 ± 3.3	66.1 ± 5.5	66.6 ± 5.5	64.9 ± 7.1	71.8 ± 4.1	67.2 ± 6.3
Thymus weight								
Absolute (g)	0.29 ± 0.06	0.25 ± 0.05	0.30 ± 0.05	0.28 ± 0.05	0.26 ± 0.06	0.26 ± 0.06	0.29 ± 0.03	0.29 ± 0.03
Relative (%)	0.40 ± 0.06	0.37 ± 0.07	0.41 ± 0.07	0.41 ± 0.07	0.38 ± 0.08	0.40 ± 0.06	0.41 ± 0.05	0.43 ± 0.05[c]

[a]Mean ± standard deviation.
[b]Significantly different from controls ($p < 0.01$).
[c]Significantly different from controls ($p < 0.05$).

N/A = not applicable.

Source: Izumi et al. (2005). Liver weight is not reported for F1/F2 offspring.

The authors considered the effects on pup thymus weight to be treatment-related, but there were some inconsistencies that suggest that the observed changes may not be toxicologically relevant. The only evidence clearly supporting an effect is the statistically significant increase ($p < 0.05$) in both absolute and relative thymus weight in F1 male pups at the high-dose of 300 mg/kg-day. Statistically significant increases ($p < 0.05$) in absolute—but not relative—thymus weight in F1 female pups at 300 mg/kg-day, and relative—but not absolute—thymus weight in F2 female pups at 300 mg/kg-day offer only ambiguous support. These changes were not internally consistent (i.e., absolute and relative weights were not both changed together) and were proportional to body weight changes observed in the same groups (nonsignificant increase in body weight in F1 female pups and nonsignificant decrease in F2 female pups).

Overall, the biological significance of the change in pup thymus weight is questionable, but if one assumes that the effect is a significant effect, then there is a potential concern for immunotoxicity and no immunological assays have been conducted. Increased thymus weight (10–27%) in young offspring may be an indicator of immunotoxicity because the thymus gland is a key organ for the immune system (i.e., processing and maturation of T-cells). Despite the lack of histological findings in parental animals (including the F1 parents that received *in utero* exposure), and the small increases in mean organ weights observed in the weanlings, the observed effect on thymus weight in the weanlings is considered to be biologically significant for this assessment in the absence of data to indicate otherwise. A LOAEL of 300 mg/kg-day based on the increased thymus weight in F2 females is identified. The NOAEL is 100 mg/kg-day.

Izumi et al. (2005) concluded that hepatocellular hypertrophy and increases in liver weight in parental rats are an adaptive, rather than adverse, effect of *n*-butylbenzene on the liver based on enzymatic induction of rat liver cytochrome P450 at an equivalent dose of 670 mg/kg as demonstrated by Imaoka and Funane (1991). The effect of hepatocellular hypertrophy may be specific to males because no histological change was observed in the liver of the female rats (but the liver weight in females were increased significantly at lower doses). Overall, these liver effects cannot be discounted because there is uncertainty of the enzymatic induction at the low-dose region (≤300 mg/kg-day) and its potential extrapolation and relevance to humans. For this review, these liver effects are considered biologically significant, and a LOAEL is established at 300 mg/kg-day based on the hepatocellular hypertrophy and is supported by (absolute and/or relative) increased liver weight in F0/F1 parent males. The NOAEL is 100 mg/kg-day.

OTHER STUDIES

Tanii et al. (1995) reported an i.p. LD50 of 1.995 g/kg for *n*-butylbenzene in mice. Following acute oral exposure to 4.3 g/kg *n*-butylbenzene, 2/10 rats died (Gerarde, 1959). Lethality was higher for branched-chain butylbenzenes in this study (8/10 died for sec-butylbenzene and 7/10 for *tert*-butylbenzene at the same dose). The leading cause of death in rats in this study was chemical-induced pneumonitis with pulmonary edema and hemorrhage, the latter often associated with hemorrhage in other tissues such as thymus, adrenal, and bladder. The study authors also reported hyperemia and vasodilation of the blood vessels of the gastrointestinal tract.

Noting that aromatic solvents including toluene, ethylbenzene, styrene, and *p*-xylene have been shown to cause irreversible hearing loss in rats, Gagnaire and Langlais (2005) tested the relative ototoxicity of 21 aromatic solvents, including *n*-butylbenzene. In their studies, groups of 7–8 young

male Sprague-Dawley rats were administered 8.47 mmol/kg of chemical (in a volume of 2 mL/kg) by gastric intubation for 5 days/week for a 2-week period[2]. Using the molecular weight of 134.22 g/mol for *n*-butylbenzene, a molar concentration of 8.47 mmol/kg is equivalent to a dose of 1137 mg/kg-day. After dosing, body weights were measured daily during the 2 weeks of treatment, and then for a subsequent 10 days after the period of treatment. The behavior and general health of rats was observed on a daily basis. At the end of the 10-day recovery period, six rats per treatment group were chosen randomly, deeply anesthetized, and perfused with buffered paraformaldehyde and glutaraldehyde. Subsequently, three left and three right cochleas were removed from the six chosen rats in each group and processed. Organs of Corti and basilar membranes were examined by light microscopy and scanning electron microscopy.

The only mortality was observed in 2/8 rats treated with isobutylbenzene (Gagnaire and Langlais, 2005). The study authors noted ataxia and hypoactivity in the rats treated with isobutylbenzene after each treatment. No treatment-related clinical signs were observed in any of the other groups—including those treated with *n*-butylbenzene. Of the 21 solvents tested, the following eight caused histological lesions (loss of hair cells) in the organ of Corti (listed from most to least toxic based on cytocochleograms[3]): allylbenzene, ethylbenzene, styrene, *n*-propylbenzene, *p*-xylene, toluene, *trans*-β-methylstyrene, and α-methylstyrene. The remaining chemicals tested, including cumene (isopropylbenzene), *n*-butylbenzene, *tert*-butylbenzene, 1,4-diethylbenzene, *sec*-butylbenzene, *p*-ethyltoluene, 2-,3- and 4-methylstyrene, *m*-xylene, *o*-xylene, and benzene did not cause biologically significant inner or outer hair cell loss and were considered to be inactive with regard to ototoxicity. Following an examination of octanol/water partition coefficients for the chemicals tested, Gagnaire and Langlais (2005) concluded that there was no correlation between ototoxicity and lipophilicity and that an unidentified structural constraint was essential to induce ototoxicity. Given that only one dose was tested, a freestanding NOAEL of 1137 mg/kg-day is identified for *n*-butylbenzene in this study. For comparative purposes, the LOAELs for ethylbenzene and *n*-propylbenzene in this study are 899 and 1018 mg/kg-day, respectively, based on molecular weights of 106.16 and 120.19 g/mol, respectively.

The RD_{50} (concentration necessary to depress the respiratory rate by 50% during acute exposure) for sensory irritation by *n*-butylbenzene was 710 ppm in a 30-minute exposure; the chemical did not cause pulmonary irritation (defined as a decrease in respiratory rate during exposure via tracheal cannula) at the RD_{50} (Nielsen and Alarie, 1982).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR *n*-BUTYLBENZENE

SUBCHRONIC p-RfD

There are no subchronic systemic toxicity studies of *n*-butylbenzene. The two-generation reproduction study of rats by Izumi et al. (2005) is comprehensive and well conducted and addresses

[2]The dose was selected on the basis of previous range-finding studies conducted with toluene. The chosen dose was associated with outer hair cell (OHC) loss in the middle turn of the organ of Corti—without causing mortality or body-weight loss.

[3]Cytocochleograms are three-dimensional graphs based on counts of the inner hair cells (IHC) and three rows of OHC in the organ of Corti.

variables relevant to neurotoxicity and endocrine disruption as well as the usual spectrum of variables typically assessed in a multigeneration reproduction study. It is the chosen principal study. Statistically significant increases ($p < 0.05$) in organ weights were observed (liver, kidneys, and adrenals in parental animals of two generations; and thymus weights in weanlings of F1 and F2 generations); only the increased liver and kidney weights were supported by histopathological changes (hepatocellular hypertrophy and hyaline droplets in proximal tubules, respectively) in F0 and F1 parent males. The study authors reported observing no treatment-related effects on reproduction, reproduction hormones, or growth and development of offspring over two generations (with exception of the increased thymus weight).

Several effects were observed at 300 mg/kg-day in parental animals (increased liver, kidney and adrenal weights, formation of hyaline droplet in proximal tubules, and hepatocellular hypertrophy), and in F2 females (increased thymus weight). Although statistically significant changes in liver and kidney weight were observed in parental animals at a dose of 100 mg/kg-day, these changes were considered minimal and were not consistently seen across generations and sexes. In addition, there are concerns about the significance of the thymus weight changes in F2 females such that this endpoint was not chosen as the critical effect for the derivation of the p-subchronic RfD. Overall, the liver effects based on the increased hepatocellular hypertrophy and liver weight are considered to be more sensitive than the kidney effects, because these effects occurred in two generations (F0 and F1 parent males) and increased liver weights were observed at lower doses (even though there were no histopathological changes at 30- and 100-mg/kg-day treatment groups in either gender). Therefore, the critical effect is hepatocellular hypertrophy with a LOAEL of 300 mg/kg-day in both F0 and F1 parent male rats.

To select a POD for subchronic p-RfD derivation, the increased incidences of hepatocellular hypertrophy in F0 and F1 parent male rats (see Table 1) as the critical effect were modeled using EPA's Benchmark Dose Software (v. 2.1). Appendix A provides details of the modeling effort and the selection of the best fitting model. The best-fitting model, as assessed by AIC (model with lowest AIC) for either data set was the gamma model. The BMD_{10} and $BMDL_{10}$ derived by this model for the F0 parent hepatocellular hypertrophy are 266 and 162 mg/kg-day, respectively. The BMD_{10} and $BMDL_{10}$ derived by this model for the F1 parent hepatocellular hypertrophy are 245 and 137 mg/kg-day, respectively. The $BMDL_{10}$ of 137 mg/kg-day based on the F1 parent hepatocellular hypertrophy is selected as the POD.

The **subchronic p-RfD** for *n*-butylbenzene is derived as follows:

Subchronic p-RfD = $BMDL_{10} \div UF$
= 137 mg/kg-day ÷ 1000
= **0.1 or 1×10^{-1} mg/kg-day**

The composite UF of 1000 is composed of the following:

- UF_H: A factor of 10 is applied to account for intraspecies variability, including variability in susceptibility in human populations and life-stages.
- UF_A: A factor of 10 is applied for animal-to-human extrapolation because data for evaluating toxicokinetic or toxicodynamic differences are insufficient.

- UF_D: A factor of 10 is applied for database inadequacies because neither general toxicity or developmental studies are available. In addition, immunological toxicity is of potential concern due to changes in thymus weight observed in F1 and F2 offspring.
- UF_L: A factor for extrapolating from a LOAEL to a NOAEL is not needed because BMD modeling was used to determine the POD.

Confidence in the principal study is medium; although the study was well conducted and well reported, it was not designed to address the full complement of variables normally addressed in a subchronic toxicity study, and it does not include clinical chemistry, hematology, or urinalysis components. Confidence in the database is low because it lacks true subchronic and developmental toxicity studies. Thus, overall confidence in the subchronic p-RfD is low.

CHRONIC p-RfD

A **chronic p-RfD** is similarly derived by applying a UF of 3000 to the $BMDL_{10}$ of 137 mg/kg-day as follows:

Chronic p-RfD = $BMDL_{10} \div UF$
= 137 mg/kg-day ÷ 3000
= **0.05 or 5×10^{-2} mg/kg-day**

The composite UF of 3000 is composed of the following:

- UF_H: A factor of 10 is applied to account for intraspecies variability, including variability in susceptibility in human populations and life-stages.
- UF_A: A factor of 10 is applied for animal-to-human extrapolation because data for evaluating toxicokinetic or toxicodynamic differences are insufficient.
- UF_D: A factor of 10 is applied for database inadequacies because neither general toxicity or developmental studies are available. In addition, immunological toxicity is of potential concern due to changes in thymus weight observed in F1 and F2 offspring.
- UF_L: A factor for extrapolating from a LOAEL to a NOAEL is not needed because BMD modeling was used to determine the POD.
- UF_S: A factor of 3 is applied for using data from the two-generational reproductive study (Izumi et al., 2005) based on the increased incidences of hepatocellular hypertrophy, in both F0 and F1 parent males. The dose-response trends are similar in both F0 and F1 parent males, which suggest longer exposure (*in utero* and 18-week exposures) to *n*-butylbenzene in F1 parent males may not lead to an increase in the incidences of hypertrophy.

Confidence in the key study (Izumi et al., 2005) is medium, as discussed above for the subchronic p-RfD. Confidence in the database for the chronic RfD is low due to the lack of subchronic, chronic, and additional developmental toxicity studies. Thus, overall confidence in the chronic p-RfD is low.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR *n*-BUTYLBENZENE

Data on the inhalation toxicity of the *n*-butylbenzene are limited to an acute respiratory irritation study that is not appropriate as the basis for the derivation of provisional RfCs.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR *n*-BUTYLBENZENE

WEIGHT-OF-EVIDENCE DESCRIPTOR

Under the 2005 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), there is **"*Inadequate Information to Assess Carcinogenic Potential*"** of *n*-butylbenzene. There are no human epidemiology studies, genotoxicity studies, or carcinogenicity assays.

QUANTITATIVE ESTIMATES OF CARCINOGENIC RISK

The lack of data on the carcinogenicity of *n*-butylbenzene precludes the derivation of quantitative estimates of risk for either oral or inhalation exposure.

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APPENDIX A. DETAILS OF BENCHMARK DOSE MODELING FOR SUBCHRONIC AND CHRONIC p-RfDs

MODEL FITTING PROCEDURE FOR QUANTAL NONCANCER DATA

The model-fitting procedure for dichotomous noncancer data is as follows. All available dichotomous models in the EPA Benchmark Dose Software (BMDS, version 2.1) are fit to the incidence data using the extra risk option. The multistage model is run for all polynomial degrees up to *n*-1 (where *n* is the number of dose groups including control). Goodness-of-fit is assessed by the χ^2 test. When several models provide adequate fit to the data (χ^2 $p \geq 0.1$), and the estimated BMDLs from these models differ by $\geq$3-fold, then the model with the lowest BMDL is selected. Otherwise, models with adequate fit are compared using the Akaike Information Criterion (AIC). The model with the lowest AIC is considered to provide the best fit to the data. When several models have the same AIC, the model resulting in the lowest BMDL is selected. In accordance with U.S. EPA (2000) guidance, benchmark doses (BMDs) and lower bounds on the BMD (BMDLs) associated with an extra risk of 10% (BMD_{10} and $BMDL_{10}$) are calculated for all models.

Model-Fitting Results for Liver Hypertrophy in F0 and F1 Males (Izumi et al., 2005)

Applying the procedure outlined above to the F0 and F1 male data on the incidences of hepatocellular hypertrophy (see Table 1), an adequate model fit was achieved with several models for both data sets. Table A-1 and A-2 show the results for the liver effect. In accordance with U.S. EPA (2000) guidance, the model with the lowest AIC was considered to provide the best fit to the data. For the F0 males, the resulting benchmark dose (BMD_{10}) and associated 95% lower confidence limit ($BMDL_{10}$) are 266 and 162 mg/kg-day, respectively. For the F1 males, the resulting benchmark dose (BMD_{10}) and associated 95% lower confidence limit ($BMDL_{10}$) are 245 and 137 mg/kg-day, respectively. Figure A-1 shows the model fit of the Gamma model to the F0 data; this model results in the lowest AIC value and best fit to the data. Figure A-2 shows the model fit of the Gamma model to the F1 data; this model results in the lowest AIC value and best fit to the data.

Table A-1. Benchmark Dose Model Predictions for Liver Hypertrophy in F0 Male Rats[a]

Model	Degrees of Freedom	χ^2	χ^2 Goodness of Fit *p*-Value	AIC	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)
Quantal Linear	3	2.44	0.49	30.52	201.25	104.39
Multistage (degree = 1)[b]	3	2.44	0.49	30.52	201.25	104.39
Multistage (degree = 2)[b]	3	0.68	0.88	27.84	214.77	148.71
Multistage (degree = 3)[b]	3	0.68	0.88	27.84	214.77	148.71
Weibull (power ≥ 1)	2	0	1	28.56	285.42	164.82
Gamma (power ≥ 1)	**3**	**0**	**1**	**26.56**	**265.73**	**161.56**
Probit	2	0	1	28.56	280.75	197.65
Log-probit (slope ≥ 1)	2	0	1	28.56	270.06	153.76
Log-logistic (slope ≥ 1)	2	0	1	28.56	284.65	161.76
Logistic	2	0	1	28.56	290.25	211.73

[a]Izumi et al., 2005.
[b]Degree of polynomial initially set to (*n* - 1) where *n* = number of dose groups including control. Betas restricted to ≥0.

Table A-2. Benchmark Dose Model Predictions for Liver Hypertrophy in F1 Male Rats[a]

Model	Degrees of Freedom	χ^2	χ^2 Goodness of Fit *p*-Value	AIC	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)
Quantal Linear	3	3.37	0.3376	31.05	130.54	71.21
Multistage (degree = 1)[b]	3	3.37	0.338	31.05	130.54	71.21
Multistage (degree = 2)[b]	3	0.97	0.81	27.47	170.34	115.86
Multistage (degree = 3)[b]	3	0.97	0.81	27.47	170.34	115.86
Weibull (power ≥ 1)	2	0	1	27.70	277.34	140.05
Gamma (power ≥ 1)	**3**	**0**	**1**	**25.70**	**244.52**	**136.74**
Probit	2	0	1	27.70	269.29	169.90
Log-probit (slope ≥ 1)	2	0	1	27.70	253.87	130.53
Log-logistic (slope ≥ 1)	2	0	1	27.70	275.43	136.95
Logistic	2	0	1	27.70	284.28	184.69

[a]Izumi et al., 2005.
[b]Degree of polynomial initially set to (*n* - 1) where *n* = number of dose groups including control. Betas restricted to ≥0.

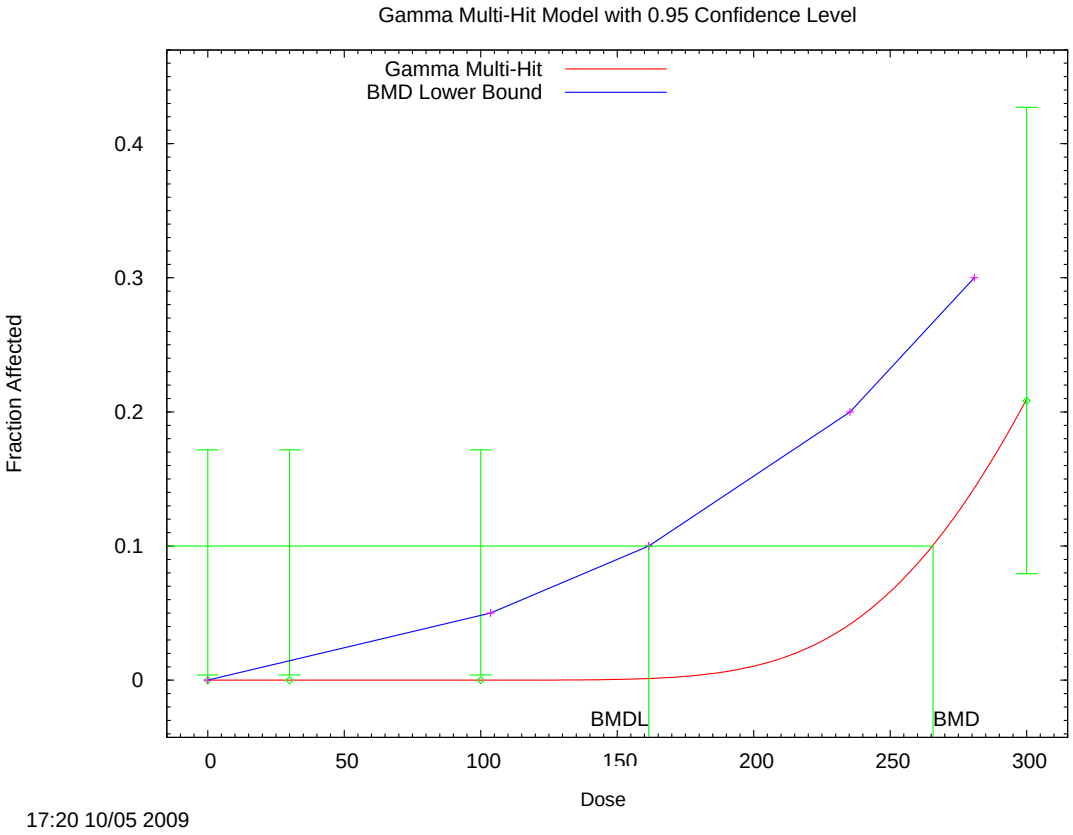

Figure A-1. Fit of Gamma Model to Data on Hepatocellular Hypertrophy in F0 Male Rats

BMDs and BMDLs indicated are associated with an extra risk of 10% and are in units of mg/kg-day

```
=================================================================
        Gamma Model. (Version: 2.13;  Date: 05/16/2008)
        Input Data File: C:\USEPA\BMDS21Beta\Temp\1tmp145B.(d)
        Gnuplot Plotting File:  C:\USEPA\BMDS21Beta\Temp\1tmp145B.plt
                                          Mon Oct 05 17:20:24 2009
 =================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response]= background+(1-background)*CumGamma[slope*dose,power],
   where CumGamma(.) is the cummulative Gamma distribution function


   Dependent variable = Incidence
   Independent variable = Dose
   Power parameter is restricted as power >=1

   Total number of observations = 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 (and Specified) Parameter Values
Background = 0.02
Slope = 0.00414503
Power = 2.63956

Asymptotic Correlation Matrix of Parameter Estimates

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

	Slope
Slope	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	NA		
Slope	0.0482501	0.0035348	0.041322	0.0551782
Power	18	NA		

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

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-12.2818	4			
Fitted model	-12.2818	1	0.000161175	3	1
Reduced model	-19.642	1	14.7205	3	0.002072

AIC: 26.5637

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	24	0.000
30.0000	0.0000	0.000	0.000	24	-0.000
100.0000	0.0000	0.000	0.000	24	-0.009
300.0000	0.2083	5.000	5.000	24	0.000

Chi^2 = 0.00 d.f. = 3 P-value = 1.0000

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

```
Confidence level =           0.95

             BMD =         265.733

            BMDL =        161.563
```

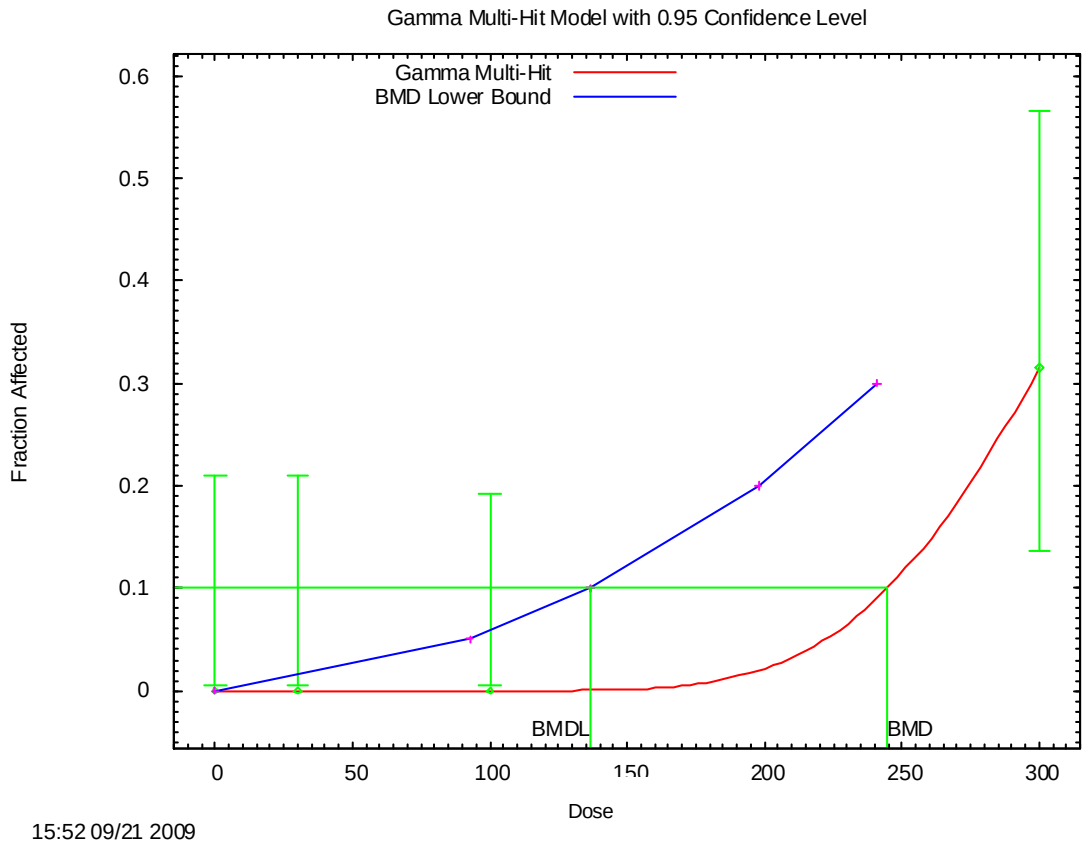

Figure A-2. Fit of Gamma Model to Data on Hepatocellular Hypertrophy in F1 Male Rats

BMDs and BMDLs indicated are associated with an extra risk of 10% and are in units of mg/kg-day

```
 ======================================================================
        Gamma Model. (Version: 2.13;  Date: 05/16/2008)
        Input Data File: C:\USEPA\BMDS21Beta\Temp\1tmp13B0.(d)
        Gnuplot Plotting File:  C:\USEPA\BMDS21Beta\Temp\1tmp13B0.plt
                                            Mon Sep 21 15:46:54 2009
 ======================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response]= background+(1-background)*CumGamma[slope*dose,power],
   where CumGamma(.) is the cummulative Gamma distribution function


   Dependent variable = Incidence
   Independent variable = Dose
   Power parameter is restricted as power >=1
```

```
Total number of observations = 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 (and Specified) Parameter Values
                   Background =        0.025
                        Slope =   0.00622162
                        Power =       2.9511


          Asymptotic Correlation Matrix of Parameter Estimates

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

                 Slope

    Slope            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
    Background                0               NA
         Slope        0.0524367       0.00388009           0.0448319           0.0600415
         Power               18               NA

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


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -11.8494         4
   Fitted model        -11.8497         1   0.000427008      3              1
  Reduced model        -21.1528         1       18.6067      3       0.0003297

          AIC:         25.6993


                                Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000          19        0.000
   30.0000     0.0000         0.000     0.000          19       -0.000
  100.0000     0.0000         0.000     0.000          21       -0.015
  300.0000     0.3158         6.000     6.000          19        0.000

 Chi^2 = 0.00      d.f. = 3        P-value = 1.0000


   Benchmark Dose Computation
```

```
Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =         244.517

            BMDL =        136.737
```