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Provisional Peer-Reviewed Toxicity Values for

tert-Amyl Alcohol
(CASRN 75-85-4)

Superfund Health Risk Technical Support Center
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Questions regarding the contents of this document may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

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COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMCL	benchmark concentration lower bound 95% confidence interval
BMD	benchmark dose
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
POD	point of departure
p-OSF	provisional oral slope factor
p-RfC	provisional reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
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

PEER-REVIEWED PROVISIONAL TOXICITY VALUES FOR *tert*-AMYL ALCOHOL (CASRN 75-85-4)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (http://hhpprtv.ornl.gov) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (www.epa.gov/iris), the respective PPRTVs are removed from the database.

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. Environmental Protection Agency (EPA) programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

QUESTIONS REGARDING PPRTVS

Questions regarding the contents and appropriate use of this PPRTV assessment should 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).

INTRODUCTION

tert-Amyl alcohol [CASRN 75-85-4, also known as amylene hydrate or 2-methyl-2-butanol (NLM, 2011a)], is used as a solvent for resins and gums and in the production of plastics, and other chemicals such as arylpyruvic acids. It is also used as a frothing and flotation agent (e.g., in ore-flotation processes) and in some pharmaceutical applications as a sedative-hypnotic drug (NLM, 2011b). *tert*-Amyl alcohol has been shown to be a major metabolite of *tert*-amyl methyl ether in rats, mice, rabbits, and humans (NLM, 2011b). The molecular formula of *tert*-amyl alcohol is $C_5H_{12}O$ (see Figure 1), and a table of physicochemical properties for *tert*-amyl alcohol is provided below (see Table 1).

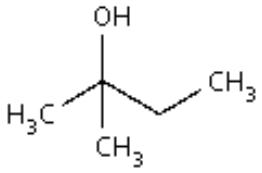

Figure 1. *tert*-Amyl Alcohol Structure

Table 1. Physicochemical Properties of *tert*-Amyl Alcohol (CASRN 75-85-4)

Property (unit)	Value
Boiling point (ºC)	102.4[a,b]
Melting point (ºC)	−9.1[a] or −8.80[a]
Density (g/cm^3)	0.8096[b]
Vapor pressure (mm Hg at 25ºC)	16.8[a] or 16.7[b]
Log octanol-water partition coefficient (unitless)	0.89[a,b]
Henry's law constant (atm-m^3/mol)	1.38×10^{-5}[a]
pH (unitless)	Neutral[b]
Solubility in water (g/100 mL at 25ºC)	110[a] or 99.1[b]
Relative vapor density (air = 1)	ND
Molecular weight (g/mol)	88.15[b]

[a]NLM (2011a).
[b]NLM (2011b).

ND = not determined.

Table 2 provides a summary of the available toxicity values for *tert*-amyl alcohol from U.S. EPA and other agencies/organizations.

Table 2. Summary of Available Toxicity Values for *tert*-Amyl Alcohol (CASRN 75-85-4)

Source/Parameter[a]	Value (Applicability)	Notes	Reference	Date Accessed
Cancer				
IRIS	NV	NA	U.S. EPA (2012b)	12-5-2011
HEAST	NV	NA	U.S. EPA (2003)	NA
IARC	NV	NA	IARC (2011)	12-5-2011
NTP	NV	NA	NTP (2011)	NA
Cal/EPA	NV	NA	Cal/EPA (2009)	NA
Noncancer				
ACGIH	NV	NA	ACGIH (2011)	NA
ATSDR	NV	NA	ATSDR (2011)	12-5-2011
Cal/EPA	NV	NA	Cal/EPA (2012, 2008)	12-5-2011
NIOSH	NV	NA	NIOSH (2007)	NA
OSHA	NV	NA	OSHA (2006)	NA
IRIS	NV	NA	U.S. EPA (2012b)	12-5-2011
Drinking water	NV	NA	U.S. EPA (2011)	NA
HEAST	NV	NA	U.S. EPA (2003)	NA
CARA HEEP	NV	NA	U.S. EPA (1994a)	NA
WHO	NV	NA	WHO (2012)	12-5-2011

[a]Sources: Integrated Risk Information System (IRIS); Health Effects Assessment Summary Tables (HEAST); International Agency for Research on Cancer (IARC); National Toxicology Program (NTP); California Environmental Protection Agency (Cal/EPA); American Conference of Governmental Industrial Hygienists (ACGIH); Agency for Toxic Substances and Disease Registry (ATSDR); National Institute for Occupational Safety and Health (NIOSH); Occupational Safety and Health Administration (OSHA); Chemical Assessments and Related Activities (CARA); Health and Environmental Effects Profile (HEEP); World Health Organization (WHO).

NA = not applicable; NV = not available.

Literature searches were conducted on sources published from 1900 through January 2013, for studies relevant to the derivation of provisional toxicity values for *tert*-amyl alcohol, CAS No. 75-85-4. The following databases were searched by chemical name, synonyms, or CAS No.: ACGIH, ANEUPL, ATSDR, BIOSIS, Cal/EPA, CCRIS, CDAT, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HERO, HMTC, HSDB, IARC, INCHEM IPCS, IPA, ITER, IUCLID, LactMed, NIOSH, NTIS, NTP, OSHA, OPP/RED, PESTAB, PPBIB, PPRTV, PubMed (toxicology

subset), RISKLINE, RTECS, TOXLINE, TRI, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, and U.S. EPA TSCATS/TSCATS2. The following databases were searched for relevant health information values or exposure limits: ACGIH, ATSDR, Cal/EPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, U.S. EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 3 provides an overview of the relevant databases for *tert*-amyl alcohol and includes all potentially relevant and repeated short-term-, subchronic-, and chronic-duration studies. Principal studies are identified in bold. The phrase "statistically significant," used throughout the document, indicates a p-value of <0.05. The phrase "biologically significant" as it pertains to changes in absolute body weight or absolute and relative liver and kidney weights indicates a >10% change from control values.

Table 3. Summary of Potentially Relevant Data for *tert*-Amyl Alcohol (CASRN 75-85-4)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Human								
1. Oral (mg/kg-d)[a]								
Acute[c]	ND							
Short-term[d]	ND							
Long-term[e]	ND							
Chronic[f]	ND							
2. Inhalation (mg/m^3)[a]								
Acute[c]	ND							
Short-term[d]	ND							
Long-term[e]	ND							
Chronic[f]	ND							
Animal								
1. Oral (mg/kg-d)[a]								
Subchronic	ND							
Chronic	ND							
Developmental	ND							
Reproductive	ND							
Carcinogenicity	ND							
2. Inhalation (mg/m^3)[a]								
Subchronic	10/10, Fischer 344, rat, inhalation, 6 hr/d, 5 d/wk, 85 d observed for males and 86 d for females	0, 7.58, 34.18, and 148.7 for males; 0, 7.61, 34.34, and 149.4 for females	Increased absolute and relative liver weight in males	34.18	84.0 for increased absolute liver weight in male rats	148.7	Dow Chemical Co (1992)	NPR

Table 3. Summary of Potentially Relevant Data for *tert*-Amyl Alcohol (CASRN 75-85-4)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Subchronic	10/10, CD-1, mouse, inhalation, 6 hr/d, 5 d/wk, 86 d observed for males and 87 d for females	0, 31.8, 143.1, and 622.8 for males; 0, 31.9, 143.8, and 625.9 for females	No significant treatment-related effects	625.9	DUB	NDr	Dow Chemical Co (1992)	NPR
	4/0, Beagle, dog, inhalation, 6 hr/d, 5 d/wk, 87 d observed	**0, 31.9, 143.8, and 625.9**	**Increased absolute and relative liver weight; cytoplasmic inclusions in liver, increased liver enzymes, and enlarged liver**	**NDr**	**7.83 for increased absolute liver weight**	**31.9**	**Dow Chemical Co (1992)**	**NPR, PS**
Chronic	ND							
Developmental	ND							
Reproductive	ND							
Carcinogenicity	ND							

[a]Dosimetry: NOAEL, BMDL/BMCL, and LOAEL values are converted to a human equivalent concentration (HEC in mg/m^3) for inhalation noncancer effects. HEC_{EXRESP} = (ppm × MW ÷ 24.45) × (hours per day exposed ÷ 24) × (days exposed ÷ total days observed) × blood-air partition coefficient (U.S. EPA, 1994b).
[b]Notes: IRIS = utilized by IRIS, date of last update; PS = principal study; PR = peer reviewed; NPR = not peer reviewed; NA = not applicable.
[c]Acute = exposure for ≤24 hr (U.S. EPA, 2002).
[d]Short-term = repeated exposure for >24 hr ≤ 30 d (U.S. EPA, 2002).
[e]Long-term = repeated exposure for >30 d ≤ 10% lifespan (based on 70-yr typical lifespan) (U.S. EPA, 2002).
[f]Chronic = repeated exposure for >10% lifespan (U.S. EPA, 2002).

DU = data unsuitable; DUB = data unamenable to BMDS; NA = not applicable; NV = not available; ND = no data; NDr = not determined; NI = not identified; NP = not provided; NR = not reported; NR/Dr = not reported but determined from data; NS = not selected.

HUMAN STUDIES

No studies were identified.

ANIMAL STUDIES

Oral Exposures

No studies were identified.

Inhalation Exposures

The effects of inhalation exposure to *tert*-amyl alcohol have not been evaluated in short-term-duration, chronic-duration, developmental toxicity, or reproductive toxicity studies on animals. However, a subchronic-duration study by Dow Chemical Co (1992) that investigated the effects of *tert*-amyl alcohol in three species was identified. This study is considered inadequate for p-RfC derivation because it is a nonpeer-reviewed and unpublished report. However, this study is suitable for the derivation of screening provisional toxicity values (see Appendix A).

Subchronic-duration Studies

The Dow Chemical Co (1992) conducted an unpublished, 87-day subchronic-duration inhalation toxicity study on rats, mice, and dogs in May of 1977 and submitted a single study report on all three species to the U.S. EPA under TSCA, Section 8(e) in April of 1992. The study predates current Good Laboratory Practice (GLP) principles, and it is unknown whether the study would be considered GLP compliant under current guidelines. For each species, animals were placed in stainless steel chambers and exposed to target atmospheric concentrations of 0-, 50-, 225-, or 1000-ppm *tert*-amyl alcohol (97.5% pure) for 6 hours per day, 5 days per week. The total study duration varied from 85−87 days (59−61 exposures) depending on the species and sex of the study animals; no explanation was given regarding why the study duration and numbers of total exposures varied. The analytical concentrations averaged 50.5, 227.6, and 990.4 ppm for the low-, middle-, and high-exposure groups for all species tested, respectively.

A portion of each study within the Dow Chemical Co (1992) report examined the clearance of *tert*-amyl alcohol from plasma in each species. The "Other Data" section of this document further discusses the results of these clearance tests.

Rat Study

The Dow Chemical Co (1992) exposed groups of Fischer 344 rats (10 per sex per group) to atmospheric *tert*-amyl alcohol. Male rats were exposed 59 times over 85 days, and females were exposed 60 times over 86 days. Utilizing the analytical concentrations, the corresponding HECs are 7.58, 34.18, and 148.7 mg/m^3 for males and 7.61, 34.34, and 149.4 mg/m^3 for females. These HECs were calculated as specified in U.S. EPA (1994b) guidance, using a molecular weight of 88.15 g/mole, adjusting for the exposure protocol (6 hours per day, 59 exposures per 85 days for male rats and 60 exposures per 86 days for female rats), and using a blood-air partition coefficient of 0.24 based on blood-air partition coefficients of 392 in rat blood (Kaneko et al., 2000a) and 1620 in human blood (Vainiotalo et al., 2007). The study authors recorded any observations of behavioral changes and signs of toxicity after treatment. Animal tissues were grossly and microscopically examined for lesions. All rats were weighed before the study, twice per week during the first week of exposure, and once per week for the duration of the study. Clinical chemistry, hematology, and urinalysis measurements were performed on all rats within 1 week of study termination. Clinical chemistry measurements included blood urea nitrogen

(BUN), serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), serum alkaline phosphatase (ALP), and glucose. Hematology measurements included packed cell volume; red, white, and differential cell counts; and hemoglobin concentration. Blood samples for clinical chemistry and hematology measurements were taken from the tail vein of fasted rats. Urinalysis parameters included pH, specific gravity, glucose, ketones, bilirubin, urobilinogen, and albumin. Urine excreted by the normal stress of handling the rats was used in the urinalysis.

After the final exposure, all rats were subjected to a gross pathological examination at the time of sacrifice. Rats were fasted overnight prior to sacrifice. At sacrifice, they were weighed, anesthetized with methoxyflurane, and, after clamping the trachea, decapitated. The study authors recorded the weights of the liver, kidney, heart, brain, and testes. The lungs and trachea of the rats were removed as a unit and inflated with 10% formalin. The eyes of the rats were examined immediately after decapitation in situ using the glass microscope slide technique under fluorescent illumination. The eyes of five rats per sex per exposure level were fixed in Zenker's solution. Representative samples of all major tissues and organs were taken from all rats and fixed in 10% phosphate-buffered formalin. The following tissues and organs were harvested from rats in this study: liver, heart, pancreas, spleen, brain, peripheral nerve, pituitary gland, spinal cord, kidneys, adrenal glands, large intestine, small intestine, stomach, cecum, mesenteric lymph node, thoracic lymph node, testes, epididymis, coagulating glands, seminal vesicles, prostrate, urinary bladder, lungs, salivary glands, skeletal muscle, aorta, adipose tissue, esophagus, thymus, parathyroid gland(s), thyroid gland, eyes, nasal turbinates, mesenteric vasculature, integument, ovaries, oviducts, and uterus. These tissues were processed by standard methods, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissue sections from five rats per sex from the control and high-exposure groups were extensively examined with a light microscope. Except for the liver which was fully examined histologically for all exposure groups, tissue sections from the remaining rats from the low- and mid-exposure groups were microscopically examined only to the extent needed to identify the target organs of toxicity and the NOAEL of this study.

Slight motor incoordination was observed in female rats in the high-exposure group following the first exposure; however, no other signs of motor incoordination were observed at any other exposure levels in males or females for the rest of the study. Excessive tearing was observed starting at the 37th exposure in both female and male rats in the mid- and high-exposure groups. Excessive tearing was more prevalent in high-exposure females, with the eyes of one particular female were observed to be swollen shut on three separate occasions. No consistent changes in mean body weight were observed among rats exposed to *tert*-amyl alcohol (see Table B-5); however, the mean body weight of the low-exposure males was statistically significantly decreased on Days 16 and 23; mean body weight of the high-exposure males was statistically significantly decreased on Days 16 and 30 of the study. The clinical chemistry results demonstrated that ALP was statistically significantly depressed in males and females in the low-exposure group but not in rats exposed to higher concentrations (see Table B-2).

Statistically significant decreases in hematology values, including packed cell volume, number of red blood cells, and hemoglobin concentration, were reported in the low-exposure males relative to the control group (see Table B-3). White blood cell counts were statistically significantly depressed in male rats in the mid- and high-exposure groups following the 54th exposure, but when measured following the 57th exposure, the same pattern was not observed

(see Table B-3). High-exposure female rats had statistically significantly depressed white blood cell counts following the 55th exposure, but similar to the males, this pattern was not observed following the 58th exposure. Female rats in the low-exposure group, however, showed a statistically significant decrease in white blood cell counts following the 58th exposure (see Table B-4). The study authors concluded that these changes in hematology values were not toxicologically significant because they were not reproducible and did not exhibit an exposure-response relationship.

The study authors observed a biologically and statistically significant increase in the absolute and relative liver weights in male rats in the high-exposure group (13% and 14% higher than the control, respectively; see Tables B-5 and B-6). A statistically significant increase in the absolute liver weight was also observed in females in the mid-exposure group (9% higher than the control; see Table B-5). However, the study authors attributed this increase to the higher mean fasted body weights, and this change was not biologically significant (i.e., did not surpass 10% of control). Additionally, the absolute heart weights of the males in the low-exposure group and females in the mid-exposure group were >10% higher than the control; however, no exposure–response relationships were evident, and the relative heart weights in these groups were only minimally changed. The study authors also stated that a statistically significant decrease in the relative heart weight (9% lower than the control) of the female rats in the high-exposure group was spontaneous and unrelated to treatment. No effects were observed in the urinalysis results of the exposed rats.

During the gross pathological examinations, slight mottling was observed in the kidneys of 8/10 male rats and 0/10 female rats in the high-exposure group versus 1/10 male rats and 0/10 female rats in the control group. The study authors did not consider this effect treatment related as it was not supported by other measures, such as kidney weight. Additionally, an increase (not statistically significant) in gray pinpoint foci was observed in the lungs of male rats exposed to *tert*-amyl alcohol, but the study authors concluded that this was not toxicologically significant because higher incidences of these foci have been observed in historical control rats.

Based on the >10% biologically significant increase in absolute and relative liver weight in the high-exposure male rats, a lowest-observed-adverse-effect level (LOAEL) of 148.7 mg/m^3 is identified with a corresponding NOAEL of 34.18 mg/m^3.

Mouse Study

The Dow Chemical Co (1992) exposed CD-1 mice (10 per sex per group) to atmospheric *tert*-amyl alcohol. Male mice were exposed 60 times over 86 days, and females were exposed 61 times over 87 days. Utilizing analytical concentrations, the corresponding HECs are 31.8, 143.1, and 622.8 mg/m^3 for males and 31.9, 143.8, and 625.9 mg/m^3 for females. These HECs were calculated as specified in U.S. EPA (1994b) guidance, using a molecular weight of 88.15 g/mole, adjusting for the exposure protocol (6 hours per day, 60 exposures per 86 days for male mice and 61 exposures per 87 days for female mice), and using a blood-air partition coefficient of 1. All mice were observed for signs of toxicity and behavioral changes and were weighed before the study, twice per week during the first week, and once per week for the remainder of the study. Clinical chemistry measurements were taken on all mice at study termination and included BUN, SGPT, SGOT, ALP, and glucose. Although not explicit in the report, no hematology measurements or urinalysis appeared to be conducted.

All mice were subjected to gross pathological examination after the final exposure postmortem. The study authors reported that the mice were not fasted the day prior to the sacrifice although the study authors provide fasted body weights in the results tables. Due to the inconsistencies in the study report, the data reported are presented exactly as given. At sacrifice, the mice were weighed, anesthetized with methoxyflurane, and, after clamping the trachea, decapitated. The study authors recorded the weights of the liver, kidney, heart, brain, and testes. The lungs and trachea of the mice were removed as a unit and inflated with 10% formalin. The eyes of the mice were examined in situ using the glass microscope slide technique under fluorescent illumination immediately after decapitation. The eyes of five mice per sex per exposure level were fixed in Zenker's solution. Representative samples of all the major tissues and organs were taken from all mice and fixed in 10% phosphate-buffered formalin. The following tissues and organs were harvested from mice in this study: liver, gallbladder, heart, pancreas, spleen, brain, peripheral nerve, pituitary gland, spinal cord, kidneys, adrenal glands, large intestine, small intestine, stomach, cecum, mesenteric lymph node, thoracic lymph node, testes, epididymides, coagulating glands, seminal vesicles, prostrate, urinary bladder, lungs, salivary glands, skeletal muscle, aorta, adipose tissue, esophagus, thymus, parathyroid gland(s), thyroid gland, eyes, nasal turbinates, mesenteric vasculature, integument, ovaries, oviducts, uterus, skeletal muscle, anterior mediastinal blood vessels, trachea, subcutaneous lymph node, cervical lymph node, cervix, and mammary gland. These tissues were processed by standard methods, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissue sections from five mice per sex from the control and 625.9 mg/m^3 groups were extensively examined with a light microscope. Tissue sections from the remaining mice from the low- and mid-exposure groups were microscopically examined only to the extent required to identify the target organs of toxicity and the NOAEL of this study.

Small, hairless patches were observed on the backs and necks of both male and female mice exposed to *tert*-amyl alcohol. These patches were observed most frequently in high-exposure males; however, the study authors concluded that these patches were not exposure-related and were most likely attributable to fighting amongst the mice. Overall changes in body-weight gains, which were derived from the fasted weights, were not statistically significant (see Table B-7). Although the body weight gains observed in the female mice in the high-exposure group were reduced compared to the control group, the study authors considered this a questionable treatment-related effect due to the high variability in the weight gain data, as evidenced by the relatively large standard deviation. BUN, SGPT, and SGOT were statistically significantly depressed in male mice exposed to *tert*-amyl alcohol (see Table B-8), but the study authors concluded that the decreases in these parameters were of unknown toxicological significance. No hematology or urinalysis results were reported for these mice. The study authors concluded that there were no treatment-related differences in the absolute organ weights (see Table B-9) or relative organ weights (see Table B-10) of the males or females. However, the study authors noted a biologically significant in the absolute liver weight (11% lower than control) and a statistically and biologically significant decrease in relative liver weight (15% lower than control) of the male mice in the low-exposure group (see Tables B-9 and B-10). The magnitude of these liver weight changes was not as great at the higher doses, therefore there is no exposure-response relationship for these effects. The noted a statistically and biologically significant decrease in the liver/body-weight ratio of the male mice in the low-exposure group was attributed by the study authors to the small increase (not statistically or biologically significant) in body weight of the group. Additionally, the female mice in the mid-exposure group showed biologically significantly decreased absolute (21% lower than control) and relative

kidney (11% lower than control) weights; however, the magnitude of these changes was not as great at the high dose indicating that there is no exposure-response relationship for these effects (see Tables B-9 and B-10). The study authors concluded that there were no treatment-related gross or microscopic changes in the examined mouse tissue samples including the lungs; however, the study authors observed an accentuation of the normal hepatocellular pattern as well as focal aggregation of mononuclear cells in the liver of 2/5 male mice in the high-exposure group (see Table B-11). The study authors determined that these findings represented normal variation rather than toxic changes, as well as the other pathological changes that were observed at similar frequencies in the other control and treatment groups.

A NOAEL of 625.9 mg/m^3 is identified based on the lack of observed systemic toxicity. A corresponding LOAEL cannot be identified because the NOAEL was the highest concentration tested.

Dog Study

The Dow Chemical Co (1992) exposed groups of four male beagle dogs to atmospheric *tert*-amyl alcohol for 87 days (61 exposures). Utilizing analytical concentrations, the corresponding HECs are 31.9, 143.8, and 625.9 mg/m^3. These HECs were calculated as specified in U.S. EPA (1994b) guidance, using a molecular weight of 88.15 g/mole, adjusting for the exposure protocol (6 hours per day, 61 exposures per 87 days), and using a blood-air partition coefficient of 1. All dogs were observed for signs of toxicity after treatment and at regular intervals, with a particular emphasis placed on examination of the nose and eyes. Ophthalmic examinations (using a slit-lamp and ophthalmoscope) were conducted on all dogs before the start of the study and during the last week of the study. All dogs were weighed before the study and once per week during the study. Clinical chemistry, hematology, and urinalysis measurements were taken on all dogs prior to the beginning of the study and during the last week of the study. Blood samples for the clinical chemistry and hematological measurements were taken from the dogs' jugular vein. Clinical chemistry measurements included BUN, SGPT, SGOT, ALP, glucose, and γ-glutamyl transpeptidase. Hematological measurements included packed cell volume; red, white, and differential cell counts; and hemoglobin concentration. Urine was extracted by catheterization analyzed for pH, specific gravity, glucose, ketones, bilirubin, urobilinogen, albumin, and sediment.

After the final exposure, all of the dogs were subjected to a gross pathological examination. The dogs were weighed, given an intravenous overdose of sodium pentobarbital, and exsanguinated prior to sacrifice, but were not fasted. Weights of the liver, kidney, heart, brain, and testes were recorded. The lungs and trachea of the dogs were removed as a unit and inflated with 10% formalin. Representative samples of all major tissues and organs were taken from all dogs and fixed in 10% phosphate-buffered formalin. The following tissues were harvested from dogs in this study: liver, heart, pancreas, spleen, brain, spinal cord, pituitary, peripheral nerve, adrenal gland, kidneys, small intestine, large intestine, stomach, gallbladder, thymus, lymph nodes, epididymides, testes, prostrate, esophagus, lungs, trachea, aorta, tonsils, parathyroid, thyroid, skeletal muscle, salivary gland, integument, eyes, tongue, nasal turbinates, adipose tissue, urinary bladder, and mesenteric vasculature. These tissues were processed by standard methods, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The tissues from all four dogs in the control and the 625.9 mg/m^3 *tert*-amyl alcohol exposure groups were extensively examined with a light microscope. Except for the liver which was fully examined histologically for all exposure groups, tissues from the remaining animals from the

low- and mid-exposure groups were microscopically examined only to the extent needed to identify the target organs for toxicity and the NOAEL of this study. To determine glycogen content, sections of the livers were stained with Periodic Acid-Schiff reagent (PAS), with and without diastase digestion.

Visible, but reversible, motor impairments were observed in all dogs in the high-exposure group. However, the dogs experienced these effects to different degrees. Blood samples collected to determine the cause of these different degrees of motor impairment showed a 4-fold difference in the concentration of *tert*-amyl alcohol. The highest concentrations were found in the most impaired dogs. Excessive tearing was observed in one dog in the high-exposure group. No significant differences were observed in the body-weight gains of dogs exposed to *tert*-amyl alcohol and control dogs throughout the duration of this study (see Table B-12). The only change in clinical chemistry parameters that the study authors considered toxicologically significant was a statistically significant increase in ALP in the high-exposure group (see Table B-13). Increased ALP is most commonly associated with bile duct obstruction, gall bladder disease, and liver disease such as hepatitis; however, the study authors did not report an increase in bilirubin. Additionally, blood glucose was statistically significantly elevated in the low-exposure group, and SGPT was statistically significantly elevated in the high-exposure group (see Table B-13). Hematology measurements demonstrated that the packed cell volume and hemoglobin concentration were both statistically significantly elevated in the low- and mid-exposure groups relative to the control group (see Table B-14); however, the study authors concluded that these results were not treatment related because the levels were similar to preexposure levels and because neither parameter was not statistically significantly elevated in the high-exposure group. Urinalysis measurements indicated that specific gravity was statistically significantly elevated only in the high-exposure group (see Table B-15). Statistically significant increases in absolute (32% higher than the control) and relative liver weight (37% higher than the control) were found in the high-exposure group (see Tables B-16 and B-17). Also, biologically significant (greater than 10% compared to controls) increases in liver weight (absolute and relative) were observed in all dose groups (except for relative liver weight in the low-exposure group). Upon further review of the individual liver-weight data for beagles in the low-exposure group, it appeared that the data for one animal may be an outlier. The value in question is 541 g reported for absolute liver weight compared to other weights in the same group of 361.08, 385.50, and 398.52 g. The study authors provided further reasoning (on page 12 of principal study) to classify this value as an outlier: "*The recorded liver weight for the remaining animal was larger than that of any other animal in the study. This appears to be a spurious value since this animal's liver was normal in size and appearance on gross examination, and no changes were found in the other measured parameters which would corroborate an effect of this magnitude on the liver*." Based on this explanation provided by the study authors, liver-weight data for this particular animal were removed from any further analysis and mean values for absolute and relative liver weight were recalculated. The average for absolute liver weight changed from 422.30 to 382.73 g, and relative liver weight changed from 3.30 to 3.03 g. Based on the recalculated averages, relative liver weight was no longer biologically significantly increased in beagles in the low-exposure group. Additionally, while the absolute and relative kidney weights were not statistically significantly elevated, they were 14% and 17% higher in the high-exposure group compared with the control group, respectively. The low-exposure group also demonstrated a 15% lower absolute kidney weight compared with the control, but the corresponding change in the relative kidney weight was only 2%. Slight changes in either measure of kidney weight were observed in the mid-exposure group.

All findings from the ophthalmic examination were normal, and no differences were observed between the exposed and control dogs. On gross examination, livers were enlarged in all dogs of the high-exposure group and in one dog of the mid-exposure group (see Table B-18). Gross and microscopic lesions were observed in the lungs of most of the exposed and control dogs, which were attributed to infection by the parasitic nematode *Filaroides hirthi*. Liver cytoplasmic eosinophilic inclusion bodies were also noted in one dog from each of low-, mid-, and high-exposure groups; none were reported in the control group (see Table B-18). Both the size and number of these inclusions were greater in the mid- and high-exposure groups than the low-exposure group, although this could not be confirmed by the data reported in the study. Though of questionable toxicological significance, the study authors concluded that these liver cytoplasmic inclusions should be considered exposure-related due to the apparent exposure-response relationship, the statistically and biologically significantly increased absolute and relative liver weights, and the clinical chemistry findings, all of which suggest that the liver is a primary target organ for *tert*-amyl alcohol toxicity.

A LOAEL of 31.9 mg/m^3 (50 ppm) is identified based on a >10% biologically significant increase in absolute liver weight. This is supported by findings of cytoplasmic eosinophilic inclusions, enlarged livers, and exposure-dependent increased serum liver enzymes. Because the low-exposure group is identified as the LOAEL, identification of a corresponding NOAEL is precluded.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

None of the following types of studies on the effects of *tert*-amyl alcohol were identified: short-term studies; immunotoxicity, neurotoxicity, carcinogenicity, genotoxicity, or mutagenicity studies; dermal studies or other routes of exposure; and mode-of-action/mechanistic studies. Several studies were identified that discuss the metabolism and toxicokinetics of *tert*-amyl alcohol and they are summarized below.

Metabolic/Toxicokinetic Studies

tert-Amyl alcohol is the primary metabolite of *tert*-amyl methyl ether. Following inhalation or gavage administration, *tert*-amyl methyl ether is readily metabolized to *tert*-amyl alcohol by demethylation of the ether group. As the primary metabolite, the toxicokinetics of *tert*-amyl alcohol have mainly been described as part of studies examining exposure to *tert*-amyl methyl ether. The previously discussed study by Dow Chemical Co (1992) examined the pharmacokinetics of *tert*-amyl alcohol after direct inhalation exposure in rats, mice, and dogs at concentrations of 50, 225, or 1000 ppm for 6 hours per day, 5 days per week, for several months. Although the study does not indicate the percentage of the inhaled dose that was absorbed, the presence of *tert*-amyl alcohol in the plasma within 30 minutes of exposure indicates that the compound is absorbed. In addition, blood-air partition coefficients of 392 in rat blood (Kaneko et al., 2000a) and 1620 in human blood (Vainiotalo et al., 2007) indicate an affinity for blood and that absorption is likely. There are no data on absorption following oral exposure. There are no distribution studies on *tert*-amyl alcohol, but data by Kaneko et al. (2000b) indicate that *tert*-amyl alcohol has an affinity for all tissues. Most of the available metabolism studies exposed animals to *tert*-amyl methyl ether, but Amberg et al. (1999) examined urinary metabolites after oral exposure to either *tert*-amyl alcohol or *tert*-amyl methyl ether and found the same metabolites (indicating that *tert*-amyl alcohol is the first step in the metabolism of *tert*-amyl methyl ether). The major urinary metabolites recovered from rats exposed to *tert*-amyl alcohol were *tert*-amyl alcohol glucuronide and 2-methyl-2,3-butanediol and its glucuronide; the

minor metabolites included free *tert*-amyl alcohol, 2-hydroxy-2-methylbutyric acid, and 3-hydroxy-3-methylbutyric acid. Mannering and Shoeman (1996) found that *tert*-amyl alcohol is an active inducer of cytochrome P4503A, in addition to inducing P4502E and P4501A to some extent, in mouse livers. The study authors suggested that *tert*-amyl alcohol may be metabolized to an olefin by P450.

tert-Amyl alcohol is rapidly cleared from the blood of exposed animals (Amberg et al., 2000). Dow Chemical Co (1992) found that the elimination of *tert*-amyl alcohol is slower in rats (half-life of 47 minutes at 50 ppm) than in mice (half-life of 29 minutes at 1000 ppm), but faster in both species compared to dogs (half-life of 69 minutes at 50 ppm); however, data do not indicate any evidence of saturation at a concentration of 1000 ppm in mice, while rats and dogs demonstrate saturation at 1000 ppm. All species demonstrated first-order clearance kinetics; however, at 1000 ppm, rats and dogs are best described by first-order kinetics assuming either Michaelis-Menten or saturation kinetics. The data indicate a low potential for accumulation in the blood of dogs exposed to concentrations >1000 ppm because similar levels were measured after 2, 3, or 4 months (Dow Chemical Co, 1992). Sumner et al. (2003c) also found that the half-life of *tert*-amyl alcohol in blood is longer in rats (1−1.7 hours) than in mice (0.2−0.8 hours). Furthermore, Sumner et al. (2003b) determined that the blood concentrations of *tert*-amyl alcohol were 2- to 3-fold higher in mice compared to rats, either receiving 500- or 2500-ppm *tert*-amyl methyl ether via inhalation (nose-only). After exposure to *tert*-amyl methyl ether, *tert*-amyl alcohol is primarily found in expired air and urine (Sumner et al., 2003a).

There is a single physiologically based pharmacokinetic (PBPK) model for *tert*-amyl alcohol (Collins et al., 1999); however, this model is not appropriate for use in dosimetric conversions because the author concluded that it underpredicted the results. In the model, *tert*-amyl alcohol has three compartments (i.e., lung, liver, and total body water) that are linked to the metabolism of *tert*-amyl methyl ether in the liver. This model was compared with data collected from male Fischer 344 rats after a 6-hour exposure to 100-, 500-, or 2500-ppm *tert*-amyl methyl ether. The *tert*-amyl alcohol model underpredicted the results. Three hypotheses were tested, and the one that fit the data best was the nonspecific binding of *tert*-amyl alcohol. It should be noted that the partition coefficients used for *tert*-amyl alcohol were actually those of *tert*-butyl alcohol because the physical and chemical properties are similar.

DERIVATION OF PROVISIONAL VALUES

Tables 4 and 5 present summaries of noncancer and cancer reference values, respectively. IRIS data are indicated in the tables, if available.

Table 4. Summary of Noncancer Reference Values for *tert*-Amyl Alcohol (CASRN 75-85-4)

Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD	UF_C	Principal Study
Subchronic p-RfD (mg/kg-d)	NDr						
Chronic p-RfD (mg/kg-d)	NDr						
Screening subchronic p-RfC (mg/m^3)[a]	Dog/M	Increased absolute liver weight	3×10^{-2}	$BMCL_{10HEC}$	7.83	300	Dow Chemical Co (1992)
Screening chronic p-RfC (mg/m^3)[a]	Dog/M	Increased absolute liver weight	3×10^{-3}	$BMCL_{10HEC}$	7.83	3000	Dow Chemical Co (1992)

[a]A provisional screening value is provided in Appendix A to this document.

NDr = not determined.

Table 5. Summary of Cancer Values for *tert*-Amyl Alcohol (CASRN 75-85-4)

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF	NDr			
p-IUR	NDr			

NDr = not determined.

DERIVATION OF ORAL REFERENCE DOSES

No studies were identified.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Derivation of Subchronic Provisional RfC (Subchronic p-RfC)

There are three subchronic-duration exposures presented in one study on *tert*-amyl alcohol in animals (see Table 3). The 12-week inhalation study performed by Dow Chemical Co (1992) is the only available study on *tert*-amyl alcohol exposure. However, Dow Chemical Co (1992) is considered inadequate for p-RfC derivation because it is not peer-reviewed and is an unpublished report. This study is suitable, however, for the derivation of screening provisional toxicity values. Appendix A provides details on the screening subchronic p-RfC.

Derivation of Chronic Provisional RfC (Chronic p-RfC)

There are no chronic-duration studies for *tert*-amyl alcohol for derivation of a chronic p-RfC. However, the unpublished subchronic inhalation study by Dow Chemical Co (1992) is suitable for derivation of a screening provisional chronic toxicity value. Appendix A provides details on the screening chronic p-RfC.

CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR

Table 6 identifies the cancer weight-of-evidence (WOE) descriptor for *tert*-amyl alcohol.

Table 6. Cancer WOE Descriptor for *tert*-Amyl Alcohol

Possible WOE Descriptor	Designation	Route of Entry (Oral, Inhalation, or Both)	Comments
"Carcinogenic to Humans"	NS	NA	No human cancer studies are available.
"Likely to Be Carcinogenic to Humans"	NS	NA	No animal cancer data are available.
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	No animal cancer data are available.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**No adequate information is available to assess the carcinogenic potential of *tert*-amyl alcohol by inhalation or oral routes of exposure.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	No evidence of carcinogenicity in humans is available.

NA = not applicable; NS = not selected.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

No studies were identified.

APPENDIX A. PROVISIONAL SCREENING VALUES

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

DERIVATION OF SCREENING PROVISIONAL ORAL REFERENCES DOSES

No studies were identified.

DERIVATION OF SCREENING PROVISIONAL INHALATION REFERENCE CONCENTRATIONS

Derivation of Screening Subchronic Provisional RfC (Subchronic p-RfC)

The portion of the Dow Chemical Co (1992) study on dogs is selected as the principal study for the derivation of the screening subchronic p-RfC. The critical effect is increased mean absolute liver weight observed in male dogs. The 12-week inhalation study performed by Dow Chemical Co (1992) is the only available subchronic-duration exposure study, but it is considered inadequate for provisional p-RfC derivation because it is not peer-reviewed and is an unpublished report. However, this study is otherwise well conducted and suitable for the derivation of a screening provisional toxicity value. This study was performed prior to the establishment of GLP principles although it appears to follow general GLP principles. This study otherwise meets the standards of study design and performance in terms of the number of study animals, examination of the potential toxicity endpoints, and presentation of information. Study details are provided in the "Review of Potentially Relevant Data" section.

Exposure concentrations from this study were adjusted for intermittent dosing [as per guidance provided by U.S. EPA (2002)], and human equivalent concentrations (HECs) were determined prior to modeling. The $LOAEL_{HEC}$ of 31.9 mg/m^3 for dogs and 148.7 for male rats was calculated by using U.S. EPA (1994b) methodology for an extrarespiratory effect as follows:

Exposure concentration adjustment for continuous exposure:

For male dogs:

$LOAEL_{ADJ}$ = $LOAEL_{ppm,\ analytical}$ × (MW ÷ 24.45) × (hours exposed ÷ 24 hours) × (days exposed ÷ 87 days)
= 50.5 ppm × (88.15 g/mol ÷ 24.45) × (6 hours ÷ 24 hours) × (61 days ÷ 87 days)
= 182.8 mg/m^3 × (6 hours ÷ 24 hours) × (61 days ÷ 87 days)
= 31.9 mg/m^3

For male rats:

$LOAEL_{ADJ}$ = $LOAEL_{ppm,\ analytical}$ × (MW ÷ 24.45) × (hours exposed ÷ 24 hours) × (days exposed ÷ 85 days)
= 990.4 ppm × (88.15 g/mol ÷ 24.45) × (6 hours ÷ 24 hours) × (59 days ÷ 85 days)
= 3570.7 × (6 hours ÷ 24 hours) × (59 days ÷ 85 days)
= 619.6 mg/m^3

HEC conversion for extrarespiratory effects:

For male dogs:

$LOAEL_{HEC}$ = $LOAEL_{ADJ}$ × $(H_{b/g})_A$ ÷ $(H_{b/g})_H$
= 31.9 mg/m^3 × 1
= 31.9 mg/m^3

For male rats:

$LOAEL_{HEC}$ = $LOAEL_{ADJ}$ × $(H_{b/g})_A$ ÷ $(H_{b/g})_H$
= 619.6 mg/m^3 × 0.24
= 148.7 mg/m^3

where:

$(H_{b/g})_A$ ÷ $(H_{b/g})_H$ = the ratio of the blood:gas (air) partition coefficient of the chemical for the laboratory animal species to the human value. In the absence of data for *tert*-amyl alcohol for beagles, the default value of 1 was used, as specified in U.S. EPA (1994b) guidance. The ratio of the blood:gas (air) partition coefficient for rats was 0.24 based on rat (Kaneko et al., 2000a) and human data (Vainiotalo et al., 2007).

The Dow Chemical Co (1992) study report includes data on three species: rats, mice, and dogs. The experimental methods and endpoints were similar across species. The most sensitive endpoints observed to be statistically and/or biologically significantly increased in the Dow Chemical Co (1992) study were absolute and relative liver weights in male beagle dogs and rats and alkaline phosphatase activity in male beagles; all of the common continuous models (i.e., Exponential, Linear, Polynomial, Power, and Hill models) available in the EPA's Benchmark Dose Software (BMDS, version 2.1.2) were fit to these data if possible; see Appendix C for modeling results and BMD methodology. Because liver-weight changes >10% are considered biologically significant at that level, all models were run with a benchmark response (BMR) of 10% relative risk. For increased absolute liver weight in male beagles, BMD modeling resulted in BMC_{10HEC} and $BMCL_{10HEC}$ values of 33.5 mg/m^3 and 7.83 mg/m^3, respectively. For increased absolute liver weight in male rats, BMD modeling provided BMC_{10HEC} and $BMCL_{10HEC}$ values of 110 mg/m^3 and 84.0 mg/m^3, respectively. For increased relative liver weight in male rats, BMD analysis resulted in BMC_{10HEC} and $BMCL_{10HEC}$ values of 102 mg/m^3 and 86.6 mg/m^3, respectively. For increased ALP activity in male beagles, all models were run with a benchmark response (BMR) of 1 standard deviation resulting in BMC_{1SD} and $BMCL_{1SD}$ values of 87.4 mg/m^3 and 57.8 mg/m^3, respectively. For increased relative liver weight in male beagles, the BMD analysis resulted in significant lack of fit (Test 3, $p < 0.10$) for all continuous models employing nonconstant variance (see Table C-2). Because these data were not amenable to BMD modeling, a NOAEL/LOAEL approach was employed to identify a potential point of departure (POD). For increased relative liver weight in male beagles, a biologically significant increase was observed in the mid-dose group, identifying a LOAEL of 143.8 mg/m^3 with a corresponding NOAEL of 31.9 mg/m^3.

Of the toxicological effects observed in male beagles and rats in the subchronic-duration study by the Dow Chemical Co (1992), the most sensitive is increased absolute liver weight in beagles with a $BMCL_{10HEC}$ of 7.83 mg/m^3. The selection of increased absolute liver weight in beagles as the critical effect is supported by exposure-dependent increased liver enzymes (statistically significant at 625.9 mg/m^3), observations of enlarged livers (statistically significant at 625.9 mg/m^3), and hepatic cytoplasmic eosinophilic inclusions (not statistically significant at any dose but considered to be exposure-related by the study authors). The selection of the $BMCL_{10HEC}$ of 7.83 mg/m^3 for increased absolute liver weight in male beagles as the POD would not only protect against this effect but also other liver effects (e.g., increased liver enzymes) that occurred at higher concentrations in dogs. Based on the toxicity findings in the three tested species, dogs are the most sensitive to the effects of *tert*-amyl alcohol. Therefore, the selection of the POD ($BMCL_{10HEC}$ of 7.83 mg/m^3) in dogs is also protective against effects observed in rats and mice. **Therefore, the $BMCL_{10HEC}$ of 7.83 mg/m^3 based on increased absolute liver weight in male beagles (Dow Chemical Co, 1992) is chosen as the POD to derive a screening subchronic p-RfC.**

The screening subchronic p-RfC for *tert*-amyl alcohol is derived as follows:

$$\textbf{Screening Subchronic p-RfC} = BMCL_{10HEC} \div UF_C$$
$$= 7.83 \text{ mg/m}^3 \div 300$$
$$= \mathbf{3 \times 10^{-2} \text{ mg/m}^3}$$

Table A-1 summarizes the uncertainty factors (UFs) for the screening subchronic p-RfC for *tert*-amyl alcohol. Confidence in the screening value is by definition, low.

Table A-1. UFs for Screening Subchronic p-RfC for *tert*-Amyl Alcohol

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicodynamic differences between dogs and humans following inhalation exposure to *tert*-amyl alcohol. The toxicokinetic uncertainty has been accounted for by calculation of a human equivalent concentration (HEC) as described in the RfC methodology (U.S. EPA, 1994b).
UF_D	10	A UF_D of 10 is applied because there are no acceptable two-generation reproductive toxicity or developmental toxicity studies via the inhalation route.
UF_H	10	A UF_H of 10 is applied for inter-individual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of *tert*-amyl alcohol in humans.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a BMCL.
UF_S	1	A UF_S of 1 is applied because a subchronic-duration study was selected as the principal study.
UF_C	300	$UF_C = UF_A \times UF_D \times UF_H \times UF_L \times UF_S$

Derivation of Screening Chronic Provisional RfC (Chronic p-RfC)

Because no chronic-duration studies exist for *tert*-amyl alcohol, the dog portion of the nonpeer-reviewed subchronic study by the Dow Chemical Co (1992) is also selected as the principal study for derivation of the screening chronic p-RfC. For the same reasons listed above in the screening subchronic p-RfC discussion, the study by Dow Chemical Co (1992) meets standards of study design and performance. Details are provided in the "Review of Potentially Relevant Data" section.

The chronic p-RfC for *tert*-amyl alcohol, based on a $BMCL_{10HEC}$ of 7.83 mg/m^3 for increased absolute liver weight in male beagles, is derived as follows:

$$\textbf{Screening Chronic p-RfC} = BMCL_{10HEC} \div UF$$
$$= 7.83\ mg/m^3 \div 3000$$
$$= \mathbf{3 \times 10^{-3}\ mg/m^3}$$

Table A-2 summarizes the UFs for the screening chronic p-RfC for *tert*-amyl alcohol. Confidence in the screening value is by definition, low.

Table A-2. UFs for Screening Chronic p-RfC for *tert*-Amyl Alcohol

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicodynamic differences between dogs and humans following inhalation exposure to *tert*-amyl alcohol. The toxicokinetic uncertainty has been accounted for by calculation of a human equivalent concentration (HEC) as described in the RfC methodology (U.S. EPA, 1994b).
UF_D	10	A UF_D of 10 is applied because there are no acceptable two-generation reproductive toxicity or developmental toxicity studies via the inhalation route.
UF_H	10	A UF_H of 10 is applied for inter-individual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of *tert*-amyl alcohol in humans.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a BMCL.
UF_S	10	A UF_S of 10 is applied because a subchronic-duration study was selected as the principal study.
UF_C	3000	$UF_C = UF_A \times UF_D \times UF_H \times UF_L \times UF_S$

APPENDIX B. DATA TABLES

Table B-1. Body-Weight Gain in Male and Female Fischer 344 Rats Exposed to *tert*-Amyl Alcohol by Inhalation for 12 Weeks[a]

Endpoint	Exposure Concentration in ppm[b]			
	0	50	225	1000
Males (59 exposures)[d]				
Number of animals	10	10	10	10
Body-weight gain (g)[c]	106.2 ± 20.1	108.6 ± 23.2	99.8 ± 17.7	104.0 ± 23.2
Females (60 exposures)[d]				
Number of animals	10	10	10	10
Body-weight gain (g)[c]	36.5 ± 9.8	40.4 ± 10.5	41.0 ± 9.2	38.4 ± 14.2

[a]Dow Chemical Co (1992).
[b]Corresponding HECs are 7.58, 34.18, and 148.7 mg/m^3 for males and 7.61, 34.34, and 149.4 mg/m^3 for females.
[c]Mean ± standard deviation; calculated from the mean body weights in the study report.
[d]The legibility of the original study makes it difficult to decipher these values.

Table B-2. Selected Clinical Chemistry Parameters in Male and Female Fischer 344 Rats Exposed to *tert*-Amyl Alcohol by Inhalation for 12 Weeks[a]

Endpoint	Exposure Concentration in ppm[b]			
	0	50	225	1000
Males (59 exposures)				
Number of animals	10	10	10	10
Serum Alkaline Phosphatase (µUnits/mL)[c]	78 ± 4	68 ± 5*	73 ± 6	84 ± 10
Females (60 exposures)				
Number of animals	10	10	10	10
Serum Alkaline Phosphatase (µUnits/mL)[c]	66 ± 7	57 ± 5*	61 ± 6	73 ± 8

[a]Dow Chemical Co (1992).
[b]Corresponding HECs are 7.58, 34.18, and 148.7 mg/m^3 for males and 7.61, 34.34, and 149.4 mg/m^3 for females.
[c]Mean ± standard deviation.

*$p < 0.05$, according to the Dunnett's test reported by the study authors.

Table B-3. Selected Hematological Values in Male Fischer 344 Rats Exposed to *tert*-Amyl Alcohol by Inhalation for 11 Weeks[a]

Endpoint	Exposure Concentration in ppm[b]			
	0	50	225	1000
54 Exposures				
Number of animals	10	10	10	10
Packed cell volume (%)[c]	49.5 ± 1.4	46.4 ± 1.7*	49.3 ± 2.1	49.3 ± 2.0
Red blood cells ($\times 10^6$/mm^3)[c]	8.79 ± 0.25	8.28 ± 0.35*	8.77 ± 0.30	8.91 ± 0.41
Hemoglobin (g/100 mL)[c]	16.0 ± 0.4	15.0 ± 0.5*	15.8 ± 0.7	15.9 ± 0.6
White blood cells ($\times 10^6$/mm^3)[c]	13.3 ± 2.3	12.7 ± 1.6	9.4 ± 0.9*	10.0 ± 1.0*
57 Exposures				
Number of animals	10	10	10	10
Packed cell volume (%)[c]	49.8 ± 1.3	47.4 ± 0.9*	49.1 ± 1.3	48.9 ± 1.4
Red blood cells ($\times 10^6$/mm^3)[c]	9.03 ± 0.34	8.39 ± 0.20*	8.75 ± 0.38	8.77 ± 0.26
Hemoglobin (g/100 mL)[c]	16.1 ± 0.5	15.5 ± 0.4*	15.9 ± 0.5	16.1 ± 0.3
White blood cells ($\times 10^6$/mm^3)[c]	12.3 ± 1.4	12.2 ± 1.4	12.4 ± 1.6	12.0 ± 1.5

[a]Dow Chemical Co (1992).
[b]Corresponding HECs are 7.58, 34.18, and 148.7 mg/m^3 for males and 7.61, 34.34, and 149.4 mg/m^3 for females.
[c]Mean ± standard deviation.

*$p < 0.05$, according to the Dunnett's test reported by the study authors.

Table B-4. Selected Hematological Values in Female Fischer 344 Rats Exposed to *tert*-Amyl Alcohol by Inhalation for 11 Weeks[a]

Endpoint	Exposure Concentration in ppm[b]			
	0	50	225	1000
55 Exposures				
Number of animals	10	10	10	10
Packed cell volume (%)[c]	49.7 ± 1.7	47.9 ± 2.0	48.6 ± 1.7	48.9 ± 1.4
Red blood cells (× 10^6/mm^3)[c]	8.54 ± 0.29	8.27 ± 0.28	8.58 ± 0.29	8.70 ± 0.51
Hemoglobin (g/100 mL)[c]	16.2 ± 0.6	16.3 ± 0.5	16.5 ± 0.4	16.3 ± 0.4
White blood cells (× 10^6/mm^3)[c]	9.6 ± 1.5	9.0 ± 1.6	8.4 ± 1.2	8.0 ± 0.9*
58 Exposures				
Number of animals	10	10	10	10
Packed cell volume (%)[c]	47.6 ± 1.1	48.5 ± 1.7	47.1 ± 1.2	46.5 ± 1.6
Red blood cells (× 10^6/mm^3)[c]	8.08 ± 0.26	7.80 ± 0.42	7.81 ± 0.36	7.83 ± 0.44
Hemoglobin (g/100 mL)[c]	15.7 ± 0.5	15.5 ± 0.8	15.5 ± 0.5	15.5 ± 0.6
White blood cells (× 10^6/mm^3)[c]	12.1 ± 1.2	10.0 ± 1.0*	11.4 ± 1.2	10.9 ± 1.2

[a]Dow Chemical Co (1992).
[b]Corresponding HECs are 7.58, 34.18, and 148.7 mg/m^3 for males and 7.61, 34.34, and 149.4 mg/m^3 for females.
[c]Mean ± standard deviation.

*$p < 0.05$, according to the Dunnett's test reported by the study authors.

Table B-5. Selected Absolute Organ Weights in Male and Female Fischer 344 Rats Exposed to *tert*-Amyl Alcohol by Inhalation for 12 Weeks[a]

Endpoint	Exposure Concentration in ppm[b]			
	0	50	225	1000
Males (59 exposures)				
Number of animals	10	10	10	10
Fasted body weight (g)[c]	304 ± 13	305 ± 16 (0.33)	301 ± 14 (−0.99)	303 ± 17 (−0.33)
Kidney (g)[c]	2.05 ± 0.11	2.06 ± 0.11 (0.49)	2.07 ± 0.12 (0.98)	2.09 ± 0.16 (1.95)
Liver (g)[c]	7.48 ± 0.50	7.45 ± 0.51 (−0.40)	7.56 ± 0.36 (1.07)	8.45 ± 0.64 (12.97)*
Brain (g)[c]	1.88 ± 0.04	1.87 ± 0.05 (−0.53)	1.89 ± 0.06 (0.53)	1.84 ± 0.06 (−2.13)
Heart (g)[c]	0.80 ± 0.05	0.89 ± 0.07 (11.25)	0.86 ± 0.07 (7.50)	0.85 ± 0.07 (6.25)
Testes (g)[c]	3.07 ± 0.10	3.02 ±0.16 (−1.63)	3.10 ± 0.11 (0.98)	3.00 ± 0.14 (−2.28)
Females (60 exposures)				
Number of animals	10	10	10	10
Fasted body weight (g)[c]	160 ± 6	167 ± 8 (4.38)	170 ± 7 (6.25)*	163 ± 11 (−1.88)
Kidney (g)[c]	1.20 ± 0.04	1.19 ± 0.08 (−0.83)	1.27 ± 0.09 (5.83)	1.14 ± 0.12 (−5.00)
Liver (g)[c]	3.84 ± 0.19	4.02 ± 0.16 (4.69)	4.20 ± 0.32 (9.34)*	4.02 ± 0.37 (4.69)
Brain (g)[c]	1.70 ± 0.04	1.73 ± 0.05 (1.76)	1.74 ± 0.03 (2.35)	1.70 ± 0.09 (0)
Heart (g)[c]	0.50 ± 0.04	0.54 ± 0.04 (8.00)	0.57 ± 0.05 (14.00)	0.52 ± 0.04 (4.00)

[a]Dow Chemical Co (1992).
[b]Corresponding HECs are 7.58, 34.18, and 148.7 mg/m^3 for males and 7.61, 34.34, and 149.4 mg/m^3 for females.
[c]Mean ± standard deviation (% change compared to control calculated as [| exposed value − control value |] ÷ control value).

*$p < 0.05$, according to the Dunnett's test reported by the study authors.

Table B-6. Selected Relative Organ Weights in Male and Female Fischer 344 Rats Exposed to *tert*-Amyl Alcohol by Inhalation for 12 Weeks[a]

Endpoint	Exposure Concentration in ppm[b]			
	0	50	225	1000
Males (59 exposures)				
Number of animals	10	10	10	10
Fasted body weight (g)[c]	304 ± 13	305 ± 16 (0.33)	301 ± 14 (−0.99)	303 ± 17 (−0.33)
Relative kidney weight[c,d]	0.67 ± 0.03	0.68 ± 0.02 (1.49)	0.69 ± 0.04 (2.98)	0.69 ± 0.04 (2.99)
Relative liver weight[c,d]	2.46 ± 0.12	2.45 ± 0.11 (−0.41)	2.52 ± 0.10 (2.44)	2.81 ± 0.10 (14.23)*
Relative brain weight[c,d]	0.62 ± 0.03	0.62 ± 0.03 (0)[e]	0.63 ± 0.03 (1.61)	0.61 ± 0.02 (−1.61)
Relative heart weight[c,d]	0.29 ± 0.01	0.29 ± 0.02 (0)	0.29 ± 0.02 (0)	0.28 ± 0.01 (−3.45)
Relative testes weight[c,d]	1.01 ± 0.05	0.99 ±0.05 (−1.98)	1.03 ± 0.05 (1.98)[e]	0.99 ± 0.04 (−1.98)
Females (60 exposures)				
Number of animals	10	10	10	10
Fasted body weight (g)[c]	160 ± 6	167 ± 8 (4.38)	170 ± 7 (6.25)*	163 ± 11 (−1.88)
Relative kidney weight[c,d]	0.75 ± 0.05	0.71 ± 0.05 (−5.33)[e]	0.75 ± 0.04 (0)	0.70 ± 0.04 (−6.67)[e]
Relative liver weight[c,d]	2.41 ± 0.11	2.41 ± 0.09 (0)	2.40 ± 0.12 (−0.41)	2.46 ± 0.11 (2.07)
Relative brain weight[c,d]	1.07 ± 0.03	1.03 ± 0.04 (−3.74)	1.03 ± 0.03 (−3.74)	1.05 ± 0.04 (−1.87)
Relative heart weight[c,d]	0.35 ± 0.02[e]	0.33 ± 0.02 (−5.71)	0.34 ± 0.02 (−2.86)	0.32 ±0.02 (−8.57)*

[a]Dow Chemical Co (1992).
[b]Corresponding HECs are 7.58, 34.18, and 148.7 mg/m^3 for males and 7.61, 34.34, and 149.4 mg/m^3 for females.
[c]Mean ± standard deviation (% change compared to control calculated as [| exposed value − control value |] ÷ control value).
[d]Relative organ weights are presented as g-organ weight/100 g-body weight.
[e]The legibility of the original study makes it difficult to decipher these values.

*$p < 0.05$, according to the Dunnett's test reported by the study authors.

Table B-7. Body-Weight Gain in Male and Female CD-1 Mice Exposed to *tert*-Amyl Alcohol by Inhalation for 12 Weeks[a]

Endpoint	Exposure Concentration in ppm[b]			
	0	**50**	**225**	**1000**
Males (60 exposures)				
Number of animals	10	10	10	10
Body-weight gain (g)[c]	5.0 ± 3.4	8.4 ± 4.5[d]	6.5 ± 3.5	6.4 ± 3.1
Females (61 exposures)				
Number of animals	10	10	10	10
Body-weight gain (g)[c]	4.7 ± 3.3	4.3 ± 3.4	5.0 ± 3.5	2.2 ± 3.7

[a]Dow Chemical Co (1992).
[b]Corresponding HECs are 31.8, 143.1, and 622.8 mg/m^3 for males and 31.9, 143.8, and 625.9 mg/m^3 for females.
[c]Mean ± standard deviation; calculated from the mean body weights in the study report.
[d]The legibility of original study makes it difficult to decipher this value.

Table B-8. Selected Clinical Chemistry Parameters in Male and Female CD-1 Mice Exposed to *tert*-Amyl Alcohol by Inhalation for 12 Weeks[a]

Endpoint	Exposure Concentration in ppm[b]			
	0	50	225	1000
Males (60 exposures)				
Number of animals	10	10	10	10
Blood urea nitrogen (mg %)[c]	31 ± 4	24 ± 1*	24 ± 4*	28 ± 4
Serum alkaline phosphatase (µUnits/mL)[c]	30 ± 8	34 ± 19	31 ± 14	31 ± 18
Serum glutamic pyruvic transaminase (µUnits/mL)[c]	62 ± 51	16 ± 15*	26 ± 12*	27 ± 19*
Serum glutamic oxaloacetic transaminase (µUnits/mL)[c]	63± 24	31± 12*	43± 16	53± 22
Females (61 exposures)				
Number of animals	10	10	10	10
Blood urea nitrogen (mg %)[c]	28 ± 5	26 ± 3	25 ± 4	27 ± 4
Serum alkaline phosphatase (µUnits/mL)[c]	40 ± 9	40 ± 10	43 ± 9	41 ± 10
Serum glutamic pyruvic transaminase (µUnits/mL)[c]	13 ± 3	13 ± 3	11 ± 2	11 ± 2
Serum glutamic oxaloacetic transaminase (µUnits/mL)[c]	37± 5	41± 9	39± 7	36± 6

[a]Dow Chemical Co (1992).
[b]Corresponding HECs are 31.8, 143.1, and 622.8 mg/m^3 for males and 31.9, 143.8, and 625.9 mg/m^3 for females.
[c]Mean ± standard deviation.

*p <0.05, according to the Dunnett's test reported by the study authors.

Table B-9. Selected Absolute Organ Weights in Male and Female CD-1 Mice Exposed to *tert*-Amyl Alcohol by Inhalation for 12 Weeks[a]

Endpoint	Exposure Concentration in ppm[b]			
	0	50	225	1000
Males (60 exposures)				
Number of animals	10	10	10	10
Fasted body weight (g)[c]	38 ± 2	40 ± 3 (5.26)	38 ± 3 (0)	38 ± 3 (0)
Kidney (g)[c]	0.65 ± 0.15	0.71 ± 0.15 (9.23)	0.67 ± 0.10 (3.08)	0.63 ± 0.07 (−3.08)
Liver (g)[c]	2.09 ± 0.24	1.86 ± 0.26 (−11.00)	2.04 ± 0.27 (−2.39)	2.13 ± 0.34 (1.91)
Brain (g)[c]	0.54 ± 0.04	0.55 ± 0.04 (1.85)	0.54 ± 0.02 (0)	0.55 ± 0.03 (1.85)
Heart (g)[c]	0.18 ± 0.03	0.17 ± 0.03 (−5.56)	0.18 ± 0.02 (0)	0.19 ± 0.03 (5.56)
Testes (g)[c]	0.28 ± 0.03	0.28 ± 0.03 (0)	0.29 ± 0.04 (3.57)	0.27 ± 0.02 (−3.57)
Females (61 exposures)				
Number of animals	10	10	10	10
Fasted body weight (g)[c]	31 ± 3	30 ± 3 (−3.23)	30 ± 3 (−3.23)	28 ± 3 (−9.68)
Kidney (g)[c]	0.38 ± 0.04	0.37 ± 0.05 (−2.63)	0.30 ± 0.03 (−21.05)	0.36 ± 0.04 (−5.26)
Liver (g)[c]	1.67 ± 0.25	1.62 ± 0.27 (−2.99)	1.54 ± 0.27 (−7.78)	1.51 ± 0.10 (−9.58)
Brain (g)[c]	0.49 ± 0.03	0.49 ± 0.03 (0)	0.49 ± 0.03 (0)	0.49 ± 0.02 (0)
Heart (g)[c]	0.14 ± 0.02	0.14 ± 0.03 (0)	0.14 ± 0.01 (0)	0.14 ± 0.02 (0)

[a]Dow Chemical Co (1992).
[b]Corresponding HECs are 31.8, 143.1, and 622.8 mg/m^3 for males and 31.9, 143.8, and 625.9 mg/m^3 for females.
[c]Mean ± standard deviation (% change compared to control calculated as [| exposed value − control value |] ÷ control value).

*$p < 0.05$, according to the Dunnett's test reported by the study authors.

Table B-10. Selected Relative Organ Weights in Male and Female CD-1 Mice Exposed to *tert*-Amyl Alcohol by Inhalation for 12 Weeks[a]

Endpoint	Exposure Concentration in ppm[b]			
	0	50	225	1000
Males (60 exposures)[e]				
Number of animals	10	10	10	10
Fasted body weight (g)[c]	38 ± 2	40 ± 3 (5.26)	38 ± 3 (0)	38 ± 3 (0)
Kidney[c,d]	1.69 ± 0.30	1.78 ± 0.35 (5.33)	1.75 ± 0.26 (3.55)	1.66 ± 0.19 (−1.78)
Liver[c,d]	5.44 ± 0.52	4.63 ± 0.44 (−14.89)*	5.28 ± 0.42 (−2.94)	5.56 ± 0.67 (2.21)
Brain[c,d]	1.40 ± 0.10	1.37 ± 0.12 (−2.14)	1.41 ± 0.08 (0.71)	1.44 ± 0.14 (2.86)
Heart[c,d]	0.40 ± 0.06	0.43 ± 0.06 (7.50)	0.48 ± 0.05 (20.00)	0.49 ± 0.07 (22.50)
Testes[c,d]	0.71 ± 0.09	0.71 ± 0.09 (0)	0.76 ± 0.06 (7.04)	0.72 ± 0.09 (1.41)
Females (61 exposures)[e]				
Number of animals	10	10	10	10
Fasted body weight (g)[c]	31 ± 3	30 ± 3 (−3.23)	30 ± 3 (−3.23)	28 ± 3 (−9.68)
Kidney[c,d]	1.24 ± 0.09	1.23 ± 0.12 (−0.81)	1.10 ± 0.08 (−11.29)	1.29 ± 0.10 (4.03)
Liver[c,d]	5.45 ± 0.36	5.36 ± 0.49 (−1.65)	5.17 ± 0.48 (−5.14)	5.31 ± 0.23 (−2.57)
Brain[c,d]	1.63 ± 0.14	1.64 ± 0.15 (0.61)	1.68 ± 0.10 (3.07)	1.74 ± 0.13 (6.75)
Heart[c,d]	0.47 ± 0.05	0.45 ± 0.07 (−4.26)	0.47 ± 0.04 (0)	0.48 ± 0.04 (2.13)

[a]Dow Chemical Co (1992).
[b]Corresponding HECs are 31.8, 143.1, and 622.8 mg/m^3 for males and 31.9, 143.8, and 625.9 mg/m^3 for females.
[c]Mean ± standard deviation (% change compared to control calculated as [| exposed value − control value |] ÷ control value).
[d]Relative organ weights are presented as g-organ weight/100 g-body weight.
[e]The legibility of the original study makes it difficult to these decipher values.

*$p < 0.05$, according to the Dunnett's test reported by the study authors.

Table B-11. Histopathology of Male CD-1 Mice Exposed to *tert*-Amyl Alcohol by Inhalation for 12 Weeks (60 Exposures)[a]

Endpoint	Exposure Concentration in ppm[b]			
	0	50	225	1000
Liver				
Accentuation of hepatolobular pattern[c]	0/5 (0)	ND	ND	2/5 (40)
Multifocal aggregates of mononuclear cells[c]	0/5 (0)	ND	ND	1/5 (20)
Focal aggregation of mononuclear cells[c]	0/5 (0)	ND	ND	2/5 (40)[d]

[a]Dow Chemical Co (1992).
[b]Corresponding HECs are 31.8, 143.1, and 622.8 mg/m^3 for males and 31.9, 143.8, and 625.9 mg/m^3 for females.
[c]Number of animals with endpoint/number of animals exposed (% affected).
[d]The legibility of the original study makes it difficult to decipher this value.

ND = not determined.

Table B-12. Body Weight Gain in Male Beagle Dogs Exposed to *tert*-Amyl Alcohol by Inhalation for 12 Weeks (61 Exposures)[a]

Endpoint	Exposure Concentration in ppm (HEC in mg/m^3)[b]			
	0 (0)	50 (31.9)	225 (143.8)	1000 (625.9)
Number of animals	4	4	4	4
Body-weight gain (kg)[c]	1.2 ± 0.3	1.0 ± 0.6	0.9 ± 1.1	1.1 ± 0.8

[a]Dow Chemical Co (1992).
[b]HEC_{EXRESP} = (ppm × MW ÷ 24.45) × (hours per day exposed ÷ 24) × (days per week exposed ÷ 87) × blood-air partition coefficient.
[c]Mean ± standard deviation; calculated from the mean body weights in the study report.

Table B-13. Selected Clinical Chemistry Parameters in Male Beagle Dogs Exposed to *tert*-Amyl Alcohol by Inhalation for 12 Weeks (61 Exposures)[a]

Endpoint	Exposure Concentration in ppm (HEC in mg/m^3)[b]			
	0 (0)	50 (31.9)	225 (143.8)	1000 (625.9)
Number of animals	4	4	4	4
Blood glucose (mg %)[c]	94 ± 7[b]	120 ± 11*	109 ± 17	107 ± 7
Blood urea nitrogen (mg %)[c,d]	19 ± 3	19 ± 2	21 ± 2	18 ± 4
Serum alkaline phosphatase (µUnits/mL)[c]	32 ± 7	39 ± 6	42 ± 7	99 ± 52*
Serum glutamic pyruvic transaminase (µUnits/mL)[c]	17 ± 2	18 ± 3	22 ± 4	26 ± 7*

[a]Dow Chemical Co (1992).
[b]HEC_{EXRESP} = (ppm × MW ÷ 24.45) × (hours per day exposed ÷ 24) × (days per week exposed ÷ 87) × blood-air partition coefficient.
[c]Mean ± standard deviation.
[d]Values were measured on Day 55.

*$p < 0.05$, according to the Dunnett's test reported by the study authors.

Table B-14. Selected Hematology Values in Male Beagle Dogs Exposed to *tert*-Amyl Alcohol by Inhalation for 11 Weeks (56 Exposures)[a]

Endpoint	Exposure Concentration in ppm (HEC in mg/m^3)[b]			
	0 (0)	50 (31.9)	225 (143.8)	1000 (625.9)
Number of animals	4	4	4	4
Packed cell volume (%)[c]	42.8 ± 2.2	48.9 ± 2.8*	49.8 ± 3.5*	44.0 ± 2.8
Hemoglobin (g/100 mL)[c]	15.5 ± 0.7	17.6 ± 1.1*	18.0 ± 1.2*	16.0 ± 0.6

[a]Dow Chemical Co (1992).
[b]HEC_{EXRESP} = (ppm × MW ÷ 24.45) × (hours per day exposed ÷ 24) × (days per week exposed ÷ 87) × blood-air partition coefficient.
[c]Mean ± standard deviation.

*$p < 0.05$, according to the Dunnett's test reported by the study authors.

Table B-15. Selected Urinalysis Values in Male Beagle Dogs Before and After Exposure to *tert*-Amyl Alcohol by Inhalation for 11 Weeks (55 Exposures)[a]

Endpoint	Exposure Concentration in ppm (HEC in mg/m^3)[b]			
	0 (0)	50 (31.9)	225 (143.8)	1000 (625.9)
Number of animals	4	4	4	4
Specific gravity (preexposure)[c]	1.032 ± 0.011	1.031 ± 0.011	1.026 ± 0.007	1.043 ± 0.011
Specific gravity (55 exposures)[c]	1.040 ± 0.06	1.055 ± 0.007	1.052 ± 0.011	1.029 ± 0.012*

[a]Dow Chemical Co (1992).
[b]HEC_{EXRESP} = (ppm × MW ÷ 24.45) × (hours per day exposed ÷ 24) × (days per week exposed ÷ 87) × blood-air partition coefficient.
[c]Mean ± standard deviation.

*$p < 0.05$, according to the Dunnett's test reported by the study authors.

Table B-16. Selected Absolute Organ Weights in Male Beagle Dogs Exposed to *tert*-Amyl Alcohol by Inhalation for 12 Weeks (61 Exposures)[a]

Endpoint	Exposure Concentration in ppm (HEC in mg/m^3)[b]			
	0 (0)	50 (31.9)	225 (143.8)	1000 (625.9)
Number of animals	4	3	4	4
Final body weight (kg)[c]	12.5 ± 0.2	12.5 ± 0.5 (0)	12.7 ± 0.6 (1.60)	12.1 ± 0.6 (−3.20)
Kidney (g)[c]	59.02 ± 4.55	50.01 ± 7.76 (−15.27)	60.52 ± 6.46 (2.54)	67.56 ± 8.20 (14.47)
Liver (g)[c]	345.58 ± 49.08	382.73 ± 17.40 (10.75)[e]	421.66 ± 47.03 (22.02)	456.24 ± 22.97 (32.02)*
Brain (g)[c]	85.51 ± 4.45	85.07 ± 4.62 (−0.51)	80.06 ± 4.12 (−6.37)	81.78 ± 1.29 (−4.36)
Heart (g)[c]	85.84 ± 8.40[d]	85.57 ± 6.28 (−0.31)	82.53 ± 10.63 (−3.86)	86.24 ± 7.42 (0.47)
Testes (g)[c]	18.31 ±1.77[d]	17.10 ± 2.50 (−6.61)	16.41 ± 0.95 (−10.38)[d]	18.74 ±1.70 (2.35)

[a]Dow Chemical Co (1992).
[b]HEC_{EXRESP} = (ppm × MW ÷ 24.45) × (hours per day exposed ÷ 24) × (days per week exposed ÷ 87) × blood-air partition coefficient.
[c]Mean ± standard deviation (% change compared to control calculated as [| exposed value − control value |] ÷ control value).
[d]The legibility of the original study makes it difficult to decipher this value.
[e]This average differs from what is reported in the principal study due to removal of an individual outlier, see study summary for full explanation.

*$p < 0.05$, according to the Dunnett's test reported by the study authors.

Table B-17. Selected Relative Organ Weights in Male Beagle Dogs Exposed to *tert*-Amyl Alcohol by Inhalation for 12 Weeks (61 Exposures)[a]

Endpoint	Exposure Concentration in ppm (HEC in mg/m^3)[b]			
	0 (0)	**50 (31.9)**	**225 (143.8)**	**1000 (625.9)**
Number of animals	4	3	4	4
Final body weight (kg)[c]	12.5 ± 0.2	12.5 ± 0.5 (0)	12.7 ± 0.6 (1.60)	12.1 ± 0.6 (−3.20)
Relative kidney weight[c,d]	0.48 ± 0.05	0.47 ± 0.06 (−2.08)	0.47 ± 0.04 (−2.08)	0.56 ± 0.09 (16.67)
Relative liver weight[c,d]	2.76 ± 0.34	3.03 ± 0.04 (9.78)[f]	3.31 ± 0.28 (19.93)	3.77 ± 0.20 (36.59)*
Relative brain weight[c,d]	0.68 ± 0.04	0.60 ± 0.05 (−11.76)[e]	0.60 ± 0.03 (−11.76)	0.68 ± 0.04 (0)[e]
Relative heart weight	0.69 ± 0.03	0.60 ± 0.04 (−13.04)	0.73 ± 0.05 (5.80)	0.71 ±0.04 (2.90)
Relative testes weight	0.15 ± 0.01	0.14 ± 0.01 (−6.67)	0.13 ± 0.01 (−13.33)	0.16 ± 0.02 (6.67)

[a]Dow Chemical Co (1992).
[b]HEC_{EXRESP} = (ppm × MW ÷ 24.45) × (hours per day exposed ÷ 24) × (days per week exposed ÷ 87) × blood-air partition coefficient.
[c]Mean ± standard deviation (% change compared to control calculated as [| exposed value − control value |] ÷ control value).
[d]Relative organ weights are presented as g-organ weight/100 g-body weight.
[e]The legibility of the original study makes it difficult to decipher these values.
[f]This average differs from what is reported in the principal study due to removal of an individual outlier, see study summary for full explanation.

*$p < 0.05$, according to the Dunnett's test reported by the study authors.

Table B-18. Selected Histopathologic and Gross Pathological Observations in the Livers of Male Beagle Dogs Exposed to *tert*-Amyl Alcohol by Inhalation for 12 Weeks (61 Exposures)[a]

Endpoint	Exposure Concentration in ppm (HEC in mg/m^3)[b]			
	0 (0)	50 (31.9)	225 (143.8)	1000 (625.9)
Enlarged liver	0/4 (0)	0/4 (0)	1/4 (25)	4/4 (100)
Accentuation of the hepatolobular pattern due to increased cytoplastic vacuolization in the centrilobular region	3/4 (75)[c]	3/4 (75)[c]	4/4 (100)	2/4 (50)
Focal or multifocal aggregates of mononuclear cells	2/4 (50)	0/4 (0)	0/4 (0)	0/4 (0)
Focal or multifocal aggregates of mononuclear and polynuclear cells	2/4 (50)	0/4 (0)	1/4 (25)	0/4 (0)
Reticuloendothelial cells containing pigment	1/4 (25)	0/4 (0)	0/4 (0)	0/4 (0)
Hepatocellular cytoplasmic eosinophilic inclusion bodies	0/4 (0)	1/4 (25)	1/4 (25)[c]	1/4 (25)[c]
Focal granulosa	0/4 (0)	0/4 (0)	2/4 (50)	2/4 (50)

[a]Dow Chemical Co (1992).
[b]HEC_{EXRESP} = (ppm × MW ÷ 24.45) × (hours per day exposed ÷ 24) × (days per week exposed ÷ 87) × blood-air partition coefficient.
[c]The legibility of original study makes it difficult to decipher these values.

APPENDIX C. BMD OUTPUTS

MODELING PROCEDURE FOR CONTINUOUS DATA

The BMD modeling of continuous data was conducted with EPA's BMDS (version 2.1.2). For increased alkaline phosphatase activity in male beagles, all continuous models available within the software were fit using a default BMR of 1 standard deviation from the control mean. For increased liver weights in male rats and beagles, all continuous models available within the software were fit using a default BMR of 10% relative risk. An adequate fit was judged based on the goodness-of-fit *p*-value ($p > 0.1$), magnitude of the scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. In addition to these three criteria for judging adequacy of model fit, a determination was made as to whether the variance across dose groups was homogeneous. If a homogeneous variance model was deemed appropriate based on the statistical test provided in BMDS (i.e., Test 2), the final BMD results were estimated from a homogeneous variance model. If the test for homogeneity of variance was rejected ($p < 0.1$), the model was run again while modeling the variance as a power function of the mean to account for this nonhomogeneous variance. If this nonhomogeneous variance model did not adequately fit the data (i.e., Test 3; *p*-value < 0.1), the data set was considered unsuitable for BMD modeling. Among all models providing adequate fit, the lowest BMCL was selected if the BMCLs estimated from different models varied greater than 3-fold; otherwise, the BMCL from the model with the lowest AIC was selected as a potential POD from which to derive the screening p-RfC values.

INCREASED ABSOLUTE LIVER WEIGHT OF MALE BEAGLES TREATED WITH *tert*-AMYL ALCOHOL FOR 12 WEEKS (Dow Chemical Co, 1992)

All available continuous models in BMDS (version 2.1.2) were fit to the increased absolute liver-weight data from male beagles exposed to *tert*-amyl alcohol for 12 weeks (Dow Chemical Co, 1992) (see Table B-16). For increased absolute liver weight, a BMR of a 10% change relative to the control mean was used. In addition, a BMR of 1 SD was also estimated for comparison purposes based on U.S. EPA (2012a) BMD guidance. The homogeneity variance (Test 2) *p*-value of greater than 0.1 indicates that constant variance is the appropriate variance model. As assessed by the goodness-of-fit test and visual inspection, the Hill model provided the best fit model (see Table C-1 and Figure C-1). Estimated doses associated with 10% relative risk and the 95% lower confidence limit on these doses (BMC_{10HEC} values and $BMCL_{10HEC}$ values, respectively) were 33.5 and 7.83 mg/m^3.

Table C-1. Model Predictions for Absolute Liver Weight in Male Beagles[a]

Model[b]	BMC_{10HEC}	$BMCL_{10HEC}$	BMC_{1SDHEC}	$BMCL_{1SDHEC}$	*p*-Value Test 2	*p*-Value Test 3	Goodness-of-Fit *p*-Value[b]	AIC	Conclusion
Exponential (M2)	279	192	292	196	0.162	0.162	0.071	130.93	Goodness-of-fit *p*-value < 0.1
Exponential (M3)	279	192	292	196	0.162	0.162	0.071	130.93	Goodness-of-fit *p*-value < 0.1
Exponential (M4)	45.5	12.7	42.5	13.4	0.162	0.162	0.607	127.90	
Exponential (M5)	45.5	12.7	42.5	13.4	0.162	0.162	0.607	127.90	
Hill	**33.5**	**7.83**	**31.0**	**8.25**	**0.162**	**0.162**	**0.829**	**127.68**	**Lowest BMCL**
Linear	256	168	266	173	0.162	0.162	0.081	130.66	Goodness-of-fit *p*-value < 0.1
Polynomial	256	168	266	173	0.162	0.162	0.081	130.66	Goodness-of-fit *p*-value < 0.1
Power	256	168	266	173	0.162	0.162	0.081	130.66	Goodness-of-fit *p*-value < 0.1

[a]Dow Chemical Co (1992).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.

AIC = Akaike's Information Criteria; BMC = benchmark concentration; BMCL = lower confidence limit (95%) on the benchmark concentration.

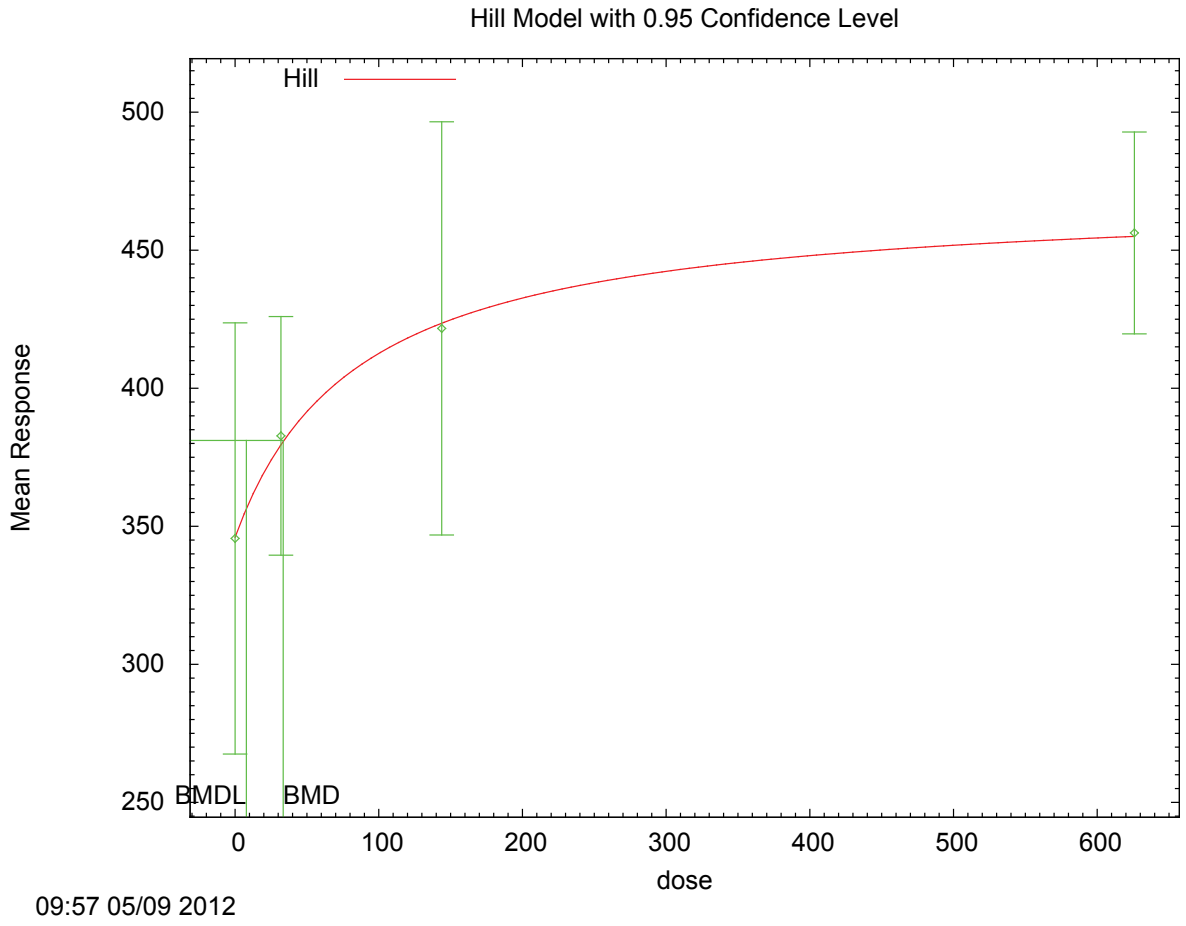

Figure C-1. Dose-Response Modeling for Increased Absolute Liver Weight in Male Beagles Treated with *tert*-Amyl Alcohol for 12 weeks (Dow Chemical Co, 1992)

Text Output for Hill BMD Model for Increased Absolute Liver Weight in Male Beagles Treated with *tert*-Amyl Alcohol for 12 weeks (Dow Chemical Co, 1992)

```
================================================================================
        Hill Model. (Version: 2.15;  Date: 10/28/2009)
        Input Data File: C:\Documents and Settings\JKaiser\Desktop\modeling
results\hil_absliv_taa_dog_dowwo541_Hil-ConstantVariance-BMR10-Restrict.(d)
        Gnuplot Plotting File: C:\Documents and Settings\JKaiser\Desktop\modeling
results\hil_absliv_taa_dog_dowwo541_Hil-ConstantVariance-BMR10-Restrict.plt
                                                Tue May 29 08:19:17 2012
 ================================================================================

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

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = mean
```

Independent variable = dose
rho is set to 0
Power parameter restricted to be greater than 1
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 =	1459.13	
rho =	0	Specified
intercept =	345.58	
v =	110.66	
n =	0.184171	
k =	203.444	

Asymptotic Correlation Matrix of Parameter Estimates

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

	alpha	intercept	v	k
alpha	1	-2.5e-007	-1.3e-007	-3.8e-007
intercept	-2.5e-007	1	-0.36	0.49
v	-1.3e-007	-0.36	1	0.5
k	-3.8e-007	0.49	0.5	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	1073.37	391.941	305.185	1841.56
intercept	346.421	16.071	314.923	377.92
v	123.903	28.5316	67.9824	179.824
n	1	NA		
k	86.2353	76.5392	-63.7787	236.249

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

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	4	346	346	49.1	32.8	-0.0514
31.9	3	383	380	17.4	32.8	0.151
143.8	4	422	424	47	32.8	-0.135
625.9	4	456	455	23	32.8	0.0561

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	-59.815784	5	129.631568
A2	-57.248826	8	130.497652
A3	-59.815784	5	129.631568
fitted	-59.839224	4	127.678448
R	-67.241843	2	138.483685

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	19.986	6	0.002785
Test 2	5.13392	3	0.1622
Test 3	5.13392	3	0.1622
Test 4	0.0468793	1	0.8286

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 =           0.1

Risk Type        =     Relative risk

Confidence level =           0.95

             BMD =        33.4678

            BMDL =        7.8333
```

INCREASED RELATIVE LIVER WEIGHT OF MALE BEAGLES TREATED WITH *tert*-AMYL ALCOHOL FOR 12 WEEKS (Dow Chemical Co, 1992)

All available continuous models in BMDS (version 2.1.2) were fit to the increased relative liver-weight data from male beagles exposed to *tert*-amyl alcohol for 12 weeks (Dow Chemical Co, 1992) (see Table B-17). For increased relative liver weight, a BMR of a 10% change relative to the control mean was used. In addition, a BMR of 1 SD was also estimated for comparison purposes based on EPA BMD guidance (U.S. EPA, 2012a). The BMD analysis resulted in significant lack of fit (goodness-of-fit $p < 0.10$, Test 4) for all continuous models employing constant variance. No available model in BMDS provided an adequate fit to the data as Test 3 for all models was less than 0.1 (see Table C-2). All of the BMD modeling results shown in Table C-2 were obtained from nonconstant variance models. Because all models for these data failed, a BMD output graph is not provided.

Table C-2. Model Predictions for Relative Liver Weight in Male Beagles[a]

Model[b]	BMC_{10HEC}	$BMCL_{10HEC}$	BMC_{1SDHEC}	$BMCL_{1SDHEC}$	*p*-Value Test 2	*p*-Value Test 3	Goodness-of-Fit *p*-Value[b]	AIC	Conclusion
Exponential (M2)	244	187	243	156	0.020	0.010	0.092	−18.79	*p*-score 3 < 0.1
Exponential (M3)	244	187	243	156	0.020	0.010	0.092	−18.79	*p*-score 3 < 0.1
Exponential (M4)	63.5	29.9	56.1	24.4	0.020	0.010	0.394	−20.82	*p*-score 3 < 0.1
Exponential (M5)	63.5	29.9	56.1	24.4	0.020	0.010	0.394	−20.82	*p*-score 3 < 0.1
Hill	54.0	18.4	47.4	21.5	0.020	0.010	0.464	−21.01	*p*-score 3 < 0.1
Linear	221	162	218	132	0.020	0.010	0.111	−19.15	*p*-score 3 < 0.1
Polynomial	221	162	218	132	0.020	0.010	0.111	−19.15	*p*-score 3 < 0.1
Power	221	162	218	132	0.020	0.010	0.111	−19.15	*p*-score 3 < 0.1

[a]Dow Chemical Co (1992).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.

AIC = Akaike's Information Criteria; BMC = benchmark concentration; BMCL = lower confidence limit (95%) on the benchmark concentration.

INCREASED ALKALINE PHOSPHATASE IN MALE BEAGLES TREATED WITH *tert*-AMYL ALCOHOL FOR 12 WEEKS (Dow Chemical Co, 1992)

All available continuous models in BMDS (version 2.1.2) were fit to the increased alkaline phosphatase data from male beagles exposed to *tert*-amyl alcohol for 12 weeks (Dow Chemical Co, 1992) (see Table B-13). The homogeneity variance (Test 2) *p*-value of less than 0.1 indicates that nonconstant variance is the appropriate variance model. As assessed by the goodness-of-fit test and visual inspection, the Exponential 2 model provided the best fit model (see Table C-3 and Figure C-2). Estimated doses associated with 10% relative risk and the 95% lower confidence limit on these doses (BMC_{1SDHEC} values and $BMCL_{1SDHEC}$ values, respectively) were 87.4 and 57.8 mg/m^3.

Table C-3. Model Predictions for Alkaline Phosphatase in Male Beagles[a]

Model[b]	BMC_{1SDHEC}	$BMCL_{1SDHEC}$	*p*-Value Test 2[b]	*p*-Value Test 3[b]	Goodness-of-Fit *p*-Value[b]	AIC	Conclusion
Exponential (M2)	**87.4**	**57.8**	**<0.0001**	**0.500**	**0.483**	**99.32**	**Lowest acceptable AIC**
Exponential (M3)	108	58.0	<0.0001	0.500	0.237	101.26	
Exponential (M4)	59.3	34.1	<0.0001	0.500	0.100	102.56	
Exponential (M5)	132	37.9	<0.0001	0.500	NDr	103.53	
Hill	132	NDr	<0.0001	0.500	NDr	103.53	BMCL not calculated
Power	132	37.9	<0.0001	0.500	<0.0001	101.53	Goodness-of-fit *p*-value < 0.1
Polynomial	1.72×10^{-6}	NDr	<0.0001	0.500	<0.0001	8	Goodness-of-fit *p*-value < 0.1, BMCL not calculated
Linear	−9999	29.2	<0.0001	0.500	0.196	36.10	

[a]Dow Chemical Co (1992).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.

AIC = Akaike's Information Criteria; BMC = benchmark concentration; BMCL = lower confidence limit (95%) on the benchmark concentration; NDr = not determinable.

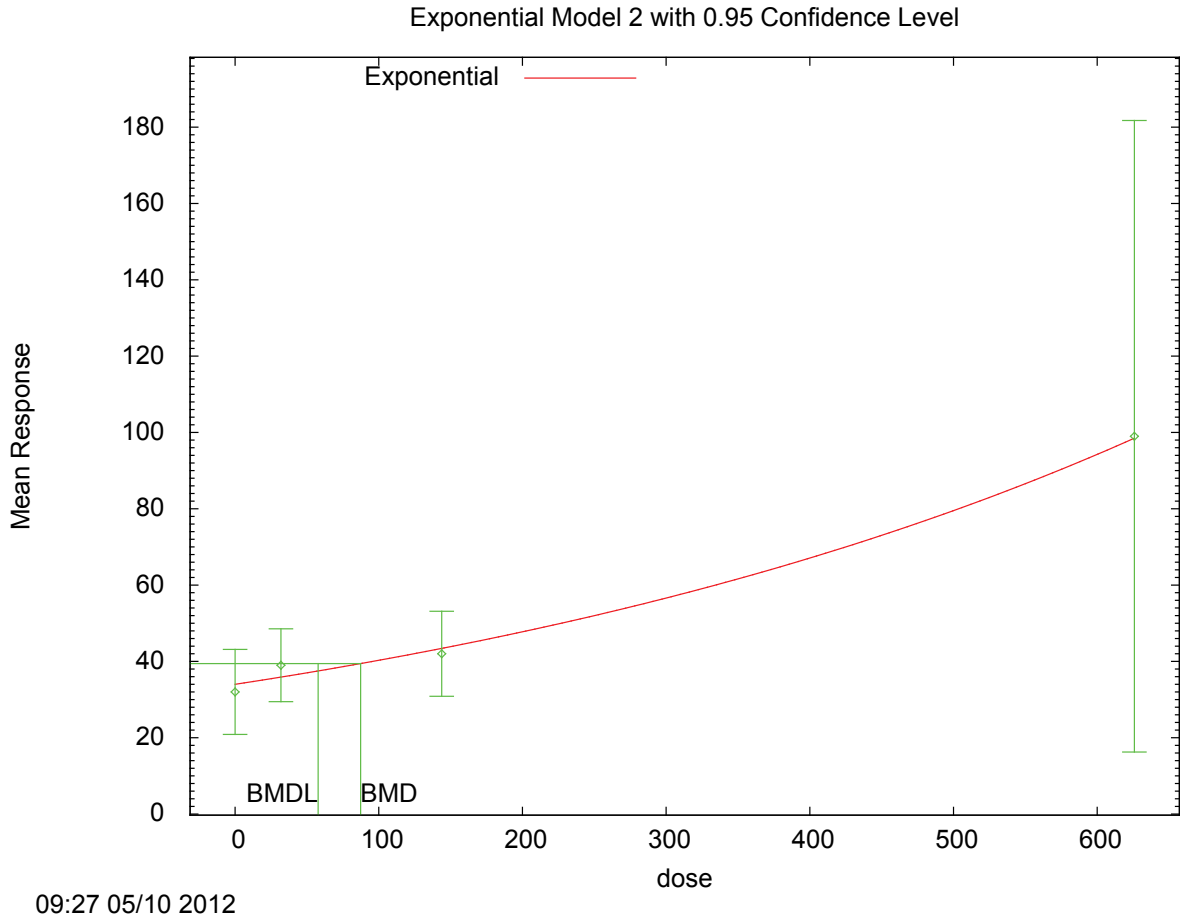

Figure C-2. Dose-Response Modeling for Increased Alkaline Phosphatase in Male Beagles Treated with *tert*-Amyl Alcohol for 12 weeks (Dow Chemical Co, 1992)

INCREASED ABSOLUTE LIVER WEIGHT OF MALE RATS TREATED WITH *tert*-AMYL ALCOHOL FOR 12 WEEKS (Dow Chemical Co, 1992)

All available continuous models in BMDS (version 2.1.2) were fit to the increased absolute liver-weight data from male rats exposed to *tert*-amyl alcohol for 12 weeks (Dow Chemical Co, 1992) (see Table B-5). For increased absolute liver weight, a BMR of a 10% change relative to the control mean was used. In addition, a BMR of 1 SD was also estimated for comparison purposes based on U.S. EPA (2012a) BMD guidance. The homogeneity variance (Test 2) *p*-value of greater than 0.1 indicates that constant variance is the appropriate variance model. As assessed by the goodness-of-fit test and visual inspection, the Exponential 2 model provided the best fit model (see Table C-4 and Figure C-3). Estimated doses associated with 10% relative risk and the 95% lower confidence limit on these doses (BMC_{10HEC} values and $BMCL_{10HEC}$ values, respectively) were 110 and 84.0 mg/m^3.

Table C-4. Model Predictions for Absolute Liver Weight in Male Rats[a]

Model[b]	BMC_{10HEC}	$BMCL_{10HEC}$	BMC_{1SDHEC}	$BMCL_{1SDHEC}$	*p*-Value Test 2	*p*-Value Test 3	Goodness-of-Fit *p*-Value[b]	AIC	Conclusion
Exponential (M2)	**110**	**84.0**	**73.4**	**55.0**	**0.367**	**0.367**	**0.798**	**−11.29**	**Lowest acceptable AIC**
Exponential (M3)	126	85.6	96.4	56.1	0.367	0.367	0.857	−9.71	
Exponential (M4)	108	80.7	71.1	52.2	0.367	0.367	0.467	−9.21	
Exponential (M5)	45.8	35.8	42.2	34.6	0.367	0.367	NDr	−7.72	
Hill	48.1	36.5	42.7	34.8	0.367	0.367	NDr	−7.72	
Linear	108	80.7	71.1	52.2	0.367	0.367	0.768	−11.21	
Polynomial	127	82.7	98.8	53.6	0.367	0.367	0.837	−9.70	
Power	125	82.8	95.6	53.6	0.367	0.367	0.858	−9.71	

[a]Dow Chemical Co (1992).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.

AIC = Akaike's Information Criteria; BMC = benchmark concentration; BMCL = lower confidence limit (95%) on the benchmark concentration; NDr = not determinable.

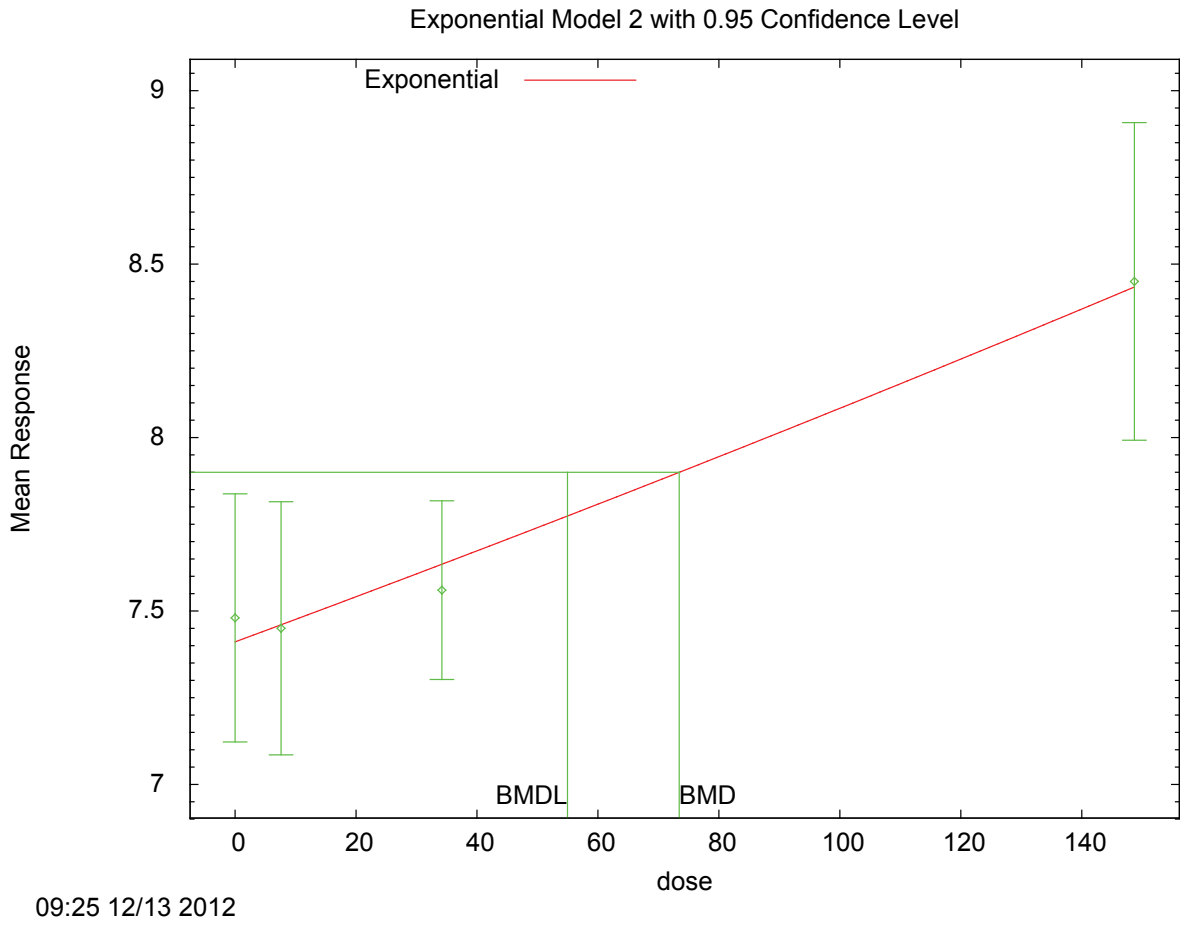

Figure C-3. Dose-Response Modeling for Increased Absolute Liver Weight in Male Rats Treated with *tert*-Amyl Alcohol for 12 weeks (Dow Chemical Co, 1992)

INCREASED RELATIVE LIVER WEIGHT OF MALE RATS TREATED WITH *tert*-AMYL ALCOHOL FOR 12 WEEKS (Dow Chemical Co, 1992)

All available continuous models in BMDS (version 2.1.2) were fit to the increased relative liver-weight data from male rats exposed to *tert*-amyl alcohol for 12 weeks (Dow Chemical Co, 1992) (see Table B-6). For increased relative liver weight, a BMR of a 10% change relative to the control mean was used. In addition, a BMR of 1 SD was also estimated for comparison purposes based on U.S. EPA (2012a) BMD guidance. The homogeneity variance (Test 2) *p*-value of greater than 0.1 indicates that constant variance is the appropriate variance model. As assessed by the goodness-of-fit test and visual inspection, the Exponential 2 model provided the best fit (see Table C-5 and Figure C-4). Estimated doses associated with 10% relative risk and the 95% lower confidence limit on these doses (BMC_{10HEC} values and $BMCL_{10HEC}$ values, respectively) were 102 and 86.6 mg/m^3.

Table C-5. Model Predictions for Relative Liver Weight in Male Rats[a]

Model[b]	BMC_{10HEC}	$BMCL_{10HEC}$	BMC_{1SDHEC}	$BMCL_{1SDHEC}$	*p*-Value Test 2	*p*-Value Test 3	Goodness-of-Fit *p*-Value[b]	AIC	Conclusion
Exponential (M2)	**102**	**86.6**	**44.2**	**35.4**	**0.925**	**0.925**	**0.8275**	**−136.02**	**Lowest acceptable AIC**
Exponential (M3)	108	86.9	51.5	35.5	0.925	0.925	0.6178	−134.15	
Exponential (M4)	99.7	83.3	42.0	33.3	0.925	0.925	0.5008	−133.95	
Exponential (M5)	40.9	35.9	36.0	24.7	0.925	0.925	NDr	−132.35	
Hill	43.8	36.5	36.4	24.6	0.925	0.925	NDr	−132.35	
Linear	99.7	83.3	42.0	33.3	0.925	0.925	0.7972	−135.95	
Polynomial	109	83.7	51.0	33.5	0.925	0.925	0.5891	−134.11	
Power	107	83.9	51.0	33.5	0.925	0.925	0.6269	−134.16	

[a]Dow Chemical Co (1992).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.

AIC = Akaike's Information Criteria; BMC = benchmark concentration; BMCL = lower confidence limit (95%) on the benchmark concentration; NDr = not determinable.

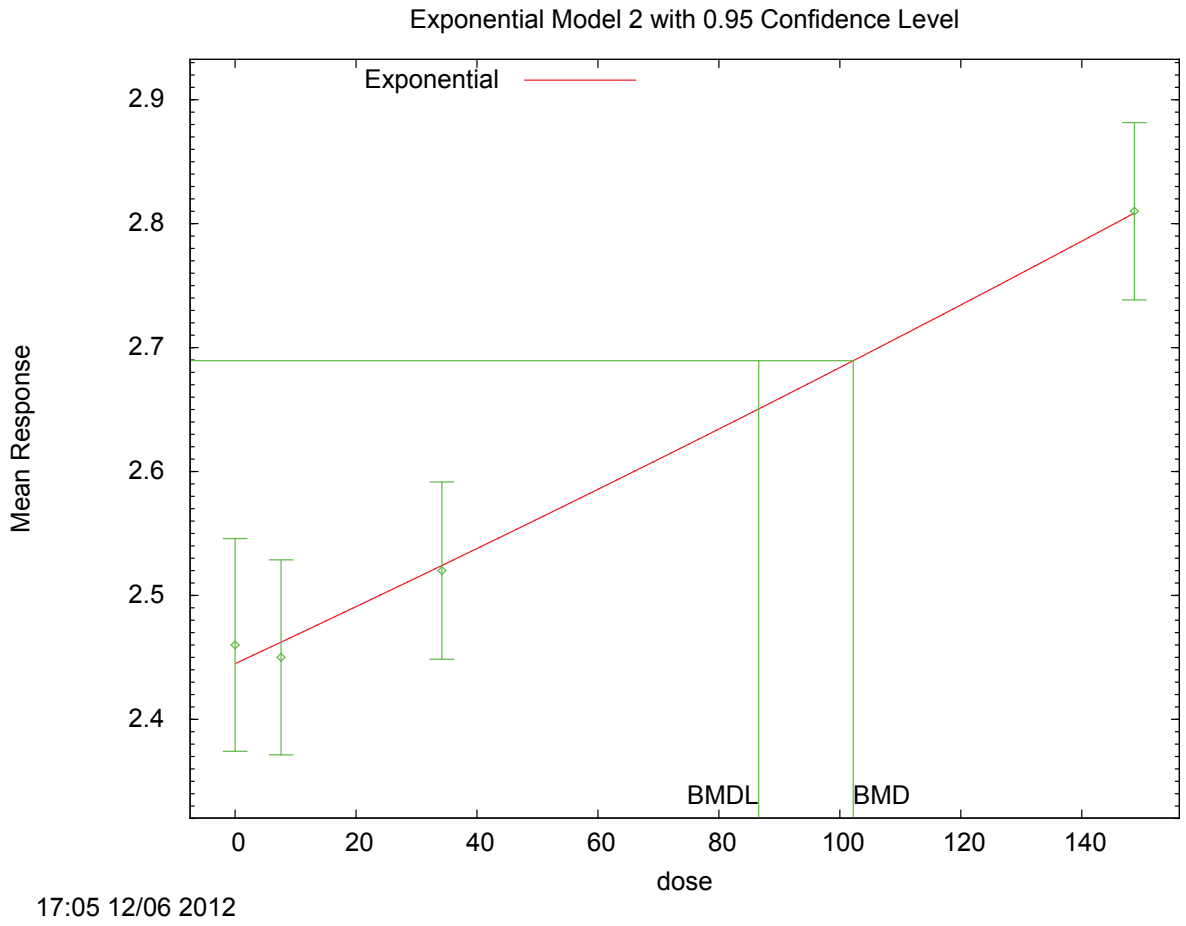

Figure C-4. Dose-Response Modeling for Increased Relative Liver Weight in Male Rats Treated with *tert*-Amyl Alcohol for 12 weeks (Dow Chemical Co, 1992)

APPENDIX D. REFERENCES

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