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Provisional Peer-Reviewed Toxicity Values for

n-Nonane
(CASRN 111-84-2)

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

Commonly Used Abbreviations

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

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR *n*-NONANE (CASRN 111-84-2)

Background

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

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

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

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

Disclaimers

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

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore,

users are strongly encouraged to read the entire PPRTV document and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

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

INTRODUCTION

No RfD, RfC, or carcinogenicity assessment for *n*-nonane is available on IRIS (U.S. EPA, 2009). *n*-Nonane is not included on the Health Effects Assessment Summary Tables (HEAST; U.S. EPA, 1997), the Drinking Water Standards and Health Advisory list (U.S. EPA, 2006), or the Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991, 1994). The Agency for Toxic Substances and Disease Registry (ATSDR) (2009) has not produced a Toxicological Profile for *n*-nonane. Toxicological Profiles on mixtures containing *n*-nonane, such as jet fuel JP-8 (ATSDR, 1998), and Total Petroleum Hydrocarbons (ATSDR, 1999), do not derive oral or inhalation MRLs for any of the individual compounds. A chronic oral RfD of 1.017 mg/kg/day has been derived for *n*-nonane by Staats Creative Sciences (SCS) for the United States Air Force (Staats, 1994) based on route-to-route extrapolation from an inhalation concentration of 1600 ppm derived from a subchronic inhalation study in rats by Carpenter et al. (1978). Although Staats (1994) used the 1600-ppm level as a NOAEL, Carpenter et al. (1978) reported the NOAEL for subchronic inhalation of *n*-nonane vapor by rats to be 590 ppm based on consistent suppression of weight gain and signs of toxic stress in rats exposed in the high-dose group to 1600-ppm *n*-nonane vapor.

No Environmental Health Criteria Document is available for *n*-nonane from the World Health Organization (WHO, 2009). The Occupational Safety and Health Administration (OSHA, 2009) has not established a permissible exposure limit (PEL) for *n*-nonane. The National Institute for Occupational Safety and Health (NIOSH, 2008) has set a recommended exposure limit (REL) of 200 ppm (1,050 mg/m^3) for *n*-nonane based on CNS effects, irritation of the eyes, skin, nose, and throat and chemical pneumonitis (aspiration liquid). The American Conference of Governmental Industrial Hygienists (ACGIH, 2007) recommends a threshold limit value (TLV) of 200 ppm—also based on CNS effects. The carcinogenicity of *n*-nonane has not been assessed by the International Agency for Research on Cancer (IARC, 2009) or the National Toxicology Program (NTP, 2005, 2009).

To identify toxicological information pertinent to the derivation of provisional toxicity values for *n*-nonane, literature searches were conducted in December 2007 using the following

databases: MEDLINE, TOXLINE (Special), BIOSIS, TSCATS1/TSCATS2, CCRIS, DART/ETIC, GENETOX, HSDB, RTECS, and Current Contents. A Voluntary Children's Chemical Evaluation Program (VCCEP) Tier 1 Pilot Submission on the *n*-Alkane Category from the American Chemistry Council *n*-Alkane VCCEP Consortium (2004) was also reviewed for relevant data. A final search for toxicological information was conducted for the period from December 2007 and September 2009.

REVIEW OF PERTINENT DATA

Human Studies

No information was located regarding the subchronic or chronic oral or inhalation toxicity of *n*-nonane in humans.

Animal Studies

Oral Exposure

Data on the subchronic oral effects of *n*-nonane in animals come from a single subchronic study by Dodd et al. (2003). Dodd et al. (2003) treated groups of 10 male C57BL/6 mice and 10 female Fischer 344 rats with doses (neat) of 0, 100, 1000, or 5000 mg/kg-day of *n*-nonane (99% purity) by gavage 7 days/week for 90 days. The test protocol required two rodent species and both male and female animals. Because of a concern for the development of α-2u-globulin nephropathy in male rats, only female rats were dosed. The study authors dosed only male mice. The dosages were established based on a 7-day range-finding study conducted by the same researchers, which are discussed in further detail below. Dodd et al. (2003) randomly assigned mice and rats to dose groups (10/group). Due to unexpected mortality in the high-dose rats during the first 4 days of dosing, two additional rats were assigned to this group. Animals were allowed free access to food and water and were housed individually in plastic cages. Body weights were determined and recorded immediately prior to the initiation of the study. Body weights and food consumption were determined and recorded weekly thereafter. Animals were fasted at least 12 hours prior to sacrifice following the 90-day exposure period.

Effects on general toxicity, neurobehavioral activity (grip strength and locomotor activity), hematology (hematocrit [HCT], hemoglobin [HGB] concentration, erythrocyte count [RBC], mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], total and differential leukocyte count [WBC], and platelet count), clinical chemistry (calcium, phosphorus, chloride, sodium, potassium, glucose, alanine aminotransferase [ALT], aspartate aminotransferase [AST], γ-glutamyl transpeptidase, alkaline phosphatase [ALP], blood urea nitrogen [BUN], albumin, globulin, total protein, creatinine, and total bilirubin), and organ weights (liver, kidneys, adrenals, gonads, spleen, lungs, and brain) were evaluated in all animals (Dodd et al., 2003). In addition, a few additional serum chemistry measurements of cholesterol, triglycerides, and magnesium were made only in rats. Gross necropsy, including examination of the external surface of the body, all the orifices, and the cranial, thoracic, and the abdominal cavities and their contents, were conducted on each animal. Histopathologic examination of 32 tissues and organs, including any gross lesions identified at necropsy, were conducted on all control and high-dose animals and on "target" tissues from low- and mid-dose animals.

Mice in the control, low-, and mid-dose groups did not exhibit any notable clinical signs of toxicity during the 90-day exposure to *n*-nonane (Dodd et al., 2003). However, rats in the control, low-, and mid-dose groups exhibited the occasional presence of dry red material around the eyes. Both mice and rats in the high-dose group exhibited general signs of toxicity in the form of wet urogenital/perianal areas, matted fur in the anal area, perianal alopecia, perianal/hindlimb erythema, dark-colored urine, diarrhea, erythema/excreta at base of tail, hunched posture, dry red material around the eyes and nose, lower jaw alopecia, and matted body fur. In addition, mice at the high dose exhibited occasional redness and swelling of the penis and scrotal area. Food consumption values and body-weight gains were not different from controls for mice. Food consumption values were significantly ($p < 0.01$) decreased during the first two weeks of the study for mid- and high-dose female rats. However, no significant differences in body-weight gain compared to controls were observed. No statistical difference between exposed and control animals in regard to grip strength was observed. There was a pattern of decreased motor activity that was observed during the first 12 weeks of the study in male mice and female rats dosed with *n*-nonane. A clear dose-response relationship, however, was not observed.

Dodd et al. (2003) reported mortality in five high-dose rats within the first 10 days of the study. Upon necropsy of these rats, gross and histologic lesions (pulmonary hemorrhage and severe transmural hemorrhagic gastritis) were observed. The authors considered these lesions to be caused by trauma during oral gavage. In addition, another high-dose rat died during Week 11, and a mid-dose rat died during Week 13. These deaths were also attributed to dosing accidents. Two high-dose mice, two mid-dose mice, and one control mouse also died before the end of the 90-day study. Again, hemorrhagic lesions were suggestive of dosing accidents.

Table 1 summarizes the statistically significant hematological changes observed in mice and rats. Dodd et al. (2003) recognized that although statistically significant differences in two hematology indices were observed among exposed animals compared to control animals, all the values were well within normal limits for each species. Furthermore, Dodd et al. (2003) stated that the occurrence of increased neutrophil percentage and corresponding decreased lymphocyte percentage is consistent with the normal physiologic responses to stress and minor inflammation—which, in turn, correlates with the histopathology alterations described below.

Table 1. Mean Hematologic Values of Male Mice and Female Rats[a]

Parameter	0 mg/kg-day		100 mg/kg-day		1000 mg/kg-day		5000 mg/kg-day	
	Mice	Rats	Mice	Rats	Mice	Rats	Mice	Rats
RBC (10^6)	11.5 ± 1.2[b]	8.9 ± 0.4	11.4 ± 0.6	8.8 ± 0.5	10.9 ± 0.9	8.7 ± 0.6	9.7 ± 1.5[c]	8.9 ± 0.8
HGB (g/dl)	16.7 ± 0.7	15.4 ± 0.6	16 ± 0.3	15.5 ± 0.8	15.5 ± 0.5	15.2 ± 1.0	14.5 ± 2.0[d]	15.5 ± 1.2
HCT (%)	53.7 ± 5.1	47.2 ± 1.7	52.4 ± 4.1	46.9 ± 2.5	49.4 ± 2.9	46.6 ± 2.9	44.1 ± 6.9[d]	47.2 ± 3.8
WBC (10^3)	5.6 ± 1.3	6.8 ± 0.8	7.1 ± 2.6	8.7 ± 1.1[c]	5.9 ± 1.4	7.9 ± 1.5	7.6 ± 2.0	9.6 ± 1.2[c]
Basophils (%)	1.2 ± 2.0	0.1 ± 0.1	0.6 ± 1.0	0.3 ± 0.2	0.9 ± 1.4	0.2 ± 0.2	0.5 ± 0.6	0.8 ± 0.7[c]
Neutrophils (%)	9.6 ± 5.5	21.1 ± 3.2	10.4 ± 8.1[d]	22.1 ± 3.9	10.7 ± 5.5[d]	24.4 ± 3.5	25.8 ± 10.9[d]	29.5 ± 7.3[c]
Lymphocytes (%)	85.6 ± 4.4	73.8 ± 3.2	86.2 ± 6.8	73.2 ± 4	85.5 ± 4.2	70.9 ± 3.6	70.1 ± 14.5[d]	65.3 ± 6.9[c]

[a]Dodd et al., 2003; C57BL/6 mice; Fisher 344 rats
[b]Mean ± SD
[c]$p < 0.05$ compared to control
[d]$p < 0.01$ compared to control

Statistically significant changes in serum chemistry in mice and rats are summarized in Table 2. Similarly to the alterations in hematology, some changes in serum chemistry in exposed animals were significantly different from control animals, but the values were well within normal limits for each species and represent mild, clinically insignificant changes (Dodd et al., 2003).

Table 2. Mean Serum Chemistry Values of Male Mice and Female Rats[a]

Parameter	0 mg/kg-day		100 mg/kg-day		1000 mg/kg-day		5000 mg/kg-day	
	Mice	Rats	Mice	Rats	Mice	Rats	Mice	Rats
Chloride (mmol/L)	115 ± 4[b]	98.7 ± 1.3	115 ± 2	98.8 ± 1.9	113 ± 1[c]	99.7 ± 0.9	111 ± 2[d]	98.3 ± 2.1
Total Protein (g/dL)	5 ± 0.3	6.3 ± 0.2	4.8 ± 0.3	6.3 ± 0.2	4.8 ± 0.1	5.9 ± 0.2[c]	4.6 ± 0.3	6.1 ± 0.3
AST (IU/L)	64.1 ± 4.4	85.6 ± 23	52.3 ± 5.4	78.5 ± 8.2	54.5 ± 13.5	83.1 ± 15	50.6 ± 5.6[c]	97.3 ± 15.3
ALT (IU/L)	16.8 ± 6.0	48.8 ± 4.1	15.8 ± 7.3	47.9 ± 7.2	24.5 ± 14.5	44.7 ± 5.8	19.3 ± 9.1	61.8 ± 5[c]
ALP (IU/L)	98.3 ± 15	127 ± 13	96 ± 17.4[c]	124 ± 21	89.5 ± 7.7[d]	113 ± 11	65.5 ± 18[d]	157 ± 53
Triglycerides (mg/dL)	NA[e]	62.2 ± 14.8	NA	69.4 ± 18.3	NA	49.8 ± 6.7	NA	37.2 ± 11.4[d]
Cholesterol (mg/dL)	NA	77.9 ± 7.5	NA	79.1 ± 5.1	NA	72.7 ± 3.2	NA	64.5 ± 6.6[c]
Albumin (g/dL)	2.6 ± 0.2	3.6 ± 0.1	2.5 ± 0.1	3.6 ± 0.1	2.4 ± 0.1[c]	3.2 ± 0.2[c]	2.2 ± 0.2[d]	3.2 ± 0.2[c]
Total Bilirubin (mg/dL)	0.4 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.3 ± <0.1	0.3 ± 0.1	0.2 ± 0.1[c]	0.3 ± 0.1

[a]Dodd et al., 2003; C57BL/6 mice; Fisher 344 rats
[b]Mean ± SD
[c]$p < 0.05$ compared to control
[d]$p < 0.01$ compared to control
[e]NA = not analyzed

Tables 3 and 4 summarize the mean absolute and relative organ weights for male mice and female rats, respectively. As shown, absolute and relative (to body and to brain) liver weights were significantly ($p < 0.05$) increased by 13–15% in female rats receiving 5000-mg/kg-day *n*-nonane and by 19–23% in male mice receiving 5000-mg/kg-day *n*-nonane. Other noteworthy changes ($p < 0.05$), occurring only in female rats, were a 73–79% increase in mean absolute and relative lung weight in the 5000-mg/kg-day group and smaller—but apparently dose-related—changes ($p < 0.05$) in adrenal (11–24% increase) and ovary (14–26% decrease) weights in the 1000- and 5000-mg/kg-day groups.

Table 3. Mean (%) Absolute and Relative Organ Weights of Male Mice[a]

Organ	Dose (mg/kg-day)			
	0	100	1000	5000
Absolute Weights				
Liver	1.14 ± 0.04[b]	1.2 ± 0.03	1.27 ± 0.06	1.4 ± 0.08[c]
Kidneys	0.45 ± 0.01	0.41 ± 0.01	0.4 ± 0.01[c]	0.4 ± 0.02[c]
Lungs	0.34 ± 0.01	0.31 ± 0.02	0.29 ± 0.02	0.28 ± 0.02
Spleen	0.05 ± <0.01	0.06 ± <0.01	0.07 ± <0.01	0.12 ± 0.04
Adrenals	0.006 ± 0.001	0.007 ± 0.001	0.005 ± 0.001	0.005 ± 0.001
Testes	0.22 ± <0.01	0.2 ± 0.01	0.21 ± 0.01	0.2 ± 0.01
Brain	0.43 ± <0.01	0.42 ± <0.01	0.42 ± <0.01	0.41 ± 0.01
Body Weight	28.5 ± 0.5	27.6 ± 0.5	27.6 ± 0.9	26.9 ± 0.7
Relative to Body Weight				
Liver	4.01 ± 0.13	4.35 ± 0.08	4.6 ± 0.11[c]	5.18 ± 0.2[c]
Kidneys	1.58 ± 0.02	1.5 ± 0.03	1.46 ± 0.02[c]	1.47 ± 0.05
Lungs	1.21 ± 0.03	1.13 ± 0.07	1.04 ± 0.06	1.04 ± 0.04
Spleen	0.19 ± 0.01	0.23 ± 0.01	0.24 ± 0.01	0.46 ± 0.14
Adrenals	0.023 ± 0.004	0.025 ± 0.004	0.018 ± 0.003	0.02 ± 0.003
Testes	0.78 ± 0.02	0.74 ± 0.03	0.77 ± 0.03	0.76 ± 0.03
Brain	1.51 ± 0.03	1.54 ± 0.02	1.53 ± 0.06	1.54 ± 0.04
Relative to Brain Weight				
Liver	266 ± 10	283 ± 7	304 ± 16[c]	339 ± 21[c]
Kidneys	105 ± 2	97.4 ± 1.4	95.8 ± 3.4	96.1 ± 4.9
Lungs	79.9 ± 1.9	73.4 ± 4.6	68.6 ± 5.5	67.7 ± 3.6
Spleen	12.7 ± 0.5	14.7 ± 0.5	15.9 ± 1.1	30.4 ± 9.6
Adrenals	1.5 ± 0.25	1.61 ± 0.26	1.22 ± 0.25	1.31 ± 0.19
Testes	51.9 ± 1.1	48.2 ± 1.7	50.4 ± 1.7	49.1 ± 1.6

[a]Dodd et al., 2003; C57BL/6 mice
[b]Mean ± SD, units are percent
[c]$p < 0.05$ compared to control

Table 4. Mean (%) Absolute and Relative Organ Weights of Female Rats[a]

Organ	Dose (mg/kg-day)			
	0	100	1000	5000
Absolute Weights				
Liver	4.19 ± 0.1[b]	4.1 ± 0.11	4.03 ± 0.09	4.82 ± 0.18[c]
Kidneys	1.17 ± 0.02	1.14 ± 0.02	1.13 ± 0.02	1.21 ± 0.04
Lungs	1.32 ± 0.12	1.25 ± 0.07	1.21 ± 0.09	2.28 ± 0.44[c]
Spleen	0.39 ± 0.01	0.38 ± 0.01	0.35 ± 0.01	0.34 ± 0.02[c]
Adrenals	0.054 ± 0.003	0.053 ± 0.002	0.060 ± 0.002	0.066 ± 0.003
Ovaries	0.091 ± 0.002	0.088 ± 0.002	0.076 ± 0.003[c]	0.067 ± 0.008[c]
Brain	1.69 ± 0.02	1.67 ± 0.01	1.64 ± 0.03	1.67 ± 0.02
Body Weight	163.3 ± 2.5	161.9 ± 1.5	154 ± 2.5	160.8 ± 4.4
Relative to Body Weight				
Liver	2.56 ± 0.04	2.53 ± 0.06	2.62 ± 0.04	3.0 ± 0.06[c]
Kidneys	0.72 ± 0.01	0.71 ± 0.01	0.74 ± 0.01	0.75 ± 0.01
Lungs	0.8 ± 0.07	0.77 ± 0.04	0.79 ± 0.05	1.43 ± 0.3[c]
Spleen	0.24 ± <0.01	0.23 ± 0.01	0.23 ± <0.01	0.21 ± 0.01[c]
Adrenals	0.033 ± 0.002	0.033 ± 0.001	0.039 ± 0.001[c]	0.041 ± 0.001[c]
Ovaries	0.056 ± 0.001	0.055 ± 0.001	0.050 ± 0.002	0.041 ± 0.004[c]
Brain	1.04 ± 0.01	1.03 ± 0.01	1.07 ± 0.01	1.04 ± 0.03
Relative to Brain Weight				
Liver	248 ± 5	245 ± 6	246 ± 4	289 ± 10[c]
Kidneys	69.3 ± 1	68.3 ± 0.6	69.2 ± 0.9	72.7 ± 2.2
Lungs	77.5 ± 6.4	75.1 ± 4.8	73.8 ± 5.1	138 ± 28[c]
Spleen	22.9 ± 0.5	22.5 ± 0.5	21.2 ± 0.4	20.4 ± 1
Adrenals	3.21 ± 0.19	3.16 ± 0.08	3.66 ± 0.13[c]	3.97 ± 0.18[c]
Ovaries	5.41 ± 0.09	5.28 ± 0.13	4.65 ± 0.18	4.0 ± 0.45[c]

[a]Dodd et al., 2003; Fisher 344 rats
[b]Mean ± SD, units are percent
[c]$p < 0.05$ compared to control

Table 5 summarizes the tissue lesion incidence reported by Dodd et al. (2003) in exposed animals. Lesions occurred primarily along the alimentary tract. Varying degrees of hyperplasia and hyperkeratosis of the squamous epithelium were found in the nonglandular stomach (forestomach) of mice and rats from all dose groups. Occasionally, erosion and ulceration of the mucosa were also present. No lesions were observed in the glandular stomach of any treated animal. Other lesions observed were mild inflammation in the proximal duodenum mucosa (high-dose rats), perianal hyperplasia accompanied by hyperkeratosis often with mild inflammation (mid- and high-dose mice and rats), and multifocal minimal-to-mild necrosis and suppurative inflammation of the nasal turbinates (high-dose mice; low-, mid-, and high-dose rats). In rats, the nasal lesions were often accompanied by pulmonary lesions (incidence not reported) consistent with aspiration of foreign material, ranging from peribronchial histiocytic infiltrates to necrohemorrhagic bronchopneumonia. Based on the pathology of these lesions and the pulmonary foreign body response observed in rats, Dodd et al. (2003) suggest that the lesions in the nasal turbinates resulted from direct contact with the gavaged test agent—rather than from specific xenobiotic targeting of nasal mucosa. Based on the lesions observed in the forestomachs of both rats and mice at all dose levels, the lowest dose tested of 100 mg/kg-day is identified as a LOAEL for the purposes of this review. A NOAEL is not identified in this study.

Table 5. Incidence of Tissue Lesions[a]

Lesion	Dose (mg/kg-day)							
	0		100		1000		5000	
	Mice	Rats	Mice	Rats	Mice	Rats	Mice	Rats
Stomach (nonglandular)–squamous epithelial hyperplasia/ hyperkeratosis	0/9	0/10	6/10	8/10	7/8	10/10	8/8	10/11
Proximal Duodenum–inflammation (mild)	0/7	0/10	0/10	0/10	0/10	0/10	0/10	2/10
Rectum–perianal hyperplasia, hyperkeratosis and inflammation	0/9	0/10	0/10	0/10	2/10	5/10	8/10	9/11
Nasal Turbinates–rhinitis	0/9	0/10	0/10	1/9	0/10	7/10	4/10	9/10

[a]Dodd et al., 2003; C57BL/6 mice; Fisher 344 rats

Inhalation Exposure

Data on the subchronic inhalation effects of *n*-nonane in animals come from a single study by Carpenter et al. (1978). Carpenter et al. (1978) exposed groups of 25 male Harlan-Wistar rats intermittently to 0-, 360-, 590-, or 1600 ppm (0-, 1888-, 3095-, or 8393 mg/m^3) of *n*-nonane (98.4% purity) for 6 hours per day, 5 days per week, for 13 weeks (total of 63 exposure days). The study authors selected the concentrations based on results of an acute 4-hour inhalation study and preliminary repeated inhalation trials performed during a preliminary investigation, as summarized further below (Carpenter et al., 1978). Eight to nine rats from each dose group were sacrificed after 63 exposure days, while the remaining rats were exposed for an additional 2 days and then sacrificed. Exposed rats were monitored for changes in general appearance and behavior, body-weight gain, hematology (HCT, RBC, reticulocyte count, total and differential WBC), clinical chemistry (ALP, ALT [SGOT], AST [SGPT], and BUN), and urinalysis (specific measurements not described). In addition, three rats from each exposure group were sacrificed for histopathologic examination of tissues (adrenal, brain, pituitary, trachea, bifurcation of the trachea, thyroid, parathyroid, lung, heart, liver, kidney, spleen, stomach, duodenum, pancreas, ileum, jejunum, colon, skeletal muscle, sciatic nerve, and bone marrow) after 19 and 38 days of exposure.

Carpenter et al. (1978) reported that two rats from the low-dose group died during the study. These rats demonstrated suppurative bronchopneumonia upon necropsy. No deaths occurred in the mid-dose group, but two rats in the high-dose group died during the first day of exposure. Necropsy revealed lung congestion and hemorrhage in these rats, but no other significant lesions were found. Carpenter et al. (1978) concluded that mortality was not dose-related and the deaths were not related to treatment by *n*-nonane. Rats in the low- and mid-dose groups did not demonstrate any changes in appearance or behavior, while rats in the high-dose group exhibited salivation, mild coordination loss, and fine tremors throughout the first 4 days of exposure, and continued to exhibit salivation and lacrimation throughout the 13-week study. High-dose rats also had statistically significantly ($p < 0.01$) decreased body-weight gain throughout the study, and significantly ($p < 0.05$) reduced mean final body weight, in comparison to control animals, as shown in Tables 6 and 7 below. Although statistically significant ($p < 0.05$), the deficit in terminal body weight is small (7% decrease) and less than what is generally considered biologically significant (10% decrease).

Table 6. Mean Final Body Weight[a]	
Concentration (mg/m^3)	**Body Weight[b] (grams)**
0	523.9 ± 56.4
1889	548.1 ± 37.6
3095	532.0 ± 58.1
8393	484.8 ± 61.2[c]

[a]Carpenter et al., 1978; Harlan-Wistar rats
[b]Mean ± SD
[c]$0.05 > p > 0.01$

Table 7. Body-Weight Gain Throughout the Study[a]		
	Concentration (mg/m^3)	
Days of Exposure	**0**	**8393**
4	23.0 ± 11.9[b]	10.4 ± 12[c]
18	139.6 ± 23.3	105.3 ± 27.1[c]
33	217.1 ± 34.7	183.8 ± 33.4[d]
47	274.7 ± 41.1	222.3 ± 47.5[d]
62	297.4 ± 62.1	267.7 ± 55.4

[a]Carpenter et al., 1978; Harlan-Wistar rats
[b]Mean ± SD; units are in grams
[c]$p < 0.001$
[d]$0.01 > p > 0.001$

Carpenter et al. (1978) noted that no significant differences were observed in urinalysis comparisons—although data are not reported. Blood chemistry values appeared normal for all parameters evaluated in treated rats except for a small, transitory, statistically significant elevation in AST in high-dose rats within the first 4 weeks of exposure ($p < 0.05$). Similar increases in AST levels were not observed after 8 or 13 weeks of exposure. All hematological parameters in treated rats appeared normal except for statistically significant increases in eosinophil counts after 8 weeks of exposure ($p < 0.05$) among rats from the mid-dose group. This effect was not observed after 13 weeks and did not demonstrate a dose-response relationship, as similar effects were not observed in rats from the high-dose group. In general, the only effects observed based on clinical chemistry and hematology were small, transient, and not dose-related.

Carpenter et al. (1978) reported that no treatment-related histopathologic lesions occurred in rats exposed to *n*-nonane. Although there were no remarkable changes in blood, urine, or tissues from rats repeatedly exposed to *n*-nonane vapor, the rats exposed to the highest level did demonstrate clinical signs of toxicity throughout the study (salivation and lacrimation; also mild coordination loss and fine tremors early in the study). The high-exposure rats also exhibited a decreased body-weight gain and slightly decreased terminal body weights (-7%) compared to control animals. The high exposure level of 8393 mg/m^3 is identified as a LOAEL based on clinical signs and body-weight changes in rats exposed to *n*-nonane vapor. The 3095 mg/m^3 exposure level is a NOAEL.

Other Studies

Acute/Short-term Toxicity

As mentioned above, Dodd et al. (2003) conducted a 7-day range-finding study, whereby male C57BL/6 mice (5/group) and female F-344 rats (5/group) were treated with 0, 700, 1800, or 3600 mg/kg-day *n*-nonane (neat) for 7 consecutive days. The exposed animals were evaluated for general toxicity, neurotoxicity, body weights, gross necropsy, and changes in organ weights. Mice from the high-dose group demonstrated increased liver and spleen weights compared to controls, and mice in the 1800-mg/kg-day dose group demonstrated increased liver weights. Rats from the high-dose group demonstrated decreased body weights compared to controls and signs of irritation in the perianal area. Neurobehavioral tests were inconclusive.

Carpenter et al. (1978) exposed groups of 16 male Harlan-Wistar rats to 4000, 8000, 16,000, or 32,000 mg/m^3 (measured concentrations of 1330, 4600, 11,000, or 23,000 mg/m^3) *n*-nonane (98.4% purity) vapors for 4 hours. Ten rats were randomly selected for LC50 determination. Mortality occurred at 11,000 mg/m^3 (1/10) and at 23,000 mg/m^3 (8/10), which resulted in an acute 4-hour LC50 of 17,000 (14,000–21,000) mg/m^3. Micropathological examination of tissues taken from six rats 14 days after each of the single 4-hour inhalation periods revealed no lesions attributable to *n*-nonane vapor inhalation.

In addition, Carpenter et al. (1978) exposed 10 female albino Harlan-Wistar rats to 12,000 mg/m^3 (measured concentration of 9200 mg/m^3) *n*-nonane vapor for 2 consecutive days. Within 3 hours of exposure on both days, rats exhibited poor coordination, tremors, and clonic spasms. Carpenter et al. (1978) exposed another group of 10 female Harlan-Wistar rats to 10,000 mg/m^3 *n*-nonane vapors for 3 consecutive days, 6 hours/day. The rats were rested for a weekend and then subjected to the same exposure for an additional 4 days. The mean measured concentration for the 7 days was 8100 mg/m^3 *n*-nonane vapor. The study authors documented minor coordination loss, mild tremors, and slight irritation of the eyes and extremities in exposed rats on Exposure Day 2. Similar effects were observed throughout the 7-day exposure period. No lesions attributable to *n*-nonane exposure were found during necropsy.

Nilsen et al. (1988) exposed male Sprague-Dawley rats to 12,663-, 18,675-, 23,281-, or 27,698-mg/m^3 *n*-nonane (>99% purity) vapors for a single 8-hour exposure. Mortality rates by exposure were 0/10, 1/10, 4/10, and 9/10, respectively. Necropsy revealed dilation of the sinusoids and marked pulmonary edema in the animals that died during treatment. The 8-hour LC50 for *n*-nonane was 23,733 mg/m^3.

Additional information, that falls outside the scope of the provisional values documents, is available from studies not discussed here. Toxicokinetic inhalation studies in rats (Zahlsen et al., 1990; Zahlsen et al., 1992; and Lof et al., 1999) reveal the accumulation of *n*-nonane in adipose tissues but not in blood or in the target tissues. Metabolism of *n*-nonane is discussed by Serve et al. (1995), Mortsen et al. (2000), and Edwards et al. (2005). Finally, Robinson (1999) developed a physiologically based pharmacokinetic (PBPK) model for inhaled *n*-nonane in the rat.

Other Routes

A series of reports by Khan et al. (1980a, 1980b, 1985) evaluated the effects in rats following an intraperitoneal (i.p.) dose of 1.0 mL/kg-day *n*-nonane for up to 7 days. Decreased body weight, increased relative liver weight, increased phenobarbital-induced sleeping times, and altered activities of hepatic and serum enzymes were observed.

Genotoxicity

Data on the genotoxic potential of *n*-nonane are limited, but they suggest that the potential for *n*-nonane to induce any significant mutagenic or cytogenetic activity is low. *n*-Nonane did not cause mutations in vitro in mutagenicity assays with *S. typhimurium* at concentrations up to 10 mg/plate with or without metabolic activation (Zeiger et al., 1992). Rivedal et al. (1992) demonstrated that *n*-nonane did not induce morphological transformation in Syrian hamster embryo cells, nor did it reduce intercellular communication in Syrian hamster embryo cells.

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

Subchronic p-RfD

Data on the subchronic oral toxicity of *n*-nonane come from a single study by Dodd et al. (2003). Dodd et al. (2003) reported proliferative forestomach lesions with varying degrees of hyperplasia and hyperkeratosis of the squamous epithelium among all groups of rats and mice with a LOAEL of 100 mg/kg-day. A NOAEL could not be determined.

The Benchmark Dose (BMD) approach was applied to the incidence data for forestomach lesions in mice and rats (see Table 5). Appendix B contains details of the modeling and a plot of the best-fitting model. For rats, a BMD of 9.62 mg/kg-day and Benchmark Dose Lower Bound (BMDL) of 3.55 mg/kg-day were calculated, although there is little confidence in these values due to irregularities in the model output (see Appendix B). For mice, the BMD is 8.43 mg/kg-day and the BMDL is 3.13 mg/kg-day. The BMDL of 3.13 mg/kg-day for mice was selected as the point of departure (POD) for derivation of the subchronic p-RfD.

A **subchronic p-RfD** is derived for *n*-nonane by dividing the BMDL of 3.13 mg/kg-day by an UF of 1000, as shown below:

$$\begin{aligned} \textbf{Subchronic p-RfD} &= \text{BMDL} \div \text{UF} \\ &= 3.13 \text{ mg/kg-day} \div 1000 \\ &= \mathbf{0.003 \text{ or } 3 \times 10^{-3} \text{ mg/kg-day}} \end{aligned}$$

The UF of 1000 is composed of the following:

- UF_A: A factor of 10 is applied for animal-to-human extrapolation to account for potential pharmacokinetic and pharmacodynamic differences between animals and humans.

- UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation because data for evaluating susceptible human response are limited.
- UF_D: A factor of 10 is applied for database limitations. Although a subchronic oral study is available for *n*-nonane that evaluated effects in two species (Dodd et al., 2003), data for evaluating developmental and reproductive toxicity are limited and might have identified adverse effects at lower levels.

Confidence in the principal study (Dodd et al., 2003) is medium because, despite the investigation of sensitive endpoints, the sample sizes are relatively small (10 per dose) and only one sex of each species was tested. Confidence in the database is low because the data set is limited to a single subchronic study and acute animal studies. Reflecting medium confidence in the principal study and low confidence in the database, confidence in the subchronic p-RfD is low.

Chronic p-RfD

No oral chronic studies on *n*-nonane are available. Although a subchronic study is available (Dodd et al., 2003), the study is not extrapolated to estimate the effects due to chronic exposure because of the high level of uncertainty (i.e. Composite UF of 3000) associated with the subchronic p-RfD. However, the Appendix A of this document contains a screening value that may be useful in certain instances. Please see the attached Appendix A for details.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR *n*-NONANE

Subchronic p-RfC

Data on the subchronic inhalation toxicity of *n*-nonane come from a single study by Carpenter et al. (1978). Carpenter et al. (1978) observed clinical signs (salivation and lacrimation) and marginally depressed body weight (-7%) in rats exposed to the LOAEL of 8393 mg/m^3 for 6 hours per day, 5 days per week, for 13 weeks. The NOAEL is 3095 mg/m^3.

BMD modeling of the body-weight data is not possible because group sizes for this endpoint are not reported. Due to interim sacrifices and occasional deaths during the study, group sizes were less than the initial 25 per group. However, reporting of study methods and results is not sufficiently detailed to develop estimated values. Likewise, incidence data for clinical signs are not reported. Therefore, a NOAEL/LOAEL approach is used to identify the NOAEL of 3095 mg/m^3 as the POD for deriving the p-RfC values.

To calculate the subchronic p-RfC for *n*-nonane, the NOAEL of 3095 mg/m^3 in male rats (Carpenter et al., 1978) is first adjusted for continuous exposure ($NOAEL_{[ADJ]}$) as recommended by U.S. EPA (1994). The $NOAEL_{[ADJ]}$ is calculated as follows (U.S. EPA, 1994):

$$\begin{aligned} NOAEL_{[ADJ]} &= (NOAEL)\ (\#\ hours/24\ hours)\ (\#\ days/7\ days) \\ &= (3095\ mg/m^3)\ (6\ hours/24\ hours)\ (5\ days/7\ days) \\ &= 553\ mg/m^3 \end{aligned}$$

The human equivalent concentration ($NOAEL_{[HEC]}$) based on the $NOAEL_{[ADJ]}$ is calculated for systemic effects (clinical signs and decreased body weight) of a Category 3 gas (relatively low solubility and low reactivity) by multiplying the $NOAEL_{[ADJ]}$ by the ratio of the blood:gas (air) partition coefficient of *n*-nonane for the laboratory animal species to the human value ($[H_{b/g}]_A/[H_{b/g}]_H$). Blood:air partition coefficients of 5.8 and 50 have been estimated in rats (Smith et al., 2005) and humans (Imbriani et al., 1985), respectively. Using these reported partition coefficients, a $NOAEL_{[HEC]}$ of 64 mg/m^3 is calculated as follows:

$$\begin{aligned} NOAEL_{[HEC]} &= NOAEL_{[ADJ]} \times (H_{b/g})_A/(H_{b/g})_H \\ &= 553\ mg/m^3 \times 1.0 \\ &= 553\ mg/m^3 \end{aligned}$$

A **subchronic p-RfC** for *n*-nonane, based on the $NOAEL_{[HEC]}$ of 553 mg/m^3 in male rats (Carpenter et al., 1978), is derived as follows:

$$\begin{aligned} \textbf{Subchronic p-RfC} &= NOAEL_{[HEC]} \div UF \\ &= 553\ mg/m^3 \div 300 \\ &= \mathbf{2\ mg/m^3} \end{aligned}$$

The UF of 300 is composed of the following:

- UF_A: A partial UF of 3 ($10^{0.5}$) is applied for interspecies extrapolation to account for potential pharmacodynamic differences between rats and humans. Converting the rat data to human equivalent concentrations by the dosimetric equations accounts for pharmacokinetic differences between rats and humans; thus, it is not necessary to use the full UF of 10 for interspecies extrapolation.
- UF_H: A 10-fold UF for intraspecies differences is applied to account for potentially susceptible individuals in the absence of quantitative information or information on the variability of response in humans.
- UF_D: An UF of 10 is included for database limitations. A single subchronic inhalation toxicity study in one animal species (rat) is available (Carpenter et al., 1978). The database lacks supporting systemic studies, multigenerational reproduction studies, and developmental toxicity studies.

Confidence in the principal study (Carpenter et al., 1978) is low-to-medium. The 13-week study in rats uses adequate numbers of animals, a wide variety of endpoints (including comprehensive histopathologic examinations) and appropriate controls. However, only male rats were tested, histopathologic examinations were limited to three animals per exposure group at two time points before the end of the study (at 19 and 38 days), and reporting of study methods and results is incomplete. Confidence in the database is low because the database lacks adequate studies of neurotoxicity, developmental toxicity, and reproductive toxicity (including multigeneration reproductive toxicity). Reflecting low-to-medium confidence in the principal study and low confidence in the database, confidence in the subchronic p-RfC is low.

Chronic p-RfC

To derive the chronic p-RfC, an additional 10-fold uncertainty factor for exposure duration is applied to the POD, resulting in a total uncertainty factor of 3000. The **chronic p-RfC** for *n*-nonane is derived below:

$$\textbf{Chronic p-RfC} = NOAEL_{[HEC]} \div UF$$
$$= 553\ mg/m^3 \div 3000$$
$$= \mathbf{0.2\ mg/m^3\ or\ 2 \times 10^{-1}\ mg/m^3}$$

The UF of 3000 is composed of the following:

- UF_A: A partial UF of 3 ($10^{0.5}$) is applied for interspecies extrapolation to account for potential pharmacodynamic differences between rats and humans. Converting the rat data to human equivalent concentrations by the dosimetric equations accounts for pharmacokinetic differences between rats and humans; thus, it is not necessary to use the full UF of 10 for interspecies extrapolation.
- UF_S: A factor of 10 is applied for using data from a subchronic study to assess potential effects from chronic exposure, because data for evaluating response after chronic exposure are not available.
- UF_H: A 10-fold UF for intraspecies differences is applied to account for potentially susceptible individuals in the absence of quantitative information or information on the variability of response in humans.
- UF_D: An UF of 10 is included for database limitations. A single subchronic inhalation toxicity study in one animal species (rat) is available (Carpenter et al., 1978). The database lacks supporting systemic studies, multigenerational reproduction studies, and developmental toxicity studies.

Confidence in the subchronic toxicity study used to derive the chronic p-RfC is low-to-medium as discussed in the subchronic p-RfC derivation. Confidence in the database is low due to the lack of a chronic study and for the reasons discussed in the subchronic p-RfC derivation. Reflecting low-to-medium confidence in the principal study and low confidence in the database, confidence in the chronic p-RfC is low.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR *n*-NONANE

Weight-of-Evidence Descriptor

Studies evaluating the carcinogenic potential of oral or inhalation exposure to *n*-nonane in humans or animals have not been located in the available literature. Genotoxicity data suggest that the potential for *n*-nonane to induce any significant mutagenic or cytogenetic activity is low. Under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), there is "*Inadequate Information to Assess* [the] *Carcinogenic Potential*" of n-nonane.

Quantitative Estimates of Carcinogenic Risk

A lack of suitable data precludes derivation of quantitative estimates of cancer risk for *n*-nonane.

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APPENDIX A. DERIVATION OF SCREENING VALUE FOR *n*-NONANE

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional toxicity values for *n*-nonane. 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.

Screening Chronic p-RfD

Data on the subchronic oral toxicity of *n*-nonane come from a single study by Dodd et al. (2003). Dodd et al. (2003) reported proliferative forestomach lesions with varying degrees of hyperplasia and hyperkeratosis of the squamous epithelium among all groups of rats and mice with a LOAEL of 100 mg/kg-day. A NOAEL could not be determined.

The Benchmark Dose (BMD) approach was applied to the incidence data for forestomach lesions in mice and rats (see Table 5). Appendix B contains details of the modeling and a plot of the best-fitting model. For rats, a BMD of 9.62 mg/kg-day and Benchmark Dose Lower Bound (BMDL) of 3.55 mg/kg-day were calculated, although there is little confidence in these values due to irregularities in the model output (see Appendix B). For mice, the BMD is 8.43 mg/kg-day and the BMDL is 3.13 mg/kg-day. The BMDL of 3.13 mg/kg-day for mice was selected as the POD for derivation of the screening chronic p-RfD.

No oral chronic studies on *n*-nonane are available. Using the BMDL of 3.13 mg/kg-day for mice based on incidence of forestomach lesions following subchronic oral exposure to *n*-nonane, a screening chronic p-RfD is derived as follows:

$$\begin{aligned} \textbf{Screening Chronic p-RfD} &= \text{BMDL} \div \text{UF} \\ &= 3.13 \text{ mg/kg-day} \div 10{,}000 \\ &= \mathbf{0.0003 \text{ or } 3 \times 10^{-4} \text{ mg/kg-day}} \end{aligned}$$

The UF of 10,000 is composed of the following:

- UF_A: A factor of 10 is applied for animal-to-human extrapolation to account for potential pharmacokinetic and pharmacodynamic differences between animals and humans
- UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation, because data for evaluating susceptible human response are limited.
- UF_S: A factor of 10 is applied for using data from a subchronic study to assess potential effects from chronic exposure, because data chronic exposure might have identified additional effects from longer exposure.

- UF_D: A factor of 10 is applied for database limitations, Although a subchronic oral study is available for nonane that evaluated effects in two species, data for evaluating developmental and reproductive toxicity are limited and might have identified effects at lower levels.

Confidence in the subchronic toxicity study used to derive the screening chronic p-RfD is medium, as discussed in the subchronic p-RfD derivation. Confidence in the database is low due to the lack of a chronic study and for the reasons discussed in the subchronic p-RfD derivation. Reflecting medium confidence in the principal study and low confidence in the database, confidence in the screening chronic p-RfD is low.

APPENDIX B. DETAILS OF BENCHMARK DOSE MODELING FOR SUBCHRONIC RfD

Model-Fitting Procedure for Quantal Data:

The incidence data were analyzed using all available models for quantal data in the benchmark dose software (BMDS) program (version 2.1) developed by the U.S. EPA. Risk was calculated as extra risk. Confidence bounds were automatically calculated by the BMDS using a maximum likelihood profile method.

Output from the BMDS program was evaluated using the criteria described in U.S. EPA (2000). Goodness-of-fit was evaluated using the chi-square statistic calculated by the BMDS program. Acceptable global goodness-of-fit is indicated by a p-value greater than or equal to 0.1. Models that did not meet this criterion were eliminated from consideration. Local fit is evaluated visually on the graphic output by comparing the observed and estimated results at each data point. $BMDL_{10}$ estimates that are within a factor of 3 are considered to show no model dependence and are ranked using the Akaike Information Criteria (AIC) reported by the BMDS program. The model with the lowest AIC is considered to provide a superior fit. When the $BMDL_{10}$ estimates vary by greater than a factor of 3, the lowest $BMDL_{10}$ value is selected as the conservative estimate for the POD.

Model-Fitting for Incidence of Forestomach Lesions in Mice and Rats (Dodd et al., 2003):

Following the above procedure, quantal models were fit to the data shown in Table 5 for incidence of forestomach lesions in mice and rats. The results are shown in Tables A-1 (rats) and A-2 (mice). Although the gamma model appeared to fit the rat data adequately ($p = 0.61$) and benchmark values were calculated ($BMD_{10} = 9.62$; $BMDL_{10} = 3.55$), the AIC was extremely high in relation to the other models and messages were contained in the output indicating that the model did not converge. Therefore, there is little confidence in this result. No other models fit the rat data adequately. For the mouse data, the log-logistic model fit the data adequately ($BMD_{10} = 8.44$; $BMDL_{10} = 3.13$). Figures A-1 (rat) and A-2 (mouse) show the fits of the models to the data.

Table A-1. Model Predictions for Forestomach Lesions in Rats						
Model	**Degrees of Freedom**	**χ^2**	**χ^2 Goodness of Fit *p*-Value[a]**	**AIC**	**BMD_{10} (mg/kg-day)**	**$BMDL_{10}$ (mg/kg-day)**
Gamma (power ≥ 1)[b]	2	1	0.6065	1434.01	9.62	3.55
Log-logistic (slope ≥ 1)	3	11.8	0.0081	22.97	3.88	1.14
Logistic	2	19.78	0.0001	47.01	280.31	136.75
Multistage (betas ≥ 0)[c]	2	21.07	0	44.99	136.80	64.06
Log-probit (slope ≥ 1)	3	3274	0	35.95	24.65	13.34
Probit	2	19.8	0.0001	47.58	359.89	212.55
Weibull (power ≥ 1)	2	21.07	0	44.99	136.80	64.06
Quantal-Linear	2	21.07	0	44.99	136.80	64.06

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Model selected for POD
[c]One degree polynomial shown. Higher degree polynomials default back to one degree.
.

Table A-2. Model Predictions for Forestomach Lesions in Mice						
Model	**Degrees of Freedom**	**χ^2**	**χ^2 Goodness of Fit *p*-Value[a]**	**AIC**	**BMD_{10} (mg/kg-day)**	**$BMDL_{10}$ (mg/kg-day)**
Gamma (power ≥ 1)	3	7.96	0.0469	26.77	26.98	15.58
Log-logistic (slope ≥ 1)[b]	3	0.52	0.9137	22.07	8.44	3.13
Logistic	2	6.52	0.0384	32.07	105.67	55.26
Multistage (betas ≥ 0)[c]	3	7.96	0.0469	26.77	26.98	15.58
Log-probit (slope ≥ 1)	3	7.9	0.0482	25.01	30.94	17.05
Probit	2	6.59	0.0371	32.10	109.93	66.28
Weibull (power ≥ 1)	3	7.96	0.0469	26.77	26.98	15.58
Quantal-Linear	3	7.96	0.0469	26.77	26.98	15.58

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Model selected for POD.
[c]One degree polynomial shown. Higher degree polynomials default back to one degree.

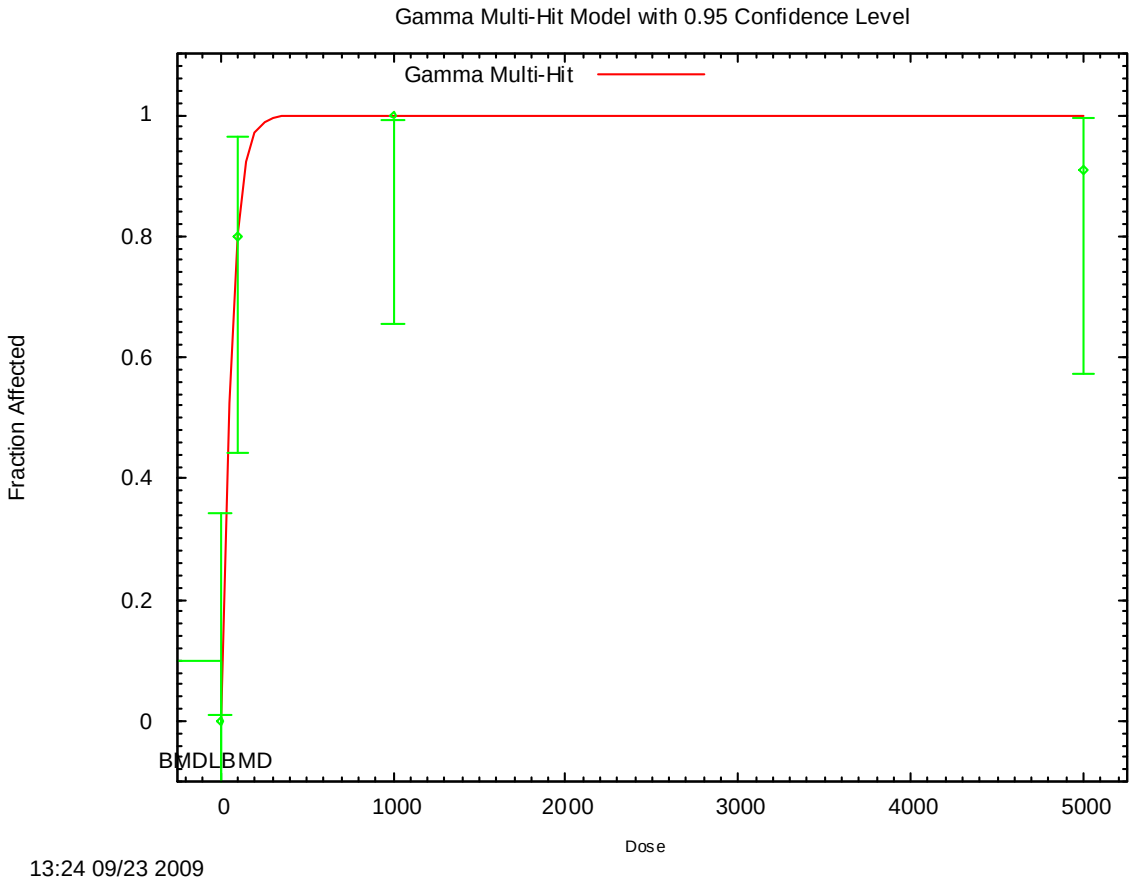

Figure A-1. Fit of Gamma Model to Incidence Data for Forestomach Lesions in Rats (Dodd et al., 2003)

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

```
 ======================================================================
        Gamma Model. (Version: 2.13;  Date: 05/16/2008)
        Input Data File: C:\USEPA\BMDS21\Data\gamdiacotorats922gammarats0922.(d)
        Gnuplot Plotting File:
C:\USEPA\BMDS21\Data\gamdiacotorats922gammarats0922.plt
                                                  Wed Sep 23 13:24:13 2009
 ======================================================================

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

   The form of the probability function is:

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


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

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


                  Default Initial (and Specified) Parameter Values
                     Background =    0.0454545
                          Slope =    0.0146706
                          Power =          1.3


           Asymptotic Correlation Matrix of Parameter Estimates

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

                  Slope        Power

     Slope      NA             NA

     Power      NA             NA


NA - This parameter's variance has been estimated as zero or less.
THE MODEL HAS PROBABLY NOT CONVERGED!!!



                                 Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background                0               NA
          Slope        0.0196736               NA                  NA
NA
          Power          1.24722               NA                  NA
NA

At least some variance estimates are negative.
THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!
Try again from another starting point.



                       Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -8.35732         4
   Fitted model        -715.714         2       1414.71      2      6.2934391e-308
  Reduced model        -25.6112         1       34.5077      3         <.0001

           AIC:         1435.43


                                 Goodness  of  Fit
                                                                  Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
```

```
  ---------------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          10        0.000
   100.0000     0.8000         8.000     8.000          10        0.000
  1000.0000     1.0000        10.000    10.000          10        0.000
  5000.0000     1.0000        11.000     9.999          11       -1.001

  Chi^2 = 1.00      d.f. = 2        P-value = 0.6059


    Benchmark Dose Computation

 Specified effect =            0.1

 Risk Type        =      Extra risk

 Confidence level =           0.95

               BMD =        9.62447

              BMDL =       3.55095
```

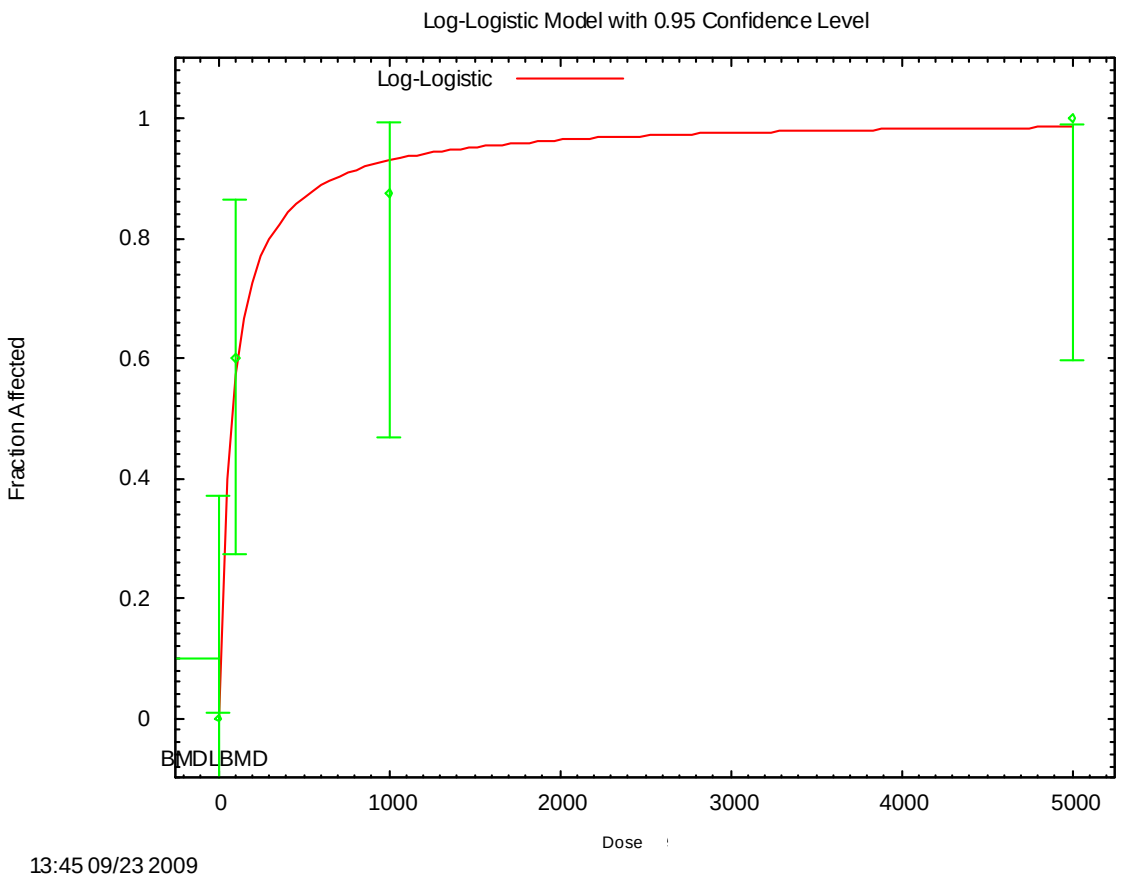

Figure A-2. Fit of Log-logistic Model to Incidence Data for Forestomach Lesions in Mice (Dodd et al., 2003)

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

```
 ======================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\USEPA\BMDS21\Data\lnldiacotomice922Loglogist0922mice.(d)
        Gnuplot Plotting File:
C:\USEPA\BMDS21\Data\lnldiacotomice922Loglogist0922mice.plt
                                                Wed Sep 23 13:45:18 2009
 ======================================================================

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

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = Percent
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 4
   Total number of records with missing values = 0
```

```
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                  Default Initial Parameter Values
                     background =            0
                      intercept =        -5.38
                          slope =            1


           Asymptotic Correlation Matrix of Parameter Estimates

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

              intercept

 intercept            1



                                 Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     background                0            *                 *                   *
      intercept         -4.32976            *                 *                   *
          slope                1            *                 *                   *

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -9.74428         4
   Fitted model        -10.0346         1      0.580634      3          0.9009
  Reduced model        -23.5554         1       27.6223      3         <.0001

           AIC:         22.0692


                                 Goodness  of  Fit
                                                                   Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ----------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000           9        0.000
  100.0000     0.5684         5.684     6.000          10        0.202
 1000.0000     0.9294         7.435     7.000           8       -0.601
 5000.0000     0.9850         7.880     8.000           8        0.349

 Chi^2 = 0.52      d.f. = 3        P-value = 0.9137
```

```
   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        8.43622

            BMDL =        3.12858
```