

Provisional Peer-Reviewed Toxicity Values for  
  
1,1-Dimethylhydrazine  
(CASRN 57-14-7)

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## COMMONLY USED ABBREVIATIONS

BMD	Benchmark Dose
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
LOAEL <sub>ADJ</sub>	LOAEL adjusted to continuous exposure duration
LOAEL <sub>HEC</sub>	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
NOAEL <sub>ADJ</sub>	NOAEL adjusted to continuous exposure duration
NOAEL <sub>HEC</sub>	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 <sub>A</sub>	animal to human uncertainty factor
UF <sub>C</sub>	composite uncertainty factor
UF <sub>D</sub>	incomplete to complete database uncertainty factor
UF <sub>H</sub>	interhuman uncertainty factor
UF <sub>L</sub>	LOAEL to NOAEL uncertainty factor
UF <sub>S</sub>	subchronic to chronic uncertainty factor

## PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 1,1-DIMETHYLHYDRAZINE (CASRN 57-14-7)

### 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

1,1-Dimethylhydrazine (1,1-DMH) is not listed on IRIS (U.S. EPA, 2009), the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006), or the HEAST (U.S. EPA, 1997). The Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991, 1994a) included a Health and Environmental Effects Profile (HEEP) for 1,1-DMH (U.S. EPA, 1984). The HEEP concluded that 1,1-DMH was a carcinogen by the oral route in mice and hamsters and derived a cancer potency factor of  $8.66 \text{ (mg/kg-day)}^{-1}$  based on the incidence of hemangiosarcoma in male Swiss mice reported by Toth (1973). The HEEP did not attempt to derive noncancer toxicity values. CalEPA (1992) derived an estimate of human cancer potency of  $2.8 \text{ (mg/kg-day)}^{-1}$ . ATSDR (1997) derived an intermediate-duration (15–364 days) inhalation minimal risk level (MRL) of  $2 \times 10^{-4}$  ppm ( $5 \times 10^{-4} \text{ mg/m}^3$ ) for 1,1-DMH based on hyaline degeneration of the gallbladder in C57BL/6 mice exposed to a lowest-observed-adverse-effect level (LOAEL) of 0.05 ppm ( $0.1 \text{ mg/m}^3$ ) for 6 hours/day, 5 days/week, for 6 months by Haun et al. (1984) and an uncertainty factor (UF) of 300 (10 for use of a LOAEL, 3 for interspecies extrapolation, and 10 for human variability). MRLs for other routes and durations were not derived due to lack of adequate data. Occupational exposure limits established for 1,1-DMH include a Threshold Limit Value (TLV) 8-hour Time-Weighted Average (TWA) of 0.01 ppm ( $2.6 \times 10^{-2} \text{ mg/m}^3$ ) with skin notation (ACGIH, 2001, 2007), a Recommended Exposure Limit (REL) of 0.06 ppm ( $0.16 \text{ mg/m}^3$ ) for 2 hours/day exposure (NIOSH, 2005), and a Permissible Exposure Limit (PEL) TWA of 0.5 ppm ( $1 \text{ mg/m}^3$ ) with skin notation (OSHA, 2009). IARC (1999) categorized 1,1-DMH as a Group 2B carcinogen, *possibly carcinogenic to humans*. The chemical was listed as “reasonably anticipated to be a human carcinogen” by NTP (2005). The toxicity of 1,1-DMH has not been reviewed by WHO (2009).

Literature searches were conducted for the period from 1965 to April 2006 to identify data relevant to the derivation of noncancer and cancer risk values for 1,1-DMH. The following databases were searched: MEDLINE (plus cancer subset, replacing CANCERLIT), TOXLINE special, TOXCENTER, CCRIS, GENETOX, HSDB, EMIC/EMICBACK, DART/ETIC, RTECS, TSCATS, and Current Contents. These searches also were updated in June 2009.

## REVIEW OF PERTINENT DATA

1,1-DMH often is produced by reduction of nitrosodimethylamine (NDMA), leaving NDMA as a contaminant in commercial 1,1-DMH. 1,1-DMH also is the major hydrolyzation product of daminozide, a pesticide.

### **Human Studies**

#### ***Oral Exposure***

No data were located regarding the oral toxicity or carcinogenicity of 1,1-DMH in humans.

#### ***Inhalation Exposure***

A retrospective study of 1193 Danish Air Force missile workers was conducted (Petersen et al., 1970) to investigate health effects from 1,1-DMH exposures. Exposure durations were estimated using questionnaires, while exposure concentrations were unknown. Medical data were obtained by tri-monthly or quarterly health examinations performed from March 1961 to January 1964, including associated blood and urine tests. Blood tests included measurement of hemoglobin (Hgb) and serum glutamate pyruvate transaminase (SGPT or ALT) concentrations, and total and differential leukocyte counts. Urinalysis included determination of urobilin, urobilinogen, protein, and glucose concentrations. No statistical analysis was reported. Forty-seven workers were deemed to have elevated ALT concentrations from at least one testing period, suggesting an effect of 1,1-DMH on the liver.

In a study of chemical laboratory workers (Shook and Cowart, 1957), 5 workers had positive cephalin flocculation tests following 3-month, 6 day/week, 10 hours/day exposures to unspecified airborne concentrations of 1,1-DMH followed by 6–8 additional 4-hour exposures over the next 3 months.

### **Animal Studies**

#### ***Oral Exposure***

Goldenthal (1989a) conducted a chronic drinking water study in mice. Charles River CD-1 mice (90/gender/group) were given 0-, 40-, or 80-ppm 1,1-DMH (100% purity) in deionized tap water with 0.25% citrate buffer (to neutralize pH) for 24 months. Body weights and food and water consumption were measured. From these data, Goldenthal (1989a) calculated average daily intake as 0, 7.34, or 13.01 mg/kg-day for males and 0, 11.59, or 21.77 mg/kg-day for females. Observations were made for mortality, hematology, and gross and histological pathology, although the blood parameters and tissues observed were not specified in the IPCS (1991) summary. Statistical analyses were performed, but the specific tests were not identified.

Mortality at the study's end was 70%, 76%, and 98% in male mice and 58%, 92%, and 92% in females exposed to increasing concentrations of 1,1-DMH. Male body weight did not exhibit a dose-related response, although water intake was reduced in both dose groups throughout the study and food consumption was reduced sporadically as well. Among females, body weight in the high dose group was significantly lower (10% reduction) than controls over

the last 6 months of exposure. Water intake in female mice was reduced during the first 13 weeks of the study, while food consumption was reduced sporadically throughout the study (Goldenthal, 1989a).

Significant changes in hematological parameters (unspecified) were observed in male mice starting at 6 months in the 13 mg/kg-day (high-dose) group and at 12 months in the 7 mg/kg-day (low-dose) group. Increases in ALT and sorbitol dehydrogenase (SDH) concentrations (magnitudes not reported) were observed at 12 months in both treated groups in both genders. Gross pathology included increased liver lobulation in treated males and development of lung and liver nodules in treated males, beginning at 8 months, and in treated females, beginning at 12 months. Several histopathological lesions were found in the liver. In treated males, multifocal chronic inflammation was exhibited from 12–24 months, while hypertrophy and necrosis were observed throughout the study. In both treated groups of both genders, hemosiderosis and splenic hematopoiesis occurred. The IPCS (1991) summary of Goldenthal (1989a) did not report incidence data for these effects.

Lung and liver tumors occurred in a dose-related manner in male and female mice (see Table 1). Hemangioma and hemangiosarcoma appear to be the most sensitive neoplastic effects observed in this species, with the IPCS (1991) summary reporting over 80% of high-dose males and females developing these tumors. It should be noted that the Finkel (1995) summary reported a somewhat lower incidence of these tumors in males (see Table 1). Occurrences of alveolar and bronchiolar neoplasms also increased with dose in both genders, but they did not increase as dramatically between the low- and high-dose groups as those observed in the liver.

<b>Table 1. Tumor Incidence in CD-1 Mice Given Pure 1,1-Dimethylhydrazine in Drinking Water for 24 Months<sup>a</sup></b>				
Tumor Type	Gender	Drinking water concentration		
		0	40 ppm <sup>c</sup>	80 ppm <sup>d</sup>
Hepatic hemangioma & hemangiosarcoma	M	9%	67%	81%
	M <sup>b</sup>	5/66	31/67	43/68
	F	4%	26%	82%
Alveolar & bronchiolar neoplasm	M	18%	45%	55%
	F	14%	50%	48%
Mortality	M	63/90	68/90	88/90
Mortality	F	52/90	83/90	83/90

<sup>a</sup>From Goldenthal (1989a) as summarized by IPCS (1991). The IPSC summary did not report statistical significance or make clear which animals were included in these percentages but implied they included all, regardless of time or cause of death.

<sup>b</sup>Goldenthal (1989a) male mouse tumor data as cited in Finkel (1995).

<sup>c</sup>40 ppm = 7.34 mg/kg-day in males and 11.59 mg/kg-day in females.

<sup>d</sup>80 ppm = 13.71 mg/kg-day in males and 21.77 mg/kg-day in females.

Several factors made interpretation of these data difficult:

- The high mortality among control animals compromised interpretation of other effects data
- The effect of the neoplasms, especially on observed mortality, could not be distinguished from noncancer effects
- The available data suggests that the maximum tolerated dose (MTD) might have been exceeded at both doses

Goldenthal (1990) conducted a second lifetime drinking water study in CD-1 mice using lower doses. In this study, mice (90/gender/group) were administered 0, 1, 5, 10 (in males), or 20-ppm (in females) 1,1-DMH (100% purity) in deionized tap water with 0.25% citrate buffer (to neutralize pH) for 24 months. Body weight and food and water intake were measured at unspecified intervals. From body weight and water consumption measurements, Goldenthal (1990) estimated average daily intake of 1,1-DMH as 0, 0.19, 0.97, or 1.9 mg/kg-day in males and 0, 0.27, 1.4, or 2.7 mg/kg-day in females. Hematological tests were conducted in 10 mice/gender/group at 6, 12, 18, and 24 months, including measurement of hemoglobin and hematocrit concentrations, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and counts of erythrocytes, platelets, and total and differential leukocytes. At 24 months, biochemical tests were performed in 10 mice/gender/group, including measurements of total bilirubin concentrations and alkaline phosphatase, aspartate aminotransferase (AST), ALT, and SDH activities. Gross and histological pathology was conducted on an unspecified number of tissues at spontaneous death, at 8 and 12 months (20 mice/gender/group), and at the study's end. Statistical comparisons were performed, but were not specified in the IPCS (1991) summary of the Goldenthal (1990) data.

Significantly increased mortality was reported only in the high-dose males. Mortality in males over the course of the study was 48%, 54%, 52%, and 68% with increasing dose. In females, mortality rates were 60%, 50%, 64%, and 76%. No consistent, dose-related changes in body weight were observed. No biologically relevant changes in hematological or biochemical measures reported. An increased incidence in gross lung nodules was reported in mid-dose males (47%) and was higher than in controls (21%) or high-dose males (26%). The only clearly nonneoplastic histological lesion reported is a dose-related, unidentified brown liver pigment, suggesting hemosiderosis. However, neither incidences nor statistical significance were reported in the IPCS (1991) summary of Goldenthal (1990).

Only high-dose females exhibited a statistically significant increase in incidence of alveolar or bronchiolar adenomas (41%) and carcinomas (14%), respectively, compared with incidence rates of 10% and 2%, respectively, for these neoplasms in controls (see Table 2). Incidence rates for other exposure groups were not reported (Goldenthal, 1990).

This study appears to have been well conducted, with 90 animals/gender/group exposed to pure test agent and observations reported for a number of parameters following exposure to multiple doses (Goldenthal, 1990).

**Table 2. Tumor Incidence in Female CD-1 Mice Given Pure 1,1-Dimethylhydrazine in Drinking Water for 24 Months<sup>a</sup>**

Tumor Type	Gender	Drinking Water Concentration	
		0	20 ppm (2.7 mg/kg-d)
Alveolar & bronchiolar adenoma	F	5/49	20/49 <sup>b</sup>
Alveolar & bronchiolar carcinoma	F	1/49	7/49 <sup>b</sup>
Mortality	F	60%	76%

<sup>a</sup>Goldenthal (1990).

<sup>b</sup>Statistically significant. IPCS (1991) did not report statistical method used or level of significance. IPCS also reported a “positive statistical trend for pulmonary neoplasms.” Tumor rates at 1, 2, 5, and 10 ppm were reported only as not significantly different from controls.

Goldenthal (1989b) also chronically exposed rats to 1,1-DMH in drinking water. Male and female Fisher 344 rats (70/gender/group) were given 0-, 1-, 50-, or 100-ppm 1,1-DMH (100% purity) in deionized tap water with 0.25% citrate buffer (to neutralize pH) for 24 months. Body weight and food and water consumption were measured. From these measurements, Goldenthal (1989b) estimated average daily doses as 0, 0.07, 3.2, or 6.2 mg/kg-day for males and 0, 0.1, 4.5, or 7.9 mg/kg-day for females. Unspecified hematological, gross, and histopathological observations were made. Statistical tests were performed, but they are not described in the IPCS (1991) summary of Goldenthal (1989b).

Body weight reductions in high-dose male rats and mid- and high-dose female rats were statistically significant but slight, ranging in magnitude from 2–5%. While food intake was unaffected by 1,1-DMH, water consumption appears to have been consistently reduced in mid- and high-dose males in the final 20 weeks of the study. Observed mortality appears to have been inversely dose-related, with rates of 36%, 36%, 28%, and 18% in males, and 32%, 24%, 28%, and 10% in females, for controls to high-dose groups. Hematological parameters were not significantly different between groups. A single gross pathological effect, cloudy corneas, was found to be slightly higher in the mid- and high-dose groups of female rats (37% and 41%, respectively) compared with controls (21%). A corresponding increase in the incidence of corneal mineralization was reported. No dose-related nonneoplastic liver effects were observed. A no-observed-adverse-effect level (NOAEL) of 0.1 mg/kg-day and LOAEL of 4.5 mg/kg-day for corneal clouding and mineralization in female rats is identified in the Goldenthal (1989b) data.

Pituitary adenomas were significantly increased in the high-dose females, while hepatocellular adenomas and carcinomas were increased in the mid- and high-dose females (see Table 3). The incidence rate of pituitary adenomas in high-dose females was 56%, compared with 32% in controls. Incidence data for pituitary tumors in males were not reported. Hepatocellular tumors were seen in 10% of mid- and high-dose females, while none were seen in the males or the controls. Goldenthal (1989b) reported a historical incidence rate for rat liver tumors of 0.5% (2/370).

**Table 3. Percent Tumor Incidence in Female Fisher 344 Rats Given Pure 1,1-Dimethylhydrazine in Drinking Water for 24 Months<sup>a</sup>**

Tumor Type	Drinking Water Concentration (Dose)			
	0	1 ppm (0.07 mg/kg-d)	50 ppm (3.2 mg/kg-d)	100 ppm (6.2 mg/kg-d)
Pituitary adenoma	32%	n/a	n/a	56% <sup>b</sup>
Total liver neoplasm	0%	n/a	10% <sup>b</sup>	10% <sup>b</sup>
Hepatocellular adenoma	0%	2%	4%	2%
Hepatocellular carcinoma	0%	0%	6%	8%
Mortality	32%	24%	28%	10%

n/a = data not available.

<sup>a</sup>Goldenthal (1989b).

<sup>b</sup>Statistically significant. IPCS (1991) did not report statistical method used or level of significance.

The study by Goldenthal (1989b) appears to have been well designed to determine the chronic neoplastic and nonneoplastic effects of 1,1-DMH in the drinking water of rats.

Earlier studies of 1,1-DMH were exclusively cancer bioassays. Roe et al. (1967) carried out a gavage study to determine the carcinogenicity of 1,1-DMH in the lungs of mice. Groups of 85 and 25 female Swiss mice were given daily doses of 0 or 5 mg 1,1-DMH (purity unspecified) in water, respectively, via stomach tube, 5 days/week, for 40 weeks. Using reference values for body weight of B6C3F1 mice (U.S. EPA, 1988, Table 1–2), the doses are estimated as 0, 134, and 142 mg/kg-day for controls, treated males, and treated females, respectively. Neither mortality nor other experimental methods were reported. The only reported pathology was lung tumor incidence in animals surviving to 40–50 weeks or 50–60 weeks of the study. Lung adenomas and adenosarcomas were found in 1/8 and 4/9 of the 40–50 and 50–60 week survivors, respectively, compared with 2/37 and 6/42 in controls for the same time periods. These differences were not statistically significant ( $p = 0.6$  using Fisher’s exact test conducted for this review), but they were limited by the lack of incidence data from unscheduled deaths of treated animals. Other study limitations included a lack of 1,1-DMH purity data, the use of a single dose, and inadequate reporting of experimental methods and noncancer effects.

Kelly et al. (1969) also evaluated pulmonary carcinogenicity in gavage-dosed mice. Two groups of 10 or 30 female CDF1 mice were given gavage doses of 0 or 0.1 mg/kg-week 1,1-DMH (purity unspecified) for 8 weeks. Surviving mice were sacrificed at 28 weeks after initiation of dosing. At necropsy, gross and microscopic observations for lung tumors and leukemia were made in lung, liver, thymus, spleen, kidney, lymph nodes, and other unspecified organs. Seventeen percent (5/30) of treated mice died prior to Week 28, compared with none of the controls. Lung tumor incidence in treated animals (1/25) was not higher than controls (1/10). No other observations were reported. Limitations of this study included a lack of reporting of chemical purity and noncancer effects, the use of weekly—rather than daily—exposures, and a duration of observation (28 weeks) that was not long enough to capture the latency period for tumor development.

Toth (1973) explored the carcinogenicity of 1,1-DMH in mice exposed to a single 1,1-DMH concentration in drinking water. Two groups of 5-week-old Swiss albino mice (100/gender/group for controls, 50/gender/group for treated mice) were given 0 or 0.01% (100 ppm) 1,1-DMH (purity unspecified) in drinking water, continuously, for up to 120 weeks. Based on observations of drinking water consumption, the Toth (1973) estimated the daily oral dose of 1,1-DMH as 0.7 mg/animal-day for males and females. Body weights were recorded weekly but were not reported. Using reference values for body weights (U.S. EPA, 1988), the doses have been calculated for this review as 19 and 20 mg/kg-day in males and females, respectively. Clinical observations were made at unspecified intervals. No hematology, serum chemistry, or urinalysis data were collected. Animals were allowed to die or were sacrificed if found in poor condition. At necropsy, organs were examined grossly. Histopathological exams were performed on lung, liver, spleen, and kidney tissue, as well as other tissues found to have gross lesions. No statistical analysis was reported by Toth (1973).

Survival was markedly decreased in treated animals when compared with controls, indicating that exposure exceeded the MTD. All treated males died after 65–75 weeks of exposure, and all treated females died after 55–65 weeks of exposure. In comparison, control males survived 115–125 weeks, while control females survived 105 to 115 weeks. No quantitative nonneoplastic effects were reported. Incidences of neoplastic pathology were reported (see Table 4). Fisher's exact test revealed statistically significant increases in incidence of four tumor types: angiosarcoma, lung adenoma and carcinoma, renal adenoma, and benign hepatoma ( $p < 0.05$ ). Angiosarcoma, primarily in the liver, was the most sensitive neoplastic effect. In treated males, 84% exhibited angiosarcomas as early as 35 weeks of exposure, while 74% of treated females had this tumor as early as 36 weeks of exposure. In comparison, 2% and 4% of control males and females, respectively, developed angiosarcomas as early as 67 and 37 weeks into the study, respectively (Toth, 1973).

The Toth (1973) study was of limited value because it utilized only one dose, precluding the ability to characterize dose-response relationships. The purity of the test agent was not reported and the single dose exceeded the MTD, prohibiting observations over a chronic, lifetime exposure.

**Table 4. Tumor Incidence in C57BL/6 Mice Given 1,1-Dimethylhydrazine of Uncertain Purity in Drinking Water for up to 120 Weeks<sup>a</sup>**

Tumor Type	Gender	Drinking Water Concentration	
		0	100 ppm <sup>b</sup>
Angiosarcoma (multisite)	M	2/110	42/50 <sup>c</sup>
	F	4/110	37/50 <sup>c</sup>
Lung adenoma and carcinoma	M	11/110	39/50 <sup>c</sup>
	F	14/110	32/50 <sup>c</sup>
Renal adenoma	M	0/110	1/50
	F	0/110	9/50 <sup>c</sup>
Hepatoma, benign	M	0/110	6/50 <sup>c</sup>
	F	0/110	0/50

<sup>a</sup>Toth (1973).

<sup>b</sup>19 mg/kg-day in males and 20 mg/kg-day females.

<sup>c</sup>Significantly different from controls ( $p < 0.05$ ) using Fisher exact test performed for this review.

Toth (1977) performed a similar assessment of 1,1-DMH carcinogenicity in hamsters from exposure to a single drinking water concentration. In this study, two groups of 50 Syrian golden hamsters per gender were given 0 (100/gender) or 0.1% (100 ppm) 1,1-DMH (purity unspecified) in drinking water until death. Using reference values for body weight and drinking water intake for hamsters (U.S. EPA, 1988), the doses are estimated as 134 and 131 mg/kg-day for males and females, respectively. Observations included clinical signs and measurement of body weight. Hematology, serum chemistry, and urinalysis were not performed. At necropsy, gross observations were made of all tissues. The liver, spleen, kidney, bladder, thyroid, heart, pancreas, testes, brain, nasal turbinates, and lungs were collected and examined for histopathology. No statistical analysis was reported.

Survival in treated hamsters was decreased relative to controls (Toth, 1977). All treated males and females died by Weeks 84–94 or 74–84, respectively, while control males and females all died by Weeks 104–114 or 84–94, respectively. None of the treated hamsters survived to lifetime, indicating that the MTD may have been exceeded. Adverse clinical signs, body weights, or abnormal gross findings at necropsy were not reported. In tests performed for this review, significant increases in cecum, blood vessel, and adrenal tumors were found ( $p < 0.05$ ) relative to controls (see Table 5). Cecum adenomas and adenocarcinomas were observed with 20% and 30% incidence in treated males and females, respectively. Angioma and angiosarcoma, primarily in the liver, were seen in 28% of treated males. However, only 4% of females exhibited this effect. The adrenal cortical adenoma incidence of 8% in females was significantly greater than the incidence in control females. However, 8% of control males and no treated males exhibited this tumor, leading to questions about the data in females.

The hamster study of Toth (1977) is of limited value because neither the purity of 1,1-DMH used nor noncancer toxicity data were reported, and only one dose was tested. In addition, the single tested dose (0.1% in drinking water) might have exceeded the MTD, resulting in early mortality of the treated animals.

Druckrey et al. (1967) exposed 20 BD rats to 70 mg/kg-day 1,1-DMH (purity unspecified) in drinking water for life. No information regarding controls was reported. At death, all animals were subjected to necropsy. Grossly observable masses were submitted for histological examination. No data were reported for mortality, clinical signs, or noncancer endpoints. Liver carcinomas (incidence unspecified) were observed. No other adverse effects were reported. The unspecified purity of 1,1-DMH, the small number of animals used, and the absence of cancer or noncancer incidence data for controls and treated animals limit the utility of this study.

**Table 5. Tumor Incidence in Syrian Golden Hamsters Given 1,1-Dimethylhydrazine of Uncertain Purity in Drinking Water for up to 120 Weeks<sup>a</sup>**

Tumor type	Gender	Drinking Water Concentration	
		0	1,000 ppm <sup>b</sup>
Angioma & angiosarcoma (multisite)	M	0/100	15/50 <sup>c</sup>
	F	1/100	10/50 <sup>c</sup>
Cecum adenoma & adenocarcinoma	M	0/100	14/50 <sup>c</sup>
	F	0/100	2/50
Adrenal cortical adenoma	M	4/100	0/50
	F	1/100	4/50 <sup>c</sup>

<sup>a</sup>Toth (1977).

<sup>b</sup>134 mg/kg-day in males and 131 mg/kg-day in females.

<sup>c</sup>Significantly different from controls ( $p < 0.05$ ) using Fisher exact test performed for this review.

No carcinogenic effects were observed by Argus and Hoch-Ligeti (1961) in rats dosed via stomach tube. A group of 25 male Wistar rats was given 0.3 mg/kg-day 1,1-DMH (purity unspecified) via stomach tube for 45 weeks. No control group was reported. Survivors were sacrificed at Week 53 of the study. All animals dying from Week 22 onward were subjected to gross necropsy and histopathological examination of liver, spleen, kidneys, lung, and any other tissues found to have gross abnormalities. No tumors were observed in any of the examined rats (0/25). Usefulness of data from this study is limited by use of 1,1-DMH of unspecified purity, the absence of a control group, the lack of nonneoplastic effects data, the small number of treated animals, and inadequate exposure duration and observation period for assessing the carcinogenicity of 1,1-DMH.

### ***Inhalation Exposure***

Weeks et al. (1963) identified inhalation LC<sub>50</sub>s in rats and dogs, and Jacobsen et al. (1955) reported LC<sub>50</sub>s in rats, mice, and hamsters (see Table 6).

Rinehart et al. (1960) exposed groups of 3 male beagle dogs to 0-, 5-, or 25-ppm 1,1-DMH (purity not reported) in air for 6 hours/day, 5 days/week, for 26 (0 and 5 ppm groups) or 13 (25 ppm group) weeks. Animals were observed for mortality and clinical signs. Blood samples were drawn daily from high-exposure animals and every fourth day, beginning on Day 2, from the low-exposure dogs. Blood was analyzed for hematocrit, Hgb, red blood cell (RBC) and white blood cell (WBC) counts, blood nonprotein nitrogen, blood sugar, and bilirubin. Sulfobromophthalein (BSP) retention also was measured. All surviving dogs were autopsied at the conclusion of their exposure period. Only terminal body-weight losses are reported. Tissues observed at autopsy for gross lesions and histopathology were the liver, spleen, brain, heart, kidneys, stomach, intestines, pancreas, adrenals, testes, bladder, and trachea.

<b>Table 6. Acute Inhalation LC<sub>50</sub>s for 1,1-Dimethylhydrazine</b>			
<b>Species</b>	<b>LC<sub>50</sub> (ppm)</b>	<b>Exposure Duration (minutes)</b>	<b>Source</b>
Rat	24,500	5	Weeks et al. (1963)
Rat	1410	60	Weeks et al. (1963)
Rat	252	240	Weeks et al. (1963)
Rat	252	240	Jacobsen et al. (1955)
Mice	172	240	Jacobsen et al. (1955)
Hamster	392	240	Jacobsen et al. (1955)
Dog	22,300	5	Weeks et al. (1963)
Dog	981	60	Weeks et al. (1963)

The 25-ppm group exhibited signs of CNS toxicity: salivation, depression, emesis, diarrhea, convulsive seizures, and death of one of the three dogs on Day 3 (Rinehart et al., 1960). Maximum mean body weight loss for the two surviving high-exposure dogs was 2.5 kg, compared with control mean body weight loss of 0.2 kg. Hgb and hematocrit concentrations and RBC counts in the high-exposure group decreased maximally to 38%, 28%, and 58% of the controls, respectively, at Week 4 and were 21%, 11%, and 39% lower than controls, respectively, at study termination. Histopathology indicated hemosiderosis of the liver and extensive heme pigment deposition in Kupffer cells and splenic sinuses. Bone marrow exhibited increased erythrocytic activity. The dog that died after the third day of exposure exhibited alveolar hemorrhage, emphysema, and atelectasis.

Effects seen in the 5-ppm group were less severe (Rinehart et al., 1960). Lethargy and mean body weight loss of 1.8 kg were observed up to Week 14, but signs of lethargy disappeared and terminal mean body weight loss was 1.5 kg (compared with 0.2 kg for controls) at 26 weeks. Week 24 concentrations of Hgb and hematocrit were reduced by 35 and 18%, respectively, but terminal concentrations were only 12% and 13% below preexposure concentrations 2 weeks later. Histopathology of the 5-ppm animals revealed splenic hemosiderosis in an unreported number of dogs. This study identified a subchronic LOAEL of 5 ppm for transient lethargy and hematological effects (hemolytic anemia) in dogs. Limitations of the study included the use of a small number of dogs (3/group), the lack of purity data for the test material, a relatively short exposure duration (5% of lifetime), few monitored endpoints, and incomplete reporting.

The same report (Rinehart et al., 1960) also described 6 hours/day, 5 day/week inhalation exposures of male Wistar rats (20/group) and female CF-1 mice (30/group) to 140-ppm 1,1-DMH (purity not reported) for 6 weeks or 75 ppm for 7 weeks. An unreported number of controls also were utilized. Observations were made for mortality and clinical signs. Body weights were measured and an unreported number of tissues examined at sacrifice for gross lesions and histopathology. Occasional tremors were seen in the 140-ppm groups of both rodent species, while occasional dyspnea and lethargy were observed in the 75-ppm groups. Nearly all (29/30) mice died by Week 2 in the 140-ppm group, while 8/30 died by Week 5 in the 75-ppm group. 1,1-DMH was less lethal to the male rats, as mortality incidences of only 1/20 and 0/30 were observed by Week 5 in the 140- and 75-ppm groups, respectively. However, periods of dyspnea and lethargy were observed in rats in the 75-ppm group. Convulsions were observed in all rodents dying prematurely. Body weight gains in 140-ppm rats and mice were reported as lower than controls through Week 2, although no weight data were shown in the report. No histological changes were observed in either rodent species. For mice, a subchronic FEL of 75 ppm was identified for mortality. For rats, this study identified a LOAEL of 75 ppm for dyspnea and lethargy. However, no LOAEL was identified in mice, because substantial deaths (8/30) among mice exposed at the lowest concentration tested.

Groups of female C57B1/6 mice (400/group), male Fisher F344 rats (200/group), male Golden Syrian hamsters (200/group), and male and female beagle dogs (4/gender/group) were exposed to 0, 0.05, 0.5, or 5 ppm for 6 hours/day, 5 days/week, for 6 months, in a study designed primarily to investigate carcinogenicity (Haun et al., 1979, 1984). Rodents and dogs were observed for approximately 18 months and 5 years, respectively, following cessation of exposure. Propellant-grade 1,1-DMH was used, which contained 0.12% (NDMA). During the exposure period, hourly observations were made for mortality and clinical signs. Body weights were measured bi-weekly during the exposure period and monthly thereafter. In dogs, blood samples were collected bi-weekly during exposure and at various times (for 0-, 0.5-, and 5-ppm groups) after exposure and examined for Hgb, hematocrit, sodium, potassium, calcium, glucose, total protein, albumin, globulin, ALT, and alkaline phosphatase concentrations and RBC, WBC, and differential cell counts. In addition, blood samples taken at study termination were examined for blood urea nitrogen (BUN), chloride, cholesterol, creatinine, AST, and BSP retention levels, prothrombin time, and cephalin flocculation. Rat and hamster blood samples taken at cessation of exposure were measured for hematocrit and RBC counts. All animals found dead or sacrificed at study termination were subjected to necropsy and histological examination of 31 tissue types. No histopathology was performed at the end of the exposure period.

No treatment-related clinical signs or changes in body weight were observed in any of the dogs (Haun et al., 1979, 1984). One dog in the 5-ppm group died at 15 months postexposure. Blood chemistry measurements revealed significantly elevated serum ALT concentrations in the 5-ppm group from Weeks 4–26 during exposure (maximum elevation above controls of 372% at Week 8; 244% at Week 26) and to 11 weeks postexposure, after which treated animals were not significantly different from controls. Histopathological examination (upon death or study termination) found no increase in nonneoplastic lesions in treated dogs. The only observation of a tumor was a metastatic reticulum cell sarcoma encapsulating the heart and portions of the lung of the dog dying at 15 months after exposure cessation.

Haun et al. (1979, 1984) attributed mortality in rodents during exposure to respiratory infection or accidents. No treatment-related clinical signs were observed during exposure. In mice, body weights were not affected by treatment. No effects on RBC counts or hematocrit were observed. Several statistically significant increases in noncancer histological lesions were observed at study termination (see Table 7). Hyaline degeneration of the gallbladder and endometrial cysts in the uterus were the most sensitive effects, with statistically significant increases in all treated groups. Lesions in the liver (congestion, angiectasis) and lung (congestion, perivascular cuffing, lymphoid hyperplasia) were significantly increased only in the 0.5- and 5-ppm groups. Incidence rates for all noncancer effects except liver angiectasis were higher among mice exposed to 0.5 ppm than 5 ppm. Although no significant differences in mortality were reported in mice, mortality at 24 months was approximately 65%, 70%, and 85% in the 0.05-, 0.5-, and 5-ppm groups, respectively. A possible explanation for the higher noncancer incidence rates in the mid-exposure group compared with the high-exposure group may be late development of effects masked by the higher mortality in the high-exposure group. However, this could not be confirmed in the absence of time-to-lesion data.

In mice, Haun et al. (1979, 1984) reported low, but statistically significant increases, in incidences of thyroid follicular cell carcinomas in the 0.5- and 5-ppm groups (see Table 8). Small, statistically significant increases in hemangiosarcoma and Kupffer cell sarcoma were observed in the 0.05- and 5-ppm groups, but not the 0.5-ppm group.

Treated rats exhibited significantly lower body weights compared with controls, although the differences were not exposure-related (Haun et al., 1979, 1984). Body weight data were not shown. No effects on RBC counts or hematocrit were observed. Histopathological exams found no significant increases in noncancer lesions. Nonsignificant increases in alveolar hyperplasia were seen in all groups (see Table 9). Fatty liver changes were nonsignificantly increased in the 0.05-ppm group and significantly decreased in the 0.5- and 5-ppm groups.

In rats, statistically significant increases were found for the incidences of pancreas islet cell adenoma at 0.5 and 5 ppm, and pituitary chromophobe adenoma at 5 ppm (see Table 10). A nonsignificant increase in bronchial adenoma was seen in the 5-ppm group (Haun et al., 1979, 1984).

Hamsters appeared to be the least susceptible of the species tested. Body weights were significantly lower in treated hamsters than controls but were not exposure-related. No effects on RBC counts or hematocrit were observed. No significant increases in noncancer lesions or tumors were seen in any treatment group (Haun et al., 1979, 1984).

**Table 7. Incidence of Noncancer Histopathological Lesions in Female C57BL/6 Mice Exposed for 6 Months via Inhalation to 1,1-Dimethylhydrazine Contaminated with NDMA, and Observed for an Additional 18 Months<sup>a</sup>**

Tissue	Lesion type	Exposure Concentration			
		0	0.05 ppm 0.13 mg/m <sup>3</sup>	0.5 ppm 1.3 mg/m <sup>3</sup>	5 ppm 13 mg/m <sup>3</sup>
Lung	congestion	179/686 (26%)	83/340 (24%)	121/331 (37%) <sup>b</sup>	98/336 (29%)
	perivascular cuffing	121/686 (18%)	54/340 (16%)	93/331 (28%) <sup>b</sup>	90/336 (27%) <sup>b</sup>
	lymphoid hyperplasia	4/686 (0.6%)	6/340 (2%)	14/331 (4%) <sup>b</sup>	8/336 (2%) <sup>b</sup>
Liver	congestion	48/681 (7%)	20/363 (6%)	47/344 (14%) <sup>b</sup>	20/342 (6%)
	angiectasis	11/681 (2%)	9/363 (2%)	2/344 (0.6%)	23/342 (7%) <sup>b</sup>
Gallbladder	hyaline degeneration	48/701 (7%)	49/374 (13%) <sup>b</sup>	45/368 (12%) <sup>b</sup>	41/360 (11%) <sup>b</sup>
Uterus	endometrial cysts	11/632 (2%)	46/348 (13%) <sup>b</sup>	67/311 (22%) <sup>b</sup>	57/312 (18%) <sup>b</sup>

<sup>a</sup>Haun et al. (1979, 1984).

<sup>b</sup>Significantly different from controls ( $p < 0.05$ ) using Fisher exact test performed for this review.

**Table 8. Tumor Incidence in Female C57BL/6 Mice Exposed for 6 Months via Inhalation to 1,1-Dimethylhydrazine Contaminated with NDMA, and Observed for an Additional 18 Months<sup>a</sup>**

Tumor type	Exposure Concentration			
	0	0.05 ppm 0.13 mg/m <sup>3</sup>	0.5 ppm 1.3 mg/m <sup>3</sup>	5 ppm 13 mg/m <sup>3</sup>
thyroid follicular cell carcinoma	2/551 (0.4%)	1/311 (0.3%)	8/278 (3%) <sup>b</sup>	5/286 (2%) <sup>b</sup>
hemangiosarcoma	5/701 (0.7%)	9/374 (2%) <sup>b</sup>	3/368 (0.8%)	17/360 (5%) <sup>b</sup>
Kupffer cell sarcoma	1/701 (0.1%)	4/374 (1%) <sup>b</sup>	0/368 (0%)	8/360 (2%) <sup>b</sup>

<sup>a</sup>Haun et al. (1979, 1984).

<sup>b</sup>Significantly different from controls ( $p < 0.05$ ) using Fisher exact test performed for this review.

**Table 9. Incidence of Noncancer Histopathological Lesions in Male F-344 Rats Exposed for 6 Months via Inhalation to 1,1-Dimethylhydrazine Contaminated with NDMA, and Observed for an Additional 18 Months<sup>a</sup>**

Lesion type	Exposure Concentration			
	0	0.05 ppm 0.13 mg/m <sup>3</sup>	0.5 ppm 1.3 mg/m <sup>3</sup>	5 ppm 13 mg/m <sup>3</sup>
Alveolar hyperplasia	8/189 (4%)	17/192 (9%)	16/182 (9%)	11/191 (6%)
Fatty liver changes	59/197 (30%)	69/193 (36%)	38/189 (20%) <sup>b</sup>	38/188 (20%) <sup>b</sup>

<sup>a</sup>Haun et al. (1979, 1984).

<sup>b</sup>Significantly different from controls ( $p < 0.05$ ) using Fisher exact test performed for this review.

**Table 10. Tumor Incidence in Male F-344 Rats Exposed for 6 Months via Inhalation to 1,1-Dimethylhydrazine Contaminated with NDMA, and Observed for an Additional 18 Months<sup>a</sup>**

Tissue	Tumor type	Exposure Concentration			
		0	0.05 ppm 0.13 mg/m <sup>3</sup>	0.5 ppm 1.3 mg/m <sup>3</sup>	5 ppm 13 mg/m <sup>3</sup>
Lung	bronchiolar adenoma	5/189 (3%)	0/192 (0%)	2/182 (1%)	10/191 (5%)
Pancreas	islet cell adenoma	0/170 (0%)	3/174 (2%)	12/169 (7%) <sup>b</sup>	6/158 (4%) <sup>b</sup>
Pituitary	chromophobe adenoma	60/171 (35%)	76/182 (42%)	75/169 (44%)	90/174 (52%) <sup>b</sup>

<sup>a</sup>Haun et al. (1979, 1984).

<sup>b</sup>Significantly different from controls ( $p < 0.05$ ) using Fisher exact test performed for this review.

The only noncancer effects reported in rodents by Haun et al. (1979, 1984) were increased incidence of some histopathological lesions in mice. However, interpretation of these data is uncertain due to the 18-month period between the end of exposure and examination. Some of the observed lesions are common lesions associated with aging (e.g., endometrial cysts). The observed increases were generally small. None of the lesions that occurred with increased incidence in more than one exposure group showed a consistent exposure-response relationship. However, data for endometrial cysts among female mice (see Table 7) appears to demonstrate a reasonable exposure-response relationship and presents the most sensitive noncancer LOAEL for inhalation exposure.

To assess whether the presence of 0.12% NDMA, a recognized liver toxicant (Anderson et al., 1978; Peto et al., 1991), in inhaled 1,1-DMH contributed to the elevation of serum ALT concentrations seen in dogs, Haun et al. (1984) also exposed beagle dogs (2/gender/group) to 5 ppm purified 1,1-DMH containing  $\leq 35$  parts per trillion (ppt) NDMA in 3 phases. In the first phase, the dogs were exposed for 6/hours/day, 5 days/week, initially for 8.5 weeks. Blood samples were collected at least bi-weekly and analyzed for Hgb, hematocrit, sodium, potassium, calcium, glucose, total protein, albumin, globulin, ALT, and alkaline phosphatase, and for RBC, WBC, and differential cell counts. BSP retention was measured at the start and end of the study. Liver biopsies were taken following 8.5 weeks exposure. The dogs were allowed to recover from surgery for 5 days, after which a 13-day continuous inhalation exposure of 5-ppm NDMA-free 1,1-DMH was administered in the second phase of exposure. In the final phase, dogs were continuously exposed for 16 days to 5-ppm 1,1-DMH containing 0.12% NDMA. At exposure termination, all dogs were sacrificed and 31 tissue types were collected and subjected to gross and histopathological examination.

Haun et al. (1984) reported no significant changes in serum ALT concentrations or other serum chemistry parameters among treated dogs during or following the intermittent and continuous exposures to NDMA-free 1,1-DMH. No significant differences were observed histopathologically in liver biopsy samples from control and treated dogs. In dogs subsequently exposed to 1,1-DMH containing NDMA, significantly higher concentrations of serum ALT, as much as 25% on days 10–16 of exposure, were observed in treated animals. BSP retention and histopathology were not significantly different between treated and control dogs. These findings suggested that the observed increases in serum ALT concentrations in dogs exposed to 5-ppm 1,1-DMH for 6 months resulted from the presence of NDMA in 1,1-DMH.

Haun et al. (1984) also conducted a chronic inhalation study in mice to examine the oncogenicity of purified 1,1-DMH containing  $\leq 35$ -ppt NDMA. Two groups of 200 female C57BL/6 mice were exposed to 0- or 5-ppm purified 1,1-DMH for 6 hours/day, 5 days/week, for 12 months, after which they were observed for a 12-month postexposure period. Body weights were measured monthly. At study termination, all surviving mice were sacrificed. Haun et al. (1984) collected 31 tissue types from animals dying prematurely or terminally sacrificed and subjected to histopathological examination. In addition, two mice from each group were sacrificed at the end of the exposure period and subjected to electron microscopy of the liver and lungs.

During the 12-month exposure period, survival was marginally reduced in the treated group (Haun et al., 1984). However, by the study's end, survival was similar for both groups. Mean body weights in treated mice were less than controls beginning at Month 7 of the study

and were 15% lower than controls at the study's end. Electron microscopy of the lung and livers of two mice/group sacrificed at the end of the exposure period showed morphology to be similar in both groups. Haun et al. (1984) reported significant increases in incidences of nonneoplastic lesions in the nasal mucosa, circulatory system, and anus of treated female mice at study termination and insignificant increases in other lesions, including gall bladder hyaline degeneration, and endometrial and ovarian cysts (see Table 11). Lesions of the nasal mucosa appear to be the most sensitive nonneoplastic endpoint in the one year inhalation study, with a squamous metaplasia rate of 11% compared with 0.5% in controls.

<b>Table 11. Incidence of Noncancer Histopathological Lesions in Female C57BL/6 Mice Exposed via Inhalation to Purified 1,1-Dimethylhydrazine for 12 Months and Examined 12 Months Later<sup>a</sup></b>			
<b>Tissue</b>	<b>Lesion Type</b>	<b>Exposure Concentration</b>	
		<b>0</b>	<b>5 ppm 13 mg/m<sup>3</sup></b>
Nasal mucosa	Suppurative inflammation	8/183	31/179 <sup>b</sup>
	Hyperplasia	1/183	7/179 <sup>c</sup>
	Squamous metaplasia	1/183	19/179 <sup>b</sup>
	Dysplasia	2/183	14/179 <sup>b</sup>
Circulatory system	Angiectasis	27/191	54/190 <sup>b</sup>
Anus	Prolapse	2/92	13/93 <sup>b</sup>
	Erosion	13/92	30/93 <sup>b</sup>
Reproductive	Endometrial cysts	0/187	6/169
	Ovary cysts	26/168	31/151
Gall bladder	Hyaline degeneration	9/158	14/156

<sup>a</sup>Haun et al. (1984).

<sup>b</sup>Significantly different from controls ( $p < 0.01$ ) using Fisher exact test.

<sup>c</sup>Significantly different from controls ( $p < 0.05$ ) using Fisher exact test.

Incidences of tumors of the lung, liver, nasal cavity, bone, and circulatory and lymphatic systems were significantly higher in mice treated with purified 1,1-DMH, compared with controls. (Haun et al., 1984) The lung, liver, and nasal mucosa appear to be the most sensitive tissues to cancer (see Table 12).

This study utilized a purified exposure agent and included extensive histopathological observations in a sufficient number of animals exposed chronically and observed over a lifetime. However, its usefulness is limited by inclusion of only a single exposure concentration in one gender of one species, a relatively short exposure duration, and very limited evaluation for noncancer endpoints during and immediately following exposure.

**Table 12. Tumor Incidence in Female C57BL/6 Mice Exposed via Inhalation to Purified 1,1-Dimethylhydrazine for 12 Months and Examined 12 Months Later<sup>a</sup>**

Tissue	Lesion Type	Exposure Concentration	
		0	5 ppm 13 mg/m <sup>3</sup>
Lung	alveolar/bronchiolar adenoma	4/187	20/186 <sup>b</sup>
Liver	hepatocellular adenoma	4/187	20/188 <sup>c</sup>
Lymphatic system	malignant lymphoma	64/191	84/190 <sup>c</sup>
Nasal mucosa	Papilloma	0/183	5/179 <sup>b</sup>
	adenomatous polyp	0/183	17/179 <sup>b</sup>
Bone	Osteoma	0/183	5/179 <sup>c</sup>
Circulatory system	Hemangioma	6/191	19/190 <sup>b</sup>

<sup>a</sup>Haun et al. (1984).

<sup>b</sup>Significantly different from controls ( $p < 0.01$ ) using Fisher exact test.

<sup>c</sup>Significantly different from controls ( $p < 0.05$ ) using Fisher exact test.

### Other Studies

Hodge (1954) identified an oral LD<sub>50</sub> of 360 mg/kg in rats. Smith and Clark (1971) reported mortality in 1/4 and 3/4 dogs given dermal applications of 300 and 1800 mg/kg, respectively for 6 hours.

Intraperitoneal (i.p.) injections of 10 mg/kg 1,1-DMH, 5 days/week for 4 weeks, in rhesus monkeys resulted in initial weight loss, 90% increase in plasma glucose, and hepatic lipid deposition (Patrick and Back, 1964). Rats were given i.p. injections of 10, 30, 50, or 70 mg/kg 1,1-DMH for 21 days (Cornish and Hartung, 1969). Significant mortality occurred in the first 3 days in rats given 30 mg/kg or higher. Swelling and lipid infiltration occurred in the 50 and 70 mg/kg survivors, while increased BUN concentrations were seen in the 50 mg/kg survivors. Dose-related increases in AST concentrations were observed in all treated groups. In mice, i.p. injections of 1,1-DMH resulted in an increased one-way mixed lymphocyte response and an inhibition of prostaglandin E2 produced by adherent splenocytes (Tarr et al., 1988).

In pregnant rats given i.p. doses of 10, 30, or 60 mg/kg 1,1-DMH on GD 6–15, reduced body weight gain was observed to be dose-related and persisted at the highest dose (Keller et al., 1984). In more than half of the birthed litters, 30% fetal resorption was seen along with a moderate increase in skeletal and soft tissue abnormalities.

Christudossa et al (2008) gave 6-week old Wistar rats a subcutaneous injection of 30 mg 1,1-DMH per kg body wt, twice a week for 20 weeks, and sacrificed the animals after 5 and 9 months of treatment. Tissue zinc concentrations showed a significant decreases ( $p < 0.05$ ) in the large intestine at 9 months, while the stomach and small intestine showed no significant changes at 5 or 9 months. Tissue CuZnSOD enzyme activity in the stomach, small intestine, and large intestine showed no significant decreases at 5 or 9 months as compared with controls. Histologically, the large intestine was normal at 9 months. Christudossa et al (2008) concluded that 1,1-DMH administered at this dosage appeared not to be carcinogenic in Wistar rats.

The results of mutagenicity studies using *S. typhimurium* (TA 97, 98, 100, 102, 1530, 1535, 1537, 1538, 1950, 2638, G-46) and *E. coli* (WP2 uvr A, WP2 uvr A trp, WP2/pKM101, WP2 uvrA/pKM101) have been inconsistent, but tend to be negative for reverse mutations (Von Wright and Tikkanen, 1980; Brusick and Matheson, 1976; Hemminki et al., 1980; Bruce and Heddle, 1979; de Flora, 1981; Tosk et al., 1979; Bartsch et al., 1980; Parodi et al., 1981; Rogan et al., 1982; Nielsen et al., 1992; Watanabe et al., 1996). However, DNA repair was observed to be positive in *E. coli* (AB1157/JC5547, 2921, 2926, 5519) and *B. subtilis* H17/M45 (Suter and Jaeger, 1982). Mitotic recombination was negative in *S. cerevisiae*, but forward mutations were seen in *A. nidulans*. In mammalian cell lines, unscheduled DNA synthesis was observed in human diploid lung cells and mouse hepatocytes, but not in rat hepatocytes (Mori et al., 1988; Brusick and Matheson, 1976). Both positive and negative results for forward mutations have been seen in mouse lymphoma cells (Rogers and Back, 1981; Brusick and Matheson, 1976). In vivo, positive results were reported for inhibition of thymidine incorporation in mouse testicular DNA, micronucleus test in female mice, and DNA damage or binding in rats (Bruce and Heddle, 1979; Parodi et al., 1981; Sagelsdorff et al., 1988; Seiler, 1977). Negative results were seen for unscheduled DNA synthesis in mice or rats, sperm abnormalities in mice, the micronucleus test in male mice, and lethal mutations in mice or fruit flies (Tyson and Mirsalis, 1985; Wyrobek and Bruce, 1975; Bruce and Heddle, 1979; Suzuki et al., 1989; Zijlstra and Vogel, 1988; Brusick and Matheson, 1976; Epstein et al., 1972).

#### **DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC RfDs FOR 1,1-DIMETHYLHYDRAZINE**

No human data were available for derivation of a subchronic or chronic provisional oral reference dose (p-RfD) for 1,1-DMH. Several studies of oral exposures in mice, rats, or hamsters reported mortality and tumor incidence but not nonneoplastic toxicity (Roe et al., 1967; Kelly et al., 1969; Argus and Hoch-Ligeti, 1961; Toth 1973, 1977; Druckrey et al., 1967). Drinking water studies by Goldenthal in mice and rats were not available for this assessment, but were summarized by IPCS (1991; Goldenthal, 1989a,b, 1990). These summaries included descriptions of observed nonneoplastic effects, but they did not report incidence rates. Thus, the lack of primary sources of quantitative data precludes the derivation of provisional RfDs. However, Appendix A of this document contains a screening chronic RfD that may be useful in certain instances. Please see the attached Appendix A for details.

#### **DERIVATION OF PROVISIONAL SUBCHRONIC RfC FOR 1,1-DIMETHYLHYDRAZINE**

Available human data were insufficiently quantitative to use to derive a subchronic or chronic provisional inhalation reference concentration (p-RfC) for 1,1-DMH. Animal data came from studies by Rinehart et al. (1960) and Haun et al. (1979, 1984) in dogs and rodents. The studies conducted by Haun et al. (1979, 1984) in rodents were designed primarily as cancer bioassays, with few endpoints examined during or immediately following exposure. Noncancer effects observed in these studies included statistically significant increases in some lesions, including some associated with aging in mice examined at 24 months of age, 18 months after

exposure had ended. Reported effects generally were small and often did not increase with exposure. However, the incidence of endometrial cysts among female mice (see Table 7) was significantly increased (13% vs. 2% among controls) at the lowest exposure (0.13 mg/m<sup>3</sup>) and increased with concentration at all exposure concentrations, except the highest.

The dog study by Haun et al. (1979, 1984) included periodic serum chemistry measurements during and immediately following the exposure period. Large increases in serum ALT, indicative of liver toxicity, were seen through most of the exposure period and for an additional 11 weeks postexposure. However, follow-up studies conducted by Haun et al. (1984) using purified 1,1-DMH demonstrated that the increase in ALT in the initial study probably resulted from exposure to NDMA, which was an impurity in the propellant-grade 1,1-DMH tested by Haun et al. (1979, 1984) in the initial study.

Rinehart et al. (1960) did not report the purity of the test material, so it is not known whether the 1,1-DMH used in this study contained NDMA or other contaminants that might have influenced the results. This study reported overt toxic effects in rodents at both tested concentrations (75 ppm and 140 ppm, for up to 7 weeks), including significant mortality in mice and dyspnea and lethargy in rats. In dogs exposed for 13–26 weeks, this study identified a LOAEL of 5 ppm (13 mg/m<sup>3</sup>) for transient lethargy and hematological effects (hemolytic anemia). Overt toxicity, including death, was observed in dogs exposed to 25 ppm (63 mg/m<sup>3</sup>). Due to the small number of dogs tested (3 per exposure concentration), the relatively short exposure duration (5% of lifetime), the limited number of endpoints monitored, the marginal quality of the reporting, and the uncertainty about potential contaminants in the test material, there is insufficient confidence in the results of this study for it to serve as the basis for p-RfC derivation.

The Haun et al. (1979, 1984) studies in female mice identify a LOAEL of 0.13 mg/m<sup>3</sup> (0.05 ppm) for endometrial cysts using standard 1,1-DMH that was contaminated with 0.12% NDMA (see Table 7). Although the test compound was contaminated with NDMA, the choice of this endpoint for the 1,1-DMH critical effect is supported by extensive reviews of NDMA data (ATSDR, 1989; ACGIH, 2001; IARC, 1978; U.S. EPA, 1993; WHO, 2002) and key NDMA data sources (Anderson et al., 1978; Peto et al., 1991; Klein et al., 1991), which reveal no evidence associating NDMA with endometrial cysts or uterine effects of any type. U.S. EPA benchmark dose (BMD) modeling software (version 1.3.2) has been used in an attempt to calculate a BMCL<sub>10</sub> (see Appendix B) using these data on exposures leading to endometrial cysts. The data generate curves that appear reasonable only when the highest exposure data are deleted (see Figure B-1). This deletion is justified because the incidence of this effect seems to level off above the middle exposure. However, none of the models provide *p*-values >0.1 (see Table B-1). Thus, the 6-month LOAEL of 0.13 mg/m<sup>3</sup> (0.05 ppm) for endometrial cysts in female mice (Haun et al., 1979, 1984) has been chosen as the point of departure (POD) for deriving the p-RfDs.

In the absence of a valid physiologically-based pharmacokinetic (PBPK) model, default assumptions (U.S. EPA, 1994b) are used to estimate a human equivalent concentration (HEC). The 6-hours/day-5-day/week mouse exposure is adjusted for duration and frequency of exposure, to represent the average exposure over a 24-hour day, 7 days/week period:

$$\text{LOAEL}_{(\text{ADJ})} = (0.13 \text{ mg/m}^3) \times (6 \text{ hr}/24 \text{ hr}) \times (5 \text{ days}/7 \text{ days}) = 2.3 \times 10^{-2} \text{ mg/m}^3$$

Because the available evidence suggest inhaled 1,1-DMH is a systemic rather than a respiratory toxicant, it is considered a Category 3 gas (U.S. EPA, 1994b). In the absence of blood:gas partition coefficients for 1,1-DMH, the dosimetric adjustment factor (DAF) is assumed to be 1.

A composite UF of 3,000 is applied to this LOAEL POD of  $2.3 \times 10^{-2} \text{ mg/m}^3$  to derive the subchronic inhalation p-RfC of  $8 \times 10^{-6} \text{ mg/m}^3$ . The composite UF of 3,000 is calculated from the following individual UFs:

- $UF_L = 10$  for using a LOAEL POD.
- $UF_S = 1$  for using data from a study in which the mice were observed for 24 months but exposed for only 6 months to derive a subchronic p-RfC.
- $UF_A = 3$  for using the human equivalent concentration of the mouse inhalation data to predict human effects.<sup>a</sup>
- $UF_H = 10$  to account for susceptible human populations.
- $UF_D = 10$  for the limited database, which included no reproductive, developmental, or multigenerational studies.

$$\begin{aligned}\text{Subchronic p-RfC} &= 2.3 \times 10^{-2} \text{ mg/m}^3 \div 3,000 \\ &= \mathbf{8 \times 10^{-6} \text{ mg/m}^3}\end{aligned}$$

Confidence in the principal study is low, primarily because of the impure form of 1,1-DMH to which experimental animals were exposed. Additional concerns result from the 18-month period between the end of exposure and examination, and the lack of increase in incidence of uterine lesions from the mid- to high-exposure mice. Low confidence in the subchronic p-RfC follows.

Although the 6-month LOAEL of  $0.13 \text{ mg/m}^3$  (0.05 ppm) for endometrial cysts in female mice (Haun et al., 1979, 1984) also has been considered for derivation of the chronic p-RfC, the composite uncertainty factor required would exceed 3,000 with application of an additional uncertainty factor for using the 6-month exposure data to derive a chronic value. Thus, derivation of a chronic p-RfC is not feasible. However, the Appendix of this document contains a screening chronic RfC that may be useful in certain instances. Please see the attached Appendix A for details.

## PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 1,1-DIMETHYLHYDRAZINE

### Weight-of-Evidence Descriptor

Under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), this assessment characterizes 1,1-DMH as “*Likely to be Carcinogenic to Humans*,” based on positive carcinogenicity data in several subchronic and chronic oral and inhalation studies in mice, rats, and hamsters. No epidemiological data were available to determine the carcinogenicity of 1,1-DMH in humans. Subchronic drinking water exposures resulted in the development of angiosarcoma in both genders of mice and hamsters (Toth, 1973, 1977). Chronic drinking water

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<sup>a</sup>Application of a dosimetric adjustment factor in the calculation of a HEC addresses the toxicokinetic aspects of the animal-to-human UF, allowing reduction from the default  $UF_A$  of 10 to 3.

exposures in mice (Goldenthal, 1989a, 1990) resulted in hemangiomas, hemangiosarcomas, and lung tumors, while female rats (Goldenthal, 1989b) exhibited pituitary and hepatocellular adenomas and hepatocellular carcinomas. Subchronic inhalation exposures resulted in hemangiosarcomas, Kupffer cell sarcomas, and thyroid follicular cell sarcomas in mice, and pancreas islet cell adenomas and pituitary chromophobe adenomas in rats (Haun et al., 1979, 1984). While the purity of 1,1-DMH was not reported in many of the studies, Haun et al. (1979, 1984) reported the presence of 0.12% NDMA, a potent multisite carcinogen (U.S. EPA, 1993), in the 1,1-DMH used for subchronic inhalation exposures, introducing uncertainty as to whether the observed carcinogenicity resulted from exposure to 1,1-DMH or NDMA. However, in a chronic, less-than-lifetime inhalation study in mice exposed to purified 1,1-DMH (Haun et al., 1984), tumor development occurred in multiple sites, including the nasal mucosa, lung, liver, lymphatic system, bone, and blood vessels, suggesting that 1,1-DMH is carcinogenic independent of adulterant NDMA.

Genotoxicity data for 1,1-DMH were equivocal regarding its potential to induce carcinogenicity by direct action on DNA. Both positive and negative results have been reported for bacterial and fungal genomic mutations and DNA repair (Von Wright and Tikkanen, 1980; Brusick and Matheson, 1976; Hemminki et al., 1980; Bruce and Heddle, 1979; de Flora, 1981; Tosk et al., 1979; Bartsch et al., 1980; Parodi et al., 1981; Rogan et al., 1982; Nielsen et al., 1992; Watanabe et al., 1996; Suter and Jaeger, 1982), DNA lesions in human and animal cell lines (Mori et al., 1988; Brusick and Matheson, 1976; Rogers and Back, 1981), and DNA binding and repair in vivo (Bruce and Heddle, 1979; Parodi et al., 1981; Sagelsdorff et al., 1988; Seiler, 1977). Lethal genetic mutations have not been observed in animals (Suzuki et al., 1989; Zijlstra and Vogel, 1988; Brusick and Matheson, 1976; Epstein et al., 1972). Available data are insufficient to determine a mode of action for tumor development.

## **Quantitative Estimates of Carcinogenic Risk**

### ***Oral Exposure***

There were no human oral data on which to base an oral cancer risk estimate for 1,1-DMH. The Goldenthal rat and mouse studies (1989a,b, 1990), when available, might provide adequate dose-response data for cancer risk derivation. The oral cancer data potentially could result in more conservative risk values than those derived from the noncancer data. However, all available data (Goldenthal, 1989 a,b, 1990; Toth, 1973, 1977) were compromised and are considered inadequate for determining a provisional oral slope factor (p-OSF) at the time of this assessment.

Among the available tumor data, the Goldenthal (1989a) male mouse hepatic hemangioma and hemangiosarcoma data (see Table 1) appeared to provide the steepest dose-response curve. Unfortunately, these data could not be used to determine a p-OSF because they were compromised by use of very high doses and by a high mortality rate among controls and treated mice. In addition, these data were available only from secondary sources and two of those sources (IPCS, 1991 and Finkel, 1995) reported dissimilar cancer incidence data among the exposed mice (see Table 1).

The Goldenthal (1990) female mouse alveolar and bronchiolar adenoma and carcinoma data (see Table 2) were similarly compromised by very high mortality rates among experimental and control animals, the use of only one treatment dose, and availability only from a secondary source: IPCS (1991).

The Goldenthal (1989b) female rat hepatocellular adenoma and carcinoma data (see Table 3) also were available only from a secondary source (IPCS, 1991) and suggested potential cancer risk substantially lower than that for either hepatic hemangioma and hemangiosarcoma (Goldenthal, 1989a) or alveolar and bronchiolar adenoma and carcinoma (Goldenthal 1990).

The mouse (Toth, 1973) and hamster (Toth, 1977) tumor data (see Tables 4 and 5, respectively) were compromised because the test chemical probably was contaminated with *n*-nitrosodimethylamine, a potent multisite carcinogen. In addition, these data were available only for a single, high treatment dose.

Although none of these data, even considered in concert, were sufficient to determine a p-OSF for cancer risk, availability of the primary Goldenthal (1989a,b, 1990) data and additional study details might allow derivation of an OSF for 1,1-DMH. When original sources for those data become available, their usefulness for deriving either a provisional or a screening OSF can be reconsidered.

### ***Inhalation Exposure***

There were no human inhalation data on which to base a cancer inhalation unit risk (IUR) estimate for 1,1-DMH and the available animal data (Haun et al., 1979, 1984) are too compromised to be adequate for determining the IUR.

Among the available tumor data, the Haun et al. (1979, 1984) male rat and female mouse data (see Tables 7–10) were severely compromised by use of 1,1-DMH that was contaminated with NDMA, which has been demonstrated to be a potent, multisite carcinogen in experimental animals (U.S. EPA, 1993). Because the contaminant NDMA was at a low concentration (0.12%) in the treatment chemical, future assessments of this chemical might consider using the NDMA data to attempt to distinguish the fractions of cancer risk attributable to NDMA and 1,1-DMH, respectively.

Other Haun et al. (1984) data used purified 1,1-DMH to determine tumor rates among female mice (see Table 12). However, these data were compromised by the use of only one exposure concentration, which makes it difficult to estimate a reasonable cancer risk curve from which a p-IUR might be calculated.

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## APPENDIX A. DERIVATION OF SCREENING VALUES FOR 1,1-DIMETHYLHYDRAZINE

For reasons noted in the main Provisional Peer-Reviewed Toxicity Value (PPRTV) document, it is inappropriate to derive subchronic and chronic p-RfDs, or a chronic p-RfC, for 1,1-Dimethylhydrazine (1,1-DMH). However, information is available for this chemical that, although insufficient to support derivation of provisional toxicity values 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 a Screening Chronic RfD

Goldenthal (1989b) reported that a single gross pathological effect, cloudy corneas, was found to be slightly higher in the mid- and high-dose groups of Fisher 344 rats fed pure 1,1-DMH in drinking water for 24 months (37% and 41%, respectively) compared with controls (21%), but not in low dose groups. Corresponding increases in the incidence of corneal mineralization were reported. Goldenthal (1989b) observed other nonneoplastic effects only in the high-dose group. Although the low dose was 50 times lower than the mid-dose at which this effect was noted, the low dose for corneal clouding and mineralization is applied as a no-observed-adverse-effect level (NOAEL) point of departure (POD). These data are insufficiently quantitative to attempt benchmark dose modeling. Although this study appeared to have been well designed, the fact that these data were available only in secondary form (IPCS, 1991) leads to low confidence, and the conclusion that this derivation can be pursued only for an oral screening toxicity value. When the Superfund Health Risk Technical Support Center obtains the original Goldenthal (1989a,b, 1990) data, the derivation of p-RfDs can be reconsidered.

Goldenthal (1989b) estimated that the 1-ppm pure 1,1-DMH in drinking water represented a dose of 0.1 mg/kg-day. Using this dose as the chronic NOAEL POD, a composite uncertainty factor (UF) of 1,000, calculated from the following individual UFs, is applied:

- $UF_A = 10$  for extrapolating from rat drinking water data to predict human effects.
- $UF_H = 10$  to account for susceptible human populations.
- $UF_D = 10$  for the limited database, which included no reproductive, developmental, or multigenerational studies.

$$\begin{aligned}\text{Screening Chronic RfD} &= 0.1 \text{ mg/kg-day} \div 1,000 \\ &= 1 \times 10^{-4} \text{ mg/kg-day}\end{aligned}$$

The lack of subchronic data reporting noncancer effects precludes derivation of a subchronic RfD.

### Derivation of a Chronic Inhalation Screening Value

A composite uncertainty factor of 10,000 has been calculated from the following individual UFs. This UF is applied to the 6-month mouse inhalation LOAEL, adjusted to a human LOAEL<sub>[HEC]</sub> POD of  $2.3 \times 10^{-2} \text{ mg/m}^3$ , for endometrial cysts (Haun et al., 1979, 1984) to derive the subchronic inhalation p-RfC.

- $UF_L = 10$  for using a lowest-observed-adverse-effect-level (LOAEL) POD.
- $UF_S = 3$  for using data from a study in which the mice were observed for 24 months but exposed for only 6 months to derive a chronic value. This UF was reduced from 10 because a follow-up one-year study, using purified 1,1-DMH, demonstrated only a statistically insignificant increase in the critical effect (endometrial cysts) among mice treated with the high dose of 5 ppm ( $HEC = 2.3 \text{ mg/m}^3$ ).
- $UF_A = 3$  for using the human equivalent concentration of the mouse inhalation data to predict human effects.<sup>b</sup>
- $UF_H = 10$  to account for susceptible human populations.
- $UF_D = 10$  for the limited database, which included no reproductive, developmental, or multigenerational studies.

$$\begin{aligned}\text{Screening Chronic RfC} &= 2.3 \times 10^{-2} \text{ mg/m}^3 \div 10,000 \\ &= 2 \times 10^{-6} \text{ mg/m}^3\end{aligned}$$

Confidence in the principal study is low because the 1,1-DMH to which experimental animals were exposed was contaminated with NDMA. Additional concerns resulted from the 18-month period between the end of exposure and examination, the lack of increase in incidence of uterine lesions from the mid- to high-exposure mice, and the statistically insignificant increase in lesions seen in the one-year study using purified 1,1-DMH. Low confidence in the Screening Chronic RfC follows.

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<sup>b</sup>Application of a dosimetric adjustment factor in the calculation of a HEC addresses the toxicokinetic aspects of the animal-to-human UF, allowing reduction from the default  $UF_A$  of 10 to 3.

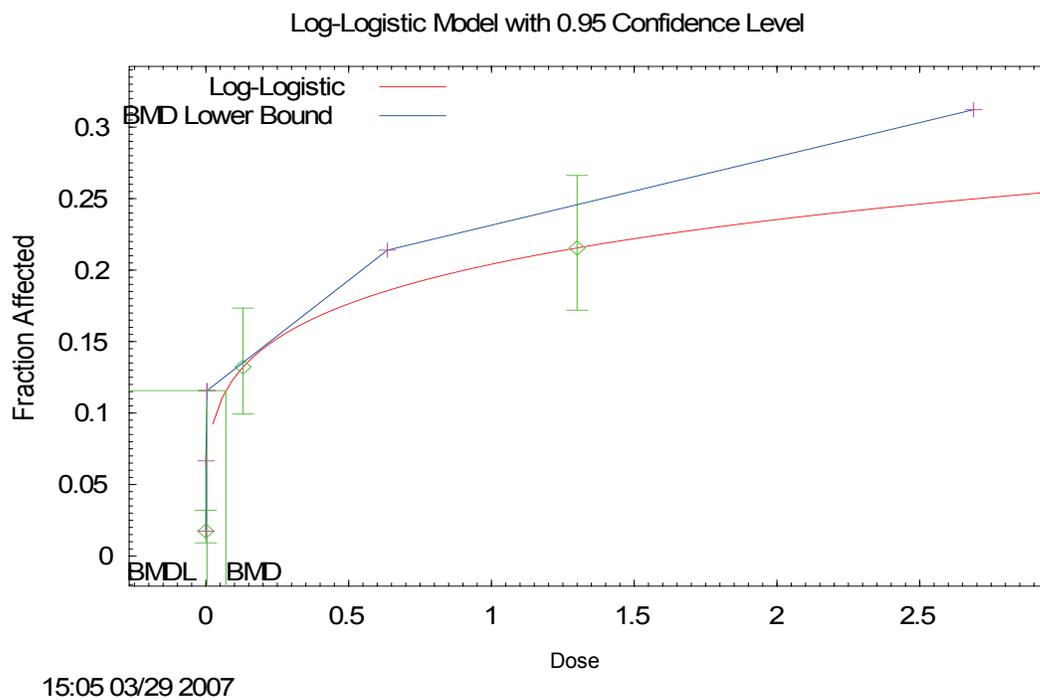
**APPENDIX B. BENCHMARK DOSE MODELING OF NONCANCER INHALATION DATA FOR 1,1-DIMETHYLHYDRAZINE: INCIDENCE OF UTERINE ENDOMETRIAL CYSTS IN C57BL/6 MICE**

<b>Table B-1. BMC Summaries for 1,1-Dimethylhydrazine<sup>a</sup> Female Mouse Endometrial Cyst Inhalation Data<sup>b</sup> with High Concentration Data Deleted; LOAEL = 0.13 mg/m<sup>3</sup></b>						
	<b>P</b>	<b>Chi<sup>2</sup></b>	<b>Σ scaled residuals<sup>c</sup></b>	<b>AIC</b>	<b>BMC (mg/m<sup>3</sup>)</b>	<b>BMCL (mg/m<sup>3</sup>)</b>
Log-log	NA	0	0	712.834	0.0698731	0.00390327
Log-probit	NA	0	0	712.834	0.0722823	0.00459426
Gamma	0	38.71	8.2	744.946	0.563999	0.446986
Probit	0	38.71	1.8	744.946	0.563999	0.446986
Quantal linear	0	38.71	8.2	744.946	0.563999	0.446986
Weibull	0	38.71	8.2	744.946	0.563999	0.446986
Multistage	0	45.41	9.4	754.163	0.858715	0.748505
Log-normal	0	46.11	9.5	755.081	0.8973	0.791855
Quantal quadratic	0	52.79	10.1	761.354	0.972032	0.855306

<sup>a</sup>Contaminated with 0.12% *n*-nitrosodimethylamine.

<sup>b</sup>Haun et al. (1979, 1984).

<sup>c</sup>Sum of absolute values of scaled residuals at lowest exposure and for controls.



**Figure B-1. Best-fitting BMC Curve for Endometrial Cysts in Mice Exposed to Airborne 1,1-DMH (Haun et al., 1979, 1984) with the Highest Concentration Deleted**