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Provisional Peer-Reviewed Toxicity Values for

Hydrazine
(CASRN 302-01-2)

Superfund Health Risk Technical Support Center
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Office of Research and Development
U.S. Environmental Protection Agency
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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
$LOAEL_{ADJ}$	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 HYDRAZINE (CASRN 302-01-2)

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 reference doses (RfD) or reference concentrations (RfC) are available for hydrazine in the Integrated Risk Information System (IRIS) database (U.S. EPA, 1991a), in the Health Effects Assessment Summary Tables (HEAST; U.S. EPA, 1997), or in the list of Drinking Water Standards and Health Advisories (U.S. EPA, 2006). However, IRIS (U.S. EPA, 1991a) does include a cancer assessment, which is discussed below. The Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991b, 1994a) included a Health and Environmental Effects Profile (HEEP) for Hydrazine and Hydrazine Sulfate (U.S. EPA, 1984) and a Health and Environmental Effects Document (HEED) for Hydrazine (U.S. EPA, 1990). No oral RfDs or inhalation RfCs were provided in the HEEP or HEED; U.S. EPA (1984, 1990) considered the data insufficient for the derivation of RfCs or RfDs for subchronic and chronic inhalation and oral exposures to hydrazine; however, a reportable quantity (RQ) of 0.454 kg (U.S. EPA, 2008) for noncancer toxicity was based on increased mortality in mice in the Haun and Kinkead (1973) inhalation study. The review of the Haun and Kinkead (1973) study in the HEED (U.S. EPA, 1990) suggested that the LOAEL concentration of 0.2 ppm (0.26 mg/m^3) was a frank effect level (FEL) in mice due to "significant" mortality; however, only 1 of 40 mice (2.5%) from this group died following 6 months of continuous exposure to hydrazine.

An Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile for Hydrazines (ATSDR, 1997) derived an intermediate-duration inhalation MRL of 0.004 ppm (5×10^{-3} mg/m^3) for exposure to hydrazine based on a LOAEL of 0.2 ppm (0.26 mg/m^3) from which they calculated a LOAEL(HEC) of 1.154 ppm (1.5 mg/m^3) for moderate fatty liver changes in female mice exposed to hydrazine for 6 months (Haun and Kinkead, 1973), and a composite uncertainty factor (UF) of 300, which was comprised of individual UFs of 10 for human variability, 10 for use of a LOAEL, and 3 for extrapolation from animals to humans following conversion to a human equivalent concentration (HEC). ATSDR (1997) did not derive acute or chronic inhalation MRLs for hydrazine, but noted adverse effects on the liver and central nervous system. ATSDR (1997) also did not derive oral MRLs for hydrazine. Studies in animals reported effects on the liver following acute-duration (Marshall et al., 1983; Wakabayashi et al., 1983) and intermediate-duration oral exposures (Biancifiori, 1970). However, these data did not define the threshold dose for hepatic effects with confidence.

CalEPA (2000) provides a chronic inhalation reference exposure level (REL) of 0.2 μg/m^3 (0.2 ppb; 2×10^{-4} mg/m^3) based on a human equivalent LOAEL concentration of 0.045 ppm (0.59 mg/m^3) for amyloidosis of the liver and thyroid in hamsters exposed by inhalation for 1 year (Vernot et al., 1985) and a composite UF of 300 (10 for human variability, 10 for use of a LOAEL, and 3 for extrapolation from animals to humans following conversion to a HEC).

Occupational exposure standards and guidelines for hydrazine include an American Conference of Governmental Industrial Hygienists threshold limit value-time-weighted average (ACGIH, 2001, 2008) of 0.01 ppm (0.013 mg/m^3), based on liver toxicity and a statistically insignificant increase in nasal tumors reported by Vernot et al. (1985) among rats exposed at 0.05 ppm (0.065 mg/m^3). Other occupational exposure standards are based primarily on skin irritation effects and include a National Institute for Occupational Safety and Health (NIOSH, 2005) 2-hour recommended exposure limit of 0.03 ppm (0.04 mg/m^3) and an Occupational Safety & Health Administration (OSHA, 2009) 8-hour time-weighted average permissible exposure limit of 1 ppm (1.3 mg/m^3).

IRIS (U.S. EPA, 1991a) and the HEAST (U.S. EPA, 1997) described hydrazine as a "Probable Human Carcinogen" (Group B2) because of tumors observed in mice, rats, and hamsters following oral, inhalation, or intraperitoneal administration, and supporting mutagenicity data. IRIS derived an oral slope factor (OSF) of 3 $(mg/kg\text{-}day)^{-1}$ based on hepatomas observed in mice given hydrazine sulfate in water by oral gavage (Biancifiori, 1970) and an inhalation unit risk of 4.9×10^{-3} $(\mu g/m^3)^{-1}$ based on nasal cavity adenomas or adenocarcinomas in male rats following inhalation exposure (MacEwen et al., 1981). The National Toxicology Program (NTP, 2005) Report on Carcinogens characterized hydrazine and hydrazine sulfate as "reasonably anticipated to be human carcinogens" based on evidence in laboratory animals. CalEPA (2005) included hydrazine and hydrazine sulfate in its List of Chemicals Known to the State to Cause Cancer or Reproductive Toxicity (updated December 2, 2005). The International Agency for Research on Cancer (IARC, 1999) assigned hydrazine to Group 2B, possibly carcinogenic to humans based on sufficient evidence for the carcinogenicity of hydrazine in animals and inadequate evidence in humans. The World Health Organization (WHO, 1987) Environmental Health Criteria document also characterized hydrazine as a possible human carcinogen based on mutagenicity data and carcinogenicity findings in animals.

Literature searches were performed for 1965 to February 2006 in TOXLINE, MEDLINE (plus PubMed cancer subset), and DART/ETICBACK. Search of the BIOSIS database was performed for 2000 to February, 2006. Databases searched without date limitations included TSCATS, RTECS, GENETOX, HSDB, and CCRIS. The search of Current Contents encompassed August 2005 to August 2008, and PubMed searches were updated in July 2009.

REVIEW OF PERTINENT DATA

Human Studies

Oral Exposure

Although hydrazine sulfate had been shown to cause tumors in laboratory animals (U.S. EPA, 1991a; Biancifiori, 1970; MacEwen et al., 1981), it also had been tested as an antitumor agent in humans. Several of these studies (Filov et al., 1995; Gold, 1975; Gershanovich et al., 1981) reported hydrazine sulfate to be effective in shrinking tumor size, suggesting possible cytotoxic properties. However, none of these studies included a control group. Other studies identified no appreciable antitumor effects, including uncontrolled studies (Lerner and Regelson, 1976; Ochoa et al., 1975; Spremulli et al., 1979; Strum et al., 1975) as well as randomized clinical trials using control groups in patients with nonsmall cell lung cancer (Chlebowski et al., 1990; Kosty et al., 1994, 1995; Loprinzi et al., 1994b) and colorectal cancer (Loprinzi et al., 1994a). Summaries of available data by the American Cancer Society (ACS, 1976), Kaegi (1998), Vickers (2004), and the University of Texas M.D. Anderson Cancer Center (UT, 2007), found the evidence for antitumor activity to be ambiguous, at best.

Chlebowski et al. (1990) noted improved survival and nutritional status among patients being treated concurrently with hydrazine sulfate and cisplatin. However, several clinical studies documented gastrointestinal (Lerner and Regelson, 1976) or neurological (Kosty et al., 1994; Loprinzi et al., 1994a) side effects, or both (Gershanovich et al., 1981; Ochoa et al., 1975) among treated patients. Hainer et al. (2000) reported that a cancer patient who had self-administered hydrazine sulfate 180 mg/day for 4 months developed fatal hepatic encephalopathy, renal failure, and profound coagulopathy.

Hydrazine sulfate is a known antagonist of pyridoxine (Hainer et al., 2000) so symptoms of central nervous system toxicity are likely to occur (UT, 2007). Ochoa et al. (1975) reported a 50% incidence of polyneuritis among 29 cancer patients treated with hydrazine sulfate. Oral and injected doses were associated with mild nausea, vomiting, anorexia, as well as the central nervous system toxicity.

Gershanovich et al. (1981) treated cancer patients, who had various types of disseminated tumors that had not responded to other forms of anticancer therapy, with one to three 60-mg tablets or capsules per day (calculated dose range of 0.86−2.57 mg/kg-day, assuming a 70-kg body weight). Treatment courses generally were for 30−45 days but occasionally for up to 6 months. Patients received from 2 to 24 courses of treatment, separated by treatment-free intervals of 14−30 days, for up to 5 years. Among the 225 cancer patients evaluated, side effects reported included nausea or vomiting (22), dizziness (13), and polyneuritis (4). However, Gershanovich et al. (1981) reported that symptoms disappeared when daily doses were reduced to 120 mg/day, suggesting this dose might be a no-observed-adverse-effect level (NOAEL). Using the most conservative assumptions (30-day treatment followed by 30 days treatment-free), these data were used to calculate an average daily dose, as follows:

$$[(120 \text{ mg/day})/70 \text{ kg}] \times (30 \text{ day treatment}/60\text{-day duration}) = 0.86 \text{ mg/kg-day}.$$

Unfortunately, this study did not provide details regarding the specific treatment durations of patients reporting side effects, and it reported no control group.

Filov et al. (1995) followed a similar protocol with a larger study group of 740 patients. All were treated with three 60-mg hydrazine sulfate tablets per day (calculated dose = 2.57 mg/kg-day). In some cases of gastrointestinal distress, patients were administered one tablet a day for 3−4 days, then two tablets a day up to the 9th day of treatment, and after that, three tablets a day. Total dose per 30−40 day course varied from 5.4 to 8.1 g. Patients typically received 2−20 courses of treatment, with 2−6 weeks treatment-free between courses. Using conservative assumptions, the average daily dose is similar to that calculated from the Gershanovich et al. (1981) data. Filov et al. (1995) reported nausea and vomiting in 5.6% of patients, and, like Gershanovich et al. (1981), reported that symptoms regressed when treatment was reduced to 120 mg/day (1.76 mg/kg-day). Filov et al. (1995) also reported peripheral nervous system effects, such as polyneuritis, in 1.8% of treated patients. Statistical analysis of these data was not reported.

Chlebowski et al. (1987) studied 101 patients with a variety of advanced cancers and at least 10% weight loss (mean = 16%). Of these patients, 71 were treated with 60-mg tablets of hydrazine sulfate, 3 times per day, while 30 were treated similarly with placebo tablets over a 30-day course of treatment. The calculated dose received by treated patients is calculated as

(180 mg/day) ÷ 70 kg = 2.57 mg/kg-day. Only 41 treated and 17 placebo patients were able to complete the repeated evaluations after 30 days. Treatment was discontinued because of "toxic effects" in 10% of hydrazine and 6% of placebo patients. A statistically significant greater percent of treated patients (83%) maintained or increased their weights while 53% of placebo-treated patients did so. Chlebowski et al. (1987) attributed the weight increases among placebo-treated patients to nutritional counseling provided to all study subjects. Table 1 summarizes the side effects of treatment.

Table 1. Percent Cancer Patients Reporting Side Effects[a]

	Hydrazine (180 mg/day)	**Placebo**
No toxic effects	71%	84%
Nausea and vomiting		
Mild	12%	12%
Moderate	5%	0%
Light-headed	17%	6%
Treatment discontinued for toxic effects	10%	6%
Polyneuritis	<1%?	0%?

[a]Chlebowski et al. (1987).

Kosty et al. (1994) randomized patients with Stage IIIB or IV locally advanced (T4) nonsmall-cell lung cancer (NSCLC) and performance status 0 or 1 to receive cisplatin and vinblastine, as well as either hydrazine sulfate 60 mg or placebo three times per day orally (estimated hydrazine dose 2.57 mg/kg-day). There were 266 eligible patients: 135 in the treatment group and 131 in the placebo group. The median survival duration was 7.78 months for the hydrazine sulfate treated group, compared with 7.70 for the placebo group ($p = 0.65$).

Objective response rates were similar for both groups. The hydrazine-treated group had 4% complete responses, 20% partial responses, and 2% regression. The placebo group had 3% complete responses, 23% partial responses, and 2% regression. The major toxicity was severe or life threatening neutropenia, which occurred in 65% of the hydrazine sulfate patients and 63% of the placebo patients. There were no differences between groups in degree of anorexia, weight gain, or loss of overall nutritional status. Sensory and motor neuropathy occurred significantly more often in patients treated with hydrazine sulfate and quality of life was significantly worse in these patients ($p = 0.004$).

Inhalation Exposure

No human studies were located regarding the inhalation toxicity of hydrazine following subchronic or chronic exposure. ATSDR (1997) and ACGIH (2001) describe case reports of the consequences of acute inhalation exposure to hydrazine. Reported effects include respiratory symptoms (pneumonia, tracheitis, and bronchitis), liver and kidney toxicity (necrosis and degeneration), and neurological effects (tremors; poor concentration and memory).
Kao et al. (2007) reported a case of reversible mild hepatotoxicity in a healthy young man following brief inhalation of an unknown concentration of hydrazine vapor. No other human data published subsequent to the data cited by ATSDR assessment have been identified. Cancer mortality studies have been conducted in workers; however, these occupational studies are not reviewed for this PPRTV document because of the existing carcinogenicity assessment for hydrazine on the IRIS database.

Animal Studies

Oral Exposure

Fitzgerald and Shank (1996) treated male Syrian golden hamsters (25−43 per dose group) with hydrazine sulfate in the drinking water at concentrations of 0, 170, 340, or 510 mg/L for 21 months. Water consumption was measured at five randomly selected 10-day intervals and body weights were measured every 5 weeks during the study. Fitzgerald and Shank (1996) used water consumption and body weight measurements to calculate the average dose of hydrazine as the free base (0, 4.2, 6.7, and 9.8 mg/kg-day, respectively). Hamsters were sacrificed if moribund or at end of the study. Three animals from each dose group were killed at 6, 12, 14, 16, 18, 20, and 21 months. Prior to sacrifice, the animals received five intraperitoneal injections of [methyl-^{3}H]-methionine at 30-minute intervals, to measure formation of 5-methylcytosine in DNA. [Methyl-^{14}C]-thymidine also was injected 1 hour prior to sacrifice to measure DNA synthesis. Histopathological examination was performed on the livers of control and treated hamsters.

A decrease in the survival rate was observed in all treated groups as compared to controls (Fitzgerald and Shank, 1996). Survival at 21 months was approximately 70, 40, 0, and <10% in the 0, 4.2, 6.7, and 9.8 mg/kg-day groups, respectively (data estimated from graph). The observed mortality occurred primarily in the second year of the study. At 40 weeks of exposure, survival for all treatment groups was similar to controls. The causes of death were not reported for animals that died during the study. Body weight gains were not notably different from the controls in any treatment group. Clinical signs of toxicity were not discussed. Histopathological evaluation indicated that nonneoplastic liver lesions, including megalocytosis, intranuclear inclusions, bile duct hyperplasia, and foci of cellular alteration, were increased in hamsters as early as around 14 months in the high-dose (9.8 mg/kg) group and 16 months in the 6.7 mg/kg-dose group. Although the incidences of these lesions were not reported,

Fitzgerald and Shank (1996) stated that the total number of lesions per animal was dose-related at 21 months. However, the study authors indicated that no dose-response relationship was apparent for any individual lesion observed during the study. Cell proliferation following cytotoxicity was not observed by Carbon-14 uptake into DNA during the 21-month study exposure period.

Fitzgerald and Shank (1996) also observed liver adenomas and carcinomas in hamsters given hydrazine sulfate. The incidence of liver adenomas was 0/25, 1/30 (3%), 4/43 (9%), and 10/40 (25%) in control, low-, mid-, and high-dose groups, respectively. Hepatocellular carcinoma was reported at incidence rates of 0/25, 0/30, 1/43 (2%), and 3/40 (8%), in control, low-, mid-, and high-dose groups, respectively. Angiosarcomas were seen in two hamsters from the control group and one hamster from the high-dose group, and leukemia was observed in one control animal. Methylated guanine adducts were found in liver DNA beginning at 6 months of exposure. Hydrazine sulfate exposure did not affect the rate of DNA synthesis or cytosine methylation. However, differences were seen in the ratio between these rates, suggesting hypomethylation of liver DNA. Linear regression analysis demonstrated a correlation between hypomethylation and the formation of hepatocellular adenomas and carcinomas.

Liver effects were observed in exposed hamsters in the two highest dose groups (6.7 and 9.8 mg/kg-day); however, the lowest dose (4.2 mg/kg-day) represented a frank effect level (FEL) for this study (Fitzgerald and Shank, 1996), due to the significant mortality observed in all dose groups. The mortality apparently was not secondary to development of tumors, as only one low-dose animal developed a tumor and that was benign (adenoma), only one mid-dose animal had a carcinoma, and the decrease in survival in the high-dose group started well before development of the first tumor in that group (40 weeks decreased survival vs. 52 weeks for adenoma and 76 weeks for carcinoma). A NOAEL could not be determined from this study.

Steinhoff et al. (1990) conducted a chronic drinking water study with hydrazine hydrate (100% purity) in SPF-bred Bor:NMRI mice. Mice (50/gender/group) were exposed to hydrazine concentrations of 0, 2, 10, or 50 ppm (mg/L) for 2 years. Drinking water consumption was measured every 2 days during the first 4 weeks of the study, and once every 4 weeks for the remainder of the study. Steinhoff et al. (1990) calculated an average daily intake of hydrazine for mice in the highest dose group (5 mg/kg-day for males, 6 mg/kg-day for females). Daily dose estimates were not provided for mice exposed to 2 or 10 mg/mL hydrazine. Using reference body weight and drinking water intake rates for $B6C3F_1$ mice with chronic exposure (U.S. EPA, 1988)[1], estimated average daily doses for the 2 and 10 mg/L dose groups are 0.47 and 2.4 mg/kg-day hydrazine for male mice and 0.48 and 2.4 mg/kg-day hydrazine for female mice, respectively. Animals from each treatment group were sacrificed by exsanguination under ether anesthesia and organs weights of the brain, heart, liver, testes, lungs, spleen, kidneys, adrenals, and ovaries were measured. Evaluation of gross changes and histopathological examination were conducted for aorta, eyelids, cecum, colon, duodenum, exorbital lacrimal gland, femur, gall bladder, brain, Harder's gland, urinary bladder, ureter, urethra, skin, heart, testes, pituitary, ileum, jejunum, larynx, bone marrow, head, nasopharyngeal space, liver, lung,

[1]Male $B6C3F_1$ mice 0.037 kg body weight and 0.0088 L/day water ingestion rate; female's 0.035 kg body weight and 0.0085 L/day water ingestion rate.

lymph nodes, stomach, mammary gland, spleen, muscle, epididymis, adrenals, sciatic nerve, optic nerve, kidneys, esophagus, ovaries, oviduct, pancreas, prostate, rectum, spinal cord, seminal vesicles, thyroid, salivary glands sternum, thymus, trachea, uterus, and tongue.

Steinhoff et al. (1990) reported a dose-dependent decrease in water consumption in mice exposed to hydrazine hydrate in their drinking water (data presented graphically). For male mice receiving 0.47, 2.4, or 5 mg/kg-day hydrazine, water consumption was reduced by 2, 27, and 51% of control rates, respectively. Water consumption was reduced by 10, 29, and 59% of controls in females exposed to 0.48, 2.4, or 6 mg/kg-day hydrazine, respectively.

Male and female mice in the highest dose group (5 or 6 mg/kg-day) exhibited clinical signs of toxicity (i.e., ruffled coats, lower vitality) and decreased weight gain beginning at 4 days of exposure and continuing throughout the study (maximal decrease in body weight of approximately 25%, data presented graphically). Steinhoff et al. (1990) reported no further information regarding the incidence or severity of clinical signs of toxicity in the high-dose group. A 5% decrease in weight gain was observed over the course of the study in mice in the 2.4 mg/kg-day dose group. Mice in the 0.47 or 0.48 mg/kg-day dose group had body weights similar to controls, although the female mice did have slight reductions in body weight gains. Steinhoff et al. (1990) reported no clinical signs of toxicity in the mid- or low-dose groups. Hydrazine exposure did not reduce survival in any treatment groups, as compared to controls. No treatment-related effects were observed in organ weights, and macroscopic examination did not yield evidence of organ or tissue damage, or carcinogenicity. Histopathological examination of tissues did not demonstrate hydrazine-related noncancer lesions or neoplastic changes. Reductions in weight gain were small and reductions in water consumption probably were related to palatability. A LOAEL of 5 mg/kg-day and a NOAEL of 2.4 mg/kg-day for hydrazine are derived from this study based on clinical signs of toxicity: ruffled coat, lower vitality, and slightly decreased body weight in male and female mice.

Bosan et al. (1987) gave hydrazine sulfate in drinking water to hamsters for 2 years at 0, 4.6, 8.3, and 10.3 mg hydrazine/kg-day. Negative controls received distilled water only. Body weights were slightly reduced, compared to controls, among treated hamsters only during the first weeks of treatment. Survival data, which was presented only graphically, indicates that all doses reduced survival over time and suggests a dose-response relationship between increasing dose and mortality. Because these survival data were presented only graphically, it is unclear whether the mortality was significantly greater among treated hamsters vs. controls, or whether the apparent dose-response relationship represented a significant trend. Bosan et al. (1987) reported extensive, dose-related necrosis, hypertrophy, and nodular hyperplasia in hamster livers, beginning after 18 months exposure, and extensive dose-related degeneration of hepatic tissue at the conclusion of the 2-year study. Unfortunately, only tumor and metabolite data were presented quantitatively, precluding further analysis of the noncancer data. The graphically presented survival data indicates ~40% mortality among control hamsters, ~45% mortality among 4.6 mg/kg-day hamsters, and ~75% mortality among 8.3 and 10.3 mg/kg-day hamsters, after 2 years exposure. Based on this report, 4.6 mg/kg-day appears to be a LOAEL for liver necrosis, hypertrophy, and nodular hyperplasia.

Biancifiori (1970) administered hydrazine sulfate in water by stomach tube to CBA/Cb/Se mice and golden hamsters. Mice (25−30/gender/group) were given daily doses of 0, 0.14, 0.28, 0.56, or 1.13 mg hydrazine sulfate on 6 days/week for 25 weeks (150 doses). Daily hydrazine dose estimates are calculated to be 0, 0.8, 1.6, 3.2, or 6.5 mg/kg-day for male mice and 0, 0.9, 1.7, 3.4, or 6.9 mg/kg-day for female mice, assuming a mouse body weight of 0.037 kg for males and 0.035 kg for females (U.S. EPA, 1988, using body weight data for $B6C3F_1$ mice) and adjusting for administration on 6 of 7 days/week. Hamsters (23−56/group, male and females combined) were given hydrazine sulfate in 60 daily doses of 0 or 3 mg, 4 days/week for 15 weeks, or 100 daily doses of 2.8 mg, 5 days/week for 20 weeks. Daily hydrazine doses are estimated to be 0, 3.1, or 3.6 mg/kg-day for male and female hamsters, assuming a reference body weight of 0.140 kg (U.S. EPA, 1988; average chronic body weights for male and female golden hamsters) and adjusting for administration either 4 or 5 days/week. Mice and hamsters were examined at natural death or were sacrificed if moribund. The liver, lungs, and various endocrine glands (not further described) were removed and processed for histopathological examination.

Oral administration of hydrazine sulfate resulted in a dose-related increase in the incidence of hepatomas in male mice (3/30, 1/26, 7/25, 12/25, and 15/25 for doses of 0, 0.8, 1.6, 3.2, or 6.5 mg/kg-day, respectively) and in female mice (1/29, 2/25, 16/24, and 15/24 for doses of 0, 1.7, 3.4, or 6.9 mg/kg-day, respectively). Biancifiori (1970) observed reddish-gray nodules were observed upon gross examination of the liver. These nodules often were cystic and filled with blood, and the liver was friable. Biancifiori (1970) also observed lung metastases in four mice treated with the highest dose of hydrazine sulfate. Multiple pulmonary tumors were present in many treated mice (incidence data not reported). Body weights were decreased (1−4 g) in control and treated mice with tumors. Body weight loss was not observed in mice without tumors. Survival time was higher in control and low-dose mice (0.8 mg/kg-day) compared to other dose groups; increased death rates in the higher dose groups were observed primarily among animals with hepatomas. Liver tumors were first observed at 39, 52, and 53 weeks in mice receiving 6.5, 3.2, or 1.6 mg/kg-day hydrazine sulfate, respectively. Noncancer lesions were not reported for mice in this study (Biancifiori, 1970).

Although Biancifiori (1970) observed no tumors in male and female hamsters exposed to hydrazine sulfate, nonneoplastic liver lesions were observed. No difference in the incidence of liver lesions was observed between genders, and combined incidences were reported for males and females. Macroscopic observations noted that livers from treated hamsters were small, grayish-yellow, and hard. Histopathology findings indicated cirrhosis, degeneration, and atrophy of parenchymal cells; increased fibrous connective tissue separating liver lobules; reticuloendothelial cell and bile duct proliferation; and degeneration of the fibrous cells in hyalinized tissue. Reticuloendothelial cell proliferation progressed from small cellular aggregates filling dilated sinusoids to cords of hyperplastic cells deposited in layers covering parenchymal tissue. Focal bile duct proliferation occurred in the fibrous stroma, leading to cystic structures where dilated bile ducts were in proximity to one another. The internal wall of the bile duct was lined with epithelial cells having hyperchromatic nuclei. Table 2 presents the incidence of liver lesions in hamsters from this study (Biancifiori, 1970). Histopathological examination of hamsters dying at different ages provided some information regarding the sequence of changes in the liver. Moderate vascular congestion and a disturbed architecture initially were present, followed by reticuloendothelial cell proliferation and cirrhosis. Hydropic degeneration and pressure atrophy were seen later, accompanied by bile duct proliferation and degeneration of the

fibrous cells of hyalinized tissue. Biancifiori (1970) observed vascular congestion in the respiratory system in treated hamsters (no additional information was provided). No treatment-related effects were seen in the thyroid, ovaries, or adrenals. Survival was drastically reduced in treated hamsters, with 34/56, 0/23, and 3/35 hamsters still alive at 48 weeks for the 0, 3.1, and 3.6 mg/kg-day dose groups, respectively. Treated hamsters bearing liver lesions lost 10−15 g in weight (no further information was reported). A FEL of 3.1 mg/kg-day is derived from this study based on reduced survival (0% at 48 weeks) and the presence of liver lesions (cirrhosis and reticuloendothelial cell proliferation) observed in hamsters given hydrazine sulfate by oral gavage. A NOAEL cannot be determined from this study.

Table 2. Incidence of Liver Lesions in Male and Female Golden Hamsters Given Hydrazine Sulfate by Oral Gavage 4 Days/Week for 15 Weeks (60 Doses) or 5 Days/Week for 20 Weeks, 100 Doses[a]

Effect	Average Daily Dose (mg/kg-day)		
	0	3.1	3.6
Cirrhosis	0/56[b]	14/23 (61%)[c]	27/35 (77%)[c]
Reticuloendothelial cell proliferation	0/56[b]	12/23 (52%)[c]	28/35 (80%)[c]
Bile duct proliferation	0/56[b]	0/23	9/35 (26%)[c]
Degenerative fibrous cells in hyalinized tissue	0/56[b]	0/23	6/35 (17%)[c]
Combined liver lesions	0/56[b]	14/23 (61%)[c]	29/35 (83%)[c]

[a]Biancifiori (1970).
[b]$p < 0.05$ by Cochran-Armitage trend test performed for this analysis.
[c]$p < 0.05$ by Fisher Exact test performed for this analysis.

Bollard et al. (2005) administered single gavage doses of hydrazine hydrochloride in saline solution to groups of 10 male Sprague-Dawley rats and groups of 8 male B6C3F mice. Doses were 0, 100, and 250 mg/kg in mice and 0, 30, and 90 mg/kg in rats. Animals were sacrificed 48 hours and 168 hours postdosing, and histopathological examinations were performed on the liver and kidneys. Urine samples were collected throughout postdose lifespan of the experimental animals and hydrazine metabolites were measured. Low-dose mice exhibited no observed effects, as did high-dose mice sacrificed 7 days postdosing. Kidney effects were observed only among the rats examined 2 days postdosing, with 3 of 5 rats at the low-dose and all 5 at the high-dose exhibiting generally minimal vacuolations and rarefaction of the kidney proximal tubules.

Bollard et al. (2005) observed generally mild lipidosis in periportal and midzonal hepatocytes among 3/4 high-dose mice and all high-dose rats examined 2 days postdosing; only one high-dose rat examined 7 days postdosing exhibited this effect, although it was classified as "moderate" severity. Glycogen vacuolation was observed among 4/5 rats in each of the four experimental groups. Bollard et al. (2005) classified the severity of this effect as "minimal" for all groups except the high-dose group examined 7 days postdosing, which exhibited generally "mild" effects. Among low-dose rats sacrificed 2 days postdosing, 1 of 5 exhibited moderate lipidosis in the midzonal region of the liver and minimal increased mitotic activity. Among the high-dose rats examined 2 days postdosing, 2/5 of exhibited minimal single-cell liver necrosis.

Liver weights among mice were essentially the same among controls and in both dose groups. Bollard et al. (2005) observed consistent liver weights between control and low-dose rats; however, high-dose rats examined 7 days postdosing exhibited notably lower liver weights than rats in other dose groups.

Analysis of urine samples revealed no notable increases in AST and ALT enzymes, which would have been indicative of liver damage in either species. Bollard et al. (2005) noted a number of species differences in metabolites measured in urine. The study authors concluded that the greater magnitude of metabolic effects observed in the rat supported the more pronounced liver pathology in the rat compared to mice, and attributed those differences to a higher activity of N-acetyl transferases in the mice.

Schiller et al. (1979) evaluated the effects of hydrazine on the development of intestinal brush border enzymes by exposing pregnant golden Syrian hamsters to a single oral gavage dose of 260 mg/kg hydrazine hydrate on Day 12 of the 16-day gestation period. Groups of offspring (n = 3) were sacrificed at 1 or 2 days before birth and 3, 4, 10, 17, 24, 25, 53, or 60 days afterbirth. Intestinal tissues were analyzed for brush border enzyme activity; fetal and neonatal animals were evaluated for cleft palate formation. Hydrazine hydrate exposure was shown to alter the pattern of typical enzyme development by decreasing or delaying the peak activity of lactase and sucrase, resulting in lower activity in adult offspring. Postnatal alkaline phosphatase activity was increased in intestinal tissue of offspring following a single oral dose of hydrazine hydrate during gestation. No incidence of cleft palate formation was observed in this study.

To determine whether hydrazine was cytotoxic to prostate cancer tumor cells, Kamradt and Pienta (1998) subcutaneously injected 24 male Copenhagen rats with MAT-LyLu Dunning rat prostate cancer cells. These rats were divided into three groups of eight, which were treated with 0, 2.57, and 3.84 mg/kg-day hydrazine sulfate in drinking water for 14 days. Kamradt and Pienta (1998) chose these doses because the "standard" dose was similar to doses used in human clinical trials and the high dose was 50% higher. One animal in the high-dose group died on Day 4. On Day 14, the researchers sacrificed the animals, excised the prostate tumors, and determined body weights and the size of the tumors by weight and 2-dimensional caliper measurements. Mean tumor weights were 2.44 g among control rats, 2.50 g in the standard dose group, and 2.10 g in the high-dose group. Kamradt and Pienta (1998) reported there was no statistically significant difference in body weights (data not reported) or tumor weights between groups (p = 0.63), based on the paired t-test. Kamradt and Pienta (1998) concluded that hydrazine sulfate was not cytotoxic to prostate cancer cells, confirming their in vitro conclusions using human and rat tumor cells (discussed below).

Inhalation Exposure

Latendresse et al. (1995) conducted acute inhalation studies with hydrazine in male and female Fischer 344 rats and male Syrian golden hamsters. Animals (5 rats/gender/group, 10 hamsters/group) were exposed to anhydrous hydrazine at concentrations of 0 or 750 ppm (982 mg/m^3) for a 1-hour exposure duration, administered only once (acute study), or once per week for 10 weeks (repeated-exposure study). Additional groups of animals (100 rats/gender/group, 100 hamsters/group) were exposed to 0, 75, or 750 ppm (0, 98, or 982 mg/m^3) for 1 hour, once per week, for 10 weeks and were held for 22 to 30 months postexposure prior to sacrifice (cancer study). These exposures are calculated to be, on average, approximately 0, 0.585, and 5.85 mg/m^3 over each week. Animals were weighed weekly before each exposure

and monthly thereafter (for animals that were held during the postexposure period). Groups of animals were sacrificed 24 hours after the first (acute study) and tenth (repeated-exposure study) exposures, or 22 to 30 months after exposure (cancer study). A complete necropsy was performed on all animals that died or were sacrificed during the study. For the acute and repeated-exposure studies, 17 tissues obtained from rats and hamsters were examined for histopathology, including the nose, lung, and liver, which were considered to be potential target tissues. For animals in the cancer study, the nose, larynx, trachea, bronchi, lungs, thyroid (rats only), and colon (hamsters only) were examined histopathologically in the high-dose and control animals. Target tissues that were identified in the high-dose group were also examined in low-dose animals.

During the 10-week exposure period, mean body weights were significantly reduced in the high concentration (weekly average = 5.85 mg/m^3) groups of male and female rats, and in the low exposure (weekly average = 0.585 mg/m^3) groups of female rats only ($p < 0.05$). Latendresse et al. (1995) did not report the magnitude of the decrease in body weight; however, review of the figure illustrating the change in body weight over time suggests that the percent reduction in body weight was very small. Recovery from body weight loss was more rapid in female rats (by 2 weeks postexposure) as compared to male rats (by 38 weeks postexposure). Male hamster body weights were reduced in the high exposure group only, during the exposure period. No treatment-related effects on mortality were observed in rats or hamsters. Nasal lesions were seen after acute exposure to 750 ppm (weekly average = 5.85 mg/m^3) in rats and hamsters. These lesions included bilateral necrosis and exfoliation of transitional, respiratory, and olfactory epithelium in the anterior nasal passages. In rats, the most severely affected regions included the lateral surfaces of the naso- and maxilloturbinates; the medial surface of the maxilloturbinate; and the dorsal and lateral walls of the dorsal lateral, middle lateral, and ventral lateral meatuses. Regions normally covered by transitional and respiratory epithelium were lined with a single layer of simple squamous epithelium. A neutrophilic response was seen in the lamina propria of exfoliated regions. Latendresse et al. (1995) considered this neutrophilic response minimal in rats, but it was more pronounced in hamsters. In both rats and hamsters, necrosis was more predominant in the olfactory epithelium of the anterior nose, while morphology consistent with apoptosis was detected slightly more posterior, suggesting an anterior to posterior severity gradient.

Following repeated exposure to 750 ppm (weekly average = 5.85 mg/m^3) in rats, nasal lesions, including squamous metaplasia, desquamation, necrosis, and apoptosis, occurred in the transitional epithelium covering the margins and the lateral surfaces of the naso- and maxilloturbinates, the dorsal and lateral wall of the lateral meatuses, and the olfactory epithelium lining the roof of the dorsal medial meatus in the anterior nose (Latendresse et al., 1995). Squamous metaplasia of the transitional epithelium and desquamation of metaplastic cells were seen in 6 of 10 rats. Apoptotic cells (i.e., shrunken, hyperchromatic, degenerated cells) were sometimes observed in the metaplastic epithelium along with nucleated squamous cells found adjacent to aggregates of sloughed squamous epithelial cells. Squamous metaplasia of the transitional epithelium was not observed in hamsters exposed to hydrazine. In the olfactory epithelium of both rats and hamsters, dead and degenerating cells were found, consistent with both necrosis and apoptosis. In contrast to the acute exposure findings, apoptosis (9/10) appeared more prevalent than necrosis (3/10) in the olfactory epithelium of the anterior nose. Segmental or patchy depletion of sensory neurons and some sustentacular cells was seen in atrophied areas of the olfactory epithelium covering the roof of the dorsal medial meatus.

Lesions were limited to the nasal cavity in rats and hamsters that were held for 22−30 months after initiation of hydrazine exposure (Latendresse et al., 1995). A low incidence of proliferative nasal lesions, including hyperplasia, adenoma, and carcinoma, was seen in rats and hamsters of both treatment groups; however, the increase in incidence of these lesions was statistically significant relative to controls among males and females exposed to a weekly average concentration of 5.85 mg/m^3. 5.85 mg/m^3 could be considered a LOAEL for averaged acute inhalation exposure to hydrazine, based on nasal lesions in rats and hamsters exposed 1 hour/week for 10 weeks to 750 ppm (982 mg/m^3). However, the extreme nature of the extrapolation from 1 hour to 168 hours per week exposure, suggests this LOAEL has limited applicability to derivation of a p-RfC.

Vernot et al. (1985) and MacEwen et al. (1981) reported results of a chronic inhalation study of hydrazine conducted in rats, mice, hamsters, and dogs. Fischer 344 rats (100/gender/treatment group, 150/gender/control group), C57BL/6 mice (females only; 400/treatment group, 800/control group), Golden Syrian hamsters (males only; 200/group) and beagle dogs (4/gender/group) were exposed to anhydrous hydrazine (99.8% purity) at concentrations of 0.05 (rats and mice only), 0.25, 1.0, or 5.0 ppm (rats and hamsters only) for 6 hours/day, 5 days/week, for a 1-year period (no exposure on weekends or holidays). Duration-adjusted exposure concentrations are 0.0116, 0.058, 0.232, or 1.16 mg/m^3. Chamber hydrazine concentrations were determined using a Technicon Autoanalyzer® proportioning pump and colorimeter and subtracting baseline concentrations of the chamber air 2 hours before introduction of hydrazine, each day. Relative humidity was maintained at 50% ± 10% and temperature at 22°C ± 2°. Animals were maintained under control conditions for postexposure holding times of 12 months for hamsters, 15 months for mice, 18 months for rats, and 38 months for dogs for oncogenic evaluation. An important flaw in this study is that control animals were not housed in the inhalation chambers. Animals were observed hourly during the exposure period and daily thereafter. Body weights of the rats, hamsters, and dogs were measured biweekly during exposure and monthly during the postexposure period. Mice were weighed monthly as cage groups throughout the study. Blood samples were obtained from the great saphenous vein of dogs biweekly during exposure and at 2, 5, 9, 14, 33, 83, 96, 121, and 152 weeks postexposure. Hematology and serum clinical determinations included red blood cell (RBC) count, white blood cell (WBC) count, hematocrit, hemoglobin, sodium, potassium, calcium, glucose, total protein, albumin, globulin, alanine aminotransferase, and alkaline phosphatase. Bromosulphalein retention times also were measured in dogs at bimonthly intervals. Necropsy was performed for all animals that died during the study or at study termination, and tissues (not specified) were prepared for histopathological examination.

Male hamsters were the only animals to experience a significant increase in mortality during the hydrazine exposure period (32−33% for all treatment groups, 19% for controls), as measured by the Fisher's Exact Test performed for this analysis ($p < 0.001$). Deaths were less than 10% in all groups of rats and mice during the exposure period. At study termination, mortality was higher for treated mice (84−87%) as compared to controls (72−79%); however, the increase in mortality was reported not to be dose-related (no further information was provided). All groups of hamsters, including the controls, experienced decreases in body weight during the exposure period (maximum loss of 20 g at 15 months; percentage change was not provided). Body weights recovered following the exposure period for hamsters in the 0, 0.058, and 0.232 mg/m^3 hydrazine groups. Body weights of hamsters in the 1.16 mg/m^3 hydrazine group remained lower than controls until 10 months postexposure. Weight gain for exposed mice and

female rats was similar to control groups during the exposure period, but it was decreased during the postexposure period (20−30 g decrease reported for female rats). Body weights for male rats exposed to 1.16 mg/m^3 hydrazine were reported to be lower than other exposure groups, as well as controls. No further information was reported for effects of hydrazine exposure on body weight. Intermittent increases in alanine aminotransferase were noted beginning at 34 months postexposure for one male dog exposed to 0.232 mg/m^3. This animal was sacrificed at 36 months postexposure for histopathological examination of tissues. Liver changes were characterized as patchy to diffuse clusters of swollen hepatocytes with highly vacuolated cytoplasm. No other clinical chemistry or histopathological effects were observed in dogs exposed to hydrazine in this study (Vernot et al., 1985).

Histopathological examination of tissues revealed no nonneoplastic effects attributable to hydrazine in mice. However, it is important to note that tissues were obtained for analysis 15 months after the termination of exposure (Vernot et al., 1985). Rats were held for 18 months postexposure prior to histopathological examination. In male and female rats exposed to 1.16 mg/m^3 hydrazine, inflammatory changes were observed in the respiratory epithelium and squamous metaplasia was evident in the nose, larynx, and trachea. Degenerative changes also were noted in reproductive tissues of female rats exposed to a weekly average of 1.16 mg/m^3 hydrazine (see Table 3). The primary nonneoplastic change observed in male hamsters examined 1 year after hydrazine exposure was generalized amyloidosis (i.e., accumulation of amyloid protein possibly related to aging), which was present in the liver, kidney, thyroid, and adrenal gland. This change was evident in 6−24% of control hamsters, but the incidence was significantly increased at all hydrazine concentrations tested in this species (see Table 4). The incidences of hemosiderosis and bile duct hyperplasia in liver, lymphadenitis in the lymph nodes, and kidney mineralization were also increased in each hamster exposure group. Adrenal degeneration and senile atrophy of the testis were observed at higher concentrations in hamsters (see Table 4). No consistent clinical or pathological effects were seen in dogs 38 months following cessation of hydrazine exposure.

The histopathology data from this study are limited in their usefulness for evaluating the noncancer health effects of inhalation exposure to hydrazine (Vernot et al., 1985). A lengthy time period elapsed between the 1-year exposure period and the time of necropsy and histopathology evaluation (18 months for rats, 15 months for mice, and 1 year for hamsters). Therefore, the observed histopathological lesions might not reflect reversible noncancer health effects that might have occurred during chronic exposure to hydrazine. Interpretation of these data also is complicated by a high background incidence of certain lesions in control animals, including pulmonary and liver effects in rats, and amyloidosis and liver hemosiderosis in hamsters. Amyloidosis, hemosiderosis, and bile duct hyperplasia were common findings in the livers of unexposed hamsters; Vernot et al. (1985) suggested that the increase in the incidence of these lesions represented a treatment-related acceleration of common aging changes in hamsters. Because histopathological evaluation was not performed for any animals immediately following the exposure period, the data might not be sufficiently sensitive for the determination of a p-RfC for hydrazine. Vernot et al. (1985) observed decreases in body weight and survival in hamsters during the exposure period; however, these effects also were seen in the control group and were not clearly related to treatment.

Table 3. Incidence (Percent) of Nonneoplastic Lesions in Rats Exposed Whole-Body to Airborne Hydrazine 6 Hours/Day, 5 Days/Week, for 1 Year and Observed for 18 Additional Months[a]

Lesion	Average Exposure Concentration[b]				
	Control	0.0116 mg/m^3	0.058 mg/m^3	0.232 mg/m^3	1.16 mg/m^3
Nasal					
Squamous metaplasia					
Males	24/146 (16)	19/96 (20)	24/94 (26)	25/97 (26)	47/99 (47)[c]
Females	28/145 (19)	18/97 (19)	23/98 (23)	24/94 (26)	28/95 (25)
Epithelial hyperplasia					
Males	4/146 (3)	9/96 (9)[c]	3/94 (3)	4/97 (4)	21/99 (21)[c]
Females	3/145 (2)	2/97 (2)	4/98 (4)	5/94 (5)	9/95 (9)[d]
Larynx					
Squamous metaplasia					
Males	2/141 (1)	2/95 (2)	2/91 (2)	3/91 (3)	18/92 (20)[c]
Females	6/138 (4)	2/91 (2)	2/91 (2)	4/91 (4)	14/91 (53)[c]
Inflammation					
Males	14/141 (9)	42/95 (44)[c]	7/91 (8)	14/91 (15)	72/92 (78)[c]
Females	22/138 (16)	11/91 (12)	4/91 (4)	10/91 (11)	48/91 (53)[c]
Trachea					
Squamous metaplasia					
Males	0/145 (0)	0/97 (0)	0/98 (0)	0/95 (0)	10/97 (10)[c]
Females	0/147 (0)	0/96 (0)	0/97 (0)	0/95 (0)	6/98 (6)[c]
Inflammation					
Males	5/145 (3)	17/97 (18)[c]	2/98 (2)	2/95 (2)	52/97 (54)[c]
Females	0/147 (0)	3/96 (3)	1/97 (1)	4/95 (4)[d]	29/98 (30)[c]
Lymph node					
Hyperplasia					
Males	4/149 (3)	5/99 (5)	3/99 (3)	5/98 (5)	5/99 (5)
Females	3/147 (2)	2/97 (2)	4/100 (4)	3/97 (3)	11/98 (11)[c]
Hepatic					
Focal cellular change					
Males	58/149 (39)	39/99 (39)	40/99 (40)	41/99 (41)	42/99 (42)
Females	57/147 (39)	42/97 (43)	36/100 (36)	58/97 (60)[c]	64/98 (65)[c]
Endometritis	8/147 (5)	5/97 (5)	0/100 (0)	6/97 (6)	21/98 (21)[c]
Salpingitis	0/147 (0)	0/97 (0)	0/100 (0)	1/97 (1)	20/98 (20)[c]
Ovarian atrophy	15/147 (10)	13/97 (13)	3/100 (3)	15/97 (15)	22/98 (22)[d]

[a]Vernot et al. (1985).
[b]Exposure concentrations listed were adjusted to reflect average exposure for 24 hrs/day, 7 days/wk, with units converted from ppm to mg/m^3.
[c]Incidence significantly greater than control, $p \leq 0.01$.
[d]Incidence significantly greater than control, $0.01 < p \leq 0.05$.

Table 4. Incidence (Percent) of Nonneoplastic Lesions in Male Hamsters Exposed Whole-Body to Airborne Hydrazine 6 Hours/Day, 5 Days/Week, for 1 Year and Observed for 12 Additional Months[a]

Lesion	Average Exposure Concentration[b]			
	Control	58 µg/m^3	232 µg/m^3	1160 µg/m^3
Liver				
Amyloidosis	42/180 (23)	67/160 (42)[c]	68/148 (46)[c]	79/159 (50)[c]
Hemosiderosis	42/180 (23)	63/160 (39)[c]	77/148 (52)[c]	94/159 (59)[c]
Bile duct hyperplasia	14/180 (8)	31/160 (19)[c]	28/148 (19)[d]	44/159 (28)[c]
Biliary cyst	45/180 (25)	45/160 (28)	42/148 (28)	55/159 (35)[d]
Spleen				
Amyloidosis	39/160 (24)	39/129 (30)	57/130 (44)[c]	60/138 (44)[c]
Lymph nodes				
Lymphadenitis	6/167 (4)	13/143 (9)[d]	17/140 (12)[c]	16/146 (11)[c]
Kidney				
Interstitial amyloidosis	15/179 (8)	19/164 (12)	21/145 (15)	28/160 (18)[c]
Glomerular amyloidosis	39/179 (22)	53/164 (32)[d]	67/145 (46)[c]	77/160 (48)[c]
Mineralization	55/179 (31)	78/164 (48)[c]	51/145 (35)	82/160 (51)[c]
Thyroid				
Amyloidosis	9/155 (6)	20/117 (17)[c]	11/127 (9)	22/137 (16)[c]
Adrenal				
Amyloidosis	38/177 (22)	49/155 (32)[d]	52/141 (37)[c]	76/153 (50)[c]
Degeneration	25/177 (14)	29/155 (19)	26/141 (18)	34/153 (22)[d]
Testis				
Senile atrophy	33/185 (18)	41/160 (26)	40/149 (27)[d]	55/159 (35)[c]
Aspermatogenesis	27/185 (15)	20/160 (13)	18/149 (12)	36/159 (23)[d]
Hypospermatogenesis	33/185 (18)	35/160 (22)	38/149 (26)	41/159 (26)

[a]Vernot et al. (1985).
[b]Exposure concentrations listed were adjusted to reflect average exposure for 24 hrs/day, 7 days/wk with units converted from ppm to µg/m^3.
[c]Incidence significantly greater than control, $p \leq 0.01$.
[d]Incidence significantly greater than control, $0.01 < p \leq 0.05$.

Although no NOAEL or LOAELs can be identified from the Vernot et al. (1985) and MacEwen et al. (1981) data in rats, mice, or dogs, a LOAEL of 0.058 mg/m^3 is identified for several effects showing dose-response trends in male hamsters, including liver, adrenal, and glomerular amyloidosis; liver hemosiderosis; bile duct hyperplasia; and lymphadenitis.

Vernot et al. (1985) also reported tumor pathology findings from this study. The incidence of benign nasal adenomatous polyps was significantly increased in the 1.16 mg/m^3 hydrazine groups of male hamsters (1/181, 0/154, 1/148, and 16/160 for 0, 0.058, 0.232, and 1.16 mg/m^3, respectively) and female rats (0/145, 2/97, 0/98, 2/94, and 28/95 for 0, 0.0116, 0.058, 0.232, and 1.16 mg/m^3, respectively). Among male rats, the incidence of this lesion was significantly increased in both the 0.232, and 1.16 mg/m^3 hydrazine groups (0/146, 2/96, 1/94, 9/97, and 58/98 for 0, 0.0116, 0.058, 0.232, and 1.16 mg/m^3, respectively). The incidence of thyroid carcinoma also was increased in male rats at 1.16 mg/m^3 hydrazine (7/146, 6/96, 5/94, 9/97, and 13/98 for 0, 0.0116, 0.058, 0.232, and 1.16 mg/m^3, respectively). Vernot et al. (1985) reported no other significant tumor findings in rats, mice, hamsters, or dogs from this study.

Haun and Kinkead (1973) conducted a 6-month inhalation study in male Sprague-Dawley rats (50/group), female ICR mice (40/group), male beagle dogs (8/group), and female rhesus monkeys (4/group). Anhydrous hydrazine (97% pure) was administered at continuous inhalation concentrations of 0, 0.2, or 1 ppm (0, 0.26 or 1.3 mg/m^3); or 0, 1, or 5 ppm (0, 1.3, or 6.5 mg/m^3) for 6 hours/day, 5 days/week. The 6 hours/day-5 days/week exposures are calculated to be equivalent to duration-adjusted weekly average concentrations of 0, 0.232, or 1.16 mg/m^3. Hydrazine concentrations were verified in the Thomas Domes that housed the animal chambers, using an AutoAnalyzer® described by Geiger (1967). Haun and Kinkead (1973) indicated only that temperature and humidity were automatically controlled, without specifying the levels. The body weights of dogs, monkeys, and rats were measured every 2 weeks throughout the study. Mice were not weighed. Bone marrow samples were obtained for analysis of the myeloid to erythroid ratio in five rats per group that were sacrificed at 8, 16, and 24 weeks of exposure. Blood samples were also obtained from these rats for hematocrit, hemoglobin, and red blood cell (RBC) determinations. Bone marrow samples from four dogs per group were examined at the end of the study. Blood samples were obtained from all monkeys and four dogs per group biweekly during the first month of the study and monthly thereafter. Hematology measurements included hematocrit, hemoglobin, RBC, white blood cell (WBC), differential, and reticulocyte counts. Clinical chemistry measurements included sodium, potassium, cholesterol, calcium, inorganic phosphorous, total bilirubin, albumin/globulin, total protein, blood urea nitrogen (BUN), glucose, creatinine, chloride, triglycerides, and alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase activities. Ten rats and mice from each exposure group were maintained until natural death and were evaluated for formation of tumors. Two dogs from each of the two highest exposure groups and control group were allowed to live 6 weeks postexposure, when blood samples were obtained for hematology and clinical chemistry analysis. Pathological evaluations (not further described) were performed on animals that died during the study or were sacrificed at study termination.

Body weights were reduced in all rat groups exposed to hydrazine (Haun and Kinkead, 1973), except the 0.26 mg/m^3 continuous exposure group. Body weights returned to control levels by 2 weeks following exposure, except for rats in the 1.16 mg/m^3 exposure group. Survival was not reduced in rats exposed to hydrazine, and no treatment related changes in hematology, clinical chemistry, myeloid to erythroid ratios in bone marrow, or organ weights were observed. Significant histopathological changes were not seen in rats exposed to 0.26 or 1.3 mg/m^3 hydrazine (continuous exposure or 6 hours/day, 5 days/week). Chronic broncho-pneumonia was observed in 19 of 30 rats exposed to 6.5 mg/m^3 hydrazine. Haun and Kinkead (1973) indicated that it was not clear whether this effect was a result of

hydrazine exposure or the presence of bacterial pathogens. However, bronchopneumonia was not seen in the control rats or the rats exposed to 0.26 or 1.3 mg/m^3 hydrazine. Bronchopneumonia contributed to reduced survival in the postexposure period (6−8 weeks after exposure) of rats exposed to 6.5 mg/m^3.

Clinical signs of toxicity observed in mice included lethargy and rough, yellow fur, during the first few weeks of exposure. Mice were not evaluated for changes in body weight, organ weight, hematology, or clinical chemistry. Hydrazine exposure reduced survival in mice, with 2.5% and 55% mortality among mice continuously exposed to 0.26 and 1.3 mg/m^3 hydrazine, and 7.5 and 35% mortality in mice exposed to 0.232 and 1.16 mg/m^3 averaged for 6 hours/day, 5 days/week, respectively. The mortality incidences reported for the 0.26 mg/m^3 continuous exposure group (1/40) and the group exposed to 0.232 mg/m^3 averaged for 6 hours/day, 5 days/week (3/40), were not significantly different from controls (0/40), according to results of Fisher Exact tests performed for this analysis. The majority of deaths occurred during the first 2−3 weeks of exposure. No mortality was observed in the controls during the 6-month study. Pathological examination of exposed mice following the 6-month exposure period revealed moderate to severe fatty liver changes in all hydrazine-treated groups. Haun and Kinkead (1973) suggested that hepatotoxicity was the cause of the excess mortality seen in mice, although the incidence of liver lesions in control and hydrazine-treated groups was not provided.

Dogs exposed to a continuous concentration of 1.3 mg/m^3 hydrazine were noticeably emaciated and one dog from this group experienced tonic seizures on three separate occasions. The body weights of dogs exposed continuously to 0.26 mg/m^3 hydrazine or to 0.232 mg/m^3 averaged for 6 hours/day, 5 days/week, were similar to controls. Significant weight loss was observed in dogs exposed continuously to 1.3 mg/m^3 hydrazine (2-kg mean weight loss at 6 weeks) or to 1.16 mg/m^3 averaged for 6 hours/day, 5 days/week (maximum loss of 0.75 kg at 4 weeks). Body weights returned to control levels by 2 weeks following exposure in dogs that were held for observation (two per group). Two of eight dogs in the 1.3 mg/m^3 continuous exposure group died following 16 weeks of exposure. Mild to moderate hematological effects, including decreased hematocrit, hemoglobin, and RBC counts, were observed in dogs exposed to 1.3 mg/m^3 hydrazine for 24 hours/day or 1.16 mg/m^3 averaged for 6 hours/day for 5 days/week. Slightly decreased myeloid to erythroid ratios, indicative of erythropoietic activity, were seen in the bone marrow from dogs exposed continuously to 1.3 mg/m^3 hydrazine. Pathological examination showed fatty livers in dogs exposed to 1.3 mg/m^3 hydrazine for 24 hours/day or 1.16 mg/m^3 averaged for 6 hours/day for 5 days/week. No central nervous system (CNS) lesions were observed in the brain of the dog that experienced seizures during exposure. Hematocrit, hemoglobin, and RBC counts returned to control values by 2 weeks postexposure in dogs held for observation (two per group); no histopathological lesions were reported in these animals. No changes in hematologic parameters or histopathology were seen in dogs exposed to 0.26 mg/m^3 for 24 hours/day or 0.232 mg/m^3 averaged for 6 hours/day, 5 days/week. Organ weights did not differ from controls in any hydrazine exposure group (Haun and Kinkead, 1973).

Haun and Kinkead (1973) observed minimal eye irritation in monkeys exposed to 1.3 mg/m^3 continuously or to 1.16 mg/m^3 averaged for 6 hours/day, 5 days/week. No significant changes in survival or body weights were observed following hydrazine exposure in monkeys.

Hematology and clinical chemistry values were reported as normal throughout the study. Slight to moderate fat accumulation was observed in the livers of exposed monkeys; however, control monkeys also showed some degree of fatty liver change.

Table 5 summarizes LOAELs and NOAELs for various endpoints and species. LOAELs of 0.26 mg/m^3 (continuous exposure) and 0.232 mg/m^3 (averaged from 1.3 mg/m^3 6 hours/day for 5 days/week) are derived from this study based on fatty liver changes in mice. An overall NOAEL was not derived from this study (Haun and Kinkead, 1973).

Table 5. 6-Month Noncancer NOAELs and LOAELs in mg/m^3 for Airborne Hydrazine[a]

Species	Concentration	Continuous Exposure NOAEL	Adjusted[b] Intermittent NOAEL	Continuous Exposure LOAEL	Adjusted[b] Intermittent LOAEL	Effect
Male Sprague-Dawley rats	0, 0.2, or 1 ppm (continuous exposure)	0.26	NA	1.3	0.232	Decreased body weight
Female ICR mice	0, 0.2, or 1 ppm (continuous exposure)	NA	NA	0.26	0.232	Moderate to severe fatty liver changes; reduced survival at 1 ppm
Male beagle dogs	0, 0.2, or 1 ppm (continuous exposure)	0.26	0.232	1.3[c]	1.16	Decreased body weight, fatty liver, hematological changes[c]
Rhesus monkeys	0, 0.2, or 1 ppm (continuous exposure)	0.26	0.232	1.3	1.16	Minimal eye irritation

[a]Haun and Kinkead (1973).
[b]6 hours/day, 5 days/week exposure, averaged over 24 hrs/day, 7 days/week.
[c]Two of eight dogs died when continuously exposed to 1.3 mg/m^3.

Comstock et al. (1954) conducted a series of experiments on the inhalation toxicity of hydrazine in female mice (strain unspecified), male Wistar rats, and male beagle dogs. Inhalation chamber concentrations were calculated and determined analytically using samples of chamber air. Measured concentrations were 25−179 times lower than calculated estimates. Comstock et al. (1954) attributed the difference to adsorption of hydrazine vapor on the walls of the chamber, as well as on the animals themselves. Initial inhalation experiments using high concentrations were terminated early, after 5 or 13 exposures, due to significant mortality in mice and rats.

Comstock et al. (1954) performed a subsequent 6-week inhalation study using average daily measured concentrations of 0 or 26 mg/mg^3 (20 ppm) hydrazine (range 2−55 mg/mg^3; 2−42 ppm). Rats (10−13/group) and mice (10/group) were exposed 6 hours/day, 5 days/week for 6 weeks. Body weights were measured 3 times/week in exposed animals and 2 times/week in controls. Pathological examinations (details not provided) were performed on animals that died in the chamber or shortly after exposure, as well as on occasional randomly selected animals.

Comstock et al. (1954) reported no behavioral or general health issues among the treated animals during the study, although treated animals lost weight during the study. The study authors indicated that the total weight loss in rats was in the range of 30−60 g, but they did not provide further information. By study termination, 11/13 rats and 7/10 mice had died. All mice died between the 11th and 14th exposure. The first rat died during the 13th exposure, and other deaths occurred intermittently throughout the remainder of the study. Histopathology evaluation revealed pulmonary effects, including edema and "patchy, localized damage" to the bronchial mucosa and fatty changes of the liver. The incidence of these effects was not reported for any group.

Comstock et al. (1954) conducted two subchronic experiments in a variety of mammals, including dogs, rats, mice, and guinea pigs. Blood and urine were collected from the dogs weekly, immediately after an exposure period. Blood samples were analyzed for specific gravity, erythrocyte and leukocyte count, differential leukocyte count, platelet count, hemoglobin, sedimentation rate, and hematocrit. Serum chemistry analyses consisted of chloride, bicarbonate, sugar, urea, potassium, sodium, cholesterol, calcium, phosphorus, and plasma protein. Urine was tested for pH, specific gravity, sugar, albumin, and microscopic examination of sediment.

In the first experiment, Comstock et al. (1954; Comstock and Oberst, 1952) exposed 2 dogs and 20 rats to 6 mg/m^3 (5 ppm) hydrazine (purity unspecified) 6 hours/day, 5 days/week, for 31 weeks. One dog and 10 rats served as controls. Both dogs lost weight (16 and 29% of original body weight) and suffered periodic loss of appetite throughout the experiment. After 11 weeks exposure, progressive increases in muscle tremors, weakness, fatigue, and vomiting that accompanied the loss of appetite were noted. Hematology evaluation revealed mild hypoglycemia and an increased count of stab cells (immature neutrophils). Autopsies revealed grossly visible areas of emphysema and atelectasis in the treated dogs' lungs, and hypertrophy of the bronchiolar musculature (details not provided). No changes were observed in the control dog. Treated rats did not experience body weight changes when compared with control rats, but they were lethargic after the 23rd week. Two rats died during the 28th week. Autopsies of two other rats at study termination showed interstitial pneumonitis and a few areas of alveolar emphysema. The six remaining rats were maintained for 6 months and then subjected to pathological examination; the lungs of these and the control animals were normal. Comstock et al. (1954; Comstock and Oberst, 1952) reported that, based on the autopsies, effects were limited to the lungs in both dogs and rats. The 6 mg/m^3 concentration in this study is a FEL for mortality in rats, and for severe body weight reductions and clinical signs in dogs.

In the second experiment, Comstock et al. (1954) exposed 4 dogs, 30 rats, 20 mice, and 10 guinea pigs to 18 mg/m^3 (14 ppm) hydrazine 6 hours/day, 5 days/week, for up to 6 months. Two control dogs were noted, but controls for the other species were not reported. According to the report, the mice were exposed 24 times (approximately 5 weeks) and survivors were autopsied. Loss of appetite in the dogs led the researchers to substitute more palatable foods and even to force feed the animals. The dogs experienced vomiting, decreased food consumption, fatigue and anorexia, as well as tremors (1/4). One of the dogs was force-fed, and another was given a diet of raw horse meat through much of the exposure period. Two dogs died prior to sacrifice—one during Week 3 and one during Week 15 of exposure; the remaining two apparently survived until study termination, about 39 weeks. Hematology findings suggested anemia, with reduced erythrocyte count and hemoglobin; in one dog, the hemoglobin dropped

from 16.1 to 9.9 g/100 cc. In one of the dogs that died prematurely during a seizure, the lungs were congested and the kidneys were observed to contain "healed infarcts," with blood in the tubules and swelling of glomerular cells. Comstock et al. (1954) suggested that the latter effects might not have been treatment-related. Autopsy of the two surviving dogs revealed pigmentation (believed by the authors to be hemosiderin) in the Kupffer cells and spleen, as well as vacuolation in the Kupffer cells. Among the rats, mice, and guinea pigs, mortality was the primary endpoint noted, in addition to lethargy in the rats. Over 139 exposures (about 28 weeks), 23/30 rats, 15/20 mice and 8/10 guinea pigs died; Comstock et al. (1954) reported that no control animals died, but the number and species of control animals were not reported. The five surviving mice were autopsied at study termination, and no pathological findings were noted.

Each of the studies described by Comstock et al. (1954) suffered from serious limitations: high variability in the chamber concentrations, limited information on study implementation and findings, variability in the diets among dogs, and significant clinical signs of toxicity and high mortality among all tested species. Further, there is significant uncertainty in the hydrazine doses received by the animals given the potential oral exposure to adsorbed hydrazine via grooming. The study limitations preclude the identification of effect concentrations from these data.

Other Studies

Intraperitoneal injection studies evaluated the hepatotoxicity of hydrazine (Timbrell et al., 1982; Scales and Timbrell, 1982). Sprague-Dawley rats (number/group not given) were injected with hydrazine hydrate (0, 10, 20, 30, 40, 50, or 60 mg/kg). Some animals received prior treatment with phenobarbital (75 mg/kg for 3 days), piperonyl butoxide (500 mg/kg, single injection 30 minutes prior to the hydrazine dose), or diethyl maleate to (400 mg/kg, single injection given 45 minutes prior to the hydrazine dose). These pretreatments were given to evaluate the importance of oxidative metabolism (induced by phenobarbital and inhibited by piperonyl butoxide) and glutathione conjugation (depletion of glutathione by diethyl maleate) to the liver toxicity of hydrazine. Animals were sacrificed at various times after hydrazine dosing. Gross examination of the abdominal and thoracic viscera was accomplished, and the liver and kidneys were removed, weighed, and prepared for evaluation by light and electron microscopy. Hepatic triglycerides and reduced glutathione were determined in liver homogenates. Hydrazine metabolism was determined in liver microsomes from treated rats.

Marked hepatocyte vacuolation, with no evidence of necrosis, was observed by light microscopy 24 hours after a single hydrazine dose of 40−60 mg/kg. Fine periportal or midzonal vacuolation was seen at 20 mg/kg but was not detected in rats given 10 mg/kg. Ultrastructural changes were observed in the liver and kidney at doses of 20 mg/kg and above. Numerous lipid vacuoles, mitochondrial swelling, and an increase in the number of microbodies associated with mitochondria were observed in hepatocytes and proximal tubule cells. Liver effects were fairly rapid, with lipid droplet accumulation and mitochondrial swelling occurring within 30 minutes of dosing. Hydrazine produced a dose-related increase in relative liver and kidney weight and hepatic triglyceride content, and a dose-related decrease in hepatic reduced glutathione content, measured 24 hours after dosing. Phenobarbital-pretreated animals showed less lipid vacuolation after hydrazine dosing and a decrease in hepatic triglyceride accumulation, as compared to nonpretreated rats. Pretreatment with piperonyl butoxide lowered the dose threshold for hydrazine. Fatty vacuolation was observed at 10 mg/kg in pretreated rats; an increase in the

severity of this effect was observed in rats given 20 mg/kg hydrazine, as compared to nonpretreated rats. Liver weights also were increased in piperonyl butoxide pretreated rats. These results suggested that the parent compound, and not a metabolite, may be responsible for the liver toxicity of hydrazine. Depletion of glutathione by pretreatment with diethyl maleate did not affect hydrazine liver toxicity.

Hepatic gene expression and lipid homeostasis were studied in C57Bl/6 mice exposed to a single oral dose of 0, 100, or 300 mg/kg hydrazine (99.7% purity) in saline solution (Richards et al., 2004). The highest dose of hydrazine (300 mg/kg) caused a 10-fold increase in plasma alanine aminotransferase (ALT) activity and produced hepatic necrosis, macrovesicular degeneration (the presence of lipid vacuoles), and steatosis. Lipid accumulation in the liver increased over time with a significant increase in lipid droplets, beginning at 2 hours after dosing. Macrovesicular degeneration was evident by 4 hours and increased in severity until 24 hours after dosing. After 24 hours, the presence of cytoplasmic vacuoles decreased and diffuse necrosis was observed. No changes in liver histopathology were observed at 100 mg/kg; however, plasma ALT activity was increased by approximately 50% (estimated from graph). The gene expression profile was evaluated 24 hours after a single oral dose of 100 mg/kg hydrazine. Hydrazine altered the hepatic expression of many genes, including those related to lipid transport, synthesis, and metabolism.

Toth (1993) reviewed several developmental toxicity studies that evaluated the effects of gestational exposure to hydrazine. Embryo lethality was observed in pregnant Wistar rats injected subcutaneously with 8 mg/kg-day hydrazine throughout gestation. Pregnant ICR mice were given intraperitoneal injections of hydrazine at doses of 4, 12, 20, 30, and 40 mg/kg-day on gestational days (GD) 6, 7, 8, and 9. Anomalies were seen at all doses, although Toth (1993) reported that the incidence of these changes was not significant at lower doses (no further information was provided). Anomalies included exencephaly, hydronephrosis, anophthalmia, and microphthalmia, hypoplasia of testes, undescended testes, cleft palate, supernumerary ribs, short ribs, and bipartite centrum.

Hydrazine administered to pregnant Fischer 344 rats by intraperitoneal injection or percutaneous exposure at doses of 0, 2.5, 5, 10, or 50 mg/kg-day on GD 6−15 resulted in a dose-related increase in litter mortality. Fetal weight loss was also seen in some dose groups. Several anomalies were observed in this study—including anophthalmia, supernumerary ribs, fused ribs, delayed ossification, hydronephrosis, hydrocephalus, and dilation of brain ventricles and right side of aorta. No further information was provided regarding these studies in the review by Toth (1993). A review by Keller (1988) suggested that hydrazine embryotoxicity occurred concurrently with maternal toxicity.

Vivekanandan et al. (2007) reported increased triglyceride, cholesterol, free fatty acids, and total lipids in both the plasma and liver tissue of rats accompanied by a fall in phospholipids (PL) in the liver tissue 24 hours after i.p. administration of 50 mg hydrazine/kg. Hydrazine treatment also caused an increase in the mobility of triglyceride and total lipids from adipose tissue.

Kamradt and Pienta (1998) tested the in vitro toxicity of hydrazine sulfate in cell cultures of LNCaP and PC-3 human prostate cancer cells and MAT-LyLu Dunning rat prostate cancer cells, using five concentrations of hydrazine sulfate, ranging from 200 nM to 1 M, plus a control culture. The human cell types were chosen to represent androgen-sensitive and androgen-resistant human prostate cancer cells. The study authors concluded that hydrazine sulfate demonstrated no growth inhibition in any of the three cell lines examined, at any of the five tested concentrations.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC RfDs FOR HYDRAZINE

The human oral exposure data for hydrazine are limited. Several uncontrolled studies with cancer patients (Filov et al., 1995; Gold, 1975; Gershanovich et al., 1981) reported tumor regression, suggesting cytotoxic effects. However, other studies that included placebo-treated control groups (Chlebowski et al., 1990; Kosty et al., 1994, 1995; Loprinzi et al., 1994a,b) as well as uncontrolled studies (Lerner and Regelson, 1976; Ochoa et al., 1975; Spremulli et al., 1979; Strum et al., 1975) have demonstrated no effects on tumors, suggesting that hydrazine is not cytotoxic. Authoritative data summaries (ACS, 1976; Kaegi, 1998; Vickers, 2004; UT, 2007) have concluded that hydrazine sulfate might not be significantly cytotoxic to cancer tumors. The conclusion of lack of cytotoxicity is supported by the results of Kamradt and Pienta (1998), which demonstrated no oral hydrazine treatment-related effects on body weight or prostate cancer tumor size in rats, and no effect in vitro on human or rat prostate cancer cells. However, human cancer patients treated with hydrazine sulfate at daily doses of 180 mg/day experienced gastrointestinal (Lerner and Regelson, 1976) or neurological (Kosty et al., 1994; Hainer et al., 2000; Loprinzi et al., 1994a) side effects, including lethargy, nausea, vomiting, dizziness, excitement, insomnia, and polyneuritis (Chlebowski et al., 1984; Filov et al., 1995; Gershanovich et al., 1981; Ochoa et al, 1975; Spremulli et al., 1979). In a case report, Hainer et al. (2000) described a cancer patient who died following 4 months self-administration of 180 mg/day hydrazine sulfate. Although Gershanovich et al. (1981) and Filov et al. (1995) reported that symptoms disappeared at a lower dose (120 mg/day), dose durations were not specifically associated with effects and no control groups were reported.

Table 6 summarizes results from the two chronic drinking water studies and one subchronic oral gavage study available for hydrazine (Fitzgerald and Shank, 1996; Steinhoff et al., 1990; Biancifiori, 1970). Based on these data, and the inhalation data (Vernot et al., 1985; Haun and Kinkead, 1973), the liver appears to be the primary target organ for hydrazine in laboratory animals. Liver lesions, including megalocytosis, intranuclear inclusions, bile duct hyperplasia, and foci of cellular alteration, were increased in hamsters given 6.7 and 9.8 mg/kg-day hydrazine (as sulfate) in their drinking water (Fitzgerald and Shank, 1996). Biancifiori (1970) noted cirrhosis of the liver and reticuloendothelial cell proliferation in hamsters given approximately 3 mg/kg-day hydrazine (as sulfate) in a subchronic oral gavage study. The authors of both studies observed significant mortality at or below doses that caused liver effects (Fitzgerald and Shank, 1996; Biancifiori, 1970), indicating that the lowest dose in each study was a FEL. Noncancer lesions were not reported for mice in the subchronic oral gavage study (hydrazine given 6 days/week for 25 weeks); however, liver tumors were seen in male and female mice at doses >3 mg/kg-day (Biancifiori, 1970).

Table 6. Noncancer Effects Reported in Oral Toxicity Studies for Hydrazine

Species	Dose/Duration	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Effect	Reference
Male Syrian golden hamsters	Sulfate 21 month drinking water study; 0, 4.2, 6.7, and 9.8 mg/kg-day	NA	4.2 (FEL)	Mortality in all dose groups; liver lesions at doses ≥6.7 mg/kg-day	Fitzgerald and Shank, 1996
SPF-bred NMRI mice (Bor:NMRI strain)	Hydrate 2 year drinking water study; 0, 0.47, 2.4, or 5 mg/kg-day (males) 0, 0.48, 2.4, or 6 mg/kg-day (females)	2.4	5	Clinical signs (ruffled coat, lower vitality), slightly decreased body weight	Steinhoff et al., 1990
Golden hamsters	Sulfate oral gavage study; 0, 3.1 mg/kg-day (4 days/week for 15 weeks), or 3.6 mg/kg-day (5 days/ week for 20 weeks)	NA	3.1 (FEL)	Reduced survival; liver toxicity (cirrhosis and reticuloendothelial cell proliferation)	Biancifiori, 1970
Human cancer patients[a]	Sulfate 0.43−1.29 mg/kg-day intermittently for 2.5 to 60 months	0.86	1.29	lethargy, nausea, vomiting, dizziness, excitement, insomnia, polyneuritis	Gershanovich et al., 1981; Filov et al., 1995

[a]Doses averaged over 24 hours/day, 7 days/week for entire dosing period using assumptions discussed in the text.

The results of the drinking water study of hydrazine hydrate in mice (Steinhoff et al., 1990) suggest that mice might be less sensitive than hamsters to hydrazine-induced hepatotoxicity and mortality. Chronic doses of 4.2 mg/kg-day have been associated with significant mortality in hamsters (Fitzgerald and Shank, 1996). However, a dose of 5 mg/kg-day in mice did not reduce survival or cause liver toxicity, although Steinhoff et al. (1990) reported clinical signs and markedly reduced body weight. Lower toxicity in the mouse drinking water study might have been related to species differences in sensitivity or the use of hydrazine hydrate in the mouse study (Steinhoff et al., 1990) as compared to use of hydrazine sulfate in the hamster studies. The Bollard et al. (2005) acute gavage study indicates that rats may be more sensitive than mice and proposes a metabolic rationale for this species difference.

Experimental animal ingestion data do not support the derivation of p-RfDs because the LOAELs for hydrazine sulfate reported in the most sensitive species (hamsters) are for frank effects—including increased mortality in all dose groups (as low as 3.1 mg/kg-day [Biancifiori, 1970])—with no NOAELs identified. Data in mice indicate a NOAEL for hydrazine hydrate of 2.4 mg/kg-day with a LOAEL of 5 mg/kg-day for various clinical signs and

slightly decreased body weight (Steinhoff et al., 1990). Use of the oral mouse NOAEL data for hydrazine hydrate is rejected because increased mortality was reported in hamsters at similar doses of hydrazine sulfate and there is no evidence that mice might be more representative of humans. Steinhoff et al. (1990) reported the only chronic data for hydrazine hydrate, and this study was conducted only in mice. Thus, it is difficult to compare the toxicity of the hydrate in mice with that of the sulfate in hamsters. However, because studies of the sulfate reported tumors in rats and mice exposed to similar doses and no such tumors have been reported in mice exposed to the hydrate, it might be a less toxic form of hydrazine.

The data from human cancer patients (Chlebowski et al., 1984, 1990; Filov et al., 1995; Gershanovich et al., 1981; Gold, 1975; Hainer et al., 2000; Kosty et al., 1994; Lerner and Regelson, 1976; Strum et al., 1975; Loprinzi et al., 1994a,b; Ochoa et al., 1975; Spremulli et al., 1979) also do not support provisional value derivation because each study contained one or more of the following flaws:

- The study did not provide details regarding the specific treatment durations of patients reporting side effects or were only 30 days duration.
- The study reported no control groups.
- The study reported only one treatment group.
- The patients were treated concurrently with other toxic chemotherapeutic agents.

Although the liver is the key target organ following inhalation (see Haun and Kinkead, 1973; Vernot et al., 1985) as well as ingestion exposure in animals (Fitzgerald and Shank, 1996; Biancifiori, 1970) and humans (Hainer et al., 2000; Kao et al. 2007), insufficient data are available to extrapolate from the inhalation data to derive oral toxicity values. No oral toxicity values are derived in this document because data for hydrazine sulfate in hamsters identify only FELs, and mouse data for hydrazine hydrate demonstrate a NOAEL that is similar to the hamster FELs for the sulfate. However, Appendix A of this document contains a "screening value" based on the human data, which may be useful in certain instances. Please see the attached Appendix A for details.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC RfCs FOR HYDRAZINE

Acute inhalation exposure to hydrazine in humans has produced respiratory symptoms, including pneumonia, tracheitis, and bronchitis; liver and kidney necrosis and degeneration; and neurological effects, including tremors, poor concentration, and memory loss (Kao et al., 2007; ACGIH, 2001; ATSDR, 1997). These case reports do not provide quantitative exposure information necessary for derivation of a p-RfC. Four animal inhalation studies evaluated the effects of hydrazine exposure in rats, mice, hamsters, dogs, or rhesus monkeys. The observed effects include nasal lesions in rats and hamsters (Latendresse et al., 1995; Vernot et al., 1985), liver toxicity in hamsters, mice (Vernot et al., 1985; Haun and Kinkead, 1973), and monkeys (Haun and Kinkead, 1973), amyloidosis in multiple organs as well as bile duct hyperplasia and lymphadenitis in hamsters (Vernot et al., 1985), kidney mineralization in hamsters (Vernot et al., 1985), and mild hematologic effects in dogs (Haun and Kinkead, 1973). At high

concentrations, airborne hydrazine exposures caused significant reduction in body weight, clinical signs of toxicity, and reduced survival (Latendresse et al., 1995; Vernot et al., 1985; Haun and Kinkead, 1973; Comstock et al., 1954).

Comstock et al. (1954) used single exposure groups with high concentrations of hydrazine. The methodological limitations of this study preclude its use for development of a p-RfC. The data from Latendresse et al. (1995) are not useful for the determination of p-RfCs because animals were exposed for only 1 hour/week for 10 weeks. The histopathology data from Vernot et al. (1985) are difficult to interpret due to the length of time between the 1-year exposure period and the necropsy and histopathology evaluation (18 months for rats, 15 months for mice, and 1 year for hamsters). In addition, interpretation of these data is complicated by a high background incidence of most histopathological lesions in control animals (i.e., pulmonary and liver effects in rats, amyloidosis, and liver hemosiderosis in hamsters). Table 4 summarizes these data. Table 5 summarizes the data from Haun and Kinkead (1973).

Both Haun and Kinkead (1973) and Vernot et al. (1985) are considered for use as the critical study to determine the subchronic and chronic p-RfCs. Although monkeys were the species most relevant to humans, these Haun and Kinkead (1973) data are not used to derive a p-RfC because the very small number of monkeys tested (4/group) provided insufficient statistical power to identify an effect level with confidence. The Haun and Kinkead (1973) data indicate a 6-month LOAEL of 0.26 mg/m^3 from continuous exposure for fatty liver changes among female mice, and a LOAEL of 0.232 mg/m^3 averaged from 6 hours/day for 5 days/week exposure. The latter airborne concentration also was a LOAEL for body weight reduction among male rats. The Vernot et al. (1985) data indicate a 1-year LOAEL of 0.058 mg/m^3, averaged from 6 hours/day for 5 days/week exposure, for multiple liver effects in male hamsters.

Hydrazine causes liver toxicity, especially indicated by amyloidosis and hemosiderosis, which are sensitive indicators of liver damage. Examples of reported liver toxicity caused by hydrazine include the following:

- Haun and Kinkead (1973) demonstrated fatty liver changes among mice following inhalation exposure.
- Comstock et al. (1954) observed hemosiderin and vacuolation in the Kupffer cells of dogs exposed via inhalation.
- Fitzgerald and Shank (1996) reported increases in megalocytosis, intranuclear inclusions, bile duct hyperplasia, and foci of cellular alteration among hamsters exposed to hydrazine sulfate via drinking water.
- Biancifiori (1970) demonstrated liver cirrhosis and reticuloendothelial cell proliferation among hamsters exposed to hydrazine sulfate via gavage.
- Timbrell et al. (1982) and Scales and Timbrell (1982) demonstrated fatty liver changes among rats following a single intraperitoneal injection of hydrazine hydrate.
- Kao et al. (2007) reported a case of reversible, mild hepatotoxicity in a healthy young man following brief inhalation of an unknown concentration of hydrazine vapor.
- Hainer et al. (2000) reported that a cancer patient who had orally self-administered hydrazine sulfate 180 mg/day for four months, developed hepatic encephalopathy, as well as renal failure and profound coagulopathy, leading to death.

Although these liver effects were observed at a fairly high incidence among control animals, apparently a function of animal ages, these data exhibit clear concentration-response relationships even after 1 year without exposure. Less clear, but reasonable, concentration-response relationships also have been observed for bile duct hyperplasia and lymph node inflammation.

Vernot et al. (1985) is chosen as the critical study, despite the shortcomings noted above, because it identifies a lower adjusted inhalation LOAEL for several potential endpoints in male hamsters and because the adversity of the liver endpoints it described are supported by results of other studies. Additionally, the data presented by Vernot et al. (1985) exhibits a dose-response relationship following 1 year of exposure for bile duct hyperplasia, and for hemosiderosis and amyloidosis in the liver (see Table 4).

Appendix B summarizes benchmark concentration (BMC) analyses on the incidence data for amyloidosis and hemosiderosis in the liver, and for bile duct hyperplasia. The data for bile duct hyperplasia and for hemosiderosis and amyloidosis in the liver are chosen for modeling because they exhibit the clearest concentration-response relationships following 1 year of exposure (see Table 4). Data from all BMC models for the incidence of bile duct hyperplasia exhibit a significant lack of fit ($p < 0.1$; see Table B-1). Therefore, a BMC and BMCL for this endpoint could not be determined. Although the unrestricted Probit model of the log-transformed amyloidosis data provides the best fit statistics (see Tables B-2 and B-3), the $BMCL_{10}$ it calculates is less than zero, and visual inspection of the curve indicates that it is superlinear (see Figure B-1). When applied to log-transformed hemosiderosis data, the unrestricted Probit model provides very good fit statistics (see Table B-4). However, the BMC_{10} it calculates is more than 10 times below the LOAEL, and the $BMCL_{10}$ is nearly 600 times lower than the LOAEL. Visual inspection of the curve indicates that it, too, is superlinear (see Figure B-2). When the hemosiderosis data were modeled without the highest dose, only the log-logistic model exhibited adequate fit to the data ($p > 0.1$; see Table B-5 and Figure B-3), calculating BMC_{10} and $BMCL_{10}$ estimates of 39.96 and 27.19 $\mu g/m^3$, respectively for liver hemosiderosis in male hamsters, following 1-year inhalation exposure to anhydrous hydrazine and an additional year of unexposed observation.

This provides two potential points of departure (POD) based on the hamster liver effects data: a BMCL of 27 $\mu g/m^3$ for hemosiderosis and a LOAEL of 58 $\mu g/m^3$ for amyloidosis and bile duct hyperplasia, for which BMD modeling proved infeasible. A NOAEL is not available for either effect. The $BMCL_{10}$ of 27 $\mu g/m^3$ for hemosiderosis is lower than the LOAEL of 58 $\mu g/m^3$ for amyloidosis and bile duct hyperplasia; thus it represents a more defensible POD (U.S. EPA, 2000); therefore, hemosiderosis is chosen as the critical effect and the $BMCL_{10}$ POD of 27 $\mu g/m^3$ is used to derive the p-RfC. Because the incidence data in Table 4 indicate that amyloidosis and bile duct hyperplasia in hamsters are not more sensitive endpoints than hemosiderosis, a p-RfC based on the POD for the hemosiderosis endpoint also should protect against amyloidosis and bile duct hyperplasia.

Hydrazine is treated as a Category 3 gas because inhalation exposure resulted in systemic effects, including the critical effect of hemosiderosis in male hamsters (Vernot et al., 1985). Following the U.S. EPA (1994b) methodology for extrarespiratory or systemic effects of a Category 3 gas, the $BMCL_{10HEC}$ is derived by multiplying the duration-adjusted $BMCL_{10}$ by the ratio of the blood:gas partition coefficients ($[H_{b/g}]_A/[H_{b/g}]_H$). In the absence of an available

blood:gas partition coefficient for hydrazine in the hamster, a value of 1 is used for the ratio of the human:hamster blood:gas partition coefficients, so the $BMCL_{10\ HEC}$ for liver amyloidosis is equal to the duration adjusted $BMCL_{10}$ of 0.027 mg/m^3. A subchronic p-RfC is calculated from the hamster $BMCL_{10HEC}$ for liver amyloidosis by applying a composite uncertainty factor of 300, as follows:

The **subchronic p-RfC** is derived as follows:

$$\begin{aligned} \textbf{Subchronic p-RfC} &= BMCL_{10HEC} \div UF \\ &= 0.027\ mg/m^3 \div 300 = 0.00009\ mg/m^3 \\ &= \mathbf{9 \times 10^{-5}\ mg/m^3} \end{aligned}$$

The composite UF of 300 includes the following individual UFs:

- UF_A = 3 reflects a factor of 1 for toxicokinetic differences across species, which has been reduced from 3 due to application of the dosimetric equations, and a factor of 3 for toxicodynamic considerations.
- UF_H = 10 accounts for potential variation in sensitivity within human populations because there is limited information on the degree to which humans of varying gender, age, health status, or genetic makeup might vary in the disposition of, or response to, hydrazine.
- UF_D = 10 for database deficiencies accounts for the lack of both multigeneration reproductive toxicity and developmental toxicity data for the inhalation exposure route. Several developmental studies were available using intraperitoneal or subcutaneous injection of hydrazine (reviewed in Toth, 1993; Keller, 1988). These studies suggest that hydrazine could cause embryo lethality and fetal anomalies at high doses. However, no oral or inhalation developmental toxicity studies are available. In addition, adequate supporting subchronic or chronic toxicity studies were lacking. The maximum database UF also is required to account for the additional uncertainties resulting from the key study (Vernot et al., 1985) having waited a full year following conclusion of exposure to conduct autopsies on the experimental animals.

Derivation of the **chronic p-RfC** uses the same liver toxicity data in male hamsters (Vernot et al., 1985), POD, and a composite UF of 1000, as follows:

$$\begin{aligned} \textbf{Chronic p-RfC} &= BMCL_{10HEC} \div UF \\ &= 0.027\ mg/m^3 \div 1000 = 0.000027\ mg/m^3 \\ &= \mathbf{3 \times 10^{-5}\ mg/m^3} \end{aligned}$$

The composite UF of 1000 includes the following individual UFs:

- UF_A = 3 reflects a factor of 1 for toxicokinetic differences across species, which has been reduced from 3 due to application of the dosimetric equations, and a factor of 3 for toxicodynamic considerations.
- UF_H = 10 accounts for potential variation in sensitivity within human populations because there is limited information on the degree to which humans of varying gender, age, health status, or genetic makeup might vary in the disposition of, or response to, hydrazine.

- UF_S = 3 to reflect the fact that the critical data comes from a study with a relatively short (1 year) chronic exposure duration for application in deriving a chronic p-RfC.
- UF_D = 10 for database deficiencies accounts for the lack of both multigeneration reproductive toxicity and developmental toxicity data for the inhalation exposure route. Several developmental studies were available using intraperitoneal or subcutaneous injection of hydrazine (reviewed in Toth, 1993; Keller, 1988). These studies suggest that hydrazine could cause embryo lethality and fetal anomalies at high doses. However, no oral or inhalation developmental toxicity studies are available. In addition, adequate supporting subchronic or chronic toxicity studies were lacking. The maximum database UF also is required to account for the additional uncertainties resulting from the key study (Vernot et al., 1985) having waited a full year following conclusion of exposure to conduct autopsies on the experimental animals, with the resulting possibility that some reversible—but relevant—endpoints might not have been observed.

Confidence in the critical study (Vernot et al., 1985) is low primarily because of the extended period between exposure and detailed evaluation of the animals. While inhalation exposure to hydrazine was evaluated in several species with an adequate number of animals used in each exposure group, effects were seen at all concentrations in the sensitive species. Therefore, a NOAEL cannot be determined. Confidence in the database is low. In addition to the critical study (Vernot et al., 1985), three other inhalation studies evaluated the effects of hydrazine exposure in laboratory animals (Latendresse et al., 1995; Haun and Kinkead, 1973; Comstock et al., 1954). While the Haun and Kinkead (1973) data support p-RfC derivations, they reported a LOAEL in mice that was four times higher than the LOAEL in hamsters indicated by Vernot et al. (1985). Neither study reports a NOAEL for the most sensitive species. Multigeneration reproductive toxicity data are not available for hydrazine, and developmental toxicity data are not available for the oral or inhalation exposure route. Low confidence in both the subchronic and chronic p-RfCs follow.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR HYDRAZINE

Weight-of-Evidence Descriptor

The IRIS cancer assessment (U.S. EPA 1991a) classified hydrazine and hydrazine sulfate as "*A Probable Human Carcinogen,*" Group B2, based on tumors observed in mice, rats, and hamsters following oral, inhalation, or intraperitoneal administration, with supporting mutagenicity data.

Quantitative Estimates of Carcinogenic Risk

IRIS (U.S. EPA, 1991a) reports an oral slope factor of 3 $(mg/kg\text{-}day)^{-1}$ based on hepatomas observed in mice given hydrazine sulfate in water by oral gavage (Biancifiori, 1970). U.S. EPA (1991a) also reports an inhalation unit risk of 4.9×10^{-3} $(\mu g/m^3)^{-1}$, which was calculated from tumor incidence data for nasal cavity adenoma or adenocarcinoma in male rats following inhalation exposure to hydrazine (MacEwen et al., 1981).

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APPENDIX A. FURTHER CONSIDERATIONS OF TOXICITY VALUES FOR HYDRAZINE (SCREENING VALUES)

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional toxicity values for hydrazine. 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.

Gershanovich et al. (1981) and Filov et al. (1995) each treated 225 and 740 cancer patients, respectively, who had tumors at various sites that had not responded to other forms of anticancer therapy, with one to three 60-mg hydrazine sulfate tablets or capsules per day. Each treatment course generally was for 30−45 days. Patients received from 2 to 40 courses of treatment, separated by treatment-free intervals of 2−6 weeks, for up to 5 years. Among the cancer patients evaluated, side effects, including nausea or vomiting, dizziness, and polyneuritis, were reported only among patients treated at the highest dose (180 mg/day). However, both studies reported that symptoms disappeared when daily doses were reduced to 120 mg/day, suggesting this dose might be a NOAEL. No other adverse effects were reported. Unfortunately, these studies did not provide details regarding the specific treatment durations of patients reporting side effects, and they reported no control groups. However, these findings are supported by other studies that demonstrated similar effects following shorter-term (generally 30-day) treatment with 180 mg/day (Lerner and Regelson, 1976; Kosty et al., 1994; Loprinzi et al., 1994a; Ochoa et al., 1975).

Using the most conservative assumptions of a series of 30-day treatments followed by 30 days treatment-free for up to 5 years, these data (Gershanovich et al., 1981; Filov et al., 1995) can be considered for use to estimate an average daily LOAEL for reversible side effects among cancer patients as follows:

$$[(180 \text{ mg/day})/70 \text{ kg}] \times (30 \text{ day treatment}/60\text{-day duration}) = 1.29 \text{ mg/kg-day}$$

Similarly, an average daily NOAEL also is calculated, as follows:

$$[(120 \text{ mg/day})/70 \text{ kg}] \times (30 \text{ day treatment}/60\text{-day duration}) = 0.86 \text{ mg/kg-day}.$$

Neither Gershanovich et al. (1981) nor Filov et al. (1995) reports control group information for comparison to the NOAEL or LOAEL. However, the POD identified here is the most conservative—even if a control group were considered. If similar effects were observed in a hypothetical control group, this could only increase the POD and result in a less conservative a POD. The duration of treatment underlying these values ranged from less than 3 months (two

treatment courses of 30−45 days separated by one 2−6 week period without treatment) up to 5 years.

A screening subchronic RfD is calculated from the human NOAEL of 0.86 mg/kg-day for side effects among cancer patients treated with hydrazine by applying a composite UF of 1000 that includes the following individual UFs:

- $UF_A = 1$. Human data are used for the POD, so no interspecies uncertainty is present.
- $UF_H = 10$ for potential human variability. Although cancer patients seemed likely to be among the more susceptible members of the human population, comparatively few effects were reported, and they included only clinically evident signs.
- $UF_S = 10$, for exposure durations that were not clearly reported and might have been as brief as 2.5 months. Although durations for some patients were as long as 5 years, exposures as long as 7 years are considered subchronic among humans.
- $UF_D = 10$ for database uncertainties. The key studies incompletely reported the relevant data and included no control groups. Studies reporting reproductive or developmental data used only the intraperitoneal or subcutaneous injection route of exposure (reviewed in Toth, 1993; Keller, 1988). Few supporting data for the oral route are available. As summarized in Table 6, Steinhoff et al. (1990) reported a chronic NOAEL in mice of 2.4 mg/kg-day. However, Biancifiori (1970) and Fitzgerald and Shank (1996) reported only FELs in hamsters—including mortality at similar doses (3.1, subchronic, and 4.2 mg/kg-day, chronic, respectively). These FELs in hamsters are less than four times the human NOAEL considered as the POD for deriving this screening value.

Screening Subchronic RfD = NOAEL/UF
= (0.86 mg/kg-day) ÷ 1000
= 0.00086 mg/kg-day
= **9×10^{-4} mg/kg-day**

APPENDIX B. BENCHMARK CONCENTRATION ANALYSES FOR DERIVATION OF THE p-RfD

U.S. EPA (2002) recommends that benchmark concentration analysis (BMC) be used to derive reference values whenever possible, and that derivation of a reference value should consider all relevant and appropriate endpoints of toxicity. In this case, incidence data for three indicators of liver toxicity, bile duct hyperplasia, hemosiderosis, and amyloidosis, are evaluated using BMC modeling. Potential points of departure values (PODs) for each effect are compared to determine the critical effect used for derivation of the provisional subchronic RfC.

All dichotomous models in the U.S. EPA Benchmark Dose Software (BMDS; Version 1.4.1b) were fit to the incidence data for bile duct hyperplasia, hemosiderosis, and amyloidosis in male hamsters exposed to airborne hydrazine (see Table 4). For each model, a benchmark response (BMR) of 10% extra risk (as recommended by U.S. EPA, 2000) is used to calculate a BMC and its lower 95% confidence limit (BMCL). Tables B-1 through B-5 show various modeling results from these endpoints, and Figures B-1 through B-3 depict the curves calculated by the models with global goodness-of-fit chi square *p*-value $\geq$0.1.

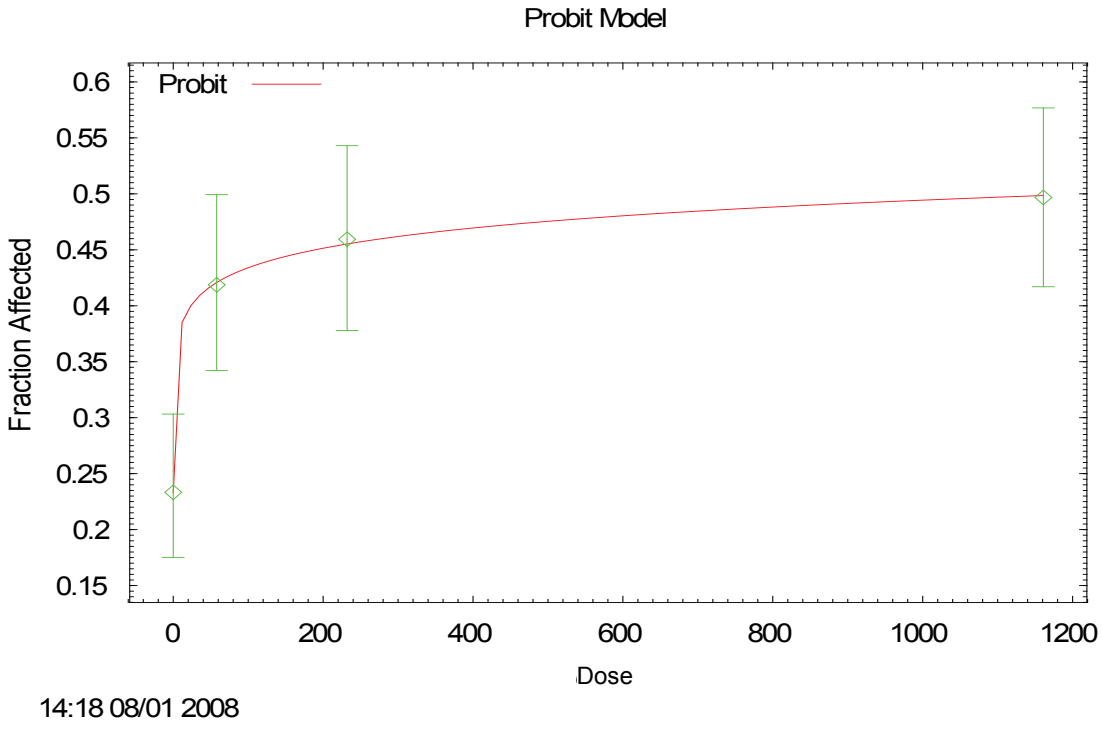

Figure B-1. Plot of Unrestricted Probit BMC Analysis for Log of Liver Amyloidosis Incidence in Male Hamsters Exposed Whole-Body to Airborne Hydrazine 6 Hours/Day, 5 Days/Week for 1 Year, After 12 Months Additional Observation (Vernot et al., 1985)

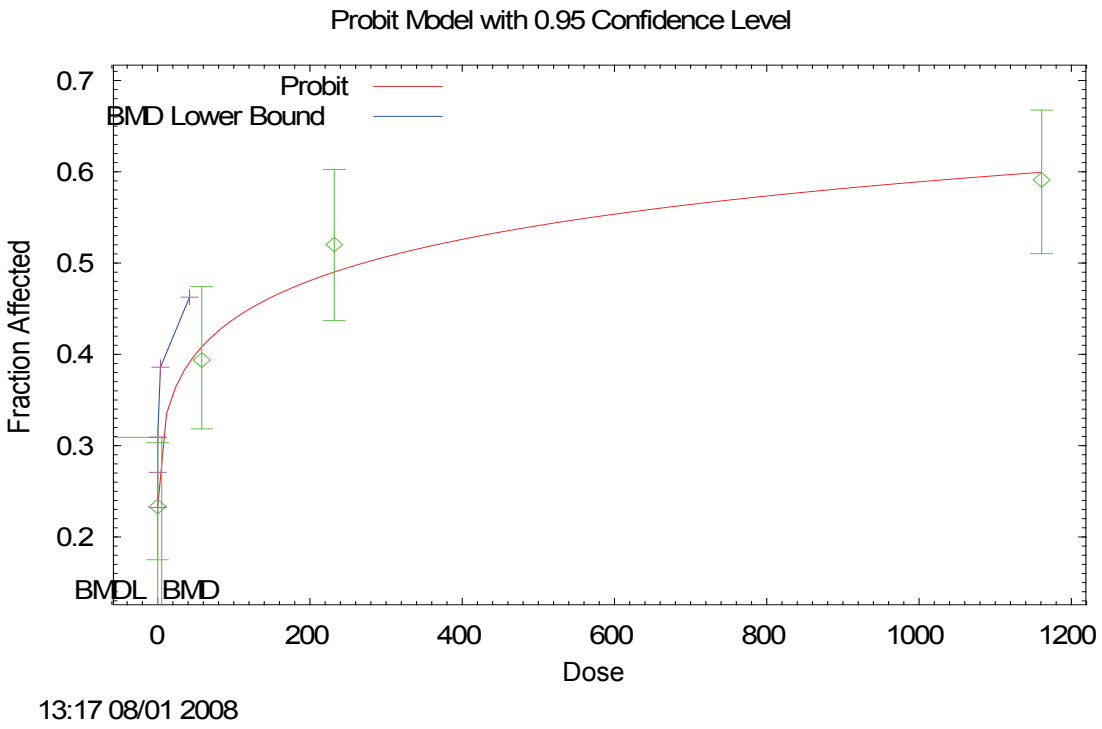

Figure B-2. Plot of Unrestricted Probit BMC Analysis for Log of Liver Hemosiderosis Incidence in Male Hamsters Exposed Whole-Body to Airborne Hydrazine 6 Hours/Day, 5 Days/Week for 1 Year, After 12 Months Additional Observation (Vernot et al., 1985)

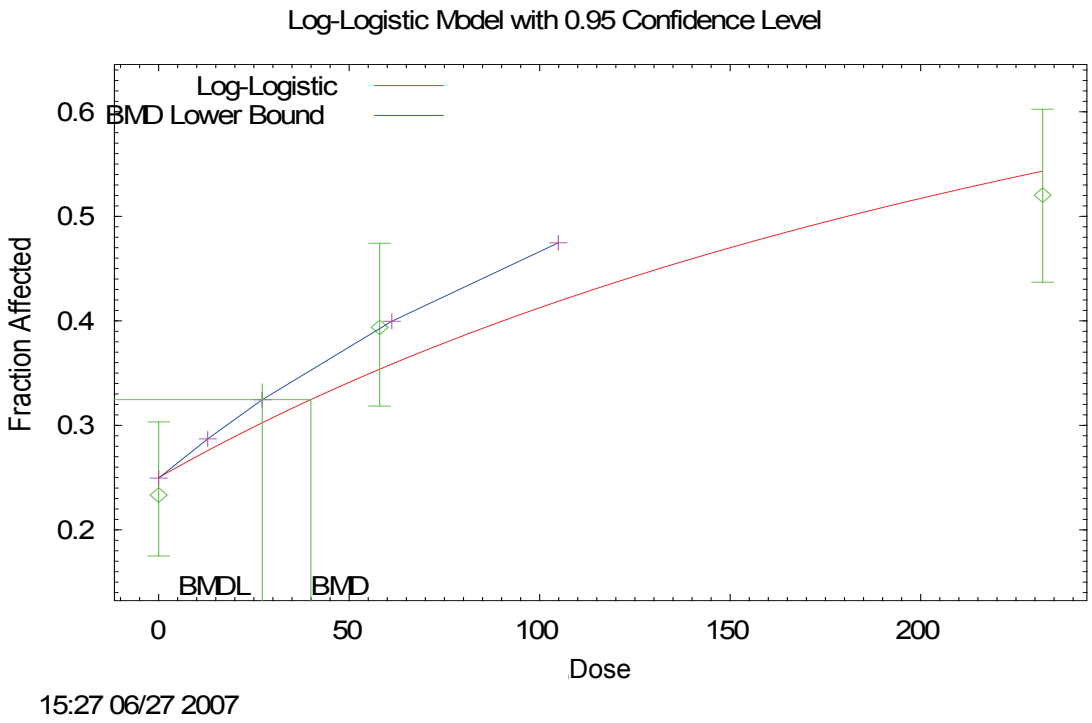

Figure B-3. Plot of Log-Logistic BMC Analysis for Liver Hemosiderosis Incidence in Male Hamsters Exposed Whole-Body to Airborne Hydrazine 6 Hours/Day, 5 Days/Week for 1 Year, After 12 Months Additional Observation (Vernot et al., 1985). The highest dose has been excluded for this analysis; LOAEL = 58 µg/m^3

Table B-1. BMC Summaries for Bile Duct Hyperplasia Incidence in Male Hamsters Exposed Whole-Body to Airborne Hydrazine[a] 6 Hours/Day, 5 Days/Week for 1 Year, After 12 Months Additional Observation[b]

	p	Chi^2	Σ scaled Residuals[c]	AIC	BMC ($\mu g/m^3$)	$BMCL_{10}$ ($\mu g/m^3$)
Gamma	0.0108	9.05	4.1	600.240	NA[d]	NA
Logistic	0.0079	9.67	4.2	601.106	NA	NA
Log-logistic	0.0119	8.86	4.1	599.978	NA	NA
Log-Probit	0.0083	9.59	4.1	600.998	NA	NA
Probit	0.0034	11.34	4.3	603.116	NA	NA
Quantal-Linear	0.0108	9.05	4.1	600.240	NA	NA
Multistage	0.0108	9.05	4.1	600.240	NA	NA
Weibull	0.0108	9.05	4.1	600.240	NA	NA

[a]LOAEL = 58 $\mu g/m^3$.
[b]Vernot et al. (1985).
[c]Sum of absolute values of scaled residuals at lowest dose and for controls.
[d]All models exhibited significant lack of fit to the data ($p < 0.1$) so calculated BMCs and BMCLs are invalid.

Table B-2. BMC Summaries for Liver Amyloidosis Incidence in Male Hamsters Exposed Whole-Body to Airborne Hydrazine[a] 6 Hours/Day, 5 Days/Week for 1 Year, After 12 Months Additional Observation[b]

	p	Chi^2	Σ scaled Residuals[c]	AIC	BMC ($\mu g/m^3$)	$BMCL_{10}$ ($\mu g/m^3$)
Gamma	0.0002	16.68	4.8	858.816	NA[d]	NA
Log-logistic	0.0003	15.96	4.7	858.017	NA	NA
Logistic	0.0002	17.44	4.9	859.670	NA	NA
Multistage	0.0002	16.68	4.8	858.816	NA	NA
Log-Probit	**0.9015**	**0.02**	**0.1**	**843.769**	**0.144238**	**0**
Log-Probit restrict slope	0.0000	29.52	5.1	872.556	NA	NA
Probit	0.0002	17.40	4.9	859.622	NA	NA
Quantal-Linear	0.0002	16.68	4.8	858.816	NA	NA
Weibull	0.0002	16.68	4.8	858.816	NA	NA

[a]LOAEL = 58 $\mu g/m^3$.
[b]Vernot et al. (1985).
[c]Sum of absolute values of scaled residuals at lowest dose and for controls.
[d]All models other than the log-probit model exhibited significant lack of fit to the data ($p < 0.1$) so calculated BMCs and BMCLs are invalid.

Table B-3. BMC Summaries for Liver Amyloidosis Incidence in Male Hamsters Exposed Whole-Body to Airborne Hydrazine[a] 6 Hours/Day, 5 Days/Week for 1 Year, After 12 Months Additional Observation[b]

	p	Chi^2	Σ scaled Residuals[c]	AIC	BMC (µg/m^3)	BMCL$_{10}$ (µg/m^3)
Gamma	0.0082	6.99	3.5	628.246	NA[d]	NA
Logistic	0.0041	8.26	3.9	629.540	NA	NA
Log-logistic	0.0141	6.03	3.1	627.283	NA	NA
Log-Probit	0.0006	11.91	4.8	633.189	NA	NA
Multistage	0.0082	6.99	3.5	628.246	NA	NA
Probit	0.0043	8.16	3.9	629.441	NA	NA
Weibull	0.0082	6.99	3.5	628.246	NA	NA

[a]Highest dose was excluded for these analyses; LOAEL = 58 µg/m^3.
[b]Vernot et al. (1985).
[c]Sum of absolute values of scaled residuals at lowest dose and for controls.
[d]All models exhibited significant lack of fit to the data ($p < 0.1$) so calculated BMCs and BMCLs are invalid.

Table B-4. BMC Summaries for Liver Hemosiderosis Incidence in Male Hamsters Exposed Whole-Body to Airborne Hydrazine[a] 6 Hours/Day, 5 Days/Week for 1 Year, After 12 Months Additional Observation[b]

	p	Chi^2	Σ scaled Residuals[c]	AIC	BMC (µg/m^3	BMCL$_{10}$ (µg/m^3)
Gamma	0.0001	18.17	3.9	852.575	NA[d]	NA
Log-logistic	0.0005	15.08	3.6	849.328	NA	NA
Logistic	0.0000	20.67	4.1	855.225	NA	NA
Multistage	0.0001	18.17	3.9	852.575	NA	NA
Log-Probit	**0.3981**	**0.71**	**0.44**	**836.849**	**5.35176**	**0.104368**
Log-Probit restrict slope	0.0000	26.09	4.4	860.693	NA	NA
Probit	0.0000	20.59	4.1	855.141	NA	NA
Quantal-Linear	0.0001	18.17	3.9	852.575	NA	NA
Weibull	0.0001	18.17	3.9	852.575	NA	NA

[a]LOAEL = 58 µg/m^3.
[b]Vernot et al. (1985).
[c]Sum of absolute values of scaled residuals at lowest dose and for controls.
[d]All models other than the log-probit model exhibited significant lack of fit to the data ($p < 0.1$) so calculated BMCs and BMCLs are invalid.

Table B-5. BMC Summaries for Liver Hemosiderosis Incidence in Male Hamsters Exposed Whole-Body to Airborne Hydrazine[a] 6 Hours/Day, 5 Days/Week for 1 Year, After 12 Months Additional Observation[b]

	p	Chi^2	Σ scaled Residuals[c]	AIC	BMC (µg/m^3)	BMCL$_{10}$ (µg/m^3)
Gamma	0.0985	2.73	2.1	621.738	NA[d]	NA
Logistic	0.0380	4.30	2.9	623.317	NA	NA
Log-logistic	**0.1920**	**1.70**	**1.6**	**620.721**	**39.9600**	**27.1939**
Log-Probit	0.0407	4.19	2.8	623.197	NA	NA
Multistage	0.0985	2.73	2.1	621.738	NA	NA
Probit	0.0067	7.35	3.7	626.320	NA	NA
Quantal-Linear	0.0985	2.73	2.1	621.738	NA	NA
Weibull	0.0985	2.73	2.1	621.738	NA	NA

[a]Highest dose was excluded for these analyses; LOAEL = 58 µg/m^3.
[b]Vernot et al. (1985).
[c]Sum of absolute values of scaled residuals at lowest dose and for controls.
[d]All models other than the log-logistic model exhibited significant lack of fit to the data ($p < 0.1$) so calculated BMCs and BMCLs are invalid.