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Provisional Peer-Reviewed Toxicity Values for

Methyl Hydrazine
(CASRN 60-34-4)

Superfund Health Risk Technical Support Center
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COMMONLY USED ABBREVIATIONS

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

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR METHYL HYDRAZINE (CASRN 60-34-4)

BACKGROUND

HISTORY

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

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

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

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

DISCLAIMERS

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

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

QUESTIONS REGARDING PPRTVS

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

INTRODUCTION

There are no RfD, RfC, or carcinogenicity assessments for methyl hydrazine (MH; structure shown in Figure 1) on the IRIS database (U.S. EPA, 2009), or in the HEAST (U.S. EPA, 1997), or on the Drinking Water and Health Advisories list (U.S. EPA, 2006). The Chemical Assessments and Related Activities (CARA) database (U.S. EPA, 1991, 1994a) lists a Health and Environmental Effects Profile (HEEP) for MH (U.S. EPA, 1984) that contains a cancer assessment, in which a human oral slope factor (OSF) of 1.09 $(mg/kg\text{-}day)^{-1}$ was derived using liver tumor incidence data from hamsters in a chronic drinking water study (Toth and Shimizu, 1973). Noncancer assessments were not developed in the HEEP.

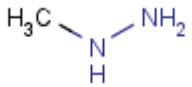

Figure 1. Chemical Structure of Methyl Hydrazine

Occupational health guidelines and standards are available for MH. The American Conference of Governmental Industrial Hygienists (ACGIH, 2001, 2008) recommends a Threshold Limit Value-time-weighted average (TLV-TWA) of 0.01 ppm (0.019 mg/m^3) with skin irritancy and animal carcinogen (A3) notations. The National Institute for Occupational Safety and Health (NIOSH, 2005) designated MH a potential human carcinogen and recommends a ceiling Recommended Exposure Limit (REL) (2 hours) of 0.04 ppm (0.08 mg/m^3) and an Immediately Dangerous to Life or Health (IDLH) concentration of 20 ppm (38 mg/m^3). The Occupational Safety and Health Administration (OSHA, 2009) has promulgated a Permissible Exposure Limit (PEL) of 0.2 ppm (0.38 mg/m^3) for MH.

ATSDR (1997) developed a toxicological profile for hydrazines, but this contains little or no toxicological information about MH per se and no oral or inhalation Minimal Risk Levels (MRLs) for MH. There is no World Health Organization (WHO, 2009) Environmental Health Criteria Document for MH, and the carcinogenicity of MH has not been evaluated by the National Toxicology Program (NTP, 2009, 2005) or the International Agency for Research on Cancer (IARC, 2009). CalEPA (2009a,b,c) has not derived chronic oral or inhalation RELs or a cancer potency factor for MH.

Literature searches were conducted for studies relevant to the derivation of provisional toxicity values for MH. Databases searched included MEDLINE, TOXLINE (BIOSIS and NTIS), TOXCENTER (Chemical Abstracts), CCRIS, DART/ETIC, DTIC, TSCATS/TSCATS 2, GENETOX, HSDB, RTECS, and Current Contents. The time period covered by most of the searches ranged from the 1960s through September 2010, although some searches covered the early literature.

REVIEW OF PERTINENT DATA

HUMAN STUDIES

In an unpublished study conducted by the Aerospace Medical Research Laboratory (AMRL), MacEwen et al. (1970) exposed volunteers to 90-ppm (170-mg/m^3) MH for 10 minutes (head-only exposure) and assessed subjective symptoms of irritation, clinical chemistry, hematology, and respiratory parameters. The volunteers were all men whose average age was 31 years old (range up to 44 years old; minimum not available due to poor quality of the available study); the group included nonsmokers, smokers, and former smokers. Preliminary experiments with one volunteer each exposed to 50 or 70 ppm (94 or 130 mg/m^3) for 10 minutes and followed for 2 weeks were conducted prior to the experiment at 90 ppm. The authors reported that there were no effects on these two volunteers, but they did not report the endpoints that were examined. A group of five volunteers was then exposed to 90-ppm MH for 10 minutes, during which, each volunteer's subjective reports of nasal and eye irritation and odor intensity were recorded. Each volunteer was subsequently exposed to 30- and 50-ppm ammonia (in random order) for comparative information on irritation intensity. Blood samples for clinical chemistry (electrolytes, calcium, inorganic phosphorus, cholesterol, total bilirubin, total protein, albumin, glucose, creatinine, chloride, uric acid, blood urea nitrogen [BUN], lactate dehydrogenase [LDH], alkaline phosphatase [ALP], and aspartate transaminase [AST, previously Serum glutamic oxaloacetic transaminase, or SGOT]) and hematology (hematocrit [Hct]; hemoglobin [Hgb]; erythrocyte [red blood cell; RBC]; and leukocyte [white blood cell; WBC] counts; reticulocytes; and Heinz bodies) were collected before exposure and 1, 7, and 14 days after exposure; hematology was also assessed 60 days after exposure. Respiratory parameters were evaluated before and after exposure as well as 60 days postexposure.

The authors reported increased moisture without tearing in most subjects, and slight reddening of the eyes in some subjects exposed to 90-ppm MH for 10 minutes. The individual reports of nasal and eye irritation intensity were not legible in the available study; however, the authors reported that the 90-ppm MH concentration was "slightly more irritant than 30-ppm NH_3 but considerably less than the 50-ppm NH_3 atmosphere." Among hematology parameters, the only finding was an increase in Heinz bodies (3–5% of erythrocytes by 7 days after exposure,

dropping to the preexposure level of 0% by 60 days after exposure). Review of the data showed that clinical chemistry and respiratory evaluations did not indicate an effect of exposure at any time point, when compared with preexposure levels. The authors attributed individual changes in respiratory parameters of two subjects to a respiratory infection in one subject and smoking in another. In a transcript of a discussion following the study, the authors indicated that urine samples were collected for analysis of glucose, albumin, and microscopic examination, and no treatment-related effects were observed. This study was reviewed and approved by the Medical Research Review Committee of the 6570th Aerospace Medical Research Laboratory at Wright-Patterson Air Force Base (MacEwen et al, 1970).

In a review of data available for use in setting Spacecraft Maximum Acceptable Concentrations (SMACs), Garcia et al. (1992) briefly reported the results of a study conducted by the White Sands Facility of the NASA Johnson Space Center (Hoffman et al., 1976 cited by Garcia et al., 1992). Efforts to obtain the original study were not successful. According to information provided in Garcia et al. (1992), 42 volunteers inhaled 0.2-ppm (0.38 mg/m^3) MH in a single sniff (volume of 30 cm^3). Garcia et al. (1992) reported that 75% of the subjects (32/42) complained of an irritating odor, while 28% (12/42) exhibited evidence of significant nasal pathology (not further characterized). No other details of the study population, exposure conditions, toxicological evaluations conducted, or findings were available in the study by Garcia et al. (1992).

ANIMAL STUDIES

Oral Exposure

The effects of oral exposure to MH in animals have been evaluated in one subchronic-duration study in mice (Kelly et al., 1969) and four chronic-duration studies, including a 40-week study in Swiss mice (Roe et al., 1967) and three lifetime exposure studies in Swiss mice and Syrian golden hamsters (Toth, 1972; Toth and Shimizu, 1973; MacEwen et al., 1970). There was also a developmental toxicity study in Sprague-Dawley rats (Slanina et al., 1993). All these studies were published in peer-reviewed journals, except MacEwen et al. (1970), which is a peer-reviewed technical report on cancer and noncancer effects. Tables 1 and 2 summarize dose-response information for the studies presented in this section.

Table 1. Incidence of Tumors in Swiss Mice Exposed to Methyl Hydrazine or Methyl Hydrazine Sulfate in Drinking Water for Life (Toth, 1972)

Tumor Type	Control[a]	0.01% MH	0.001% MH Sulfate
Male			
Dose	**0**	**17.8 mg/kg-day**	**2.8 mg/kg-day**
Lung adenomas or adenocarcinomas	11/110	11/50[b]	23/50[c]
Malignant lymphoma	2/110	0/50	8/50[c]
Hepatoma	0/110	3/50[b]	0/50
Cholangioma	0/110	2/50	0/50
Cholangiocarcinoma	0/110	1/50	0/50
Angioma of liver and lymph node	0/110	1/50	1/50
Female			
Dose	**0**	**20.3 mg/kg-day**	**2.2 mg/kg-day**
Lung adenomas or adenocarcinomas	14/110	12/50[d]	23/50[c]
Hepatoma	0/110	3/50[b]	0/50
Cholangioma	0/110	6/50[c]	0/50
Cholangiocarcinoma	0/110	1/50	0/50
Angioma of liver	0/110	4/50[c]	3/50[b]

[a]Untreated control data from a similarly designed study of hydrazine sulfate (Toth, 1969)
[b]Significantly different from controls by Fisher's exact test conducted for this evaluation; $p < 0.05$
[c]$p < 0.01$
[d]$p = 0.06$

Table 2. Incidence of Tumors in Syrian Golden Hamsters Exposed to Methyl Hydrazine in Drinking Water for Life (Toth and Shimizu, 1973)

Tumor Type	Control	0.01% MH
Male		
Dose	**0**	**8.2 mg/kg-day**
Malignant histiocytoma of liver	0/97[a]	27/50[b]
Cecal tumor	1/97	7/50[b]
Female		
Dose	**0**	**9.0 mg/kg-day**
Malignant histiocytoma of liver	0/99	16/49[b]
Cecal tumor	1/99	9/49[b]

[a]Number affected/number exposed
[b]Significantly different from controls by Fisher's exact test conducted for this evaluation; $p < 0.01$

Subchronic-Duration Studies—MH was evaluated in a subchronic-duration study of carcinogenicity in mice (Kelly et al., 1969). Kelly et al. (1969) administered MH (purity not specified) to 30 female CDF_1 mice (7–8 weeks old) by gavage in water at a total dose of 3.7 mg/mouse once a week for 8 weeks (0.53 mg/mouse-day) (Kelly et al., 1969). Using the body weight of 27 g reported by the authors for treated mice at Study Week 12 (additional body-weight data not reported), the estimated weekly dose per unit body weight was 20-mg/kg MH. A control group of 10 females was given saline by gavage, and both treated and control groups were observed for 20–25 weeks following the last dose. Body weight and mortality were

recorded at Week 12 after study commencement. Upon sacrifice, gross observations for pulmonary tumors and leukemia were undertaken and histologically verified by examinations of lung, liver, thymus, spleen, kidney, lymph nodes, and other (unspecified) organs. Other endpoints (e.g., nonneoplastic effects) were not investigated or not reported. Mortality was increased in the treated mice (70% compared to 0% in controls); the authors did not discuss timing or potential causes of death. There were no lung tumors or leukemias in the nine surviving mice; data on other tumor types were not reported. This study identifies a Frank Effect Level (FEL) of 20 mg/kg-week for mice based on high mortality.

Chronic-Duration Studies—MH sulfate (purity not specified) was administered to 25 female Swiss mice (age not reported) by gavage in water at a dose level of 0.5 mg/mouse for 5 days/week, for 40 weeks (Roe et al., 1967). A range-finding study using groups of five mice, reported briefly by the study authors indicated that doses of 2, 8, or 32 mg/mouse, 5 days/week were lethal to all mice within the first week of treatment, while all survived 0.5 mg/mouse. The study authors chose this dose for the main study. Using the default reference average body weight of 0.035 kg for chronic exposure in female mice ($B6C3F_1$ strain used by default; U.S. EPA, 1988), the estimated dose of MH sulfate per unit body weight was 14 mg/kg-day (10 mg/kg-day adjusted for continuous exposure). A group of 85 untreated mice served as controls. Evaluations were limited to gross and histological examinations for lung tumors in 10 treated and 37 control survivors at study Weeks 40–50 and in 9 treated and 42 control survivors at Weeks 50–60. The incidence of lung tumors and the total number of lung tumors were not increased by treatment with MH sulfate. Nonneoplastic effects were not reported, so effect levels could not be determined.

Groups of 50 male and 50 female Swiss mice (6 weeks old) were exposed to drinking water containing 0.01% MH or 0.001% MH sulfate (purities not reported) for life (Toth, 1972). The experiments did not use concurrent control groups; rather, control data on 110 male and 110 female untreated mice from the same colony used in a similarly designed study of hydrazine sulfate and reported by Toth (1969) were used for comparison. Reported average daily consumption of MH was 0.66 mg/mouse for males and 0.71 mg/mouse for females; consumption of MH sulfate was 0.102 mg/mouse for males and 0.078 mg/mouse for females. Using default chronic reference average body weights of 0.037 and 0.035 kg for male and female mice, respectively ($B6C3F_1$ default; U.S. EPA, 1988), the estimated doses per unit body weight were 17.8 and 20.3 mg/kg-day for MH and 2.8 and 2.2 mg/kg-day for MH sulfate (males and females, respectively). Treated drinking water was prepared three times per week. Survival, body weight, comprehensive gross pathology, and limited histopathology (liver, kidneys, spleen, lungs, and organs showing gross changes) were evaluated, but survival and tumor incidence and latency data were the only results reported. Survival was reduced in the MH group, with no male mice surviving past 60 weeks and no female mice surviving past 70 weeks, whereas MH sulfate had no apparent effect on survival at Week 70 (83% in males and 84% in females compared to 67 and 37% in controls, respectively) or Week 110 (19% males and 10% females compared to 10 and 1% in controls). As survival was affected at the only dose of MH tested (17.8–20.3 mg/kg-day), this dose is a FEL. Other effect levels could not be determined.

As evidenced in Table 1, incidences of lung tumors (adenomas and adenocarcinomas) were higher in the mice exposed to 0.001% MH sulfate and 0.01% MH (Toth, 1972) in comparison to the unexposed control incidences reported by Toth (1969). Although MH sulfate was more potent than MH in inducing lung tumors, the average latency period was shorter in

mice of both sexes exposed to 0.01% MH (51 vs. 74–95 weeks in controls and MH sulfate treatment groups, respectively). The incidence of malignant lymphoma in male mice exposed to MH sulfate was also significantly increased relative to the control data (see Table 1). The authors noted that several other tumor types were observed in animals treated with MH (benign and malignant liver and bile duct tumors in both sexes), but not in controls, and attributed the tumors to treatment (see Table 1). Because the survival of mice treated with MH was markedly reduced, the tumor incidences associated with this treatment may be underestimated relative to longer-exposure durations. In addition, the lack of a concurrent control group increases the uncertainty in the findings of this study.

Groups of 50 male and 50 female Syrian golden hamsters (6 weeks old) were exposed to 0.01% MH (purity not specified) in drinking water for life and compared with 100 male and 100 female untreated controls (Toth and Shimizu, 1973). Reported average daily intake of MH for the males and females was 1.1 and 1.3 mg/hamster, respectively. Using default chronic reference average body weights of 0.134 and 0.145 kg for male and female Syrian golden hamsters (U.S. EPA, 1988), respectively, estimated doses per unit body weight for males and females were 8.2 and 9.0 mg/kg-day, respectively. Treated drinking water was prepared three times per week. Survival, body weight, comprehensive gross pathology, and limited histopathology (liver, kidneys, spleen, bladder, thyroid, heart, pancreas, testes, brain, nasal turbinate, lungs, and organs showing gross changes) were evaluated, but survival and tumor incidence and latency data were the only results reported. Survival was reduced in treated male and female hamsters during the second year of the study; survival to 90 weeks was 16 and 2% in treated males and females, respectively, versus 32 and 20% in control males and females, respectively. No treated animals remained alive after 100 weeks. Apart from survival, no noncancer endpoints were reported; thus, nonfrank-effect levels cannot be identified for this study. Incidences of liver and cecum tumors were statistically significantly increased in exposed hamsters of both sexes ($p < 0.01$, Fisher's exact test conducted for this review; see Table 2). The average latency period (animal age) for the liver tumors (malignant histiocytomas = Kupffer's cell sarcomas) was 78 weeks in males and 70 weeks in females. The tumors were not seen in any control animals. Tumors of the cecum (polyploid adenomas and adenocarcinomas) were found with average latency periods of 77 and 64 weeks in males and females, respectively. Cecal tumors were observed in only two control animals—one male after 84 weeks and one female after 53 weeks. Other tumors occurred at low incidence and were not attributed to treatment by the researchers.

An unpublished study designed to replicate the hamster carcinogenicity findings of Toth and Shimizu (1973) was conducted by MacEwen and Vernot (1975). In the study, the authors raised concerns regarding the stability of MH, postulating that the hamsters in the study by Toth and Shimizu (1973) may not have been exposed to MH—but, rather, to its oxidation products. Preliminary tests reported by MacEwen and Vernot (1975) showed that approximately 60% of the MH content could be lost over 24 hours from a 0.01% MH-tap water solution. The authors also observed that the pH of the MH-water solution had an effect on decomposition, and adjusting the pH to 3.5 with HCl reduced the loss of the MH content to approximately 5%. Additional experiments demonstrated that adjustment of the drinking water to pH 3.5 with HCl did not affect body-weight gain or water consumption. Based on these observations, an experiment was conducted using three groups of male Syrian golden hamsters: 30 were exposed to 0.01% MH as the free base in drinking water (unadjusted pH group), 30 were exposed to 0.01% MH in drinking water adjusted to pH 3.5 with HCl (acidic pH group), and 17 were

exposed to drinking water alone adjusted to pH 3.5 with HCl (control). Test solutions in the main study were changed daily. No MH purity was reported. The hamsters (5 months old) were exposed to the test solutions for life. Study endpoints included survival, body weight (monthly), water consumption (daily), and limited hematology (RBC and Hct on five animals/group after 7, 11, and 15 months; bone marrow myeloid/erythroid (M/E) ratio in two acidic group animals and one control animal at end of study [83 weeks]). The authors estimated the nominal (unadjusted for loss) average daily doses of MH to be 7.3 mg/kg-day in the unadjusted pH group and 7.5 mg/kg-day in the acidic pH group. Complete necropsies with limited histopathology (liver, kidney, spleen, heart, lung, trachea, esophagus, thyroid, urocyst, testes, and gross lesions) were conducted on 13, 25, and 25 animals in the control, unadjusted, and acidic groups following death or sacrifice at the end of the study.

Survival of hamsters through the 80th week of treatment was not affected by treatment in either MH group (24, 17, and 17% in control, unadjusted MH, and acidic MH groups, respectively) (MacEwen and Vernot, 1975). The authors reported that the hamsters exposed to MH unadjusted for pH exhibited lower mean body weights beginning in the fourth month of exposure (statistical analysis not reported; data presented graphically). Animals exposed to the acidic MH solution had lower mean body weights after the 15th month of treatment. Based on the graphical data, mean terminal body weights appeared to be about 20% lower than controls in the unadjusted MH group and 10% lower than controls in the adjusted MH group. Hematology analysis showed reduced RBC and Hct in both MH groups at all time points; however, statistical analysis was not conducted, and the available data were inadequate for independent statistical analysis (variability was not reported). Evaluation of the bone marrow M/E ratio showed reduced values (0.5–0.7) for the two animals examined from the acidic MH group compared with the ratio of 1.9 observed in the one control; however, the small number of animals evaluated limits conclusions that can be drawn from this observation. Neither group exposed to MH exhibited a statistically significant increase in any tumor type or in the total number of tumors across sites. This study identifies a LOAEL of 7.3 mg/kg-day for body weight decrement of at least 10% and possible hematologic effects. A NOAEL was not determined.

There are several important differences in the two hamster studies that may have contributed to the different results for carcinogenicity. First, the hamsters used in the unpublished study were older at commencement of exposure (5 months) than the 6-week-old hamsters in the study by Toth and Shimizu (1973); as a result, the exposure duration in the study by MacEwen and Vernot (1975) was shorter (both studies featured lifetime exposure), and any enhancement in carcinogenicity associated with exposure to younger animals would not have been replicated. Second, MacEwen and Vernot (1975) used smaller groups (30/dose) of male hamsters only, while Toth and Shimizu (1973) used 50 hamsters/sex/dose. Third, MacEwen and Vernot (1975) took measures to ensure the stability of MH in water in their study, including daily changing of test solutions (versus three times per week in the Toth and Shimizu, 1973 study) and inclusion of treatment groups with and without adjustment to pH 3.5, noting that at this pH, the MH loss from 0.01% solution over 24 hours was much lower (approximately 5%) than at neutral pH (up to 60%). Additionally, as already stated, MacEwen and Vernot (1975) suggested that the hamsters in the study by Toth and Shimizu (1973) may have been exposed to oxidation products of MH rather than the compound itself.

Reproductive/developmental Studies—Slanina et al (1993) performed a embriotoxicity and teratogencity study with rat intravenous (i.v.) infusion as pilot experiment (Experiment 1), and a follow-up study with orally-administered MH (Experiment 2) as follow:

Experiment 1: Groups of three pregnant Sprague-Dawley rats received a constant i.v. daily dose of 0 (physiological saline solution), 1.2, 3.0 (low dose range), 4.2, 6.0 (intermediate dose range), 9.0, and 13.2 mg/kg-day (high dose range), respectively, at an infusion rate of 10 µL/h from GDs 6 to 13 (Experiment 1). Throughout the experiment animals were inspected daily for signs of maternal toxicity and weight gain. On Day 19 of gestation, the animals were sacrificed with halothane and examined for embryotoxicity, external and skeletal malformations.

Signs of apparent maternal toxicity were seen after continuous i.v. infusion of MH in the high dose range groups. Five out of 33 treated dams died before the end of the experiment in the highest dose group (13.2 mg/kg-day). One or several occasions of convulsions were observed in the high dose range groups (9.0–13.2 mg/kg-day). No apparent sings of maternal toxicity were observed in the intermediate and low dose range groups (1.2–6.0 mg/kg-day). A significant ($p < 0.01$, two-sample test of proportions) dose-related increase in the number of resorptions starting with the second lowest dose group was observed. The number of dams with at least one resorption was 70.6% and 100% in the 3.0- and 4.2-mg/kg-day dose groups, respectively, as compared to 21.1% of controls. For the only dam which became pregnant in the 6.0-mg/kg-day dose group, eight out of nine embryos were resorbed. A statistical difference ($p < 0.01$) for pregnancy rate was observed in the dose groups 4.2 and 6.0 mg/kg-day (43% and 93% of the animals, respectively, compared to 14% in control groups). The study authors indicated a nonstatistically significant increase of some minor abnormalities (e.g., oedema and anemia, extremely small fetuses), fetal body weights, or incidence of fetal malformations were observed compared to the control group.

As follow-up study of the dramatically decreased pregnancy rate after continuous i.v. infusion of MH pregnant rats observed in the experiment 1, Slanina et al. (1993) treated pregnant (plug-positive) Sprague-Dawley rats with a single gavage dose of 0 (corresponding amount of physiological saline), 1, or 5-mg/kg MH (with highest purity available) in distilled water on Gestation Day (GD) 6 (Experiment 2). Determination of MH in serum was performed in 6 out of 16 animals in the low-dose group and in all animals in the high-dose group. There were 16 dams in each exposure group and 24 controls. The dams were sacrificed on GD 19, at which time, uteri were removed, and numbers of corpora lutea, implantations, resorptions, and live and dead fetuses were recorded. Live fetuses were weighed and examined for external and skeletal malformations; visceral malformations were not evaluated. Preimplantation loss (calculated as percent of corpora lutea) was statistically significantly increased in the high-dose group. The data was presented as mean ± SD preimplantation losses per litter as follow: control, low-, and high-dose groups were 22.17 ± 0.50, 29.78 ± 0.40, and 40.83 ± 0.63, respectively; $p < 0.05$ for the high-dose group. The incidence of females with resorptions or dead fetuses was higher in the high-dose group (62.5%) than in controls (37.5%), but the difference was not statistically significant. Fetal body weight and rates of external and skeletal malformations were not affected by MH exposure. This study identifies a developmental LOAEL of 5 mg/kg based on increased preimplantation losses; the NOAEL is 1 mg/kg. Maternal effect levels could not be determined due to the lack of reported maternal evaluations. This effect is supported by the results of the experiment 1, an intravenous (i.v.) experiment with six dose levels, which showed a significant, dose-related increase in the incidence of females with resorptions/dead fetuses and a decrease in

pregnancy rate with increasing doses of MH. Based on the results of the oral study, the researchers attributed the decrease in pregnancy rate in the i.v. experiment to preimplantation loss, which was not recorded directly in the i.v. experiment.

Inhalation Exposure

No published studies of inhalation exposure to MH in animals were identified in the literature searches. The AMRL conducted a series of subchronic- and chronic-duration inhalation studies (exposure durations from 3 months to 1 year) with a variety of species (Kinkead et al., 1985; Darmer and MacEwen, 1973; MacEwen and Haun, 1971; Haun, 1970; Kroe, 1971). None of these studies was published in peer-reviewed journals. Reports of these studies (discussed below) were limited by poor descriptions of study design and findings, and occasionally, legibility issues.

Subchronic-Duration Studies—Groups of 80 male Sprague-Dawley rats, 8 female beagle dogs, and 4 female Rhesus monkeys were exposed to concentrations of 0-, 0.04-, or 0.1-ppm MH continuously (purity not specified) for 90 days (Darmer and MacEwen, 1973). Body weights were measured before and after exposure, as well as at 2-week intervals during exposure. Blood was collected from 30 rats/dose group after 45 and 90 days of exposure, and from dogs and monkeys before exposure, biweekly during exposure, and at exposure termination. Hematology parameters included Hct, Hgb, RBC, reticulocytes, WBC, and Heinz bodies. In addition, serum levels of total inorganic phosphorus and ALP were analyzed. Erythrocyte fragility tests were performed on blood samples collected from dogs at termination. At the end of exposure, the 20 rats not sacrificed earlier for hematology analyses were sacrificed, as were all dogs and monkeys, for gross pathology evaluations. Organ weights (heart, lung, liver, spleen, and kidney) were measured in rats only. The authors reported that tissues were collected for histopathology evaluation but did not present the findings of such evaluation. Concentrations of MH were analyzed daily using a colorimetric method calibrated to a known concentration of the compound; the authors reported average concentrations over the 90 days of 0.0462 and 0.100 ppm (0.087 and 0.19 mg/m^3) for the low- and high-exposure groups, respectively.

In rats, body weight was depressed in the high-exposure group through most of the exposure period; the authors reported that the difference was statistically significantly different from control at most measurements (Darmer and MacEwen, 1973). Based on data presented graphically, the difference from control was much less than 10% throughout the study. Statistically significant decreases in Hct (p <0.01), Hgb (p < 0.05), and RBC (p <0.01) were observed in both exposure groups at the 45-day measurement; at the 90-day measurement, only RBC (p < 0.01) in the high-exposure group was significantly different from controls. Table 3 shows the results. Total phosphorus was increased (8–13% higher than controls; p < 0.05) at both exposure levels at the 90-day measurement; there was no effect on serum ALP. The organ-weight data showed no effect of treatment on absolute or relative organ weights. The authors reported that there were no gross necropsy findings. Histopathology findings were not discussed. A LOAEL of 0.10 ppm (0.19 mg/m^3) and NOAEL of 0.046 ppm (0.087 mg/m^3) can be identified in rats based on reduced RBC persisting to 90 days.

Table 3. Hematology and Serum Chemistry Mean Values in Albino Sprague-Dawley Rats Exposed to Methyl Hydrazine by Continuous Inhalation for 90 Days (Darmer and MacEwen, 1973)

	Control	0.046 ppm	0.10 ppm
Number of Animals Examined	**30**	**30**	**30**
45 days			
Erythrocyte count (× 10)	8.2	7.6[a]	7.5[a]
Hemoglobin content (g %)	16.0	15.6[b]	15.0[a]
Hematocrit (vol %)	44	42[a]	41[a]
Total phosphorus (mg %)	7.1	8.1	7.3
Alkaline phosphatase (IU)	154	142	146
90 days			
Erythrocyte count (× 10)	7.0	7.6	6.1[b]
Hemoglobin content (g %)	16.7	15.7	15.4
Hematocrit (vol %)	44	44	43
Total phosphorus (mg %)	6.2	6.7[b]	7.0[b]
Alkaline phosphatase (IU)	117	117	117

[a]$p < 0.01$
[b]Significantly different from control at $p < 0.05$

In dogs exposed to the high concentration, there was evidence of hemolysis (reduced Hct, Hgb, and RBC, and increased osmotic fragility of erythrocytes) as well as increases in serum phosphorus and ALP (Darmer and MacEwen, 1973). No effects on these parameters were observed in the 0.046-ppm group. Table 4 provides the pertinent data. At necropsy, the livers of the dogs in the high-exposure group exhibited a "nutmeg" appearance, which the authors considered to be evidence of passive congestion; the incidence was not reported, and additional details were not provided. This study identified a LOAEL of 0.10 ppm (0.19 mg/m^3) in dogs based on hematology and serum chemistry changes and gross liver pathology; the NOAEL is 0.046 ppm (0.087 mg/m^3).

A monkey in the 0.046-ppm group died after 10 days of treatment (Darmer and MacEwen, 1973). Necropsy of the animal revealed amyloidosis, described as a preexisting condition, and the authors did not consider the death to be related to MH exposure. The data showed no effects of treatment on hematology parameters in monkeys (see Table 4). The authors reported that no gross pathology related to treatment was observed. This study suggests a NOAEL of 0.10 ppm (0.19 mg/m^3) in monkeys; although limited evaluations were performed (as in the other species), and group sizes were small.

Table 4. Hematology and Serum Chemistry Mean Values in Beagle Dogs and Rhesus Monkeys Exposed to Methyl Hydrazine by Continuous Inhalation for 90 Days (Results At Termination) (Darmer and MacEwen, 1973)

	Control	0.046 ppm	0.10 ppm
Dogs			
Number of Animals Examined	**8**	**8**	**8**
Hematology			
Erythrocyte count ($\times 10^6$)	6.26	5.41	4.73[a]
Hemoglobin content (g %)	18.1	17.0	15.1[a]
Hematocrit (vol %)	49	47	44[a]
Clinical chemistry			
Alkaline phosphatase	63	85	356[a]
Total phosphorus (mg %)	4.0	4.7	4.9[b]
Monkeys			
Number of Animals Examined	**4**	**4**	**4**
Hematology			
Erythrocyte count ($\times 10^6$)	5.20	4.44	4.72
Hemoglobin content (g %)	13.8	12.7	13.8
Hematocrit (vol %)	40	38	38

[a]$p < 0.01$
[b]Significantly different from control at $p < 0.05$

Chronic-Duration Studies—Rats, mice, dogs, and monkeys were exposed to MH (purity not specified) on an intermittent (6 hours/day, 5 days/week) or continuous basis for approximately 6 months (MacEwen and Haun, 1971; Kroe, 1971; Haun, 1970). These experiments are unpublished, and there are inconsistencies among the reports. Groups of 50 Wistar rats, 40 ICR mice, 8 beagle dogs, and 4 Rhesus monkeys were exposed to 0 or 0.2 ppm (0 or 0.38 mg/m^3) continuously; 0, 0.2, or 1 ppm (0, 0.38, or 1.9 mg/m^3) intermittently; or 0, 2, or 5 ppm (0, 3.8, or 9.4 mg/m^3) intermittently. There were inconsistencies among the reports; for example, MacEwen and Haun (1971) and Haun (1970) reported that female monkeys, dogs, and mice were used in all of the 6-month studies, while Kroe (1971) reported that the mice exposed to 2.0 and 5.0 ppm were male, and the dogs and monkeys exposed to 0.2 and 1.0 ppm were male. The methods and evaluations conducted were poorly reported; however, based on the results reported, the following parameters were evaluated: clinical signs and mortality in all animals; biweekly body weight in rats; monthly electroencephalogram (EEG) measurements in monkeys; biweekly hematology (8 indices) and clinical chemistry (15 indices) in dogs and monkeys; bone marrow M/E ratio in dogs; gross pathology in all animals; organ weights (heart, lungs, liver, kidneys, and spleen) in rats; and histopathology in 10 rats/group, 10 mice/group, and all dogs and monkeys at the end of the exposure period. The histological examinations included the liver, kidneys, spleen, heart, and lungs in all species, and the brain and unspecified endocrine glands in dogs and monkeys. All result data were presented graphically, and incidences of histopathologic findings were not reported.

In rats, there were no deaths, and no clinical signs of toxicity were reported (MacEwen and Haun, 1971; Kroe, 1971; Haun, 1970). Rats exhibited reduced body-weight gain with continuous exposure at 0.2 ppm and intermittent exposure at ≥1 ppm; body weight was not affected in the 0.2-ppm intermittent group. The authors did not indicate the methods of statistical analysis; however, body-weight differences were reported to be statistically significantly different from controls ($p < 0.01$) at Weeks 7, 9, and 13 for the 0.2-ppm continuous exposure and at Weeks 1–9 for the 1-ppm intermittent exposure. Visual examination of the growth curves indicate that the mean weights of the 0.2-ppm continuous and 1-ppm intermittent exposure groups were no more than approximately 5% lower than the controls during the first 13 weeks; data after Week 13 were not considered reliable by the authors due to heat stress (from equipment malfunction) in the control animals. At 2- and 5-ppm intermittent exposures, the study authors not that rat growth was significantly decreased from Weeks 10 and 12, respectively, until the end of the study; at Week 26, body weights in these groups were approximately 10 and 20% less than controls, respectively (based on visual inspection of data presented graphically). The study authors indicated that relative kidney and spleen weights were significantly ($p < 0.01$) increased in rats exposed to 2 or 5 ppm intermittently, but data and statistical methods were not given. It is not clear whether organ weight measurements were made in the lower exposure groups. According to the study authors, histologic examination of 10 rats/group did not indicate treatment-related changes at any exposure level (data not shown). A LOAEL of 2 ppm (3.8 mg/m^3) for intermittent exposure (adjusted to 0.68 mg/m^3 of continuous exposure) is identified for rats based on body-weight reduction of about 10%. The NOAEL for body-weight changes (organ weights not reported for this exposure group) was 1 ppm (1.9 mg/m^3) for intermittent (adjusted to 0.34 mg/m^3 of continuous exposure). By continuous exposure, 0.2 ppm (0.38 mg/m^3) was a NOAEL in rats.

In mice, mortality was increased at ≥2 ppm; the authors reported 1/40, 6/40, and 9/40 deaths in the control, 2-, and 5-ppm intermittent exposure groups, respectively (MacEwen and Haun, 1971; Haun, 1970; Kroe, 1971). Cause(s) and/or timing of deaths were not reported. In addition to the deaths attributed to treatment, the study authors reported that seven other mice from the 5-ppm exposure group died accidentally (no further information provided). Mice exposed to 5 ppm reportedly showed clinical signs of rough yellowed coats and occasional lethargy. Kroe (1971) reported pathology findings on 10 mice/group, but they did not report incidences. Findings reported in mice exposed to 2- and 5-ppm MH included centrilobular or periportal cholestasis, bile duct proliferation, centrilobular hepatic hemosiderosis, splenic hemosiderosis, and renal tubular hemosiderosis. Hemosiderosis of the liver, spleen, and renal tubules was also observed in the mice exposed to 0.2 ppm (intermittently or continuously) and 1 ppm; cholestasis and bile duct proliferation were not observed in these groups. The authors reported that hemosiderosis was more severe in the 0.2-ppm continuous group, followed by the 1- and 0.2-ppm intermittent groups, and that the effects in the 0.2-ppm intermittent group was "significantly more than nonexposed controls"; however, data and statistics were not reported. These results suggest a LOAEL for hemosiderosis of the liver, spleen, and renal tubules in mice given 0.2 ppm (0.38 mg/m^3) by intermittent exposure (adjusted to 0.068 mg/m^3 of continuous exposure). The lack of incidence information for this effect, however, renders the LOAEL uncertain.

No dogs died during the experiment (MacEwen and Haun, 1971; Kroe, 1971; Haun, 1970). Exposure to 5 ppm was associated with apparent conjunctivitis in dogs as indicated by prominent nictitating membranes and photophobia. The effect on the nictitating membranes was

observed as early as Week 2 and continued throughout the study, was minimal or absent following weekends of no exposure, and increased in severity following several daily exposures. No clinical signs were observed at ≤2 ppm. Hematological effects that were generally concentration-related and suggestive of hemolytic anemia were observed at all exposure levels, including both continuous and intermittent exposure to 0.2 ppm. These effects included decreases in RBC, Hct, Hgb, and bone marrow M/E ratio and increases in methemoglobin, Heinz body formation, and RBC fragility that were statistically significant at all exposure levels but more severe at 2 and 5 ppm. Clinical chemistry findings in dogs included dose-related increases in serum bilirubin, ALP, and total phosphorus levels in all exposure groups throughout the study, with increases of 2-fold or greater in all but the 0.2-ppm intermittent exposure group. Histopathology examinations in dogs revealed periportal intracanalicular cholestasis of the liver at all concentrations and hepatic and renal hemosiderosis at 2 and 5 ppm. Moderate lymphoid hyperplasia was reported in the lower exposure groups but not the higher exposure groups. A LOAEL of 0.2 ppm (0.38 mg/m^3), due to intermittent exposure (adjusted to 0.068 mg/m^3 of continuous exposure), is identified for dogs based on evidence of hemolytic anemia (hematology and serum chemistry changes as well as histopathology) and hepatic cholestasis. A NOAEL was not identified.

There were no deaths or clinical signs of toxicity among monkeys (MacEwen and Haun, 1971; Kroe, 1971; Haun, 1970). Body weights were not recorded. Hematology findings in monkeys included decreased Hct, Hgb, and RBC, as well as increased reticulocytes. Based on graphical presentation of data for the 2- and 5-ppm groups, RBC and reticulocyte counts were affected at both concentrations, but Hct and Hgb levels were only clearly affected at 5-ppm MH. No data were presented on these endpoints in monkeys exposed to 0.2 or 1 ppm. In addition to the hematology changes noted above, the authors reported the presence of Heinz bodies (one to five Heinz bodies in 100 RBCs) in all exposed groups of monkeys. No dose- or species-related effects were evident in monkeys or dogs that were observed. There were no histopathology findings in monkeys. Due to the lack of information on hematology results in the lower exposure groups, it is not possible to determine effect levels for monkeys.

Kinkead et al. (1985) detailed the results of longer experiments by the same laboratory (AMRL) in rats, mice, hamsters, and dogs exposed via inhalation (purity not reported) for 6 hours/day, 5 days/week, for 1 year. F344 rats (100/sex/group and 150/sex/controls, 10 weeks of age at start) were exposed to concentrations of 0, 0.02, 0.2, 2.0, or 5.0 ppm (0, 0.038, 0.38, 3.8, or 9.4 mg/m^3); C57BL/6J mice (400 females/group, 10 weeks of age at start) were exposed to concentrations of 0, 0.02, 0.2, or 2.0 ppm (0, 0.038, 0.38, or 3.8 mg/m^3); Syrian golden hamsters (200 males/group, 12 weeks of age at start) were exposed to concentrations of 0, 0.2, 2.0, or 5.0 ppm (0, 0.38, 3.8, or 9.4 mg/m^3); and beagle dogs (4/sex/group, 11–20 months of age at start) were exposed to 0, 0.2, or 2.0 ppm (0, 0.38, or 3.8 mg/m^3). Body weights were recorded biweekly for rats, hamsters, and dogs, and monthly for mice. Blood was collected biweekly during the exposure period from dogs for hematology (Hct, Hgb, RBC, and WBC) and clinical chemistry (ALP, alanine aminotransferase [ALT, previously serum glutamic pyruvic transaminase, or SGPT], bilirubin, glucose, triglycerides, iron, and sedimentation rate) evaluations. Methemoglobin levels were measured in dogs once every 3 months during exposure. Liver function was assessed using the bromosulphophthalein (BSP) retention test in dogs at the end of exposure. Rats, mice, and hamsters were observed untreated for 1 year after the conclusion of the exposure period, while dogs were observed for 5 years. At the end of the observation period, all animals were necropsied, and 33 tissues from each animal were examined

microscopically. The prolonged postexposure observation period prior to sacrifice and pathology evaluation (1 year in rodents and 5 years in dogs) is a limitation of the study for assessment of noncancer effects, allowing ample time for recovery of reversible nonneoplastic effects. No information on survival or clinical signs was reported for any species tested. Statistical tests used in the study were not reported.

Growth curves for rats showed body-weight decrements for both sexes (Kinkead et al., 1985). The authors reported that body weights were statistically significantly lower than controls during the exposure period in all groups of treated males and in the 2- and 5-ppm groups of females (data and *p*-value not given). Examination of the graphs indicated that body weights at the end of the exposure period were decreased by at least 10% in all exposed male rats and in the 5-ppm group of female rats. However, except for the 5-ppm groups in both sexes, there was no evidence of a dose response. Body weights in the 0.02-, 0.2-, and 2-ppm groups were similar throughout the exposure and postexposure periods in both sexes. It is, therefore, unclear whether this represents a treatment-related effect at the lower exposure levels. Review of the data shown indicated that there were no exposure-related increases in the incidences of any nonneoplastic or neoplastic lesions upon histopathology examination 1 year after treatment ended; statistically significant decreases in the incidences of some tumor types were associated with treatment. A NOAEL of 2 ppm (3.8 mg/m^3) and a LOAEL of 5 ppm (9.4 mg/m^3) are identified for rats based on decreased body weight clearly related to MH exposure.

Data on body weights of mice were not reported; histopathology findings were the only results given (Kinkead et al., 1985). Tumors of the nasal mucosa, lung, and liver, as well as hemangiomas (sites not specified), were increased in incidence in exposed mice when compared with unexposed controls (Kinkead et al., 1985). Table 5 shows the tumor incidences. Although the incidences of nasal tumors were not statistically distinguishable from controls, several different tumor types (adenomas, adenomatous polyps, osteomas, and epithelial neoplasms) were observed at the highest exposure, and no nasal tumors were observed in controls. The authors indicated that nasal tumors are rare in untreated mice and considered these tumors to be biologically significant. The incidence of hemangiomas at the highest exposure was not legible in the available version of the report; however, the authors reported that the incidence was "markedly increased." The incidences of several nonneoplastic lesions were also reported to be increased in treated mice (see Table 5), although interpretation of these data is uncertain. Due to the prolonged period of nonexposure and late sacrifice, reversible effects due to treatment would not be observable, and age-related changes may confound treatment-related findings. Also in the case of this study, tumors found in several organs may confound the results for nonneoplastic lesions in the same organs. For example, it is uncertain whether the liver cysts that developed in mice represent a distinct morphological entity from the adenomas and carcinomas that were apparent in the same organ, or whether hepatocyte pleomorphism reported as a distinct nonneoplastic lesion is related to the neoplastic effect in the liver. The low incidence and lack of a clear step-wise dose-response for some lesions (e.g., nasal lesions) also argues against these lesions being related to treatment. Due to the uncertain interpretation of the pathology data in this study, a NOAEL and a LOAEL were not identified for the mouse.

Table 5. Pathology Changes in Female C57BL/6J Mice Exposed to Methyl Hydrazine by Inhalation for 1 Year (Kinkead et al., 1985)

	Control	0.02 ppm	0.2 ppm	2.0 ppm
NeoplasticLesions				
Nasal adenoma	0/367[a]	1/354	0/349	1/355
Nasal adenomatous polyp	0/367	0/354	0/349	4/355
Nasal osteoma	0/367	0/354	0/349	3/355
Nasal and respiratory epithelial neoplasms	0/367	2/354	1/349	4/355
Lung adenoma	13/364	16/354	23/347	56/360[b]
Lung carcinoma	0/364	1/354	2/347	3/360
Liver adenoma	6/373	2/357	5/357	20/363[b]
Liver carcinoma	2/373	4/357	4/357	14/363[b]
Hemangioma	5/387	9/371	5/368	2?/371[b,c]
Nonneoplastic Lesions				
Nasal inflammation	10/367	35/354[b]	17/349	28/355[b]
Mandibular lymph node plasmacytosis	17/322	50/344[b]	46/330[b]	31/329
Mandibular lymph node hemorrhage	2/322	7/344	7/330	10/329[d]
Liver cysts	3/373	4/357	13/357[d]	39/363[b]
Bile duct hyperplasia	2/373	2/357	1/357	17/363[b]
Hepatocyte pleomorphism	11/373	6/357	11/357	33/363[b]
Gallbladder crystals	10/303	7/295	8/315	53/312[b]
Angiectasis	16/387	26/371	29/368[d]	59/371[b]
Kidney hydronephrosis	4/374	11/362	6/353	14/365[d]

[a]Number affected/number examined
[b]$p < 0.01$
[c]? represents illegible digit in available report
[d]Significantly different from control at $p < 0.05$

Treated male hamsters exhibited effects on growth (Kinkead et al., 1985). Body-weight decrements were observed in all treated groups, but a clear dose-response relationship was not evident. At the end of exposure, body weights of treated hamsters appeared to be between 5 and 10% lower than controls based on visual inspection of data presented graphically. Body weight was decreased throughout exposure in the 5.0-ppm group, from about Week 16 on in the 2.0-ppm group, and from about Week 36 in the 0.2-ppm group. Neoplastic changes in the nares and adrenals were observed in the hamsters (see Table 6). Nasal adenomas were increased in the high-exposure group, and nasal adenomatous polyps were increased in both the mid- and high-exposure groups. Benign adenomas of the adrenal cortex were also increased in incidence in the high-exposure group. As was observed for mice, the incidence of a number of nonneoplastic lesions were reported to be increased in treated hamsters (see Table 6), but, again, the low incidence, lack of clear progressive dose-response, and/or potential confounding by tumor- or age-related changes make interpretation of these data highly uncertain. Subsequently, no NOAEL or LOAEL can be identified.

Table 6. Pathology Changes in Male Syrian Golden Hamsters Exposed to Methyl Hydrazine by Inhalation for 1 Year (Kinkead et al., 1985)

	Control	0.2 ppm	2.0 ppm	5.0 ppm
Neoplastic Lesions				
Nasal adenoma	1/190[a]	0/177	0/180	7/177[b]
Nasal adenomatous polyp	0/190	0/177	9/180[c]	11/177[c]
Adrenal cortical adenoma (benign)	16/191	16/173	10/172	23/176[c]
Nonneoplastic Lesions				
Nasal submucosal cysts	35/190	52/177[b]	56/180[c]	46/177
Rhinitis	12/190	21/177[b]	25/180[b]	28/177[c]
Nasal hyperplasia	0/190	0/177	2/180	4/177
Pulmonary atelectasis	0/189	2/177	5/174[b]	7/174[c]
Hepatitis	20/194	15/175	24/177	31/174[b]
Biliary cysts	41/194	67/175[c]	73/177[c]	76/174[c]
Interstitial fibrosis of kidney	75/195	83/179	105/176[c]	96/177[b]

[a]Number affected/number examined
[b]Significantly different from control at $p < 0.05$
[c]$p < 0.01$

Kinkead et al. (1985) reported hematology, clinical chemistry, and histopathology findings for treated dogs. Apart from methemoglobin and serum ALT levels (shown in Table 7), hematology and clinical chemistry data were reported graphically. A review of graphs of hematology data indicated that both exposed groups of dogs exhibited dose-related decreases in RBC, Hgb, and Hct throughout the exposure period. Methemoglobin levels were increased relative to controls in the 2.0-ppm group throughout exposure and in the 0.2-ppm group at the 6-month time point (see Table 7). Serum ALT levels were markedly increased in the 2.0-ppm group (between 4- and 6-fold higher than controls throughout the entire exposure period, based on graphical data; levels at termination reported in Table 7) but were not different from controls at 0.2 ppm. Liver function, as measured by BSP retention, was also affected at the high exposure; retention was significantly ($p < 0.01$) increased in the 2.0-ppm group (see Table 7). The authors reported that there were no treatment-related nonneoplastic or neoplastic lesions observed upon histopathology examination of dogs 5 years after the end of exposure (data not shown). These data indicate a LOAEL of 0.2 ppm (0.38 mg/m^3) for beagle dogs based on hematology effects.

Table 7. Selected Changes (Mean Values) in Dogs Exposed to Methyl Hydrazine by Inhalation for 1 Year (Kinkead et al., 1985)

	Control	0.2 ppm	2.0 ppm
Number of Animals Examined	**4**	**4**	**4**
Hematology			
Methemoglobin (% Hgb): 3 months	0.791	0.753	1.019[a]
Methemoglobin (% Hgb): 6 months	0.806	1.084[b]	1.833[a]
Methemoglobin (% Hgb): 9 months	0.794	0.847	0.972[b]
Methemoglobin (% Hgb): 12 months	0.834	0.913	1.336[a]
Clinical chemistry			
AST (IU/L): 12 months	50.0	75.0	228.3[a]
Other			
BSP retention (% at 10 minutes): 12 months	14.9	20.3	34.5[a]

[a]Significantly different from control at $p < 0.05$
[b]$p < 0.01$

OTHER STUDIES

Genotoxicity

Tables 8 and 9 summarize in vitro and in vivo genotoxicity data for MH, respectively. Genotoxicity data for MH are mixed but suggest that this compound may be mutagenic under some circumstances. Specifically, increased mutation frequencies have been observed in several *Salmonella typhimurium* strains (TA100, TA1535, and TA1537) when tested in suspension assays (Matsushita et al., 1993; Rogan et al., 1982; Brusick and Matheson, 1976), while negative results were observed in these strains in plate incorporation assays (Mortelmans et al., 1986; Brusick and Matheson, 1976). Poso et al. (1995) observed increased mutation frequencies when *S. typhimurium* TA102 was tested in a plate incorporation assay; this strain also yielded positive results in a suspension assay (Matsushita et al., 1993). Tests for mutations in DNA repair-deficient strains of *Escherichia coli* have yielded positive results (Poso et al., 1995; Von Wright et al., 1977). When MH was tested for forward mutation in Chinese hamster lung fibroblast V79 cells, weakly positive results were reported (Kuszynski et al., 1981); this study was reported only as an abstract. No increase in forward mutations was observed in mouse lymphoma L5178Y cells (Rogers and Back, 1981; Brusick and Matheson, 1976). Tests for DNA repair in ACI rat and C3H/HeN mouse hepatocytes were positive without metabolic activation (Mori et al., 1988). MH did not induce unscheduled DNA synthesis in human fibroblast WI-38 cells when tested with or without metabolic activation (Brusick and Matheson, 1976). Ehrlich ascites liver cells incubated with MH have shown evidence of single-strand DNA breaks (Moroson and Furlan, 1969).

The few available in vivo studies of genotoxicity, including dominant lethal tests in mice and rats exposed via intraperitoneal injection, as well as tests for unscheduled DNA synthesis in the liver of rats exposed via gavage, have given negative results (Brusick and Matheson, 1976; Beije and Olsson, 1990). Host-mediated assays using *S. typhimurium* in mice exposed orally to MH gave equivocal results (Von Wright and Tikkanen, 1980b).

Table 8. Results of In Vitro Genotoxicity Studies of Methyl Hydrazine

Test System	Endpoint	MH			Result[a]			Reference
					Metabolic activation			
		Purity	Vehicle	Dose/Concentration Tested	+S9	–S9	Cytotoxicity[b]	
S. typhimurium TA1535, TA1537, TA1538, TA98, TA100	Reverse mutation (plate assay)	NR	DMSO	0.0001–5.0 µL/plate	–	–	NR	Brusick and Matheson, 1976 (unpublished)
S. typhimurium TA1535	Reverse mutation (suspension assay)	NR	DMSO	1–5 µL/mL	NT	+	NR	Brusick and Matheson, 1976 (unpublished)
S. typhimurium TA100	Reverse mutation	NR	NR	1–3 µmol	–	–	At >3 µmol	Von Wright and Tikkanen, 1980b
S. typhimurium TA1535, 1537	Reverse mutation (suspension assay)	≥98%	Distilled water	100–1000 µg/plate	+ at cytotoxic concentration	+ at cytotoxic concentration	At 200–500 µg/plate	Rogan et al., 1982
S. typhimurium TA1535, TA1537, TA97, TA98, TA100	Reverse mutation (plate assay)	NR	Distilled water	1–100 µg/plate	–	–	NR	Mortelmans et al., 1986
S. typhimurium TA102, TA100	Reverse mutation (suspension assay)	NR	NR	Up to 2 µmol for TA100 and 10 µmol for TA102	+	–	NR	Matsushita et al., 1993
S. typhimurium TA102	Reverse mutation (plate assay)	NR	Distilled water	0.5– 2.0 µmol/plate	+	NT	NR	Poso et al., 1995
Saccharomyces cerevisae D4	Gene recom-bination	NR	DMSO	0.000 – 5.0 µL/plate	–	–	NR	Brusick and Matheson, 1976 (unpublished)
E. coli WP2*uvrA*-	DNA repair	NR	DMSO	0.0001– 5.0 µL/plate	–	–	NR	Brusick and Matheson, 1976 (unpublished)
E. coli WP2 and CM871	DNA repair	NR	Distilled water	NR	+ for repair-deficient CM871	NT	NR	Poso et al., 1995
E. coli WP2 *try,hcr*	Reverse mutation	NR	Water	5–20 µg/mL	NT	+ at cytotoxic concentration	Yes >5 µg/mL	Von Wright et al, 1977
E. coli pol A_1^+, pol A_1^-, WP2 *try,hcr,* B/r WP2*try*	DNA repair	NR	NR	0.5–1.0 mg	NT	+	NR	Von Wright et al., 1977

Table 8. Results of In Vitro Genotoxicity Studies of Methyl Hydrazine

Test System	Endpoint	MH			Result[a]			Reference
					Metabolic activation			
		Purity	Vehicle	Dose/Concentration Tested	+S9	–S9	Cytotoxicity[b]	
E. coli WP2B/r *trp;*WP2B/r *uvrA, trp;* CM871 *uvrA,recA,lexA,trp*	SOS induction	NR	NR	0.5–2.0 µmol (spot test); 0.5–1.0 µmol/mL (liquid incubation test)	NT	+, greater response in repair-deficient strains	NR	Von Wright and Tikkanen 1980a
Chinese hamster lung fibroblasts V79 cells	Forward mutation	NR	NR	NR	Weakly +	Weakly +	NR	Kuszynski et al., 1981 (abstract)
L5178Y mouse lymphoma cells	Forward mutation	NR	DMSO	0.0005– 0.1 µL/mL	–	–	NR	Brusick and Matheson, 1976 (unpublished)
L5178Y mouse lymphoma cells	Forward mutation	NR	DMSO	0.1–5 mM	–	–	At 5 mM	Rogers and Back, 1981
ACI rat hepatocytes	DNA repair	NR	NR	10^{-5}–10^{-4} M MH sulfate	NT	+	At 10^{-3} M	Mori et al., 1988
C3H/HeN mouse hepatocytes	DNA repair	NR	NR	10^{-5}–10^{-3} M MH sulfate	NT	+	None	Mori et al., 1988
Human fibroblast WI-38 cells	Unscheduled DNA synthesis	NR	DMSO	0.1–1.0 µL/mL (without activation) 0.1–0.5 µL/mL (with activation)	–	–	NR	Brusick and Matheson, 1976 (unpublished)

[a]+ = active; – = inactive; NR = not reported; NT = not tested
[b]Defined for this review as survival < 50%
DMSO = dimethyl sulfoxide, DNA = deoxyribonucleic acid, NR = not reported, NT = not tested

Table 9. Results of In Vivo Genotoxicity Studies of Methyl Hydrazine

Species/Test System	Endpoint	Dose and Route	Result[a]	Reference
Mouse	Dominant lethal mutation	0.26–26 mg/kg via i.p. injection	–	Brusick and Matheson, 1976 (unpublished)
Rat	Dominant lethal mutation	0.22–22 mg/kg via i.p. injection	–	Brusick and Matheson, 1976 (unpublished)
Rat liver	Unscheduled DNA synthesis in liver	gavage, 30 mg/kg	–	Beije and Olsson, 1990 (abstract)

[a] – = inactive

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR METHYL HYDRAZINE

SUBCHRONIC AND CHRONIC p-RfD

There are no human studies of oral exposure to MH. The database of animal toxicological studies of oral exposure includes one subchronic-duration study in mice (Kelly et al., 1969), two chronic-duration studies each in mice and hamsters (MacEwen and Vernot, 1975; Toth and Shimizu, 1973; Toth, 1972; Roe et al., 1967), and a developmental toxicity study in rats (Slanina et al., 1993). The subchronic- and chronic-duration studies were primarily aimed at assessing carcinogenicity of MH, and most did not report any noncancer endpoints other than mortality. Of the available studies, only MacEwen and Vernot (1975) and Slanina et al. (1993) provided enough information on noncancer endpoints to identify a LOAEL.

The LOAEL identified for the data in MacEwen and Vernot (1975) was 7.3 mg/kg-day, the only dose tested, for reduced body weight (at least 10%) and possible hematologic effects in hamsters. The use of a single dose level precluded modeling of these data. The developmental toxicity study (Slanina et al., 1993) identified a LOAEL of 5 mg/kg (single dose) for increased preimplantation losses; the NOAEL was 1 mg/kg. The data for percent preimplantation loss were modeled using the EPA Benchmark Dose Software (BMDS v. 2.1), but adequate model fit was not achieved. Appendix B presents details of the benchmark dose (BMD) modeling. As a consequence, the NOAEL of 1 mg/kg-day associated with the developmental toxicity study (Slanina et al., 1993) was selected as the point of departure (POD) for both subchronic and chronic p-RfD derivation.

A **subchronic and a chronic p-RfD** were derived by dividing the NOAEL of 1.0 mg/kg-day by a UF of 1000, as shown below:

Subchronic and Chronic p-RfD = NOAEL ÷ UF
= 1.0 mg/kg-day ÷ 1000
= **0.001 mg/kg-day or 1×10^{-3} mg/kg-day**

The composite UF of 300 was composed of the following UFs:

- UF_H: A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response in humans
- UF_A: A UF_A of 10 is applied for animal-to-human extrapolation to account for potential toxicokinetic and toxicodynamic differences between rats and humans. There are no data to determine whether humans are more or less sensitive than rats to the developmental toxicity of MH
- UF_D: A UF_D of 10 is selected because the database includes a single developmental toxicity study in rats (Slanina et al., 1993) with only one day dosing (GD 6) and limited developmental endpoints tested, no two-generation reproduction studies, and there is a clear indication for hematological effects as well as hemosiderosis of the liver, kidney, and spleen during inhalation exposure (MacEwen and Haun, 1971; Kinkead et al., 1985)
- UF_L: A UF_L of 1 is applied because the POD was developed using a NOAEL.
- UF_S: A UF_S of 1 is applied because further adjustment for duration is not warranted when developmental toxicity data are used to develop a POD.

Confidence in the key study (Slanina et al., 1993) is low. This study included three dose groups with group sizes of 16–24 animals and identified clear NOAEL and LOAEL values. However, the dams were exposed on a single day (GD 6), so effects on other developmental stages could not be assessed. The toxicologic endpoints examined were uterine contents and external and skeletal malformations; visceral malformations were not evaluated, and no assessment of maternal toxicity was included. The oral experiment was supported by consistent findings in an i.v. experiment with six dose levels reported in the same paper. Confidence in the database for noncancer effects of oral MH is low. All oral subchronic- and chronic-duration studies were designed as cancer bioassays, with little or no investigation of noncancer endpoints. Developmental toxicity has been studied in only one species, and no studies of reproductive toxicity are available. Low confidence in the subchronic and chronic p-RfD follows.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR METHYL HYDRAZINE

There are no studies of subchronic- or chronic-duration human exposure to MH via inhalation. All of the available animal studies of inhaled MH are unpublished. These include 90-day studies of continuous exposure to MH in rats, dogs, and monkeys (Darmer and MacEwen, 1973); 6-month studies of intermittent (6 hours/day, 5 days/week) or continuous exposure in rats, mice, dogs, and monkeys (MacEwen and Haun, 1971; Kroe, 1971; Haun, 1970); and 1-year studies of intermittent exposure in rats, mice, hamsters, and dogs (Kinkead et al., 1985). Table 10 provides a summary of the effect levels identified from the available studies. These studies provide consistent evidence of hemolytic effects in several species, as well as hepatic changes in dogs and hamsters exposed for ≥90 days. Because all of the relevant studies are unpublished, it is not appropriate to derive provisional values. However, Appendix A of this document contains a screening value that may be useful in certain instances.

Table 10. Summary of Inhalation Noncancer Dose-Response Information for Methyl Hydrazine

Species and Study Type (*n*/sex/group)	Exposure	NOAEL (mg/m^3)	LOAEL (mg/m^3)	Responses at the LOAEL	Comments	Reference
Subchronic-Duration studies						
Rats 80 M/group	0, 0.046, 0.1 ppm (0, 0.087, 0.19 mg/m^3), continuously for 90 days	0.087 HEC:[a] 0.087	0.19 HEC: 0.19	Hematology changes (decreased RBC)	Evaluations limited to body weight, limited hematology and serum chemistry, and gross pathology	Darmer and MacEwen, 1973
Dogs 8 F/group	0, 0.046, 0.1 ppm (0, 0.087, 0.19 mg/m^3), continuously for 90 days	0.087 HEC: 0.087	0.19 HEC: 0.19	Hematology (decreased RBC, Hgb, Hct, increased osmotic fragility) and serum chemistry changes (increased ALP) and gross liver pathology	Evaluations limited to body weight, limited hematology and serum chemistry, and gross pathology	Darmer and MacEwen, 1973
Monkeys 4 F/group	0, 0.046, 0.1 ppm 0, 0.087, 0.19 mg/m^3), continuously for 90 days	0.19 HEC: 0.19	NA	None	Evaluations limited to hematology and gross pathology	Darmer and MacEwen, 1973
Chronic-Duration studies						
Wistar rats 50 M/group	0, 0.2, 1.0, 2.0, 5.0 ppm (0, 0.38, 1.9, 3.8, 9.4 mg/mg^3) 6 hours/day, 5 days/week, for about 6 months	1.9 HEC: 0.34	3.8 HEC: 0.68	Body weight decreased approximately 10%	Hematology not examined in rats	MacEwen and Haun, 1971; Kroe, 1971; Haun, 1970
Wistar rats 50 M/group	0, 0.2 ppm (0, 0.38 mg/m^3) continuously for 6 months	0.38 HEC: 0.38	NA	None	Hematology not examined in rats	MacEwen and Haun, 1971; Kroe, 1971; Haun, 1970

Table 10. Summary of Inhalation Noncancer Dose-Response Information for Methyl Hydrazine

Species and Study Type (*n*/sex/group)	Exposure	NOAEL (mg/m^3)	LOAEL (mg/m^3)	Responses at the LOAEL	Comments	Reference
F344 Rats 100/sex/treatment group 150/sex controls	0, 0.02, 0.2, 2.0, 5.0 ppm (0, 0.038, 0.38, 3.8, 9.4 mg/m^3) 6 hours/day, 5 days/week, for 1 year	3.8 HEC: 0.68	9.4 HEC: 1.68	Decreased body weight clearly related to MH exposure	Body-weight decreases at lower exposures not dose related	Kinkead et al., 1985
ICR mice 40/group	0, 0.2, 1.0, 2.0, 5.0 ppm (0, 0.38, 1.9, 3.8, 9.4 mg/mg^3) 6 hours/day, 5 days/week, for about 6 months	NA	0.38 HEC: 0.068	Hemosiderosis of the liver, spleen, and kidneys	Hematology not examined in mice. Sex of treated mice reported inconsistently by different authors (see study summary)	MacEwen and Haun, 1971; Kroe, 1971; Haun, 1970
ICR mice 40/group	0, 0.2 ppm (0, 0.38 mg/m^3) continuously for 6 months	NA	0.38 HEC: 0.38	Hemosiderosis of the liver, spleen, and kidneys	Hematology not examined in mice. Sex of treated mice reported inconsistently by different authors (see study summary)	MacEwen and Haun, 1971; Kroe, 1971; Haun, 1970
Beagle dogs 8/group	0, 0.2, 1.0, 2.0, 5.0 ppm (0, 0.38, 1.9, 3.8, 9.4 mg/mg^3) 6 hours/day, 5 days/week, for about 6 months	NA	0.38 HEC: 0.068	Hematologic and histopathologic evidence of hemolytic anemia; liver cholestasis	Sex of treated dogs reported inconsistently by different authors (see study summary)	MacEwen and Haun, 1971; Kroe, 1971; Haun, 1970
Beagle dogs 8/group	0, 0.2 ppm (0, 0.38 mg/m^3) continuously for 6 months	NA	0.38 HEC: 0.38	Hematologic and histopathologic evidence of hemolytic anemia; liver cholestasis	Sex of treated dogs reported inconsistently by different authors (see study summary)	MacEwen and Haun, 1971; Kroe, 1971; Haun, 1970
Beagle dogs 4/sex/group	0, 0.2, 2.0 ppm (0, 0.38, 3.8 mg/m^3) 6 hours/day, 5 days/week, for 1 year	NA	0.38 HEC: 0.068	Hematology changes (decreased RBC, Hgb, Hct; increased methemoglobin)		Kinkead et al., 1985

Table 10. Summary of Inhalation Noncancer Dose-Response Information for Methyl Hydrazine

Species and Study Type (*n*/sex/group)	Exposure	NOAEL (mg/m^3)	LOAEL (mg/m^3)	Responses at the LOAEL	Comments	Reference
C57BL/6J mice 400 female/group	0, 0.2, 2.0 ppm (0, 0.38, 3.8 mg/m^3) 6 hours/day, 5 days/week, for 1 year	NA	NA	NA	The low incidence and lack of a clear step-wise-response for lesions such as nasal lesions to be treatment related	Kinkead et al., 1985
Syrian golden hamsters 200 males/group	0, 0.2, 1.0, 2.0, 5.0 ppm (0, 0.38, 1.9, 3.8, 9.4 mg/m^3) 6 hours/day, 5 days/week, for about 6 months	NA	NA	NA	Body weights of treated hamsters was decreased throughout exposure in the 5-ppm (9.4-mg/m^3) group. Nonstatistically significant increase of nonneoplastic lesions	Kinkead et al., 1985

[a]HEC calculated as follows: $NOAEL_{HEC}$ = NOAEL × exposure hours/24 hours × exposure days/7 days × dosimetric adjustment
For systemic effects, the dosimetric adjustment is the ratio of the animal:human blood:gas partition coefficients for MH (in the absence of experimental values, a default value of 1 was used)

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR METHYL HYDRAZINE

WEIGHT-OF-EVIDENCE DESCRIPTOR

Under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), the available evidence suggests that MH is "*Likely to be Carcinogenic to Humans"* based on positive results in some (but not other) oral animal studies (discussed below), increased incidences of lung and liver tumors and hemangiomas in female mice exposed via inhalation for 1 year (Kinkead et al., 1985), and increased incidences of nasal and adrenal tumors in male hamsters exposed via inhalation for 1 year (Kinkead et al., 1985). Genotoxicity data for MH are mixed but suggest that this compound may be mutagenic under some circumstances.

The oral cancer data for MH include a study of increased incidences of lung and liver tumors in male and female mice exposed via drinking water for life (Toth, 1972). However, this study did not include a concurrent control group (the reference group was studied separately as part of another, previous experiment), and animals may have been exposed to oxidation products of MH, rather than the chemical itself (low stability of MH in water at neutral pH was demonstrated by MacEwen and Vernot, 1975; solutions were changed only three times per week in the Toth, 1972 study). Low survival in treated mice (no male mice surviving past 60 weeks and no female mice surviving past 70 weeks) also complicates interpretation of these findings. Also in this study, a 10-fold lower concentration of MH sulfate, which did not affect survival, produced a much larger increase in lung tumor incidence. However, lung tumors were not increased by MH sulfate in another study of mice that featured gavage (in water) exposure at a higher dose (Roe et al., 1967) but was limited by small group size (n = 25) and relatively short exposure duration (40 weeks).

The oral cancer data also include a study of increased incidences of malignant histiocytomas of the liver and tumors of the cecum in male and female hamsters exposed via drinking water for life (Toth and Shimizu, 1973). It has been suggested that exposure of treated animals in this study was to oxidation products of MH, rather than the chemical itself (MacEwen and Vernot, 1975). A second study in hamsters conducted at the same drinking water concentration as the Toth and Shimizu (1973) study, but including daily changes of test solution and adjustment of pH to 3.5 to reduce loss of MH from solution, found no increases in tumors (MacEwen and Vernot, 1975). However, this study started with older animals (5 months versus 6 weeks), thereby reducing exposure duration (exposure was lifetime in both studies), and group sizes were smaller (30 males in each of two treatment groups [adjusted pH and unadjusted] and only 17 controls, versus 50/sex/treated group and 100/sex/ control group in Toth and Shimizu, 1973).

QUANTITATIVE ESTIMATES OF CARCINOGENIC RISK

Oral Exposure

The database for oral carcinogenicity of MH is limited by (1) lack of a concurrent control in the study of mice (Toth, 1972); (2) reduced survival in the study of mice (Toth, 1972); (3) questions about the stability of the treatment compound in drinking water in both the Toth (1972) mouse and Toth and Shimizu (1973) hamster studies; and (4) inconsistent findings in two studies in hamsters (MacEwen and Vernot, 1975; Toth and Shimizu, 1973) that used the same exposure concentration. Furthermore, available oral studies demonstrating treatment-related induction of

tumors (Toth and Shimizu, 1973; Toth, 1972) each used a single concentration of MH in drinking water, providing only limited dose-response information. As a consequence of the uncertainties in the available database for oral carcinogenicity of MH, a provisional OSF was not derived for this compound.

Inhalation Exposure

No human inhalation exposure data were located. The animal data available are from the 1-year bioassay conducted by Kinkead et al. (1985), an unpublished technical report for a chronic-duration inhalation toxicity study. Kinkead et al. (1985) was the only study that demonstrated increased incidences of tumors after inhalation exposure. In female $B6C3F_1$ mice, there were increased incidences of lung adenomas, liver adenomas, liver carcinomas, and hemangiomas (Kinkead et al., 1985). In male hamsters, the incidences of nasal adenomas, nasal adenomatous polyps, and adrenal cortical adenomas were significantly increased (Kinkead et al., 1985). Because the incidence of hemangiomas in the high-dose group was illegible in the available report, no modeling was performed on this data set. Because the principal study is unpublished, it is not appropriate to derive provisional values. However, Appendix A presents a screening provisional inhalation unit risk value (Screening p-IUR).

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APPENDIX A. DERIVATION OF AN INHALATION SCREENING VALUE FOR METHYL HYDRAZINE

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

To provide a basis for comparing the studies, NOAEL and LOAEL values were adjusted for continuous exposure and then converted to human equivalent concentrations (HECs). First, exposure was adjusted to equivalent continuous exposure according to the equation below:

$$NOAEL_{ADJ} = NOAEL\ (mg/m^3) \times \text{hours per day} \div 24 \times \text{days per week} \div 7$$

Then, treating MH as a Category 3 gas for effects on extrarespiratory endpoints, the dosimetric adjustments were made using the ratio of animal:human blood:gas partition coefficients for MH (U.S. EPA, 1994b). However, blood:gas partition coefficients for MH were not located for any species. In the absence of blood:gas partition coefficients, the default ratio of 1.0 was used to perform the dosimetric adjustment. For each study, the duration-adjusted effect level was multiplied by the corresponding dosimetric adjustment to calculate the HEC:

$$NOAEL_{HEC} = NOAEL_{ADJ} \times \text{Dosimetric Adjustment}$$

Where:

Dosimetric Adjustment = ratio of animal:human blood:gas partition coefficients (default = 1).

Table 10 includes the HECs.

SCREENING SUBCHRONIC p-RfC

Table 10 summarizes inhalation noncancer dose-response data for MH and converted HECs for both subchronic- and chronic-duration studies in rats, mice, hamsters, dogs, and monkeys (Darmer and MacEwen, 1973; MacEwen and Haun, 1971; Kroe, 1971; Haun, 1970; Kinkead et al., 1985). Darmer and MacEwen (1973) is the only available inhalation subchronic-duration study and involved rats, dogs, and monkeys. Darmer and MacEwen (1973) reported that hematologic effects of continuous exposure to 0.1 ppm (0.19 mg/m^3) monomethyl hydrazine (MMH) showed dose-response consistency with other previous studies. However, continuous exposure at 0.046 ppm (0.08 mg/m^3) did not significantly alter the hematology of the treated and animals and had no effect on rat growth. On the basis of these changes in hematologic parameters (RBC, Hgb, and Hct), as well as serum chemistry parameters (ALP and

total phosphorus), in both rats and dogs (see Tables 3 and 4), $NOAEL_{HEC}$ and $LOAEL_{HEC}$ values for rats and dogs were the same (0.087 and 0.19 mg/m^3, respectively). The study in monkeys did not identify any effects at the highest concentration tested ($NOAEL_{HEC}$ of 0.19 mg/m^3). The data were reported without any measures of variability (e.g., standard deviation), precluding benchmark dose modeling. Consequently, the $NOAEL_{HEC}$ of 0.087 mg/m^3 for both rats and dogs was selected as the POD for screening subchronic p-RfC derivation.

The **screening subchronic p-RfC** for MH was calculated as the $NOAEL_{HEC}$ of 0.087 mg/m^3 divided by an uncertainty factor (UF) of 300, as shown below:

Screening Subchronic p-RfC = $NOAEL_{HEC} \div UF$
= 0.087 mg/m^3 ÷ 300
= **0.00029 or 3 × 10^{-4} mg/m^3**

The composite UF of 300 was composed of the following UFs:

- UF_A: A factor of 3 ($10^{0.5}$) is applied for animal-to-human extrapolation to account for the toxicodynamic portion of the UF_A because the toxicokinetic portion ($10^{0.5}$) has been addressed in the dosimetric conversions.
- UF_H: A factor of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response in humans
- UF_D: A factor of 10 is selected because there are no acceptable two-generation reproduction studies or developmental studies, and there is no indication of any other studies that may be relevant to the database UF.
- UF_L: A factor of 1 is applied because the POD was developed using a NOAEL.
- UF_S: A factor of 1 is applied because the POD was developed using a subchronic-duration study.

Confidence in the key study (Darmer and MacEwen, 1973) is low. This study included three exposure groups with group sizes of 80 rats and eight dogs and identified clear NOAEL and LOAEL values for effects (hematology changes) shown consistently in several studies and species. However, the study is unpublished and, thus, has not been subjected to peer review. Only a single sex (male rats and female dogs) was tested in each species. The toxicologic endpoints examined were limited to body weight, hematology, serum chemistry, and gross pathology; histopathology evaluations were not reported. Confidence in the database for noncancer effects of subchronic-duration inhalation exposure to MH is low, as the database is limited to one unpublished study in rats, dogs, and monkeys (Darmer and MacEwen, 1973). There are no studies examining developmental or reproductive effects after inhalation of MH, and developmental toxicity has been demonstrated in one oral study (Slanina et al., 1993). Low confidence in the screening subchronic p-RfC follows.

SCREENING CHRONIC p-RfC

Table 10 shows the HECs for 6-month and 1-year studies in rats, mice, and dogs (Kinkead et al., 1985; MacEwen and Haun, 1971; Kroe, 1971; Haun, 1970). As the table indicates, the most sensitive endpoints were hematological and/or histopathological evidence of hemolytic anemia in dogs and hemosiderosis of the liver, spleen, and kidneys in mice exposed to a HEC of 0.068 mg/m^3 for 6 months or 1 year. Reported changes at this exposure level included decreases in RBC, Hgb, and Hct; increases in RBC fragility, methemoglobin, and Heinz bodies;

and hemosiderosis of the spleen, liver, and kidneys. Liver cholestasis, as indicated by histopathology and serum chemistry (increased serum ALP and bilirubin), was also evident in dogs exposed at this level in the 6-month study. Similar liver effects were seen in the 6-month mouse study and the 1-year dog study but at higher concentrations. NOAEL values were not established. No standard deviation was reported, which made the data in these studies insufficient to perform benchmark dose modeling. Consequently, the $LOAEL_{HEC}$ of 0.068 mg/m^3 for both mice and dogs was selected as the POD for screening chronic p-RfC derivation.

The **screening chronic p-RfC** for MH was calculated as the $LOAEL_{HEC}$ of 0.068 mg/m^3 divided by a UF of 3000, as shown below:

$$\begin{aligned}\textbf{Screening Chronic p-RfC} &= LOAEL_{HEC} \div UF \\ &= 0.068\ mg/m^3 \div 3000 \\ &= \mathbf{0.00002\ or\ 2 \times 10^{-5}\ mg/m^3}\end{aligned}$$

The composite UF of 3000 was composed of the following UFs:

- UF_A: A factor of 3 ($10^{0.5}$) is applied for animal-to-human extrapolation to account for the toxicodynamic portion of the UF_A because the toxicokinetic portion ($10^{0.5}$) has been addressed in the dosimetric conversions.
- UF_H: A factor of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response in humans
- UF_D: A factor of 10 is selected because there are no acceptable two-generation reproduction studies or developmental studies, and there is no indication of any other studies that may be relevant to the database UF. All of the available studies are unpublished, and none of them included lifetime exposure.
- UF_L: A factor of 10 is applied for using a POD based on a LOAEL because a NOAEL cannot be determined from the available data.
- UF_S: A factor of 1 is applied because a chronic-duration study was utilized as the critical study.

Confidence in the key mouse and dog studies (Kinkead et al., 1985; MacEwen and Haun, 1971; Kroe, 1971; Haun, 1970) is low. The studies included multiple exposure groups but did not identify a NOAEL. Group sizes were large for mice but small for dogs. The studies are all unpublished and, thus, have not been subjected to peer review; in addition, much of the data were reported graphically and without information on the nature or results of statistical analysis. The critical hematology endpoints were not measured directly in mice but were only indicated indirectly by histopathology. The 1-year exposure duration, while chronic in duration, did not represent a lifetime exposure in any of the species tested. Confidence in the database for noncancer effects of chronic-duration inhalation exposure to MH is low. The database includes 6-month and 1-year studies in rats, mice, hamsters, dogs, and/or monkeys (Kinkead et al., 1985; MacEwen and Haun, 1971; Kroe, 1971; Haun, 1970); however, few studies identified NOAEL levels (see Table 10). All of the available studies are unpublished, and none of them included lifetime exposure. There were reporting inconsistencies among reports of the same studies; for example, MacEwen and Haun (1971) and Haun (1970) reported that female monkeys, dogs, and mice were used in all of the 6-month studies, while Kroe (1971) reported that the mice exposed to 2.0 and 5.0 ppm were male, and that the dogs and monkeys exposed to 0.2 and 1.0 ppm were

male. The studies by Kinkead et al. (1985) employed prolonged postexposure observation periods (1 year in rodents and 5 years in dogs) prior to pathology evaluations, allowing for possible recovery from reversible noncancer effects and age- and tumor-related confounding of noncancer lesions. There are no studies examining developmental or reproductive effects of inhalation of MH; developmental toxicity has been demonstrated in one oral study (Slanina et al., 1993). Low confidence in the screening chronic p-RfC follows.

SCREENING INHALATION UNIT RISK (IUR)

Inhalation data are sufficient to derive a quantitative estimate of cancer risk for MH; this derivation is shown below. Data from the 1-year bioassay conducted by Kinkead et al. (1985) were used as the basis for the quantitative cancer assessment, as this was the only study that demonstrated increased incidences of tumors after inhalation exposure. In female $B6C3F_1$ mice, there were increased incidences of lung adenomas, liver adenomas, liver carcinomas, and hemangiomas (Kinkead et al., 1985). In male hamsters, the incidences of nasal adenomas, nasal adenomatous polyps, and adrenal cortical adenomas were significantly increased (Kinkead et al., 1985). Because the incidence of hemangiomas in the high-dose group was illegible in the available report, no modeling was performed on this data set. Table A-1 shows the modeling that was performed for the remaining data sets.

Table A-1. Dose-Response Data for Derivation of Inhalation Unit Risk (Kinkead et al., 1985)

Species and Sex	Target Organ	Tumor Type	Exposure Concentration (mg/m^3)			
			Control	**0.038**	**0.38**	**3.8**
Female mouse	Lung	Adenoma	13/364[a]	16/354	23/347	56/360[b]
	Liver	Adenoma	6/373	2/357	5/357	20/363[b]
	Liver	Carcinoma	2/373	4/357	4/357	14/363[b]
			Control	**0.38**	**3.8**	**9.4**
Male hamster[c]	Nasal cavity	Adenoma	1/190	0/177	0/180	7/177[d]
	Nasal cavity	Adenomatous polyp	0/190	0/177	9/180[b]	11/177[b]
	Adrenal cortex	Adenoma	16/191	16/173	10/172	23/176[b]

[a]Number affected/number examined
[b] $p < 0.01$
[c]Incidence of hemangioma data was not included because it was not quantified in the Kinkead et al. (1985) study
[d]Significantly different from control at $p < 0.05$

Dose-response modeling of the data in Table A-1 was performed to obtain a POD for a quantitative assessment of cancer risk. The POD is an estimated concentration (expressed in human-equivalent terms) near the lower end of the observed range that marks the starting point for extrapolation to lower doses. Each tumor type was modeled individually. Combining tumors at a single site (e.g., liver adenomas and carcinomas in mice, or nasal cavity adenomas and adenomatous polyps in hamsters) was considered but was not possible because the summary data were presented only for individual tumor types in the original study and the individual animal data were not available.

Appendix C provides details of the modeling efforts and the selection of best-fitting models. In accordance with EPA (2000) guidance, BMC and BMCL values associated with a

BMR (benchmark response) of 10% extra risk were calculated. Table A-2 compares the BMC_{10} and $BMCL_{10}$ values estimated from the best-fitting models for the various tumor types. The $BMCL_{10}$ values were adjusted to equivalent continuous exposure concentrations $BMCL_{10ADJ}$, and HECs were then calculated using the dosimetric adjustment appropriate to the observed tumor type, as shown in the following equations:

$$BMCL_{10ADJ} = BMCL_{10} \times \text{exposure hours} \div 24 \text{ hours} \times \text{exposure days} \div 7 \text{ days}$$
$$= BMCL_{10} \times 6 \text{ hours} \div 24 \text{ hours} \times 5 \text{ days} \div 7 \text{ days}$$

$$BMCL_{10HEC} = BMCL_{10ADJ} \times \text{dosimetric adjustment}$$

Table A-2. Comparison of BMC_{10} and $BMCL_{10}$ Values for Lung, Nasal, and Adrenal Tumors in Female Mice and Male Hamsters Exposed to Methyl Hydrazine[a]

Species and Sex	Target Organ	Tumor Type	BMC_{10}[b] (mg/m^3)	$BMCL_{10}$[b] (mg/m^3)	$BMCL_{10ADJ}$[c] (mg/m^3)	Dosimetric Adjustment[d]	$BMCL_{10HEC}$[e] (mg/m^3)
Female mouse	Lung	Adenoma	3.12	2.3	0.41	3.54 ($RGDR_{PU}$)	1.4
	Liver	Adenoma	8.82	5.8	1.04	1.0 (blood:gas)	1.0
Male hamster	Nasal cavity	Adenoma	13.46	11.1	1.98	0.059 ($RGDR_{ET}$)	0.12
	Nasal cavity	Adenomatous polyp	12.36	8.7	1.55	0.059 ($RGDR_{ET}$)	0.092
	Adrenal cortex	Adenoma	11.60	9.2	1.64	1.0 (blood:gas)	1.6

[a]See Appendix C for details of modeling
[b]Unadjusted for continuous exposure and before conversion to human equivalent concentration
[c]Exposure concentration adjusted to equivalent continuous exposure concentration based on treatment 6 hours/day, 5 days/week, as follows: $BMCL_{10ADJ} = BMCL_{10} \times 6$ hours/24 hours × 5 days/7 days
[d]Dosimetric adjustment is calculated according to endpoint, as follows:
For systemic effects, it is the ratio of the animal:human blood:gas partition coefficients for MH (in the absence of experimental values, a default value of 1 was used);
For respiratory effects, it is the RGDR for the affected portion of the respiratory tract (pulmonary for lung adenomas in mice and extrathoracic for nasal tumors in hamsters), calculated as the ratio of the animal:human minute volume/surface area ratios using default values from EPA (1994b)
[e]Human equivalent concentration calculated as product of adjusted LOAEL and dosimetric adjustment, as follows: $BMCL_{10HEC} = BMCL_{10ADJ} \times$ Dosimetric adjustment

For tumors in the respiratory tract, the dosimetric adjustment is the regional gas deposition ratio (RGDR) for the affected portion of the respiratory tract (pulmonary for lung adenomas in mice and extrathoracic for nasal tumors in hamsters). An RGDR(ET) was calculated as the dosimetric adjustment for nasal (extrathoracic) tumors in male hamsters with chronic-duration exposure, as follows (equation 4-18 and default values from U.S. EPA,1994b):

$$\begin{aligned}\text{Hamster RGDR(ET)} &= (MV_a \div S_a) \div (MV_h \div S_h) \\ &= (0.057 \text{ L/min}/14 \text{ cm}^2) \div (13.8 \text{ L/min} \div 200 \text{ cm}^2) \\ &= 0.0041 \text{ L/min-cm}^2 \div 0.069 \text{ L/min-cm}^2 \\ &= 0.059\end{aligned}$$

Where:

RGDR(ET) = regional gas dose ratio for the extrathoracic area of the respiratory tract
MV_a = animal minute volume (hamster = 0.057 L/min, based on default body weight of 0.134 kg for male hamster in a chronic-duration study; see U.S. EPA, 1994b)
MV_h = human minute volume (13.8 L/min)
S_a = surface area of the extrathoracic region in the animal (hamster = 14 cm^2)
S_h = surface area of the extrathoracic region in the human (200 cm^2)

Similarly, an RGDR(PU) of 3.54 was calculated as the dosimetric adjustment for pulmonary tumors in female mice with chronic exposure according to Equation 4-28 (pulmonary RGDR for Category 1 gas) in EPA (1994b) using default values for body weight (0.0353 kg for mice, 70 kg for humans), ventilation rate (0.0413 L/minute for mice, 13.8 L/minute for humans), and pulmonary surface area (0.05 m^2 for mice, 54 m^2 for humans) in EPA (1994b).

The dosimetric adjustment for the remaining, systemic (extrarespiratory) tumors is the ratio of animal:human blood:gas partition coefficients (U.S. EPA, 1994b). In the absence of chemical-specific blood:gas partition coefficients for MH in humans or animals, the default value of 1.0 was used.

Among the data sets modeled, the lowest $BMCL_{10HEC}$ values calculated as described above were 0.09 and 0.1 mg/m^3 based on modeling of nasal adenomatous polyps and nasal adenomas in hamsters, respectively. The low value of 0.09 mg/m^3 was selected as the POD for derivation of the IUR.

The mode of action for tumors produced by MH has not been elucidated; thus, the default linear methodology was applied. In order to linearly extrapolate cancer risks from the $BMCL_{10HEC}$ to the origin, a **Screening p-IUR** was calculated as the ratio $BMR/BMCL_{10HEC}$ (0.1/0.09 mg/m^3), as follows:

$$\begin{aligned}\textbf{Screening p-IUR} &= BMR \div BMCL_{10HEC} \\ &= 0.1 \div 0.09 \text{ mg/m}^3 \\ &= \mathbf{1 \ (mg/m^3)^{-1}}\end{aligned}$$

The screening provisional IUR for MH should not be used with exposures exceeding the POD ($BMCL_{10HEC}$ = 0.09 mg/m^3), because at exposures above this level, the fitted dose-response model better characterizes what is known about the carcinogenicity of MH.

APPENDIX B. DETAILS OF BENCHMARK DOSE MODELING FOR SUBCHRONIC AND CHRONIC RfD

MODEL-FITTING PROCEDURE FOR CONTINUOUS DATA

The BMD modeling for continuous data was conducted with EPA's BMD software (BMDS v. 2.1). For the continuous data, the original data were modeled with all the continuous models available within the software with a default BMR of one standard deviation (SD). An adequate fit was judged based on the goodness-of-fit *p*-value ($p > 0.1$), scaled residual at the range of benchmark response (BMR), and visual inspection of the model fit. In addition to the three criteria for judging the adequate model fit, whether the variance needed to be modeled, and if so, how it was modeled also determined the final use of the model results. If a homogenous variance model was recommended based on statistics (Test 2) provided from the BMD modeling results, the final BMD results would be estimated from a homogenous variance model. If the test for homogenous variance (Test 2) was negative ($p < 0.1$), the model was run again while applying the power model integrated into the BMDS to account for nonhomogenous variance (known as the nonhomogenous variance model). If the nonhomogenous variance model did not provide an adequate fit to the variance data (Test 3: $p < 0.1$), the data set would be considered unsuitable for BMD modeling. Among all the models providing adequate data fit (goodness-of-fit *p*-value ≥ 0.1), the lowest BMDL will be selected if the BMDLs estimated from different models vary over a wide range (not quantified); otherwise, the BMDL from the model with the lowest Akaike Information Criterion (AIC) would be considered appropriate for the data set.

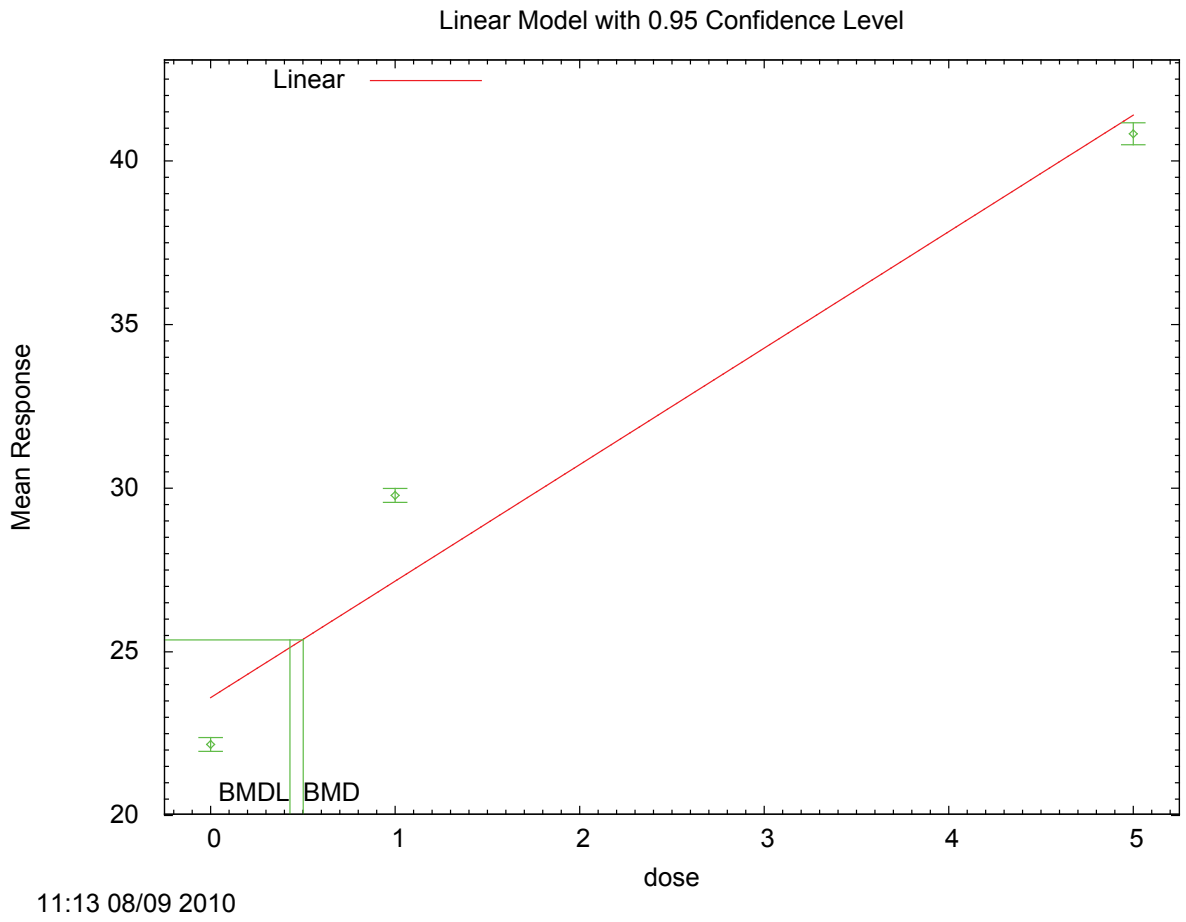
MODEL-FITTING RESULTS FOR PERCENT PREIMPLANTATION LOSS IN RATS (SLANINA ET AL., 1993)

The data for percent preimplantation loss associated with MH administration (mean ± SD [*n*] preimplantation losses per litter of 22.17 ± 0.50 [24], 29.78 ± 0.40 [16], and 40.83 ± 0.63% [16], for 0-, 1-, and 5-mg/kg doses, respectively) were modeled using the EPA Benchmark Dose Software (BMDS v. 2.1). The models were run with a BMR of 1 SD from the control mean, as recommended by EPA (2000). With only three dose groups, the linear model was the only continuous variable model available (the larger models have too many parameters for the number of data points, leaving insufficient degrees of freedom to assess model fit). While the homogenous variance model provided adequate fit to the variance data, the means did not fit the linear model. Table B-1 shows the modeling results. Thus, this data set was not suitable for BMD modeling.

Table B-1. Model Predictions for Percent Preimplantation Loss in Rat (Slanina et al., 1993)

Model	Variance *p*-Value[a]	Means *p*-Value[a]	AIC	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)
Linear, homogenous variance[b]	0.1975	<0.0001	126.81	0.50	0.43

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria
[b]Coefficients restricted to be positive



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Polynomial Model. (Version: 2.13; Date: 04/08/2008)
Input Data File: C:\USEPA\BMDS21\Data\MMH\lin_MMH-slamine_SDMHH-Slanine-Linear.(d)
Gnuplot Plotting File: C:\USEPA\BMDS21\Data\MMH\lin_MMH-slamine_SDMHH-Slanine-Linear.plt
Mon Aug 09 11:13:53 2010

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BMDS Model Run

~~~~~~~~~~

The form of the response function is:

Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

Dependent variable = Mean
Independent variable = Dose
rho is set to 0
~~~~~~~~~~

Signs of the polynomial coefficients are not restricted
A constant variance model is fit

Total number of dose groups = 3
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values
alpha = 0.266104
rho = 0 Specified
beta_0 = 24.0167
beta_1 = 3.455

Asymptotic Correlation Matrix of Parameter Estimates

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

	alpha	beta_0	beta_1
alpha	1	1.5e-009	2.8e-009
beta_0	1.5e-009	1	-0.63
beta_1	2.8e-009	-0.63	1

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
alpha	3.1815	0.601247	2.00308	4.35992
beta_0	23.5802	0.306592	22.9793	24.1811
beta_1	3.55573	0.112489	3.33525	3.7762

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	24	22.2	23.6	0.5	1.78	-3.87
1	16	29.8	27.1	0.4	1.78	5.93
5	16	40.8	41.4	0.63	1.78	-1.19

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	10.610004	4	-13.220007
A2	12.232083	6	-12.464166
A3	10.610004	4	-13.220007
fitted	**-60.405886**	**3**	**126.811772**
R	-142.616844	2	289.233688

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	309.698	4	<.0001
Test 2	3.24416	2	0.1975
Test 3	**3.24416**	**2**	**0.1975**
Test 4	142.032	1	<.0001

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

Specified effect = 1

Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 0.501635

BMDL = 0.429715

APPENDIX C. DETAILS OF BENCHMARK DOSE MODELING FOR INHALATION UNIT RISK

MODEL-FITTING PROCEDURE FOR CANCER INCIDENCE DATA

The model-fitting procedure for dichotomous cancer incidence data is as follows. The multistage cancer model in the EPA BMDS is fit to the incidence data using the extra risk option. The multistage cancer model is run for all polynomial degrees up to n-1 (where n is the number of dose groups including control). Adequate model fit is judged by three criteria: goodness-of-fit p-value ($p > 0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMDL is selected as the POD when the difference between the BMDLs estimated from these models is high (unquantified); otherwise, the BMDL from the model with the lowest Akaike Information Criterion (AIC) is chosen. In accordance with EPA (2000) guidance, BMDs and BMDL values associated with a BMR of 10% extra risk are calculated.

MODEL-FITTING RESULTS FOR LUNG ADENOMA IN FEMALE MICE EXPOSED TO METHYL HYDRAZINE BY INHALATION FOR 1 YEAR (KINKEAD ET AL., 1985)

Applying the procedure outlined above to the data for lung adenoma in female mice exposed to MH, adequate fit was achieved with all models. Table C-1 shows the modeling results. The higher-degree polynomial models defaulted back to the 1-degree model, so that all of the models gave the same result. Figure C-1 shows the fit of the multistage cancer, 1-degree model to the data. The benchmark concentration (BMC_{10}) and associated 95% lower confidence limit ($BMCL_{10}$) for this data set were 3.12 and 2.34 mg/m^3, respectively.

Table C-1. Model Predictions for Lung Adenoma in Female Mice Exposed to Methyl Hydrazine by Inhalation for 1 Year (Kinkead et al., 1985)

Model	Degrees of Freedom	χ^2	χ^2 Goodness-of-Fit p-Value[a]	AIC	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)
Multistage cancer, 1-degree[b]	**2**	**1.30**	**0.52**	**728.30**	**3.12**	**2.34**
Multistage cancer, 2-degree[b]	2	1.30	0.52	728.30	3.12	2.34
Multistage cancer, 3-degree[b]	2	1.30	0.52	728.30	3.12	2.34

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria
[b]Betas restricted to ≥0

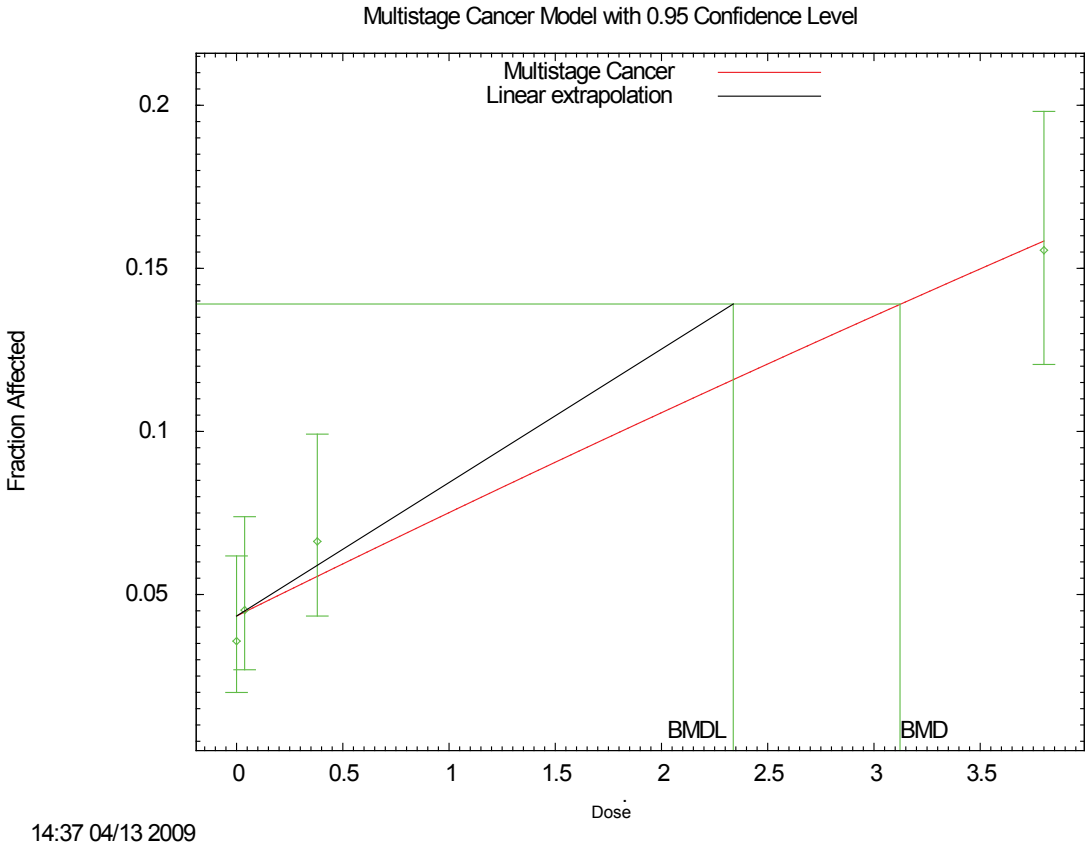

Figure C-1. Fit of Multistage Cancer, 1-Degree Model to Data on Lung Adenoma in Female Mice Exposed to Methyl Hydrazine by Inhalation for 1 Year (Kinkead et al., 1985).

Note: BMC and BMCL indicated are associated with an extra risk of 10% and are in units of mg/m^3.

MODEL-FITTING RESULTS FOR LIVER ADENOMA IN FEMALE MICE EXPOSED TO METHYL HYDRAZINE BY INHALATION FOR 1 YEAR (KINKEAD ET AL., 1985)

Applying the procedure outlined above to the data for liver adenoma in female mice exposed to MH, adequate model fit was achieved with all models. Table C-2 shows the modeling results. BMCLs from models providing adequate fit did not differ by more than 3-fold. In accordance with EPA (2000) guidance, the model with the lowest AIC, the 1-degree model, was selected as the source of the POD. Figure C-2 shows the fit of the multistage cancer, 1-degree model to the data. For this data set, the resulting BMC_{10} and $BMCL_{10}$ were 8.82 and 5.78 mg/m^3, respectively.

Table C-2. Model Predictions for Liver Adenoma in Female Mice Exposed to Methyl Hydrazine by Inhalation for 1 Year (Kinkead et al. (1985)

Model	Degrees of Freedom	χ^2	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)
Multistage cancer, 1-degree[b]	**2**	**2.08**	**0.35**	**299.76**	**8.82**	**5.78**
Multistage cancer, 2-degree[b]	1	1.88	0.17	301.65	6.30	4.70
Multistage cancer, 3-degree[b]	1	1.88	0.17	301.65	6.30	4.39

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria
[b]Betas restricted to ≥0

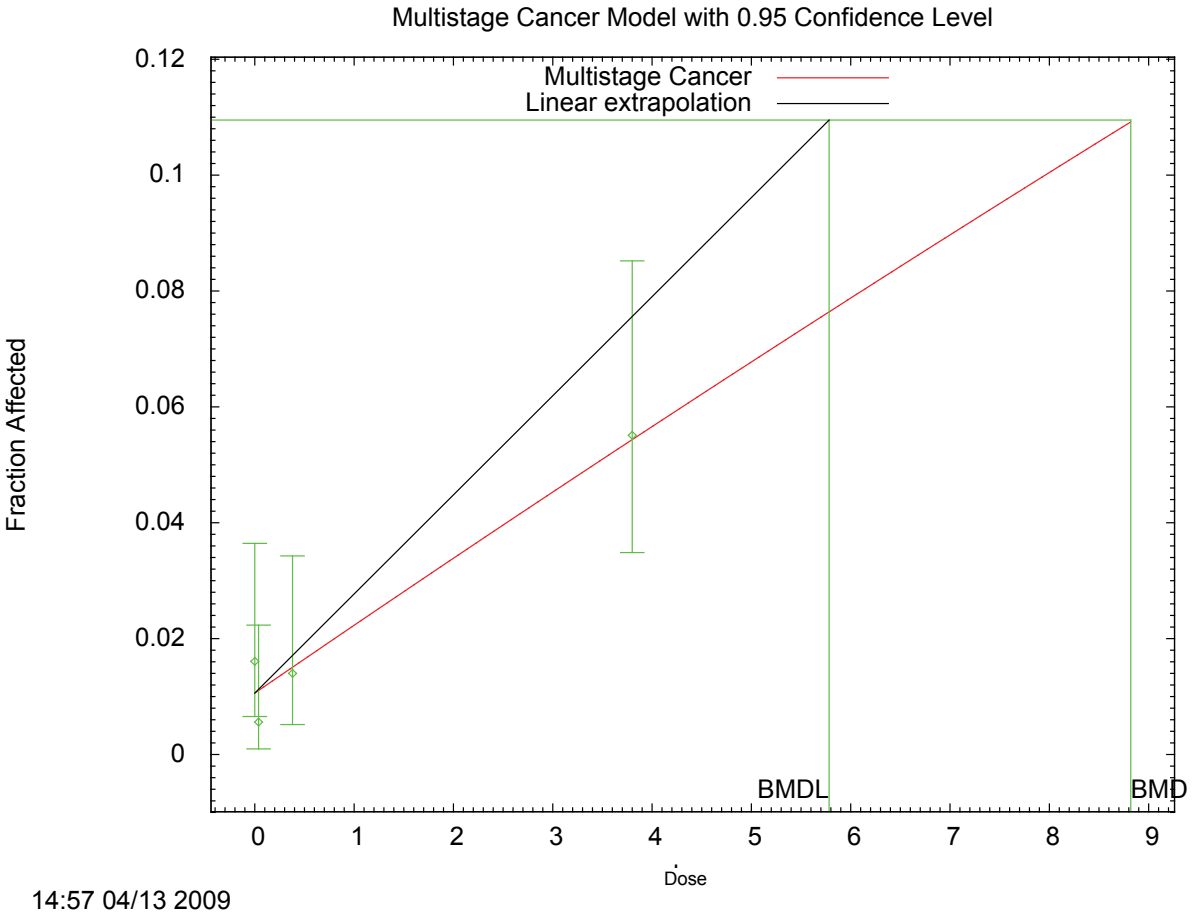

Figure C-2. Fit of Multistage Cancer, 1-Degree Model to Data on Liver Adenoma in Female Mice Exposed to Methyl Hydrazine by Inhalation for 1 Year (Kinkead et al. 1985).

Note: BMC and BMCL indicated are associated with an extra risk of 10% and are in units of mg/m^3.

MODEL-FITTING RESULTS FOR LIVER CARCINOMA IN FEMALE MICE EXPOSED TO METHYL HYDRAZINE BY INHALATION FOR 1 YEAR (KINKEAD ET AL., 1985)

Applying the procedure outlined above to the data for liver carcinoma in female mice exposed to MH, all of the models achieved adequate fit, but the BMD calculations failed (see Table C-3). Dropping the highest dose was considered but rejected because the only evidence for an effect of treatment was at the high dose. This data set proved to be unsuitable for BMD modeling.

Table C-3. Model Predictions for Liver Carcinoma in Female Mice Exposed to Methyl Hydrazine by Inhalation for 1 Year (Kinkead et al., 1985)

Model	Degrees of Freedom	χ^2	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)
Multistage cancer, 1-degree[b]	2	0.69	0.71	235.98	Not applicable	Not applicable
Multistage cancer, 2-degree[b]	2	0.69	0.71	235.98	Not applicable	Not applicable
Multistage cancer, 3-degree[b]	2	0.69	0.71	235.98	Not applicable	Not applicable

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria
[b]Betas restricted to ≥0

MODEL-FITTING RESULTS FOR NASAL ADENOMA IN MALE HAMSTERS EXPOSED TO METHYL HYDRAZINE BY INHALATION FOR 1 YEAR (KINKEAD ET AL., 1985)

Applying the procedure outlined above to the data for nasal adenoma in male hamsters exposed to MH, adequate model fit was achieved with multistage cancer, 2- and 3-degree models. For the 1-degree model, model fit was marginal, and the BMD calculation failed. Table C-4 shows the modeling results. BMCLs from models providing adequate fit did not differ by more than 3-fold. In accordance with EPA (2000) guidance, the model with the lowest AIC, the 3-degree model, was selected as the basis for the POD. Figure C-3 shows the fit of the multistage cancer, 3-degree model to the data. For this data set, the resulting BMC_{10} and $BMCL_{10}$ were 13.46 and 11.07 mg/m^3, respectively.

Table C-4. Model Predictions for Nasal Adenoma in Male Hamsters Exposed to Methyl Hydrazine by Inhalation for 1 Year (Kinkead et al. (1985)

Model	Degrees of Freedom	χ^2	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)
Multistage cancer, 1-degree[b]	2	4.69	0.096	82.54	Not applicable	Not applicable
Multistage cancer, 2-degree[b]	2	2.93	0.23	79.65	16.92	12.59
Multistage cancer, 3-degree[b]	**2**	**2.30**	**0.32**	**78.43**	**13.46**	**11.07**

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria
[b]Betas restricted to ≥0

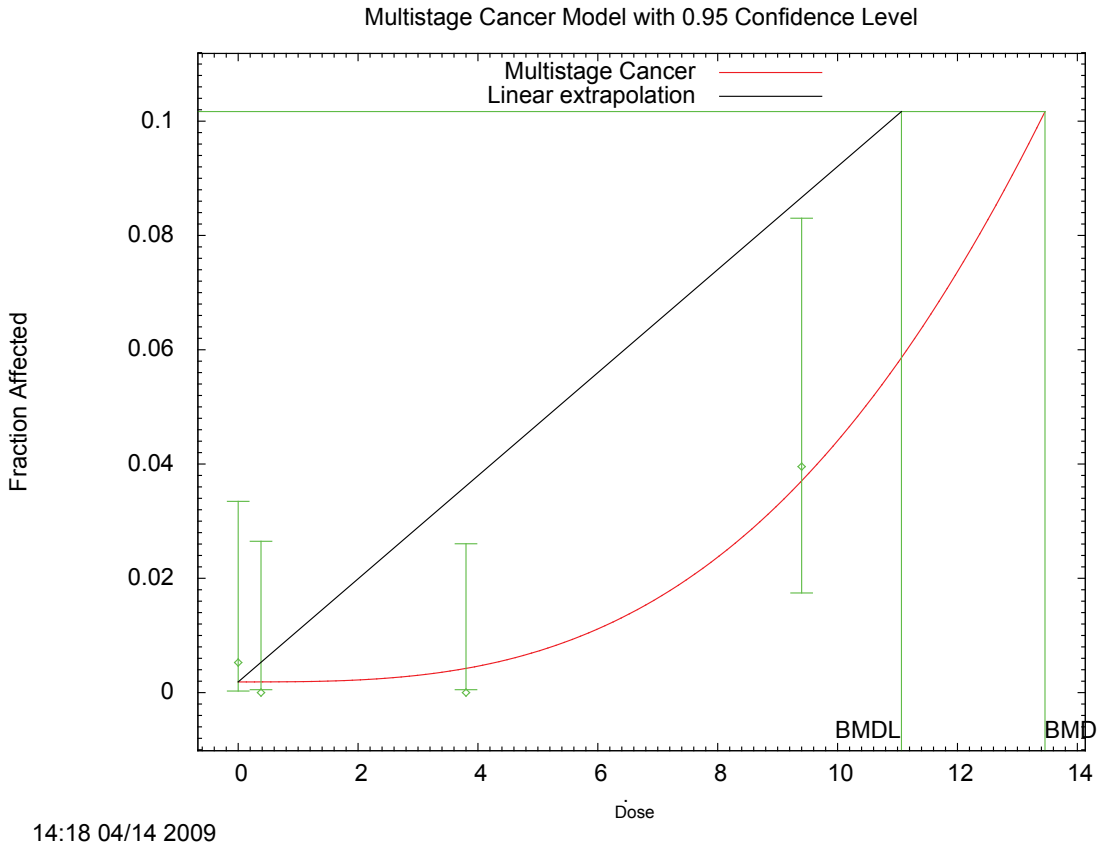

Figure C-3. Fit of Multistage Cancer, 3-Degree Model to Data on Nasal Adenoma in Male Hamsters Exposed to Methyl Hydrazine by Inhalation for 1 Year (Kinkead et al. (1985).

Note: BMC and BMCL indicated are associated with an extra risk of 10% and are in units of mg/m^3.

MODEL-FITTING RESULTS FOR NASAL ADENOMATOUS POLYPS IN MALE HAMSTERS EXPOSED TO METHYL HYDRAZINE BY INHALATION FOR 1 YEAR (KINKEAD ET AL., 1985)

Applying the procedure outlined above to the data for nasal adenomatous polyps in male hamsters exposed to MH, adequate model fit was achieved with all models. Table C-5 shows the modeling results. The higher-degree polynomial models defaulted back to the 1-degree model, so that all of the models gave the same result. Figure C-4 shows the fit of the multistage cancer, 1-degree model to the data. For this data set, the resulting BMC_{10} and $BMCL_{10}$ were 12.36 and 8.74 mg/m^3, respectively.

Table C-5. Model Predictions for Nasal Adenomatous Polyps in Male Hamsters Exposed to Methyl Hydrazine by Inhalation for 1 Year (Kinkead et al. (1985)

Model	Degrees of Freedom	χ^2	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)
Multistage cancer, 1-degree[b]	**3**	**3.04**	**0.39**	**159.26**	**12.36**	**8.74**
Multistage cancer, 2-degree[b]	3	3.04	0.39	159.26	12.36	8.74
Multistage cancer, 3-degree[b]	3	3.04	0.39	159.26	12.36	8.74

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria
[b]Betas restricted to ≥0

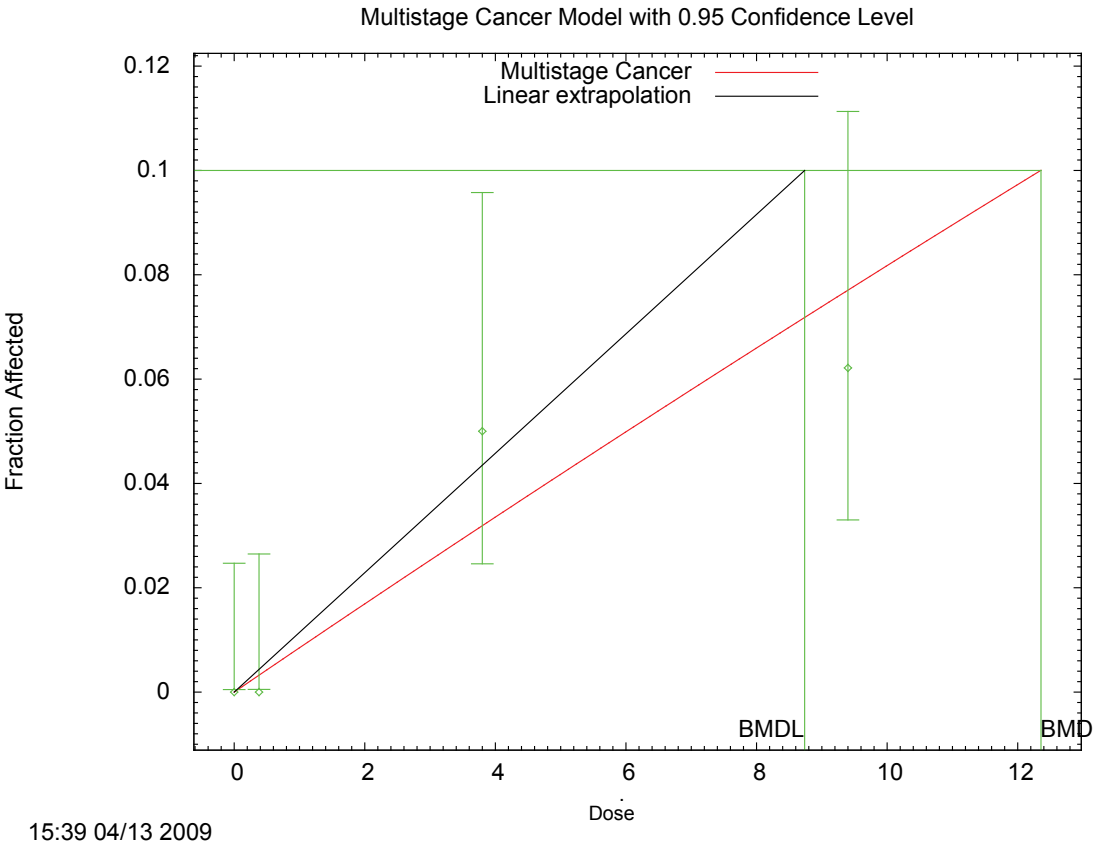

Figure C-4. Fit of Multistage Cancer, 1-Degree Model to Data on Nasal Adenomatous Polyps in Male Hamsters Exposed to Methyl Hydrazine by Inhalation for 1 Year (Kinkead et al., 1985).

Note: BMC and BMCL indicated are associated with an extra risk of 10% and are in units of mg/m^3.

MODEL-FITTING RESULTS FOR ADRENAL CORTICAL ADENOMA IN MALE HAMSTERS EXPOSED TO METHYL HYDRAZINE BY INHALATION FOR 1 YEAR (KINKEAD ET AL., 1985)

Applying the procedure outlined above to the data for adrenal cortical adenoma in male hamsters exposed to MH, adequate model fit was achieved with all models. Table C-6 shows the modeling results. BMCLs from models providing adequate fit did not differ by more than 3-fold. In accordance with EPA (2000) guidance, the model with the lowest AIC, the 3-degree model, was selected as the source of the POD. Figure C-5 shows the fit of the multistage cancer, 3-degree model to the data. For this data set, the resulting BMC_{10} and $BMCL_{10}$ were 11.60 and 9.19 mg/m^3, respectively.

Table C-6. Model Predictions for Adrenal Cortical Adenoma in Male Hamsters Exposed to Methyl Hydrazine by Inhalation for 1 Year (Kinkead et al., 1985)

Model	Degrees of Freedom	χ^2	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)
Multistage cancer, 1-degree[b]	2	3.40	0.18	437.11	24.96	10.86
Multistage cancer, 2-degree[b]	2	2.32	0.31	435.89	13.43	9.33
Multistage cancer, 3-degree[b]	**2**	**1.85**	**0.40**	**435.34**	**11.60**	**9.19**

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria
[b]Betas restricted to ≥0

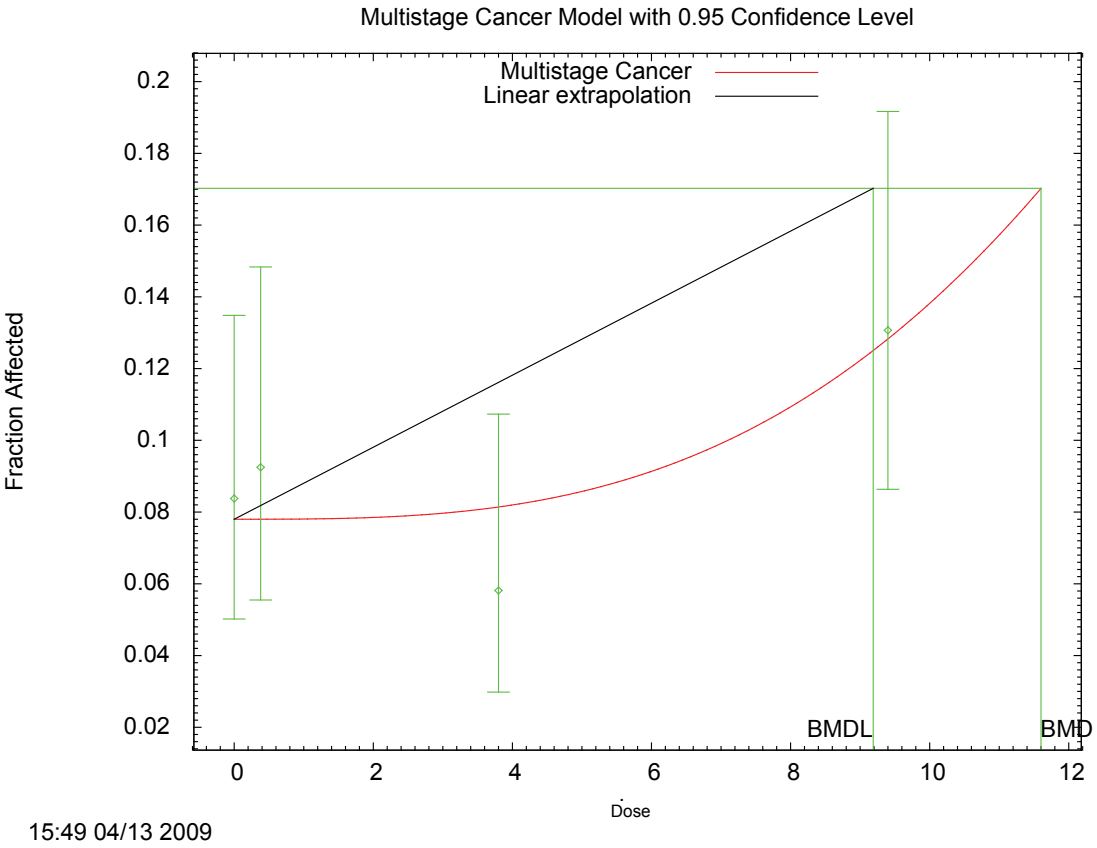

Figure C-5. Fit of Multistage Cancer, 3-Degree Model to Data on Adrenal Cortical Adenoma in Male Hamsters Exposed to Methyl Hydrazine by Inhalation for 1 Year (Kinkead et al., 1985).

Note: BMC and BMCL indicated are associated with an extra risk of 10% and are in units of mg/m^3.