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TOXICOLOGICAL REVIEW

OF

1,2-DIBROMOETHANE

(CAS No. 106-93-4)

In Support of Summary Information on the Integrated Risk Information System (IRIS)

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U.S. Environmental Protection Agency
Washington, DC

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FOREWORD

The purpose of this Toxicological Review is to provide scientific support and rationale for the hazard and dose-response assessment in IRIS pertaining to chronic exposure to 1,2-dibromoethane. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of 1,2-dibromoethane.

In Section 6, *Major Conclusions in the Characterization of Hazard and Dose Response,* EPA has characterized its overall confidence in the quantitative and qualitative aspects of hazard and dose response by addressing knowledge gaps, uncertainties, quality of data, and scientific controversies. The discussion is intended to convey the limitations of the assessment and to aid and guide the risk assessor in the ensuing steps of the risk assessment process.

For other general information about this assessment or other questions relating to IRIS, the reader is referred to EPA's IRIS Hotline at 202-566-1676.

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1. INTRODUCTION

This document presents background information and justification for the Integrated Risk Information System (IRIS) Summary of the hazard and dose-response assessment of 1,2-dibromoethane. IRIS Summaries may include an oral reference dose (RfD), inhalation reference concentration (RfC) and a carcinogenicity assessment.

The RfD and RfC provide quantitative information for noncancer dose-response assessments. The toxicity values are based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis but may not exist for other toxic effects such as some carcinogenic responses. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime. It is expressed in units of mg/kg-day. The inhalation RfC is analogous to the oral RfD, but provides a continuous inhalation exposure estimate. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory or systemic effects). It is generally expressed in units of mg/m^3.

The carcinogenicity assessment provides information on the carcinogenic hazard potential of the substance in question and quantitative estimates of risk from oral and inhalation exposure. The information includes a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen and the conditions under which the carcinogenic effects may be expressed. Quantitative risk estimates are presented in three ways to better facilitate their use: (1) generally, the *slope factor* is the result of application of a low-dose extrapolation procedure and is presented as the risk per mg/kg-day of oral exposure; (2) the *unit risk* is the quantitative estimate in terms of either risk per µg/L drinking water or risk per $µg/m^3$ air breathed; and (3) the 95% lower bound and central estimate on the estimated concentration of the chemical substance in drinking water or air that presents cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000.

Development of these hazard identification and dose-response assessments for 1,2-dibromoethane has followed the general guidelines for risk assessment as set forth by the National Research Council (1983). EPA guidelines that were used in the development of this assessment may include the following: *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S.

EPA, 1986a), *Guidelines for Mutagenicity Risk Assessment* (U.S. EPA, 1986b), *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991), *Guidelines for Reproductive Toxicity Risk Assessment* (U.S. EPA, 1996b), *Guidelines for Neurotoxicity Risk Assessment* (U.S. EPA, 1998a), *Draft Revised Guidelines for Carcinogen Assessment* (U.S. EPA, 1999), *Recommendations for and Documentation of Biological Values for Use in Risk Assessment* (U.S. EPA, 1988), (proposed) *Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity* (U.S. EPA, 1994a), *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994b), *Use of the Benchmark Dose Approach in Health Risk Assessment* (U.S. EPA, 1995), *Science Policy Council Handbook: Peer Review* (U.S. EPA, 1998b, 2000a), *Science Policy Council Handbook*: *Risk Characterization* (U.S. EPA, 2000b), *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000c), *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 2000d), and *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002).

The literature search strategy employed for this compound was based on the CASRN and at least one common name. Any pertinent scientific information submitted by the public to the IRIS Submission Desk was also considered in the development of this document. The relevant literature was reviewed through May 2003.

2. CHEMICAL AND PHYSICAL PROPERTIES RELEVANT TO ASSESSMENT

1,2-Dibromoethane, also known as ethylene dibromide, is a colorless, heavy liquid that has a mildly sweet, chloroform-like odor (HSDB, 1999). It is sparingly soluble in water and miscible with most organic solvents. It is soluble in alcohol, ether, acetate, and benzene. The physical properties of 1,2-dibromoethane are listed in Table 2-1.

Prior to the phaseout of leaded gasoline in the United States, 1,2-dibromoethane was primarily used as an anti-knock compound. Sources of 1,2-dibromoethane included emissions and exhaust from vehicles using leaded gasoline. Its use as a fumigant for citrus, grain, and soil was discontinued in 1984 (U.S. Environmental Protection Agency [EPA], 2000e). It is currently used as a solvent for resins, gums, and waxes; as a chemical intermediate in the synthesis of dyes and pharmaceuticals; and as a precursor in the synthesis of vinyl chloride. Also, 1,2-dibromoethane appears to be formed naturally by microalgae growth and has been detected in ocean waters and air.

1,2-Dibromoethane exhibits low-to-moderate soil adsorption, with experimental K_{oc} values ranging from 14 to 160, indicating that 1,2-dibromoethane will leach quickly into groundwater. 1,2-Dibromoethane volatilizes readily from surface soil as predicted by its relatively high vapor pressure (11.2 mm Hg at 25°C). 1,2-Dibromoethane is very stable towards hydrolysis (half-life, $T_{1/2}$ = 13.2 years at pH 7 and 20°C) and is more likely to undergo aerobic biodegradation in the soil rather than abiotic degradation. After 8 weeks under anaerobic conditions in the presence of denitrifying bacteria, no biodegradation was observed compared with 97% degradation to ethylene under aerobic conditions.

In aquatic environments, the primary removal process for 1,2-dibromoethane is evaporation: the volatilization half-life from a typical lake or river is 1–5 days. Biodegradation of 1,2-dibromoethane in groundwater can be slow (with half-lives in months), and biotic hydrolysis only readily occurs in the presence of a natural catalyst such as hydrogen sulfide. The presence of hydrogen sulfide increases the rate of hydrolysis from several years to approximately 2 months.

In the ambient atmosphere, 1,2-dibromoethane exists as a vapor, and, although it

undergoes degradation in a reaction with photochemically produced hydroxyl radicals, it is likely to be persistent. Direct photolysis is not likely to occur.

Table 2-1. Chemical and physical properties of 1,2-dibromoethane

Property	Value	Reference
Molecular weight	187.88	HSDB, 1999
Density at 25°C	2.172 g/mL	
Melting point	9.8°C	
Boiling point	131-132°C	
Vapor pressure at 25°C	11.2 mm Hg	
Henry's Law constant	8.2×10^{-4} atm-m^3/mol	
Water solubility at 25°C	4150 mg/L	
K_{oc}	66	

1 ppm = 7.68 mg/m^3 at 25°C and 760 mm Hg.

3. TOXICOKINETICS RELEVANT TO ASSESSMENTS

3.1. ABSORPTION

1,2-Dibromoethane absorption via the gastrointestinal tract was described by Hissink et al. (2000) using data from Roth et al. (1993). Hissink et al. (2000) found that orally exposed rats appeared to absorb 1,2-dibromoethane via two first-order processes presumed to be from the stomach to the intestines and from the intestines to the liver. For the purposes of their models (see section 3.5), Hissink et al. (2000) estimated rat absorption parameters from *in vivo* oral and intravenous (i.v.) exposures and assumed human absorption was not different from that of rats. For rats dosed orally (gavage) with 50 and 150 mg 1,2-dibromoethane/kg, absorption was reported to be fast, with blood concentrations nearing estimated C_{max} levels within 30 minutes. Oral exposure to 1 gram of 1,2-dibromoethane resulted in serum 1,2-dibromoethane concentrations of approximately 1 ppm (0.1% of the dose based on blood volume) in one minipig 15 minutes after compound administration (Kirby et al., 1980). Very rapid 1,2-dibromoethane metabolism was considered as causing relatively low serum 1,2-dibromoethane concentrations. Inhalation studies (National Toxicology Program [NTP], 1982; Stinson et al., 1981; Nitschke et al., 1981; Reznik et al., 1980; Short et al., 1978; Smith and Goldman, 1983) show that 1,2-dibromoethane is absorbed via the inhalation route of exposure and distributed systemically. Stott and McKenna (1984) showed that 1,2-dibromoethane is about 50% absorbed when presented to either the upper or lower respiratory tract of Fisher 344 rats at a flow rate equivalent to the animals' respiratory minute volume (53 mL/min). Following dermal exposure to 1 mL 1,2-dibromoethane in guinea pigs, 1,2-dibromoethane blood levels increased rapidly to 2.1 μg/mL after 1 hour and decreased slightly to 1.8 μg/mL after 6 hours (Jakobson et al., 1982).

3.2. METABOLISM

1,2-Dibromoethane is metabolized by two major pathways, cytochrome-P450-monooxygenase and glutathione (GSH) conjugation via glutathione-S-transferase (GST). These pathways are depicted in Figures 3-1 and 3-2. Oxidative metabolism by cytochrome-P450 leads to the formation of the reactive metabolite 2-bromoacetaldehyde (Hill et al., 1978) via dehydrohalogenation of a *gem*-halohydrin. This route has been demonstrated to account for 80%

of the metabolism of 1,2-dibromoethane in the rat (van Bladeren et al., 1981). 2-Bromoacetaldehyde can then be converted to s-(2-hydroxyethyl) glutathione (HEG) and S-carboxymethylglutathione (CMG) through several different pathways involving either direct interaction with GSH or oxidative metabolism to 2-bromoethanol and 2-bromoacetic acid followed by conjugation with GSH (Jean and Reed, 1992). However, only the former pathway involving direct interaction of 2-bromoacetaldehyde with GSH is believed to be catalyzed by GSTs (Jean and Reed, 1992). Under hypoxic conditions, free radical intermediates have been generated in microsomal and hepatocyte assays (Tomasi et al., 1983).

1,2-Dibromoethane can also conjugate directly with GSH by a GST-mediated reaction to form S-(2-bromoethyl)GSH (Jean and Reed, 1992), a half-mustard that can spontaneously rearrange to an episulfonium ion, thiiranium, and is further hydrolyzed to S-(β-hydroxyethyl)GSH; or it can bind to DNA (Hodgson and Levi, 1994; Jean and Reed, 1992; Peterson et al., 1988). S-(2-bromoethyl)GSH can also undergo further GSH conjugation to form S,S-1,2-ethanediyl-bis-GSH (Jean and Reed, 1992). Formation of these GSH-containing metabolites correlated with a 71% depletion of intracellular GSH. In vitro studies have shown that approximately 60% of the episulfonium ion is trapped as S,S-ethanediyl-bis-GSH with the remainder reacting with water to form S-hydroxyethylGSH (Cmarik et al., 1990). The episulfonium ion is believed to be responsible for the genotoxicity of 1,2-dibromoethane. The major adduct derived from the episulfonium pathway is S-[2-N^7-guanyl)ethyl]GSH (Koga et al., 1986). However, N^2- and O^6-guanyl adducts may also contribute (Cmarik et al., 1992; Kim and Guengerich, 1997; Kim and Guengerich, 1998). These may explain the predominance of GC:AT transitions in *Escherichia coli (*Foster et al., 1988) and *Drosophila melanogaster* (Ballering et al., 1994).

The half-mustard (Ozawa and Guengerich, 1983) and 2-bromoacetaldehyde (Guengerich and Persmark, 1994) can react with DNA to generate miscoding adducts, although the rate of reaction of 2-bromoacetaldehyde with DNA has been shown to be rather slow (Guengerich et al., 1981). The *in vitro* rate of hydrolysis of S-(2-bromoethyl)GSH is 1.6/min^{-1} with a $T_{1/2}$ of 0.44 min (Wheeler et al., 2001).

In vivo metabolic studies have identified a number of urinary metabolites following 1,2-dibromoethane exposure. Nachtomi et al. (1966) identified S-(hydroxyethyl)mercapturic acid as a major urinary metabolite and S-(β-hydroxyethyl)cysteine as a minor metabolite following oral

administration of 100 mg/kg 1,2-dibromoethane in albino rats. S-(hydroxyethyl)mercapturic acid, thiodiacetic acid, and thiodiacetic acid sulfoxide have been identified as major urinary metabolites following oral administration of 1,2-dibromoethane in Wistar rats (Wormhoudt et al. 1998). Thiodiacetic acid formation is dependent on cytochrome-P450 oxidation for formation and not GSH conjugation (Wormhoudt et al., 1997). S-[2-(N^7-guanyl)ethyl]-N-acetylcysteine, which is derived from the nucleic acid adduct S-[2-(N^7-guanyl)ethyl]GSH, has also been identified as a urinary metabolite in rats following intraperitoneal injection (Kim and Guengerich, 1989).

Van Bladeren et al. (1981) reported that the oxidative route compared to the conjugative route occurred in a ratio of about 4:1 in rats. This would mean that 1,2-dibromoethane is preferentially metabolized to 2-bromoacetaldehyde and then conjugated with GSH. The cytochrome-P450 isozyme responsible for the oxidation of 1,2-dibromoethane to 2-bromoacetaldehyde appears to be CYP2E1. Wormhoudt et al. (1996a) found that microsomes from Wistar rats pretreated with pyrazole, an inducer of CYP2E1, had a turnover (V_{max}/K_m) of 1,2-dibromoethane to 2-bromoacetaldehyde 74 times greater than microsomes from rats pretreated with β-naphthoflavone, an inducer of CYP2A1. Similarly, heterologously expressed CYP2E1 had a catalytic efficiency in terms of V_{max}/K_m 100 times greater than CYP2B6 and 600 times greater than CYP2A6 (Wormhoudt et al., 1996b). The same study found that heterologously expressed CYP1A1, CYP1A2, CYP2C8, CYP2C9, CYP2C18, CYP3A4, and CYP3A5 had no ability to metabolize 1,2-dibromoethane to 2-bromoacetaldehyde. Microsomes from 21 different human livers were able to catalyze the oxidation of 1,2-dibromoethane to 2-bromoacetaldehyde with activities that ranged from 22.2 to1027.6 pmol/min-mg of protein (Wormhoudt et al., 1996b). This oxidation was significantly inhibited by specific CYP2E1 inhibitors, disulfiram and diethyldithiocarbamate.

The results of several experiments suggest that of the several mammalian GSH transferases that can catalyze conjugation with GSH (Cmarik et al., 1990), theta-class GSH transferase (GSTT) may be most important for conjugation of 1,2-dibromoethane. Investigation of human erythrocyte cytosol from 12 people not exposed to 1,2-dibromoethane revealed that two of the cytosols did not catalyze GSH conjugation with 1,2-dibromoethane (Ploemen et al., 1995). Every cytosol had similar activity toward the classic GSH substrate, 1-chloro-2,4-dinitrobenzene. However, the two cytosol enzymes incapable of catalyzing 1,2-dibromoethane-GSH conjugation were also incapable of catalyzing GSH conjugation with 1,2-epoxy-3-(p-nitrophenoxy)-propane

(EPNP). EPNP is a highly selective substrate for GSTT, and this suggests that GSTT is specific for GSH conjugation of 1,2-dibromoethane in human erythrocyte cytosol. Human GSTT is polymorphic in humans (Pemble et al., 1994; Warholm et al., 1995; Nelson et al., 1995; Kempkes et al., 1996). If the carcinogenicity of 1,2-dibromoethane is attributable only to a conjugate formed only by GSTT, people with a null genotype leading to no activity for this enzyme may not be as susceptible to cancer from 1,2-dibromoethane (see discussion in section 4.7).

In vitro experiments found *Salmonella typhimurium* expressing human GST-θ had greater genotoxicity following 1,2-dibromoethane exposure than strains that did not express this enzyme (Thier et al., 1996). Simula et al. (1993) reported that GST-α expression increased the mutagenicity of 1,2-dibromoethane in an *S. typhimurium* assay but GST-π did not. The authors did not investigate the role of GST-θ.

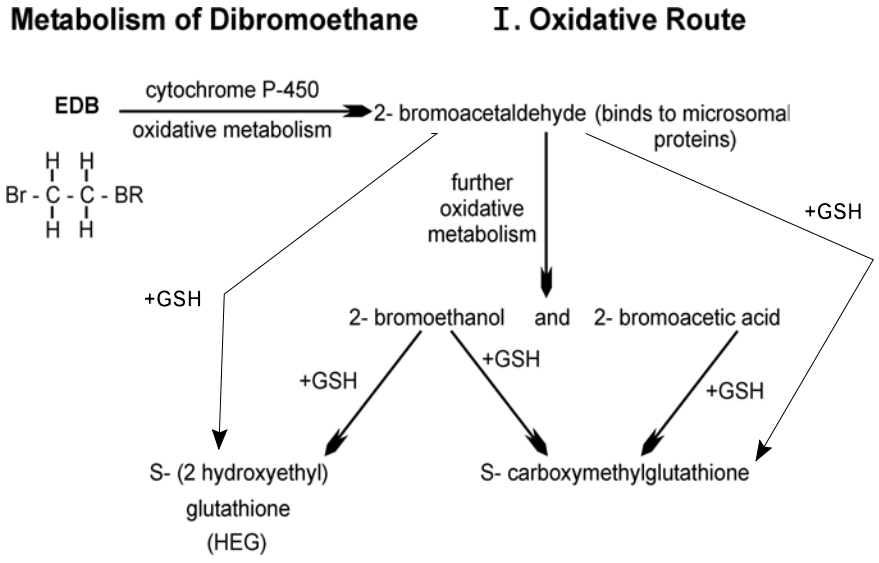

Figure 3-1. Metabolism of dibromoethane by the oxidative route.

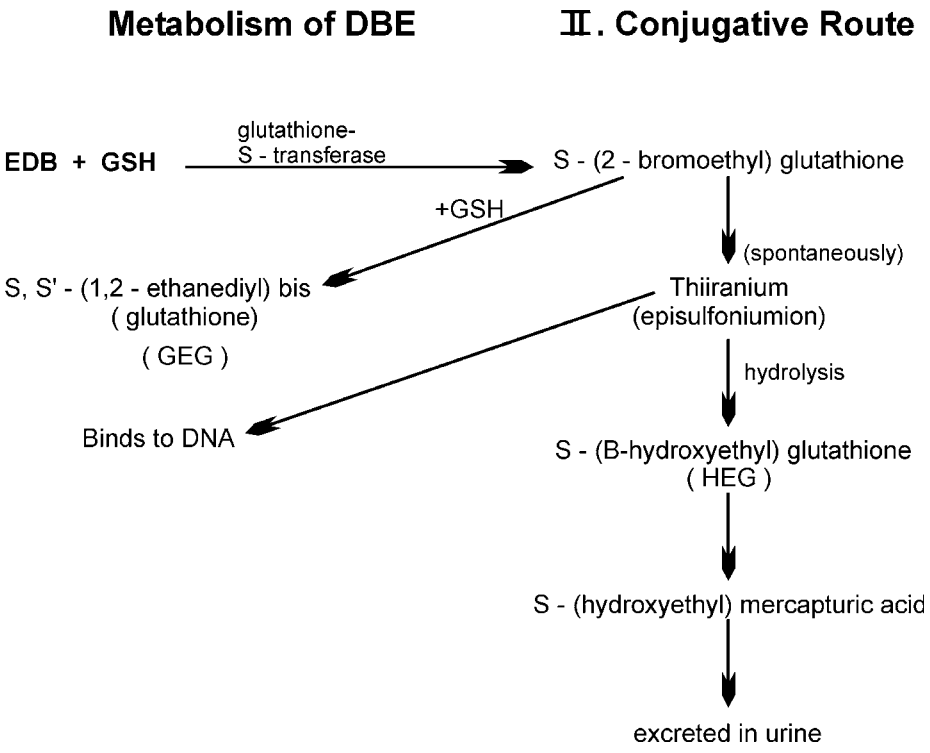

Figure 3-2. Metabolism of dibromoethane by the conjugative route.

3.3 DISTRIBUTION

Following oral administration of 15 mg/kg ^{14}C-1,2-dibromoethane in rats, retention of the compound 24 hours after administration was limited to 3% of administered label in organs with the majority of the dose retained in the kidney, liver, and spleen (Plotnick et al., 1979). Forty-eight hours after exposure, 1.1% of administered label was present in the liver. Disulfiram, a compound known to enhance the toxicity of 1,2-dibromoethane in animals, significantly increased the tissue concentration of ^{14}C-1,2-dibromoethane in liver, kidneys, spleen, testes, and brain of male Sprague-Dawley rats that consumed a diet containing 0.05% disulfiram for 12 days prior to oral intubation with 15 mg/kg ^{14}C-1,2-dibromoethane (Plotnick et al., 1979). Also, label associated with liver nuclei was significantly increased in disulfiram-treated rats. As would be expected, urinary elimination of ^{14}C-1,2-dibromoethane was decreased significantly with increased tissue binding.

One hundred sixty-eight hours after i.v. (10 and 50 mg/kg) or oral (50 and 150 mg/kg) administration of ^{14}C-1,2-dibromoethane, <1% of administered label was found in the liver, lungs, and kidneys and 0.3% was present in erythrocytes (Wormhoudt et al., 1998). Short et al. (1979), who monitored total radioactivity in whole organs (kidney, stomach, liver, and testes) and tissue fractions 4 hours after oral administration of 10 and 100 mg/kg ^{14}C-1,2-dibromoethane, found that label was greater in the kidney, liver, and stomach than in testes. A portion of the label in these tissues was covalently bound to DNA, RNA, and protein.

In mice, irreversibly bound metabolites of ^{14}C-1,2-dibromoethane (2.6 mg/kg) were reported to be highest in the nasal mucosa, followed by the liver, lung, and kidney, 3 hours after intraperitoneal (i.p.) injection (Brittebo et al., 1989). Similarly, Hill et al. (1978) reported significant macromolecular binding to epithelial tissues of the respiratory tract, liver, kidney, and small intestine of rats following i.p. injection of 0.8 mg/kg ^{14}C-1,2-dibromoethane. In one male cynomolgous monkey administered 4 μmol/kg ^{14}C-1,2-dibromoethane intraperitoneally, the liver and kidney proximal tubules had the highest amount of administered radioactivity per mg of tissue, but very little binding was observed in the lung and other organs of the respiratory tract (Brandt et al., 1987). When tissues from a female monkey were incubated with 20 μM ^{14}C-1,2-dibromoethane, the distribution of bound metabolites in the kidney was identical to that observed *in vivo*. The authors also described a distinct zone of binding in the adrenal zona reticularis, both *in vitro* and *in vivo*. Significant levels of radiolabeled metabolites irreversibly bound to the

adrenal cortex, nasal cavity, lung, and other tissues of rats (Sprague-Dawley and Fischer) and C57BL mice were also observed by Kowalski et al. (1985) after i.v. and i.p. injection of ^{14}C-1,2-dibromoethane. For results in fetal tissues, see section 4.7.1.

3.4. EXCRETION

1,2-Dibromoethane is eliminated mainly in the urine. In vivo metabolic studies have identified a number of urinary metabolites, including S-(hydroxyethyl)mercapturic acid and S-(β-hydroxyethyl)cysteine following oral administration of 100 mg/kg 1,2-dibromoethane in albino rats (Nachtomi et al., 1966)). S-(hydroxyethyl)mercapturic acid, thiodiacetic acid, and thiodiacetic acid sulfoxide have been identified as major urinary metabolites following oral administration of 1,2-dibromoethane in Wistar rats (Wormhoudt et al., 1998). S-[2-(N^7-guanyl)ethyl]-N-acetylcysteine, which is derived from the nucleic acid adduct S-[2-(N^7-guanyl)ethyl]GSH, has also been identified as a urinary metabolite in rats following intraperitoneal injection (Kim and Guengerich, 1989).

Following oral administration of 15 mg/kg ^{14}C-1,2-dibromoethane in rats, 72% of the dose was excreted in the urine and 1.65% in the feces (Plotnick et al., 1979). Forty-eight hours later, 73% of the dose had been accounted for in the urine and 3% in the feces. Similar results were reported by Wormhoudt et al. (1998), who found that following i.v. (10 and 50 mg/kg) or oral (50 and 150 mg/kg) administration of ^{14}C-1,2-dibromoethane, 75 - 82% of the radioactivity was excreted in the urine within 48 hours, 3.2 - 4% was eliminated in the feces within 48 hours, and 0.53 - 7.2% was eliminated in the expired air within 2 hours. The only major difference between the two routes of administration was that a much higher percentage of the dose was eliminated in the expired air following i.v. administration.

3.5. PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODELS

Hissink et al. (2000) have developed a PBPK model for 1,2-dibromoethane for rats and humans that is largely based on *in vitro* data published by Ploemen et al. (1997). Due primarily to the higher relative ventilation rate, cardiac output, and metabolic rate of rats, the Hissink et al. (2000) model predicts that blood concentrations of 1,2-dibromoethane and the metabolites of both

pathways (P450 oxidative and GST conjugation) described above would be higher in rats than in humans. Their model predicts that this would be the case for average humans and for humans with extremely high contributions from one or the other pathway (i.e., high GST/P450 or P450/GST contribution ratios). Assuming that a GSH conjugate is the toxicant and that total GSH conjugate level correlates to the specific toxic episulfonium ion would suggest that humans may be less sensitive than rats to the genotoxic and carcinogenic effects of 1,2-dibromoethane. The model has not been fully validated, however, and makes several assumptions that affect the conclusions, including the following: (1) there is no P450 activity in human kidneys but significant P450 activity in rat kidneys; (2) there is considerably lower GSH activity in human skeletal muscle, lung, and stomach compared with rat; and (3) that steady state levels were reached in blood after an 8-hour exposure. The model only simulated an 8-hour exposure, and longer simulation runs are needed to evaluate steady-state levels and subsequent differences in GSH conjugate levels. The model also does not include terms for GSH synthesis and degradation rates (also needed for chronic exposures), factors that can greatly affect GSH conjugate levels. It also does not attempt to distinguish (or correlate) the episulfonium conjugate from all other GSH conjugates or the P450 metabolite conjugates from the parent compound GSH conjugates. Given these limitations, it would not be appropriate to use the Hissink et al. (2000) model at this time for quantitative (route-to-route or animal-to-human) extrapolations. However, the Hissink et al. (2000) report and model provide useful information regarding the mode of action of 1,2-dibromoethane, particularly with respect to the cancer effects of 1,2-dibromoethane.

4. HAZARD IDENTIFICATION

4.1. STUDIES IN HUMANS

4.1.1. Lethality

Olmstead (1960) described a case report of a 43-year old woman who ingested capsules containing 1,2-dibromoethane. Symptoms included abdominal pain, nausea, vomiting, diarrhea, darkening of the urine, tachypnea, and marked agitation; she died 54 hours after ingesting of the capsules. Histological examination revealed massive central lobular necrosis of the liver with focal proximal tubular epithelial damage in the kidney. Olmstead (1960) commented that these changes were similar to those observed in various experimental animals following oral administration of 1,2-dibromoethane.

Six cases of suicidal poisoning via ingestion of 1,2-dibromoethane were reported by Saraswat et al. (1986). Two of the six individuals died. In one of these individuals, postmortem examination revealed massive liver necrosis; ulceration of the oral cavity; congestion and erosion of the stomach; congestion of the lungs, spleen, brain, and kidneys; pulmonary edema; and cloudy swelling of the kidney with occasional tubular necrosis. The other individual showed centrilobular necrosis of the liver and congestion of the lungs and stomach. Clinical signs observed in those who survived ingestion of 1,2-dibromoethane included nausea, vomiting, and burning of the throat.

1,2-Dibromoethane was lethal to two workers following acute exposure to 1,2-dibromoethane in a tank (Letz et al., 1984). One worker exhibited metabolic acidosis, central nervous system depression, and liver damage. The other worker displayed metabolic acidosis and hepatic and renal failure. Elevated serum bromide concentrations were detected in both cases prior to death.

4.1.2. Reproductive Toxicity

Semen quality has been studied in papaya workers with long-term exposure to 1,2-dibromoethane used in the fumigation of papaya (Ratcliffe et al., 1987). Workers at six papaya fumigation plants located near Hilo, Hawaii, were assessed for potential 1,2-dibromoethane-related reproductive toxicity.

Exposure of the papaya workers to 1,2-dibromoethane was characterized in detail by Clapp (1986). The workers were exposed to 1,2-dibromoethane for an average of 5 years. Samples were reported to be collected on at least two separate days to give an estimate of exposure during the workweek. Three to four packers/sorters and one to two forklift operators were sampled per plant for an 8-hour work shift; in three of the plants, air samples were taken both in 1982 and 1983. In these three plants, there is a considerable amount of variation between the 1982 and 1983 mean air sample concentrations measured for the same plant. Full-shift exposures of 16 to 175 ppb (0.1 to 1.4 mg/m^3) among the six plants investigated were reported with a geometric mean of 88 ppb (0.68 mg/m^3) and peak exposures as high as 262 ppb (2.0 mg/m^3). Significant plant-to-plant variation was reported: full-shift exposures for papaya packers/sorters ranged from 36 to 148 ppb (0.3 - 1.1 mg/m^3) and those for forklift operators ranged from 16 to 175 ppb (0.1 - 1.4 mg/m^3). A sugar processing plant adjacent to one of the fumigation plants served as a control group for exposed workers.

Semen was collected and delivered for analysis within 1 hour of collection (Ratcliffe et al., 1987). The following potentially confounding variables were considered: tobacco smoking (current, ex-smokers, and nonsmokers), marijuana use (times per week), alcohol consumption (drinks per week), caffeine consumption (cups of coffee and/or tea per day), history of urogenital disorders, prescription medication taken in the past year, history of fever in the past three months, abstinence time, subject age, sample age, and racial background. The only significant difference between control and exposed workers was marijuana use, which was higher in exposed workers (41.3%) than in controls (20.9%).

Ratcliffe et al. (1987) reported summary air exposure data, but there was moderate dermal exposure that could not be quantified (Schrader et al., 1988). Semen of exposed workers exhibited significantly decreased average sperm count per ejaculate and percentage of viable and motile sperm. There were statistical increases in certain types of morphological abnormalities

(tapered heads, absent heads, and abnormal tails) in exposed workers. There was also a significant increase in percentage of subjects with sperm counts fewer than 20 million in exposed workers (21.7% compared to 4.7% in controls). The highly variable inhalation exposures and the confounding dermal exposures preclude the use of this population for the development of an RfC.

A comparison of 1,2-dibromoethane-exposed cohorts of forestry workers in Colorado (short-term exposure) and papaya workers from the Ratcliffe et al. (1987) study (long-term exposure) was performed by Schrader et al. (1988). Ten 1,2-dibromoethane-exposed and six unexposed forestry workers were identified for the study. Schrader et al. (1988) reported that 8-hour air samples were collected for three days during the six-week fumigation season and several short-term (15-minute and 1-hour) samples were also taken. Short-term exposure concentrations ranged from non-detectable levels to 2165 ppb (16.6 mg/m^3) for workers filling truck tanks with 1,2-dibromoethane, 57 to 525 ppb (0.4 to 4.0 mg/m^3) for workers spraying log piles, and 8 to 184 ppb (0.1 to 1.4 mg/m^3) for workers pouring an 1,2-dibromoethane emulsion on log piles. The results of the 8-hour samples were not reported, but a time-weighted average exposure of 60 ppb (0.5 mg/m^3) was reported. It should be noted that dermal exposure was recognized as a major potential route of exposure. Schrader et al. (1988) stated that dermal exposure in forestry workers was excessive, and the papaya workers described in Ratcliffe et al. (1987) were subject to moderate dermal exposure. Attempts to quantify the dermal route of exposure were unsuccessful. Exposed and control worker ejaculates were collected 1–2 weeks before exposure and during the last week of exposure.

When postexposure semen samples of forestry workers were compared to those collected pre-exposure, sperm velocity was significantly decreased in all 10 exposed workers compared to controls, and nine exposed workers had significantly decreased semen volume compared to controls. Sperm viability, sperm concentration, semen pH, sperm morphology, and sperm morphometry of exposed workers were not significantly different from controls. Sperm motility was a measured parameter, but there was no explicit indication of the percent of motile sperm in the report. It is assumed that there was no effect of 1,2-dibromoethane on motility.

These results contrast with those of papaya workers described in Ratcliffe et al. (1987). Schrader et al. (1988) suggest that the differences in toxic responses between the two studies were due to the duration of exposure. Markers of mature sperm function, such as sperm velocity, might be expected to be altered during short-term exposure, but morphogenic effects, as seen in

Ratcliffe et al. (1987), would not be observed unless exposure occurred for at least the duration of one spermatogenic cycle (74 days). Therefore, Schrader et al. (1988) conclude that the two studies complement each other when the duration of exposure (6 weeks vs. 5 years) is considered.

Wong et al. (1979) conducted a retrospective evaluation of reproductive performance of male workers in four chemical plants that produced 1,2-dibromoethane during the 1958-1977 time period. This was done by comparing actual numbers of live births delivered by their wives compared to the expected numbers of live births derived from national fertility tables published by the National Center for Health Statistics. In addition to 1,2-dibromoethane, one plant produced dibromochloropropane (a known male reproductive toxicant), another produced "other brominated compounds," workers in another plant were also probably exposed to ethylene dichloride (EDC), and the remaining plant was limited to 1,2-dibromoethane production. 1,2-Dibromoethane was monitored through industrial hygiene studies, except at one plant in which 1,2-dibromoethane levels were not determined. Observed and expected births were adjusted for maternal age, parity, race, and calendar year for all 1,2-dibromoethane-exposed workers at all four plants. Workers were classified as being exposed to either < 0.5 ppm (< 3.8 mg/m^3) or 0.5–5.0 ppm (3.8 - 38 mg/m^3). There was no difference between observed and expected births in wives of workers for three of the plants. There was, however, a significant difference (< 0.05) pertaining to the plant producing 1,2-dibromoethane and also using EDC: the 1,2-dibromoethane levels at this plant ranged from 0.1 to 4 ppm (0.8 to 30 mg/m^3). Considering the limited exposure data and co-exposure to other chemicals, no conclusions can be drawn concerning the potential antifertility effect of 1,2-dibromoethane from this study.

Sperm counts have been assessed in agricultural workers with known exposure to 1,2-dibromoethane (Takahashi et al., 1981). Volunteers were asked to complete a medical history questionnaire related to possible factors that could affect spermatogenesis. Agricultural workers and unexposed controls were asked to provide semen samples. Sperm count, morphology, and motility were determined 0.5–1 hour after collection. Co-exposure to dibromochloropropane (DBCP) also occurred in agricultural workers, but levels of DBCP and 1,2-dibromoethane exposure could not be precisely determined. The only observed adverse effect in the workers was significantly lower sperm counts compared to controls. Conclusions about the effect of 1,2-dibromoethane on male fertility cannot be determined from this study because of a lack of exposure data and co-exposure to DBCP, a well-documented gonadotoxin.

Fertility history was evaluated for male workers employed in a 1,2-dibromoethane production facility (Turner and Barry, 1979) by examining family size. A total of 82 married workers employed at the time of the study (1977) was identified, 41 of whom were determined to have very low or no exposure to 1,2-dibromoethane, while the remaining 41 had some exposure to 1,2-dibromoethane. Of those thought to have some exposure, 13 were regular process workers, 17 were process operators with variable exposure, and 11 were maintenance workers with sporadic potential exposure. In addition, 75 process workers were identified from company records of all married employees who had left employment by the time of the survey. Presumably, this earlier employed group would have had higher exposure to 1,2-dibromoethane than in the first set identified, but no information was mentioned concerning exposure categories. No exposure measurements or frequency information was available for any of the workers, however. A comparison group of 80 men was selected for this historical group from the patients of a local general practitioner, excluding any ever employed at the facility. For all groups of men, the investigators compared average number of children per family on joining the company with the average number of children at the time of the survey and concluded that there were no statistical differences among any of the groups. Among those employed at the time of the survey, average family sizes were slightly higher among those thought to be exposed to 1,2-dibromoethane (2.18 to 2.85 children per family) than for those thought not to be exposed (1.95). Ages of the men were similar, and average number of years employed when the children were born varied from 1.5 to 4.5 among those with exposure and was 5 years for those without exposure. For the historical group and its control, family sizes were very similar at 1.97 and 1.98 children/family, respectively; however, no information was provided regarding comparability of ages of the men or of the amount of time over which the fertility rates were evaluated. Due to several limitations of the study design– lack of exposure data, small sample size (especially within exposure categories), and apparent lack of control regarding whether any of the families were trying to have more children– this study is inconclusive regarding the effect of 1,2-dibromoethane on male fertility.

4.1.3. Cancer

Mortality of workers occupationally exposed to 1,2-dibromoethane has been investigated in several studies (Ott et al., 1980; Sweeney et al., 1986). Ott et al. (1980) investigated the cause of death of 161 workers occupationally exposed to 1,2-dibromoethane in two production facilities,

one in operation from 1942 to 1969 and the other from the mid-1920s to 1976. The study primarily focused on cancer mortality and respiratory disease. Quantitative data from which to calculate an 8-hour time-weighted average (TWA) were not available for the first facility. However, area sampling data from 1950, 1952, and 1971 - 72 and personal air monitoring in 1975 allowed for estimation of 1,2-dibromoethane exposure in the second facility. Area samples from 1950 ranged from 1 - 10.6 ppm (7.7 - 81.4 mg/m^3), 19 - 31 ppm (146 - 238 mg/m^3) in 1952, 0 - 110 ppm (0 - 845 mg/m^3) from 1971 - 1972, and 1.8 - 96 ppm (14 - 737 mg/m^3) in 1975. An estimated TWA of 3.5 ppm (26.9 mg/m^3) was calculated for 1971 - 1972 and 5 ppm (38.4 mg/m^3) for 1975.

In the first facility, two deaths from malignant neoplasms were observed compared to 3.6 expected. No other organic bromide compounds were manufactured at this facility and exposure was primarily limited to 1,2-dibromoethane, bromine, ethylene, sulfur dioxide, and chlorine. In the second facility, 5 deaths were attributed to malignant neoplasms compared to 2.2 expected. However, this facility manufactured other organic bromide chemicals, such as vinyl bromide, trimethylene chlorobromide, propylene chlorobromide, ethyl bromoacetate, isobutyl bromide, and acetylene tetrabromide, to which workers were potentially exposed. In addition to organic bromide chemicals, workers in the second plant were also indirectly exposed to allyl chloride, benzene, bromochloromethane, carbon tetrachloride, chloroform, ethyl bromide, hydrogen bromide, methylene chloride, methylene dibromide, tert-bromobutyl phenol, and tert-butyl phenol.

The neoplasms were not tissue-specific as can be seen from the following incidence: three lung, two stomach, one prostate, one reticulum-cell sarcoma, one pancreas, and one unknown. In addition, two of the lung neoplasms were associated with workers who had prior history of working with arsenicals which can also cause this type of cancer. The authors did not count these two workers as contributors to the total neoplasm population from this facility because of their prior arsenical exposure. Also, the two workers who succumbed to stomach cancer were father and son and were reported to have a family history of cancer. Smoking history for neoplasm-related deaths was available for one of nine workers. The study is inconclusive in regards to 1,2-dibromoethane as a potential human carcinogen because of co-exposure to other potential carcinogens.

Sweeney et al. (1986) studied the cause-specific mortality of 156 male workers in a

chemical plant that manufactured tetraethyl lead. The study was undertaken to investigate an apparent cluster of three cases of multiple myeloma and four cases of brain cancer. In this historical prospective study, employees who worked at least 1 day between 1952 and 1977 were eligible for the study. Other chemicals used in the tetraethyl lead manufacturing processes were ethylene dibromide, ethylene dichloride, chloroethane, ethylene, inorganic lead, and dyes. Environmental exposure data were available for some chemicals, but the work history records were not sufficiently detailed to construct exposure indices. Consequently, the exposure levels of the various chemicals and particular combinations of chemicals could not be determined.

The standardized mortality ratios (SMRs) for carcinomas at several sites were slightly elevated: colon and rectum (5 observed vs. 3.7 expected); trachea, bronchus, and lung (14 observed vs. 12.5 expected); and brain (4 observed vs 1.88 expected). No SMRs were statistically significantly elevated, however. The investigators reported that there was low power for detecting excess risk of mortality from multiple myeloma (27% at a 5% significance level), brain cancer (31%), or other rare cancers. Concerning the apparent clusters, it was determined that there had been some misclassification of original diagnoses, as one brain cancer was actually a metastatic carcinoma of the lung. One of the three multiple myeloma cases died subsequent to the end date of the study, however, and was not included in the analysis. It is not clear why the study period ended in 1977, given that the study's purpose was to investigate these specific cases.

Mortality in the Sweeney et al. (1986) study from all causes was lower than that predicted based on the death rates of United States males (156 observed vs. 211 expected). This is common in occupational studies and is frequently characterized as the "healthy worker effect." Ideally, the most appropriate comparison group would have been a group of workers exposed to similar levels of the same chemicals except ethylene dibromide. Overall, the study is inconclusive, given the small study size and co-exposure to other chemicals. However, it does not rule out an association of increased cancer incidence with exposure to 1,2-dibromoethane.

Turner and Barry (1979) evaluated mortality due to cancer and other causes in two 1,2-dibromoethane production facilities operated by the same company. One facility (Factory A) operated from 1940 to 1970, while the second (Factory B) started operating in 1952 and was still in operation at the time of the study (1977). Records for men who had been employed at least 4 years during the operation of the facility, with potential exposure to 1,2-dibromoethane, were examined. No exposure measurements or frequency information was available for any of the

workers, however. From Factory A, 117 men were identified with potential exposure to 1,2-dibromoethane for at least 4 years, 34 of whom had died at the time of the study. From Factory B, 274 men were identified with potential exposure to 1,2-dibromoethane for at least 4 years, 26 of whom had died by the time of the study. Death rate per 1000 man-years was calculated within broad age-at-death categories (25-44, 45-64, 65-74, and 75 years and over) due to the small number of subjects and compared with analogous death rates in the local population in 1961 and 1970 to help consider possible differences associated with date of death. Death rates for all causes and for cancer only were similar or lower in the exposed groups than in the local population for all age groups, except in the 75 years and over group (Factory A only; there were none in this age group in the Factory B set). In the oldest age group, the death rate among exposed workers was 149.9 per 1000 man-years for all causes, while the analogous death rate for the local population was 136.5 in 1961 and 135.8 in 1970. For cancer, the death rate was 21.3, while the analogous rate in the local population was 16.2 in 1961 and 17.0 in 1970; however, there was only one cancer case in the exposed group. Given the extremely small study size, lack of exposure information, and insufficient allowance for cancer latency, especially for Factory B, this study is inconclusive regarding the effect of 1,2-dibromoethane on carcinogenicity.

4.2. PRECHRONIC AND CHRONIC STUDIES AND CANCER BIOASSAYS IN ANIMALS

4.2.1. Carcinogenicity Bioassays and Chronic Oral Studies

The National Cancer Institute (NCI) (1978) examined the potential carcinogenicity of 1,2-dibromoethane in rats and mice. Male and female Osborne-Mendel rats and B6C3F_1 mice (50/sex/species/exposure group; n = 20 in untreated control group and n = 20 in vehicle control group) were administered 1,2-dibromoethane in corn oil by gastric intubation for 5 days/week until sacrificed.

Rats: The initial doses utilized for male and female rats were 40 and 80 mg/kg-day. However, high treatment-related mortality (18/50 males and 20/50 females) caused a discontinuation in the intubation of the high-dose group after treatment in week 16. Intubation of this group was suspended for 13 weeks and then restarted at week 30. At this time the surviving

rats received the low-dose regimen. All surviving male and female rats in both dosage groups were sacrificed at weeks 49 and 61, respectively. Time-weighted average low- and high-doses were 38 and 41 mg/kg-day for male rats, and 37 and 39 mg/kg-day for female rats.

The treated and vehicle control rats were placed on test simultaneously at the age of 8 weeks with intubation of vehicle controls suspended after 49 weeks, followed by a 14-day observation period. All male and female vehicle controls were sacrificed in week 63 at the age of 71 weeks. Gavage of female vehicle controls was suspended after 61 weeks and was followed by a 2-week observation period. Untreated controls (5 weeks of age) were placed on test 15 weeks after the start of the treated rats and vehicle controls. Thus, all untreated (without vehicle) controls were on test for 107 weeks.

Treatment-related effects included squamous cell carcinoma of the forestomach in rats of both sexes, judged by the investigators to be a possible cause of the high mortality. There was a positive association ($p < 0.001$) in both groups between increasing dosage and accelerated mortality. Because 40% of high-dose females died in week 15 either during intubation or shortly thereafter, it was suggested that acute toxic reactions were the likely cause of those deaths. However, squamous cell carcinomas (in all low-dose females surviving beyond week 15) were also considered by the investigators to be associated with mortality in this group. There was no mention in the report if gavage error contributed to the incidence of early mortality.

There were statistically significant increases in tumor incidence for both male and female rats, both at the point of contact (forestomach) and systemically. Crude incidences of forestomach tumors were 90% in low-dose males and 80% in low-dose females, but 66% and 58% in high dose animals. Lower incidence in the high-dose group may have been due to the higher rate of early deaths. Metastases of the forestomach tumors to multiple organs were common. There was an elevated incidence of hepatocellular carcinoma in high-dose female rats only. Hemangiosarcoma, particularly of the spleen, was observed in male and female animals. Males also had a small incidence of hemangiosarcoma in other organs: liver, kidney, pancreas, and abdominal cavity. The incidence of hemangiosarcomas was statistically significant for low-dose animals only. The incidence of these selected neoplastic lesions in the rat is summarized in Table 4-1.

Non-neoplastic lesions in the high-dose animals of both sexes included hyperkeratosis and

acanthosis of the forestomach (12/50 males and 18/50 females). The incidence of hyperkeratosis and acanthosis was lower in low-dose animals with only 4/50 females (compared with 1/20 untreated controls) and no males presenting this adverse effect. Peliosis (mottled-blue liver) hepatitis was observed in 0/40 controls, 10/50 low-dose, and 9/50 high-dose males and in 0/40 controls, 1/47 low-dose, and 5/48 high-dose females. Inflammation of the liver was also present in 1/40 controls, 4/50 low-dose, and 5/50 high-dose males and in 0/40 controls, 4/47 low-dose, and 2/48 high-dose females. Degeneration of the adrenal cortex was noted in 0/40 controls and 13/48 and 9/47 low- and high-dose males. The incidence of adrenocortical degeneration was slightly lower in females (1/40 controls, 3/44 low-dose, and 8/45 high-dose animals).

Testicular atrophy was observed in 11/20 untreated controls, 0/20 vehicle controls, and 14/49 and 18/50 low- and high-dose males, respectively. Because the untreated controls were on test for a far longer period (107 weeks) than the treated or vehicle controls, the vehicle controls are the appropriate reference group. It was stated that necropsy was performed on each animal regardless of whether it died, was sacrificed while moribund, or was at the end of the study. Thus, the incidence data for testicular atrophy for only those male rats that survived until the end of study (35 weeks) were likely higher than the data given for the original 50 rats (18 of which died early). The results suggest that the low dose (38 mg/kg-day) was a lowest-observed adverse-effect level (LOAEL), indicating that 1,2-dibromoethane induced early development of testicular lesions.

Mice: Male and female mice were initially treated with low and high doses of 60 and 120 mg/kg/day, respectively. At week 11, low- and high-dose concentrations were increased to 100 and 200 mg/kg-day, respectively. Treatment with increased doses continued for 2 weeks and then returned to initial concentrations at week 13. The high-dose treatments were further decreased to 60 mg/kg/day in week 40. At week 54, compound treatment was ceased in both low- and high-dose groups. All surviving male mice and high-dose female mice were sacrificed by week 78, while low-dose females were sacrificed at week 90. Time-weighted average low- and high-doses were 62 and 107 mg/kg/day, respectively, for mice of both sexes.

Mortality was high in all treated groups ($p < 0.001$). Only 20/50 low- and 10/50 high-dose males survived for at least 58 weeks. Due to excessive mortality, males were sacrificed at week 78. Of the males that survived to at least week 26, 44/46 low-dose and 29/40 high-dose males exhibited squamous-cell carcinoma of the forestomach. In females, 28/50 low-dose and

8/50 high-dose animals survived at least 70 weeks. Low- and high-dose females were terminated at weeks 90 and 78, respectively. As in males, early development of squamous-cell carcinoma of the forestomach was observed, with the first occurrence in the low-dose group at week 40 and the first occurrence in the high-dose group at week 34. Of the high-dose females that survived to at least week 34, 28/35 exhibited squamous-cell carcinoma of the forestomach.

Squamous-cell carcinoma of the forestomach was the primary tumor observed in both sexes. Similar to rats, this neoplasm metastasized throughout the abdominal cavity and lung. In addition, lung adenomas were observed in all mouse exposure groups of both sexes and were considered compound-related. There was a significant positive association between dosage and incidence for both sexes. Although there was little evidence of lung carcinomas (one in the low-dose females), the adenomas nevertheless are considered evidence of a carcinogenic response and are relevant for human risk assessment. The incidence of these selected neoplastic lesions in the mouse is summarized in Table 4-2.

Non-neoplastic lesions were observed primarily in the forestomach of treated mice. Acanthosis was observed in 0/40 controls, 1/50 low-dose, and 5/49 high-dose males and in 0/40 controls and 9/50 high-dose females. Hyperkeratosis of the forestomach was also observed in 13/49 high-dose males and in 0/40 controls, 1/49 low-dose, and 12/50 high-dose females. Testicular atrophy was also observed in 10/47 high-dose male mice (none in 39 control animals or in 45 low-dose animals). Thus, 1,2-dibromoethane appears to have caused early development of testicular atrophy as it had in male rats.

The carcinogenicity of 1,2-dibromoethane and its potential metabolites was the focus of a study by Van Duuren et al. (1985). Groups of 30 male and 30 female B6C3F_1 mice were administered bromoacetaldehyde, bromoethanol, or 1,2-dibromoethane in drinking water at a concentration of 4 mM for each compound for 15–18 months. Untreated control groups, consisting of 50 mice of each sex, were given distilled drinking water. Based on measured drinking water consumption, the authors estimated that 1,2-dibromoethane-treated male mice received 116 mg/kg/day, and 1,2-dibromoethane-treated female mice received 103 mg/kg/day on average.

Van Duuren et al. reported that 1,2-dibromoethane-treated animals had significant mortality and weight loss that were not observed in the other treatment groups. Survival in males

was approximately 25% at week 65 when the group was terminated, while survival in females dropped to this level by about week 74. 1,2-Dibromoethane-induced squamous carcinoma of the forestomach was observed in 26 of 28 male mice necropsied and in 22 of 29 female mice. In addition, five forestomach papillomas were observed in these 29 females. Males also exhibited eight squamous carcinomas of the glandular stomach. As in the NCI study, there were metastases of the squamous carcinomas to other organs. Bromoethanol induced leukemia (2/29 in both males and females compared with 2/50 for female controls and none in males) and had a high incidence (10/29 males and 9/29 females compared with 1/50 in each of the control groups) of forestomach papillomas. The incidence of tumor-bearing mice treated with bromoacetaldehyde was lower than untreated controls. The authors concluded that it was unlikely that bromoacetaldehyde or bromoethanol were the activated carcinogenic intermediates of 1,2-dibromoethane.

Table 4-1. Incidence of tumors in Osborne-Mendel rats in 1,2-dibromoethane oral gavage bioassay

Organ/tissue Tumor	Control 0 mg/kg-day		Vehicle control 0 mg/kg-day		38 mg/kg-day		41 mg/kg-day	
	incid.	%	incid.	%	incid.	%	incid.	%
Males								
Stomach Forestomach papilloma or tumor	0/20	0	0/20	0	45/50	90	33/50	66
Circulatory system Hemangiosarcoma	0/20	0	0/20	0	11/50	22	4/50	8
Thyroid gland Follicular cell adenoma or carcinoma	1/20	5	0/20	0	5/50	10	8/49	16
Females								
Forestomach Tumors	0/20	0	0/20	0	40/50	80	29/50	58
Liver Hepatocellular carcinoma	0/20	0	0/20	0	1/47	2	5/48	10
Circulatory system Hemangiosarcoma	0/20	0	0/20	0	1/49	2	3/48	6
Adrenals Adrenocortical carcinoma	0/20	0	0/20	0	0/44	0	4/45	9

Source: NCI, 1978.

Table 4-2. Incidence of tumors in B6C3F1 mice in 1,2-dibromoethane oral gavage bioassay

Organ/tissue Tumor	Control 0 mg/kg-day		Vehicle control 0 mg/kg-day		62 mg/kg-day		107 mg/kg-day	
	incid.	%	incid.	%	incid.	%	incid.	%
Males								
Forestomach Squamous cell papilloma or carcinoma	0/20	0	0/20	0	45/50	90	31/49	63
Lung Adenoma	0/20	0	0/20	0	4/45	8	10/47	21
Females								
Forestomach Papillomas or tumors	0/20	0	0/20	0	47/48	92	28/50	56
Lung Adenoma	0/20	0	0/20	0	10/48	20	5/50	10

Source: NCI, 1978.

4.2.2. Carcinogenicity Bioassay and Chronic Inhalation Studies

The National Toxicology Program (NTP, 1982) performed an inhalation carcinogenicity bioassay in rats and mice. Male and female Fischer 344 rats and $B6C3F_1$ mice (n = 50 per sex, species, and exposure group) were exposed to 0, 10, or 40 ppm (0, 77, or 307 mg/m^3) 1,2-dibromoethane for 6 hr/day, 5 days/week. The study was designed to assess potential adverse effects of 1,2-dibromoethane following 103 weeks of exposure. However, high mortality in both species prompted early termination in some of the exposure groups.

Rats: High-exposure male rats exhibited high mortality (90%) resulting in termination of that exposure group at week 88. Similarly, high-exposure female rats exhibited high mortality (84%) and were terminated at week 91. Mortality in control and low-exposure rats of both sexes were comparable.

Mean body weights of high-exposure rats of either sex were decreased compared to

controls throughout the study. However, body weight data were reported graphically in the text, and determination of the week that the decrease in body weight became significant (≥10% of controls) is difficult to determine. Nasal cavity tumors were the primary neoplastic lesion observed in rats. The total numbers of animals with primary nasal cavity tumors were significantly increased ($p < 0.001$) in 1,2-dibromoethane-exposed male rats (0/50 control, 39/50 low-exposure, and 41/50 high-exposure) and female rats (1/50 control, 34/49 low-exposure, and 43/50 high-exposure). These summary statistics were presented in Tables 5 and 6 of the NTP report. Table 4-3 is a summary of the incidences of nasal cavity tumor types, including those from animals that died on study.

Other neoplastic lesions were also observed. Hemangiosarcoma of the spleen was observed in 1 low-exposure and 15 high-exposure male rats, and this tumor type was also observed in 5 high-exposure females. Male rats had a dose-dependent increase in mesothelioma of the tunica vaginalis (1/50 control, 13/50 low-exposure, and 26/50 high-exposure). Female rats had a statistically significant increase in mammary fibroadenomas in both exposure groups (4/50 control, 29/49 low-exposure, and 24/50 high-exposure). In addition, 4/50 high-exposure females were observed to have adenocarcinoma of the mammary glands compared to 1/50 for controls. Lung carcinoma (4/50) and adenoma (1/50) were also reported in high-exposure females.

Several non-neoplastic lesions were considered related to treatment. A dose-dependent increase in hepatic necrosis was observed in 2/50 control, 6/50 low-exposure, and 19/50 high-exposure males and 2/50 control, 3/49 low-exposure, and 13/48 high-exposure females. Toxic nephropathy was observed in 4/50 low-exposure and 28/50 high-exposure males and 8/50 high-exposure females. This lesion was not observed in any of the controls. Dose-dependent testicular degeneration (1/50 control, 10/50 low-exposure, and 18/49 high-exposure) and atrophy (1/50 control, 2/50 low-exposure, and 5/49 high-exposure) was observed in male rats, and spermatic granulomas were observed in high-exposure males (2/49). Female rats were observed to have a dose-dependent degeneration of the adrenal cortex (4/50 control, 7/49 low-exposure, and 13/47 high-exposure). Adrenocortical degeneration was only observed in one male from each exposure group. Retinal atrophy was also observed in 1/50 low-exposure male, 10/50 low-exposure females, and 5/50 high-exposure females.

Mice: As mentioned previously, high mortality prompted early termination of some of the mouse exposure groups. Low-exposure female mice displayed moderate mortality (62%) with

controls displaying 20% mortality. Exposures were not terminated until the end of the experiment (104-106 weeks). High-exposure female mice exhibited excessive mortality (86%) with treatment terminated at week 90. Mortality was high in exposure and control groups of male mice, and all male mice were sacrificed at 78 weeks. The principal cause of mortality in male mice was ascending, suppurative urinary tract infection, progressing to necrotic and ulcerative lesions around the urethral opening; chronic or suppurative cystitis; and ascending, suppurative pyelonephritis. These effects in the male mice were not related to exposure.

Mean body weights of high-exposure mice were decreased compared to controls throughout the study. However, body weight data were reported graphically in the text, and determination of the week that decrease in body weight became significant ($\geq$10% of controls) is difficult to determine. As in rats, the principal neoplastic lesions observed were manifest in the respiratory tract. However, tumors were primarily found in the lung of mice and not the nasal cavities. The total numbers of animals with lung tumors were significantly increased ($p < 0.001$) in high-exposure male mice (0/41 control, 3/48 low-exposure, and 25/46 high-exposure) and female mice (4/49 control, 11/49 low-exposure, and 42/50 high-exposure) ($p < 0.045$ and < 0.001, respectively). These summary statistics were presented in Tables 8 and 9 of the NTP report. Table 4-4 is a summary of the incidence of lung tumor types, including those from animals that died on study.

In addition to the above-mentioned lung neoplasms, high-exposure females had an increased incidence of carcinoma (6/50), adenoma (2/50), and adenomatous polyp (3/50) of the nasal cavity. Hemangiosarcomas were observed in 2 high-exposure males, 11 low-exposure females, and 23 high-exposure females, and hemangiomas occurred in 2 high-exposure males, 1 low-exposure female, and 4 high-exposure females. These lesions were primarily observed in the retroperitoneal cavity in areas adjacent to the adrenal glands, kidneys, ovaries, and uteri of female mice. Occasionally the hemangiosarcoma and hemangioma invaded the adjacent organ. Fibrosarcoma was observed in 2 high-exposure males, 5 low-exposure females, and 15 high-exposure females, with the majority of fibrosarcomas located in subcutaneous tissues. Malignant mammary tumors (adenocarcinoma, adenocarcinoma with squamous metaplasia, or adenosquamous carcinoma) were reported in 2/50 controls, 18/50 low-exposure, and 10/50 high-exposure females.

Non-neoplastic lesions were generally not observed in male mice probably due to the high

mortality. The majority of non-neoplastic lesions observed in female mice were located in the respiratory tract. Dose-dependent epithelial hyperplasia of the lung alveoli, bronchioles, and bronchi was observed. Hyperplasia was also observed in the nasal cavities of high-exposure females (13/50). Suppurative inflammation of the nasal cavity was also observed in low-exposure (4/50) and high-exposure (20/50) females. In addition, adenomatous hyperplasia of the lung was reported in high-exposure females (37/50). In other tissues of female mice, dose-dependent hematopoiesis in the spleen was observed (0/50 control, 8/49 low-exposure, and 16/49 high-exposure), and a low, dose-dependent incidence of hepatic necrosis was also reported (0/50 control, 2/50 low-exposure, and 5/50 high-exposure).

Proliferative lesions in the nasal epithelium have been reported in mice following long-term inhalation exposure to 1,2-dibromoethane (Stinson et al., 1981). Groups of 50 male and 50 female B6C3F_1 mice were exposed to 10 or 40 ppm (77 or 307 mg/m^3) 1,2-dibromoethane 6 hours/day, 5 days/week for 103 (10 ppm) or 90 (40 ppm) weeks. At 10 ppm (77 mg/m^3), 1 male and 3 female mice developed focal epithelial hyperplasia, which increased in incidence to 10 male and 11 female mice at 40 ppm (307 mg/m^3) exposure. Benign neoplasms were observed in the 40 ppm (307 mg/m^3) exposure groups of male and female mice and identified as squamous papilloma (three in males and seven in females) and adenomas (two females); the latter were also observed to have squamous papilloma. Benign neoplasms first appeared in male mice at 59 weeks and in female mice at 79 weeks. Carcinomas were present in seven female mice exposed to 40 ppm (307 mg/m^3) 1,2-dibromoethane. The first carcinoma appeared at 45 weeks, and carcinomas were identified as squamous carcinoma (n = 2), adenocarcinoma (n = 2), and mixed carcinoma (n = 3). Sarcomas were observed in one 10 ppm (77 mg/m^3) female (characterized as poorly differentiated) and two 40 ppm (307 mg/m^3) females (hemangiosarcoma). Mortality was not reported, and no other toxicological parameters were monitored.

4.2.3. Subchronic Inhalation Studies

Preliminary to chronic bioassays, the NTP (1982) conducted subchronic inhalation studies in rats and mice. Male and female Fischer 344 rats (n = 4 to 6 per sex and exposure group) and B6C3F_1 mice (n = 10 per sex and exposure group) were exposed to 0, 3, 15, or 75 ppm (0, 23, 115, or 576 mg/m^3) 1,2-dibromoethane, 6 hours/day, 5 days/week for 13 weeks. No deaths were reported for rats at any exposure group. High-exposure female rats had depressed weight gain, and male rats exhibited a dose-dependent depression of weight gain for all exposures. In rats of

both sexes exposed to 75 ppm (576 mg/m^3) 1,2-dibromoethane, swelling and/or vacuolation of adrenal cortical cells and decreases in thyroid follicular size were observed. In mice, 4/10 males in the 3 ppm (23 mg/m^3) exposure group and 1 female in the 75 ppm (576 mg/m^3) exposure group died prior to the termination of the study. A dose-dependent decrease in body weight was observed for both sexes. Eye irritation was observed in both sexes in the 75 ppm (576 mg/m^3) exposure group at weeks 12 and 13. In the high-exposure mice, 3 males and 9 females exhibited megalocytic cells in the lining of the bronchioles. Based on the frank effects observed at 75 ppm (576 mg/m^3), 10 and 40 ppm (77and 307 mg/m^3) exposures to 1,2-dibromoethane were chosen for chronic toxicity and cancer studies described above.

Nitschke et al. (1981) described the results of a study designed principally to evaluate the role of 1,2-dibromoethane in inducing nasal lesions. Male and female F344 rats were exposed by inhalation to 1,2-dibromoethane at 0, 3, 10, or 40 ppm (0, 23, 77, or 307 mg/m^3) for 6 hours/day, 5 days/week for 13 weeks. Forty male and 20 female rats were used per exposure group, and serial sacrifices of 10 males per exposure group were conducted at 1, 6, and 13 weeks; 10 females per exposure group were sacrificed at 13 weeks. The remaining male and female animals were sacrificed 88–89 days postexposure. No treatment-related effects were observed in the urinalysis of male rats. However, the female rats in the 40 ppm (307 mg/m^3) exposure group exhibited a slight decrease in specific gravity of the urine compared to controls; this parameter returned to normal in the postexposure period. No hematological effects of toxicological significance were observed in any of the exposure groups.

Table 4-3. Nasal cavity tumor types in rats following chronic inhalation of 1,2-dibromoethane

Tumor type	Control male	10 ppm male	40 ppm male	Control female	10 ppm female	40 ppm female
Adenomatous polyp	0/50	18/50	5/50	0/50	5/50	5/50
Adenoma	0/50	11/50	0/50	0/50	11/50	3/50
Adenocarcinoma	0/50	20/50	28/50	0/50	20/50	29/50
Carcinoma	0/50	0/50	21/50	0/50	0/50	25/50
Squamous cell carcinoma	0/50	3/50	3/50	1/50	1/50	5/50

Source: NTP, 1982.

Table 4-4. Lung tumor types in mice following chronic inhalation of 1,2-dibromoethane

Tumor type	Control male	10 ppm male	40 ppm male	Control female	10 ppm female	40 ppm female
Carcinoma-bronchus	0/41	0/48	0/46	0/49	1/49	4/50
Adenoma-bronchus	0/41	0/48	2/46	0/49	0/49	5/50
Adenomatous polyp-bronchus	0/41	0/48	3/46	0/49	0/49	1/50
Adenomatous polyp-bronchiole	0/41	0/48	2/46	0/49	1/49	2/50
Alveolar/bronchiolar adenoma	0/41	0/48	11/46	3/49	7/49	13/50
Alveolar/bronchiolar carcinoma	0/41	3/48	19/46	1/49	5/49	37/50

Source: NTP, 1982.

Males exposed to 40 ppm (307 mg/m^3) showed significantly decreased body weights throughout most of the 13-week exposure period, which returned to control levels during the recovery period. No significant differences in body weight were observed for any other exposure groups. Relative liver and kidney weights were significantly elevated in the 40 ppm (307 mg/m^3) males at 6 and 13 weeks. Females in the 40 ppm (307 mg/m^3) exposure group had elevated liver weights only. Organ weights returned to control levels during the recovery period. The principal histopathological finding was scattered-to-diffuse nasal epithelial hyperplasia with focal necrosis

at all sacrifice periods for animals exposed to 40 ppm (307 mg/m^3). This increased in severity at week 6 and progressed to diffuse or focal nonkeratinizing squamous metaplasia of the respiratory epithelium by week 13. Males in the 10 ppm exposure group exhibited single or multiple nasal epithelial hyperplasia foci at all three sacrifice intervals; this effect was also present in 10 ppm females at 13 weeks. The respiratory epithelial effects in the 10 and 40 ppm (77 and 307 mg/m^3) groups had completely resolved, except for one animal, during the recovery period. No testicular, kidney, liver, or lung effects were observed. Thyroid and adrenals, a target of 1,2-dibromoethane in the NTP (1982) subchronic study, were not examined by histopathology. The study authors identified 3 ppm (23 mg/m^3) as the no-observed adverse effect level (NOAEL) from these results.

Reznik et al. (1980) also examined the respiratory system in both the rat and mouse exposed subchronically to 1,2-dibromoethane. Male and female F344 rats (5 animals/sex/exposure group) and B6C3F$_1$ mice (10 animals/sex/exposure group) were exposed by inhalation to 0, 3, 15, or 75 ppm (0, 23, 115, or 576 mg/m^3) 1,2-dibromoethane for 6 hr/day, 5 days/week, for 13 weeks. Apparently, there was no mortality as none was reported. Histomorphological changes were observed in the nasal cavity of both species exposed to 75 ppm (576 mg/m^3) 1,2-dibromoethane with a much lower incidence in rats at 15 ppm (115 mg/m^3). The concentration-dependent changes included cytomegaly, focal hyperplasia, squamous metaplasia, and loss of cilia. Rats and mice exposed to 75 ppm (576 mg/m^3) showed severe necrosis and atrophy of the olfactory epithelium. No lesions were noted in any other tissue (e.g., liver, kidney, and testis). NOAELs identified in this study were 3 ppm (23 mg/m^3) in rats and 15 ppm (115 mg/m^3) in mice. LOAELs were 15 ppm (115 mg/m^3) in rats and 75 ppm (576 mg/m^3) in mice.

Rowe et al. (1952) reported the results of a study that examined the toxicity of 1,2-dibromoethane (99% pure) to rats, rabbits, guinea pigs, and monkeys following inhalation exposure. Chamber concentrations were within 10% of desired concentrations. Examination of tissues (lung, heart, liver, kidney, spleen, testis, pancreas, and adrenal gland) was performed with light microscopy. The strains of the animals were not specified. Rats were exposed to 50 ppm (384 mg/m^3) 1,2-dibromoethane for 7 hours/day, 5 days/week, for 91 days. High mortality (50%) in male rats was attributed to pneumonia and infections of the upper respiratory tract. Male rats also exhibited statistically significant increases in relative lung, kidney, and liver weights and decreased testicular weight. In females, 4/20 animals died before study termination, and relative liver and kidney weights were increased while spleen weight was decreased. Histological examination did not reveal any significant changes except patches of pneumonic consolidation in

male rats. Guinea pigs were exposed in the same manner as rats, except that exposure was terminated after 80 days. Body weight gain was depressed in both sexes, but mortality was not different than in controls. Microscopic examination of tissues revealed a slight central fatty degeneration of the liver and slight internal congestion and edema of the kidney tubular epithelium. No other changes were observed. There were no apparent effects of toxicological significance in rabbits exposed to 50 ppm (384 mg/m^3) 1,2-dibromoethane for 7 hr/day, 5 days/week, for 84 days. There were slight, but not significant, increases in liver and kidney weights.

Monkeys exposed to 50 ppm (384 mg/m^3) 1,2-dibromoethane for 7 hr/day, 5 days/week, for 70 days exhibited fatty degeneration of the liver and increased relative kidney weight. Animals were also described as appearing ill, nervous, and unkempt throughout the experimental period. In addition, the same species were exposed to 25 ppm (192 mg/m^3) 1,2-dibromoethane 7 hr/day, 5 days/week, for 213, 205, 214, and 200 days for rats, guinea pigs, rabbits, and monkeys, respectively. No adverse effects were noted in any species except for high mortality in male rats (50%) and male and female guinea pigs (50 and 25%, respectively).

The investigators stated that rabbits and monkeys and probably rats and guinea pigs can tolerate daily repeated 7-hour exposures to 25 ppm (192 mg/m^3) 1,2-dibromoethane without adverse effects. However, this statement should be regarded with extreme caution due to the limitations of this study. Evidence from the previously mentioned subchronic studies (Nitschke et al., 1981; Reznik et al., 1980) suggests that the nasal cavity in rats is the major target organ following inhalation exposure to 1,2-dibromoethane. This tissue was not examined by Rowe et al. (1952). In addition, the study is limited because of the number of guinea pigs (7 per sex in 50 ppm exposure group, 8 per sex in 25 ppm exposure group), rabbits (3 male and 1 female for both exposure groups), and monkeys (1 per sex for both exposure groups) used in this study. The use of a larger number of animals might have detected significant adverse effects. Also, the study provided limited details of methods used.

4.2.4. Other Studies

Male Fischer 344 rats (eight animals per dose group) were given 40 or 80 mg/kg 1,2-dibromoethane in corn oil by gavage 5 days per week for 2 weeks (Ghanayem et al., 1986). Fifty

percent of high-dose rats exhibited an increased incidence of forestomach cellular proliferation compared to none in the low-dose group, vehicle controls, and two negative control groups. Hyperkeratosis was also significantly increased in high-dose animals. The study authors concluded that induced forestomach cellular proliferation provides a "favorable environment" for neoplastic development in the forestomach.

The potential influence of disulfiram on the metabolism and carcinogenicity of 1,2-dibromoethane has been studied (Wong et al., 1982). During the oxidative metabolism of 1,2-dibromoethane, 2-bromoacetaldehyde is formed, which then undergoes further oxidative metabolism or conjugation with GSH. Disulfiram inhibits aldehyde dehydrogenase and may alter the metabolism of 1,2-dibromoethane by preventing further metabolism of 2-bromoacetaldehyde. The study authors hypothesized that because disulfiram is used to treat alcoholics, alcoholics might be at a greater risk to 1,2-dibromoethane toxicity due to modified metabolism. To test this hypothesis, four groups of 48 male and 48 female Sprague-Dawley rats received either control air, control air and 0.05% disulfiram in the diet, 20 ppm (154 mg/m^3) 1,2-dibromoethane and control diet, or 20 ppm (154 mg/m^3) 1,2-dibromoethane and 0.05% disulfiram in the diet for 18 months. 1,2-Dibromoethane air concentrations were maintained for 7 hr/day, 5 days/week.

Rats in the control air/0.05% disulfiram group showed decreased body weight gain throughout the experimental period. They also had consistently lower body weight gains than rats exposed to 1,2-dibromoethane alone. Rats in the 20 ppm (154 mg/m^3) 1,2-dibromoethane/0.05% disulfiram group displayed lower body weight gains compared to all other exposure groups throughout the experiment. Weight gain reduction appeared to be correlated with decreased food consumption except in animals exposed to 1,2-dibromoethane alone. Excessive mortality was observed in animals receiving 1,2-dibromoethane/control diet and 1,2-dibromoethane/disulfiram compared to controls and disulfiram-diet rats. 1,2-Dibromoethane/control rats had normal hematological parameters, but 1,2-dibromoethane/disulfiram animals showed decreased hematocrit, hemoglobin, and red blood cell (RBC) counts. Control air/disulfiram animals had an increased incidence of hemosiderosis in the spleen, while females displayed an increase in mammary tumors.

Tumor incidence is listed in Table 4-5. Rats exposed to 1,2-dibromoethane alone had an increased incidence of splenic hemangiosarcoma and adrenal tumors with males exhibiting an increase in subcutaneous mesenchymal tumors and females having a high incidence of mammary

tumors. 1,2-Dibromoethane/disulfiram rats exhibited an increase in liver, kidney, and thyroid tumors compared to rats receiving 1,2-dibromoethane or disulfiram alone. Hemangiosarcoma was present in the liver, spleen, and mesentery, and males had an increase in lung tumors and testicular atrophy when compared to animals receiving 1,2-dibromoethane alone. From this study, it appears that disulfiram increases the toxicity and carcinogenicity of 1,2-dibromoethane.

Table 4-5. Enhancement of 1,2-dibromoethane-induced tumor with disulfiram coadministration in rats

	Control/ control diet		Control/ disulfiram diet		1,2-Dibromoethane/ control diet		1,2-Dibromoethane/ disulfiram diet	
Tumor type	**Male[a]**	**Female[a]**	**Male[a]**	**Female[a]**	**Male[b]**	**Female[a]**	**Male[a]**	**Female[c]**
Liver	0	0	1	0	2	3	36	32
Kidney	0	0	0	0	33	1	17	7
Adrenal	2	1	1	0	11	6	6	8
Subcutaneous	3	0	1	0	11	1	4	4
Thyroid	4	5	1	1	3	1	18	18
Lung	0	0	0	0	3	0	9	2
Hemangiosarcoma								
Spleen	0	0	0	0	6	0	30	19
Mesentery	1	8	4	18	5	9	15	11

[a] Groups consisted of 48 rats at the initiation of the study; all were examined histopathologically.
[b] Group consisted of 48 rats at theinitiation of the study, but two rats were not examined due to autolysis.
[c] Group consisted of 48 rats at the initiation of the study, but three rats were not examined due to autolysis.

Source: Wong et al. (1982).

1,2-Dibromoethane has been evaluated in the A/J mouse lung tumor bioassay by several routes of exposure (Stoner et al, 1986; Adkins et al, 1986). Stoner et al. (1986) exposed groups of approximately 16 male and 16 female A/J mice to 1,2-dibromoethane either by gavage at 840 mg/kg or intraperitoneally at 168, 420, or 840 mg/kg. Control groups received a comparable injection of vehicle, trycaprylin-2 for the gavage study and tricaprylin-1 for the intraperitoneal study. Injections were administered 3 times per week for a total of 24 injections. The mice were observed until 24 weeks after the first administration, then sacrificed and examined for lung

tumors. The results are summarized in Table 4-6. Both male and female mice showed increased tumor incidence at 840 mg/kg, both by oral and intraperitoneal administration, of at least twice the corresponding control response. The response in the high-dose female mice by the intraperitoneal route, at 14/16 (88%), was markedly higher than that in the high-dose male mice (44%). The authors concluded that 1,2-dibromoethane was active in only the females at only the highest dose when given intraperitoneally and inactive in both sexes when given orally. Note that these studies have limited power to detect increases in tumor incidence, relative to chronic studies; that is, if each treatment group had started with 50 mice, all of the high-dose responses, except in the male mice treated intraperitoneally, would have been statistically significantly increased relative to vehicle control. While this outcome is driven in part by the lower than average response in the vehicle control mice, at about 14 - 20% compared with about 30% across all of the untreated and vehicle controls, this experiment does not clearly rule out the possibility that oral administration of 1,2-dibromoethane is associated with induction of lung adenomas in A/J mice.

In a second set of studies, Adkins et al. (1986) exposed groups of 30 and 60 female A/J mice by inhalation to 0, 20 or 50 ppm 1,2-dibromoethane for 6 hr/day, 5 days/week, for 6 months (24 weeks) and then sacrificed and examined for lung tumors. In the first study, which started with 30 mice per group, 51% of the control animals and 100% of all surviving dibromoethane-exposed animals developed lung adenomas. A dose-related increase in pulmonary adenoma formation was observed in the second study with 60 mice per group: 26%, 68%, and 100% of the surviving control, low-dose, and high-dose mice, respectively, developed lung adenomas. The authors concluded that the two studies together indicated a concentration-related increase in the frequency and incidence of adenoma formation, significant and reproducible at 50 ppm. These data are also summarized in Table 4-6.

These studies demonstrate qualitative evidence of lung tumor induction by several routes of exposure. Because only results from animals who survived the 24-week experimental period are considered in the A/J mouse lung tumor assay, it is possible that tumor incidences are underreported and would therefore be inadequate for a quantitative dose-response assessment. The evidence does not clarify whether lung tumors are solely the result of portal of entry effects in the case of inhalation exposure to dibromoethane but does demonstrate that lung tumors can result from systemic exposure to dibromoethane.

Table 4-6. Lung tumor incidence in A/J mice following exposure to 1,2-dibromoethane via several routes of exposure

Sex	Exposure level	Number of mice placed on test	Number of mice surviving at 24 weeks	Number (%) of surviving mice with lung tumors	
Oral exposure[a]					
Male	840 mg/kg, 3 times/week	16	16	7	(44)
	0 mg/kg, 3 times/week	16	15	-[c]	(20)
Female	840 mg/kg, 3 times/week	16	16	5	(31)
	0 mg/kg, 3 times/week	16	14	-	(14)
Intraperitoneal exposure[a]					
Male	840 mg/kg, 3 times/week	16	16	7	(44)
	420 mg/kg, 3 times/week	16	15	3	(20)
	168 mg/kg, 3 times/week	15	14	2	(14)
	0 mg/kg, 3 times/week	16	15	-	(30)
Female	840 mg/kg, 3 times/week	16	16	14	(88)
	420 mg/kg, 3 times/week	16	16	9	(56)
	168 mg/kg, 3 times/week	17	17	4	(24)
	0 mg/kg, 3 times/week	16	15	-	(30)
Inhalation[b]					
Female	50 ppm, 6h/d, 5d/wk	30	11	-	(100)
	20 ppm, 6h/d, 5d/wk	30	11	-	(100)
	0 ppm, 6h/d, 5d/wk	30	30	-	(51)
Female	50 ppm, 6h/d, 5d/wk	60	57	-	(100)
	20 ppm, 6h/d, 5d/wk	60	57	-	(68)
	0 ppm, 6h/d, 5d/wk	60	58	-	(26)

[a] Source: Stoner et al. (1986).
[b] Source: Adkins et al. (1986).
[c] Only the percentage was reported.

4.3. REPRODUCTIVE AND DEVELOPMENTAL STUDIES IN ANIMALS - ORAL AND INHALATION

4.3.1. Inhalation Studies

The potential effects of 1,2-dibromoethane on reproduction in male and female rats have been reported (Short et al., 1979). Male Charles River CD rats (9-10/group) were exposed whole-body to 0, 19, 39, and 89 ppm (0, 146, 300, and 684 mg/m^3) 1,2-dibromoethane for 7 hours/day, 5 days/week, for 10 weeks, and females (20/group) were exposed to 0, 20, 39, and 80 ppm (0, 154, 300, and 614 mg/m^3) 1,2-dibromoethane for 7 hours/day, 7 days/week, for 3 weeks. Males in the 89 ppm (684 mg/m^3) exposure group and females in the 80 ppm (614 mg/m^3) exposure group gained less weight, consumed less food, and had higher mortality rates (21% males, 20% females) than controls. In the 89 ppm (684 mg/m^3) group, testicular weight and testosterone concentrations were significantly reduced, and none of the males in this group were able to impregnate non-exposed females after the 10-week exposure period, compared to a 90% impregnation rate for the other exposed males. Also, atrophy of the testis, epididymis, prostate, and seminal vesicle was observed in the 89 ppm (684 mg/m^3) group. No treatment-related reproductive effects were observed in males exposed to 19 or 39 ppm (146 or 300 mg/m^3) 1,2-dibromoethane. The litters from these males were normal with respect to total implants, viable implants, and resorptions. The fact that measures of the quality and count of sperm were not taken is considered a significant study limitation, however, given the effects observed in other studies of human and bull sperm following 1,2-dibromoethane exposure.

After females were exposed for 3 weeks, they were mated with non-exposed males and vaginal smears were taken. Vaginal smears were normal in the 20 and 39 ppm (154 and 300 mg/m^3) exposure groups, but the 80 ppm (614 mg/m^3) group was in constant diestrus and did not begin a normal cycle until 3 or 4 days postexposure. This resulted in fewer females in this group mating during a 10-day mating period with non-exposed males. For all 1,2-dibromoethane exposure groups, all mated females were pregnant when sacrificed at mid-gestation and had normal uterine contents for total implants, viable implants, and resorptions. Hormone levels were not measured. In the high exposure group, there was an incidence of 6/20 animals with mild vacuolated degeneration of the epithelium of the uterus (3/20 in controls) and 3/20 incidence of ovarian cysts (0/20 in controls). The study authors concluded that, although adverse reproductive

effects were observed in both sexes, these effects only occurred at concentrations that were associated with significant morbidity and mortality.

The effects of 1,2-dibromoethane administered by inhalation to rats and mice during gestation were also reported by Short et al.(1978). Pregnant Charles River CD rats (15-17/group) and CD-1 mice (18-22/group) were exposed whole-body at concentrations of 0, 20, 38, and 80 ppm (0, 154, 292, and 614 mg/m^3) for 23 hr/day. Exposure began on day 6 of gestation and lasted for 10 days. High mortality was observed in rats exposed to 80 ppm (614 mg/m^3) 1,2-dibromoethane, and weight loss was apparent in the 38 and 80 ppm (292 and 614 mg/m^3) exposure groups. Feed consumption was decreased in all exposure groups and failed to recover in the high-exposure group after exposure. Total number of implants was decreased, and the number of resorptions increased in the rat high-exposure group. However, there was no examination of the uterus at necropsy to definitively determine the number of implantation sites. Inasmuch as there was no effect of exposure in the Short et al. (1979) intermittent-exposure study, the effects seen here are likely due to the continuous exposure. Decreased fetal weight was noted in the 38 ppm (292 mg/m^3) exposure group. No viable fetuses were observed in the high-exposure group. None of the external or soft tissue anomalies (occluded nasal passage, hydronephrosis, solidified kidney cortex, distended urinary bladder, inferior vena cava hemorrhage, and blunt snout) noted in rat fetuses were dose-dependent.

Mice exhibited high mortality in the 38 ppm (292 mg/m^3) group and complete mortality in the 80 ppm (614 mg/m^3) group. Weight gain was reduced in mice that were exposed to 20 and 38 ppm (154 and 292 mg/m^3) 1,2-dibromoethane but returned to normal in all but one animal in the 38 ppm (292 mg/m^3) group. From this study, it appears that pregnant mice may be more sensitive to 1,2-dibromoethane than pregnant rats. Also, the CD-1 may be more sensitive than the $B6C3F_1$ as mortality was not seen (Reznik et al., 1980) in the latter strain after 13 weeks of exposure to levels higher than 38 ppm (292 mg/m^3). The 20 ppm (154 mg/m^3) mice had an increase in late resorptions and decreased fetal weight compared to controls, and mice exposed to 38 ppm (292 mg/m^3) 1,2-dibromoethane had a decrease in viable fetuses, increased resorptions, and reduced fetal body weights. Although the observed fetotoxic and teratogenic effects occurred at exposures that also caused maternal toxicity, it can be difficult to distinguish direct effects of 1,2-dibromoethane on the fetus from secondary effects resulting from maternal toxicity.

Smith and Goldman (1983) examined potential behavioral effects in offspring of rats

exposed to 1,2-dibromoethane. Pregnant female Long-Evans hooded rats (12/group) were exposed to 0, 0.43, 6.67, or 66.67 ppm (0, 3, 51, or 512 mg/m^3) 1,2-dibromoethane by inhalation for 4 hr/day, 3 days/week from day 3 to 20 of gestation. Defecation during exposure was directly related to the concentration of 1,2-dibromoethane ($p < 0.001$). Mid- and high-exposure animals defecated significantly more ($p < 0.01$ and $p < 0.05$, respectively) than controls. There was also an inverse relationship between exposure and weight gain that was statistically significant. There was no significant difference in the number of delivering females or litter size, but low- and mid-exposure pups weighed significantly more than controls while high-exposure pups weighed significantly less than controls. These weight effects in pups were not observed by day 66 post-gestation.

In newborn animals, rotorod performance on days 30 and 63 post-gestation was significantly ($p < 0.005$) increased in the mid- and high-exposure groups (6 and 6 per group). The toxicological significance of an increase in rotorod performance is not clear since there was a differential effect at certain rod speeds as well as a sex times speed interaction. The terminal performances of the mid- and high-exposure offspring in T-maze discrimination were also significantly ($p < 0.001$) different, with the high-dose group performing better than control. No other behavioral parameters in offspring were influenced by exposure. Measures of maternal behavior (nest rating and pup retrieval) were not influenced by exposure to 1,2-dibromoethane. The authors concluded that 1,2-dibromoethane produced long-term and possibly permanent alterations in the behavior of exposed offspring. The increased defecation and decreased weight gain ($p < 0.05$) in dams suggest maternal stress could have influenced behavior in the offspring, but the number of neonates tested was too small to make a definitive conclusion.

4.3.2. Oral Studies

Several studies have examined the potential reproductive toxicity of 1,2-dibromoethane in bulls after oral treatment. Amir and Ben-David (1973) examined the effects of 1,2-dibromoethane on bull spermatozoa. Three bulls (15 - 20 months) were administered (by gelatin capsules) 10 doses of 1,2-dibromoethane (4 mg/kg) on alternate days. Semen was collected 2 - 3 times per week before, during, and for 2 - 3 months after treatment. During the third week after the start of treatment, sperm abnormalities became evident. 1,2-Dibromoethane-induced effects in the sperm included coiled tails, acrosomic effects, acrosome loss, decreased motility,

degeneration, and disintegration. From the beginning of the fourth week and until day 40 after the first treatment, approximately 90 - 100% of the sperm were observed to be abnormal. Gradually, sperm abnormalities decreased, and, approximately 60 days after the first treatment (one month post-treatment), the percent of sperm abnormalities had returned to control levels.

Amir and Volcani (1967) provided further evidence of the effect of 1,2-dibromoethane on sperm by examining bull testes histologically. Three bull calves (4 days old) were orally treated with 2 mg/kg 1,2-dibromoethane for 17.5 - 22.5 months. Semen was collected with the aid of an artificial vagina for 4 - 6 six months prior to castration of one testis of each bull. Histological examination of the castrated testis revealed a depopulation in the majority of seminiferous tubules, the lumens of which were either empty or filled with cell debris. The caput and corpus epididymis were empty of spermatozoa and connective-tissue cells were thickened around the ductus. A high pseudostratified epithelium was also observed in both the caput and corpus. 1,2-Dibromoethane administration was discontinued after castration, and recovery of semen properties was monitored. In two bulls, recovery of semen properties was complete within 3 - 4 months. However, the third animal had decreased sperm density and motility for several more months although no sperm morphological abnormalities were observed. Seven months after castration, the bulls were slaughtered and the remaining testis was examined histologically. Seminiferous tubules of two of the bulls were normal, but in the third animal the majority of the seminiferous tubules remained inactive, showing hyalinization and hyperplasia of the interstitial tissue. The caput and corpus epididymis were normal in the two bulls but were still abnormal in the third animal.

The effects of 1,2-dibromoethane on sperm production in bulls have also been studied (Amir and Volcani, 1965). Four bull calves (4 days old) were fed 1,2-dibromoethane for 14–16 months. During the first 3 months of the calves' life, 2 mg/kg-day of 1,2-dibromoethane was fed to calves in milk. 1,2-Dibromoethane was then administered in feed (2 mg/kg-day) for an additional 9 months. After the first year of life, the method of administration was again altered by administering 4 mg/kg of 1,2-dibromoethane to calves in gelatin capsules on alternate days. 1,2-Dibromoethane treatment did not appear to affect the growth or health of the animals compared to controls. The libido of the treated bulls was similar to that of untreated animals. However, effects on the sperm were observed when semen was collected at termination of 1,2-dibromoethane administration. These consisted of abnormalities (tailless, coiled tails, pyriform heads), low sperm density, and poor sperm motility. Recovery after discontinuation of the

treatment varied from 10 days to approximately 3 months in different animals.

Amir (1973) provided evidence that 1,2-dibromoethane affected the shape of the spermatozoa during maturation in the epididymis and during spermogenesis. In this experiment, two bulls (15 - 20 months old) were orally administered 4 mg/kg 1,2-dibromoethane on alternate days for 12 and 21 days (7 and 10 doses, respectively). Smears of testicular spermatozoa, different parts of the epididymis, and the ductus deferens were analyzed for morphological abnormalities. In the animal that received seven doses of 1,2-dibromoethane, approximately 50% of spermatozoa from the testis and 10% of the spermatozoa from the first two segments of the caput epididymis had misshapen heads. Various segments of the epididymis also contained sperm with tail and acrosomal defects. In the animals that received 10 doses, almost the entire spermatozoa population of both the testis and caput epididymis had misshapen heads. The number of spermatozoa in the corpus and caput epididymides with tail and acrosomal defects also increased.

Amir and Lavon (1976) examined the protein changes in the epididymal and ejaculated spermatozoa of young (15 - 18 months) and old (4.5 - 5.5 years) bulls following 1,2-dibromoethane treatment. Bulls were administered 10 doses of 4 mg/kg 1,2-dibromoethane orally on alternate days. Treatment with 1,2-dibromoethane did not significantly change total nitrogen, amino acid, or lipoprotein content of epididymal and ejaculated spermatozoa. However, the amino acid composition of spermatozoan proteins did reveal an increase in the percent isoleucine and tyrosine of the caput epididymis, arginine, and glycine in the cauda epididymis, and proline in ejaculate. Ejaculate lipoproteins had an increase in percent half-cystine and tyrosine and a decrease in percent threonine, serine, glutamic acid, and isoleucine.

In addition to reporting on abnormal sperm, Amir et al. (1977) reported a reduction in DNA and protein content of sperm in three bulls treated with 10 oral doses of 4 mg/kg 1,2-dibromoethane on alternate days. Semen was collected twice weekly during treatment and for 5 weeks posttreatment and analyzed for morphological changes and DNA and protein content. DNA and protein content decreased during the first 13 days postexposure but returned to normal by days 20 and 27 postexposure for DNA and protein, respectively. A statistically significant decrease in DNA content was observed in the corpus and cauda epididymis. Protein content was only significantly reduced in the cauda epididymides. The study authors hypothesized that 1,2-dibromoethane-induced sperm abnormalities might have been due to an alkylating effect of the

chemical on the normal amino acid sequence of the sperm proteins during the replacement of the somatic histones by sperm histones in late spermiogenesis.

Amir (1975) studied individual differences in the response of bulls to 1,2-dibromoethane treatment. Thirteen young (15 - 24 months) and two adult (4.5 - 5 years) bulls received 10 oral doses (by gelatin capsules) of 4 mg/kg 1,2-dibromoethane on alternate days. In untreated animals, only 2 - 4% of spermatozoa had misshapen heads. However, in treated young animals, a "large proportion" of spermatozoa had misshapen heads at 1 day postexposure. The area of the genital tract with the greatest percentage of abnormal sperm varied among individual animals, but generally, the ductus efferentes had the highest proportion (50 - 90%). In young bulls, the maximum percentage (80 - 100%) of spermatozoa with misshapen heads that appeared in the ejaculate varied from 2 to 10 days after end of treatment. Reasons for this variation may be differences in the sperm transit time through the epididymis as well as the variation in the release time of the affected spermatozoa from the testis. The study author states that the effects of 1,2-dibromoethane treatment was more acute in adult bulls. Sperm concentration was only slightly decreased in young bulls but was significantly decreased in adults. Also, the percentage of sperm with misshapen heads returned to control levels (~ 5%) by week 5 postexposure in young bulls; but, in adults, the percentage of abnormal spermatozoa at week 5 postexposure was approximately 45% and remained elevated at 16 weeks postexposure (25%).

In all of these studies on bulls, the experimental design employed sample sizes that were too small to indicate statistically significant increases in effects observed. However, the power of all of these studies has been examined and found to be low for a number of reasons (Dobbins, 1987). Despite statistical problems with these studies, they provide a substantial qualitative evidence that bull sperm is sensitive to 1,2-dibromoethane exposure.

4.4. OTHER STUDIES

4.4.1. Reproductive/Developmental

The effects of 1,2-dibromoethane on semen quality and fertility in the rabbit have been evaluated (Williams et al., 1991). Male New Zealand white rabbits (8–10 per group) were given 1,2-dibromoethane in corn oil at 0, 15, 30, or 45 mg/kg-day for 5 days by subcutaneous administration. Weekly semen samples were collected for 6 weeks pre-exposure, during exposure, and for 12 weeks postexposure. Semen samples were analyzed for sperm concentration, number, morphology, viability, motion parameters, pH, osmolality, volume, fructose, citrate, carnitine, protein, and acid phosphatase. Male fertility was assessed at 4 and 12 weeks by artificial insemination of three females/male with 1 million motile sperm.

Significant mortality (30%) was observed in the 45 mg/kg dose group. Food consumption was decreased in dosed animals. There was no change in group mean body weight for any dose group compared to controls. Liver function enzymes (SDH and ALT) were significantly elevated in three surviving animals from the 45 mg/kg dose group. In the 45 mg/kg dose group, curvilinear velocity, straight-line velocity, percent motility, and amplitude of lateral head displacement were the only sperm characteristics statistically decreased by 1,2-dibromoethane exposure. Motility was also decreased in the 30 mg/kg dose group. The low- and mid-dose groups had significant decreases in ejaculate volume, and there was a dose-dependent decrease in pH. Male fertility, fetal structural development, litter size, and mean fetal weight were not affected by 1,2-dibromoethane exposure. There was no discussion about fetal survival. The toxicological implications of this study are limited considering the route of administration.

The binding of 1,2-dibromoethane to fetal epithelial tissue in mice has been reported (Kowalski et al., 1985, 1986). Pregnant C57BL mice in different stages of gestation (days 13–17) were injected i.v. with ^{14}C-1,2-dibromoethane (1.2–1.6 mg/kg) and then sacrificed. In addition, three fetuses were injected in utero on days 17 or 18 of gestation to circumvent the effect of maternal disposition on the fate of 1,2-dibromoethane in fetal tissues. Autoradiography and computer-assisted image analysis were utilized to investigate the binding of 1,2-dibromoethane to fetal epithelial tissue. Metabolites were not identified. At day 13 of gestation, radioactivity was uniformly distributed in fetuses. Average radioactivity amounted to 6 and 55% of maternal blood and liver levels, respectively, and was completely extracted by organic solvents. The fetuses

from dams treated on days 16 or 17 of gestation had a high concentration of radioactivity in the epithelia of the oral cavity, esophagus, forestomach, nasal mucosa, trachea, bronchi, and liver and in the thymus, lens, and choroid plexus. The radioactivity of the last three tissues was completely extractable by organic solvents, but the epithelial- and liver-associated radioactivity was only partially extractable. The distribution of radioactivity in fetuses treated in utero was similar to that of fetuses from dams treated on days 16 and 17. In vitro studies with excised fetal tissues were performed to assess possible fetal epithelial metabolism of 1,2-dibromoethane. The results indicated that fetal epithelia can produce 1,2-dibromoethane metabolites that bind to tissue.

Abnormal sperm have been observed in rams following subcutaneous treatment with 1,2-dibromoethane (Eljack and Hrudka, 1979). Rams were administered 1,2-dibromoethane (7.8–13.5 mg/kg-day) subcutaneously for 12 days. Sperm motility began to decline during week 5 after start of compound administration and declined maximally between weeks 9 and 10. Acrosomal and nuclear abnormalities were also observed. The acrosomal abnormalities began to appear in week 5 and were characterized by enlarged and misshapen apical segments. Nuclear abnormalities appeared later and were characterized by a misshapen nuclei and the formation of nuclear cristae.

The spermicidal effect of 1,2-dibromoethane in bulls and rams was reviewed by Amir (1991). Differences in the pathology of spermatozoic effects between the two species was discussed. While in the bulls, the abnormal spermatozoa issued from the affected spermatids were also collected in the ejaculates; this was not the case with treated rams. In the rams, the abnormal spermatids seem to be phagocytised in the epididymis before their arrival in the ejaculate. In addition, whereas the alkylating effect of 1,2-dibromoethane occurred also in the upper parts of the epididymis of the bulls, causing tail and acrosome defects to the spermatozoa, in the rams such an effect seems to occur all along the epididymal duct. These differences between bulls and rams in the sites of the genital tract where the chemical takes effect, and in the mechanism of this effect, are an indication of probable differences in the physiology of the reproductive tract between these species.

A model to assess potential developmental toxicity of dihaloalkanes in humans has been described (Mitra et al., 1992). Glutathione S-transferase isozymes from human fetal liver were purified and used to investigate the potential embryotoxicity of 1,2-dibromoethane in rat embryos in culture. Five isozymes were detected in the human fetal liver. All enzymes were capable of

metabolizing 1,2-dibromoethane. 1,2-Dibromoethane activation by one of the isozymes, designated P-3, resulted in toxicity to cultured rat embryos. 1,2-Dibromoethane metabolism by GST caused significant decreases in crown-rump length, yolk sac diameter, somite number, and composite score for different morphological features. Central nervous and olfactory structures were most severely affected. Yolk sack circulation and allantois were also affected. The conclusion drawn was that 1,2-dibromoethane is a suspected developmental toxicant in humans.

In a study by Brown-Woodman et al. (1998), three solvents--chloroform, dichloromethane, and dibromoethane--were examined for embryotoxic/teratogenic potential using rat embryo culture. The results showed that each of the solvents had a concentration-dependent embryotoxic effect on the developing rat embryo *in vitro*. The effect and no-effect concentrations (expressed in µmol/mL culture medium), respectively, for each of the halogenated hydrocarbons tested were dibromoethane--0.33, < 0.18; chloroform--2.06, 1.05; dichloromethane--6.54, 3.46. Histological studies were performed after exposure of rat embryos to an embryotoxic level of each of the halogenated hydrocarbons studied for increasing time periods up to the standard 40-hour culture. Marked cell death in the neuroepithelium of the developing neural tube was a prominent feature in all embryos exposed to an embryotoxic level of these solvents for periods of 16 hours or longer.

Bishop et al. (1997) examined alterations in the reproductive patterns of female mice exposed to 1,2-dibromoethane. Female mice were given a single i.p. injection of 100 or 150 mg/kg 1,2-dibromoethane and allowed to mate with untreated males for the duration of the female reproductive life span. 1,2-Dibromoethane treatment had no effect on total pups born, number of litters per female, or first and second litter size.

4.4.2. Developmental Neurotoxicity

Fanini et al. (1984) studied the effects of paternal exposure of rats to 1,2-dibromoethane on behavior in developing offspring. Male Fischer 344 rats were treated i.p. with a daily dose of 1.25, 2.5, 5.0, or 10 mg/kg 1,2-dibromoethane for 5 successive days and then mated with untreated females at 4 or 9 weeks after treatment. A comprehensive behavioral assessment of motor reflexes and motor coordination was conducted up to 21 days of age.

Paternal 1,2-dibromoethane exposure did not alter the development of surface righting ability in 3 - 6-day-old neonates or the ability of 10- and 15-day-old neonates to demonstrate negative geotaxis. The acquisition of cliff avoidance in the F_1 progeny bred at week 4 was suppressed in progeny of 5 mg/kg males on days 4 and 5, but cliff avoidance was not significantly different than controls after day 5. Cliff avoidance was not significantly different than in control F_1 progeny bred at week 9.

Swimming direction in week 4 progeny was significantly different (swimming in circles rather than straight) than controls on days 6 and 8, but this was not observed on days 10 or 12. No effect on swimming direction was observed in week 9 progeny. However, the ability of week 9 progeny to raise their heads higher with age when forced to swim was slower compared to controls. Week 4 progeny did not exhibit this trait. Rats typically swim with hindlimbs while keeping the forelimbs stationary, but significantly fewer animals swam in this manner on day 16 in week 4 progeny compared to controls. Open-field ambulation was significantly repressed in weeks 4 and 9 F_1 progeny on days 14 and 21. While the results are suggestive of developmental neurotoxicity, none of these effects exhibited a linear dose-response relationship. The study authors state that this is typical of behavioral teratology studies. The authors also hypothesize that the premeiotic stages of spermatogenesis are sensitive to the genotoxic effects of 1,2-dibromoethane.

Hsu et al. (1985) examined the activities of various neurotransmitter enzymes in the developing brain of F_1 progeny of 1,2-dibromoethane-treated males. Male Fisher 344 rats were treated intraperitoneally with 5 daily doses of 1 mg/kg-day 1,2-dibromoethane. The activities of choline acetyltransferase, acetylcholinesterase, and glutamic acid decarboxylase were examined in various brain regions of the F_1 progeny from 7 to 90 days of age. Selected brain regions included the cerebellum, corpus striatum, frontal cortex, hippocampus, and hypothalamus.

Choline acetyltransferase was significantly decreased in the hypothalamus of 7-day-old rats but was significantly increased in the cerebellum, corpus striatum, hippocampus, and hypothalamus of 21-day-old rats. Acetylcholinesterase was significantly increased in the corpus striatum and hippocampus of 7-day-old rats, decreased in the cerebellum, corpus striatum, and hippocampus of 14-day-old rats, and increased in the hypothalamus and hippocampus of 21-day-old rats. However, acetylcholinesterase was decreased in the cerebellum of 21-day-old rats. Glutamic acid decarboxylase was increased in the corpus striatum of 21-day-old rats, but

decreased in the frontal cortex of 21- and 90-day-old rats. Although this study did not examine behavior, the study authors considered that these alterations might have been associated with behavioral abnormalities observed in developing offspring by Fanini et al. (1984).

4.4.3. Genotoxicity

The evidence for 1,2-dibromoethane's potential genotoxicity is strong. 1,2-Dibromoethane is a direct-acting mutagen in bacteria. 1,2-Dibromoethane was positive for *S. typhimurium* revertant strains TA1535, TA100, and TA98 (Barber et al., 1981). Metabolic activation was not necessary for the mutagenic effects. 1,2-Dibromoethane induced point mutations in *S. typhimurium* strains TA1535 and TA100, *S. coelicolor*, and *A. nidulans* (Carere and Morpurgo, 1981). Wheeler et al. (2001) has shown that expression of a variety of GSTs within *S. typhimurium* 1535 caused a dose-dependent increase in the number of revertants upon incubation with 1,2-dibromoethane. The half-mustard, S-(2-bromoethyl)GSH, resulted in a significant increase in the number of revertants with *S. typhimurium* (without expressed GSTs) with the response dependent on whether the leaving group was Br-, Cl-, or Fl-. The first Br-leaving group of 1,2-dibromoethane appeared to be associated with the highest reversion rate fastest decomposition rate for the half-mustard. It was hypothesized that the stability of the half-mustard likely plays an important role in its ability to enter cells and cause mutations.

1,2-Dibromoethane has also been shown to induce reproducible positive responses in chromosomal aberrations and sister chromatid exchanges in Chinese hamster ovary cells (Ivett et al., 1989; Tan and Hsie, 1981; Brimer et al., 1982; Ballering et al., 1998; Graves et al., 1996). 1,2-Dibromoethane enhanced the production of micronuclei in tetrads of microsporogenesis of Tradescantia (Ma et al., 1978).

1,2-Dibromoethane has been demonstrated to cause hepatic DNA damage in rats following oral administration (Kitchin and Brown, 1986, 1987). 1,2-Dibromoethane also induced DNA damage in the stomach, kidney, liver, lung, and bladder in mice when administered intraperitoneally (Sasaki et al., 1998). The 1,2-dibromoethane-induced DNA damage could not be attributed to toxic cell death. DiRenzo et al. (1982) demonstrated that 1,2-dibromoethane can bind covalently to calf thymus DNA *in vitro*. Following i.p. administration, label was shown to bind DNA in the liver, kidney, stomach, and lung of rats and mice (Arfellini et al., 1984); binding

was highest in the liver and kidney. S-[2-(N_7-guanyl)ethyl]glutathione has been identified as the major DNA adduct in rats following treatment with 1,2-dibromoethane (Kim et al., 1990; Koga et al., 1986).

1,2-Dibromoethane was negative when tested for dominant lethal and electrophoretically-detectable specific-locus mutations in germ cells of male DBA/2J mice following i.p. injection of 100 mg/kg 1,2-dibromoethane (Barnett et al., 1992). 1,2-Dibromoethane was also negative when tested for micronucleated reticulocyte induction in mice (Asita et al., 1992). A slight but significant increase in sister chromatid exchange was noted in mice administered 1,2-dibromoethane by the i.p. route; however, the increase was not dose-related (Krishna et al., 1985). Kale and Baum (1979) reported sex-linked recessive lethal mutations in spermatozoa of *D. melanogaster*. In a later study, Kale and Baum (1983) provided evidence that *D. melanogaster* embryonic spermatogonia are particularly sensitive to 1,2-dibromoethane exposure.

Dusek et al. (2003) used chick embryo in ovo to investigate the effects of 1,2-dibromoethane on hematopoiesis at a developmental stage where the primitive erythroid cells divide and differentiate in circulation. Early after 1,2-dibromoethane treatment on embryonic day 3, annexin V/propidium iodide labelling showed acute cell death of erythroid elements, which was subsequently compensated for by the release of immature cells into the circulation. At the same time, the comet assay indicated increased DNA damage in 1,2-dibromoethane-exposed blood cells when compared with controls. After embryonic day 5, there was no indication for ongoing prominent cell death in the 1,2-dibromoethane-treated group. However, the DNA damage assessed by the comet assay persisted until embryonic day 10 in the peripheral blood cells and for even longer in cells from thymus and bursa. The kinetics of DNA fragmentation in both erythroid and lymphoid cells implied genotoxic damage by 1,2-dibromoethane to the stem cells of the definitive elements and transmission of this damage through the successive cell generations.

Bjorge et al. (1996) paper tested testicular cells, prepared from human organ transplant donors and from Wistar rats, for DNA damage caused by 15 known reproductive toxicants. Four chemicals induced significant levels of single-stranded DNA breaks in testicular cells from both species: styrene oxide (> or = 100 microM, rat and human), 1,2-dibromoethane (> or = 100 microM, rat; 1000 microM human), thiram (> or = 30 microM, rat; > or = 100 microM, human), and chlordecone (300 microM, rat; > or = 300 microM, human).

1,2-Dibromoethane was positive when tested for gene mutations in two human lymphoblastoid cell lines, AHH-1 and TK6 (Crespi et al., 1985). For the AHH-1 line, gene mutations were measured at the hypoxanthine guanine phosphoribosyl transferase locus, while, for the TK6 line, gene mutations were measured at the thymidine kinase locus. 1,2-Dibromoethane-induced sister chromatid exchanges were detected in human peripheral lymphocyte cultures (Tucker et al., 1984). 1,2-Dibromoethane induced both dose- and time-dependent increases in micronuclei in both mononucleated and binucleated human peripheral lymphocytes (Channarayappa et al., 1992).

1,2-Dibromoethane exposed papaya workers (n = 60) described by the Ratcliffe et al. study (1987) were assessed for genotoxic damage by monitoring sister chromatid exchanges and chromosomal aberrations (Steenland et al., 1986). As previously described (section 4.1.2.), workers from a nearby sugar plant served as controls (n = 42). Exposure to 1,2-dibromoethane was not associated with sister chromatid exchanges. There was a statistically significant increase in chromosomal exchanges, but this was the least frequent chromosomal aberration observed in this study. The study authors considered it possible that this finding was due to chance, given that multiple comparisons were made and that no significance was found when combining both types of chromosomal aberrations (exchanges and deletions). Therefore, the study authors concluded that exposure to low concentrations of 1,2-dibromoethane was not associated with chromosomal aberrations or sister chromatid exchanges.

Steenland et al. (1985) performed a cytogenetic examination of forestry workers and controls described in the Schrader et al. (1988) study (section 4.1.2.). Sister chromatid exchanges and chromosomal aberrations were assessed in peripheral lymphocytes. There was no significant increase in either sister chromatid exchanges or chromosomal aberrations in 1,2-dibromoethane-exposed forestry workers.

4.4.4. Acute Toxicity

Rowe et al. (1952) performed a comprehensive acute oral and inhalation toxicity study in the rat, mouse, guinea pig, chicks, and rabbits. The acute oral LD_{50} s (mg/kg) were 146 (male rats), 117 (female rats), 420 (female mice), 55 (female rabbits), 79 (male and female chicks), and 110 (male and female guinea pigs). For the acute inhalation study, rats were exposed to

100–10,000 ppm 1,2-dibromoethane for up to 16 hours while guinea pigs were exposed to 200 or 400 ppm for up to 7 hours. The 9-hour LC_{50} for rats was approximately 200 ppm. All guinea pigs exposed to 200 or 400 ppm for 2–7 hours died.

Centrilobular necrosis and sinusoidal dilations in the liver were observed in adult male albino rats treated with 110 mg/kg 1,2-dibromoethane by oral intubation (Broda et al., 1976). The centrilobular necrotic changes were reported by the authors to be similar to those caused by carbon tetrachloride.

Storer and Conolly (1983) conducted a comparative genotoxicity and acute hepatoxicity study of 1,2-dibromoethane in mice. Non-necrogenic doses of 1,2-dibromoethane (0.25 or 0.5 mmol/kg) were administered to male $B_6C_3F_1$ mice by i.p. injection. DNA damage was then assessed by an alkaline DNA unwinding assay, which assessed single strand breaks or alkali-labile sites in hepatic DNA. The high dose caused a significant decrease in percent double-stranded DNA recovered. Liver and kidney damage were assessed following single i.p. injections of 0, 0.5, 0.75, 1.0, or 1.5 mmol/kg 1,2-dibromoethane. 1,2-Dibromoethane was observed to be hepatotoxic as measured by a dose-dependent increase in liver weight, serum IDH, and serum AAT. Renal toxicity was also observed as a dose-dependent increase in kidney weight and BUN. Four of five animals died following i.p injection of 1.5 mmol/kg 1,2-dibromoethane.

4.5. SYNTHESIS AND EVALUATION OF MAJOR NONCANCER EFFECTS AND MODE OF ACTION–ORAL AND INHALATION

The epidemiological studies pertaining to subchronic and chronic effects focused primarily on reproductive and cytogenetic endpoints. The human data suggest that 1,2-dibromoethane is a male reproductive toxin. Decreased sperm count, ejaculate volume, and motility, and abnormal sperm morphology, have been reported in workers following long-term inhalation exposure to 1,2-dibromoethane (Ratcliffe et al., 1987). Workers exposed to 1,2-dibromoethane for 6 weeks displayed decreased sperm velocity and volume (Schrader et al., 1988). Also, male workers in a plant manufacturing 1,2-dibromoethane exhibited a significant decrease in fertility (Wong, 1979). However, these studies have at least one limitation (e.g., inadequate exposure data, potential exposure to other reproductive toxins, moderate-to-extensive dermal exposure potential, or other confounding factors) that renders any interpretation,

particularly a quantitative assessment, of the evidence regarding the potential of inhaled 1,2-dibromoethane to induce reproductive effects in humans inconclusive.

The evidence that inhaled 1,2-dibromoethane is associated with reproductive and developmental effects in laboratory animals is incontrovertible. Reproductive and developmental effects have been reported in rats and mice following inhalation exposure (Short et al., 1978, 1979). Effects in male rats included decreased testicular weight, decreased serum testosterone levels, testicular atrophy, and impairment of reproductive performance. Testicular atrophy has also been observed in male mice. Reported developmental effects in rats and mice consisted of decreased fetal body weight, increased resorptions, decreased fetal survival, and/or skeletal anomalies; however, these reproductive and developmental effects occurred at doses associated with significant toxicity and/or mortality in parental/maternal animals. There are also indications that there may be species and strain differences in response among pregnant animals. Oral administration of 1,2-dibromoethane also has been shown to adversely affect male reproductive endpoints. When 1,2-dibromoethane was administered orally to bulls at doses that did not affect the growth or health of the animals, it was shown to adversely affect various sperm parameters. Adverse effects included altered sperm morphology, decreased motility, and depleted sperm from seminiferous tubules. In addition, the spermicidal effect of 1,2-dibromoethane occurs during spermatogenesis, indicating that the effect is not direct. Overall, the data indicate that 1,2-dibromoethane is a male reproductive toxin in animals.

Cytogenetic studies in humans are quite limited. Steenland et al. (1985, 1986) found no evidence of genotoxicity following inhalation exposure to 1,2-dibromoethane. However, concentrations to which workers were exposed were quite low and may have been below levels that would induce DNA damage in humans. Genetic mutations have been observed in human peripheral lymphocyte cultures (Channarayappa et al., 1992; Tucker et al., 1984), and DNA damage has been noted in rats and mice (Arfellini et al., 1984; Kitchin and Brown, 1986, 1987).

Animal studies have demonstrated noncancer effects in rats and mice after subchronic- and chronic-duration inhalation or oral exposure to 1,2-dibromoethane. Early mortality, depression of body weight gain, and nonneoplastic lesions of the respiratory system, liver, kidney, testis, eye, and adrenal cortex in rats and mice were reported in a chronic inhalation study (NTP, 1982). Proliferative lesions of the nasal epithelium in mice have also been reported after chronic inhalation exposure to 1,2-dibromoethane (Stinson et al., 1981). It appears the respiratory

system, particularly the nasal epithelium, is the target tissue following inhalation exposure in both species. Excessive mortality, weight gain depression, testicular atrophy, forestomach lesions, and liver and adrenocortical degeneration were reported in rats after long-term oral exposure to 1,2-dibromoethane (NCI, 1978). In mice, long-term oral exposure to 1,2-dibromoethane was associated with body weight depression, high mortality, and testicular atrophy. The systemic effects associated with long-term oral exposure are generally consistent with those resulting from inhalation dosing. The results of the NCI study (1978) suggest that the forestomach is the target organ following oral exposure in rats and mice.

The results of a subchronic inhalation study in rats and mice revealed weight gain depression, swelling of adrenocortical cells, decreases in thyroid follicle size, and formation of megalocytic cells of the lining of bronchioles in rats and mice (NTP, 1982). In addition, Nitschke et al. (1981) reported elevated relative liver and kidney weights, focal epithelial hyperplasia of the nares, and diffuse respiratory hyperplasia. Similar respiratory effects were reported by Reznik et al. (1980), and Rowe et al. (1952) reported adverse liver and kidney effects in rats, guinea pigs, and monkeys. The subchronic toxicity data are in general consistent with reported chronic effects.

Some of the effects of 1,2-dibromoethane, particularly effects in the liver and nasal tract, are clearly related to its cytotoxicity. The mechanism of 1,2-dibromoethane-mediated cytotoxicity has been studied in isolated rat hepatocytes (Khan et al., 1993). It was demonstrated that microsomal cytochrome P-450-dependent oxidative metabolism of 1,2-dibromoethane produces the metabolite 2-bromoacetaldehyde. The results suggest that the cytotoxic mechanisms for 1,2-dibromoethane may possibly be attributed to lipid peroxidation and/or protein binding induced by 2-bromoacetaldehyde. In addition, the study authors considered that the conjugation of 1,2-dibromoethane with GSH may also contribute to cytotoxicity. Botti et al. (1982, 1986, 1989a, 1989b) and Masini et al. (1986) provided evidence that 1,2-dibromoethane-induced depletion of hepatic mitochondrial GSH correlated with hepatotoxicity and perturbations in mitochondrial Ca^{2+} homeostasis.

The results of *in vitro* and *in vivo* experiments suggest that the renal toxicity of 1,2-dibromoethane may be due to its biotransformation by GSH conjugation followed by further conversion in the kidney to highly reactive metabolites (Novotna et al., 1994). Repeated administration of 1,2-dibromoethane to rats has been shown to enhance the content of GSH in the liver and kidney (Mann and Darby, 1985). It has been suggested that lipid peroxidation may play a role in the 1,2-dibromoethane-induced pathogenesis of liver cell necrosis (Albano et al., 1984).

4.6. WEIGHT-OF-EVIDENCE EVALUATION AND CANCER CHARACTERIZATION –SYNTHESIS OF HUMAN, ANIMAL, AND OTHER SUPPORTING EVIDENCE, CONCLUSIONS ABOUT HUMAN CARCINOGENICITY, AND LIKELY MODE OF ACTION

4.6.1. Human

In a cancer study of 161 workers at two 1,2-dibromoethane manufacturing plants, Ott et al. (1980) reported that total cancer deaths of workers exposed to 1,2-dibromoethane did not exceed those expected based on national rates. There was an increase in deaths due to malignant neoplasms at one plant while the population at the second plant actually had fewer deaths due to malignant neoplasms than expected. Similarly, Sweeney et al. (1986) studied the cause-specific mortality of 156 male workers in a chemical plant that manufactured tetraethyl lead. The findings of both studies are inconclusive due to the small sample size, lack of control group, poorly characterized exposure assessment, and exposure to other potential or known carcinogens. Therefore, human data are inconclusive regarding the potential carcinogenicity of 1,2-dibromoethane to humans.

4.6.2. Animal

The results of animal oral and inhalation bioassays have demonstrated that 1,2-dibromoethane is a carcinogen in rats and mice of both sexes at multiple sites. Long-term oral administration of 1,2-dibromoethane was associated with forestomach carcinomas, hemangiosarcomas, and lung adenomas or carcinomas in rats and mice as well as hepatocellular and adrenocortical carcinomas (female rats) and thyroid follicular cell adenomas (male rats) (NCI, 1978; Van Duuren et al., 1985). The majority of the cancers associated with oral dosing were forestomach carcinomas. The relevance of forestomach effects to humans has been questioned, particularly for nongenotoxic chemicals whose mode of action is believed to involve irritation and cell proliferation from long-term exposure (Poet et al., 2003). It is true that the forestomach is not present in humans and contains features, such as minimal vascularization and stratified squamous cells, that result in a longer residence time of food-borne agents than is received by comparable human organs such as the oesophagus and the glandular stomach (Grice,

1988; Poet et al., 2003). In this case, however, effects in this organ are believed to be of potential relevance to humans because 1,2-dibromoethane and other genotoxic chemicals do not appear to require precursor events (e.g., irritation) associated with long residence time to induce these kinds of tumors. 1,2-Dibromoethane does not appear to cause significant irritation in the forestomach and was reported to induce forestomach tumors after just 168 days of exposure (NCI, 1978).

Long-term inhalation exposure of rats and mice to 1,2-dibromoethane resulted in nasal cavity carcinomas and adenocarcinomas, alveolar/bronchiolar carcinomas, splenic hemangiosarcomas, mammary gland adenocarcinomas, subcutaneous fibrosarcomas, and tunica vaginalis mesotheliomas in rats and mice (NTP, 1982; Stinson et al., 1981; Wong et al., 1982). The majority of the cancers were in the lungs of mice and in the nasal cavities of rats. The NTP (1982) inhalation study was well designed, using an adequate number of animals of both sexes, but was limited because of excessive mortality in the high-dose groups of both species, moderate mortality in low-dose female mice, and excessive mortality in male mice not related to 1,2-dibromoethane exposure. The Wong et al. (1982) study, which reported that disulfiram enhanced the toxicity and carcinogenicity of 1,2-dibromoethane, is limited because there was only one exposure dose.

1,2-Dibromoethane has been reported to be a direct acting mutagen in *S. typhimurium* assays (Barber et al., 1981). 1,2-Dibromoethane has also been shown to induce point mutations in *S. typhimurium* strains TA 1535 and TA 100, *S. coelicolor*, and *A. nidulans* (Carere and Morpungo, 1981). 1,2-Dibromoethane-induced chromosomal aberrations and sister chromatid exchanges have been demonstrated in Chinese hamster ovary cells (Ballering et al., 1998; Brimer et al., 1982; Graves et al., 1996; Ivett et al., 1989; Tan and Hsie, 1981;). 1,2-Dibromoethane has also been shown to bind to DNA *in vivo* and *in vitro* (Arfellini et al., 1984; Kim et al., 1990; Koga et al., 1986), and DNA damage has been reported in rats and mice following oral and i.p. administration (Kitchin and Brown, 1986, 1987; Sasaki et al., 1998). In *D. melanogaster*, 1,2-dibromoethane induced sex-linked recessive lethal mutations in spermatozoa and mutations in embryonic spermatogonia (Kale and Baum, 1979, 1983). 1,2-Dibromoethane has also been shown to produce mutations in human cells lines AHH-1 and TK-6 (Crespi et al., 1985), and sister-chromatid exchanges and increases in micronuclei have been demonstrated in human peripheral lymphocyte cultures (Channarayappa et al., 1992; Tucker et al., 1984). The above studies indicate that 1,2-dibromoethane is genotoxic in a variety of test systems.

4.6.3. Mode of Action

The genotoxicity of 1,2-dibromoethane is thought to be related to its conjugation with GSH as catalyzed by glutathione S-transferase (Cmarik et al., 1990; Inskeep and Guengerich, 1984; Sundheimer et al., 1982; Van Bladeren et al., 1980, 1982). The conjugation results in the formation of an episulfonium ion that can react with DNA (Peterson et al., 1988). As mentioned previously, the major DNA adduct formed is S-[2-(N^7-guanyl)ethyl]glutathione. Findings from a forward mutation assay utilizing the bacteriophage M13 *lacZ* gene and mutation spectra have established the importance of this adduct in 1,2-dibromoethane-mediated mutagenicity (Cmarik et al., 1992).

The results of a study designed to examine the ability of purified rat and human glutathione S-transferases to conjugate 1,2-dibromoethane with glutathione revealed that the metabolism of 1,2-dibromoethane by glutathione-S-transferase and the genotoxic effects of 1,2-dibromoethane are similar for rats and humans (Cmarik et al., 1990). Additional evidence that 1,2-dibromoethane is genotoxic via modification at ring nitrogens in DNA, primarily at the N^7-guanine site, was obtained from the mutation spectra of 1,2-dibromoethane in excision repair-proficient and repair-deficient strains of *D. melanogaster* (Ballering et al., 1994).

Working et al. (1986) also provided some evidence that the conjugation of 1,2-dibromoethane with GSH and its subsequent metabolism may be involved in its genotoxic properties. The ability of 1,2-dibromoethane to cause DNA damage was associated with unscheduled DNA synthesis (UDS) in rat hepatocytes and spermatocytes exposed both *in vitro* and *in vivo*. Inhibition of cytochrome P-450-mediated oxidation *in vitro* did not affect 1,2-dibromoethane-induced UDS in either cell type; however, depletion of cellular GSH inhibited the induction of UDS in both cell types. Inhibition of hepatic mixed-function oxidases *in vivo* was associated with positive UDS response to 1,2-dibromoethane in spermatocytes, but there was no effect on 1,2-dibromoethane-induced UDS in hepatocytes.

1,2-Dibromoethane has been demonstrated to act as an initiator of cell transformation in the two-stage BALB/c3T3 cell transformation test (Colacci et al., 1995, 1996). The cell transformation test is regarded as a model system for carcinogenesis *in vivo*. Utilizing γ-glutamyl-transpeptidase-positive foci as an early histochemical marker for hepatocarcinogenesis, 1,2-dibromoethane has been shown to possess promoter activity in the rat liver (Milks et al., 1982). 1,2-Dibromoethane has been demonstrated to induce a mitogenic response in the rat liver

(Ledda-Columbano et al., 1987a; Nachtomi and Farber, 1978; Nachtomi and Sarma, 1977). A single oral administration of 1,2-dibromoethane to male rats was reported to induce cell proliferation in the kidney, as monitored by increased thymidine incorporation into DNA and by mitotic index (Ledda-Columbano et al., 1987b). It has been suggested that minor perturbations in Ca^{2+} levels might play a role in triggering cell proliferation, while a more severe interference with the homeostatic control of Ca^{2+} may lead to cell death (Ledda-Columbano et al., 1987b; Nachtomi and Farber, 1978).

4.6.4. Weight-of-Evidence Characterization

Under the *Draft Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1999), 1,2-dibromoethane is considered “likely to be carcinogenic to humans” based on strong evidence of carcinogenicity in animals and inconclusive evidence of carcinogenicity in an exposed human population. This weight-of-evidence carcinogenicity characterization replaces the previous classification of "B2; probable human carcinogen," entered on IRIS on September 7, 1988. The new classification and slope factor estimates are based on a review of newer data and a reanalysis of the data used in the earlier assessment. Based on the consistent findings of several studies reporting increased incidences of a variety of tumors in rats and mice of both sexes by different routes of administration at both the site of application and at distant sites, it can be concluded that there is strong evidence of the carcinogenicity of 1,2-dibromoethane in animals. The available evidence further supports a conclusion that 1,2-dibromoethane is a genotoxic carcinogen based on evidence from a variety of *in vitro* and *in vivo* test systems.

4.7. SUSCEPTIBLE POPULATIONS

As has been described, GSTs are believed to play an important role in the mode of action for 1,2-dibromoethane carcinogenicity. Human GSTs comprise several subfamilies of isoenzymes: principally GSTM, GSTP, and GSTT. A polymorphism in the GSH conjugation of 1,2-dibromoethane by GSTT was demonstrated in the cytosol derived from human erythrocytes (Guengerich et al., 1995; Ploemen et al., 1995). Erythrocyte cytosols from 2 out of 12 subjects were unable to catalyze the conjugation of 1,2-dibromoethane with GSH due to a mutation of GSTT. The relevance of this genetic polymorphism to interindividual differences in response to 1,2-dibromoethane and in response to other carcinogens is not clear. However, deletions in

subunit 1 of the GSTT gene (GSTT1) are known to produce null genotypes that lead to absence of activity of these enzymes (Seow et al., 2002). Further, the expression of the rat theta class glutathione-S-transferase 5-5 (which is structurally similar to the human theta class GSTT) in *S. typhimurium* TA1535 increased the mutagenicity of 1,2-dibromoethane (Thier et al., 1996). Moreover, the mutagenicity of 1,2-dibromoethane was enhanced (compared to controls) in *S. typhimurium* TA1535 cells expressing the human theta ortholog GSTT1-1 (the homodimer of GSTT1) (Thier et al., 1996). GSTT1-1 polymorphism is apparently responsible for the bimodal distribution of sensitivity to sister chromatid exchange induction observed after *in vitro* exposure to butadiene diepoxide and other chemicals (Thier et al., 1996). While this polymorphism may reduce human susceptibility to 1,2-dibromoethane induced cancers, it should be noted that GST polymorphisms resulting in null or low activity of this genotype are generally thought to increase overall cancer risk (Seow et al., 2002).

DeLeve (1997) addressed the issue of whether variations in endogenous GSH in human cells could modify the genotoxicity of 1,2-dibromoethane. The incidence of sister chromatid exchanges in normal fibroblasts and in fibroblasts obtained from two human individuals with greatly reduced intracellular GSH levels due to hereditary generalized GSH synthetase deficiency, an inborn error of GSH metabolism, was studied. The induction of sister chromatid exchanges was significantly lower in the fibroblasts with GSH synthetase deficiency compared to control cells. DeLeve (1997) concluded that low endogenous GSH levels may protect against 1,2-dibromoethane-induced genotoxicity in human fibroblasts. In addition, DeLeve (1997) noted that little is known about the range of normal intracellular GSH in the population.

As mentioned previously, 2-bromoacetaldehyde is formed during the oxidative metabolism of 1,2-dibromoethane and undergoes further metabolism or conjugation with GSH (Wong et al., 1982). There may be considerable interhuman variability in their ability to catalyze the oxidation of 1,2-dibromoethane to 2-bromoacetaldehyde. Microsomes from 21 different human livers were able to catalyze the oxidation of 1,2-dibromoethane to 2-bromoacetaldehyde with activities that ranged from 22.2 to1027.6 pmol/min-mg of protein (Wormhoudt et al., 1996b). It has also been suggested that since disulfiram is used to treat alcoholics, these individuals may be at a greater risk to 1,2-dibromoethane toxicity (Wong et al., 1982). Disulfiram inhibits aldehyde dehydrogenase and may alter the metabolism of 1,2-dibromoethane by preventing the further metabolism of 2-bromoacetaldehyde. Disulfiram has been reported to enhance the carcinogenicity of 1,2-dibromoethane (Elliott and Ashby, 1980).

4.7.1. Possible Childhood Susceptibility

There are no human studies indicating that children are more susceptible to the toxic effects of 1,2-dibromoethane. However, there is evidence in mice that fetal epithelia can bind ^{14}C-1,2-dibromoethane nonvolatile metabolites after i.v. injection to pregnant animals in different stages of gestation (Kowalski et al., 1986). High-level binding was observed in the oral epithelium, nasal mucosa, and forestomach. These results suggest that fetuses are likely to be exposed to 1,2-dibromoethane from maternal circulation. The embryotoxic potential of 1,2-dibromoethane to humans has been suggested by the results of an *in vitro* study with cultured rat embryos in which it was shown that bioactivation of 1,2-dibromoethane by GST induced manifestations of embryotoxicity (Mitra et al., 1992).

It has been concluded that children's respiratory vulnerability is in part due to the fact that they have narrower airways than those of adults, and thus irritation that would produce only a slight response in an adult can result in potentially significant obstruction in the airways of a young child.[1] As such, the nasal inflamation effects of 1,2-dibromoethane may have a more significant health impact for infants and small children.

4.7.2 Possible Gender Differences

There are no human or animal data that suggest that gender differences in toxicity or carcinogenicity might occur as a result of exposure to 1,2-dibromoethane.

[1] *Ambient Air Pollution: Respiratory Hazards to Children* statement by the American Academy of Pediatrics, online at http://www.aap.org/policy/04408.html - also the topic of the journal *Pediatrics*, Volume 92, No. 3, 1993 (which could not be retrieved prior to submitting these comments).

5. DOSE-RESPONSE ASSESSMENTS

5.1. ORAL REFERENCE DOSE

An RfD can be derived based upon results of a rat chronic oral exposure study reported by NCI (1978).[2] In this study 50 Osborne-Mendel rats/sex/group were administered 1,2-dibromoethane in corn oil, by gastric intubation. The initial doses utilized for male and female rats were 40 and 80 mg/kg-day. High treatment-related mortality (18/50 males and 20/50 females) caused a discontinuation in the intubation of the high-dose group after treatment in week 16. Intubation of this group was suspended for 13 weeks and then restarted at week 30. At this time the surviving rats received the low-dose regimen. All surviving male and female rats in both dosage groups were sacrificed at weeks 49 and 61, respectively. The authors calculated time-weighted average low- and high-doses of 38 and 41 mg/kg-day for male rats, and 37 and 39 mg/kg-day for female rats.

Peliosis was chosen as one of three co-critical endpoints for use in RfD derivation. Among male rats, liver peliosis was observed in 0/40 control, 10/50 low-dose, and 9/50 high-dose groups.[3] Among female rats, peliosis was observed in 0/40 control, 4/47 low-dose, and 2/48 high-dose groups. Peliosis is marked by engorgement of the liver with blood due to blockage of the lumen of the sinus or destruction of the epithelial wall of the sinusoid. Peliosis is not considered to be a precursor to liver cancer. Although hepatocellular carcinomas were detected in 5/48 female rats, the increase was not statistically significant. No increases in hepatocellular tumors were detected in males. Squamous cell tumors found in the liver were the result of metastases from forestomach tumors.

Another co-critical endpoint in this study is the induction of testicular atrophy. The incidence of atrophy was 0/20 in vehicle controls, 14/49 in the low-dose group, and 18/50 in the

[2]NCI also studied mice, but high mortality in both dose groups of male and female mice precludes the use of these bioassays for derivation of an RfD.

[3]Mortality adjusted incidence used for the BMD analysis of this data was 4/42 and 9/25 in the low and high dose groups, respectively. (See Table B-1 and output files in Appendix B.)

high dose group.[4] Testicular atrophy was also noted in 11/20 untreated control rats sacrificed at 107 weeks. Testicular atrophy in the latter group are likely to be age related, since they were not seen in 61 week controls and because the duration was much longer than for exposed rats. The 61 week vehicle controls are therefore considered to be the appropriate control group

Although tumors of the tunica vaginalis, the serous covering of the testes, were reported in the NCI (1978) study, testicular atrophy is not considered a precursor to this effect. The tunica albuginea, a dense, fibrous membrane, lies between the testis and the tunica vaginalis. Thus, the tunica vaginalis is neither in direct contact with the testes nor is it composed of structurally or functionally related tissue. The reported testicular effects can, therefore, be considered a noncarcinogenic endpoint separated from nearby tunica vaginalis tumors.

Testicular effects were also reported in bulls administered oral doses of 2-4 mg/kg 1,2-dibromoethane (Amir and Ben-David, 1973; Amir and Volcani, 1965, 1967). Although doses were lower, these studies were not selected for RfD development because of the small numbers of animals and the use of one exposure level and because they are ruminants with a significantly different physiology. Moreover, an allometric adjustment would result in a dose quite similar to those used in the NCI (1978) study.[5] These bull studies, however, provide supporting evidence for testicular effects of low-dose 1,2-dibromoethane.

A third co-critical endpoint, was adrenal cortical degeneration (0/40 controls, 13/48 low-dose, and 9/47 high-dose) in the male Osborne-Mendel rats of the NCI (1978) study.[6] A similar effect was observed in the female rats of this study (1/40 controls, 3/44 low-dose, and 8/45 high-dose animals) and female F344 rats of the NTP (1982) chronic inhalation study. NCI (1978) reported an increased incidence of adrenal tumors in female Osborne-Mendel rats following oral exposure, and Wong et al. (1982) identified an increased incidence of adrenal tumors in both male

[4]Mortality adjusted rates used for the BMD analysis of this data were 14/43 and 18/36 in the low and high dose groups, respectively. (See Table B-1 and output files in Appendix B.)

[5]The allometric adjustment refers to the scaling of doses between species according to body mass raised to the 3/4 power which the Agency has endorsed for carcinogens. The presumption of this adjustment is that equal doses in these units (i.e., $mg/kg^{3/4}/day$) when administered daily over a lifetime, will result in equal risk across mammalian species (USEPA, 2002a). The bulls were assumed to weigh 1000 kg (Amir, 1975). After allometric adjustment, the doses given to the NCI (1978) male rats were less than 2 times, and therefore similar to, the doses given to the Amir and Volcani (1965; 1967) bulls (11 vs 21 $mg/kg^{3/4}/day$).

[6]Mortality adjusted rates used for the BMD analysis of this data were 13/48 and 9/26 in the low and high dose groups, respectively. (See Table B-1 and output files in Appendix B.)

and female Sprague-Dawley rats following inhalation exposure. However, adrenal tumors were not observed in male Osborne-Mendel rats of the NCI (1978) oral study and were not observed in the F344 rats of either sex in the NTP (1982) inhalation study. Thus, a clear association between this degenerative effect and adrenal tumors cannot be established, and use of this endpoint in support of a noncancer RfD is deemed appropriate.

Table 5-1. Oral subchronic and chronic studies in laboratory animals

Reference	Species (strain)	Sex	Animals/ dose	Exposure Regimen	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)
NCI, 1978	Rat	M	50	49 weeks, 5d/wk	--	38[a]
	(Osborne-Mendel)	F	50	61 weeks, 5d/wk	--	37[a]
Amir and Volcani, 1967	Bull (Calves)	M	3	17.5-22.5[b] Months	--	2[c]
Amir and Volcani, 1965	Bull (Calves)	M	4	14-16[b] Months	--	2[c]

[a] Critical effects were peliosis and adrenal cortical degeneration in males and females and testicular atrophy in males.
[b] Animals were dosed orally via milk (1-3 mo), feed (4-9 mo) and via gelatin capsules (> 1 yr).
[c] Critical effects were adverse alterations in various sperm parameters and testicular histology.

5.1.1. Methods of Analysis

RfDs can be derived by either development of a benchmark dose or through determination of a NOAEL or a LOAEL. TWA doses for male and female rats of the NCI (1978) study were very similar, but a higher incidence and severity of effects were observed in male rats at the low dose. Adjustment of the lower TWA low dose for intermittent exposure of 5 days/week (38 mg/kg-day × 5/7) results in a LOAEL of 27 mg/kg-day. A benchmark dose analysis was performed for all three of the co-critical endpoints (Appendix B, Table B-1). This analysis was done using both the initial, unadjusted doses of 40 and 80 mg/kg-day and TWA doses reported by the authors. Because the peliosis and adrenal cortical degeneration effects occurred at a much greater incidence towards the end of the study, the BMD assessments that used TWA doses may be more appropriate for these endpoints. However, because the incidence of testicular atrophy was similar at the beginning, middle, and end of the study (6/20 at 9-24 wks; 4/10 at 25-39 wks; 4/9 at 40-44 wks and 4/11 at 45-49 wks) the dose rate may be more critical to the occurrence of this effect. However, there is not enough data to make a definitive determination in this regard.

Depending on whether unadjusted or TWA doses were used, $BMDL_{10}$ estimates for these three endpoints ranged from approximately 7-10 mg/kg-day. Because of high mortality and unusual dosing in the high dose group, there is a great deal of uncertainty associated with these BMD results, and they are only provided here in support of the NOAEL/LOAEL approach. Adjustment of the lower TWA low dose for intermittent exposure of 5 days/week (38 mg/kg-day × 5/7) results in a LOAEL of 27 mg/kg-day.

Table 5-2 Application of uncertainty factors (UFs) for RfD calculation

POD and UF Factors	NOAEL/ LOAEL
Point of Departure (POD)-based on testicular, liver, and adrenal effects in male rats and adjusted for intermittent exposure.	**LOAEL = 27 (mg/kg-day)**
UF_H = Variation from average humans to sensitive humans	**10**
UF_A = Uncertainty in extrapolating from rodents to humans	**10**
UF_S = Uncertainty in extrapolating from subchronic to chronic effect levels	**1**
UF_L = Uncertainty in extrapolating from LOAELs to NOAELs (NOAEL/LOAEL approach)	**10**
UF_D = Uncertainty in database	**10**
$UF_{(Total)}$	**10,000[a]**
RfD (mg/kg-day)	**9E-3**

[a]The $UF_{(Total)}$ is reduced from 10,000 to recommended maximum uncertainty factor of 3000 for the purposes of calculating the final RfD due to recognized overlap in UFs (U.S.EPA, 2002a, page 4-41; U.S.EPA, 1994; Dourson and Stara, 1983).

5.1.2. RfD Derivation

The adjusted daily dose of 27 mg/kg can be considered a LOAEL for peliosis (20% response), testicular atrophy (29% response), and adrenal cortical degeneration (27% response). Because testicular atrophy occurs with high incidence in aged untreated rats, the lack of testicular atrophy in the vehicle control group at 61 weeks suggests that 1,2-dibromoethane hastens the onset of testicular atrophy. Uncertainty factors of 10 for interspecies variability, 10 for intraspecies variability in sensitivity, and 10 for adjustment from a LOAEL to a NOAEL were assigned, as there was no information available that suggested other values were appropriate.

A 10-fold uncertainty factor accounting for the extent and quality of the database was

deemed necessary due primarily to the poor quality of the principal study, the lack of high quality developmental and reproductive studies by the oral route of exposure, and limited studies in bulls that suggest adverse effects on sperm at low doses. High mortality in the principal study (NCI, 1978) causes considerable uncertainty with respect to the exposures that the animals received and with respect to the responses that might have been observed had the animals survived to term. The lack of a multigeneration study is also of concern in light of the genotoxicity of 1,2-dibromoethane, because any genetic damage to the germ cells of the F1 generation would not be detected until the F2 generation. Developmental toxicity studies covering major organogenesis (but not studies covering the entire period of gestation) are available in two species via the inhalation route, and inhalation systemic toxicity studies that evaluated the respiratory tract are available in two species. There is also some limited evidence for neurobehavioral developmental effects caused by 1,2-dibromoethane as well as endocrine disruption (based on effects on other endocrine organs as well as changes in hormone levels).

A subchronic to chronic uncertainty factor was not considered necessary because all animals of the low dose group were continuously exposed for approximately one year. This results in a overall uncertainty factor, $UF_{(Total)}$, of 10,000. In general, the individual uncertainty factors that comprise the $UF_{(Total)}$ are expected to be conservative with respect to the behavior of the average chemical (Dourson and Stara, 1983). For this reason, the Agency has recommended the application of a maximum uncertainty factor of 3000 for the purposes of calculating RfDs and RfCs (U.S.EPA, 2002a, pages 4-41; U.S.EPA, 1994b). Application of a total uncertainty factor of 3,000 to the LOAEL of 27 mg/kg-day yields an RfD of 9 E-3 mg/kg-day.

5.2. INHALATION REFERENCE CONCENTRATION (RfC)

An RfC can be derived based upon the NTP (1982) bioassay of 1,2-dibromoethane. In this study the noncarcinogenic effects observed are hepatic necrosis (male and female rats), testicular degeneration (male rats), retinal atrophy (female rats), adrenal cortical degeneration (female rats), splenic hematopoiesis (female mice), and inflammation of the nasal cavity (female mice).[7] The critical liver endpoint differs somewhat from that which was used to develop the oral

[7]The NTP (1982) study of male mice was not considered as relevant for derivation of an RfC because of high mortality in control and exposed groups due to complications from urinary tract infections that were not exposure related.

RfD (peliosis). They are, however, both measures of liver toxicity and are likely to be closely related. Because liver cancer induction was not statistically significantly increased in either sex following inhalation exposure to 1,2-dibromoethane and because necrosis is not considered a necessary precursor to induction of liver cancer, necrosis is considered to be a suitable endpoint for quantifying the noncancer effects of 1,2-dibromoethane.

Table 5-3. Inhalation subchronic and chronic studies in laboratory animals[a]

Reference	Species (strain)	Sex	No./ dose group	Exposure duration	NOAEL (mg/m^3)	LOAEL (mg/m^3)
NTP, 1982	Rat (F344)	M	50	103 weeks	--	76.8
		F	50	103 weeks	--	76.8
NTP, 1982	Mouse (B6C3F1)	M	48	78 weeks [b]	–	76.8
		F	50	106 weeks	--	76.8
Stinson et al., 1981	Mouse (B6C3F1)	M	50	103 weeks	–	76.8
		F	50	103 weeks	--	76.8
Nitschke et al., 1981[c]	Rat (F344)	M	10	13 weeks [d]	23	76.8
		F	10	13 weeks [e]	23	76.8
Reznik et al., 1980[c]	Rat (F344)	M	5	13 weeks [d]	23	115
		F	5	13 weeks [e]	23	115
Reznik et al., 1980[c]	Mouse (B6C3F1)	M	10	13 weeks [d]	115	576
		F	10	13 weeks [e]	115	576

[a] Results of Rowe et al. (1952) not included because of the many limitations of that investigation.
[b] Mortality was high in exposure and control groups of male mice.
[c] Study was designed principally to evaluate the role of 1,2-dibromoethane in promoting nasal lesions.
[d] Forty males per exposure group; serial sacrifices of 10 males per exposure group were conducted at 1, 6, and 13 weeks; remaining animals were sacrificed 88–89 days postexposure.
[e] Twenty females per exposure group; 10 females per exposure group were sacrificed at 13 weeks; remaining animals were sacrificed 88–89 days postexposure.

Table 5-4. Reproductive and developmental inhalation studies in laboratory animals

Reference	Species (strain)	Sex	#/Dose group	Exposure Duration	NOAEL (mg/m^3)	LOAEL (mg/m^3)
Short et al., 1978	Rat (Charles River CD)	M&F	15-17	10 days [a]	154	292 [b]
Short et al., 1978	Mouse (CD-1)	M&F	18-22	10 days [a]	--	154 [b]
Short et al., 1979	Rat (Charles River CD)	M F	9-10 20	10 weeks [c] 3 weeks [c]	300 300	684 [d] 614 [d]
Smith and Goldman, 1983	Rat (Long-Evans)	F	12	Days 3 to 20 of gestation [e]	3.3	51 [f]

[a] For 23 hr/day beginning on day 6 of gestation.
[b] Developmental effects plus some maternal toxicity.
[c] For 7 hr/day, 5 days/week.
[d] Reproductive effects plus significant morbidity and mortality.
[e] For 4 hr/day, 3 days/week.
[f] Based on behavioral effects in offspring.

5.2.1. Methods of Analysis

Because the NTP study demonstrated adequate spacing of exposure levels with increasing response levels with increasing exposure levels, the inhalation toxicity of 1,2-dibromoethane was evaluated using benchmark dose (BMD) analysis. A summary of the dose-response data and results and the actual EPA BMDS model runs are provided in Table B-2 of Appendix B. The benchmark doses were estimated for both 10% and 5% extra risk. An extra risk of 10% has generally been the default benchmark response (BMR) level for quantal data because it is at or near the limit of sensitivity in most bioassays. The Agency's benchmark dose technical guidance (U.S.EPA, 2000c) does indicate that a lower BMR can be used if a study has "greater than usual sensitivity." However, this study cannot be said to have greater than usual sensitivity because it involved only two dose groups and high mortality in all dose groups. In addition, responses in the low dose group were in the range of or greater than 10% for virtually all endpoints under consideration. BMD estimates for lower response levels are more dependent on model choice (i.e., the range of BMD and BMDL estimates are more variant across models). Therefore, the BMDL for an extra risk of 10% is used for the RfC derivation.

5.2.2. RfC Derivation

To derive an RfC, the $BMDL_{10}$ values presented in Table B-2 of Appendix B were adjusted to equivalent continuous exposures, converted to human equivalent concentrations (HECs), and then divided by uncertainty factors. The lowest of the resulting values was determined to be the RfC.

Human equivalent exposures were estimated following the EPA RfC methodology (U.S.EPA, 1994b). 1,2-Dibromoethane is relatively insoluble in water and demonstrates systemic toxicity, although there was some respiratory tract toxicity that may or may not be considered portal of entry effects. Therefore, 1,2-dibromoethane is considered a Category 2 gas. For Category 2 gases, HEC values are calculated using methods for category 1 gases for portal-of-entry effects and category 3 methods for systemic effects (U.S.EPA, 1994b). Thus, in Table 5-5, the EPA RfC method for Category 3 gases was used to derive $BMDL_{10}$ (HEC)s for the liver, testicular, retinal, adrenal, and splenic effects, and the method for Category 1 gases was used to derive $BMDL_{10}$(HEC) for nasal effects. The NTP (1982) data for nasal inflammation in female mice resulted in the lowest $BMDL_{10}$(HEC) of 2.8 mg/m^3. Figure 5-1 is a plot showing the selected, BMDS log-probit model results for this endpoint. The model runs that resulted in the $BMDL_{10}$ estimates for nasal inflammation and other effects are summarized in Appendix B, Table B-2.

An uncertainty factor of 3 was applied for interspecies pharmacodynamics as a consequence of considering human equivalent dosimetry above and due to the lack of data suggesting a more or less divergent response in humans. An uncertainty factor of 10 for intraspecies variability in sensitivity results was applied, as well as a default value due to the lack of data indicating a different degree of variability in humans.

An uncertainty factor for less than lifetime exposure is considered to be unnecessary because the principal study was carried out for at least 88 weeks. A database uncertainty factor of 10 is applied. High mortality in the principal study (NTP, 1982) causes considerable uncertainty with respect to the exposures that the animals received and with respect to the responses that might have been observed had the animals survived to term. A one-generation inhalation reproductive toxicity study is available but no multigeneration study. The lack of the multigeneration study is of particular concern in light of the genotoxicity of 1,2-dibromoethane,

Table 5-5. HEC estimates from BMDLs derived from NTP (1982); Table B-2, Appendix B

	Male Rats		Female Rats			Female Mice	
	Hepatic necrosis (mg/m^3)[a]	**Testicular degeneration (mg/m^3)**	**Hepatic necrosis (mg/m^3)**	**Adrenal cortical degeneration (mg/m^3)**	**Retinal atrophy (mg/m^3)**	**Splenic hematopoiesis (mg/m^3)**	**Nasal inflammation (mg/m^3)**
NOAEL	NA[b]	NA	NA	NA	NA	NA	NA
LOAEL	76.8	76.8	76.8	76.8	76.8	76.8	76.8
BMDS model[c]	Probit	LogLogistic	LogProbit	LogLogistic	LogLog	LogLogistic	LogProbit
BMD_{10}	131.774	53.2579	172.374	124.823	125.806	59.554	102.192
$BMDL_{10}$	105.343	35.0725	122.02	66.495	105.41	40.2456	80.1088
$BMDL_{10}$ (ADJ)[d]	18.8	6.3	21.8	12.0	18.8	7.2	14.3
$BMDL_{10}$ (HEC)[e]	18.8	6.3	21.8	12.0	18.8	7.2	2.8

[a]Assuming a temperature of 25°C, a barometric pressure of 760 mm Hg, and a molecular weight for 1,2-dibromoethane of 187.88, 1 ppm = 7.68 mg/m^3 (187.88/24.45).
[b]NA=not applicable.
[c]In accordance with EPA draft guidance (U.S.EPA, 2000d), the selected models were chosen on the basis of goodness of fit criteria (AIC and chi-square residual values) and visual inspection.
[d]Adjustment to continuous exposure involved multiplying the BMDL by 5 d/7 d × 6 hr/24 hr.
[e]HEC values were calculated in accordance with U.S. EPA (1994b) RfC methods. For extrarespiratory effects, a default adjustment factor of 1.0 was used for adjusting from ADJ to HEC values because 1,2-dibromoethane blood:air partition coefficients are not known for the experimental species and humans. For the respiratory effect (nasal inflammation), the HEC was calculated for an effect in the extrathoracic (ET) region. Minute $volume_{mouse}$ = 0.041 L/min, minute $volume_{human}$ = 13.8 L/min, surface $area(ET)_{mouse}$ = 3 cm^3, surface $area(ET)_{human}$ = 200 cm^2. Regional gas dose ratio(ET) = [minute $volume_{mouse}$/surface $area(ET)_{mouse}$]/[minute $volume_{human}$/surface $area(ET)_{human}$] = 0.198. BMDL(HEC) = BMDL(ADJ) × regional gas dose ratio(ET) = 14.3 mg/m^3 × 0.198 = 2.8 mg/m^3.

because any genetic damage to the germ cells of the F1 generation would not be detected until the F2 generation. Furthermore, the absence of an evaluation of sperm in reproductive toxicity study is of concern in light of the effects observed in humans and bulls. Developmental toxicity studies covering major organogenesis (but not studies covering the entire period of gestation) are available in two species via the inhalation route, and inhalation systemic toxicity studies that evaluated the respiratory tract are also available in two species. There is also some limited evidence for neurobehavioral developmental effects caused by 1,2-dibromoethane as well as endocrine disruption (based on effects on other endocrine organs as well as changes in hormone levels).

The composite uncertainty factor is 300 (10 for UF_H, 3 for UF_A, and 10 for UF_D). Application of this composite factor to the $BMDL_{10}$(HEC) of 2.8 mg/m^3 yields an RfC of 9 E-3 mg/m^3.

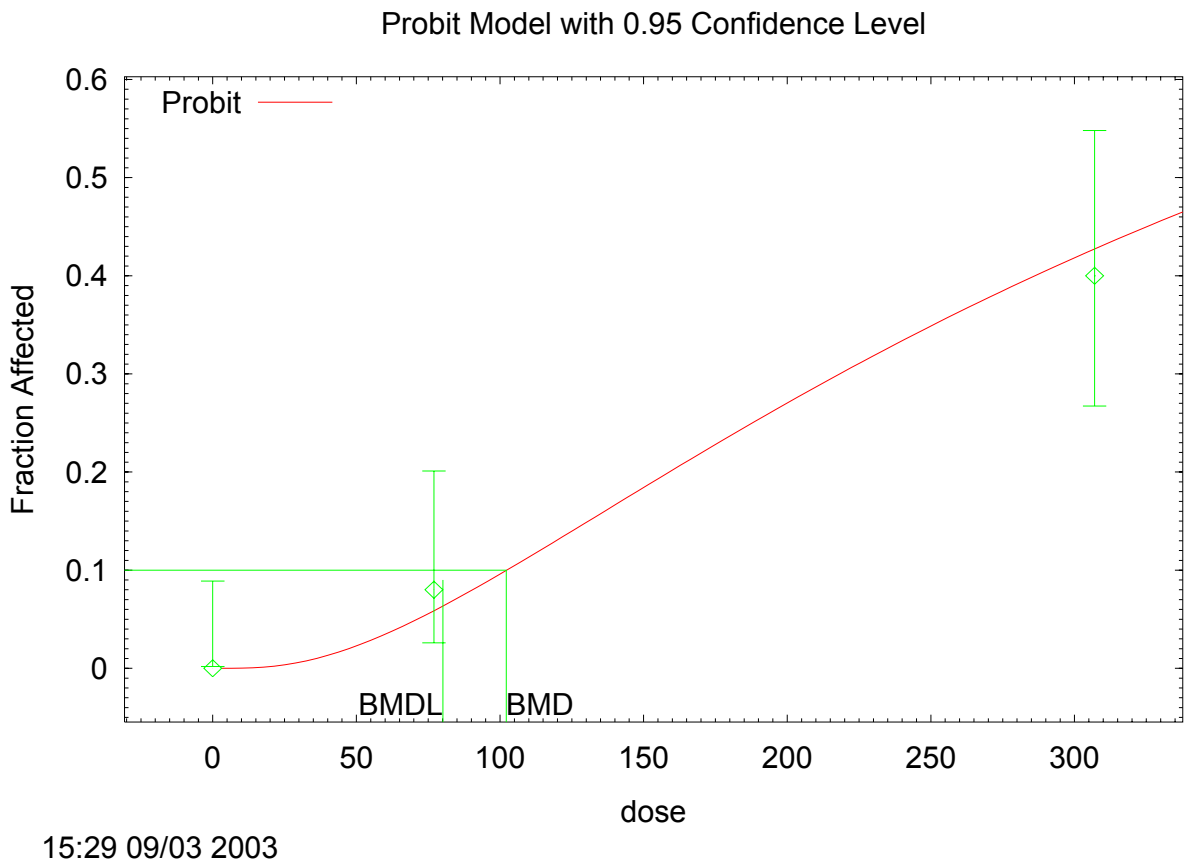

Figure 5-1: Log-Probit Model of Nasal Inflammation in Female Mice (NTP (1982)

5.3 CANCER ASSESSMENT

There are no definitive reports of cancer in humans associated with exposure to 1,2-dibromoethane; the available epidemiological studies have numerous limitations (section 4.1.3.) and are inconclusive. Chronic bioassays in rats and mice by both oral and inhalation routes provide evidence of tumors in multiple organ systems and also at direct points of contact (e.g., nasal cavity and lung tumors following inhalation and forestomach tumors following ingestion).

NCI (1978) provided evidence for the induction of forestomach squamous cell carcinoma

and hemangiosarcoma in male and female rats, thyroid follicular cell adenomas in male rats, and hepatocellular carcinomas and adrenocortical carcinomas in female rats following gavage administration of 1,2-dibromoethane. In addition, there were increases in forestomach tumors and lung adenomas in mice of both sexes. The effects in rats and mice are supported by carcinogenic findings (forestomach tumors) in a drinking water study in mice (Van Duuren et al., 1985), conducted at a single dose comparable to the high dose in the NCI mouse study. NTP (1982) provided evidence of 1,2-dibromoethane-induced nasal cavity tumor and other benign and malignant tumors in male and female Fischer 344 rats and in female $B6C3F_1$ mice in a 2-year inhalation cancer bioassay. Further, screening level evidence from A/J mouse lung tumor assays supports tumor induction by the oral, inhalation, dermal, and intraperitoneal routes of exposure (Adkins et al., 1986; Stoner et al., 1986; Van Duuren et al., 1979). In addition, 1,2-dibromoethane has been reported to be a direct acting mutagen in *S. typhimurium* assays and has also been shown to induce point mutations in *S. typhimurium*. 1,2-Dibromoethane has also been demonstrated to induce chromosomal aberrations and sister chromatid exchanges in Chinese hamster ovary cells and bind to DNA *in vivo* and *in vitro.*

This weight-of-evidence carcinogenicity characterization and quantitative estimate of carcinogenicity from oral exposure replace the previous classification of "B2; probable human carcinogen," and oral slope factor of 85 mg/kg/day entered on IRIS on September 7, 1988. The new classification and slope factor estimate are based on a review of newer data and a reanalysis of the data used in the earlier assessment. This is based on the consistent findings of several studies reporting increased incidences of a variety of tumors in rats and mice of both sexes by different routes of administration at both the site of application and at distant sites. It can be concluded that there is strong evidence of the carcinogenicity of 1,2-dibromoethane in animals. The available evidence further supports a conclusion that 1,2-dibromoethane is a genotoxic carcinogen based on evidence from a variety of *in vitro* and *in vivo* test systems. Under the *Draft Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1999), 1,2-dibromoethane is considered "likely to be carcinogenic to humans" based on strong evidence of carcinogenicity in animals and inconclusive evidence of carcinogenicity in an exposed human population.

There is some indication that a glutathione-dependent metabolite may be implicated in 1,2-dibromoethane's carcinogenic activity (as reported by Hissink et al., 2000), but the available evidence does not make any quantitative estimates possible. The carcinogenicity of 1,2-dibromoethane is evaluated according to the linear approach as described in U.S. EPA (1999), because 1,2-dibromoethane has demonstrated genotoxicity and not enough in addition is known

about the mode of action to support a nonlinear low-dose extrapolation (see section 4.6.3.).

5.3.1. Oral Carcinogenicity

5.3.1.1. *Choice of Oral Study/Data with Rationale and Justification*

The study by NCI (1978) was used for development of an oral slope factor. Although the drinking water study by Van Duuren et al. (1985) used an adequate number of animals and examined proper endpoints, the study is limited for development of an oral slope factor because only one dose level was examined. The NCI (1978) study used an adequate number of test animals and two dose levels plus untreated and vehicle control groups, and examined appropriate toxicological endpoints.

5.3.1.2. *Oral Dose-Response Data*

In the NCI (1978) study, male and female Osborne-Mendel rats and B6C3F_1 mice were administered 1,2-dibromoethane by gavage 5 days/week. High mortality in both species in all exposure groups necessitated reduced dosage levels, reduced frequency of dosing (see section 4.2.1.), and early termination of the studies. Time-weighted average low- and high-doses were 38 and 41 mg/kg/day for male rats, 37 and 39 mg/kg/day for female rats, and 62 and 107 mg/kg/day for mice of both sexes. Male and female rats were sacrificed at weeks 49 and 61, respectively. All surviving male mice and high-dose female mice were sacrificed at week 78, while low-dose females were sacrificed at week 90.

Tumor incidences were elevated with increasing exposure level at several sites: forestomach squamous cell carcinoma, hemangiosarcoma, thyroid follicular cell adenomas in male and female rats, hepatocellular carcinomas in female rats, and forestomach squamous cell carcinoma and lung adenoma in both sexes of mice. Benign and malignant tumors were combined for sites where an eventual progression from the benign to the malignant form was plausible (for example, lung alveolar/bronchiolar adenomas or carcinomas, and forestomach squamous cell papillomas or carcinomas). These data are summarized in Table 5-6.

Because there was high mortality in both species that resulted in early termination of the study, statistical procedures that can reflect the influence of intercurrent mortality on site-specific

tumor incidence rates were used to evaluate the tumor incidence levels. The individual animal data were not included in the bioassay report and were requested from NTP/NCI for this purpose (see Appendix C for a listing of the tumor incidence data by time of death). Subsequent to the completion of the NCI study of 1,2-dibromoethane, the NTP has adopted the Poly-3 procedure (Bailer and Portier, 1988) for adjusting tumor incidence rates for intercurrent mortality. The procedure is based on the observation that the cumulative incidence of tumors tends to increase with time raised to the second through the fourth powers for a large proportion of cases. In the Poly-3 procedure, for a study of T weeks duration, an animal that is removed from the study after t weeks ($t < T$) without a specified type of tumor of interest is given a weight of $(t/T)^3$. An animal that survives until the terminal sacrifice at T weeks is assigned a weight of $(T/T)^3 = 1$. An animal that develops the specific type of tumor of interest obviously lived long enough to develop the tumor and is also assigned a weight of 1. The Poly-3 tumor incidence, adjusted for intercurrent mortality up to time T, is the number of animals in a dose group with the specified type of tumor divided by the sum of the weights (the effective number of animals at risk). The tumor incidences adjusted using this procedure are also provided in Table 5-6 with the results of applying the Cochran-Armitage test for trend to the adjusted incidences.

Note that the low-dose female rats and both sexes of mice all had adjusted incidences of 100% for forestomach tumors, while the low-dose male rats had an adjusted incidence of 95%. Considering only the administered dose rate and adjusted tumor incidence at the low dose, female rats were slightly more sensitive than male rats to 1,2-dibromoethane exposure. In addition, forestomach tumors appeared the earliest in the female rat study, at week 12 in both dose groups, contrasted with week 15 in the high-dose male rats and week 31 in the low-dose male rats.

5.3.1.3. *Oral Dose Adjustments and Extrapolation Methods*

In preparation for carrying out dose-response analyses of the tumor data, adjustments to the administered doses for approximating human equivalent, continuous exposure levels were considered. Following EPA default procedures, the time-weighted daily average doses were converted to human equivalent doses on the basis of $(\text{body weight})^{3/4}$ (U.S.EPA, 1992). This adjustment is summarized in Table 5-7.

The dose levels as reported by NCI had been averaged over the period of observation in terms of weeks, with time-weighted average low and high doses of 38 and 41 mg/kg/day for male rats, and 37 and 39 mg/kg/day for female rats. Although some of the survival-adjusted incidence

of lesions and tumors in the high-dose rats were no higher than in the low dose groups, there is some evidence that there was a dose rate effect - that is, that the rate at which the 1,2-dibromoethane was administered was more directly related to the effects seen than was the time-weighted average. The tumor incidence by time curves shown in Figures C-1 through C-11 (Appendix C) illustrates that, for many of the significant tumor sites, the incidence in the high-dose group started earlier than in the corresponding low-dose group. One exception might be the forestomach tumors in female rats (Figure C-4, Appendix C), for whom the incidence in the two groups was very similar. However, since the incidence in the low-dose female rats was effectively 100% after adjusting for competing causes of mortality, the observation that the high dose female rats did not reach 100% much sooner does not really inform a characterization of a dose rate effect. In addition, the mice in the van Duuren et al. study (1985) received a daily oral exposure that was slightly higher than the high dose in the NCI mouse study. Their response was slightly less than the NCI mice, most likely attributable to drinking water administration rather than the oral gavage in the NCI study - another example of dose rate differences. Most notably,18 high dose male rats died in week 15, three of which had forestomach tumors, while in the low-dose group the first forestomach tumor was not observed until week 31. For this reason dose averaging over the period of the study may not be the most representative measure of exposure.

Another adjustment typically made to extrapolate to continuous daily exposure, that is lowering each dose by multiplying by (5 days)/(7 days)=0.71, was not incorporated prior to dose-response modeling, also in recognition of the possible dose rate effect. However, the assumption that a cumulative amount of exposure delivered over different time periods producing a similar effect may be more likely to hold at very low exposures. Since this is a linear adjustment, it can be incorporated after dose-response modeling as an alternative characterization to compare results.

Because the studies all ended before the usual 104 weeks, an adjustment to extrapolate to lifetime human exposure was considered. EPA typically adjusts each dose level by a factor related to the Poly-3 adjustment. That is, each dose is adjusted by multiplying by $(T/104)^3$, where T is the time of final sacrifice in a given dose group. When all groups have been terminated at the same time, this adjustment is linear, and can be applied before or after modeling is completed. The rat studies were terminated at approximately 50% of their intended length, which results in lowering the male and female doses by factors of 10 and 5, respectively. It was decided to consider the adjustment as an alternative characterization after the modeling is complete. Although the female mouse groups were terminated at different times, at 90 (low-dose) and 78 (high-dose) weeks, it was decided to apply a composite lifetime equivalent adjustment after modeling, to parallel the

risk estimates derived from the rat study. Calculation of the lifetime exposure adjustments is summarized in Table 5-7.

The results of the oral bioassays were characterized by fitting dose-response models to the tumor results showing significant elevations with increasing exposure. Because there was high mortality in both species that also resulted in early termination of each study, models which can reflect the influence of intercurrent mortality on site-specific tumor incidence rates were considered. EPA has generally used two approaches. Modest effects on survival can be addressed by omitting the animals in each treatment group who died before the first occurrence of the tumors being analyzed. In these bioassays, however, effects on survival were not modest. Consequently, for the quantal model analyses, intercurrent mortality was addressed using the Poly-3 adjusted data discussed in section 5.3.1.2. The poly-3 adjustment is an approximate adjustment that may not characterize the extremes of tumor incidence (Bailer and Portier, 1988), however. When tumors appear earlier with increasing exposure levels, the multistage-Weibull model is the preferred model because it incorporates the time at which death-with-tumor occurred (e.g., U.S.EPA: 1988b - 1,2-dibromoethane; 2001 - bromate; 2002b - 1,3-butadiene). However, the multistage-Weibull model cannot accommodate variable dosing schedules as in this study. Consequently, the more approximate approach using the Poly-3 adjusted data was the most suitable dose-response method for these data.

Dose-response analyses were conducted from the individual animal data for sites demonstrating an increased cancer incidence summarized in Table 5-6. Etiologically different tumor types were not combined across sites prior to modeling because the numbers of animals at risk differed by tumor site, depending on the patterns of intercurrent mortality.

EPA generally uses the multistage model with quantal cancer data, to estimate a 95% upper confidence limit (UCL) on cancer risk (extra risk) for humans. The multistage model has the form

$$P(d) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + ... + q_k d^k)],$$

where P(d) represents the lifetime risk (probability) of cancer at dose (i.e., human equivalent exposure concentration in this case) d, and parameters $q_i \geq 0$, for i = 0, 1, ..., k. The model parameters and 95% UCL were calculated using the multistage model in the EPA BMDS software. Extra risk over the background tumor rate is defined as [P(d) - P(0)]/[1 - P(0)]. Point estimates of the dose coefficients (q_is), and consequently the extra risk function, at any dose d are calculated by

maximizing the likelihood function with respect to the tumor incidence data. The incremental lifetime unit cancer risk for humans (q_1*) is defined as the 95% UCL on the parameter q_1, which is the linear dose coefficient. This 95% UCL represents a plausible upper bound on the true risk.

5.3.1.4. *Oral Slope Factor*

The results of applying quantal models to the Poly-3 adjusted tumor incidence data are provided in Table 5-8. The data for forestomach tumors for female rats and both sets of mice could not be adequately fit by the available models. For the remaining tumor data, a point of departure (PoD) near the lower end of the observed data was selected for linear extrapolation to low doses, consistent with the *Draft Guidelines for Carcinogen Risk Assessment* (U.S.EPA, 1999). An oral slope factor for each of these tumor sites was calculated by dividing the BMR level by the corresponding BMDL for these points of departure. A slope factor for each data set not fit by a model (e.g., forestomach tumors) was approximated by dividing the response at the low dose – 100% in each case – by the low dose.

Under the assumption that dose rate is the most important dose metric, estimated human equivalent oral slope factors ranged from 0.013 to 0.12 $(mg/kg/day)^{-1}$, for less than lifetime exposure. The highest slope factor corresponded to forestomach tumors in male rats. Adjustment for lifetime exposure, using the default adjustments listed in Table 5-7, leads to a range of 0.065 to 1.0 $(mg/kg/day)^{-1}$ for oral slope factors, as presented in the last column of Table 5-8.

The approximate slope factors for the other forestomach tumor (female rats; male and female mice) sets were at least as high, which is notable because these were central tendency estimates. No useful upper bound estimate was possible with the response already at 100%. These estimates and the estimate from the male rats are only useful if it can be assumed that carcinogenicity associated with 1,2-dibromoethane follows a linear relationship throughout the range of doses below 93%-100% response.

There is some concern that the forestomach tumors may result primarily as a portal of entry effect and may not have a dose-response pattern that extends linearly from the observed responses. The hemangiosarcomas and other tumors demonstrate absorption of 1,2-dibromoethane, although it is not clear whether absorption was impacted by adverse effects in the forestomach. In addition, there is considerable uncertainty in extrapolating from the period of the experiment, 49 weeks for the male rats, to full lifetime exposure. Given the multiplicity of tumor sites, however, basing the

slope factor on one tumor site underestimates oral carcinogenic potential of 1,2-dibromoethane, all else being equal.

In order to gain some understanding of the total risk from multiple tumor sites in male and female rats, it was assumed that the more significant tumor types observed were mechanistically independent - that is, that the occurrence of hemangiosarcomas, say, was not dependent upon whether there were forestomach tumors. Accordingly, a statistically appropriate upper bound risk was estimated using the following steps: (1) the central tendency, or maximum likelihood estimates (MLE) of unit potency were summed across forestomach tumors, hemangiosarcomas, and thyroid follicular cell adenomas for male rats and across hemangiosarcomas, hepatocellular carcinomas, adrenocortical carcinomas in female rats; (2) an estimate of the 95% upper bound on the summed unit risk was calculated by assuming a normal distribution for the individual risk estimates, and deriving the variance of the risk estimate for each tumor site from its 95% upper confidence limit (UCL) according to the formula

$$95\%\ \text{UCL} = \text{MLE} + 1.645 \cdot \text{s.d.},$$

where 1.645 is the t-statistic corresponding to a one-sided 95% confidence interval and >120 degrees of freedom, and the standard deviation (s.d.) is the square root of the variance of the MLE. The variances were summed across tumor sites to obtain the variance of the sum of the MLE. The 95% UCL on the sum of the individual MLEs was calculated from the variance of the sum using the same formula.

Summing the cancer risks in this manner, after the dose-response for each tumor site has been evaluated, is superior to EPA's previous practice of carrying out one dose-response analysis of tumor-bearing animals. The primary reason is that the biological relevance of the multistage model is maximized by allowing different multistage models to be fit to qualitatively different tumor types that might not be expected to develop through exactly the same modes of action. Time courses in the tumor types evaluated here did vary, for example. In this case, however, these summed estimates are approximate because the risk estimates could not be taken from analogous segments of the respective dose-response curves. For example, the risk for the male forestomach tumors comes from the portion of the dose-response near 90% response, while the risks for the other two sites are from a much lower portion (<20%) of their respective dose-response curves.

The resulting 95% UCL on the slope factor for the summed risk of forestomach tumors,

hemangiosarcomas, and thyroid follicular cell adenomas for male rats was 0.13 $(mg/kg/day)^{-1}$. The slope factor for forestomach tumors was nearly an order of magnitude higher than for the other two tumor sites, and the variability in the slope factor based on forestomach tumors alone was the greatest of the three sites, so the other sites end up having very little effect on the upper bound of the summed risks. Since risk values are rounded to one significant figure, the summed cancer slope factor is equivalent to that for forestomach tumors alone.

For comparison, the sum of the three significant tumor sites for females rats, excluding the forestomach tumors, has a 95% UCL of 0.044 $(mg/kg/day)^{-1}$. If the summed risk estimate is combined with the approximate slope factor estimated for female rat forestomach tumors of 0.1 $(mg/kg/day)^{-1}$, this results in an estimate of 0.14 $(mg/kg/day)^{-1}$. Although this risk estimate is higher than that obtained from the male rats, the contribution of risk from the forestomach tumors for female rats is relatively uncertain–there was no dose-response information between 0% and 100% response levels (and the modeling approach could not provide a confidence interval). The lowest response level for the males was still relatively high, close to 90%, but a confidence limit was estimable. The slope factor should be based on the sum of the male rat tumors slope factors rather than the sum of the female rat slope factors.

At low doses, it is not known whether or not there would be a dose rate effect. Without information to the contrary, the estimated cancer slope factor should be adjusted to daily exposure by multiplying by (7 days)/(5 days). The recommended oral slope factor for approximately half a lifetime of exposure is 0.13 $(mg/kg/day)^{-1} \times 7/5 = 0.18$ $(mg/kg/day)^{-1}$.
For application to lifetime exposures, the default lifetime exposure adjustment factor for male rats of 0.1, described in Table 5-7, leads to a slope factor of 1.8 $(mg/kg/day)^{-1}$. This slope factor should not be used with exposures greater than approximately 0.5 mg/kg/day (i.e, the human equivalent lifetime exposure level corresponding to 90% risk of forestomach tumors), since the observed dose-response would not be expected to continue linearly above this estimated lifetime-equivalent exposure level.

An oral slope factor of 85 $(mg/kg/day)^{-1}$ was listed previously on IRIS (U.S. EPA, 1988b). The earlier assessment used the multistage-Weibull model, which has a form similar to the multistage model (Equation 5-1):

$$P(d,t) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + ... + q_k d^k)*(t - t_0)^z], \quad (5\text{-}2)$$

with the addition of the time t that a tumor was observed, raised to the z power. The model fit to the NCI (1978) data fit z = 7.6 to the time that tumors were observed, which contrasts with the power of 3 used in the current analysis, through the Poly-3 adjustment for deaths occurring before the end of the study, and through the lifetime exposure adjustment for extrapolating from the end of the study to full lifetime. These modeling differences resulted in a less extreme extrapolation to lifetime exposure from the truncated bioassay that was available. Several quantitative considerations and assumptions were also updated in the reanalysis, including the use of (body weight)$^{3/4}$ scaling rather than surface area scaling, (body weight)$^{2/3}$, to estimate human equivalent doses; estimation of risk close to the range of the observed data rather than extrapolated to the exposure expected to be associated with 1×10^{-6} extra risk; and extrapolation to a human lifetime of 70 rather than 76.2 years.

Table 5-6. Observed and adjusted tumor incidences (and percentages) in rats and mice exposed by oral gavage to 1,2-dibromoethane

Tumor site	Incidence adjustment	Dose groups[a] Tumor incidence[b]						Trend test p-value[c]
Male rats		**0 mg/kg/day**		**Low dose**		**High dose**		
Forestomach papillomas or tumors	None (observed)	0/20	0%	45/50	90.0%	33/50	66.0%	
	Poly-3	0/13	0%	45/50	90.0%	33/34	97.1%	<0.001
Hemangiosarcoma	None (observed)	0/20	0%	11/50	22.0%	4/50	8.0%	
	Poly-3	0/13	0%	11/42	26.2%	4/23	17.4%	0.12[d]
Thyroid follicular cell adenoma or carcinoma	None (observed)	0/20	0%	5/50	10.0%	8/50	16.0%	
	Poly-3	0/13	0%	5/39	12.8%	8/23	36.4%	0.001
Female Rats								
Forestomach papillomas or tumors	None (observed)	0/20	0%	40/50	80%	29/50	58%	
	Poly-3	0/19	0%	40/40	100%	29/29	100%	<0.001
Hemangiosarcoma	None (observed)	0/20	0%	0/50	0%	3/50	6.0%	
	Poly-3	0/19	0%	0/20	0%	3/17	17.6%	0.026
Hepatocellular carcinoma or neoplastic nodule	None (observed)	0/20	0%	1/50	2.0%	6/50	12.0%	
	Poly-3	0/19	0%	1/20	5.0%	6/18	33.3%	0.006
Adrenocortical carcinoma	None (observed)	0/20	0%	1/50	2.0%	4/50	8.0%	
	Poly-3	0/19	0%	1/21	4.8%	4/17	23.5%	<0.001
Male mice								
Forestomach papillomas or tumors	Observed	0/20	0%	45/50	90%	31/50	64.0%	
	Poly-3	0/18	0%	45/45	100%	31/32	96.9%	<0.001
Alveolar/bronchiolar adenoma	Observed	0/20	0%	4/50	8%	10/50	20.0%	
	Poly-3	0/18	0%	4/20	20%	10/18	55.6%	<0.001
Female mice								
Forestomach papillomas or tumors	Observed	0/20	0%	47/48	97.9%	28/50	56.0%	
	Poly-3	0/18	0%	47/47	100%	28/31	93.3%	<0.001
Alveolar/bronchiolar adenoma	Observed	0/20	0%	10/48	20.0%	5/50	10.0%	
	Poly-3	0/18	0%	10/30	33.3%	5/18	27.8%	0.027

[a] The NCI bioassay doses were administered 5 days/week. The doses reported by NCI (1978) reflect averaging over the total number of weeks of the study, but not over 7 days/week.
[b] Numbers of animals at risk for observed incidences do not always agree with those given in Table 4-1 because the individual animal data tables containing the times of observation did not include notations of tissues missing due to autolysis, etc.
[c] Cochran-Armitage test for trend, using the Poly-3 adjusted incidence data.
[d] Trend test for male rat hemangiosarcomas was not statistically significant (the dose-response was not monotonically increasing), the low-dose response (26%) was statistically significantly elevated relative to control (Fisher's exact test, $p = 0.04$).
Source: NCI, 1978.

Table 5-7. Human equivalent exposures and adjustment factors for extrapolating from less-than-chronic exposure to lifetime exposure for the exposure periods in the NCI gavage study of 1,2-dibromoethane (NCI, 1978)

Sex, species	Bioassay doses (mg/kg/day)			Body weight[a] (kg)	Human equivalent exposures[b] (mg/kg/day)	Time of terminal sacrifice (weeks)	Lifetime exposure adjustment factor[c]
Male rats	Low	Weeks 1-49[d]	40	0.45	11	49	0.10
	High	Weeks 1-16 17-28 29-49[d]	80 0 40		22		
Female rats	Low	Weeks 1-61[d]	40	0.30	10	61	0.20
	High	Weeks 1-16 17-28 29-61[d]	80 0 40		20		
Male mice	Low	Weeks 1-10 11-12 13-53	60 100 60	0.030	8.6	78	0.42
	High	Weeks 1-10 11-12 13-39 40-53	120 200 120 60		17		
Female mice	Low	Weeks 1-10 11-12 13-53	60 100 60	0.025	8.2	90	0.64
	High	Weeks 1-10 11-12 13-39 40-53	120 200 120 60		16	78	0.42

[a] Body weights are lifetime averages, rounded to the nearest 0.05 kg (rats) or 0.005 kg (mice).
[b] The doses initially administered by NCI (1978) were adjusted for human equivalence by multiplying by [animal body weight (kg)/70 kg]$^{0.25}$.
[c] Lifetime exposure adjustment factor = $(t/104)^3$, where t is the time of final sacrifice in a particular dose group.
[d] Male rats were purposely not dosed during weeks 42 and 46, female rats not during weeks 42, 47, 52, and 56.

Table 5-8. Estimation of benchmark doses (BMD), lower 95% confidence limits (BMDL), and oral slope factors; using Poly-3 adjusted tumor incidence rates (see Table 5-1), for animals exposed orally to 1,2-dibromoethane (NCI, 1978)

Sex, species	Tumor type	Point of departure			Partial lifetime exposure oral slope factor[a] $(mg/kg/day)^{-1}$	Lifetime-adjusted oral slope factor[b] $(mg/kg/day)^{-1}$
		Benchmark response	BMD, mg/kg/day	BMDL, mg/kg/day		
Male rats	Forestomach	90%	11.9	9.1	0.10	1.0
	Hemangiosarcoma	20%	12.8	8.6	0.023	0.23
	Thyroid follicular cell adenoma	12.5%	10.8	5.7	0.022	0.22
Female rats	Forestomach[c]	100%	10	-	(0.1)	(0.50)
	Hemangiosarcoma	10%	18	7.9	0.013	0.065
	Hepatocellular carcinoma	15%	11	6.5	0.023	0.12
	Adrenocortical carcinoma	10%	10	5.4	0.018	0.090
Male mice	Forestomach[c]	100%	8.6	-	0.12	0.29
	Lung adenoma	30%	9.3	6.1	0.049	0.12
Female mice	Forestomach[c]	100%	8.2	-	0.12	0.23
	Lung adenoma	25%	8.6	5.8	0.043	0.082

[a] Slope factors were estimated by dividing the BMR (expressed as a proportion) by the BMDL. The slope factors should not be used with exposures higher than the corresponding BMDL, because the dose-response relationships tend to be nonlinear above the point of departure. They also only describe risk for exposure lasting the specified percentage of a lifetime.

[b] Slope factors were adjusted for lifetime exposure equivalence using the sex- and species-specific adjustments from Table 5-7, under the assumption that tumor incidence over time increases with the third power of time.

[c] Because there were no data available between 0% and 100% responses, curve fitting with meaningful confidence bounds is not possible. An approximate slope factor is derived by dividing the proportion responding at the lowest dose by that dose, expressed as the human equivalent dose, given in the BMD column.

5.3.2. Inhalation Carcinogenicity

5.3.2.1. *Choice of Inhalation Study/Data with Rationale and Justification*

Three studies were identified that reported 1,2-dibromoethane-induced tumors following inhalation. Stinson et al. (1981) reported benign neoplasms and carcinomas of the nasal cavity in male and female B6C3F_1 mice. Although the study was well designed and an adequate number of test animals were used, this study is limited for the development of an inhalation slope factor because only the nasal cavities of the animals were examined. NTP (1982) demonstrated that the nasal cavity is not necessarily the most sensitive site of tumor formation in mice. Therefore the Stinson et al. (1981) study was not used because similarly sensitive sites (lung, circulatory system) were not examined. The study by Wong et al. (1982) is also not suitable for the development of an inhalation slope factor because only one dose group was examined. The NTP (1982) study was well-conducted, used an adequate number of test animals and dose levels, and examined appropriate toxicological endpoints. Therefore, the study by NTP (1982) was used for development of an inhalation unit risk.

5.3.2.2. *Inhalation Dose-Response Data*

In the NTP (1982) study, groups of 50 F344 rats and B6C3F_1 mice of each sex were exposed by inhalation to concentrations of 10 or 40 ppm 1,2-dibromoethane, 6 hours per day for 5 days per week. Untreated controls consisted of 50 rats and 50 mice of each sex exposed in chambers to ambient air. Terminal sacrifices were conducted at 106 weeks in control animals and at 104 weeks in low-dose animals. Survival in low-dose and control rats was similar for both sexes. Terminal sacrifices were conducted at 79 weeks in the male mice, 89 weeks in the high-dose male rats and 91 weeks in the high-dose female rats and mice. Although the treated male mice demonstrated histopathology similar to that seen in the female mice, high mortality in all groups that was not related to treatment and that started by week 10 of the study made these data unsuitable for quantitative assessment.

Because there was increased mortality in both species that resulted in early termination of the study, statistical procedures that can reflect the influence of intercurrent mortality on site-specific tumor incidence rates were used to evaluate the tumor incidence levels. The Poly-3 procedure, described in section 5.3.3., was used for these data. Tumor incidences were statistically significantly elevated with increasing exposure level at several sites: nasal cavity and circulatory

system (hemangiosarcoma) in all three data sets; mesothelioma in male rats; mammary fibroadenoma or adenocarcinoma in female rats; alveolar/bronchiolar adenoma or carcinoma in female rats and mice; and adenomas or carcinomas of the bronchus, subcutaneous fibrosarcomas, or mammary adenocarcinomas in female mice. These data are summarized in Table 5-9. The individual times of tumor observations for each tumor type analyzed are listed in Appendix C2.

5.3.2.3. *Inhalation Dose Adjustments and Extrapolation Methods*

In order to extrapolate to low environmental exposure, the results of the inhalation bioassay were characterized by fitting dose-response models to the tumor results showing significant elevations with increasing exposure. Differences in survival and time course of tumor observation among dose groups were addressed using both quantal dose-response models (with Poly-3 adjusted data) and the multistage-Weibull model.

Human equivalent exposures were estimated following the EPA RfC methodology (U.S.EPA, 1994b). 1,2-Dibromoethane is relatively insoluble in water and demonstrates systemic toxicity although there was some respiratory tract toxicity which may or may not be considered portal of entry effects. Therefore, 1,2-dibromoethane is considered a Category 2 gas. Following the RfC Methodology, the respiratory tract effects were assessed alternatively as portal of entry effects or systemic effects while the rest of the effects were assessed as systemic effects.

For systemic effects, conversion to human equivalent concentrations involves comparison of the blood:air partition coefficients for humans, mice, and rats (U.S.EPA, 1994b). Gargas et al. (1989) reported a blood:air partition coefficient for rats of 119 for 1,2-dibromoethane. For their pharmacokinetic model, Hissink et al. (2000) assumed that the value for humans would be the same as for rats (see section 3). Without further information, the same assumption is made for this assessment. Therefore, no adjustment for interspecies pharmacokinetics is assumed to be necessary to estimate human equivalent concentrations for systemic effects. The equivalent average continuous concentrations for systemic effects are respectively, (10 ppm) × (30 hrs per wk)/(24 hrs per day × 7 days per wk) = 1.8 ppm and (40 × 30)/(24 × 7) = 7.1 ppm.

For portal of entry effects, the human equivalent concentration is derived by multiplying the duration-adjusted concentrations by an interspecies dosimetric adjustment for gas:respiratory effects in affected regions of the lung. For example, for effects seen in male rats in the extra-thoracic region, the adjustment uses the following calculation (U.S. EPA, 1994b):

$$RGDR(ET) = (MV_a/S_a)/(MV_h/S_h), \quad \text{(Equation 5-3)}$$

where

$RGDR(ET)$ =		regional gas dose ratio for the nasal cavity (extra-thoracic area of the respiratory system)
MV_a	=	animal minute volume (male rat: 0.21 L/min)
MV_h	=	human minute volume (13.8 L/min)
S_a	=	surface area of the extra-thoracic region of the animal respiratory system (rat: 15.0 cm^2)
S_h	=	surface area of the extra-thoracic region of the human respiratory system (200 cm^2)

Using these default values, the $RGDR(ET)_{rat, male} = (0.21/15)/(13.8/200) = 0.20$. The resulting adjustments for rats and female mice are summarized in Table 5-10. In addition, female rats and mice were also observed to have tumors in other regions of the respiratory tract. The corresponding RGDRs are also summarized in Table 5-10.

Because the high-dose groups in all three studies were terminated slightly earlier than the remaining groups, an adjustment to extrapolate to lifetime human exposure was applied to these exposure levels prior to quantal dose-response modeling. Unlike the oral studies (see section 5.3.1.3.), the early termination was only approximately 10% of the intended length and only affected one group in each set. The high-dose male rat exposure level was multiplied by $(t/104)^3 = (89/104)^3 = 0.63$, and the female rat and mouse exposure levels were multiplied by $(91/104)^3 = 0.67$.

In addition to a quantal analysis (as described in section 5.3.1.3), the characteristics of the dose-response relationships for different tumor sites were assessed through time-to-tumor analyses in order to adjust for competing mortality from cancer at other sites and differing time courses of tumor incidence with increasing dose. The general model used for the time-to-tumor (or time-to-response) analyses was the multistage-Weibull model, which has the form

$$P(d,t) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + ... + q_k d^k)*(t - t_0)^z]$$

where $P(d,t)$ represents the probability of a tumor (or other response) by age t (in bioassay weeks) for dose d (i.e., human equivalent exposure), and parameters $z \geq 1$, $t_0 \geq 0$, and $q_i \geq 0$ for i = 0, 1, ..., k,

where k = the number of dose groups - 1. The parameter t_0 represents the time between when a potentially fatal tumor becomes observable and when it causes death (see below). The analyses were conducted using the computer software TOX_RISK version 5.2 (Crump, 2000), which is based on Weibull models drawn from Krewski et al. (1983). Parameters are estimated using the method of maximum likelihood. Note that it was not necessary to adjust the administered dose for lifetime exposure prior to modeling, because the software program characterizes the tumor incidence over time from which it provides an extrapolation to lifetime exposure.

Tumor types were categorized by tumor context as either fatal or incidental tumors, in order to adjust appropriately for competing risks. Incidental tumors are those tumors thought not to have caused the death of an animal, while fatal tumors are thought to have resulted in animal death. For the rats, nasal cavity tumors were treated as fatal tumors unless observed at the terminal sacrifice in which case they were considered incidental. Furthermore, these tumors were considered rapidly fatal, and t_0 was set equal to 0 as there were insufficient data to reliably estimate t_0 in any event. Tumors at all other sites were treated as incidental for the rats. These determinations are consistent with the determination made by EPA for 1,3-butadiene (U.S. EPA, 2002b). The work of Portier et al. (1986) in analyzing tumor types in NTP historical controls lends support to these tumor context assumptions. For the mice, there were more tumor types observed than for the rats, and it was not clear which tumor type may have been most uniformly the cause of death. It was not possible to carry out an animal by animal determination of cause of death. Consequently, all of the significant female mouse tumors were considered incidental.

Specific n-stage Weibull models were selected for the individual tumor types for each sex based on the values of the log-likelihoods according to the strategy used by EPA (U.S.EPA, 2002b). If twice the difference in log-likelihoods was less than a chi-square with degrees of freedom equal to the difference in the number of stages included in the models being compared, the models were considered comparable and the most parsimonious model (i.e., the lowest-stage model) was selected.

5.3.2.4. *Inhalation Unit Risk*

The results of applying quantal models to the Poly-3 adjusted tumor incidence data are provided in Table 5-11. In several cases, the multistage model could not provide an adequate fit ($p > 0.1$). The log-logistic model was applied in these cases. The model output is provided in Appendix C2. Consistent with the *Draft Guidelines for Carcinogen Risk Assessment* (U.S.EPA,

1999), a point of departure near the lower end of the observed data was selected for linear extrapolation to low doses. An inhalation unit risk for each tumor site was calculated by dividing the BMR level by the corresponding BMCL. Estimated unit risks ranged from 0.039 $(ppm)^{-1}$ to 4.8 $(ppm)^{-1}$. The highest slope factor for each species/sex combination resulting from quantal dose-response modeling corresponded to nasal cavity tumors.

The results of applying the multistage-Weibull data to the time-to-tumor data are summarized in Table 5-12, and the model output and dose-response curves are provided in Appendix C2. The maximum likelihood estimates of the BMDs and 95% lower bounds (BMDLs) for 10% extra risk for each tumor are provided, consistent with the BMDS technical guidance (U.S.EPA, 2000d). Currently, the TOX_RISK software does not provide estimates corresponding to risks higher than 10%, so the unit risks were based on the $BMDL_{10}$s. The highest slope factor for each species/sex combination resulting from time-to-tumor modeling corresponded to nasal cavity tumors. However, approximate points of departure can be estimated from the central tendency risk estimate at the lower end of the observed data range for each tumor site and are provided in Table 5-13. These are provided only for comparison, since an estimate of the upper bound on risk is not available; these approximate risks follow the same patterns as the other unit risks, with the nasal cavity tumors showing the highest risk.

Unit risks calculated using the time-to-tumor approach were similar to those calculated using the quantal approach, within a factor of 3. Goodness of fit varied between the two approaches, with fits from one model not uniformly better than the other. The highest unit risks within each sex and species corresponded to nasal cavity tumors in all cases, with nasal cavity tumors an order of magnitude higher in male and female rats than in female mice. Because there did not appear to be substantial model dependence in the results, the highest unit risks were used to develop the overall unit risk. The quantal dose-response curves for these two data sets are provided in Appendix C2, Model Outputs C-9 and C-15. An inhalation unit risk for exposure to 1,2-dibromoethane is calculated by dividing the response rate of 0.87 (87%) by the $BMCL_{87}$ for nasal cavity tumors in male rats, or 0.87/ 0.18 ppm = 4.8 $(ppm)^{-1}$. At 25°C and standard pressure (760 mm Hg), 1 ppm × (molecular wt)/24.5 mg/m^3. The molecular weight of 1,2-dibromoethane is 188. Thus, one ppm is equivalent to 188/24.5 = 7.7 mg/m^3 of 1,2-dibromoethane. Hence, the inhalation unit risk can be expressed as 4.8 $(ppm)^{-1}$/7.7 $[(mg/m^3)/ppm] \approx 0.6\ (mg/m^3)^{-1}$.

This unit risk should not be used with exposures greater than 0.18 ppm, or 0.023 mg/m^3. Above this level, the dose-response is not linear, and the modeled dose-response pattern should be used to

estimate risk.

This inhalation unit risk is approximately 3-fold higher than the inhalation unit risk of 0.22 $(mg/m^3)^{-1}$ listed previously on IRIS (U.S. EPA, 1988b). The use of the RfC methodology to characterize human equivalent exposures in the nasal region contributes a 5-fold increase over the previous unit risk, all else being equal. The changes in cancer risk assessment since that time account for the remaining difference, primarily extrapolating linearly from a point within the observed data rather than from a modeled estimate of 1×10^{-6} risk.

There are several areas of uncertainty. First, there is uncertainty associated with extrapolating to low doses from relatively high responses in the rats, greater than 70% in the low dose groups. These studies did continue for close to the full lifetime, however, unlike the oral study. Second, there is some uncertainty involving the appropriate dose metric for some of the respiratory tumors. For the results from both modeling approaches, the unit risks for the respiratory sites are also expressed in terms of systemic toxicity rather than portal of entry effects, that is, as if the observed toxicity occurred after absorption and systemic distribution of the carcinogenic moiety. In the case of the alveolar/bronchiolar adenomas in female rats and mice, there is some indication from the oral study that these tumors can occur after ingestion of 1,2-dibromoethane, at least in the female mice. Following the RfC methodology, if systemic toxicity were solely responsible for these tumors, then the unit risks for these sites should be about 2- to 3-fold higher than if the tumors were due solely to portal of entry effects. There is no evidence that the nasal cavity tumors would result from systemic toxicity.

Last, reliance on single tumor sites probably somewhat underestimates the carcinogenic potential of 1,2-dibromoethane by the inhalation route. Using the same analysis that was applied to the oral slope factors to consider total risk from multiple tumor sites (see section 5.3.1.4), the combined risk of the significant tumors for male and female rats and for female mice was considered. As with those analyses, these sums are approximate (see section 5.3.1.4 for details). For the rats, the risks of nasal cavity tumors were clearly much larger than for the other sites, so it is not surprising that the final outcome only increases to 5.0 $(ppm)^{-1}$, which when converted to units of mg/m^3 still rounds to 0.6 $(mg/m^3)^{-1}$.

For the female rats, the sum of the five significant sites increases the unit risk for nasal cavity tumors more than for the males, with a sum of 3.9 $(ppm)^{-1}$ compared with 3.5 $(ppm)^{-1}$ for nasal cavity tumors alone. For the female mice, however, four of the six sites were very similar,

with respiratory (lung/bronchial or alveolar/bronchiolar) adenomas or carcinomas somewhat lower. The resulting 95% UCL on the slope factor for all six sites was 0.86 $(ppm)^{-1}$, almost three times higher than the risk for nasal cavity tumors alone, but roughly a factor of six lower than the unit risk based on male rat nasal cavity tumors.

Table 5-9. Observed and adjusted tumor incidence rates in rats and mice exposed to 1,2-dibromoethane by inhalation

Tumor site	Incidence adjustment	Administered concentration						Trend test p-value[d]
		0 ppm		10 ppm		40 ppm		
Male rats								
Nasal cavity tumors[a]	None (observed)	1/50	2.0%	39/50	78.0%	41/50	82.0%	
	Poly-3	1/46	2.2%	39/45	86.6%	41/43	95.3%	<0.001
Hemangiosarcoma	None (observed)	0/50	0%	1/50	2.0%	15/50	30.0%	
	Poly-3	0/46	0%	1/43	2.2%	15/28	53.6%	<0.001
Mesothelioma, tunica vaginalis	None (observed)	1/50	2.0%	8/50	16.3%	25/50	50.0%	
	Poly-3	1/46	2.1%	8/43	18.6%	25/35	71.4%	<0.001
Female Rats								
Nasal cavity tumors[b]	None (observed)	1/50	2.0%	34/49	70.8%	43/50	86.0%	
	Poly-3	1/47	2.1%	34/46	73.9%	43/46	93.5%	<0.001
Hemangiosarcoma	None (observed)	0/50	0%	0/49	0%	5/50	10.0%	
	Poly-3	0/47	0%	0/42	0%	5/26	19.2%	<0.001
Mammary fibroadenoma	None (observed)	4/50	8.0%	29/49	59.2%	24/50	48.0%	
	Poly-3	4/47	8.5%	29/46	63.0%	24/34	70.6%	<0.001
Mammary adenocarcinoma	None (observed)	1/50	2.0%	0/49	0%	4/50	8.0%	
	Poly-3	1/47	2.1%	0/42	0%	4/26	15.4%	0.023
Alveolar/bronchiolar adenoma/carcinoma	None (observed)	0/50	0%	0/49	0%	5/50	10.0%	
	Poly-3	0/47	0%	0/42	0%	5/25	20.0%	<0.001
Female Mice								
Nasal cavity tumors[c]	None (observed)	0/50	0%	0/50	0%	8/50	16.0%	
	Poly-3	0/46	0%	0/38	0%	8/27	29.6%	<0.001
Hemangiosarcoma	None (observed)	0/50	0%	12/50	24.0%	25/50	50.0%	
	Poly-3	0/46	0%	12/40	30.0%	25/35	71.4%	<0.001
Alveolar/bronchiolar adenoma/carcinoma	None (observed)	4/50	8.0%	11/50	22.0%	41/50	82.0%	
	Poly-3	4/46	8.7%	11/40	27.5%	41/44	93.2%	<0.001
Lung/bronchial adenoma/carcinoma	None (observed)	0/50	0%	1/50	2.0%	8/50	16.0%	
	Poly-3	0/46	0%	1/38	2.6%	8/26	30.8%	<0.001
Fibrosarcoma	None (observed)	0/50	0%	5/50	10.0%	11/50	22.0%	
	Poly-3	0/46	0%	5/39	12.8%	11/27	40.7%	<0.001
Mammary adenocarcinoma	None (observed)	2/50	4.0%	14/50	28.0%	9/50	18.0%	
	Poly-3	2/46	4.3%	14/40	35.0%	9/27	33.3%	0.001

[a] Adenoma, carcinoma, adenocarcinoma, adenomatous polyp, papillary adenoma, squamous cell carcinoma, or squamous cell papilloma.
[b] Adenoma, carcinoma, adenocarcinoma, adenomatous polyp, papillary adenoma, papillary polyp, or squamous cell carcinoma.
[c] Adenoma or carcinoma. [d] Cochran-Armitage test for trend, using the Poly-3 adjusted incidence data.
Source: NTP 1982.

Table 5-10: Summary of regional gas dose ratios for estimating human equivalent exposures corresponding to respiratory tumors observed in NTP (1982) inhalation bioassay

Sex, species	Body weight, kg	Minute volume[a], L/min	Affected respiratory regions	Surface area[b]	Regional gas dose ratio[c]	Human equivalent continuous[d] concentrations	
						Low-dose, ppm	High-dose, ppm
Male rats	0.30	0.21	Extra-thoracic (nasal cavity)	15.0 cm^2	0.20	0.36	1.42
Female rats	0.20	0.15	Extra-thoracic (nasal cavity) Pulmonary	15.0 cm^2 0.34 m^2	0.14 1.73	0.25 3.1	0.99 12.3
Female mice	0.035	0.041	Extra-thoracic (nasal cavity) Tracheobronchial Pulmonary	3.0 cm^2 3.5 cm^2 0.05 m^2	0.20 2.7 3.2	0.36 4.86 5.8	1.42 19.2 22.7

[a] Minute volumes were estimated using the allometric equations provided in the RfC methodology document (U.S. EPA, 1994b):

MV_{mouse}: $\ln(MV) = 0.326 + 1.05 \ln(BW)$

MV_{rat}: $\ln(MV) = -0.578 + 0.821 \ln(BW)$

[b] Surface areas provided in the RfC methodology document (U.S. EPA, 1994b). In addition, the corresponding surface areas for humans:

Extra-thoracic (nasal cavity): 200 cm^2

Tracheobronchial: 3,200 cm^2

Pulmonary: 54 m^2

[c] $RGDR = (MV_a/S_a)/(MV_h/S_h)$, where

RGDR = regional gas dose ratio for a specific area of the respiratory system

Mv_a = animal minute volume

Mv_h = human minute volume (13.8 L/min)

S_a = surface area of the specified region of the animal respiratory system

S_h = surface area of the specified region of the human respiratory system

[d] Administered concentrations were low dose, 10 ppm, and high dose, 40 ppm. A continuous exposure adjustment was included by multiplying by (5 days/7 days) × (6 hours/24 hours) = 0.178. Human equivalent continuous concentrations were estimated by multiplying equivalent continuous exposures (not shown) by the regional gas dose ratio.

Table 5-11. Estimates of benchmark concentration (BMC), lower 95% confidence limits (BMCL), and unit risks; using Poly-3 incidence rates[a], for animals exposed by inhalation to 1,2-dibromoethane (NTP, 1982)

Sex, species	Tumor type	Point of departure			Unit risk $(ppm)^{-1}$	
		BMR	BMC, ppm	BMCL, ppm	Regional respiratory dosimetry[c]	Systemic dosimetry[d]
Male rats	Nasal tumors	87%	0.38	0.18	4.8	0.96
	Hemangiosarcoma	10%	1.9	1.5	NR	0.067
	Mesothelioma	20%	1.9	1.3	NR	0.15
Female rats	Nasal tumors	70%	0.26	0.20	3.5	0.49
	Alveolar/bronchiolar adenoma/carcinoma	10%	6.6	3.4	0.029	0.051
	Hemangiosarcoma	10%	3.9	2.0	NR	0.050
	Mammary fibroadenoma[b]	55%	1.9	1.2	NR	0.46
	Mammary adenocarcinoma	10%	5.7	2.6	NR	0.039
Female mice	Nasal tumors	25%	0.96	0.73	0.34	0.068
	Lung/bronchial adenoma/carcinoma	10%	5.4	3.3	0.03	0.082
	Alveolar/bronchiolar adenoma/carcinoma	30%	6.0	4.8	0.062	0.20
	Hemangiosarcoma	35%	1.8	1.4	NR	0.25
	Fibrosarcoma	15%	1.7	1.1	NR	0.14
	Mammary adenocarcinoma[b]	25%	2.1	1.3	NR	0.19

[a] Tumor incidence data (Poly-3 incidence rates in Table 5-9) were fit using the general form of the multistage model: $P(d) = 1 - \exp(-q_0 - q_1 d - ... - q_6 d^6)$, except where p-values are footnoted (see footnote b).
[b] In cases where the multistage model did not provide an adequate fit ($p<0.1$), the log-logistic model was used: $P(d) = q_0 + (1- q_0)/[1+\exp(-a-b*\ln(d)]$.
[c] Reported modeling results reflect RGDR dosimetry adjustments as summarized in Table 5-10. NR indicates that regional respiratory dosimetry was not relevant for particular tumor sites.
[d] Reported unit risks reflect use of human equivalent lifetime concentrations. For respiratory tract endpoints, unit risks corresponding to systemic toxicity rather than portal of entry effects were estimated by multiplying the RGDR-based unit risks by the corresponding RGDR adjustments.

Table 5-12. Estimates of benchmark concentration (BMC) associated with an extra risk of 10%, lower 95% confidence limits (BMCL), and unit risks; using multistage-Weibull time-to-tumor modeling[a], for animals exposed by inhalation to 1,2-dibromoethane (NTP, 1982)

		Point of departure		Unit risk[c] $(ppm)^{-1}$	
Sex, species	Tumor type	BMC_{10}, ppm	$BMCL_{10}$, ppm	Regional respiratory dosimetry[b]	Systemic dosimetry[c]
Male rats	Nasal tumors	0.065	0.053	1.9	0.38
	Hemangiosarcoma	3.1	2.3	NR	0.040
	Mesothelioma	0.92	0.69	NR	0.14
Female rats	Nasal tumors	0.057	0.046	2.2	0.31
	Alveolar/ bronchial adenoma/ carcinoma	1.7	0.64	0.16	0.27
	Hemangiosarcoma	7.5	3.8	NR	0.026
	Mammary fibroadenoma	0.042	0.030	NR	3.3
	Mammary adenocarcinoma	1.7	0.71	NR	0.14
Female mice	Nasal tumors	0.86	0.84	0.12	0.024
	Alveolar/ bronchiolar adenoma/ carcinoma	3.7	2.2	0.045	0.14
	Lung/bronchial adenoma/ carcinoma	9.3	4.4	0.022	0.059
	Hemangiosarcoma	0.69	0.052	NR	0.19
	Fibrosarcoma	1.9	1.1	NR	0.090
	Mammary adenocarcinoma	2.2	1.2	NR	0.083

[a] Individual tumor incidence data (Appendix C-2) were fit using the multistage-Weibull model: $P(d) = 1 - \exp[(-q_0 - q_1 d - ... - q_6 d^6)t^z]$.

[b] Reported modeling results reflect RGDR dosimetry adjustments as summarized in Table 5-10. NR indicates that regional respiratory dosimetry was not relevant for particular tumor sites.

[c] Reported unit risks reflect use of human equivalent lifetime concentrations.

Table 5-13. Approximate unit risks, using central tendency dose-response estimates from multistage-Weibull time-to-tumor modeling, for animals exposed by inhalation to 1,2-dibromoethane (NTP, 1982)

Sex, species	Tumor type	Point of departure		Central tendency unit risk, $(ppm)^{-1}$
		BMR[a]	Low dose[b], ppm	
Male Rats	Nasal tumors	0.92	0.36	2.6
	Hemangiosarcoma	0.03	1.8	0.017
	Mesothelioma	0.21	1.8	0.12
Female rats	Nasal tumors	0.82	0.36	2.3
	Alveolar/ bronchiolar adenoma/ carcinoma	0.033	3.1	0.011
	Hemangiosarcoma	0.026	1.8	0.014
	Mammary fibroadenoma	0.73	1.8	0.41
	Mammary adenocarcinoma	0.048	1.8	0.027
Female mice	Nasal tumors	0.043	0.36	0.12
	Alveolar/ bronchiolar adenoma/ carcinoma	0.084	5.8	0.014
	Lung/bronchial adenoma/ carcinoma	0.049	4.9	0.010
	Hemangiosarcoma	0.31	1.8	0.17
	Fibrosarcoma	0.088	1.8	0.049
	Mammary adenocarcinoma	0.16	1.8	0.089

[a] Central tendency BMR estimated using time-to-tumor models referenced in Table 5-12.
[b] Low dose (100 ppm) adjusted by site for sex- and species-specific RGDR dosimetry, as summarized in Table 5-10.

6. MAJOR CONCLUSIONS IN THE CHARACTERIZATION OF HAZARD AND DOSE RESPONSE

6.1. HUMAN HAZARD POTENTIAL

1,2-Dibromoethane is a colorless liquid that has a chloroform-like odor and evaporates easily. It has limited solubility in water but is miscible and soluble in many organic solvents. 1,2-Dibromoethane was used primarily as an anti-knock compound in leaded gasoline and also has been used as a fumigant for grain, fruits, and soil. Today, it is more likely to be used as a solvent in resins, gums, and waxes, and as a intermediate in dye and pharmaceutical manufacturing. Past exposure from 1,2-dibromoethane was primarily from emissions and exhaust from vehicles using leaded gasoline and from its use as a fumigant. However, with restrictions on the use of leaded gasoline and limited fumigation practices, exposure to 1,2-dibromoethane has decreased.

It appears from both human and animal studies that 1,2-dibromoethane is rapidly absorbed by the oral, inhalation, and dermal routes. Animal studies indicate that 1,2-dibromoethane is metabolized by two pathways: oxidation by P450-monooxygenases and GSH conjugation mediated by glutathione-*S*-transferase. 1,2-Dibromoethane is eliminated mainly in the urine as mercapturic acid derivatives. However, a small amount of 1,2-dibromoethane is eliminated in the expired air and feces.

No subchronic- or chronic-duration human studies were located concerning ingestion of 1,2-dibromoethane. Noncancer effects reported in experimental animals orally exposed to 1,2-dibromoethane include weight gain depression, high mortality, hyperkeratosis and acanthosis of the forestomach, liver and adrenal cortex degeneration, and testicular atrophy (NCI, 1978). In mice, weight gain depression, high mortality, and testicular atrophy have been reported (NCI, 1978). All non-neoplastic changes reported following oral exposure to 1,2-dibromoethane have occurred at doses that also produced cancer. In bulls, oral administration of 1,2-dibromoethane produced adverse alterations in various sperm parameters and testicular histology (Amir and Volcani, 1965, 1967). Although doses were lower, these studies were not selected for RfD development because of the small numbers of animals and use of one exposure level and because bulls are ruminants with a significantly different physiology. Moreover, an allometric adjustment

would result in a dose quite similar to those used in the NCI (1978) study.[8] These bull studies, however, provide supporting evidence for testicular effects of low-dose 1,2-dibromoethane.

In humans, inhalation exposure to 1,2-dibromoethane in the workplace has been reported to cause adverse reproductive and fertility effects (Ratcliffe et al., 1987; Schrader et al., 1988; Wong et al., 1979). Specifically, decreases in average sperm count, percentage of viable sperm, and percentage of motile sperm have been documented following long-term exposure. Morphological abnormalities in sperm, such as tapered heads, absent heads, and abnormal tails, have also been reported following chronic exposure. Short-term exposures have been associated with sperm abnormalities in workers exposed to 1,2-dibromoethane. After six weeks of exposure to 1,2-dibromoethane, sperm velocity and semen volume were reported to decrease. Decreased reproductive performance of occupationally exposed workers was assessed by the number of live births to exposed workers' wives. Poor exposure data and moderate-to-extensive exposure by the dermal route limit the value of these findings for risk assessment purposes. Reproductive studies in laboratory animals (Short et al., 1978) provide useful quantitative information for risk assessment purposes but suffer from a lack of sperm quality and count measures.

In chronic animal studies, weight gain depression, high mortality, hepatic necrosis, nephropathy, testicular atrophy, and degeneration of the adrenal cortex have only been reported in rats and mice at exposures that also cause cancer. The results of subchronic inhalation studies revealed weight gain depression, swelling of adrenocortical cells, decreases in thyroid follicle size, and formation of megalocytic cells of the lining of bronchioles in rats and mice (NTP, 1982; Nitschke et al., 1981; Reznik et al., 1980). In rats, relative liver and kidney weights, focal epithelial hyperplasia of the nares, and diffuse respiratory hyperplasia have also been reported. Cancers have not been reported following subchronic-duration inhalation exposure to 1,2-dibromoethane.

There are no reports of cancer in humans associated with exposure to 1,2-dibromoethane. However, the human studies have serious limitations, such as poor exposure assessment and co-exposure to other potential carcinogens. Oral exposure to 1,2-dibromoethane induces cancer of the forestomach in rats and mice (NCI, 1978). The relevance of forestomach effects to humans has been questioned, particularly for nongenotoxic chemicals whose mode of action is believed to involve irritation and cell proliferation from long-term exposure (Poet et al., 2003). While the

[8]After allometric adjustment, the doses given to the NCI (1978) male rats were less than 2 times, and therefore similar to, the doses given to the Amir and Volcani (1965, 1967) bulls (11 vs 21 mg/kg$^{3/4}$/day).

forestomach contains features, such as minimal vascularization and stratified squamous cells, which result in a longer residence time of food-borne agents than is received by the oesophageal tissue or the glandular stomach (Grice, 1988; Poet et al., 2003), effects in this organ are believed to be relevant to 1,2-dibromoethane and other genotoxic chemicals that do not appear to require precursor events (e.g., irritation) associated with long residence time to induce tumors. Hemangiosarcoma in male rats, hepatocellular carcinoma in female rats, and lung cancer in mice were also reported following oral exposure to 1,2-dibromoethane (NCI, 1978). Chronic-duration inhalation exposure produces tumors of the nasal cavity in rats and lung tumors in mice (NTP, 1982). Hemangiosarcoma, mesothelioma of the tunica vaginalis, mammary carcinoma, lung adenoma, and fibrosarcoma have also been reported following long-term exposure to 1,2-dibromoethane (NTP, 1982).

There is also no evidence from human studies that 1,2-dibromoethane is genotoxic. Steenland et al. (1985, 1986) performed a cytogenetic examination on exposed workers to investigate induction of sister chromatid exchanges and chromosomal aberrations in peripheral lymphocytes and found no significant increase in either parameter. However, exposure concentrations were low and may not have been capable of inducing chromosomal damage. In contrast to human studies, there is strong evidence from *in vitro* and *in vivo* animal studies that 1,2-dibromoethane is genotoxic. 1,2-Dibromoethane is a direct-acting mutagen in bacteria. 1,2-Dibromoethane was positive for *S. typhimurium* revertant strains TA1535, TA100, and TA98 (Barber et al., 1981) and induced point mutations in *S. typhimurium* strains TA1535 and TA100, *S. coelicolor*, and *A. nidulans* (Carere and Morpurgo, 1981). 1,2-Dibromoethane has been shown to induce chromosomal aberrations and sister chromatid exchanges in Chinese hamster ovary cells (Ivett et al., 1989; Tan and Hsie, 1981; Brimer et al., 1982; Ballering et al., 1998; Graves et al., 1996). 1,2-Dibromoethane has also been reported to induce gene mutations in two human lymphoblastoid cell lines, AHH-1 and TK6 (Crespi et al., 1985), and sister chromatid exchanges in human peripheral lymphocyte cultures (Tucker et al., 1984). In vivo, 1,2-dibromoethane induced DNA damage in rats following oral administration (Kitchin and Brown, 1986, 1987; Sasaki et al., 1998). Intraperitoneal administration of radiolabeled 1,2-dibromoethane has been shown to bind DNA in the liver, kidney, stomach, and lung of rats and mice (Arfellini et al., 1984), and *S*-[2-(N^7-guanyl)ethyl]glutathione has been identified as the major DNA adduct formed in rats following treatment with 1,2-dibromoethane (Kim et al., 1990; Koga et al., 1986).

The genotoxicity of 1,2-dibromoethane is thought to be related to its conjugation with GSH as catalyzed by glutathione-*S*-transferase, which results in the formation of an episulfonium ion that can react with DNA to form *S*-[2-(N^7-guanyl)ethyl]glutathione DNA. 1,2-Dibromoethane has

been reported to cause DNA damage and UDS in rat hepatocytes and spermatocytes exposed both *in vitro* and *in vivo,* and inhibition of cytochrome P-450-mediated oxidation in either cell type did not inhibit UDS. However, depletion of cellular GSH inhibited the induction of UDS in both cell types, which suggests that GSH conjugation and not P450 oxidation is responsible for the genotoxic effects of 1,2-dibromoethane. Inhibition of hepatic mixed-function oxidases *in vivo* was associated with positive UDS response to 1,2-dibromoethane in spermatocytes, but there was no effect on 1,2-dibromoethane-induced UDS in hepatocytes.

1,2-Dibromoethane-induced cytotoxicity may be dependent on its metabolism by cytochrome P450 and/or conjugation with GSH. Microsomal cytochrome P-450-dependent oxidative metabolism of 1,2-dibromoethane produces the metabolite 2-bromoacetaldehyde. This metabolite has been reported to cause lipid peroxidation and protein binding. Glutathione conjugation may also contribute to cytotoxicity. Depletion of hepatic mitochondrial GSH by 1,2-dibromoethane has been correlated with hepatotoxicity and perturbations in mitochondrial Ca^{2+} homeostasis. The results of *in vitro* and *in vivo* experiments suggest that the renal toxicity of 1,2-dibromoethane may be due to its biotransformation by GSH conjugation followed by further conversion in the kidney to highly reactive metabolites. It has been suggested that lipid peroxidation may play a role in the 1,2-dibromoethane-induced pathogenesis of liver cell necrosis.

The available evidence further supports a conclusion that 1,2-dibromoethane is a genotoxic carcinogen. Under the *Draft Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1999), 1,2-dibromoethane is classified as "likely to be carcinogenic to humans" via both the oral and inhalation routes of exposure based on strong evidence of carcinogenicity in animals and inconclusive evidence of carcinogenicity in an exposed human population. Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a), 1,2-dibromoethane would be classified as Group B2 –Probable Human Carcinogen.

In conclusion, while the potential for human exposure to 1,2-dibromoethane is limited, studies suggest that even low levels of 1,2-dibromoethane exposure can pose considerable health risks. 1,2-Dibromoethane is rapidly absorbed by all potential routes of human exposure and is a likely human carcinogen and reproductive toxicant. There is also some limited evidence for neurobehavioral developmental effects caused by 1,2-dibromoethane as well as endocrine disruption (based on effects on other endocrine organs as well as changes in hormone levels). As is discussed in Chapter 5, the database associated with 1,2-dibromoethane's potential to cause effects on the developing fetus and newborn is limited. Additional research in this area could increase the certainty of this assessment.

6.2. DOSE RESPONSE

An RfD of 9E-3 mg/kg-day was derived. It is based on liver, testicular, and adrenal effects observed in male rats following chronic oral exposure. The RfD is supported by a benchmark dose analysis of these effects and is based on a LOAEL of 27 mg/kg-day and application of an uncertainty factor of 3000, which was reduced from an overall uncertainty factor of 10,000 (10 for interspecies, 10 for intraspecies, 10 for LOAEL to NOAEL extrapolation, 10 for database deficiency) in recognition of the lack of independence of the individual factors and that the multiplication of four or five values of 10 is likely to yield unrealistically conservative RfCs (Dourson and Stara, 1983; U.S. EPA, 1994, 2002).

An RfC of 9E-3 mg/m^3 was derived based on induction of liver pathology in both male and female rats using benchmark dose methodology in a lifetime inhalation bioassay (NTP, 1982). The RfC was calculated by application of uncertainty factors 3 for interspecies, 10 for intraspecies, and 10 for database uncertainty to the BMDL(HEC) of 2.8 mg/m^3.

A cancer oral slope factor of 2 $(mg/kg\text{-}day)^{-1}$ was calculated from the carcinogenicity bioassay in male rats (NCI, 1978) using benchmark dose methodology. An inhalation cancer slope factor estimate of 0.6 $(mg/m^3)^{-1}$ was calculated from an inhalation carcinogenicity bioassay in male rats (NTP 1982).

Confidence in the study utilized to derive the RfD and oral cancer slope factor is low to medium. Although the critical study was of chronic duration and involved a large number of animals, high mortality, close dose spacing, and the absence of a NOAEL made this study difficult to assess. Confidence in the oral database is also considered to be medium. Although oral data on reproductive/developmental effects are very limited, some indication of doses that might cause these effects can be obtained from gavage studies in bulls and inhalation studies in rats and mice. The overall confidence in these oral benchmarks is considered to be low to medium.

Confidence in the study used to derive the RfC and inhalation cancer slope factor is medium. The NTP (1982) inhalation study was well designed, using an adequate number of animals of both sexes, but was limited because of excessive mortality in the high-dose groups of both species, moderate mortality in low-dose female mice, and excessive mortality in male mice not related to 1,2-dibromoethane exposure. Confidence in the inhalation database is medium.

There are systemic inhalation toxicity studies in two species, one-generation (but no multigeneration) reproductive study, and developmental toxicity studies in two species that did not cover the full period of gestation. Although animal studies have shown that reproductive/developmental effects in females are likely to occur only at doses inducing maternal toxicity, the possibility remains that sperm quality may be adversely affected at lower doses. The overall confidence in these inhalation benchmarks is medium.

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APPENDIX A. External Peer Review–Summary of Comments and Disposition

The Toxicological Review that supports the IRIS file for 1,2-dibromoethane has undergone both internal peer review performed by scientists within EPA or other federal agencies and a more formal external peer review performed by scientists chosen by EPA's contractor in accordance with U.S. EPA (1994c). Comments made by the internal reviewers were addressed prior to submitting the documents for external peer review and are not part of this appendix. Public comments also were read and carefully considered. The three external peer reviewers were tasked with providing written answers to general questions on the overall assessment and on chemical-specific questions in areas of scientific controversy or uncertainty. A summary of comments made by the external reviewers and EPA's response to these comments follows.

General Charge Question 1. *Are you aware of any other data/studies that are relevant (i.e., useful for the hazard identification or dose-response assessment) for the assessment of the adverse health effects, both cancer and noncancer, of this chemical?*

Comment: Reviewers identified specific studies (see below) addressing carcinogenicity that they felt had not been adequately considered in the assessment.

A/J mice studies and other secondary oncogenicity studies: Stoner et al. (1986), Adkins et al (1986), and Van Duuren et al. (1979) studies should be considered.

Response: We agree that the studies identified [Stoner et al. (1986), Adkins et al (1986), Van Duuren et al. (1979)] are relevant. They have been summarized and considered in the weight of evidence.

Chronic bioassay: While the Van Duuren (1985) study was described in the assessment, one reviewer felt it had not been adequately considered in the dose-response assessment.

Response: We agree with the comment, and have more thoroughly characterized the consistency of this drinking water study with the oral gavage study. In the case of the mouse oral gavage study, the change in dosing regimen did not result in two similar dose levels, however, as with the rats. Drinking water is a more realistic exposure medium, though, so, although this study used much higher dose levels and reported less complete tumor incidence data (no times of observation and no information concerning which animals had multiple tumors), it should be considered more thoroughly.

Epidemiology studies: Sweeney et al. (1986) and Turner and Barry (1979) should be considered.

Response: EPA agrees that Sweeney et al. (1986) should be included in the document and it is included in Section 4 with a qualitative discussion of the limitations of the study and its use in the quantitative assessment of the carcinogenicity of this chemical. There are several limitations

to this study. Levels of 1,2-dibromoethane were not reported, except that they were below OSHA standards (20 ppm) and NIOSH recommended standards. 1,2-Dibromoethane was apparently added to tetraethyl lead to reduce the deposition of inorganic lead on engine parts and was used continuously because of the chemical plant's start-up, so workers were exposed from the beginning of the study period, however. Another limitation of the study was lack of a more comparable control group, unexposed workers. This study neither establishes nor dismisses an association between occupational 1,2-dibromoethane exposure and carcinogenicity.

Turner and Barry (1979) came to the attention of one reviewer as a secondary citation. As indicated by the same reviewer, this study had major limitations, including lack of information concerning duration and magnitude of exposure, number of workers studied, and length of time elapsing since first exposure, which make the study inconclusive and of little or no value to this assessment. However, its contributions and limitations have been summarized.

PBPK studies: Hissink et al. (2000) and Ploemen et al. (1997) should be considered.

Response: EPA agrees and the studies identified [Hissink et al. (2000) and Ploemen et al. (1997)] have been summarized and considered in the document for their relevance in characterizing human relevance and potential use for route-to-route extrapolation and for the estimation of human equivalent concentrations from laboratory animal studies. Given the limitations of these studies, however (see Section 3.5), it would not be appropriate to use the Hissink et al. (2000) model at this time for quantitative (route-to-route or animal-to-human) extrapolations. However, the Hissink et al. (2000) report and model provide useful information regarding the mode of action of 1,2-dibromoethane, particularly with respect to the cancer effects of 1,2-dibromoethane.

Comment: One reviewer suggested that EPA should consider requiring additional studies of (presumably pesticide) registrants to characterize the dose-response for developmental neurotoxicity (adverse behavioral effects) and the endocrine disruptive potential of 1,2-dibromoethane.

Response: Additional studies in these areas may help to improve the certainty of the RfC and RfD. The extent to which additional studies in these areas would benefit the 1,2-dibromoethane risk assessment is addressed in Section 6 of the EDB IRIS toxicological review document.

General Charge Question 2. *For the RfD and RfC, has the most appropriate critical effect been chosen (i.e., that adverse effect appearing first in a dose-response continuum)? For the cancer assessment, are the tumors observed biologically significant? relevant to human health? Points relevant to this determination include whether or not the choice follows from the dose-response assessment, whether the effect is considered adverse, and if the effect (including tumors observed in the cancer assessment) and the species in which it is observed is a valid model for humans.*

Comment: With respect to the RfD, one reviewer questioned whether all co-critical effects were identified and discussed. Another reviewer did not feel that the Agency had adequately justified

not using a benchmark dose approach on the oral data.

Response: A discussion of co-critical endpoints, including liver, testicular, and adrenal cortical effects has been added to Section 5.1. A benchmark dose analysis of these data was performed and is discussed in Section 5.1.1. Details are included in Appendix B (Table B-1 and associate output files) of the toxicological review. The RfD estimates that result from the BMD (5E-3 mg/kg/day) and NOAEL/LOAEL (9E-3 mg/kg/day) assessment approaches are very similar. Because of high mortality and unusual dosing in the high dose group, there is a great deal of uncertainty associated with these BMD results and they are only provided in support of the NOAEL/LOAEL approach.

Comment: With respect to the RfC, one reviewer suggested that all co-critical effects be considered and analyzed via the benchmark dose approach.

Response: A benchmark dose analysis of all co-critical endpoints, including liver, testicular, adrenal cortical, splenic, and nasal effects, has been added to Section 5.2. The details of this analysis are provided in Appendix B of the toxicological review.

Comment: One reviewer pointed out that 1,2-dibromoethane is most likely a Category 2 gas, and the portal of entry effects should be reevaluated accordingly.

Response: 1,2-Dibromoethane is relatively insoluble in water and demonstrates systemic toxicity, although there was some respiratory tract toxicity that may or may not be considered portal of entry effects. EPA agrees that dosimetry for 1,2-dibromoethane's effects at points of contact should take into account EPA's RfC Methodology (U.S.EPA, 1994b) for Category 2 gases. Following the RfC Methodology, the respiratory tract effects were assessed alternatively as portal of entry effects or systemic effects while the rest of the effects were assessed as systemic effects. This approach has been incorporated into the assessment (e.g., Table 5-4 of the toxicological review and Table 1 of the summary document and associate descriptive text), and the new human equivalent concentration (HEC) estimates have resulted in the critical effect for the RfC changing from liver necrosis to nasal inflammation.

Comment: Two reviewers requested a better rationale for the use of forestomach tumors in the cancer risk assessment.

Response: The Agency believes that forestomach tumors caused by genotoxic carcinogens such as 1,2-dibromoethane are more applicable to humans than forestomach tumors caused by nongenotoxic mechanisms that require cellular damage, turnover, and a long residence time of the chemical in the forestomach. Additional rationale/explanation of the use of forestomach tumors for the 1,2-dibromoethane assessment and their applicability to humans has been added to Sections 4.6, 6, and other sections of the toxicological review.

General Charge Question 3. *Have the noncancer and cancer assessments been based on the most appropriate studies? These studies should present the critical effect/cancer (tumors or*

appropriate precursor) in the clearest dose-response relationship. If not, what other study (or studies) should be chosen and why?

Comment: All reviewers felt that the appropriate studies were chosen.

General Charge Question 4. *In the IRIS Summary document, studies included in the RfD and RfC under the heading "Supporting/Additional Studies" are meant to lend scientific justification for the designation of critical effect by including any relevant pathogenesis in humans, any applicable mechanistic information, any evidence corroborative of the critical effect, or to establish the comprehensiveness of the database with respect to various endpoints (such as reproductive/developmental toxicity studies). Should other studies be included under the "Supporting/Additional" category? Should some studies be removed?*

Comment: One reviewer felt that the summary document was too short and needed more detail to support the choice of study, species, sex, and critical effect for both the RfC and RfD.

Response: Additional detail and supporting documentation has been added to the summary document.

General Charge Question 5. *For the noncancer assessments, are there other data that should be considered in developing the uncertainty factors or the modifying factor? Do the data support the use of different values than those proposed?*

Comment: For the RfD, the reviewers agreed with the uncertainty factors that were applied, but one reviewer disagreed with the rational for the 3-fold database uncertainty factor. This reviewer pointed out that the lack of oral reproductive and developmental studies should be stressed as a primary basis for this UF.

Response: The Agency agrees that the rationale for the RfD database UF should include the lack of oral reproductive and developmental toxicity studies, and it has been revised in both Chapter 5 of the toxicological review and Section I.A.3. of the IRIS summary document to take into account the reviewer's comments. In fact, the RfD database UF has been increased to 10 to account for this uncertainty and the problems with the critical study associated with the high mortality and odd dosing regimen of the high-dose group.

Comment: For the RfC, two reviewers questioned the lack of a database UF and one reviewer questioned the rationale used for the application of an effect level extrapolation factor (ELF, comparable to a LOAEL to NOAEL UF) to the $BMDL_{10}$ point of departure.

Response: In the external review draft of this assessment, the Agency did not apply a database UF, but did apply an ELF. After considering the reviewer comments, the Agency agrees that a database uncertainty factor is warranted due to the lack of any multigenerational reproductive toxicity studies given the genotoxicity of this compound and the spermatotoxicity concerns. Given that the merits and approach for the application of an ELF are still under discussion within

the Agency and the point of departure in this case is the lower bound 95% confidence limit on the dose that causes a 10% increase in a minimal effect, the Agency has determined that the application of an ELF is not warranted in this case. The overall UF remains 300 but is now based on 10 for UF_H, 3 for UF_A, and 10 for UF_D.

General Charge Question 6. *Do the confidence statements and weight-of-evidence statements present a clear rationale and accurately reflect the utility of the studies chosen, the relevancy of the effects (cancer and noncancer) to humans, and the comprehensiveness of the database? Do these statements make sufficiently apparent all the underlying assumptions and limitations of these assessments? If not, what needs to be added?*

Comment: Two reviewers felt that the confidence statements should be improved for both the RfD and RfC and that lower confidence should be placed on the RfD. One reviewer felt that the confidence discussions should be included in Section 6 of the toxicological review.

Response: The Agency generally agreed with the reviewer comments, and the confidence statements have been revised and expanded accordingly.

Specific Charge Question 1. *Regarding the RfD and RfC*

> *(a) Is the Agency justified in not making use of the bull studies of sperm effects to quantify noncancer risk?*

Comment: All reviewers agreed that the bull studies should not be used to quantify human risk, citing the small sample size and differences in physiology (including absorption and metabolism) between bulls and humans. One reviewer felt that the latter reason was more valid than the former because of the consistent adverse response observed in these studies.

Response: The text in Sections 4.3.2 and 6 has been modified to emphasize the physiological differences between bulls and humans as the primary reason these studies were not used as the basis for the RfD.

> *(b) Is liver necrosis an appropriate noncancer endpoint for derivation of an RfC?*

Comment: All reviewers felt that liver necrosis was an appropriate endpoint, but one reviewer suggested that the nasal inflammation endpoint in mice was also appropriate and might result in a lower value if the RfC were derived using the method described in EPA (1994b) for calculating HEC values for category 1 gases.

Response: The current EPA practice is to perform "endpoint specific" HEC calculations. In other words, HEC values are calculated using EPA (1994b) methods for category 1 gases for portal-of-entry effects and category 3 methods for systemic effects. The HEC for nasal inflammation effects was originally calculated using the method described for category 3 gases. When the HEC was recalculated using the method for category 1 gases, the resultant HEC value

was lower than the liver necrosis HEC value and was thereby used to derive the revised RfC of 9E-3 mg/m^3.

Specific Charge Question 2. *Regarding the cancer assessment*

> *(a) Were the adjustments made to account for early tumor formation and mortality adequate and clear?*

Comment: Two reviewers noted that the cancer dose-response modeling was carried out using a nonstandard EPA method.

Response: An interim approach that approximated the multistage-Weibull model has been deleted. The cancer dose-response modeling was carried out using the multistage-Weibull model for time-to-tumor. These results are presented in parallel with the results from the survival-adjusted tumor incidences. Upon further consideration, the multistage-Weibull model appears not to be suitable for use with the oral data because of the unusual dosing schedule that was used; the multistage-Weibull model currently available can only handle a single level of exposure per group when dose rate is an issue. The multistage-Weibull is still superior to the multistage model when survival has been differentially impacted, leading to competing causes of death confounding the response patterns, and when tumors occur earlier with increasing exposure, as was stated in the document. A more transparent explanation supporting the use of the multistage-Weibull model has been added. The output from the multistage model for all cancer dose-response analyses has also been added.

> *(b) Was it appropriate to attempt a low dose extrapolation from the high tumor incidence estimates obtained after the lifetime extrapolation approach?*

Comment: All reviewers agreed that low-dose extrapolation was appropriate and that the linear approach should be used.

> *(c) Was the use of forestomach tumors adequately justified given the absence of this organ in humans?*

Comment: Two reviewers agreed that the use of forestomach tumors was appropriate. One reviewer indicated that use of forestomach tumors was questionable because the NCI study was a gavage study and the tumors could have been by [long-term contact and] irritation that would not be relevant to humans.

Response: The rationale for using the forestomach tumors has been enhanced in the text of the toxicological review in Sections 4.6, 5, and 6. Because EDB is genotoxic, the occurrence of these tumors may not depend on irritation and cell damage caused by long retention times in the forestomach compartment of rodents (an argument that has been made for lack of relevancy to humans). Thus, it is felt that these tumors must be considered. Some expert consultation had led to the conclusion that the forestomach tumors should be treated as incidental since it was not

clear that death had been caused by the tumor and not some other more acute lesion. After more review, it appears that the forestomach tumors should be treated as the most likely cause of death for all animals who had them in the oral study, except those whose tumors were only detected at the terminal sacrifice. The other tumor types in the oral study have now been taken to be incidental, although in the few early deaths where there were no forestomach tumors some of these may have been the cause of death.

The discussion of forestomach tumors in the weight-of-evidence section (Section 4.6) has been expanded to include the following discussion:

> The relevance of forestomach effects to humans has been questioned, particularly for nongenotoxic chemicals whose mode of action is believed to involve irritation and cell proliferation from long-term exposure (Poet et al., 2003). It is true that the forestomach is not present in humans and contains features, such as minimal vascularization and stratified squamous cells, that result in a longer residence time of food-borne agents than is received by comparable human organs such as the oesophagus and the glandular stomach (Grice, 1988; Poet et al., 2003). In this case, however, effects in this organ are believed to be of potential relevance to humans because 1,2-dibromoethane and other genotoxic chemicals do not appear to require precursor events (e.g., irritation) associated with long residence time to induce these kinds of tumors. 1,2-Dibromoethane does not appear to cause significant irritation in the forestomach and was reported to induce forestomach tumors after just 168 days of exposure (NCI, 1978).

Other

Comment: In several areas of the noncancer and cancer portions of the assessment, reviewers noted instances of tables being mislabeled or missing. They suggested adding tables or adding information to existing tables in order to summarize study information (study characteristics, results, statistical significance). Inconsistent interpretation of observed effects was also noted. Numerous instances were identified where additional study information would be useful.

Response: Inconsistencies in the document have been corrected, and the requested information has been added to the text and in additional tables.

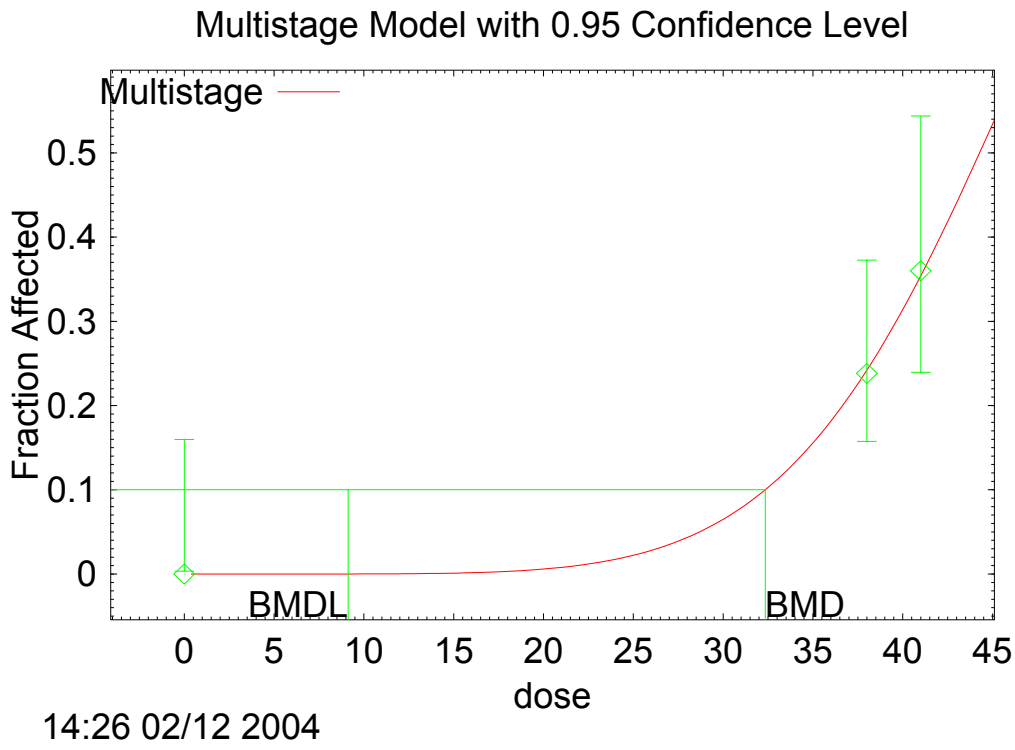
APPENDIX B. BMDS Analyses of Noncancer Endpoints

Table B-1. BMDS analysis of NCI (1978) in support of RFD

Model		Peliosis in male rats (see pp. B-2 to B-4)[a]		Testicular atrophy in male rats (see pp. B-5 to B-8)[a]		Adrenal cortical degeneration in male rat (see pp. B-9 to B-11)[a]	
		No dose adjustment	TWA dose adjustment	No dose adjustment	TWA dose adjustment	No dose adjustment	TWA dose adjustment
Multistage	Power	1	6	1	7	1	3
	BMD_{10}	17.0924	32.3459	11.5101	31.3928	15.9817	26.1145
	$BMDL_{10}$	11.9529	**9.12312**	**8.68059**	**6.77996**	11.4453	**8.46243**
	AIC	80.9598	80.7837	106.298	106.182	92.4547	91.6386
	p-value	0.9119	0.9964	0.9389	0.9958	0.6547	0.9878
Weibull	BMD_{10}	17.0924	32.8565	11.5101	31.8256	15.9817	28.6819
	$BMDL_{10}$	11.9529	9.12815	**8.68059**	6.78526	11.4453	8.47521
	AIC	80.9598	82.7764	106.298	108.173	92.4547	93.614
	p-value	0.9119	1.0000	0.9389	0.9999	0.6547	1.0000
Gamma	BMD_{10}	17.0924	32.6612	11.5101	30.2683	15.9817	29.5879
	$BMDL_{10}$	11.9529	9.1141	**8.68059**	6.65175	11.4453	8.47521
	AIC	80.9598	80.7968	106.298	106.403	92.4547	93.614
	p-value	0.9119	0.9898	0.9389	0.8918	0.6547	1.0000
Logistic	BMD_{10}	34.7812	32.8668	26.2594	31.9776	33.2869	30.205
	$BMDL_{10}$	26.6526	21.2288	20.6013	18.675	25.5276	20.0266
	AIC	86.6093	82.7831	113.248	108.175	98.8978	93.6949
	p-value	0.1038	0.9521	0.0614	0.9754	0.0540	0.8137
LogLogist	BMD_{10}	14.89	33.2451	9.88164	32.5999	13.6897	29.3368
	$BMDL_{10}$	**9.59883**	7.65899	6.19692	5.29211	**9.05438**	6.96311
	AIC	80.8128	82.7764	108.173	108.173	92.0322	93.614
	p-value	0.9820	1.0000	1.0000	1.0000	0.8114	1.0000
Probit	BMD_{10}	32.6319	33.1771	24.7944	32.4969	31.1452	29.4539
	$BMDL_{10}$	25.0429	19.6937	19.5476	17.0531	23.9958	18.6165
	AIC	86.1626	82.7764	112.678	108.173	98.4693	93.6245
	p-value	0.1193	0.9989	0.0727	0.9999	0.0604	0.9338
LogProbit	BMD_{10}	26.0742	33.6301	19.5799	33.0559	24.5429	29.9603
	$BMDL_{10}$	19.937	15.3227	15.4431	12.0592	19.063	14.5032
	AIC	81.8126	82.7764	106.87	108.173	93.8791	93.614
	p-value	0.5923	1.0000	0.7020	1.0000	0.3186	1.0000
First occurrence of effect (weeks)[b]		Low dose - 39 High dose - 36		Low dose - 38 High dose - 15		Low dose - 41 High dose - 35	
$BMDL_{10}$ (mg/m^3)		**9.59883**	**9.12312**	**8.68059**	**6.77996**	**9.05438**	**8.46243**

[a] The output file for the selected model (usually that which resulted in the lowest AIC) is included in this Appendix.
[b] An attempt was made account for early mortality. In general, rats that died before the first occurrence of the effect (see Appendix C) were excluded from the analysis of that effect. However, 13 rats that died at 15 weeks without testicular atrophy were excluded from the analysis even though this effect was observed in 5 rats at that time.

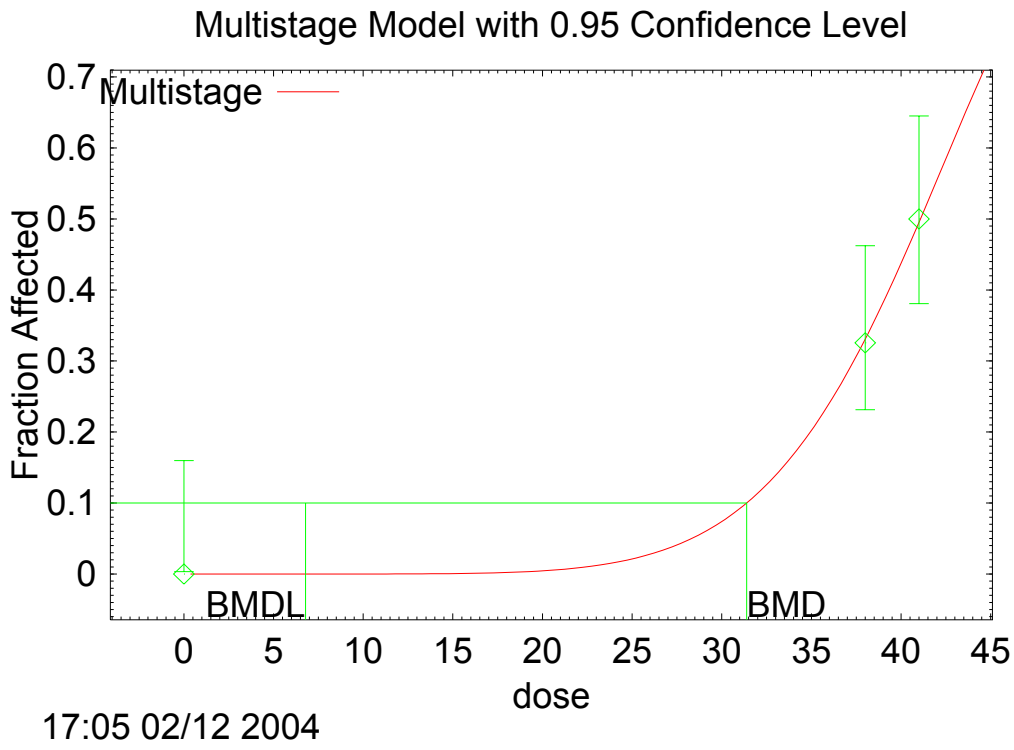
Output B-1. Peliosis in male rats




```
 ======================================================================
         Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
         Input Data File: F:\BMDS\DATA\EDB\MALERATORAL\PMULT.(d)
         Gnuplot Plotting File:  F:\BMDS\DATA\EDB\MALERATORAL\PMULT.plt
                                                Thu Feb 12 09:44:29 2004
 ======================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

Observation # < parameter # for Multistage model.
   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4-beta5*dose^5-beta6*dose^6)]

   The parameter betas are restricted to be positive


   Dependent variable = Peliosis
   Independent variable = Dose

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 7
 Total number of specified parameters = 0
 Degree of polynomial = 6

 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
                     Background =           0
```

```
                        Beta(1) =           0
                        Beta(2) =           0
                        Beta(3) =           0
                        Beta(4) =           0
                        Beta(5) =           0
                        Beta(6) =           0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(1)    -Beta(2)    -Beta(3)
-Beta(4)    -Beta(5)  have been estimated at a boundary point, or have been specified by the
user,  and do not appear in the correlation matrix )

                       Beta(6)

   Beta(6)             1


                           Parameter Estimates

       Variable           Estimate             Std. Err.
     Background                  0                NA
        Beta(1)                  0                NA
        Beta(2)                  0                NA
        Beta(3)                  0                NA
        Beta(4)                  0                NA
        Beta(5)                  0                NA
        Beta(6)       9.19938e-011       3.90849e-011

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

                         Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model         -39.3882
   Fitted model         -39.3918    0.00729548      2          0.9964
  Reduced model         -45.6631       12.5499      2        0.001883

           AIC:          80.7837


                      Goodness  of  Fit

     Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
  ------------------------------------------------------------------------
i: 1
    0.0000     0.0000         0.000         0          20       0.000
i: 2
   38.0000     0.2419        10.161        10          42      -0.021
i: 3
   41.0000     0.3540         8.850         9          25       0.026

 Chi-square =       0.01     DF = 2        P-value = 0.9964


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        32.3459

            BMDL =        9.12312
```

Output B-2. Testicular atrophy in male rats




```
=================================================================
          Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
          Input Data File: F:\BMDS\DATA\EDB\MALERATORAL\TDMULT.(d)
          Gnuplot Plotting File:  F:\BMDS\DATA\EDB\MALERATORAL\TDMULT.plt
                                                Thu Feb 12 09:32:35 2004
 =================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

Observation # < parameter # for Multistage model.
   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4-beta5*dose^5-beta6*dose^6-beta7*dose^7)]

   The parameter betas are restricted to be positive


   Dependent variable = TD
   Independent variable = Dose

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 8
 Total number of specified parameters = 0
 Degree of polynomial = 7


 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
                     Background = 2.04281e-014
                        Beta(1) =            0
                        Beta(2) =            0
                        Beta(3) =            0
                        Beta(4) =            0
                        Beta(5) =            0
                        Beta(6) =            0
                        Beta(7) =            0
**** WARNING:  Completion code = -4.  Optimum not found. Trying new starting pont****

**** WARNING 0:  Completion code = -4 trying new start****

**** WARNING 1:  Completion code = -4 trying new start****

**** WARNING 2:  Completion code = -4 trying new start****

**** WARNING 3:  Completion code = -4 trying new start****

**** WARNING 4:  Completion code = -4 trying new start****

**** WARNING 5:  Completion code = -4 trying new start****

**** WARNING 6:  Completion code = -4 trying new start****

**** WARNING 7:  Completion code = -4 trying new start****

**** WARNING 8:  Completion code = -4 trying new start****

**** WARNING 9:  Completion code = -4 trying new start****


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(1)    -Beta(2)    -Beta(3)
-Beta(4)    -Beta(5)    -Beta(6)
                have been estimated at a boundary point, or have been specified by the user,
                and do not appear in the correlation matrix )

                Beta(7)

   Beta(7)            1


                          Parameter Estimates

       Variable           Estimate             Std. Err.
     Background                  0                    NA
        Beta(1)                  0                    NA
        Beta(2)                  0                    NA
        Beta(3)                  0                    NA
        Beta(4)                  0                    NA
        Beta(5)                  0                    NA
        Beta(6)                  0                    NA
        Beta(7)        3.50648e-012         9.6754e-013

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


                       Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model         -52.0865
   Fitted model         -52.0908    0.00849527      2          0.9958
 Reduced model         -62.2989       20.4248      2         <.0001

           AIC:          106.182
```

Goodness of Fit

	Dose	Est._Prob.	Expected	Observed	Size	Chi^2 Res.
i: 1						
	0.0000	0.0000	0.000	0	20	0.000
i: 2						
	38.0000	0.3305	14.211	14	43	-0.022
i: 3						
	41.0000	0.4949	17.815	18	36	0.021

Chi-square = 0.01 DF = 2 P-value = 0.9958

Benchmark Dose Computation

Specified effect = 0.1

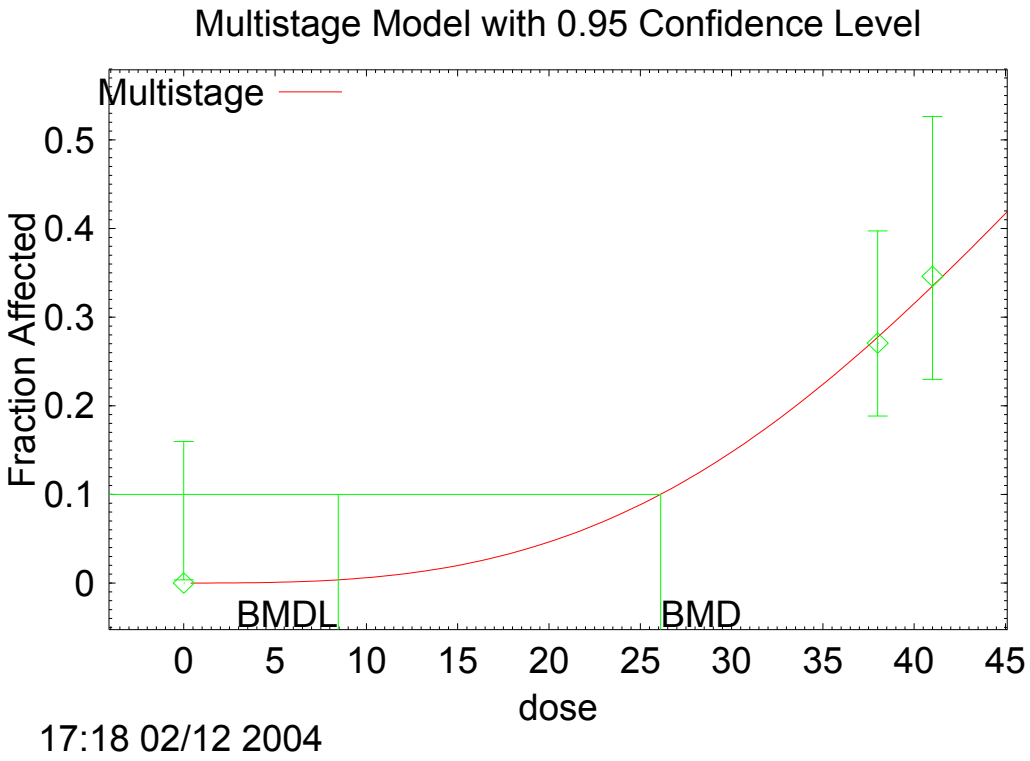
Risk Type = Extra risk

Confidence level = 0.95

BMD = 31.3928

BMDL = 6.77996

Output B-3. Adrenal cortical degeneration in male rats




```
 ======================================================================
         Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
         Input Data File: F:\BMDS\DATA\EDB\MALERATORAL\TDMULT.(d)
         Gnuplot Plotting File:  F:\BMDS\DATA\EDB\MALERATORAL\TDMULT.plt
                                                Thu Feb 12 09:08:13 2004
 ======================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

Observation # < parameter # for Multistage model.
   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive


   Dependent variable = ACD
   Independent variable = Dose

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 4
 Total number of specified parameters = 0

 Degree of polynomial = 3


 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
                    Background =           0
                       Beta(1) =           0
                       Beta(2) =           0
                       Beta(3) = 6.04978e-006


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -Background    -Beta(1)    -Beta(2)
                have been estimated at a boundary point, or have been specified by the user,
                and do not appear in the correlation matrix )

               Beta(3)

   Beta(3)           1



                        Parameter Estimates

       Variable           Estimate             Std. Err.
     Background                  0                   NA
        Beta(1)                  0                   NA
        Beta(2)                  0                   NA
        Beta(3)        5.91603e-006        2.31258e-006

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


                       Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model         -44.807
   Fitted model        -44.8193     0.0246029      2          0.9878
  Reduced model        -51.1468       12.6797      2        0.001765

          AIC:          91.6386


                     Goodness  of  Fit

     Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
  ------------------------------------------------------------------------
i: 1
    0.0000     0.0000         0.000         0          20       0.000
i: 2
   38.0000     0.2772        13.306        13          48      -0.032
i: 3
   41.0000     0.3348         8.706         9          26       0.051

 Chi-square =       0.02     DF = 2        P-value = 0.9878


   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =        26.1145

            BMDL =        8.46243
```

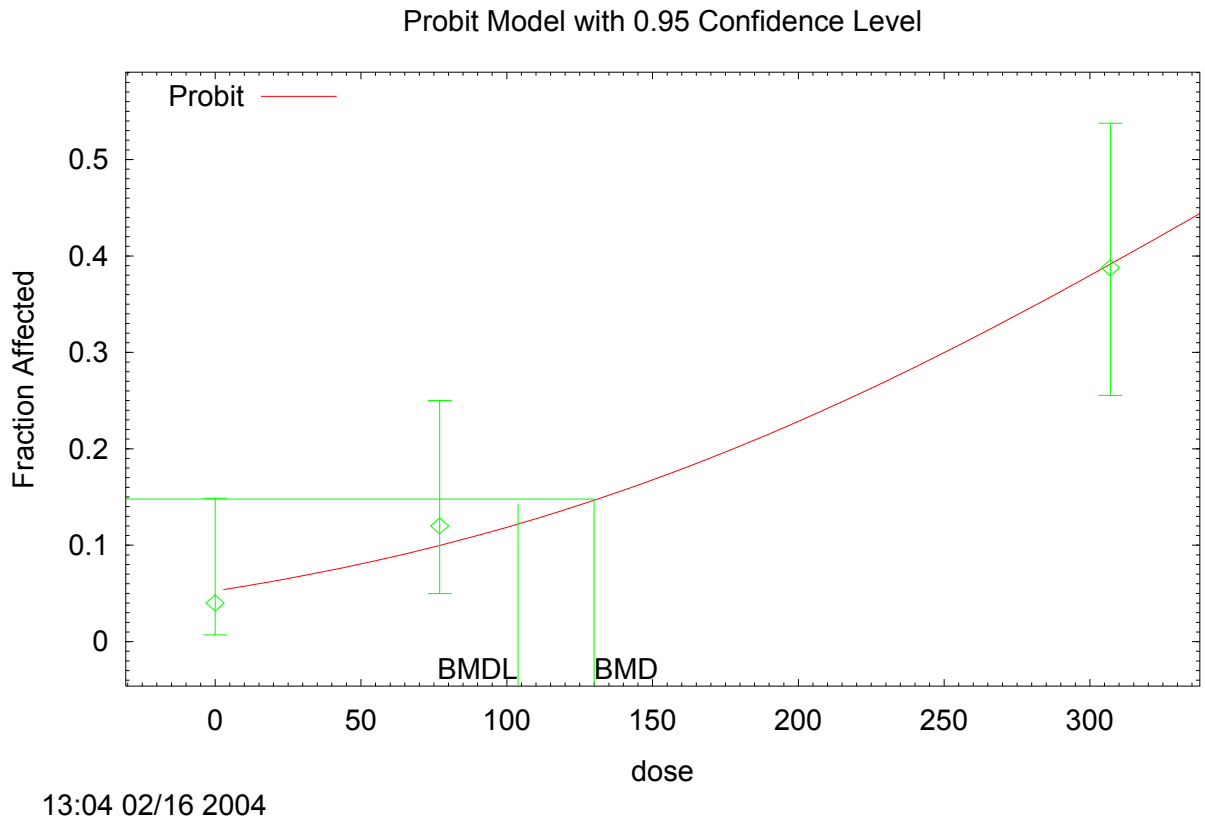
Table B-2. BMDS analysis of NTP (1982) study in support of RfC development

Model	Male rats (see pp. B-2 to B-9)[a]		Female rats (see pp. B-10 to B-17)[a]			Female mice (see pp. B-18 to B-25)[a]	
	Hepatic necrosis (mg/m^3)	Testicular degeneration (mg/m^3)	Hepatic necrosis (mg/m^3)	Adrenal cortical degeneration (mg/m^3)	Retinal atrophy (mg/m^3)	Splenic hematopoiesis (mg/m^3)	Nasal inflammation (mg/m^3)
Multistage **Degree**	2	1	1	1	1	2	1
AIC	125.893	130.016	100.267	127.524	105.441	109.213	97.8497
p-value	Undefined	0.1750	0.3801	0.8796	0.0026	0.3972	0.7308
BMD_{10}/BMD_{05}	91.71/46.99	64.98/31.64	127.3/46.99	133.7/65.07	Ind	69.61/33.89	69.07/33.63
$BMDL_{10}/BMDL_{05}$	53.26/25.93	46.00/22.4	80.38/25.93	76.83/37.40	Ind	50.53/24.60	50.11/24.40
Weibull **AIC**	125.893	130.016	101.438	127.524	105.441	109.213	99.1781
p-value	Undefined	0.1750	Undefined	0.8796	0.0026	0.3972	1.0000
BMD_{10}/BMD_{05}	90.75/48.97	64.98/31.64	180.9/48.97	133.7/65.07	Ind	69.61/33.89	92.05/53.15
$BMDL_{10}/BMDL_{05}$	53.26/25.93	46.00/22.4	86.16/25.93	76.83/37.40	Ind	50.53/24.60	52.20/25.41
Gamma **AIC**	125.893	130.016	101.438	127.524	107.847	109.213	99.1781
p-value	Undefined	0.1750	Undefined	0.8796	Undefined	0.3972	1.0000
BMD_{10}/BMD_{05}	90.51/49.38	64.98/31.64	176.8/49.38	133.7/65.07	Ind	69.61/33.89	91.60/53.87
$BMDL_{10}/BMDL_{05}$	53.26/25.93	46.00/22.4	86.16/25.93	76.83/37.40	Ind	50.53/24.60	52.20/25.41
Logistic **AIC**	124.454	134.001	99.4539	127.741	105.579	117.737	102.199
p-value	0.4584	0.0228	0.9009	0.6239	0.0029	0.0136	0.1525
BMD_{10}/BMD_{05}	142.0/85.93	Ind	187.7/85.93	180.2/102.8	Ind	Ind	161.5/109.5
$BMDL_{10}/BMDL_{05}$	114.0/66.07	Ind	148.8/66.07	130.6/73.98	Ind	Ind	129.6/80.51
LogLogist **AIC**	125.893	129.198	101.438	127.506	105.41	108.411	99.1781
p-value	Undefined	0.3300	Undefined	0.9452	0.0025	0.6274	1.0000
BMD_{10}/BMD_{05}	89.86/50.56	53.26/25.23	177.4/50.56	124.8/59.13	Ind	59.55/28.21	90.94/54.76
$BMDL_{10}/BMDL_{05}$	44.74/21.19	**35.07/16.61**	80.26/21.19	**66.50/31.50**	Ind	**40.25/19.06**	46.31/21.94
Probit **AIC**	124.302	133.606	99.4839	127.703	105.565	117.25	101.717
p-value	0.5248	0.0266	0.8311	0.6527	0.0028	0.0156	0.1871
BMD_{10}/BMD_{05}	131.8/77.79	Ind	177.4/77.79	173.3/96.77	Ind	Ind	148.2/98.3
$BMDL_{10}/BMDL_{05}$	**105.3/60.04**	Ind	138.2/60.04	122.9/68.47	Ind	Ind	118.8/72.45
LogProbit **AIC**	124.557	134.738	99.4453	128.174	107.847	117.94	97.7045
p-value	0.4091	0.0102	0.9336	0.4103	Undefined	0.0034	0.7543
BMD_{10}/BMD_{05}	120.4/83.76	Ind	172.4/83.76	196.3/136.5	Ind	Ind	102.2/71.06
$BMDL_{10}/BMDL_{05}$	87.37/60.75	Ind	**122.0/60.75**	126.9/88.22	Ind	Ind	**80.11/55.71**
First occurrence of effect (weeks)[b]	Low dose - 7 High dose - 53	Low dose - 7 High dose - 50	Low dose - 13 High dose - 67	Low dose - 13 High dose - 63	Low dose - 52 High dose - 63		
$BMDL_{10}/BMDL_{05}$	**105.3/60.04**	**35.07/16.61**	**122.0/60.75**	**66.50/31.50**	**NA**	**40.25/19.06**	**80.11/55.71**

[a] TheBMD/BMDL data in this table are rounded to four significant figures. The output file for the selected model (based on AIC and visual fit) is included in this Appendix. Benchmark doses were estimated for both 10% and 5% extra risk. An extra risk of 10% has generally been the default benchmark response (BMR) level for quantal data unless a study has "greater than usual sensitivity" (U.S. EPA, 2000). Ind = Indeterminate because p-value < 0.1.

[b] An adjustment to account for early mortality was considered but not applied. Few deaths occurred prior to the first occurrence of these effects in rats (see Appendix C). While first occurrence data were not available for female mice, mortality did not begin to increase in either exposure group until week 60, and there is no reason to believe that an irritant effect such as nasal inflammation would have a delayed onset beyond this time point.

Output B-4. Hepatic necrosis in male rats of NTP (1982)




```
 ========================================================================
         Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
         Input Data File: C:\BMDS\DATA\MTBE\CHUNFEMALES\UNSAVED1.(d)
         Gnuplot Plotting File:  C:\BMDS\DATA\MTBE\CHUNFEMALES\UNSAVED1.plt
                                                Mon Feb 16 13:05:37 2004
 ========================================================================

 Hepatic Necrosis in Male Rats of NTP (1982)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = CumNorm(Intercept+Slope*Dose),

   where CumNorm(.) is the cumulative normal distribution function


   Dependent variable = COLUMN3
   Independent variable = COLUMN1
   Slope parameter is not restricted

   Total number of observations = 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 (and Specified) Parameter Values
background = 0 Specified
intercept = -1.6355
slope = 0.0044451

Asymptotic Correlation Matrix of Parameter Estimates

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

	intercept	slope
intercept	1	-0.81
slope	-0.81	1

Parameter Estimates

Variable	Estimate	Std. Err.
intercept	-1.61217	0.219178
slope	0.00430755	0.000976355

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-59.9467			
Fitted model	-60.1512	0.409113	1	0.5224
Reduced model	-70.709	21.5247	2	<.0001

AIC: 124.302

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0535	2.673	2	50	-0.4232
77.0000	0.1002	5.009	6	50	0.4666
307.0000	0.3860	19.300	19	50	-0.08718

Chi-square = 0.40 DF = 1 P-value = 0.5248

Benchmark Dose Computation

Specified effect = 0.1

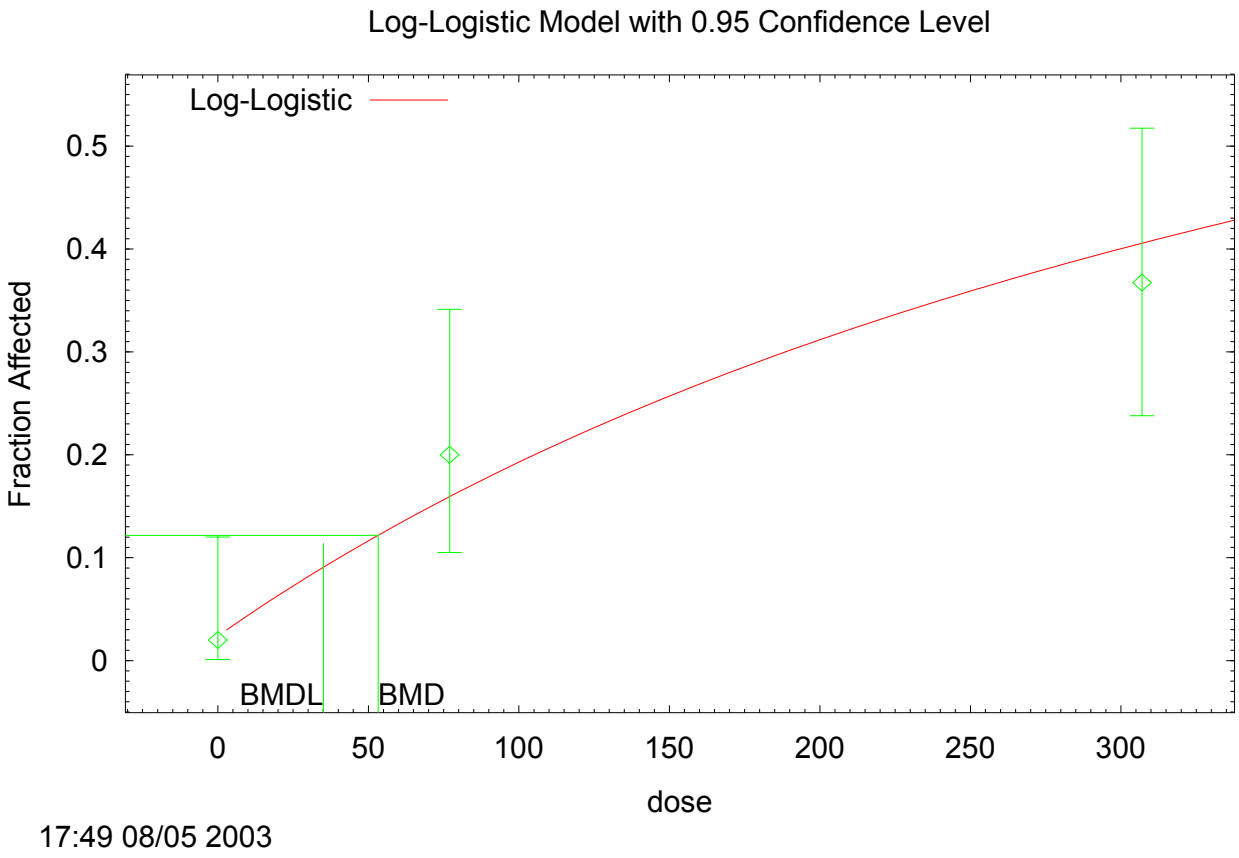
Risk Type = Extra risk

Confidence level = 0.95

BMD = 131.774

BMDL = 105.343

Output B-5. Testicular degeneration in male rats of NTP (1982)




```
 ===========================================================
         Logistic Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:20 $
         Input Data File: F:\BMDS\DATA\1,2-dibromoethane\INHALATION\1,2-
dibromoethane\MR_TD_LOGLOGISTIC.(d)
         Gnuplot Plotting File:  F:\BMDS\DATA\1,2-dibromoethane\INHALATION\1,2-
dibromoethane\MR_TD_LOGLOGISTIC.plt
                                                  Thu Jul 31 08:55:46 2003
 ===========================================================

 Testicular Degeneration in Male Rats of NTP (1982)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

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


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

   Total number of observations = 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
```

User has chosen the log transformed model

Default Initial Parameter Values
background = 0.02
intercept = -6.08038
slope = 1

Asymptotic Correlation Matrix of Parameter Estimates

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

	background	intercept
background	1	-0.39
intercept	-0.39	1

Parameter Estimates

Variable	Estimate	Std. Err.
background	0.023983	0.0231825
intercept	-6.17237	0.272892
slope	1	NA

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

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-62.141			
Fitted model	-62.5988	0.915693	1	0.3386
Reduced model	-73.4374	22.5929	2	<.0001

AIC: 129.198

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0240	1.199	1	50	-0.1841
77.0000	0.1591	7.954	10	50	0.7913
307.0000	0.4050	19.847	18	49	-0.5376

Chi-square = 0.95 DF = 1 P-value = 0.3300

Benchmark Dose Computation

Specified effect = 0.1

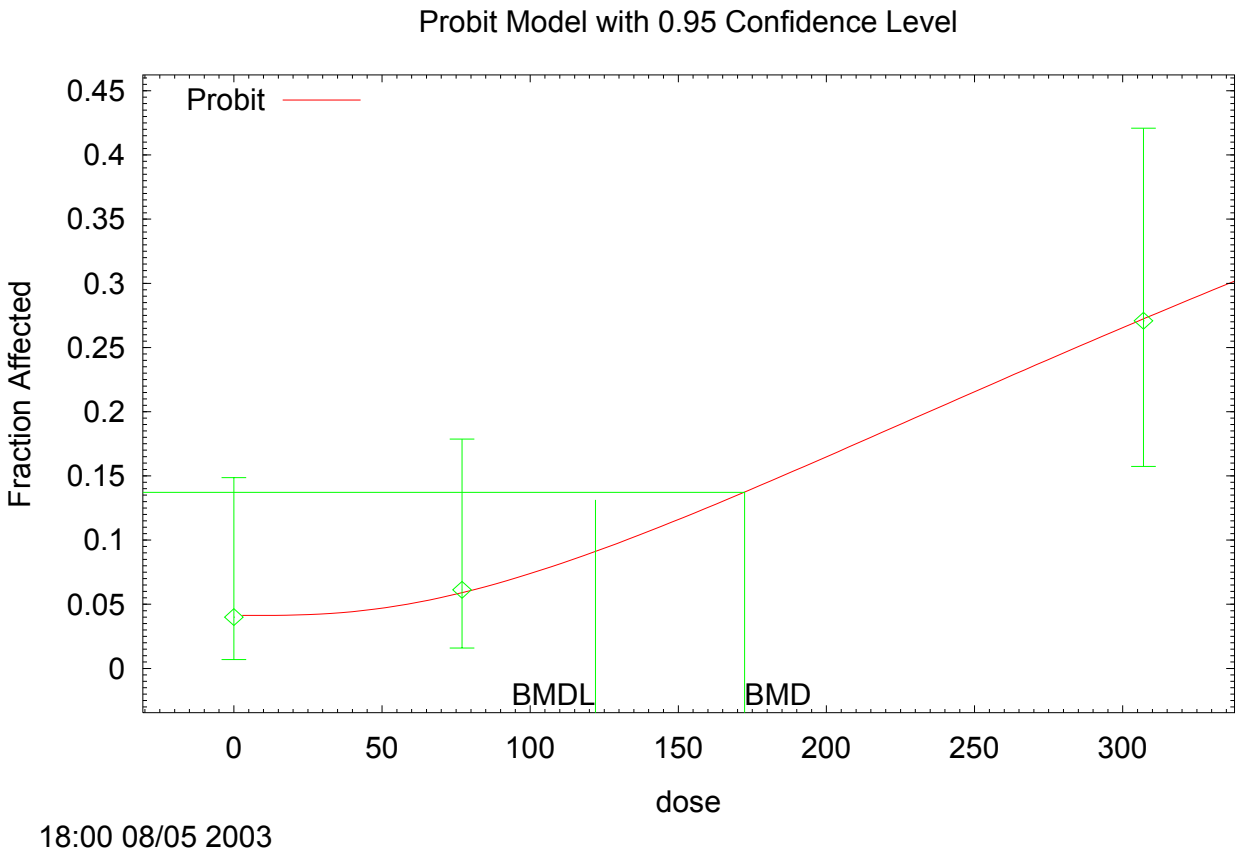
Risk Type = Extra risk

Confidence level = 0.95

BMD = 53.2579

BMDL = 35.0725

Output B-6. Hepatic necrosis in female rats of NTP (1982)




```
============================================================
          Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
          Input Data File: F:\BMDS\DATA\1,2-dibromoethane\INHALATION\1,2-
dibromoethane\FR_HN_LOGPROBIT.(d)
          Gnuplot Plotting File:  F:\BMDS\DATA\1,2-dibromoethane\INHALATION\1,2-
dibromoethane\FR_HN_LOGPROBIT.plt
                                    Thu Jul 31 10:39:58 2003
============================================================

 Heoatic Necrosis in Female Rats of NTP (1982)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = Background
               + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),

   where CumNorm(.) is the cumulative normal distribution function


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

   Total number of observations = 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
```

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
background = 0.04
intercept = -6.39367
slope = 1

Asymptotic Correlation Matrix of Parameter Estimates

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

	background	intercept
background	1	-0.41
intercept	-0.41	1

Parameter Estimates

Variable	Estimate	Std. Err.
background	0.0413485	0.0231704
intercept	-6.43122	0.228121
slope	1	NA

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

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-47.7192			
Fitted model	-47.7226	0.0069185	1	0.9337
Reduced model	-54.6511	13.8638	2	0.0009761

AIC: 99.4453

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0413	2.067	2	50	-0.04789
77.0000	0.0590	2.892	3	49	0.06572
307.0000	0.2720	13.056	13	48	-0.01819

Chi-square = 0.01 DF = 1 P-value = 0.9336

Benchmark Dose Computation

Specified effect = 0.1

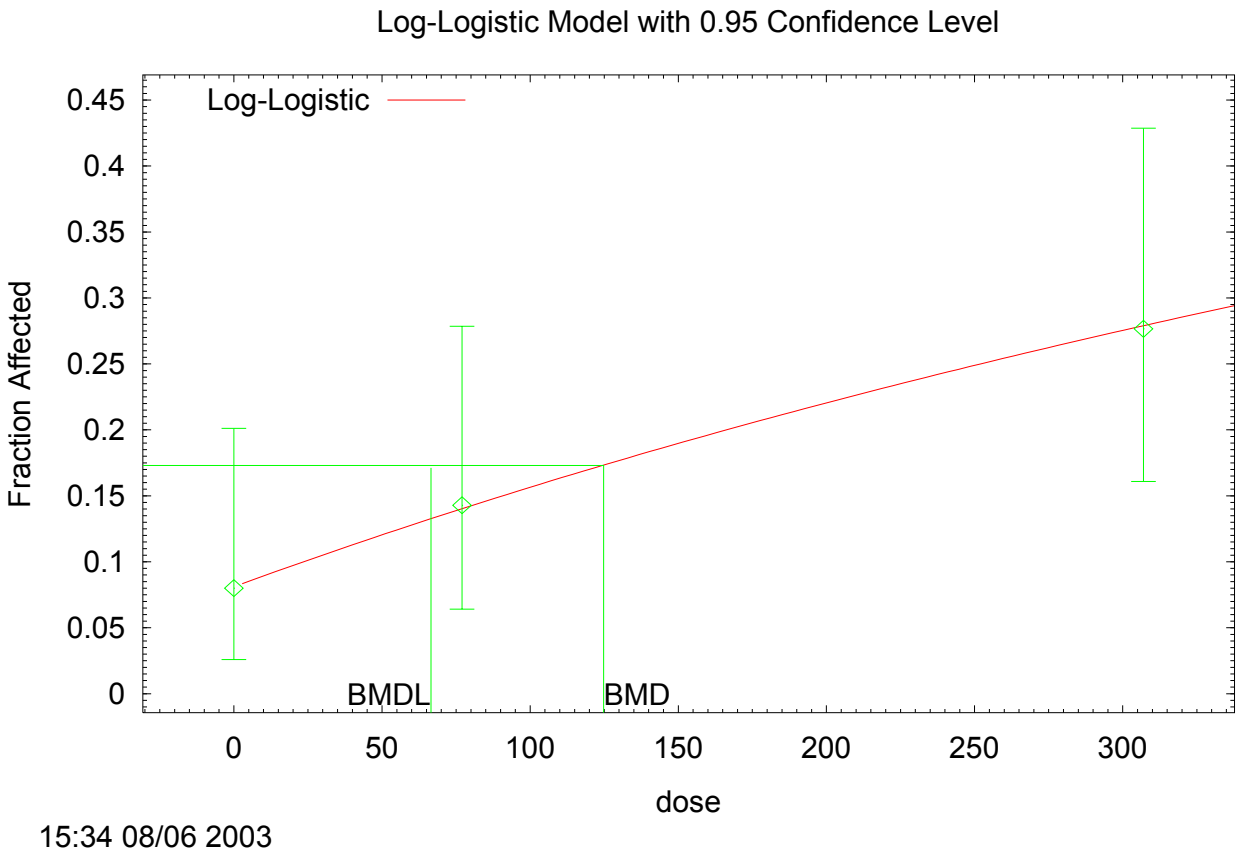
Risk Type = Extra risk

Confidence level = 0.95

BMD = 172.374

BMDL = 122.02

Output B-7. Adrenal cortical degeneration in female rats of NTP (1982)




```
============================================================
          Logistic Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:20 $
          Input Data File: F:\BMDS\DATA\1,2-dibromoethane\INHALATION\1,2-
dibromoethane\FR_ACD_LOGLOGISTIC.(d)
          Gnuplot Plotting File:  F:\BMDS\DATA\1,2-dibromoethane\INHALATION\1,2-
dibromoethane\FR_ACD_LOGLOGISTIC.plt
                                    Thu Jul 31 10:58:48 2003
============================================================

 Adrenal Cortical Degeneration in Female Rats of NTP (1982)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

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


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

   Total number of observations = 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



   User has chosen the log transformed model
```

Default Initial Parameter Values
background = 0.08
intercept = -6.99302
slope = 1

Asymptotic Correlation Matrix of Parameter Estimates

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

	background	intercept
background	1	-0.56
intercept	-0.56	1

Parameter Estimates

Variable	Estimate	Std. Err.
background	0.0811145	0.0352056
intercept	-7.02412	0.460426
slope	1	NA

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

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-61.7505			
Fitted model	-61.7529	0.00471493	1	0.9453
Reduced model	-65.2427	6.9844	2	0.03043

AIC: 127.506

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0811	4.056	4	50	-0.02887
77.0000	0.1401	6.863	7	49	0.05649
307.0000	0.2783	13.082	13	47	-0.02653

Chi-square = 0.00 DF = 1 P-value = 0.9452

Benchmark Dose Computation

Specified effect = 0.1

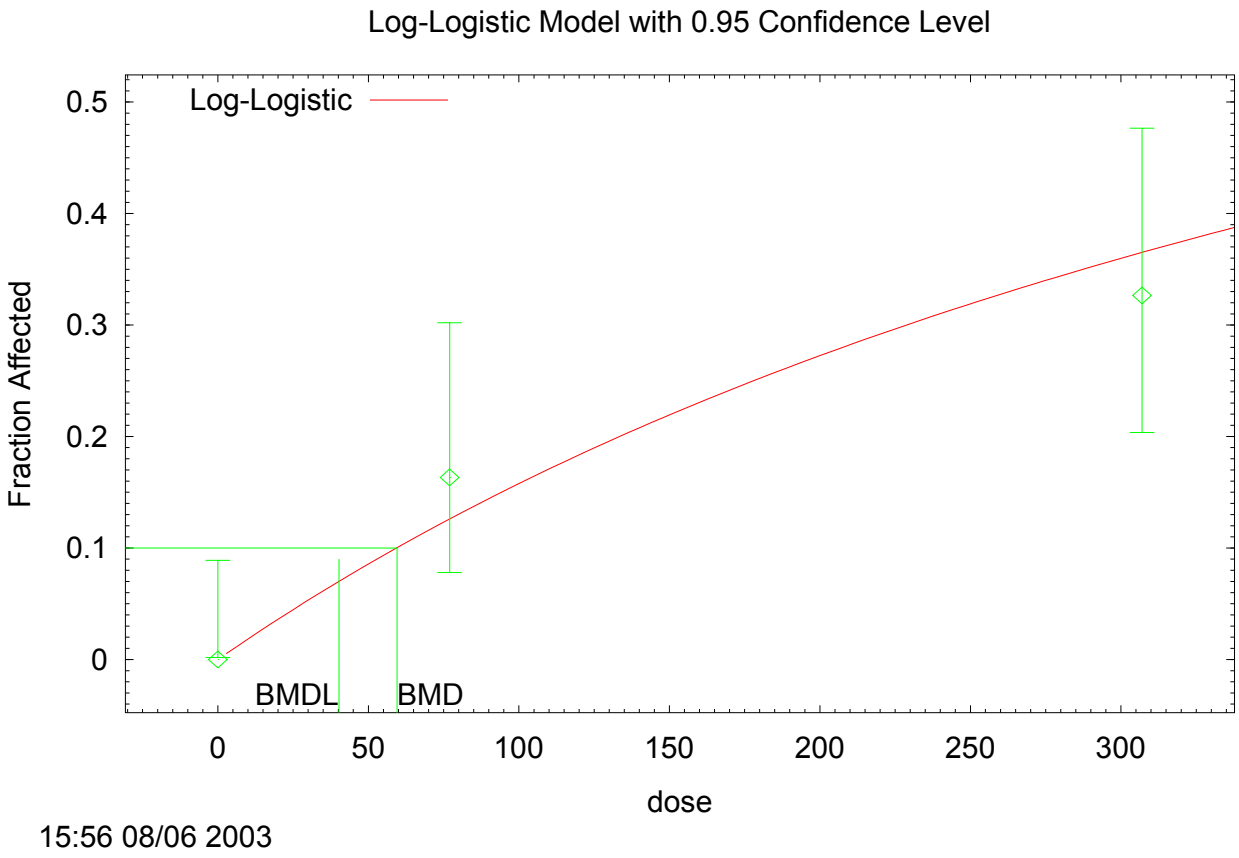
Risk Type = Extra risk

Confidence level = 0.95

BMD = 124.823

BMDL = 66.495

Output B-8. Splenic hematopoiesis in female mice of NTP (1982)




```
============================================================
         Logistic Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:20 $
         Input Data File: C:\BMDS\DATA\1,2-dibromoethane\FM_SH_LOGLOGIST.(d)
         Gnuplot Plotting File:  C:\BMDS\DATA\1,2-dibromoethane\FM_SH_LOGLOGIST.plt
                                                 Wed Jul 02 11:11:32 2003
============================================================

 Splenic Hematopoiesis in Female Mice of NTP (1982)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

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


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

   Total number of observations = 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


   User has chosen the log transformed model
```

Default Initial Parameter Values
background = 0
intercept = -6.2138
slope = 1

Asymptotic Correlation Matrix of Parameter Estimates

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

	intercept
intercept	1

Parameter Estimates

Variable	Estimate	Std. Err.
background	0	NA
intercept	-6.28411	0.244499
slope	1	NA

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

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-52.7602			
Fitted model	-53.2053	0.890189	2	0.6408
Reduced model	-65.5992	25.678	2	<.0001

AIC: 108.411

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	50	0
77.0000	0.1256	6.155	8	49	0.7952
307.0000	0.3642	17.845	16	49	-0.5477

Chi-square = 0.93 DF = 2 P-value = 0.6274

Benchmark Dose Computation

Specified effect = 0.1

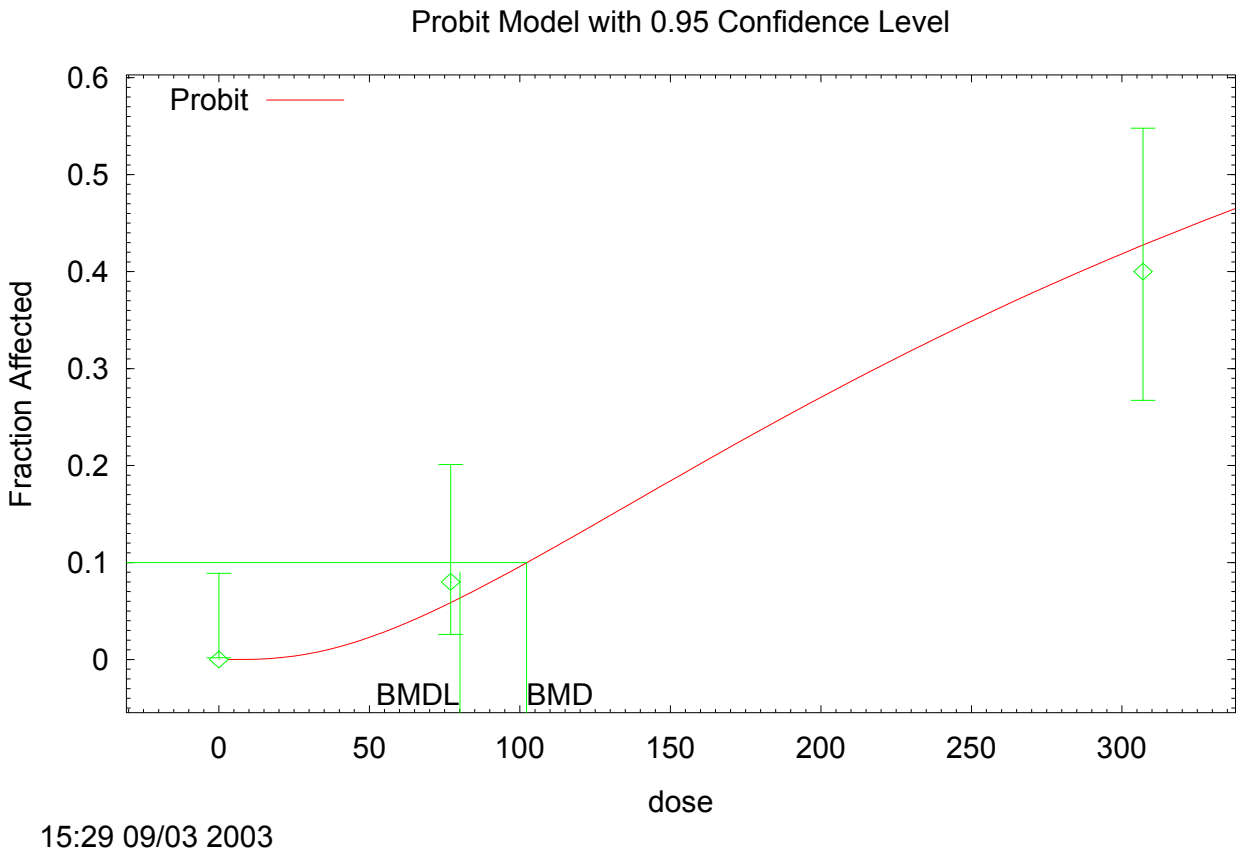
Risk Type = Extra risk

Confidence level = 0.95

BMD = 59.554

BMDL = 40.2456

Output B-9. Nasal inflammation in female mice of NTP (1982)




```
=====================================================================
         Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
         Input Data File: F:\BMDS\DATA\1,2-dibromoethane\INHALATION\1,2-
dibromoethane\FM_NI_LOGPROBIT.(d)
         Gnuplot Plotting File:  F:\BMDS\DATA\1,2-dibromoethane\INHALATION\1,2-
dibromoethane\FM_NI_LOGPROBIT.plt
                                                Fri Aug 29 14:46:40 2003
 =====================================================================

 Nasal Inflammation in Female Mice, LogProbit
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = Background
               + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),

   where CumNorm(.) is the cumulative normal distribution function


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

   Total number of observations = 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
```

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values

background =	0
intercept =	-5.86426
slope =	1

Asymptotic Correlation Matrix of Parameter Estimates

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

	intercept
intercept	1

Parameter Estimates

Variable	Estimate	Std. Err.
background	0	NA
intercept	-5.9084	0.149992
slope	1	NA

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

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-47.5891			
Fitted model	-47.8522	0.526361	2	0.7686
Reduced model	-65.9505	36.7229	2	<.0001

AIC: 97.7045

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	50	0
77.0000	0.0588	2.942	4	50	0.6359
307.0000	0.4280	21.398	20	50	-0.3997

Chi-square = 0.56 DF = 2 P-value = 0.7543

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 102.192

BMDL = 80.1088

APPENDIX C. Dose-Response Analyses of Cancer Endpoints

C-1. Analyses in support of slope factor for oral exposure

Table C-1. Number of animals with and without specified tumor types at time of death, male rats orally exposed to 1,2-dibromoethane

Group	Week of death	Forestomach tumors		Hemangiosarcomas		Thyroid follicular cell adenoma/carcinoma	
		Death with tumor	Death without tumor	Death with tumor	Death without tumor	Death with tumor	Death without tumor
Control	28	0	1	0	1	0	1
	29	0	1	0	1	0	1
	49	0	9	0	9	0	9
	63	0	9	0	9	0	9
Low-dose	31	1	0	1	0	0	1
	32	1	0	0	1	0	1
	34	2	0	2	0	0	2
	35	1	0	0	1	0	1
	36	1	0	0	1	0	1
	37	1	0	0	1	0	1
	38	1	0	1	0	0	1
	39	2	0	0	2	0	2
	40	1	0	0	1	0	1
	41	1	0	0	1	0	1
	42	1	0	0	1	0	1
	43	5	1	0	6	0	6
	44	3	0	0	3	1	2
	45	0	0	0	0	0	0
	46	2	0	0	2	0	2
	47	2	0	0	2	0	2
	48	5	0	1	4	0	5
	49	15	4	6	13	4	15
High-dose	9	0	1	0	1	0	1
	15	3	15	0	18	1	17
	24	1	0	0	1	0	1
	26	0	1	1	0	0	1
	30	1	0	0	1	0	1
	31	1	0	0	1	0	1
	34	1	0	0	1	0	1
	35	1	0	0	1	1	0
	36	1	0	0	1	0	1
	38	2	0	0	2	0	2
	39	2	0	0	2	0	2
	40	1	0	0	1	1	0
	41	4	0	0	4	0	4
	42	1	0	1	0	0	1
	44	3	0	0	3	1	2
	45	2	0	1	1	1	1
	47	1	0	0	1	0	1
	49	8	0	1	7	3	6

Source: NCI, 1978.

Table C-2. Number of animals with and without specified tumor types at time of death, female rats orally exposed to 1,2-dibromoethane

		Forestomach tumors		Hemangioarcoma		Hepatocellular carcinomas		Adrenocortical carcinomas	
Group	Week	Death with tumor	Death without tumor	Death with tumor	Death without tumor	Death with tumor	Death without tumor	Death with tumor	Death without tumor
Control	49	0	1	0	1	0	1	0	1
	63	0	19	0	19	0	19	0	19
Low-dose	1	0	5	0	5	0	5	0	5
	3	0	1	0	1	0	1	0	1
	4	0	1	0	1	0	1	0	1
	5	0	1	0	1	0	1	0	1
	11	0	1	0	1	0	1	0	1
	12	1	1	0	2	0	2	0	2
	24	1	0	0	1	0	1	0	1
	25	1	0	0	1	0	1	0	1
	28	1	0	0	1	0	1	0	1
	34	1	0	0	1	0	1	0	1
	35	1	0	0	1	0	1	0	1
	38	2	0	0	2	0	2	0	2
	39	1	0	0	1	0	1	0	1
	42	1	0	0	1	0	1	0	1
	43	1	0	0	1	0	1	0	1
	44	1	0	0	1	0	1	0	1
	45	2	0	0	2	0	2	0	2
	46	4	0	0	4	0	4	0	4
	48	2	0	0	2	0	2	0	2
	49	4	0	0	4	0	4	0	4
	50	2	0	0	2	0	2	0	2
	51	1	0	0	1	0	1	0	1
	52	2	0	0	2	0	2	0	2
	53	1	0	0	1	0	1	0	1
	54	2	0	0	2	0	2	0	2
	56	2	0	0	2	0	2	0	2
	57	2	0	0	2	0	2	0	2
	59	1	0	0	1	0	1	0	1
	60	1	0	0	1	0	1	0	1
	61	2	0	0	2	1	1	1	1
High-dose	1	0	2	0	2	0	2	0	2
	12	1	0	0	1	0	1	0	1
	14	0	1	0	1	0	1	0	1
	15	2	18	0	20	0	20	0	20
	33	1	0	0	1	1	0	0	1
	39	1	0	0	1	0	1	0	1
	40	1	0	0	1	0	1	0	1
	41	1	0	0	1	0	1	1	0
	42	2	0	1	1	0	2	0	2
	45	2	0	0	2	0	2	0	2
	47	1	0	0	1	0	1	0	1
	48	1	0	0	1	0	1	0	1
	50	1	0	0	1	0	1	0	1
	51	1	0	0	1	1	0	1	0
	53	4	0	0	4	1	3	0	4
	54	1	0	0	1	0	1	0	1
	55	1	0	0	1	0	1	0	1
	56	3	0	1	2	1	2	1	2
	58	3	0	0	3	0	3	0	3
	59	1	0	1	0	0	1	1	0
	61	1	0	0	1	1	0	0	1

Source: NCI, 1978.

Table C-3. Number of animals with and without specified tumor types at time of death, male mice orally exposed to 1,2-dibromoethane

		Forestomach tumors		Lung adenomas	
Group	Week	Death with tumor	Death without tumor	Death with tumor	Death without tumor
Control	11	0	1	0	1
	36	0	1	0	1
	59	0	18	0	18
Low-dose	12	0	1	0	1
	19	0	1	0	1
	21	0	1	0	1
	24	1	0	0	1
	26	0	1	0	1
	29	1	0	0	1
	33	1	0	0	1
	36	2	0	0	2
	40	1	0	0	1
	42	2	0	0	2
	43	2	1	0	3
	45	2	0	0	2
	46	2	0	0	2
	48	1	0	0	1
	49	1	0	0	1
	50	2	0	0	2
	52	3	0	0	3
	53	2	0	0	2
	54	1	0	0	1
	56	1	0	0	1
	58	2	0	1	1
	59	1	0	0	1
	60	1	0	0	1
	64	3	0	0	3
	65	1	0	0	1
	66	2	0	1	1
	68	1	0	1	0
	69	2	0	0	2
	72	3	0	0	3
	73	1	0	0	1
	74	1	0	1	0
	78	2	0	0	2

Table C-3. Number of animals with and without specified tumor types at time of death, male mice orally exposed to 1,2-dibromoethane (continued)

		Forestomach tumors		Lung adenomas	
Group	Week	Death with tumor	Death without tumor	Death with tumor	Death without tumor
High-dose	12	0	4	0	4
	13	0	4	0	4
	14	0	1	0	1
	21	0	1	0	1
	26	1	2	1	2
	27	0	1	0	1
	32	1	0	0	1
	34	0	1	0	1
	38	0	1	0	1
	39	0	2	0	2
	41	1	0	1	0
	42	0	1	0	1
	43	1	0	1	0
	44	2	0	0	2
	45	2	0	1	1
	46	1	0	0	1
	47	1	0	0	1
	48	2	0	0	2
	49	2	0	0	2
	52	3	0	2	1
	53	2	0	0	2
	54	1	0	0	1
	55	1	0	0	1
	57	1	0	0	1
	59	2	1	1	2
	60	1	0	1	0
	61	1	0	0	1
	65	1	0	0	1
	66	1	0	1	0
	68	1	0	0	1
	74	1	0	0	1
	77	1	0	1	0

Source: NCI, 1978.

Table C-4. Number of animals with and without specified tumor types at time of death, female mice orally exposed to 1,2-dibromoethane

		Forestomach tumors		Lung adenomas	
Group	Week	Death with tumor	Death without tumor	Death with tumor	Death without tumor
Control	15	0	1	0	1
	51	0	1	0	1
	59	0	9	0	9
	60	0	9	0	9
Low-dose	18	0	1	0	1
	40	2	0	0	2
	43	1	0	0	1
	50	1	0	1	0
	52	1	0	0	1
	54	1	0	0	1
	55	2	0	0	2
	57	0	0	0	0
	58	1	0	1	0
	59	1	0	0	1
	61	1	0	0	1
	63	1	0	0	1
	65	2	0	0	2
	66	2	0	0	2
	67	1	0	0	1
	68	1	0	0	1
	69	1	0	0	1
	70	2	0	1	1
	73	2	0	0	2
	75	3	0	0	3
	76	3	0	0	3
	77	2	0	2	0
	78	1	0	1	0
	79	1	0	0	1
	82	2	0	1	1
	83	1	0	0	1
	85	2	0	0	2
	86	2	0	0	2
	90	7	0	3	4

Table C-4. Number of animals with and without specified tumor types at time of death, female mice orally exposed to 1,2-dibromoethane

		Forestomach tumors		Lung adenomas	
Group	Week	Death with tumor	Death without tumor	Death with tumor	Death without tumor
High-dose	12	0	9	0	9
	13	0	4	0	4
	27	0	1	0	1
	28	0	1	0	1
	34	1	0	0	1
	37	1	0	0	1
	39	1	0	0	1
	40	1	0	0	1
	41	0	1	0	1
	42	0	1	0	1
	43	1	0	0	1
	44	1	1	0	2
	49	0	1	1	0
	50	1	0	1	0
	51	1	0	0	1
	52	1	0	1	0
	53	2	1	0	3
	54	0	1	0	1
	55	2	0	0	2
	57	1	0	0	1
	58	1	0	0	1
	61	1	0	0	1
	62	1	0	0	1
	65	1	0	0	1
	66	1	0	0	1
	67	1	0	0	1
	69	1	0	0	1
	70	1	0	0	1
	71	1	0	0	1
	73	1	0	0	1
	76	2	0	0	2
	78	2	1	2	1

Source: NCI, 1978.

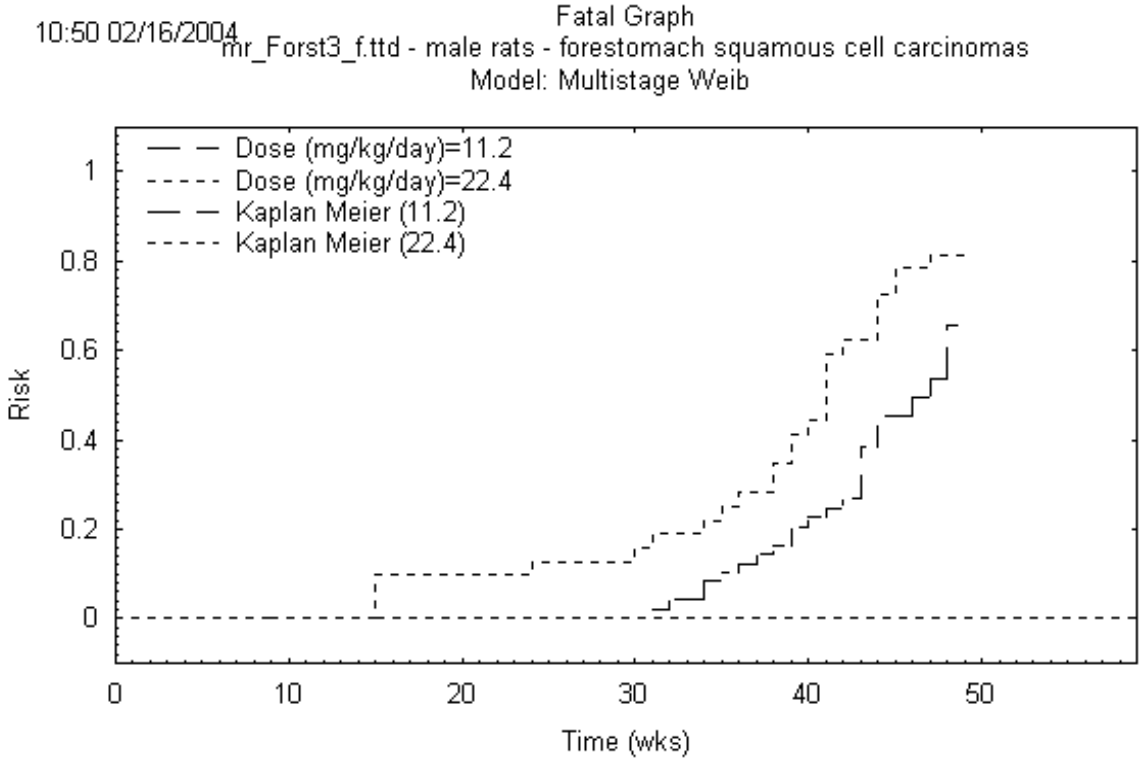


Figure C-1. Kaplan-Meier hazard curves for the incidence of forestomach squamous cell carcinomas in male rats in the oral gavage study (NCI, 1978).

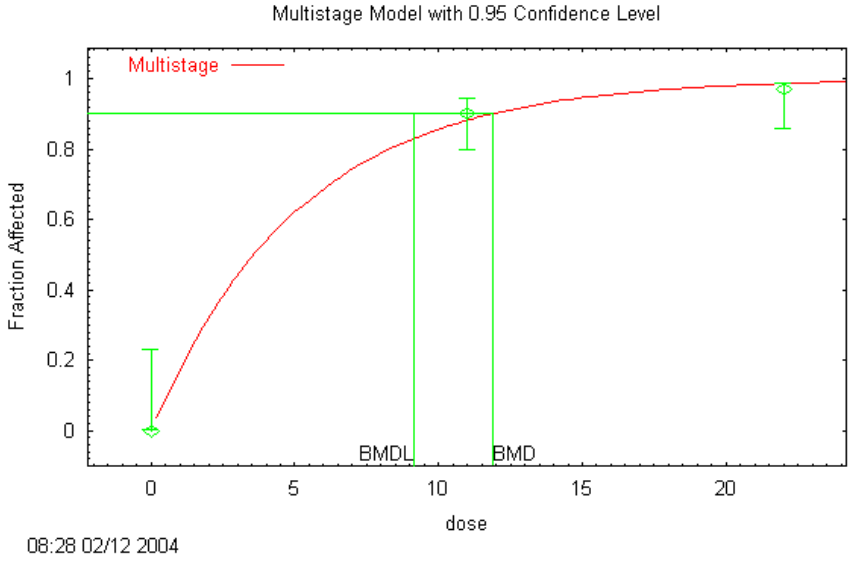
Output C-1. Multistage analysis of forestomach tumors in male rats, 1,2-dibromoethane oral gavage exposure

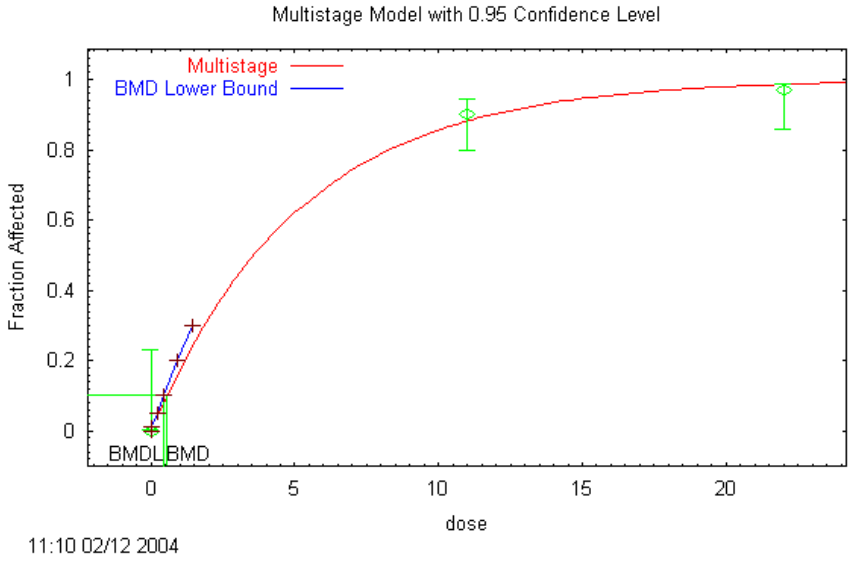
```
BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = fs_tumors
   Independent variable = hec_feb04

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 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
                    Background =     0.164564
                       Beta(1) =     0.160289
                       Beta(2) =            0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(2)
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)

   Beta(1)            1


                         Parameter Estimates

       Variable           Estimate             Std. Err.
     Background                  0                   NA
        Beta(1)           0.193784            0.0322577
        Beta(2)                  0                   NA

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


                       Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model         -20.7657
   Fitted model         -21.0724      0.613548      2          0.7358
  Reduced model         -47.9793       54.4274      2         <.0001

           AIC:          44.1449


                     Goodness  of  Fit

     Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
  ----------------------------------------------------------------------
i: 1
    0.0000     0.0000         0.000         0          13       0.000
i: 2
   11.0000     0.8814        44.068        45          50       0.178
i: 3
   22.0000     0.9859        33.521        33          34      -1.105
```

Chi-square = 0.74 DF = 2 P-value = 0.6899

Benchmark Dose Computation

Specified effect =	0.1	Specified effect =	0.9
Risk Type =	Extra risk	Risk Type =	Extra risk
Confidence level =	0.95	Confidence level =	0.95
BMD =	0.5437	BMD =	11.8822
BMDL =	0.418668	BMDL =	9.14972





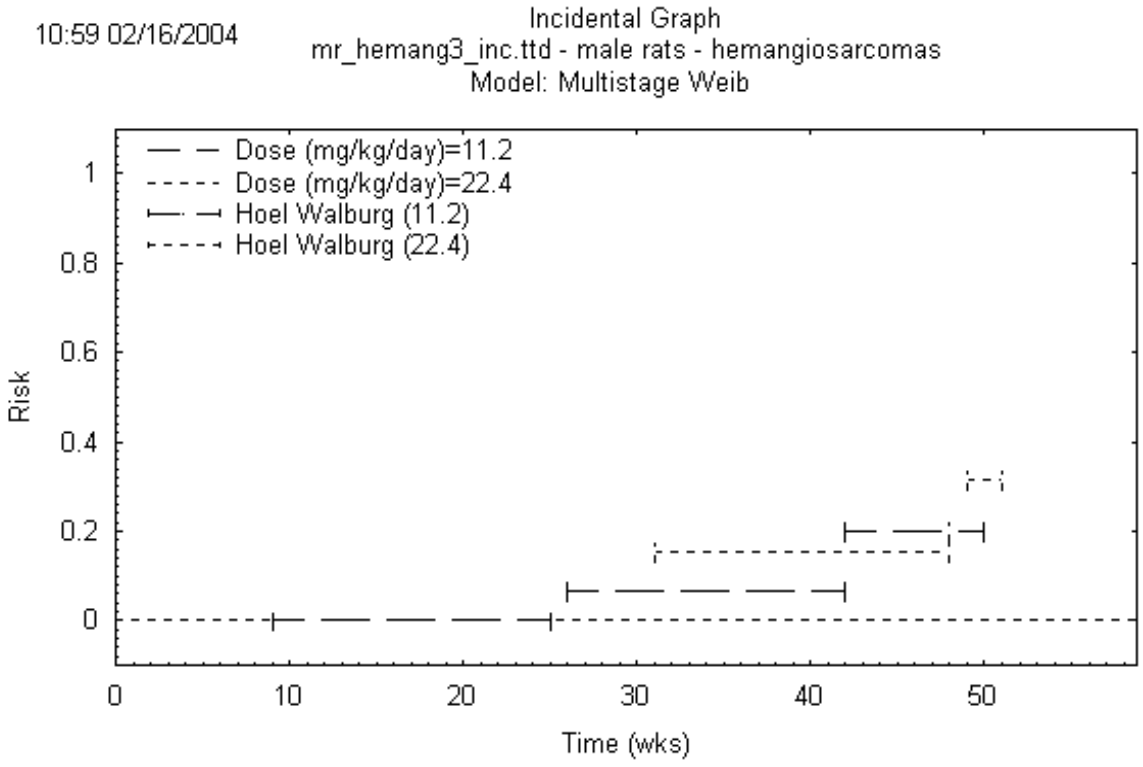


Figure C-2. Cumulative incidence curves for hemangiosarcomas in male rats in the oral gavage study (NCI, 1978.).

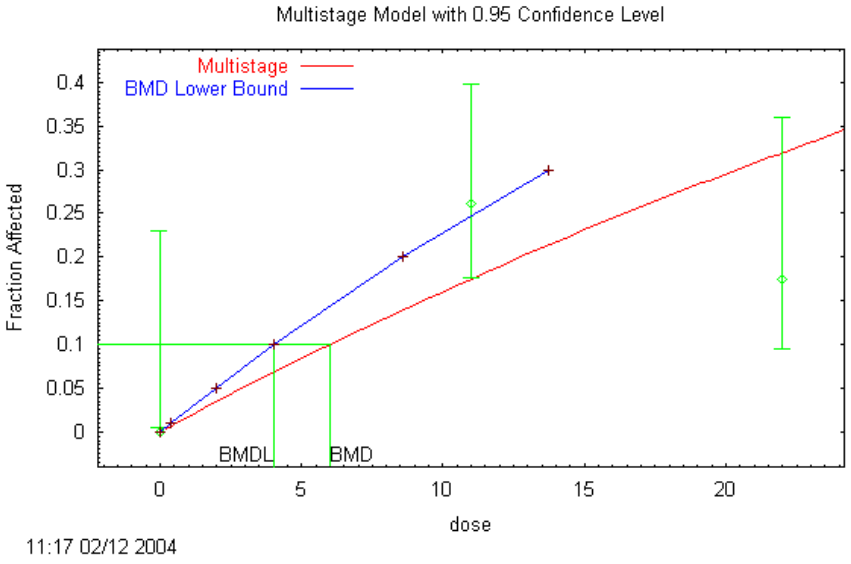
Output C-2. Multistage analysis of hemangiosarcomas in male rats, 1,2-dibromoethane oral gavage exposure

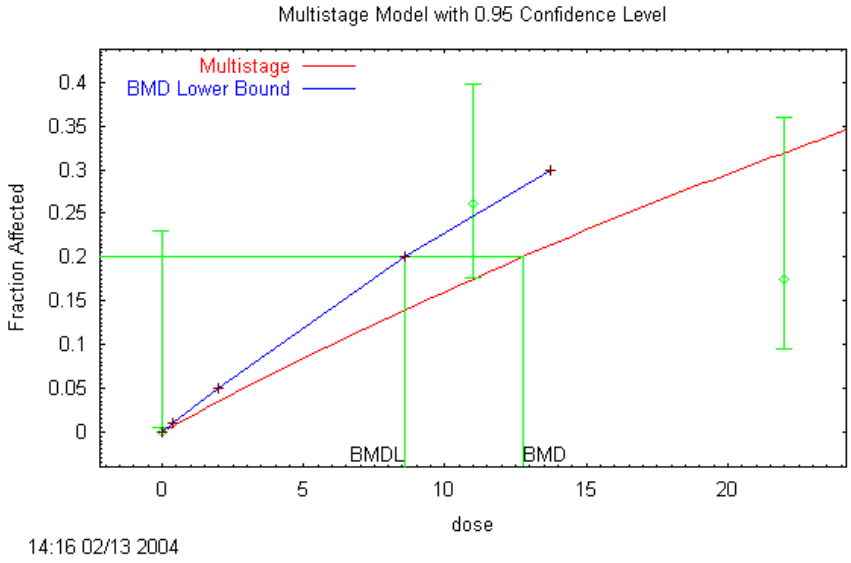
```
The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = hemang
   Independent variable = hec_feb04

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 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
                    Background =    0.0670325
                       Beta(1) =   0.00868433


           Asymptotic Correlation Matrix of Parameter Estimates

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

                Beta(1)

   Beta(1)            1



                         Parameter Estimates

       Variable           Estimate             Std. Err.
     Background                  0                    NA
        Beta(1)          0.0174672           0.00979878

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



                       Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model         -34.7785
   Fitted model         -37.0119        4.4667      2          0.1072
  Reduced model          -38.185       6.81305      2         0.03316

           AIC:          76.0237


                     Goodness  of  Fit

     Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
  ----------------------------------------------------------------------
i: 1
    0.0000     0.0000         0.000         0          13       0.000
i: 2
   11.0000     0.1748         7.342        11          42       0.604
i: 3
   22.0000     0.3191         7.338         4          23      -0.668
```

Chi-square = 4.44 DF = 2 P-value = 0.1087

Benchmark Dose Computation

Specified effect =	0.1	Specified effect =	0.2
Risk Type =	Extra risk	Risk Type =	Extra risk
Confidence level =	0.95	Confidence level =	0.95
BMD =	6.0319	BMD =	12.775
BMDL =	4.05142	BMDL =	8.58053





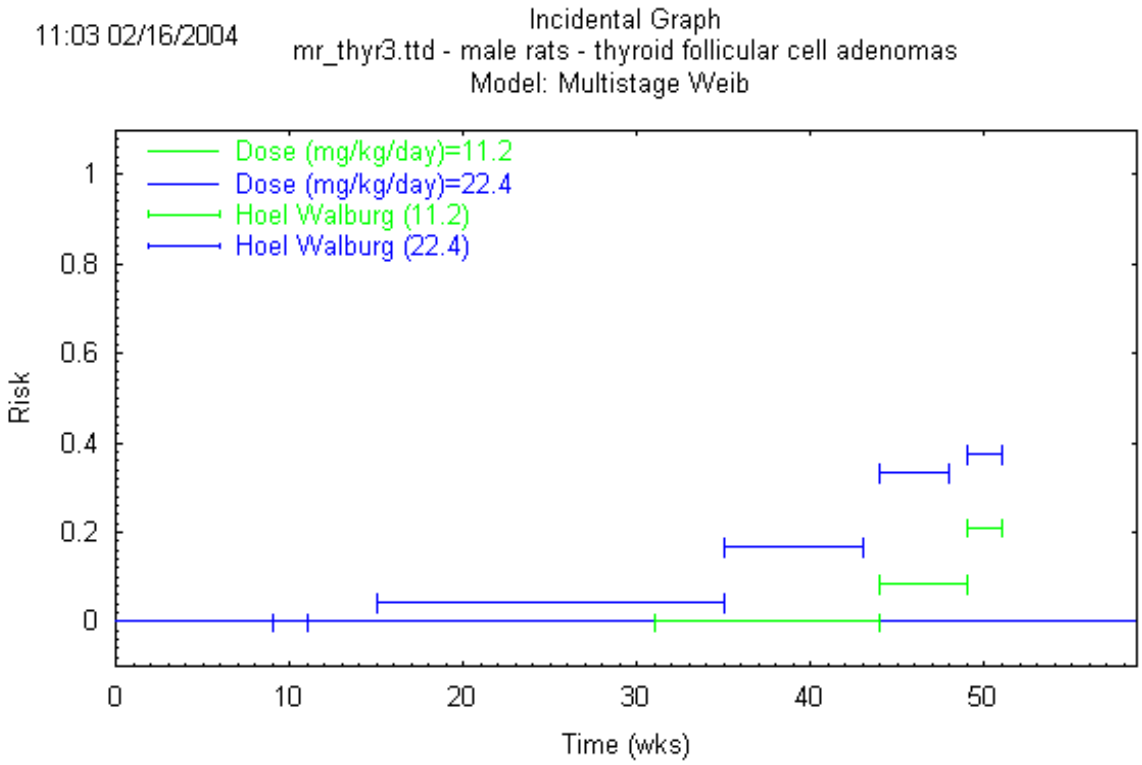


Figure C-3. Cumulative incidence curves for thyroid follicular cell adenomas or carcinomas in male rats in the oral gavage study (NCI, 1978).

Output C-3. Multistage analysis of thyroid follicular cell adenomas in male rats, 1,2-dibromoethane oral gavage exposure

```
BMDS MODEL RUN
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = tfca
   Independent variable = hec_feb04

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 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
                     Background =           0
                        Beta(1) =    0.0194293


           Asymptotic Correlation Matrix of Parameter Estimates

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

                Beta(1)

   Beta(1)            1


                          Parameter Estimates

       Variable           Estimate             Std. Err.
     Background                  0                   NA
        Beta(1)          0.0159794          0.00900218

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


                        Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model         -29.7955
   Fitted model         -30.1036      0.616179      2          0.7348
  Reduced model         -34.5849       9.57879      2        0.008317

           AIC:          62.2073


                     Goodness  of  Fit

     Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
  ----------------------------------------------------------------------
i: 1
    0.0000     0.0000         0.000         0          13       0.000
i: 2
   11.0000     0.1612         6.286         5          39      -0.244
```
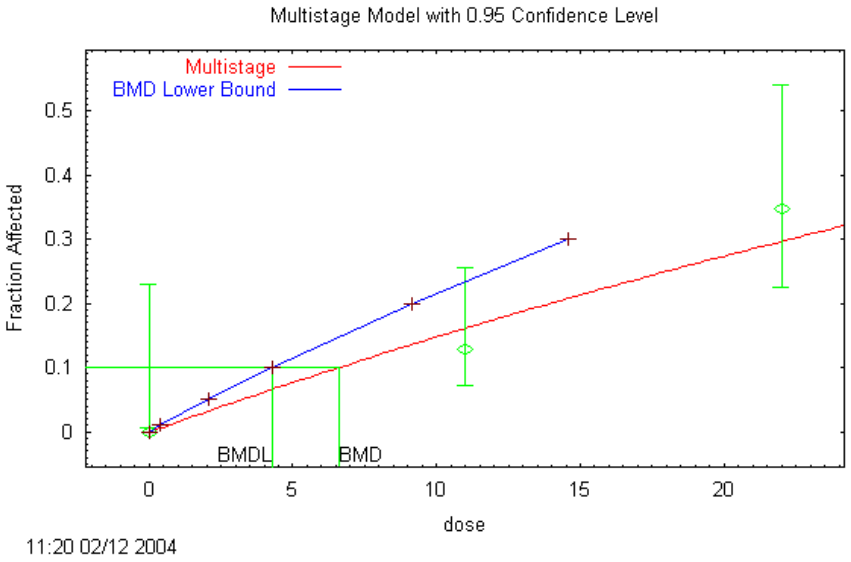
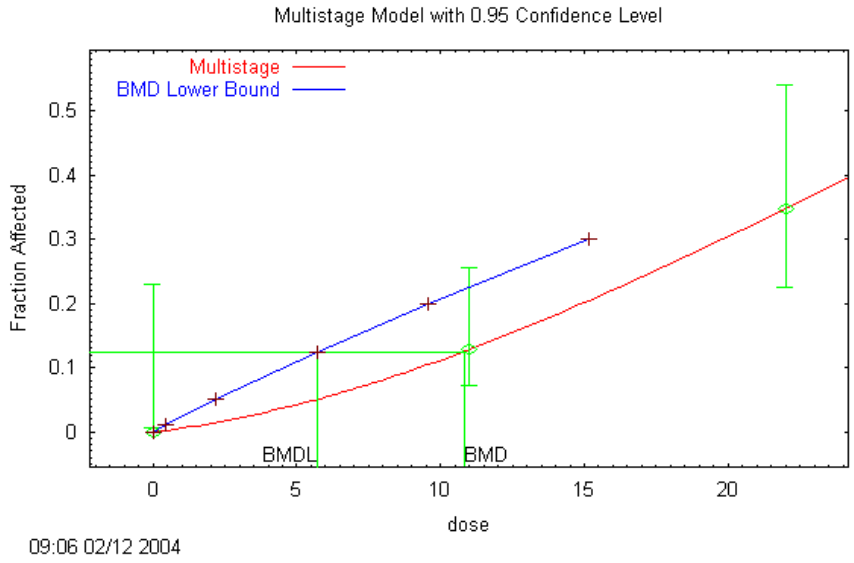

```
i: 3
   22.0000      0.2964          6.817          8           23        0.247

 Chi-square =        0.61      DF = 2         P-value = 0.7388

   Benchmark Dose Computation

 Specified effect =            0.1          Specified effect =          0.125
 Risk Type        =      Extra risk         Risk Type        =      Extra risk
 Confidence level =           0.95          Confidence level =           0.95
               BMD =        6.59354                        BMD =        10.8101
              BMDL =        4.30664                       BMDL =        5.72909
```





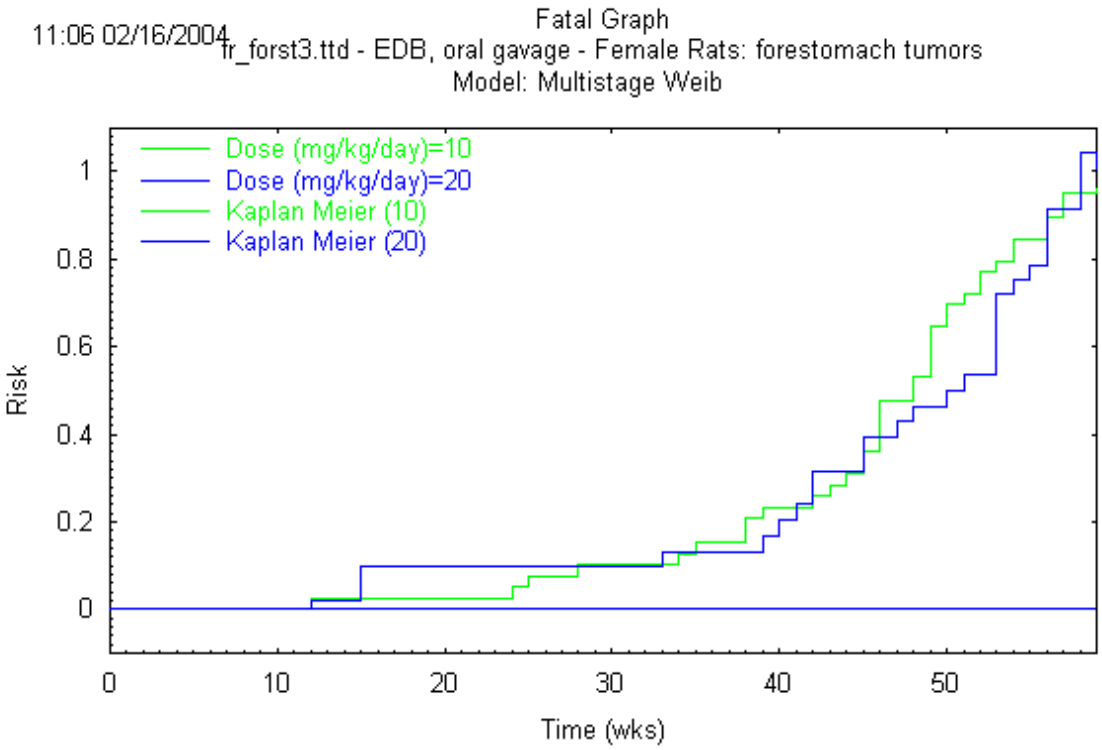


Figure C-4. Kaplan-Meier hazard curves for the incidence of forestomach squamous cell carcinomas in female rats in the oral gavage study (NCI, 1978).

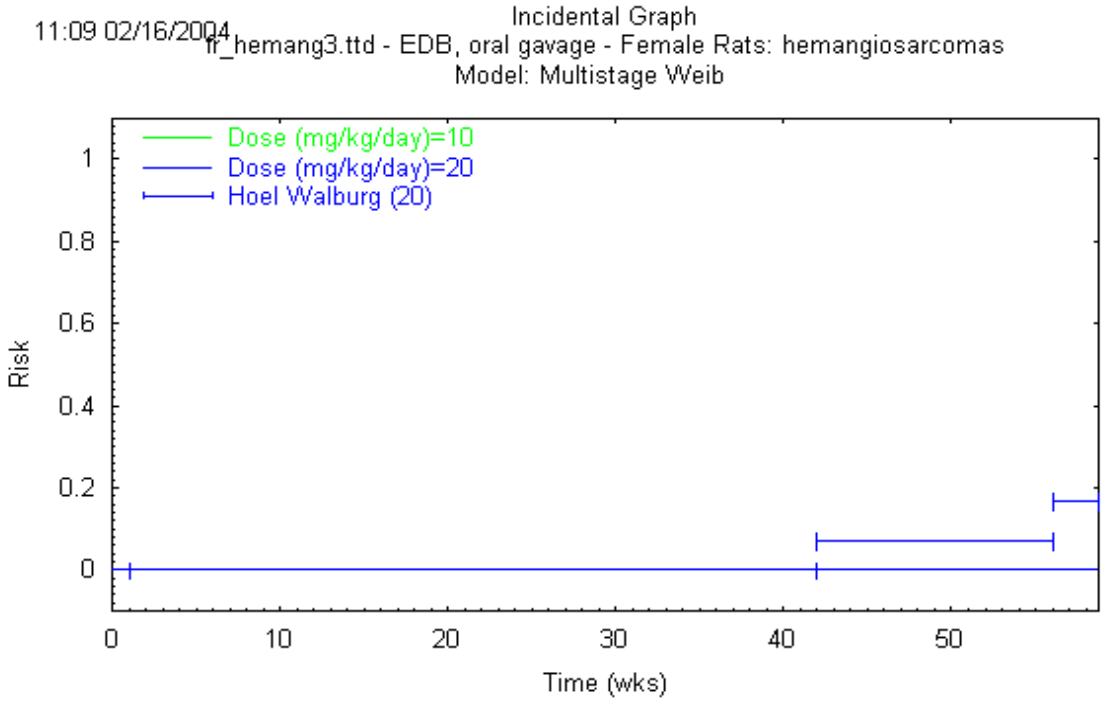


Figure C-5. Cumulative incidence curves for hemangiosarcomas in female rats in the oral gavage study (NCI, 1978).

Output C-4. Multistage analysis of hemangiosarcomas in female rats, 1,2-dibromoethane oral gavage exposure

```
BMDS MODEL RUN
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = hemang
   Independent variable = mg_kg_day

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 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
                     Background =           0
                        Beta(1) =   0.0097078

           Asymptotic Correlation Matrix of Parameter Estimates

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

                Beta(1)

   Beta(1)            1


                           Parameter Estimates

       Variable           Estimate             Std. Err.
     Background                  0                   NA
        Beta(1)         0.00588915            0.0102062

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


                         Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model         -7.92199
   Fitted model         -9.41847       2.99296      2          0.2239
  Reduced model         -11.6984        7.5528      2         0.02291

           AIC:          20.8369


                      Goodness  of  Fit

     Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
  ----------------------------------------------------------------------
i: 1
    0.0000     0.0000         0.000         0          19       0.000
i: 2
   10.0000     0.0572         1.144         0          20      -1.061
i: 3
```
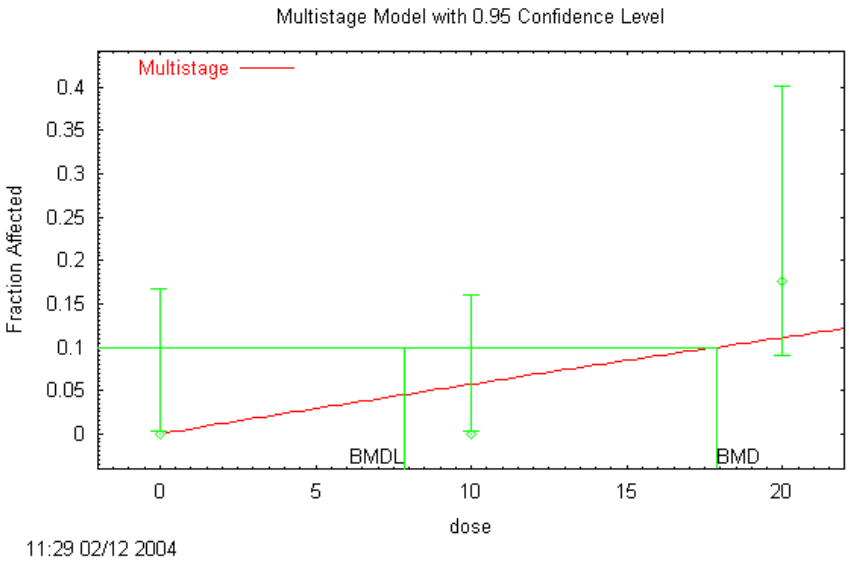

```
   20.0000      0.1111          1.889          3           17        0.662

 Chi-square =       1.95     DF = 2        P-value = 0.3775

   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        17.8906

            BMDL =        7.87117
```



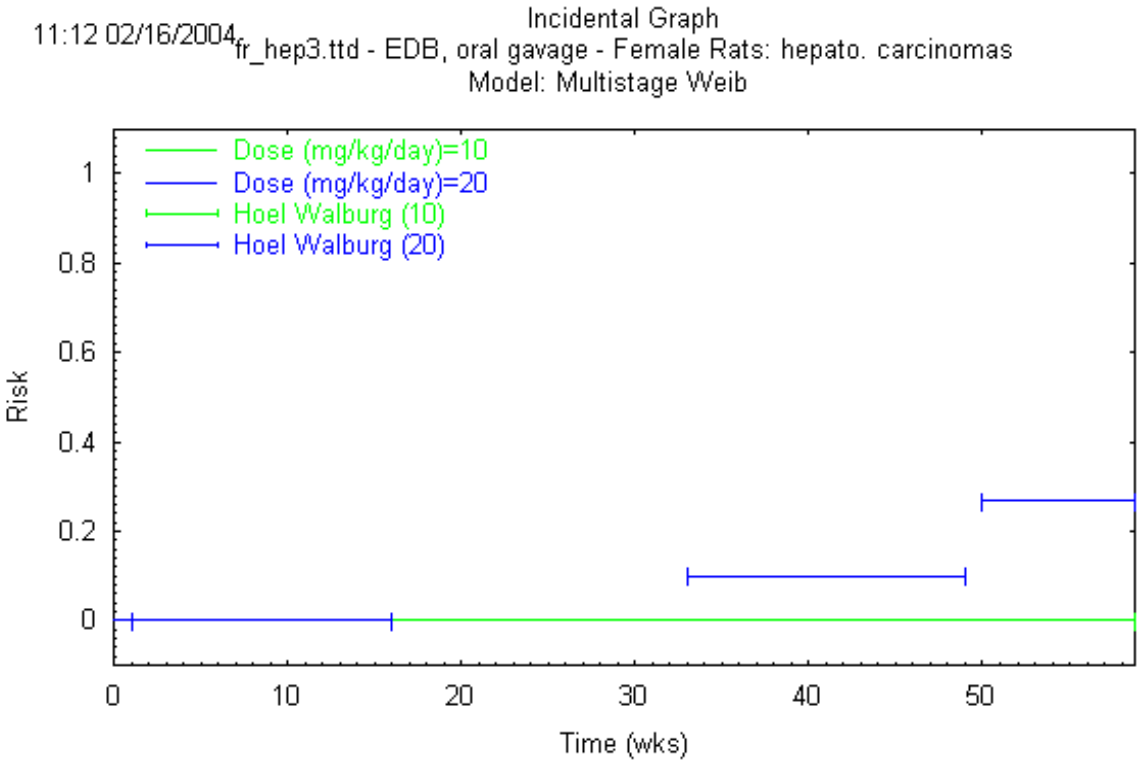


Figure C-6. Cumulative incidence curves for hepatocellular carcinomas and neoplastic nodules in female rats in the oral gavage study (NCI, 1978).

Output C-5. Multistage analysis of hepatocellular carcinomas in female rats, 1,2-dibromoethane oral gavage exposure

```
BMDS MODEL RUN
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = hepcarc
   Independent variable = mg_kg_day

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 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
                     Background =           0
                        Beta(1) =    0.0202733


           Asymptotic Correlation Matrix of Parameter Estimates

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

                Beta(1)

   Beta(1)            1


                         Parameter Estimates

       Variable           Estimate             Std. Err.
     Background                  0                   NA
        Beta(1)          0.0142265            0.0112183

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


                       Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model        -15.4276
   Fitted model        -16.5126        2.1701      2          0.3379
  Reduced model        -21.2314       11.6077      2        0.003016

           AIC:         35.0252


                     Goodness  of  Fit

     Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
  ----------------------------------------------------------------------
i: 1
    0.0000     0.0000         0.000         0          19       0.000
i: 2
   10.0000     0.1326         2.652         1          20      -0.718
```
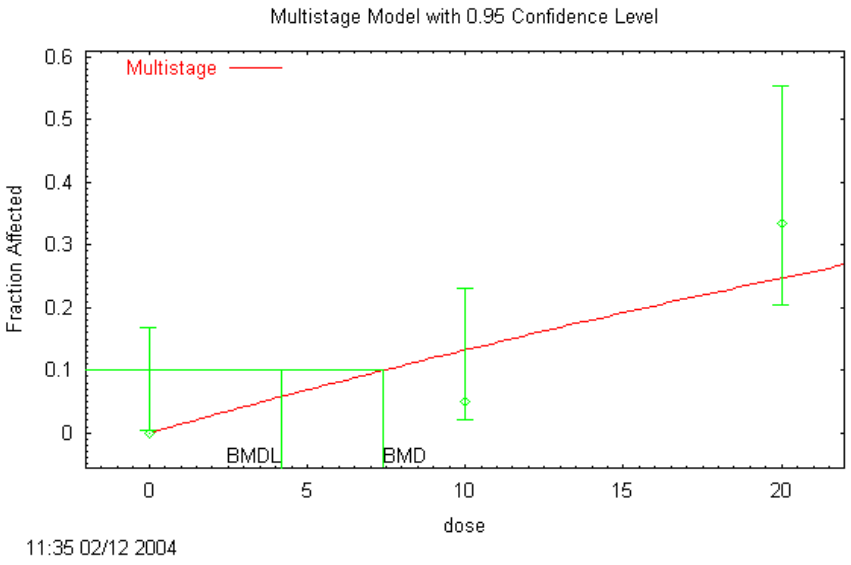
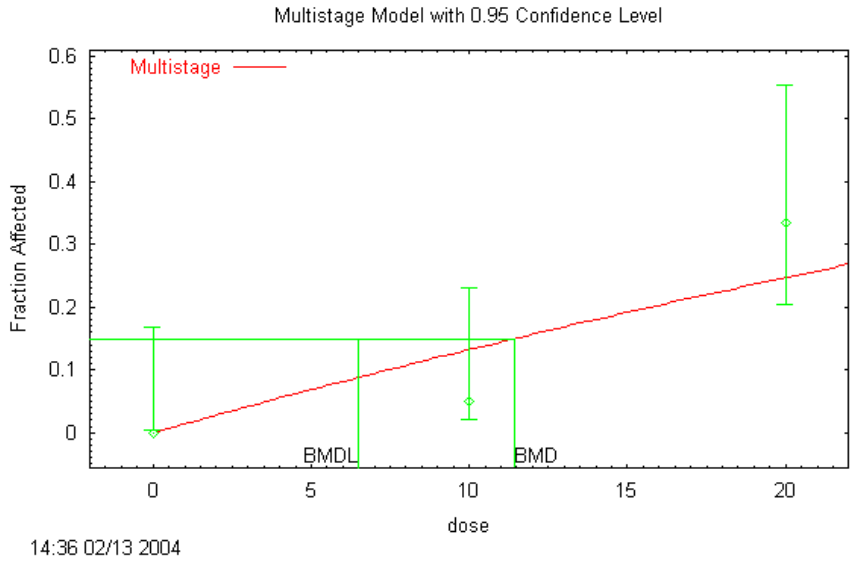

```
i: 3
   20.0000      0.2476          4.457          6           18        0.460

 Chi-square =        1.90      DF = 2        P-value = 0.3875

   Benchmark Dose Computation

 Specified effect =            0.1          Specified effect =           0.15

 Risk Type        =      Extra risk         Risk Type        =      Extra risk

 Confidence level =           0.95          Confidence level =           0.95

               BMD =        7.40594                       BMD =        11.4237

              BMDL =        4.20627                      BMDL =        6.48818
```





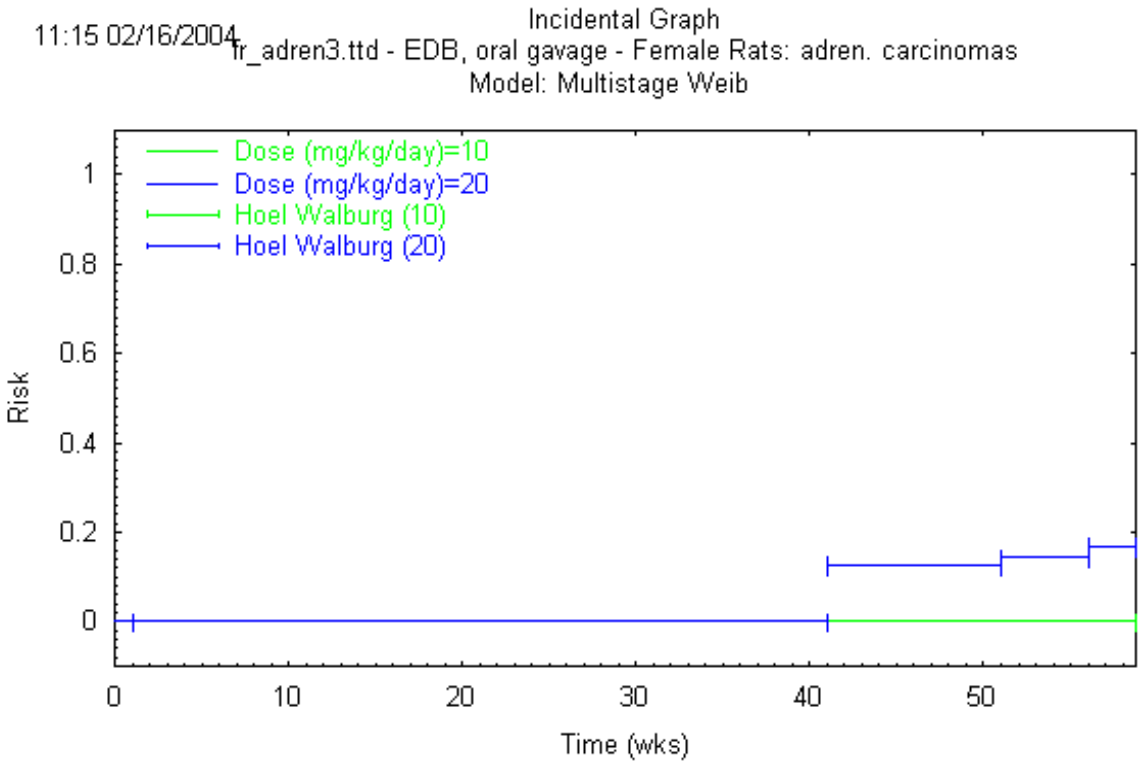
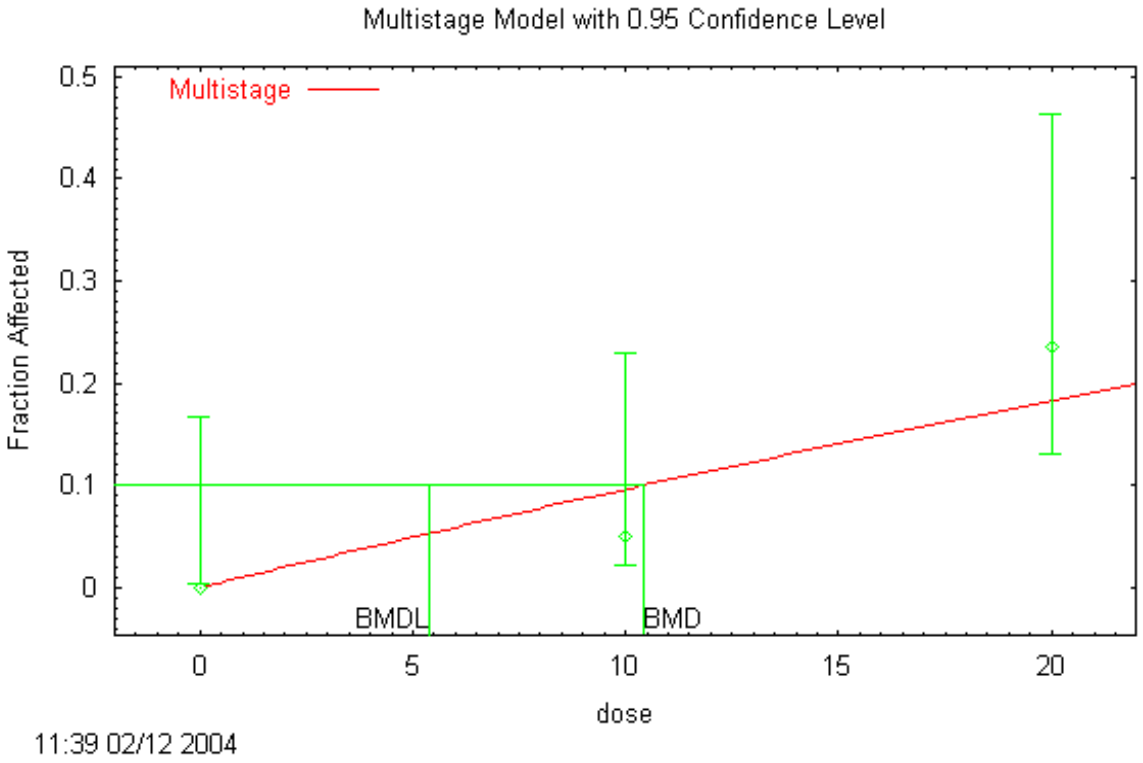


Figure C-7. Cumulative incidence curves for adrenocortical carcinomas and neoplastic nodules in female rats in the oral gavage study (NCI, 1978).

Output C-6. Multistage analysis of adrenocortical carcinomas in female rats, 1,2-dibromoethane oral gavage exposure

```
BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = adren
   Independent variable = mg_kg_day

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 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
                     Background =            0
                        Beta(1) =    0.0134132


           Asymptotic Correlation Matrix of Parameter Estimates

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

                Beta(1)

   Beta(1)            1



                         Parameter Estimates

      Variable           Estimate             Std. Err.
    Background                  0                   NA
       Beta(1)          0.0101304            0.0111373

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



                       Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model         -13.2454
   Fitted model         -13.6828      0.874853      2          0.6457
  Reduced model         -16.8494       7.20797      2         0.02722

           AIC:          29.3657


                     Goodness  of  Fit

     Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
  ----------------------------------------------------------------------
i: 1
```

```
    0.0000      0.0000          0.000          0           19        0.000
i: 2
   10.0000      0.0963          1.927          1           20       -0.532
i: 3
   20.0000      0.1834          3.118          4           17        0.346

 Chi-square =       0.80     DF = 2        P-value = 0.6706


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        10.4005

            BMDL =        5.39277
```



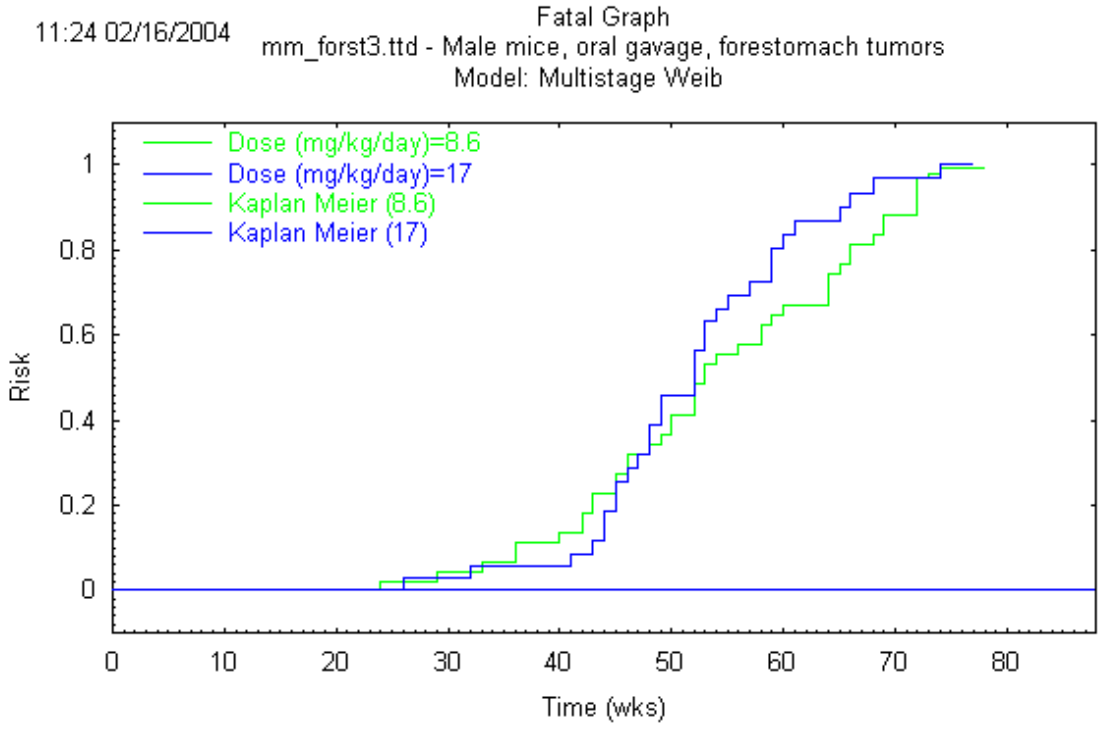


Figure C-8. Kaplan-Meier hazard curves for the incidence of forestomach squamous cell carcinomas in male mice in the oral gavage study (NCI, 1978).

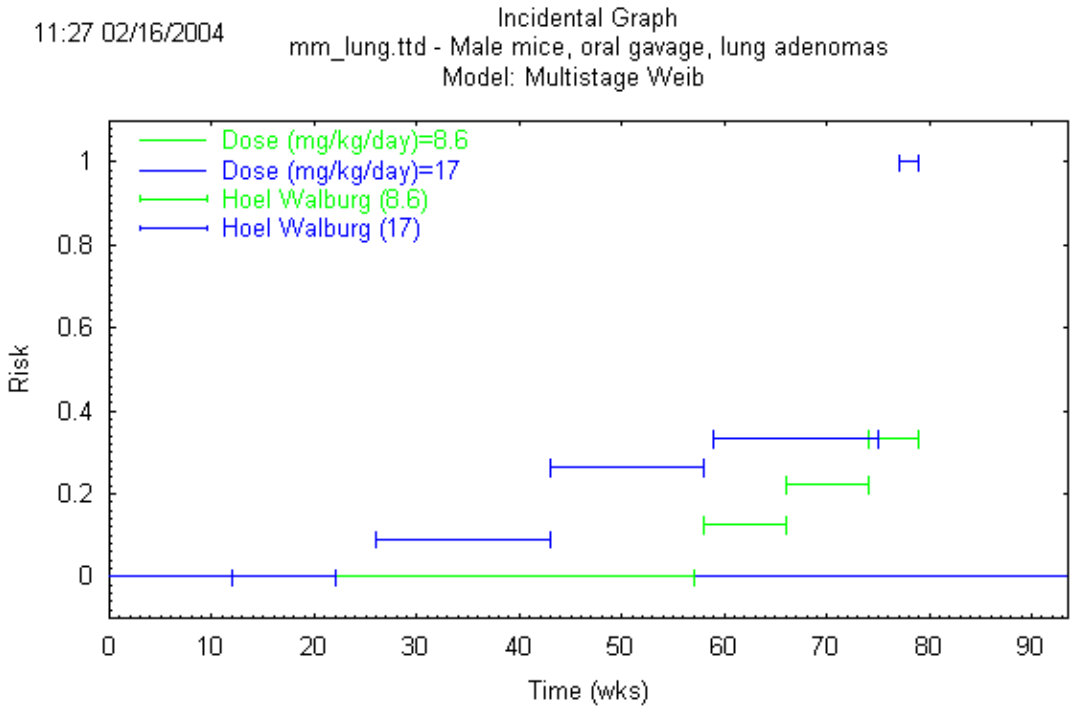


Figure C-9: Cumulative incidence curves for lung adenomas in male mice in the oral gavage study (NCI, 1978).

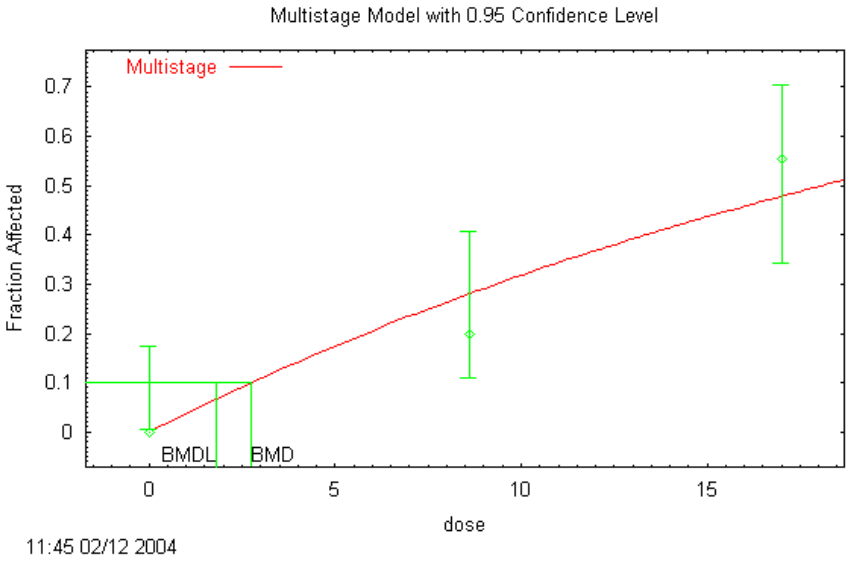
Output C-7: Multistage analysis of alveolar/bronchiolar adenomas in male mice, 1,2-dibromoethane oral gavage exposure

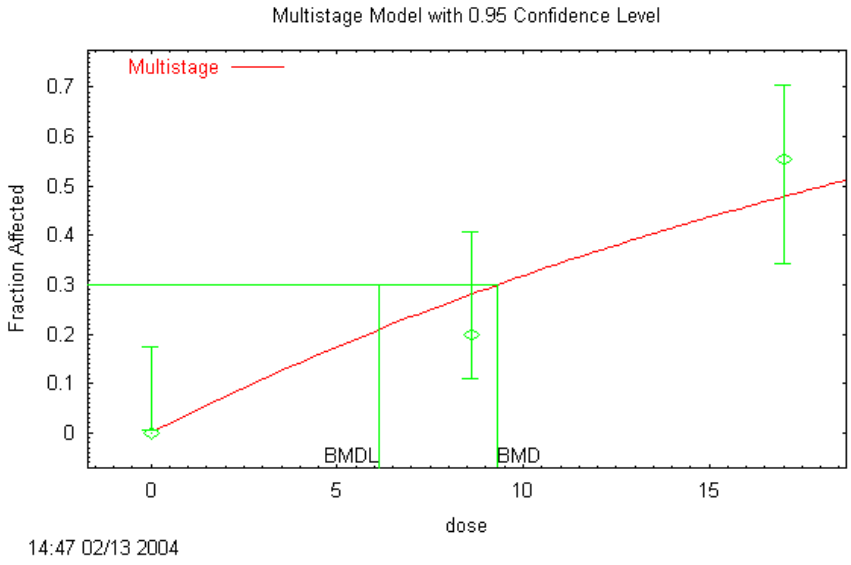
```
BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1)]

   The parameter betas are restricted to be positive

   Dependent variable = lung_ad
   Independent variable = dose_feb04

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1

 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
                     Background =            0
                        Beta(1) =    0.0476155

           Asymptotic Correlation Matrix of Parameter Estimates

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

                Beta(1)

   Beta(1)            1


                          Parameter Estimates

       Variable           Estimate             Std. Err.
     Background                  0                   NA
        Beta(1)          0.0382824            0.0159921

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


                       Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model         -22.3734
   Fitted model         -22.9321       1.11758      2          0.5719
  Reduced model         -31.4908       18.2348      2       0.0001097

           AIC:          47.8643


                     Goodness  of  Fit

     Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
  ----------------------------------------------------------------------
i: 1
    0.0000     0.0000         0.000         0          18       0.000
i: 2
    8.6000     0.2805         5.610         4          20      -0.399
i: 3
   17.0000     0.4784         8.611        10          18       0.309
```

Chi-square = 1.07 DF = 2 P-value = 0.5850

Benchmark Dose Computation

Specified effect =	0.1	Specified effect =	0.3
Risk Type =	Extra risk	Risk Type =	Extra risk
Confidence level =	0.95	Confidence level =	0.95
BMD =	2.75219	BMD =	9.31695
BMDL =	1.81432	BMDL =	6.14197





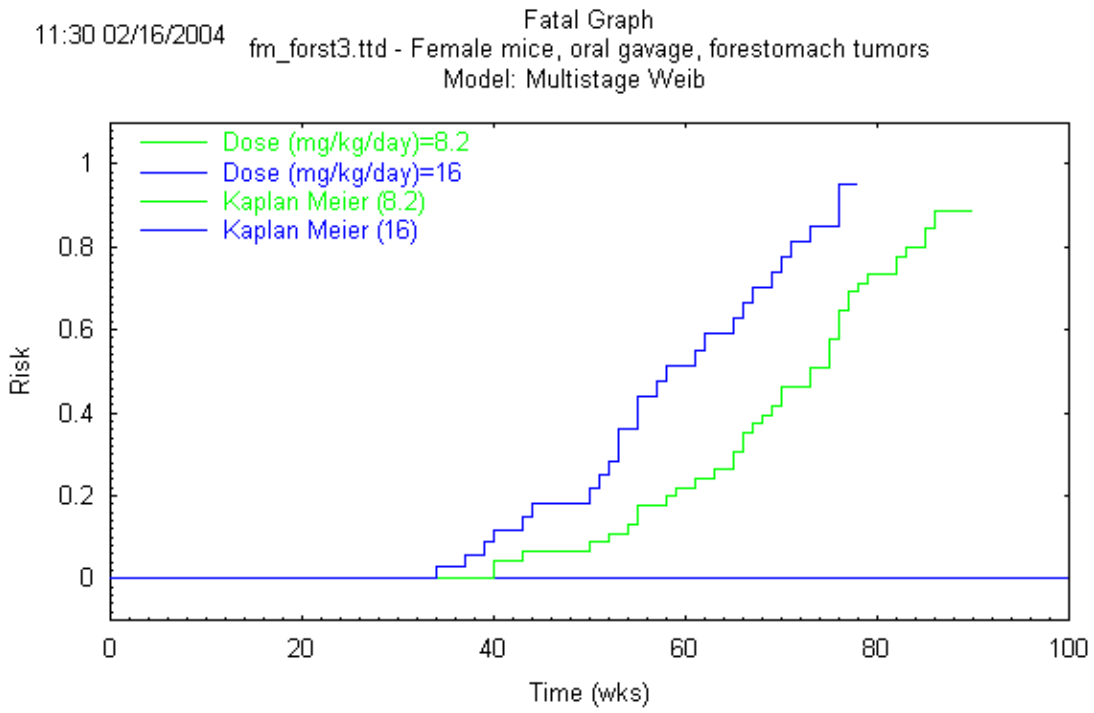


Figure C-10. Kaplan-Meier hazard curves for the incidence of forestomach squamous cell carcinomas in female mice in the oral gavage study (NCI, 1978).

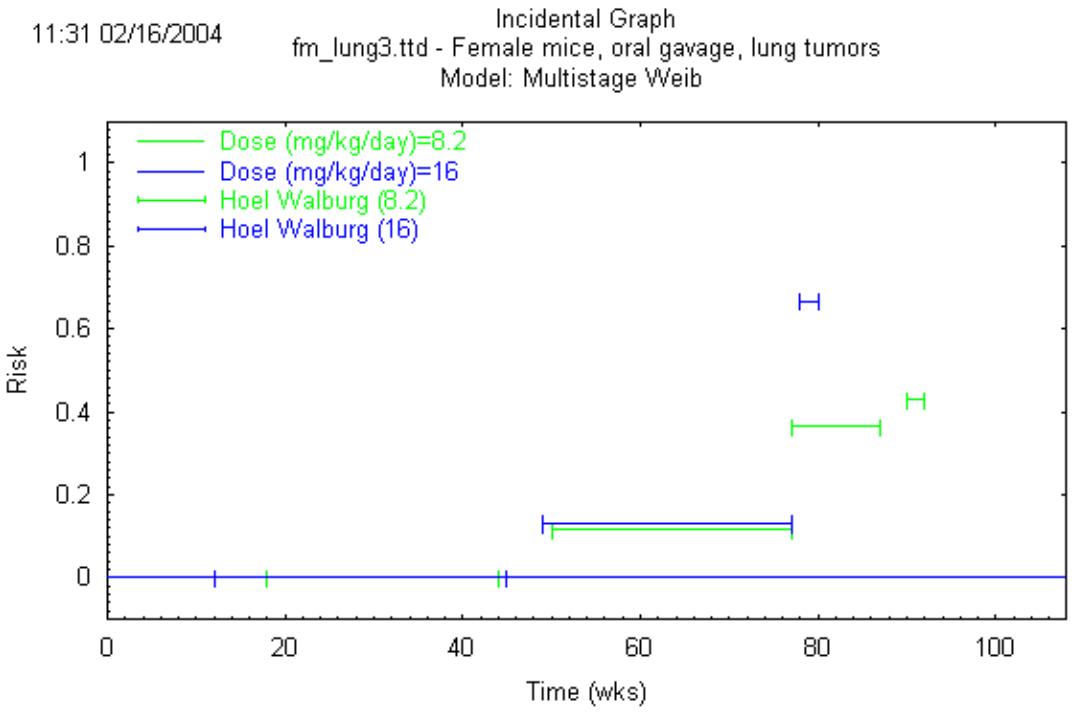
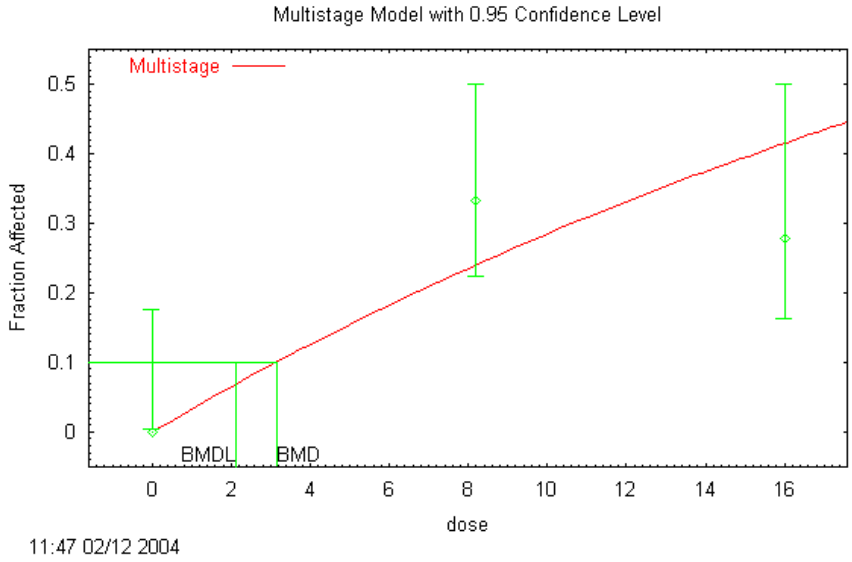


Figure C-11. Cumulative incidence curves for lung adenomas in female mice in the oral gavage study (NCI, 1978).

Output C-8. Multistage analysis of alveolar/bronchiolar adenomas in female mice, 1,2-dibromoethane oral gavage exposure

```
BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive

   Dependent variable = lung_ad
   Independent variable = dose_feb04

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2

 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
                     Background =    0.0746256
                        Beta(1) =    0.0205875
                        Beta(2) =            0

           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(2)
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)

   Beta(1)            1


                         Parameter Estimates

      Variable           Estimate             Std. Err.
    Background                  0                   NA
       Beta(1)          0.0335146            0.0159519
       Beta(2)                  0                   NA

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


                        Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model         -29.7306
   Fitted model         -31.1232       2.78529      2          0.2484
  Reduced model         -35.3734       11.2855      2        0.003543

           AIC:          64.2465


                     Goodness  of  Fit

     Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
  ----------------------------------------------------------------------
i: 1
    0.0000     0.0000         0.000         0          18       0.000
i: 2
    8.2000     0.2403         7.209        10          30       0.510
```

```
i: 3
   16.0000      0.4151          7.471          5           18       -0.565

 Chi-square =        2.82      DF = 2        P-value = 0.2442

   Benchmark Dose Computation

 Specified effect =            0.1               Specified effect =           0.25

 Risk Type        =       Extra risk             Risk Type        =       Extra risk

 Confidence level =           0.95               Confidence level =           0.95

               BMD =        3.14372                           BMD =        8.58379

              BMDL =        2.10812                          BMDL =        5.75613
```



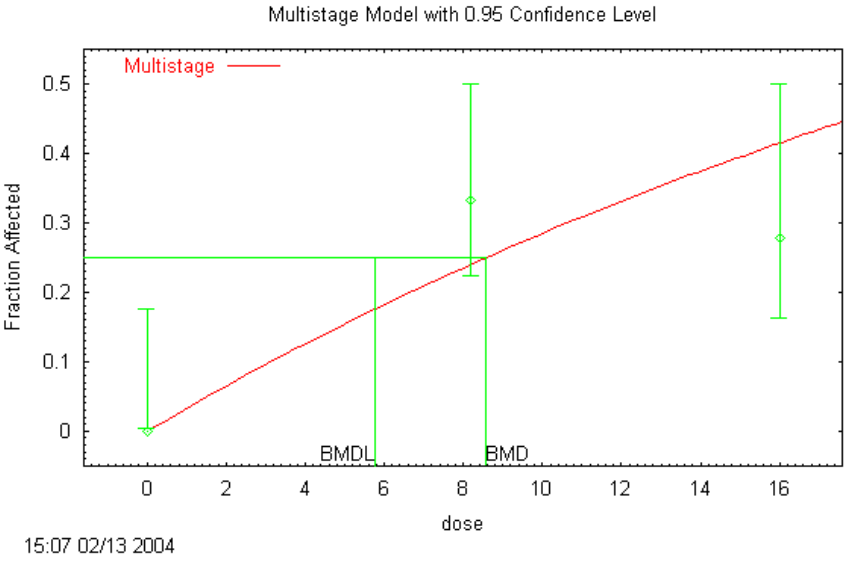


Table C-5. Number of animals with and without specified tumor types at time of death, male rats exposed by inhalation to 1,2-dibromoethane

Group	Week	All nasal tumors		Hemangiosarcomas		Mesothelioma	
		Death with tumor	Death without tumor	Death with tumor	Death without tumor	Death with tumor	Death tumor
Control	77	0	1	0	1	0	1
	88	0	1	0	1	0	1
	89	0	1	0	1	0	1
	90	0	1	0	1	0	1
	93	0	2	0	2	0	2
	97	0	1	0	1	0	1
	99	0	1	0	1	0	1
	102	0	1	0	1	0	1
	103	0	3	0	3	0	3
	104	1	18	0	19	1	18
	106	0	19	0	19	0	19
Low-dose	7	0	1	0	1	0	1
	38	0	1	0	1	0	1
	56	0	1	0	1	0	1
	85	0	1	0	1	0	1
	86	0	1	0	1	0	1
	93	0	1	0	1	0	1
	95	0	1	0	1	0	1
	96	1	1	1	1	1	1
	97	1	0	0	1	0	1
	98	1	0	0	1	0	1
	99	1	0	0	1	0	1
	102	3	0	0	3	0	3
	104	32	3	0	35	7	28
High-dose	43	1	0	0	1	0	1
	50	0	1	1	0	1	0
	53	0	1	0	1	1	0
	56	1	0	0	1	1	0
	62	0	1	0	1	0	1
	63	0	1	1	0	1	0
	64	2	0	0	2	1	1
	67	1	1	0	2	1	1
	68	2	0	0	2	1	1
	69	0	1	0	1	0	1
	70	2	2	1	3	3	1
	71	0	1	1	0	0	1
	74	1	0	0	1	0	1
	76	2	0	1	1	1	1
	77	1	0	1	0	1	0
	78	1	0	0	1	0	1
	80	5	0	2	3	0	5
	81	2	0	0	2	1	1
	82	3	0	0	3	1	2
	83	1	0	0	1	0	1
	84	3	0	0	3	1	2
	85	2	0	1	1	0	2
	86	2	0	0	2	1	1
	87	2	0	2	0	2	0
	88	1	0	1	0	1	0
	89	5	1	3	3	6	0

Source: NTP, 1982.

Table C-6. Number of animals with and without specified tumor types at time of death, female rats exposed by inhalation to 1,2-dibromoethane

		Nasal tumor		Fibroadenoma		Mammary adenocarcinoma	
Group	Week	Death with tumors	Death without tumors	Death with tumors	Death without tumors	Death with tumors	Death without tumors
Control	59	0	1	0	1	0	1
	88	0	1	0	1	0	1
	93	0	1	0	1	0	1
	97	1	0	0	1	0	1
	98	0	1	0	1	0	1
	101	0	2	0	2	0	2
	103	0	1	0	1	0	1
	104	0	21	3	18	0	21
	106	0	21	1	20	1	20
Low-dose	8	0	1	0	1	0	1
	13	0	1	0	1	0	1
	52	1	0	1	0	0	1
	79	0	1	0	1	0	1
	82	0	1	1	0	0	1
	98	3	2	5	0	0	5
	99	1	0	1	0	0	1
	104	29	9	21	17	0	38
High-dose	54	0	1	0	1	0	1
	55	0	1	0	1	0	1
	60	1	0	0	1	0	1
	63	2	0	1	1	0	2
	67	0	1	0	1	1	0
	69	1	1	0	2	0	2
	71	1	0	0	1	0	1
	72	1	1	1	1	0	2
	73	2	0	0	2	1	1
	76	1	0	0	1	0	1
	78	1	0	0	1	0	1
	79	1	0	0	1	0	1
	80	1	0	0	1	0	1
	82	1	0	1	0	0	1
	83	2	0	2	0	0	2
	84	3	0	1	2	1	2
	85	1	0	0	1	0	1
	86	3	0	1	2	0	3
	87	2	0	2	0	0	2
	88	1	0	1	0	0	1
	89	5	1	5	1	0	6
	90	2	0	1	1	0	2
	91	11	0	8	3	1	10

Table C-6. Number of animals with and without specified tumor types at time of death, female rats exposed by inhalation to 1,2-dibromoethane (continued)

		Hemangiosarcoma		Alveolar/bronchiolar adenoma/carcinoma	
Group	Week	Death with tumor	Death without tumor	Death with tumor	Death without tumor
Control	59	0	1	0	1
	88	0	1	0	1
	93	0	1	0	1
	97	0	1	0	1
	98	0	1	0	1
	101	0	2	0	2
	103	0	1	0	1
	104	0	21	0	21
	106	0	21	0	21
Low-dose	8	0	1	0	1
	13	0	1	0	1
	52	0	1	0	1
	79	0	1	0	1
	82	0	1	0	1
	98	0	5	0	5
	99	0	1	0	1
	104	0	38	0	38
High-dose	54	0	1	0	1
	55	0	1	0	1
	60	0	1	0	1
	63	0	2	0	2
	67	0	1	0	1
	69	0	2	0	2
	71	0	1	0	1
	72	0	2	0	2
	73	1	1	0	2
	76	0	1	0	1
	78	0	1	0	1
	79	0	1	0	1
	80	0	1	0	1
	82	0	1	0	1
	83	0	2	0	2
	84	0	3	0	3
	85	0	1	1	0
	86	0	3	0	3
	87	1	0	1	1
	88	1	1	0	1
	89	0	6	1	5
	90	0	2	0	2
	91	2	9	2	9

Source: NTP, 1982.

Table C-7. Number of animals with and without specified tumor types at time of death, female mice exposed by inhalation to 1,2-dibromoethane

		Nasal tumors		Hemangiosarcoma		Alveolar/bronchiolar adenoma/carcinoma	
Group	Week	Death with tumor	Death without tumor	Death with tumor	Death without tumor	Death with tumor	Death without tumor
Control	24	0	1	0	1	0	1
	85	0	1	0	1	0	1
	86	0	1	0	1	0	1
	94	0	1	0	1	0	1
	95	0	1	0	1	0	1
	96	0	1	0	1	0	1
	98	0	1	0	1	0	1
	100	0	1	0	1	0	1
	101	0	1	0	1	0	1
	104	0	22	0	22	3	19
	106	0	19	0	19	1	18
Low-dose	4	0	1	0	1	0	1
	54	0	1	0	1	0	1
	56	0	1	0	1	0	1
	62	0	1	0	1	0	1
	66	0	1	0	1	0	1
	73	0	1	0	1	0	1
	82	0	1	0	1	0	1
	84	0	1	0	1	1	0
	90	0	1	1	0	0	1
	91	0	3	1	2	0	3
	94	0	1	1	0	0	1
	95	0	3	1	2	1	2
	96	0	3	1	2	3	0
	97	0	2	0	2	1	1
	98	0	3	0	3	0	3
	100	0	2	2	0	0	2
	101	0	3	1	2	1	2
	102	0	2	1	1	0	2
	104	0	19	3	16	4	15
High-dose	19	0	1	0	1	0	1
	45	1	0	0	1	0	1
	50	0	1	0	1	1	0
	63	0	3	1	2	2	1
	65	1	0	0	1	1	0
	66	0	1	1	0	0	1
	68	0	1	1	0	1	0
	70	0	2	1	1	2	0
	71	0	2	0	2	1	1
	73	1	0	0	1	1	0
	74	0	1	0	1	1	0
	75	1	0	0	1	1	0
	77	0	2	1	1	1	1
	78	0	1	0	1	1	0
	79	1	3	3	1	4	0
	81	2	0	1	1	2	0
	82	0	3	2	1	2	1
	83	0	2	2	0	2	0
	84	0	1	0	1	1	0
	85	0	3	3	0	3	0
	86	1	2	1	2	3	0
	87	0	1	1	0	0	1
	89	0	3	2	1	2	1
	90	0	1	1	0	1	0
	91	0	8	4	4	8	0

Table C-7. Number of animals with and without specified tumor types at time of death, female mice exposed by inhalation to 1,2-dibromoethane (continued)

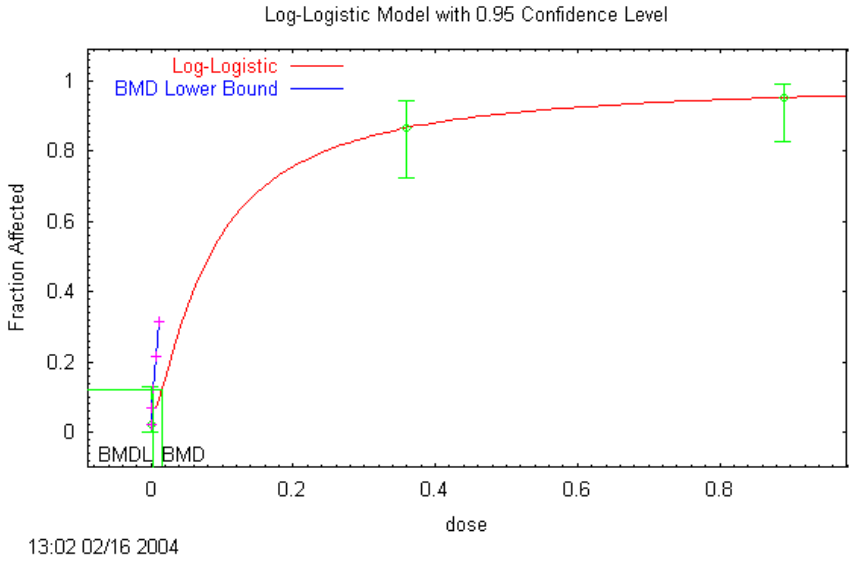
		Lung/bronchial adenoma/carcinoma		Fibrosarcoma		Mammary adenocarcinoma	
Group	Week	Death with tumor	Death without tumor	Death with tumor	Death without tumor	Death with tumor	Death without tumor
Control	24	0	1	0	1	0	1
	85	0	1	0	1	0	1
	86	0	1	0	1	0	1
	94	0	1	0	1	0	1
	95	0	1	0	1	0	1
	96	0	1	0	1	0	1
	98	0	1	0	1	0	1
	100	0	1	0	1	0	1
	101	0	1	0	1	1	0
	104	0	22	0	22	1	21
	106	0	19	0	19	0	19
Low-dose	4	0	1	0	1	1	0
	54	0	1	1	0	0	1
	56	0	1	0	1	0	1
	62	0	1	0	1	0	1
	66	0	1	0	1	0	1
	73	0	1	0	1	0	1
	82	0	1	0	1	0	1
	84	0	1	1	0	0	1
	90	0	1	0	1	0	1
	91	0	3	0	3	1	2
	94	0	1	0	1	0	1
	95	0	3	0	3	1	2
	96	0	3	0	3	0	3
	97	1	1	0	2	0	2
	98	0	3	2	1	2	1
	100	0	2	0	2	0	2
	101	0	3	0	3	2	1
	102	0	2	0	2	2	0
	104	0	19	1	18	5	14
High-dose	19	0	1	0	1	0	1
	45	0	1	0	1	0	1
	50	0	1	1	0	1	0
	63	0	3	0	3	1	2
	65	0	1	0	1	0	1
	66	0	1	0	1	0	1
	68	0	1	0	1	0	1
	70	0	2	0	2	1	1
	71	1	1	0	2	0	2
	73	0	1	0	1	0	1
	74	1	0	0	1	0	1
	75	0	1	0	1	1	0
	77	1	1	1	1	0	2
	78	0	1	0	1	0	1
	79	1	3	1	3	2	2
	81	0	2	1	1	1	1
	82	0	3	1	2	0	3
	83	0	2	0	2	0	2
	84	1	0	0	1	0	1
	85	1	2	1	2	2	1
	86	0	3	1	2	0	3
	87	0	1	0	1	0	1
	89	1	2	3	0	0	3
	90	0	1	1	0	0	1
	91	1	7	0	8	0	8

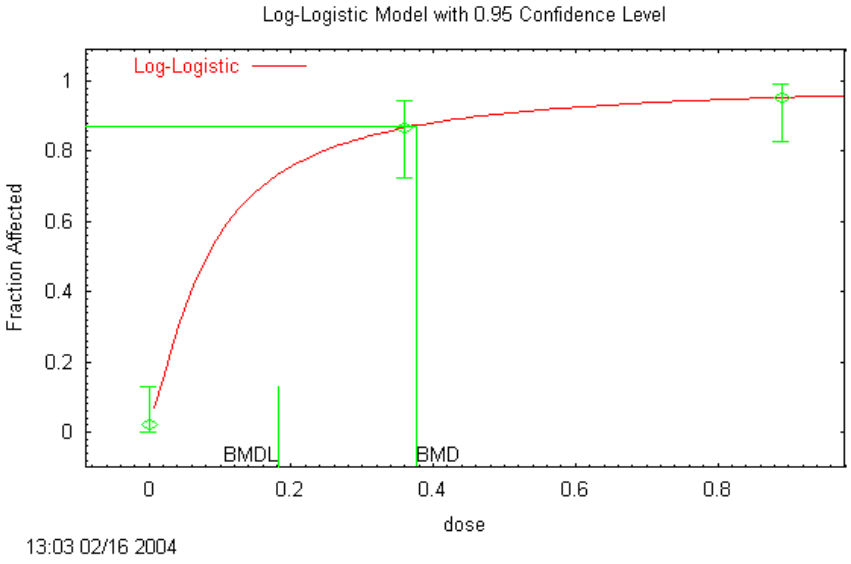
Source: NTP, 1982.

Output C-9. Multistage analysis of nasal cavity tumors in male rats, 1,2-dibromoethane inhalation exposure

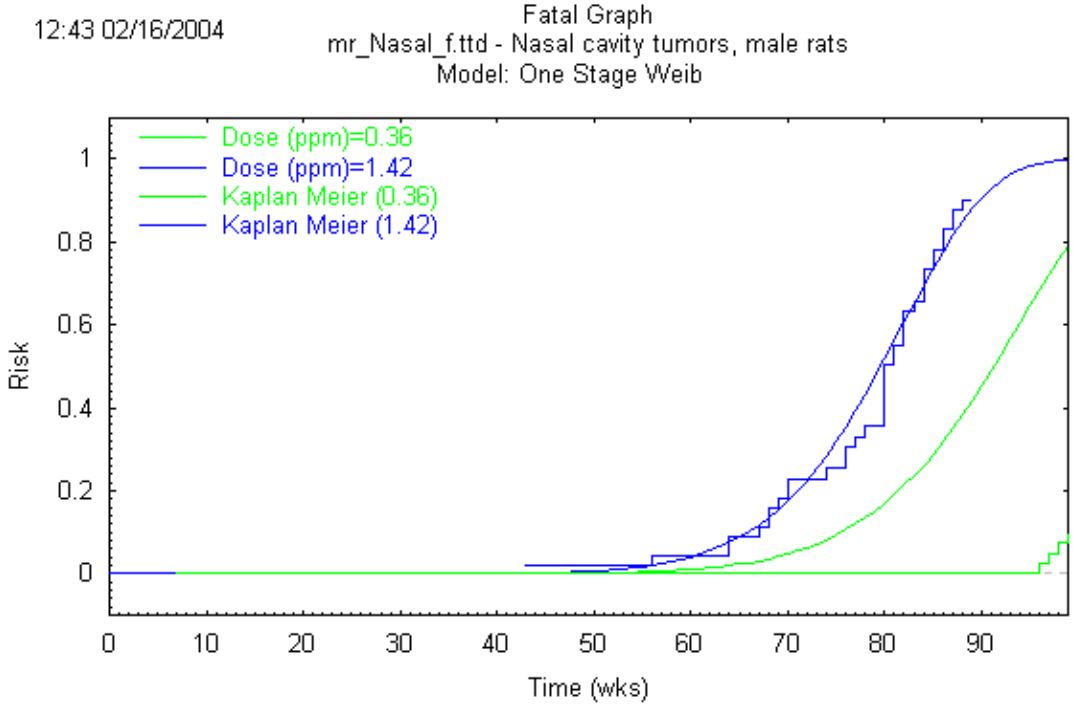
```
BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

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


   Dependent variable = nasal_tum
   Independent variable = rgdr_ppm
   Slope parameter is restricted as slope >= 1

   Total number of observations = 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



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =    0.0217391
                     intercept =      3.14555
                         slope =      1.27162


          Asymptotic Correlation Matrix of Parameter Estimates

            background    intercept        slope

background           1       -0.028       0.0028

 intercept       -0.028            1         0.89

     slope       0.0028         0.89            1


                         Parameter Estimates

       Variable           Estimate            Std. Err.
     background          0.0217391           0.0215013
      intercept            3.14555            0.820541
          slope            1.27162             0.93693


                       Analysis of Deviance Table

      Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model        -30.5769
   Fitted model        -30.5769         0      0         NA
  Reduced model        -89.9347   118.716      2         <.0001

          AIC:         67.1538


                     Goodness  of  Fit

                                                                 Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------
    0.0000      0.0217       1.000           1          46             0
    0.3600      0.8667      39.000          39          45             0
    0.8900      0.9535      41.000          41          43             0

 Chi-square =       0.00     DF = 0        P-value =     NA


   Benchmark Dose Computation
```

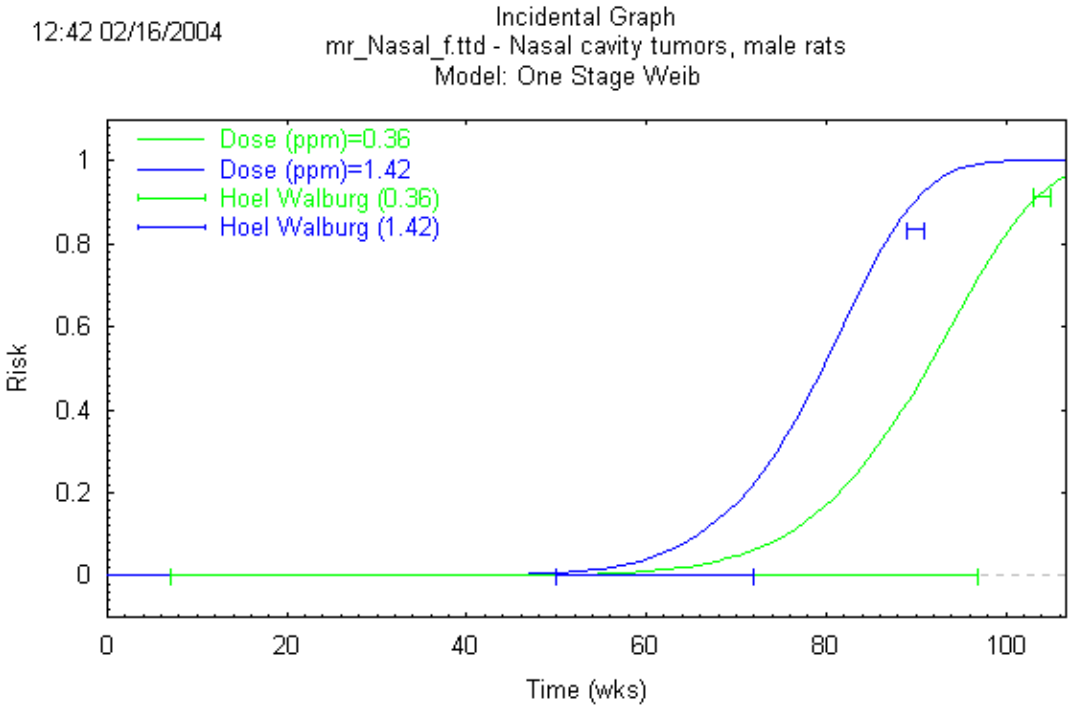
Specified effect =	0.1	Specified effect =	0.87
Risk Type =	Extra risk	Risk Type =	Extra risk
Confidence level =	0.95	Confidence level =	0.95
BMD =	0.0149722	BMD =	0.375782
BMDL =	0.0030344	BMDL =	0.182764





Output C-10. Multistage-Weibull analysis of nasal cavity tumors in male rats, 1,2-dibromoethane inhalation exposure



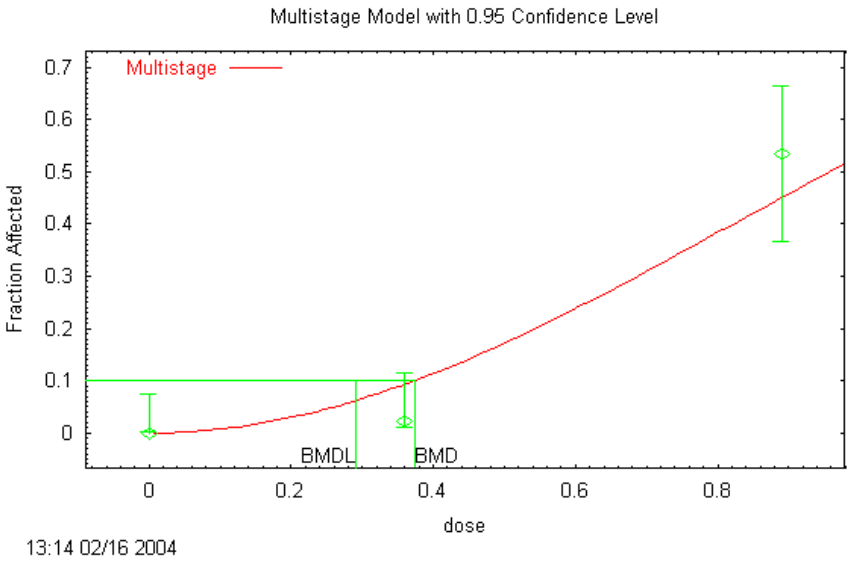


```
Generating Model Fit Table ---
TITLE: Nasal cavity tumors, male rats

             Model: One Stage Weib         Dataset: C:\Program
Files\TOX_RISK\edb_inh\mr_Nasal_f.ttd
Functional form: 1 - EXP[( -Q0 - Q1 * D ) * (T - T0)^Z]
         Maximum Log-Likelihood =  -1.785287e+002

       Parameter Estimates :
                           Q 0 = 1.347227E-022
                           Q 1 = 4.773207E-020
                           Z   = 1.000000E+001
                           T0  = 0.000000E+000   Set by User


      Avg. Doses         -------------------- Number --------------------
        (ppm)              of animals       with fatal    with incidental
                                              tumors          tumors
         0                    50                1              0
         0.36                 50                7             32
         1.42                 50               36              5



              Model: One Stage Weib     Age Begins: 0     Age Ends: 70
     Target Species: Human              Weeks/Year: 52   Days/Week:  7
              Route: Air                                 Hours/Day : 24
    Animal to human conversion method: PPM IN AIR

          Unit Potency [ per mg/kg/day ] (computed for Risk of 1.0E-6)
Lower Bound = Not Reqstd   MLE = 7.1965E-001   Upper Bound(q1*) = 8.8228E-001

 Induction Time (T0) Set by User to 0


                                  Dose Estimates (ppb)
                                95.00 %                          95.00 %
  Incid Extra Risk   Time     Lower Bound          MLE          Upper Bound
     1.0000E-006      70.00   5.0690E-004      6.2145E-004     Not Reqstd
     1.0000E-005      70.00   5.0690E-003      6.2145E-003     Not Reqstd
     0.0001           70.00   5.0692E-002      6.2148E-002     Not Reqstd
     0.0010           70.00   5.0715E-001      6.2176E-001     Not Reqstd
     0.01             70.00   5.0945E+000      6.2458E+000     Not Reqstd
     0.10             70.00   5.3407E+001      6.5476E+001     Not Reqstd
```

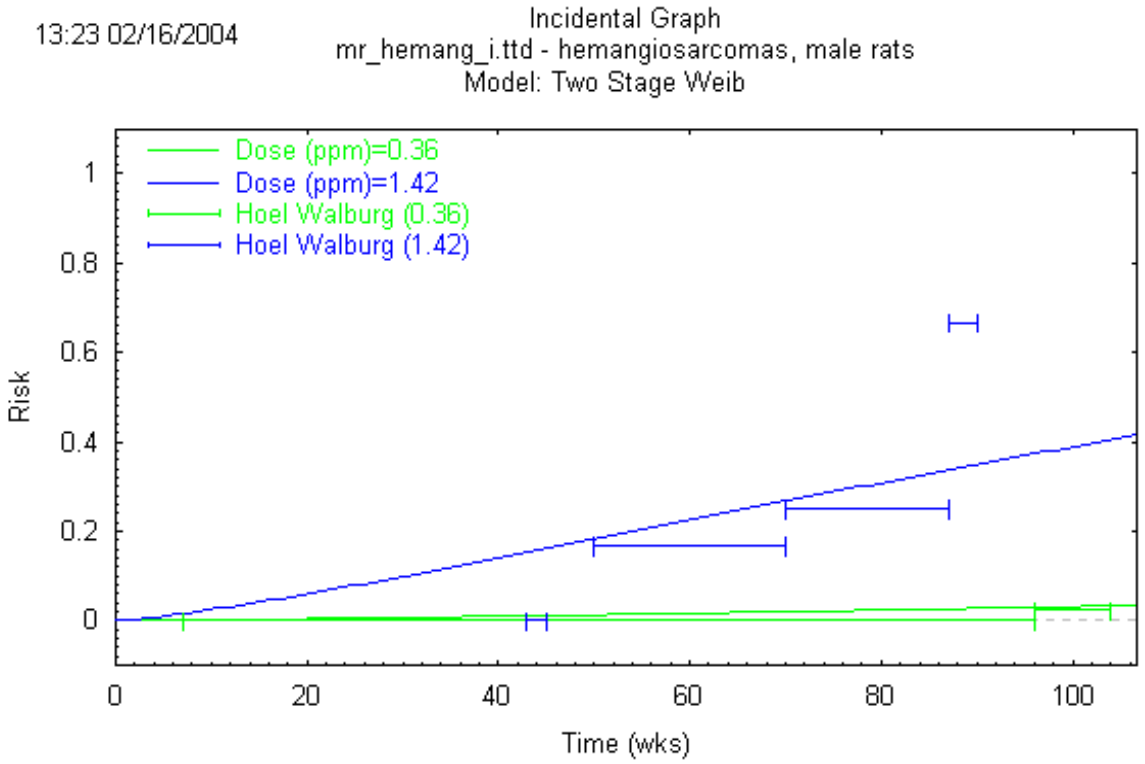
Output C-11. Multistage analysis of hemangiosarcomas in male rats, 1,2-dibromoethane inhalation exposure

```
BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = hemang
   Independent variable = rgdr_ppm

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 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
                     Background =            0
                        Beta(1) =            0
                        Beta(2) =      1.01882


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(1)
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

                Beta(2)

   Beta(2)            1



                          Parameter Estimates

       Variable           Estimate             Std. Err.
     Background                  0                NA
        Beta(1)                  0                NA
        Beta(2)            0.75631            0.293177

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



                       Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model         -24.0861
   Fitted model         -26.2309       4.28957      2          0.1171
  Reduced model         -46.6858       45.1993      2         <.0001

           AIC:          54.4618


                     Goodness  of  Fit

     Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
  ----------------------------------------------------------------------
i: 1
    0.0000     0.0000         0.000         0          46       0.000
```

```
i: 2
    0.3600      0.0934          4.015          1           43       -0.828
i: 3
    0.8900      0.4507         12.619         15           28        0.343

 Chi-square =        3.31      DF = 2         P-value = 0.1906


   Benchmark Dose Computation

 Specified effect =             0.1

 Risk Type        =       Extra risk

 Confidence level =            0.95

              BMD =        0.373241

             BMDL =        0.291394
```



Output C-12. Multistage-Weibull analysis of hemangiosarcomas in male rats, 1,2-dibromoethane inhalation exposure




```
Generating Model Fit Table ---
TITLE: hemangiosarcomas, male rats

              Model: Two Stage Weib         Dataset: C:\Program
Files\TOX_RISK\edb_inh\mr_hemang_i.ttd
Functional form: 1 - EXP[( -Q0 - Q1 * D - Q2 * D^2) * (T - T0)^Z]
         Maximum Log-Likelihood =  -3.508137e+001

       Parameter Estimates :
                            Q 0 = 0.000000E+000
                            Q 1 = 0.000000E+000
                            Q 2 = 6.309854E-004
                            Z   = 1.293779E+000
                            T0  = 0.000000E+000   Set by User


      Avg. Doses         -------------------- Number --------------------
        (ppm)              of animals       with fatal     with incidental
                                              tumors          tumors
          0                   50                0              0
          0.36                50                0              1
          1.42                50                0             15



Generating Extrapolated Doses Table ---
TITLE: hemangiosarcomas, male rats

             Dataset: C:\Program Files\TOX_RISK\edb_inh\mr_hemang_i.ttd
                                             Exposure Pattern
               Model: Two Stage Weib     Age Begins: 0     Age Ends: 70
      Target Species: Human              Weeks/Year: 52   Days/Week:  7
               Route: Air                                 Hours/Day : 24
     Animal to human conversion method: PPM IN AIR

          Unit Potency [ per mg/kg/day ] (computed for Risk of 1.0E-6)
Lower Bound = Not Reqstd   MLE = 2.3189E-004   Upper Bound(q1*) = 7.0002E-002
```

Induction Time (T0) Set by User to 0

		Dose Estimates (ppb)		
		95.00 %		95.00 %
Incid Extra Risk	Time	Lower Bound	MLE	Upper Bound
1.0000E-006	70.00	6.3887E-003	1.9286E+000	Not Reqstd
1.0000E-005	70.00	6.3884E-002	6.0988E+000	Not Reqstd
0.0001	70.00	6.3857E-001	1.9287E+001	Not Reqstd
0.0010	70.00	6.3583E+000	6.1003E+001	Not Reqstd
0.01	70.00	6.1072E+001	1.9335E+002	Not Reqstd
0.10	70.00	4.6604E+002	6.2601E+002	Not Reqstd

Output C-13. Multistage analysis of mesotheliomas in male rats, 1,2-dibromoethane inhalation exposure

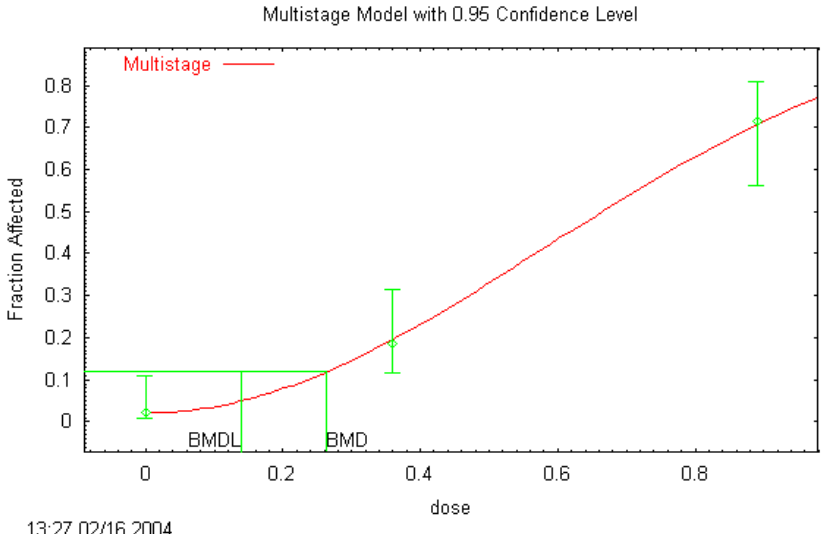
```
BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = meso
   Independent variable = rgdr_ppm

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 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
                     Background =    0.0134084
                        Beta(1) =            0
                        Beta(2) =      1.56244


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Beta(1)
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

             Background      Beta(2)

Background            1        -0.49

   Beta(2)        -0.49            1



                         Parameter Estimates

       Variable           Estimate            Std. Err.
     Background           0.0208905            0.11861
        Beta(1)                   0              NA
        Beta(2)             1.52272           0.433051

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



                        Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model          -46.416
   Fitted model         -46.4358     0.0395632      1          0.8423
  Reduced model         -72.8358       52.8395      2         <.0001

           AIC:          96.8716


                      Goodness  of  Fit

     Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
  ----------------------------------------------------------------------
```

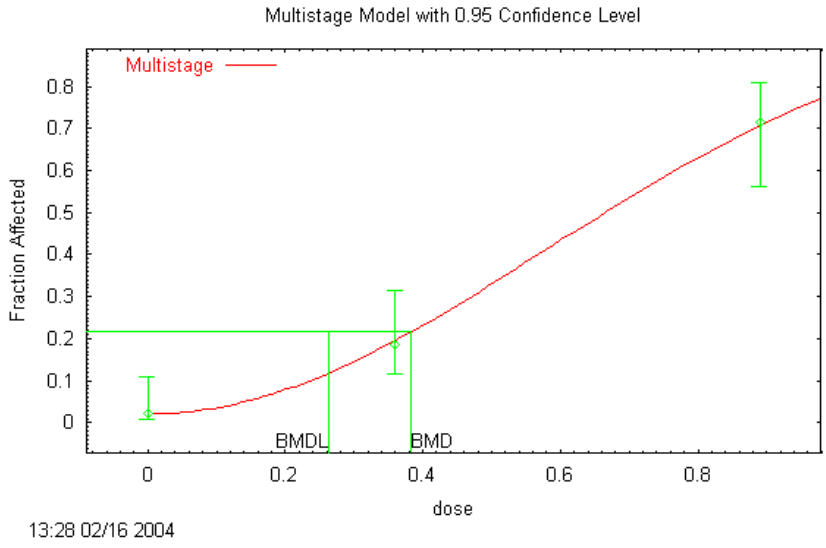
```
i: 1
    0.0000      0.0209          0.961          1           46        0.041
i: 2
    0.3600      0.1962          8.438          8           43       -0.065
i: 3
    0.8900      0.7069         24.742         25           35        0.036

 Chi-square =        0.04     DF = 1         P-value = 0.8431
```

Benchmark Dose Computation

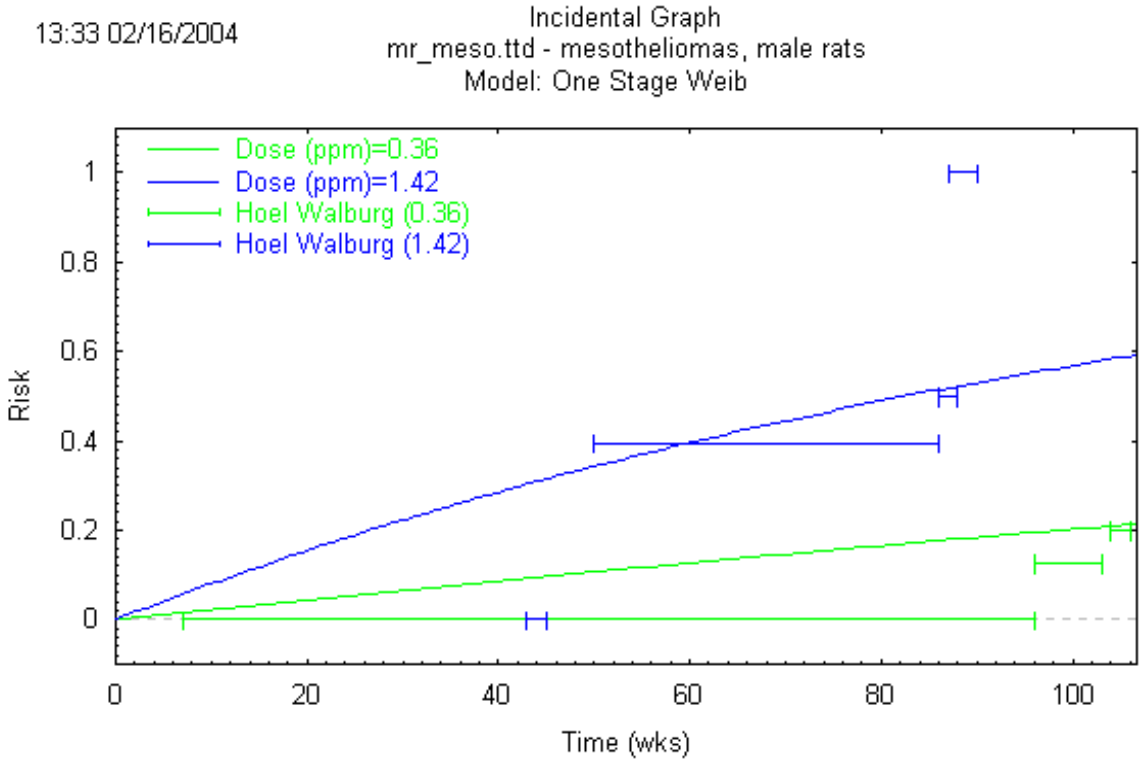
Specified effect =	0.1
Risk Type =	Extra risk
Confidence level =	0.95
BMD =	0.263045
BMDL =	0.138834

Specified effect =	0.2
Risk Type =	Extra risk
Confidence level =	0.95
BMD =	0.382809
BMDL =	0.263662





Output C-14. Multistage-Weibull analysis of mesotheliomas in male rats, 1,2-dibromoethane inhalation exposure




```
Generating Model Fit Table ---
TITLE: mesotheliomas, male rats

              Model: One Stage Weib         Dataset: C:\Program Files\TOX_RISK\edb_inh\mr_meso.ttd
Functional form: 1 - EXP[( -Q0 - Q1 * D ) * (T - T0)^Z]
         Maximum Log-Likelihood =  -6.157661e+001

       Parameter Estimates :
                            Q 0 = 1.735778E-004
                            Q 1 = 5.786966E-003
                            Z   = 1.000000E+000
                            T0  = 0.000000E+000   Set by User


      Avg. Doses          -------------------- Number --------------------
        (ppm)               of animals       with fatal    with incidental
                                               tumors          tumors
         0                    50                0              1
         0.36                 50                0              8
         1.42                 50                0             25



Generating Extrapolated Doses Table ---
TITLE: mesotheliomas, male rats

             Dataset: C:\Program Files\TOX_RISK\edb_inh\mr_meso.ttd
                                          Exposure Pattern
               Model: One Stage Weib     Age Begins: 0     Age Ends: 70
     Target Species: Human               Weeks/Year: 52   Days/Week:  7
               Route: Air                                 Hours/Day : 24
    Animal to human conversion method: PPM IN AIR

          Unit Potency [ per mg/kg/day ] (computed for Risk of 1.0E-6)
Lower Bound = Not Reqstd   MLE = 2.5763E-001   Upper Bound(q1*) = 3.4365E-001

 Induction Time (T0) Set by User to 0
```

		Dose Estimates (ppb)		
		95.00 %		95.00 %
Incid Extra Risk	Time	Lower Bound	MLE	Upper Bound
1.0000E-006	70.00	1.3014E-003	1.7360E-003	Not Reqstd
1.0000E-005	70.00	1.3014E-002	1.7360E-002	Not Reqstd
0.0001	70.00	1.3015E-001	1.7360E-001	Not Reqstd
0.0010	70.00	1.3021E+000	1.7368E+000	Not Reqstd
0.01	70.00	1.3080E+001	1.7447E+001	Not Reqstd
0.10	70.00	1.3712E+002	1.8290E+002	Not Reqstd

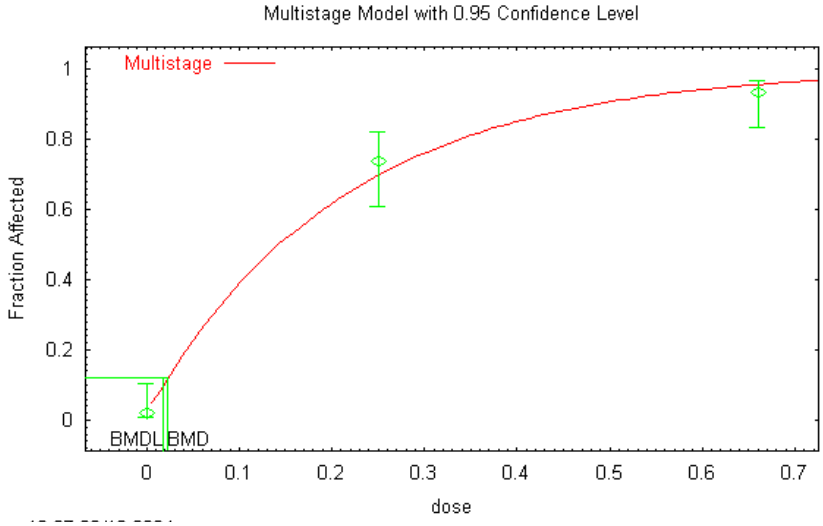
Output C-15. Multistage analysis of nasal cavity tumors in female rats, 1,2-dibromoethane inhalation exposure

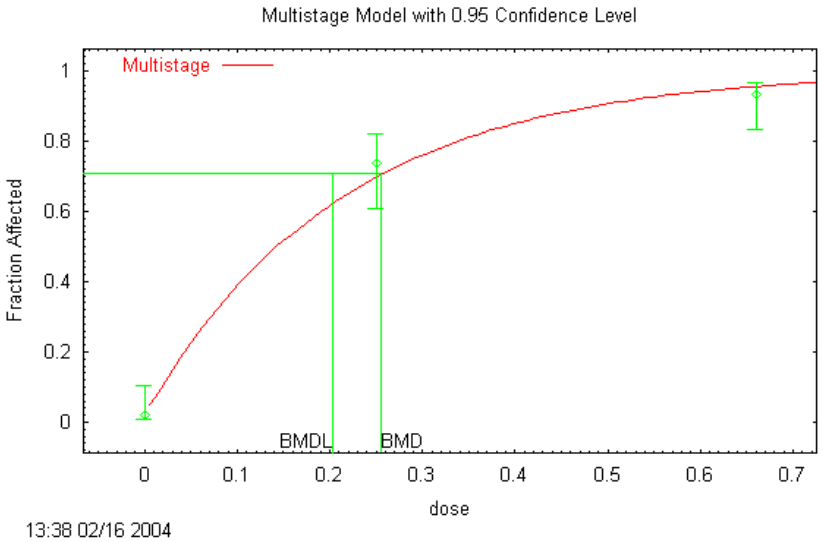
```
BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = all_nasal
   Independent variable = rgdr_ppm

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 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
                     Background =     0.132247
                        Beta(1) =      4.03267
                        Beta(2) =            0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Beta(2)
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

             Background      Beta(1)

Background            1        -0.48

   Beta(1)        -0.48            1



                         Parameter Estimates

       Variable           Estimate            Std. Err.
     Background           0.0220652           0.143887
        Beta(1)             4.70131           0.855238
        Beta(2)                   0              NA

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



                        Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model         -42.3319
   Fitted model         -42.7387     0.813627      1          0.3671
  Reduced model         -95.3053      105.947      2         <.0001

           AIC:          89.4774


                      Goodness  of  Fit

     Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
  ----------------------------------------------------------------------
```

```
i: 1
    0.0000      0.0221          1.037          1           47       -0.037
i: 2
    0.2500      0.6981         32.112         34           46        0.195
i: 3
    0.6600      0.9561         43.979         43           46       -0.507

 Chi-square =        0.87     DF = 1         P-value = 0.3523
```

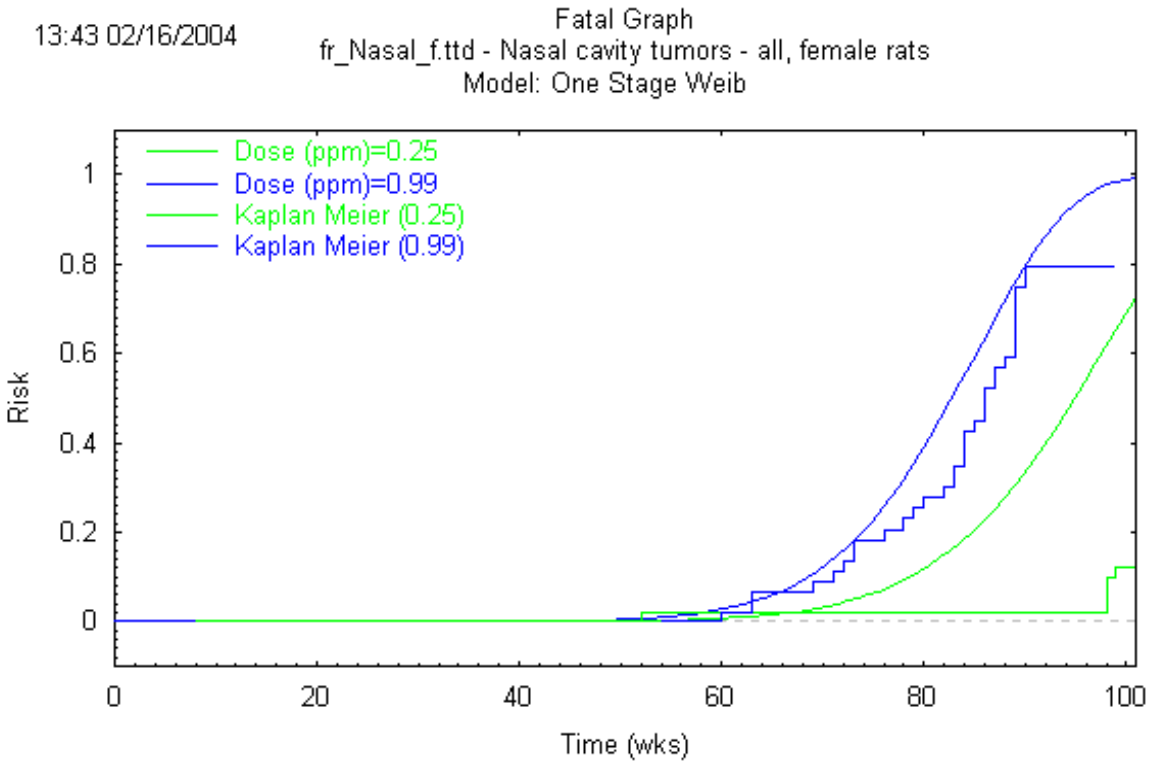
Benchmark Dose Computation

Specified effect =	0.1	Specified effect =	0.7
Risk Type =	Extra risk	Risk Type =	Extra risk
Confidence level =	0.95	Confidence level =	0.95
BMD =	0.0224109	BMD =	0.256093
BMDL =	0.0177547	BMDL =	0.202887

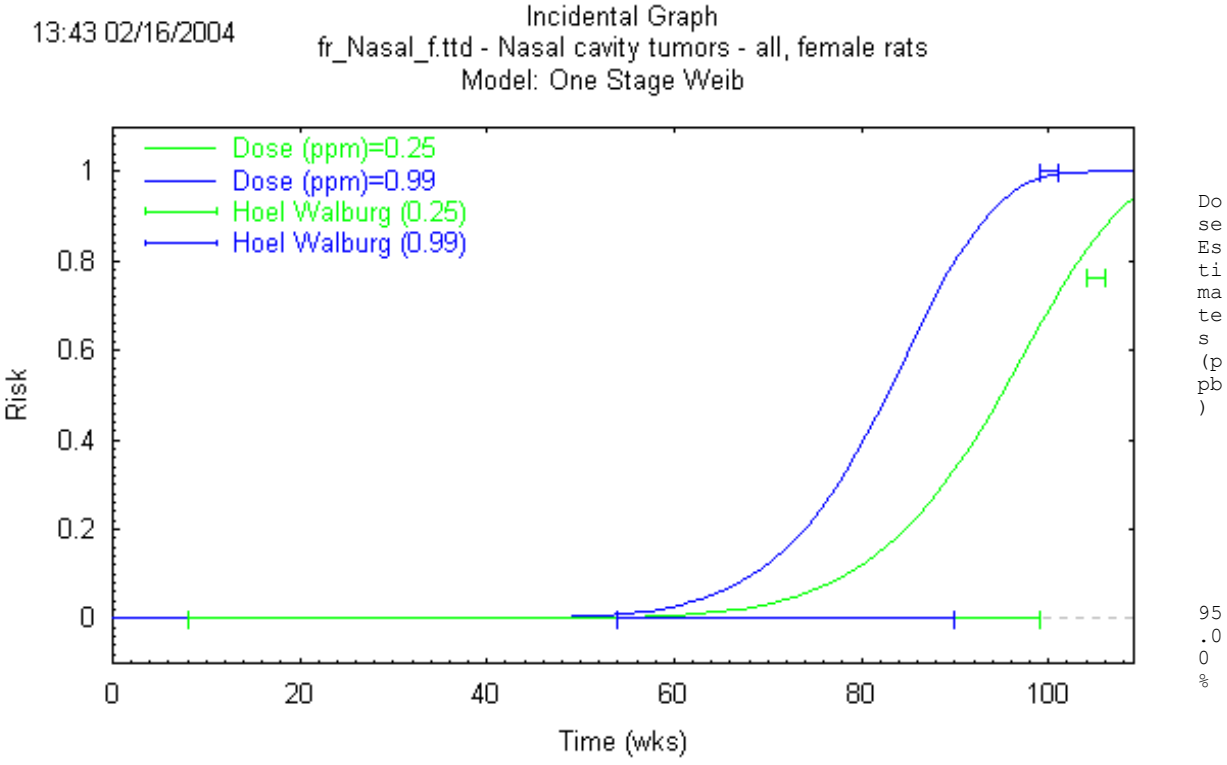




Output C-16. Multistage-Weibull analysis of nasal cavity tumors in female rats, 1,2-dibromoethane inhalation exposure



```
Generating Model Fit Table ---
TITLE: Nasal cavity tumors - all, female rats

              Model: One Stage Weib         Dataset: C:\Program
Files\TOX_RISK\edb_inh\fr_Nasal_f.ttd
Functional form: 1 - EXP[( -Q0 - Q1 * D ) * (T - T0)^Z]
         Maximum Log-Likelihood =  -1.673437e+002

       Parameter Estimates :
                             Q 0 = 1.275305E-022
                             Q 1 = 4.632330E-020
                             Z   = 1.000000E+001
                             T0  = 0.000000E+000   Set by User


      Avg. Doses         -------------------- Number --------------------
        (ppm)              of animals       with fatal    with incidental
                                              tumors          tumors
        0                    50                1              0
        0.25                 50                5             29
        0.99                 49               32             11


Generating Extrapolated Doses Table ---
TITLE: Nasal cavity tumors - all, female rats

             Dataset: C:\Program Files\TOX_RISK\edb_inh\fr_Nasal_f.ttd
                                          Exposure Pattern
               Model: One Stage Weib     Age Begins: 0     Age Ends: 70
      Target Species: Human              Weeks/Year: 52   Days/Week:  7
               Route: Air                                 Hours/Day : 24
     Animal to human conversion method: PPM IN AIR

          Unit Potency [ per mg/kg/day ] (computed for Risk of 1.0E-6)
Lower Bound = Not Reqstd   MLE = 8.2967E-001   Upper Bound(q1*) = 1.0275E+000

 Induction Time (T0) Set by User to 0
```



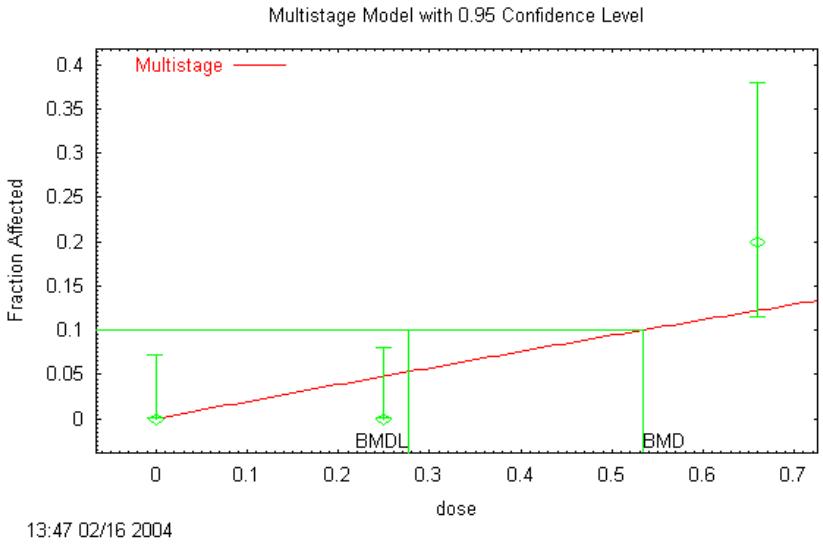
95.00 %

Incid Extra Risk	Time	Lower Bound	MLE	Upper Bound
1.0000E-006	70.00	4.3525E-004	5.3904E-004	Not Reqstd
1.0000E-005	70.00	4.3525E-003	5.3904E-003	Not Reqstd
0.0001	70.00	4.3527E-002	5.3906E-002	Not Reqstd
0.0010	70.00	4.3546E-001	5.3931E-001	Not Reqstd
0.01	70.00	4.3744E+000	5.4175E+000	Not Reqstd
0.10	70.00	4.5858E+001	5.6793E+001	Not Reqstd

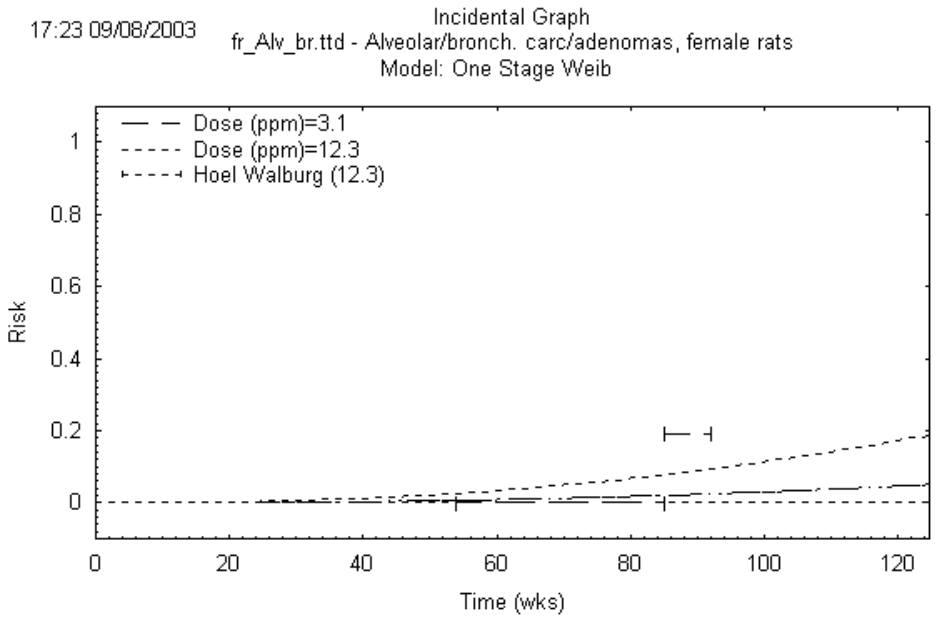
Output C-17. Multistage analysis of alveolar/bronchiolar adenomas, carcinomas in female rats, 1,2-dibromoethane inhalation exposure

```
BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = alv_br
   Independent variable = rgdr_ppm

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 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
                     Background =            0
                        Beta(1) =     0.358396


           Asymptotic Correlation Matrix of Parameter Estimates

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

                Beta(1)

   Beta(1)            1



                           Parameter Estimates

       Variable           Estimate             Std. Err.
     Background                  0                   NA
        Beta(1)           0.197519             0.252845

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



                        Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model         -12.5101
   Fitted model         -15.1907       5.36137      2         0.06852
  Reduced model         -20.5225       16.0249      2       0.0003313

           AIC:          32.3815


                     Goodness  of  Fit

     Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
  ----------------------------------------------------------------------
i: 1
    0.0000     0.0000         0.000         0          47       0.000
i: 2
    0.2500     0.0482         2.024         0          42      -1.051
```

```
i: 3
    0.6600      0.1222          3.056          5           25        0.725

 Chi-square =        3.54      DF = 2         P-value = 0.1707


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.533421

            BMDL =       0.276777
```



Output C-18. Multistage-Weibull analysis of alveolar/bronchiolar adenomas, carcinomas in female rats, 1,2-dibromoethane inhalation exposure

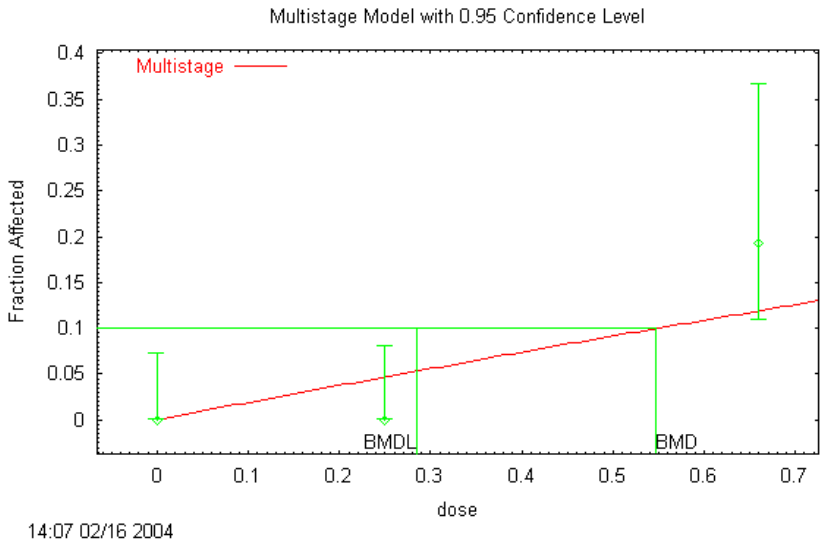



```
Model: One Stage Weib
Dataset: C:\Program Files\TOX_RISK\edb_inh\fr_Alv_br.ttd
Functional form: 1 - EXP[( -Q0 - Q1 * D ) * (T - T0)^Z]
         Maximum Log-Likelihood =  -1.706675e+001

       Parameter Estimates :
                            Q 0 = 0.000000E+000
                            Q 1 = 1.213408E-007
                            Z   = 2.453743E+000
                            T0  = 0.000000E+000


      Avg. Doses          -------------------- Number --------------------
        (ppm)               of animals       with fatal    with incidental
                                               tumors         tumors
         0                    50                 0             0
         3.10                 50                 0             0
        12.30                 50                 0             5

                                            Exposure Pattern
              Model: One Stage Weib     Age Begins: 0     Age Ends: 70
       Target Species: Human            Weeks/Year: 52   Days/Week:  7
              Route: Air                                 Hours/Day : 24
     Animal to human conversion method: PPM IN AIR

          Unit Potency [ per mg/kg-day ] (computed for Risk of 1.0E-6)
Lower Bound = Not Reqstd   MLE = 2.7040E-002   Upper Bound(q1*) = 7.3685E-002

                                  Dose Estimates (ppb)
                                95.00 %                          95.00 %
  Incid Extra Risk   Time     Lower Bound          MLE          Upper Bound
     1.0000E-006      70.00   6.0694E-003      1.6540E-002     Not Reqstd
     1.0000E-005      70.00   6.0694E-002      1.6540E-001     Not Reqstd
     0.0001           70.00   6.0697E-001      1.6540E+000     Not Reqstd
     0.0010           70.00   6.0724E+000      1.6548E+001     Not Reqstd
     0.01             70.00   6.0999E+001      1.6623E+002     Not Reqstd
     0.10             70.00   6.3947E+002      1.7426E+003     Not Reqstd
```

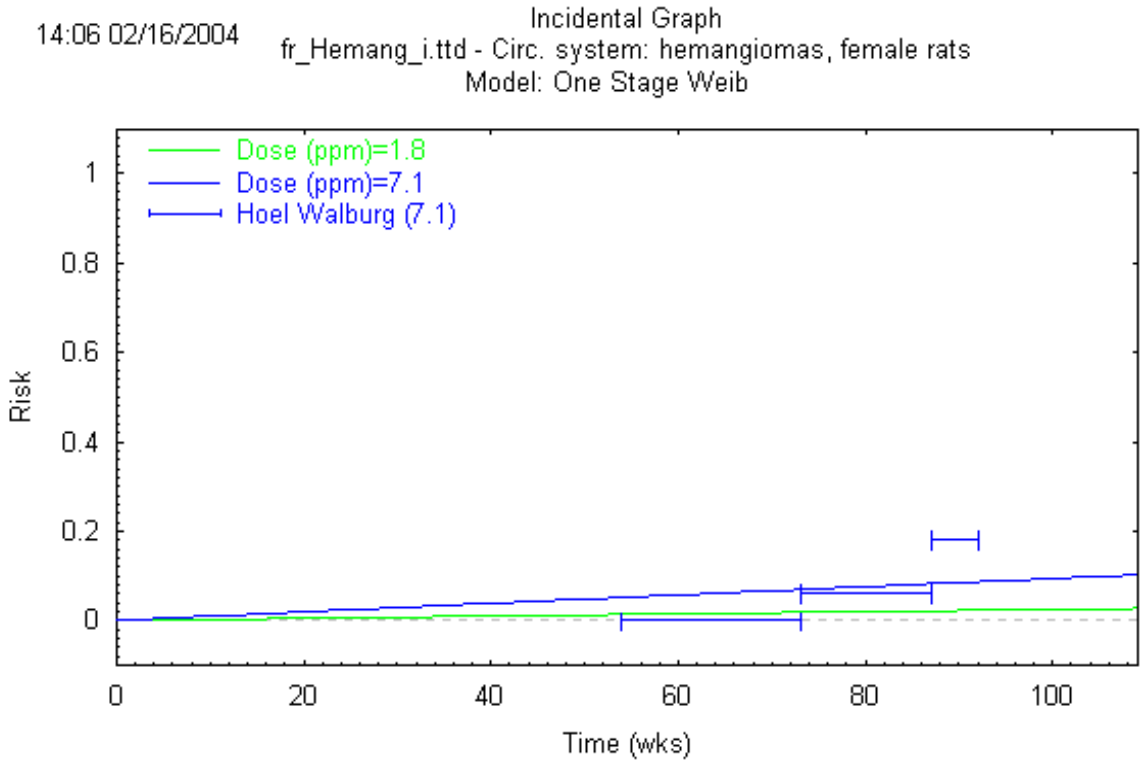
Output C-19. Multistage analysis of hemangiosarcomas in female rats, 1,2-dibromoethane inhalation exposure

```
BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = hemang
   Independent variable = rgdr_ppm

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 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
                     Background =           0
                        Beta(1) =     0.343027


           Asymptotic Correlation Matrix of Parameter Estimates

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

                Beta(1)

   Beta(1)            1



                           Parameter Estimates

       Variable           Estimate             Std. Err.
     Background                  0                   NA
        Beta(1)            0.192493            0.249396

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



                         Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model         -12.7283
    Fitted model        -15.3194       5.18217      2         0.07494
   Reduced model        -20.5672       15.6776      2       0.0003941

           AIC:          32.6389


                      Goodness  of  Fit

     Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
  ----------------------------------------------------------------------
i: 1
    0.0000     0.0000         0.000         0          47       0.000
i: 2
```

```
    0.2500      0.0470          1.973          0           42       -1.049
i: 3
    0.6600      0.1193          3.102          5           26        0.695

 Chi-square =       3.39     DF = 2        P-value = 0.1837


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.547347

            BMDL =       0.284013
```



Output C-20. Multistage-Weibull analysis of hemangiosarcomas in female rats, 1,2-dibromoethane inhalation exposure




```
Generating Model Fit Table ---
TITLE: Circ. system: hemangiomas, female rats

             Model: One Stage Weib         Dataset: C:\Program
Files\TOX_RISK\edb_inh\fr_Hemang_i.ttd
Functional form: 1 - EXP[( -Q0 - Q1 * D ) * (T - T0)^Z]
         Maximum Log-Likelihood =  -1.736830e+001

       Parameter Estimates :
                           Q 0 = 0.000000E+000
                           Q 1 = 1.388308E-004
                           Z   = 1.000000E+000
                           T0  = 0.000000E+000   Set by User


      Avg. Doses          -------------------- Number --------------------
        (ppm)               of animals       with fatal    with incidental
                                               tumors         tumors
         0                    50                 0             0
         1.80                 50                 0             0
         7.10                 50                 0             5



Generating Extrapolated Doses Table ---
TITLE: Circ. system: hemangiomas, female rats

             Dataset: C:\Program Files\TOX_RISK\edb_inh\fr_Hemang_i.ttd
                                          Exposure Pattern
               Model: One Stage Weib     Age Begins: 0     Age Ends: 70
      Target Species: Human              Weeks/Year: 52   Days/Week:  7
               Route: Air                                 Hours/Day : 24
     Animal to human conversion method: PPM IN AIR

          Unit Potency [ per mg/kg/day ] (computed for Risk of 1.0E-6)
Lower Bound = Not Reqstd   MLE = 6.2570E-003   Upper Bound(q1*) = 1.2277E-002
```

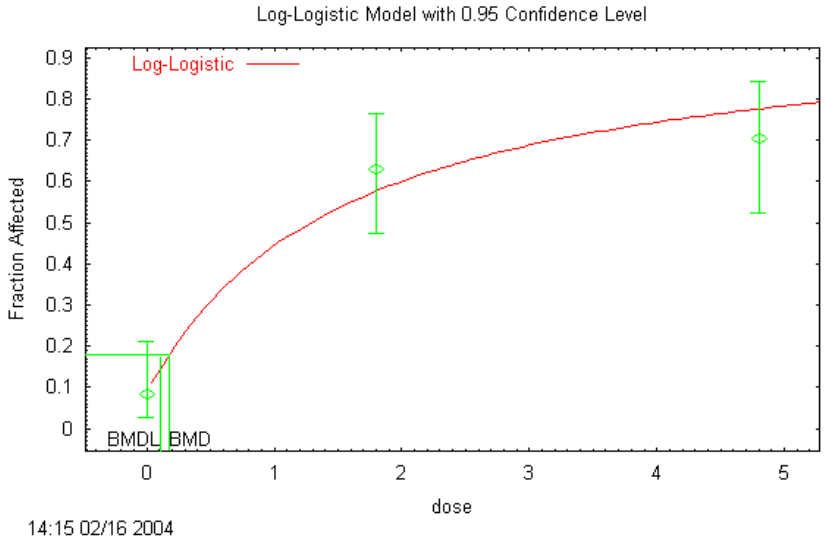
Induction Time (T0) Set by User to 0

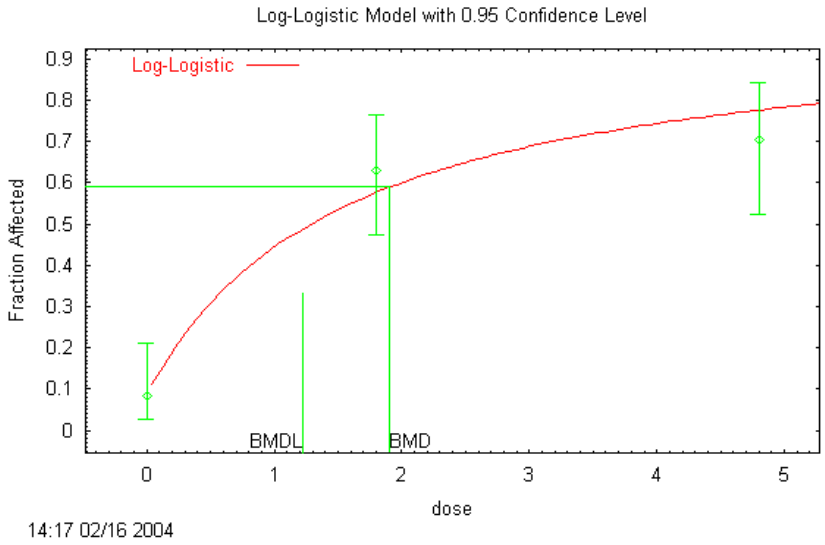
		Dose Estimates (ppb)		
		95.00 %		95.00 %
Incid Extra Risk	Time	Lower Bound	MLE	Upper Bound
1.0000E-006	70.00	3.6427E-002	7.1476E-002	Not Reqstd
1.0000E-005	70.00	3.6428E-001	7.1476E-001	Not Reqstd
0.0001	70.00	3.6429E+000	7.1479E+000	Not Reqstd
0.0010	70.00	3.6446E+001	7.1512E+001	Not Reqstd
0.01	70.00	3.6611E+002	7.1836E+002	Not Reqstd
0.10	70.00	3.8380E+003	7.5307E+003	Not Reqstd

Output C-21. Multistage analysis of mammary fibroadenomas in female rats, 1,2-dibromoethane inhalation exposure

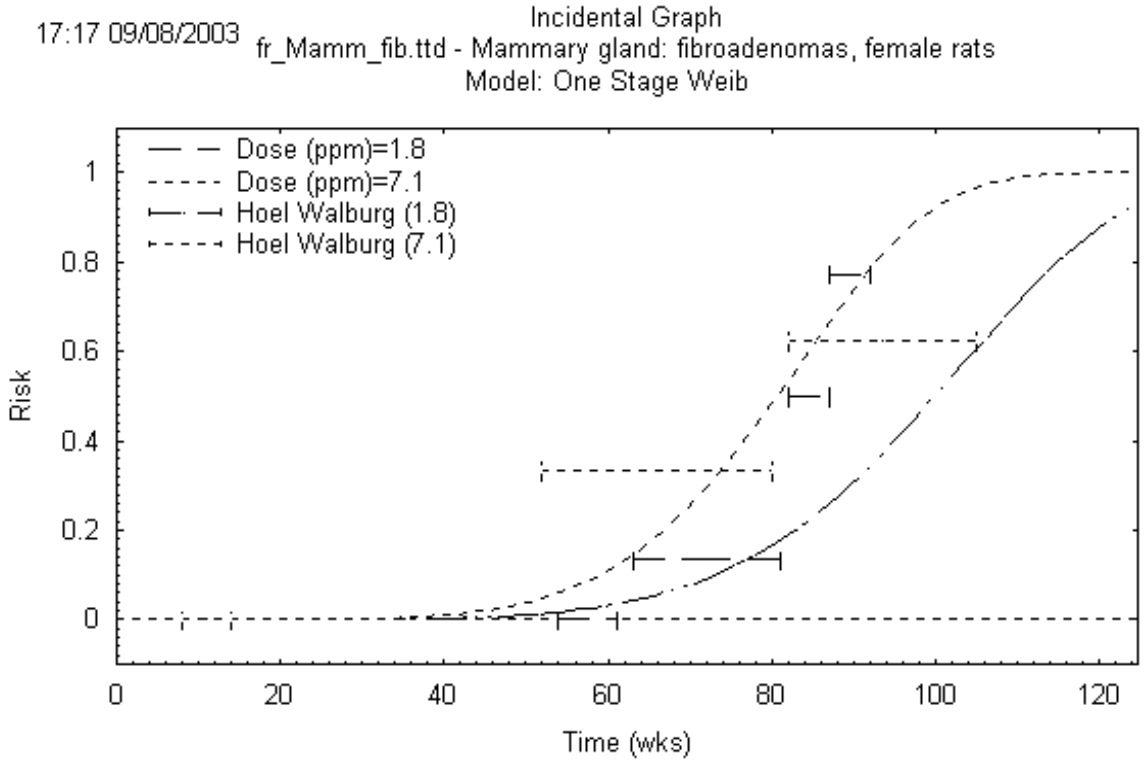
```
BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

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


   Dependent variable = fibro_inc
   Independent variable = ppm
   Slope parameter is restricted as slope >= 1

   Total number of observations = 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



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =    0.0851064
                     intercept =    -0.381425
                         slope =            1


           Asymptotic Correlation Matrix of Parameter Estimates

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

             background    intercept

background            1         -0.3

 intercept         -0.3            1


                         Parameter Estimates

      Variable           Estimate             Std. Err.
    background           0.0874464           0.0417909
     intercept           -0.445308            0.268769
         slope                   1                  NA

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


                       Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model         -64.5786
    Fitted model        -65.3126       1.46797      1          0.2257
  Reduced model         -87.3632       45.5692      2         <.0001

           AIC:          134.625


                     Goodness  of  Fit

                                                                 Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ----------------------------------------------------------------------
    0.0000      0.0874          4.110          4           47     -0.05679
    1.8000      0.5762         26.504         29           46       0.7447
```

```
   4.8000       0.7761          26.386          24            34       -0.9816

Chi-square =        1.52      DF = 1         P-value = 0.2174


  Benchmark Dose Computation

Specified effect =            0.1               Specified effect =           0.55

Risk Type        =       Extra risk             Risk Type        =       Extra risk

Confidence level =           0.95               Confidence level =           0.95

             BMD =       0.173441                           BMD =        1.90785

            BMDL =       0.111687                          BMDL =        1.22856
```





Output C-22. Multistage-Weibull analysis of mammary fibroadenomas in female rats, 1,2-dibromoethane inhalation exposure



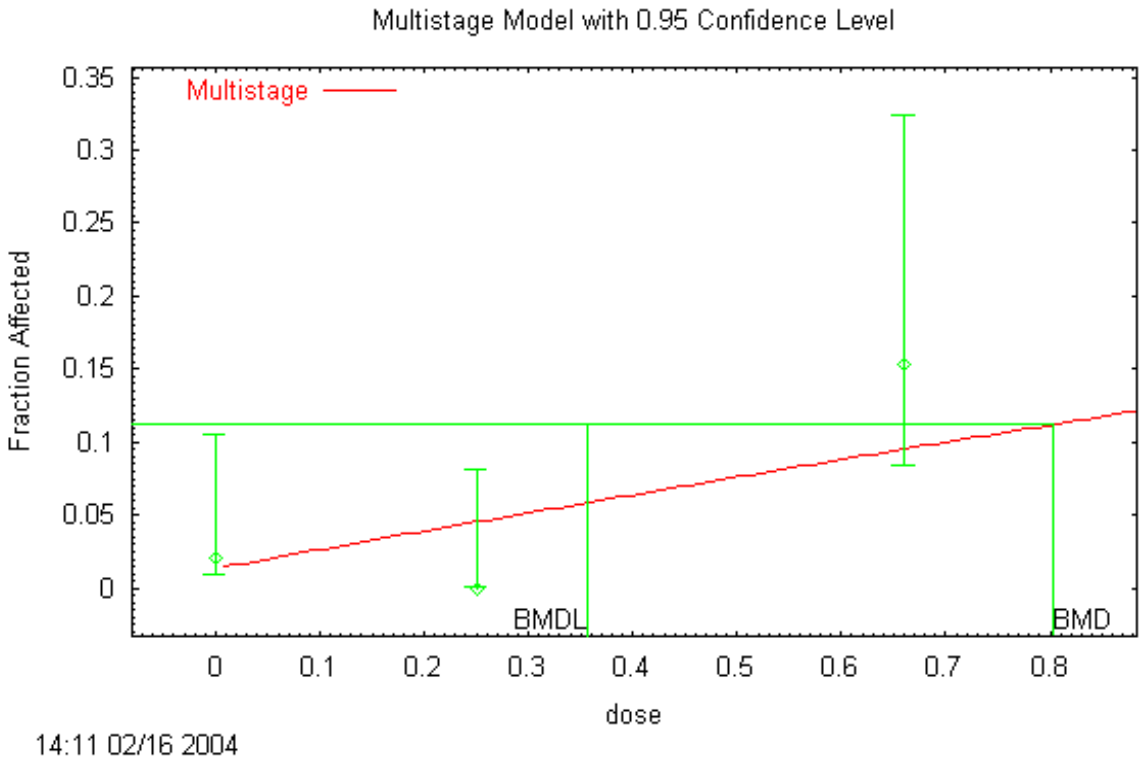

```
Model: One Stage Weib
Dataset: C:\Program Files\TOX_RISK\edb_inh\fr_Mamm_fib.ttd
Functional form: 1 - EXP[( -Q0 - Q1 * D ) * (T - T0)^Z]
         Maximum Log-Likelihood =  -7.896265e+001

       Parameter Estimates :
                           Q 0 = 6.239703E-014
                           Q 1 = 3.012200E-013
                           Z   = 6.030535E+000
                           T0  = 0.000000E+000


      Avg. Doses          -------------------- Number --------------------
        (ppm)               of animals       with fatal     with incidental
                                               tumors          tumors
          0                    50                0              4
          1.80                 50                0             29
          7.10                 50                0             24


                                          Exposure Pattern
             Model: One Stage Weib     Age Begins: 0     Age Ends: 70
      Target Species: Human            Weeks/Year: 52   Days/Week:  7
             Route: Air                                 Hours/Day : 24
     Animal to human conversion method: PPM IN AIR

          Unit Potency [ per mg/kg-day ] (computed for Risk of 1.0E-6)
Lower Bound = Not Reqstd   MLE = 1.1295E+000   Upper Bound(q1*) = 1.5809E+000

                                  Dose Estimates (ppb)
                                95.00 %                          95.00 %
  Incid Extra Risk   Time     Lower Bound          MLE          Upper Bound
     1.0000E-006      70.00   2.8289E-004      3.9597E-004     Not Reqstd
     1.0000E-005      70.00   2.8290E-003      3.9597E-003     Not Reqstd
     0.0001           70.00   2.8291E-002      3.9599E-002     Not Reqstd
     0.0010           70.00   2.8304E-001      3.9616E-001     Not Reqstd
     0.01             70.00   2.8432E+000      3.9796E+000     Not Reqstd
```

```
     0.10             70.00   2.9806E+001      4.1719E+001     Not Reqstd
```

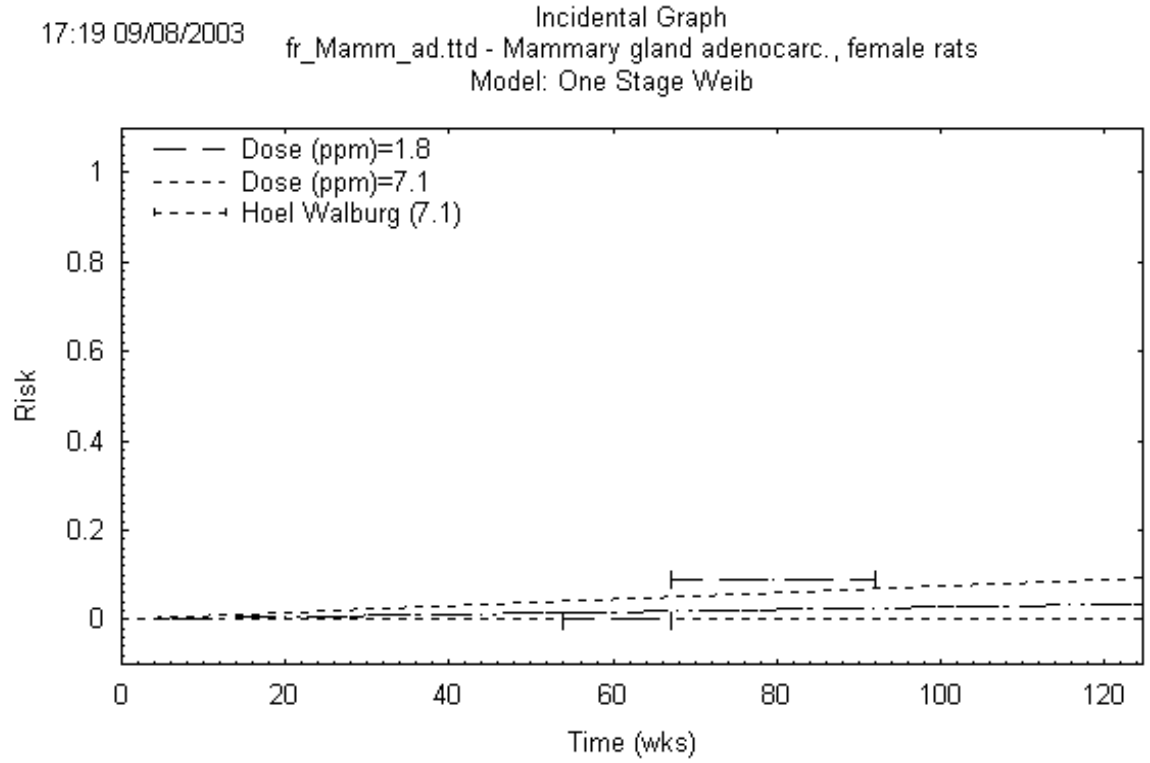
Output C-23. Multistage analysis of mammary adenocarcinomas in female rats, 1,2-dibromoethane inhalation exposure

```
=====================================================================
          Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
          Input Data File: F:\KHOGAN02\_BMDS\EDB_INH_FR.(d)
          Gnuplot Plotting File:  F:\KHOGAN02\_BMDS\EDB_INH_FR.plt
                                                  Mon Feb 16 14:11:39 2004
 =====================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = m_aden
   Independent variable = rgdr_ppm

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 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
                     Background =            0
                        Beta(1) =     0.238933


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1        -0.59

   Beta(1)        -0.59            1



                          Parameter Estimates

       Variable           Estimate            Std. Err.
     Background           0.0136816           0.116137
        Beta(1)            0.131115           0.303951



                       Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model         -16.0018
   Fitted model         -18.4844       4.96513      1         0.02586
  Reduced model         -20.5672       9.13067      2         0.01041

           AIC:          40.9688


                     Goodness  of  Fit

     Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
  ----------------------------------------------------------------------
i: 1
    0.0000     0.0137         0.643         1          47       0.563
```

```
i: 2
    0.2500      0.0455          1.910          0           42       -1.048
i: 3
    0.6600      0.0954          2.482          4           26        0.676

 Chi-square =       3.23      DF = 1         P-value = 0.0723


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.803575

            BMDL =       0.357022
```



Output C-24. Multistage-Weibull analysis of mammary adenocarcinomas in female rats, 1,2-dibromoethane inhalation exposure




```
Model: One Stage Weib
Dataset: C:\Program Files\TOX_RISK\edb_inh\fr_Mamm_ad.ttd
Functional form: 1 - EXP[( -Q0 - Q1 * D ) * (T - T0)^Z]
         Maximum Log-Likelihood =  -2.060090e+001

       Parameter Estimates :
                            Q 0 = 1.146848E-004
                            Q 1 = 9.364217E-005
                            Z   = 1.000000E+000
                            T0  = 0.000000E+000


      Avg. Doses          -------------------- Number --------------------
        (ppm)               of animals       with fatal    with incidental
                                               tumors          tumors
         0                    50                 0              1
         1.80                 50                 0              0
         7.10                 50                 0              4


               Model: One Stage Weib     Age Begins: 0     Age Ends: 70
      Target Species: Human              Weeks/Year: 52   Days/Week:  7
               Route: Air                                 Hours/Day : 24
     Animal to human conversion method: PPM IN AIR

          Unit Potency [ per mg/kg-day ] (computed for Risk of 1.0E-6)
Lower Bound = Not Reqstd   MLE = 2.7175E-002   Upper Bound(q1*) = 6.6137E-002

                                  Dose Estimates (ppb)
                                95.00 %                          95.00 %
  Incid Extra Risk   Time     Lower Bound          MLE          Upper Bound
     1.0000E-006      70.00   6.7621E-003      1.6457E-002      Not Reqstd
     1.0000E-005      70.00   6.7622E-002      1.6458E-001      Not Reqstd
     0.0001           70.00   6.7625E-001      1.6458E+000      Not Reqstd
     0.0010           70.00   6.7655E+000      1.6466E+001      Not Reqstd
     0.01             70.00   6.7962E+001      1.6540E+002      Not Reqstd
     0.10             70.00   7.1246E+002      1.7340E+003      Not Reqstd
```

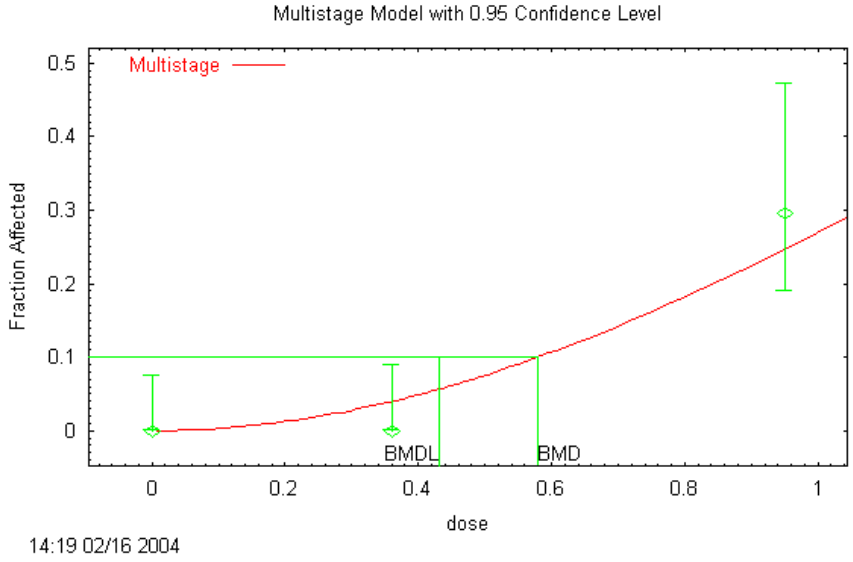
Output C-25. Multistage analysis of nasal cavity tumors in female mice, 1,2-dibromoethane inhalation exposure

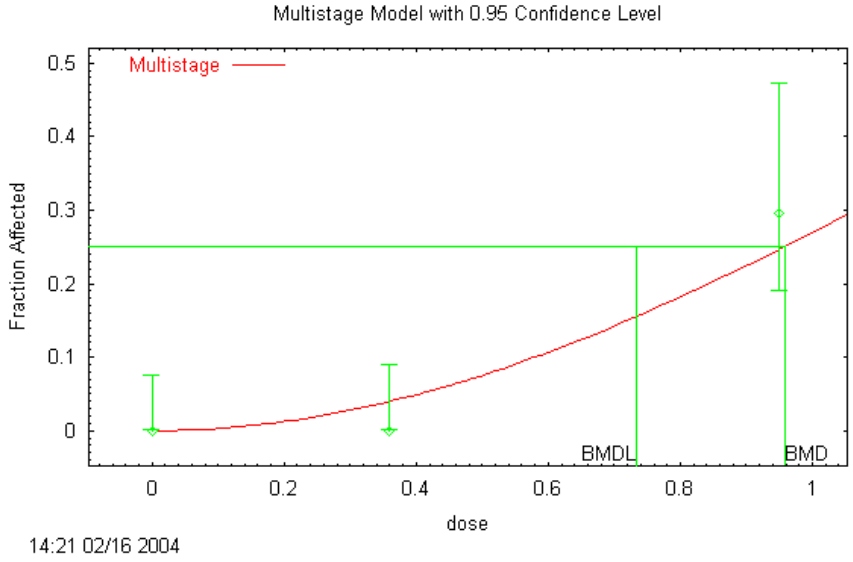
```
BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = all_nasal
   Independent variable = rgdr_ppm

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 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
                     Background =            0
                        Beta(1) =            0
                        Beta(2) =     0.412082


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(1)
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

                Beta(2)

   Beta(2)            1



                          Parameter Estimates

       Variable           Estimate             Std. Err.
     Background                  0                   NA
        Beta(1)                  0                   NA
        Beta(2)           0.313575            0.224054

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



                       Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model         -16.4077
   Fitted model         -18.1251        3.4347      2          0.1795
  Reduced model         -28.7452        24.675      2         <.0001

           AIC:          38.2501


                     Goodness  of  Fit

     Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
  ----------------------------------------------------------------------
i: 1
    0.0000     0.0000         0.000         0          46       0.000
```

```
i: 2
    0.3600      0.0398          1.513          0           38       -1.041
i: 3
    0.9500      0.2465          6.655          8           27        0.268

 Chi-square =       1.94     DF = 2        P-value = 0.3797
```

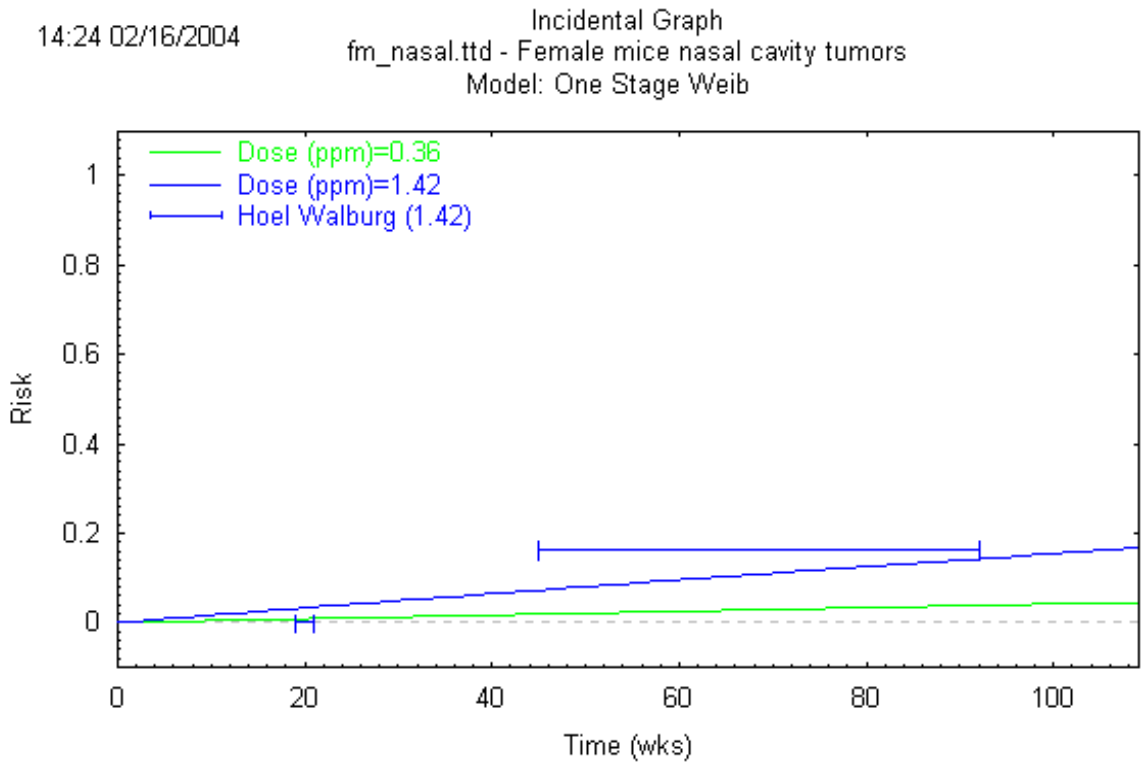
Benchmark Dose Computation

Specified effect =	0.1	Specified effect =	0.25
Risk Type =	Extra risk	Risk Type =	Extra risk
Confidence level =	0.95	Confidence level =	0.95
BMD =	0.579653	BMD =	0.957824
BMDL =	0.431521	BMDL =	0.733903





Output C-26. Multistage-Weibull analysis of nasal cavity tumors in female mice, 1,2-dibromoethane inhalation exposure




```
Generating Model Fit Table ---
TITLE: Female mice nasal cavity tumors

              Model: One Stage Weib         Dataset: C:\Program
Files\TOX_RISK\edb_inh\fm_nasal.ttd
Functional form: 1 - EXP[( -Q0 - Q1 * D ) * (T - T0)^Z]
         Maximum Log-Likelihood =  -2.495443e+001

       Parameter Estimates :
                            Q 0 = 0.000000E+000
                            Q 1 = 1.177299E-003
                            Z   = 1.000000E+000
                            T0  = 0.000000E+000   Set by User


      Avg. Doses         -------------------- Number --------------------
        (ppm)              of animals       with fatal     with incidental
                                              tumors          tumors
          0                   50                0              0
          0.36                50                0              0
          1.42                50                0              8



Generating Extrapolated Doses Table ---
TITLE: Female mice nasal cavity tumors

             Dataset: C:\Program Files\TOX_RISK\edb_inh\fm_nasal.ttd
                                              Exposure Pattern
               Model: One Stage Weib     Age Begins: 0     Age Ends: 70
      Target Species: Human              Weeks/Year: 52   Days/Week:  7
               Route: Air                                 Hours/Day : 24
     Animal to human conversion method: PPM IN AIR

          Unit Potency [ per mg/kg/day ] (computed for Risk of 1.0E-6)
Lower Bound = Not Reqstd   MLE = 5.4729E-002   Upper Bound(q1*) = 8.0545E-002
```

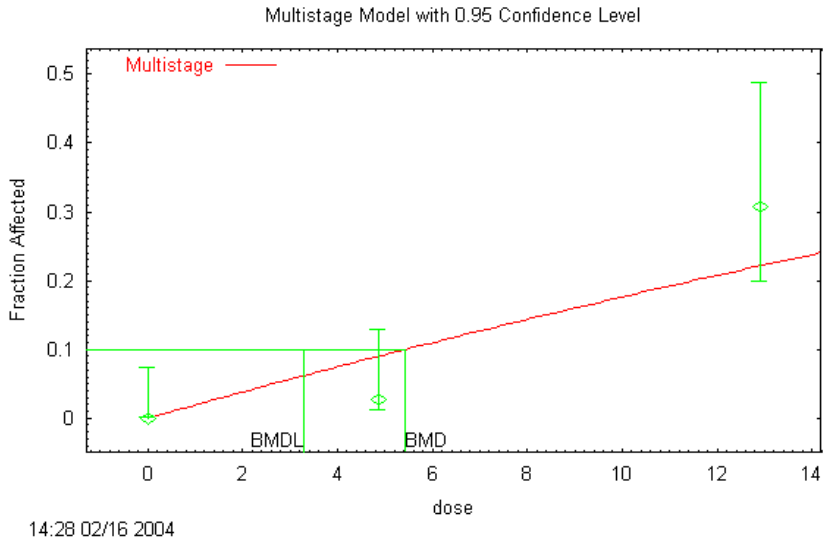
Induction Time (T0) Set by User to 0

		Dose Estimates (ppb)		
		95.00 %		95.00 %
Incid Extra Risk	Time	Lower Bound	MLE	Upper Bound
1.0000E-006	70.00	5.5495E-003	8.1673E-003	Not Reqstd
1.0000E-005	70.00	5.5496E-002	8.1674E-002	Not Reqstd
0.0001	70.00	5.5498E-001	8.1677E-001	Not Reqstd
0.0010	70.00	5.5523E+000	8.1714E+000	Not Reqstd
0.01	70.00	5.5775E+001	8.2084E+001	Not Reqstd
0.10	70.00	8.3863E+002	8.6051E+002	Not Reqstd

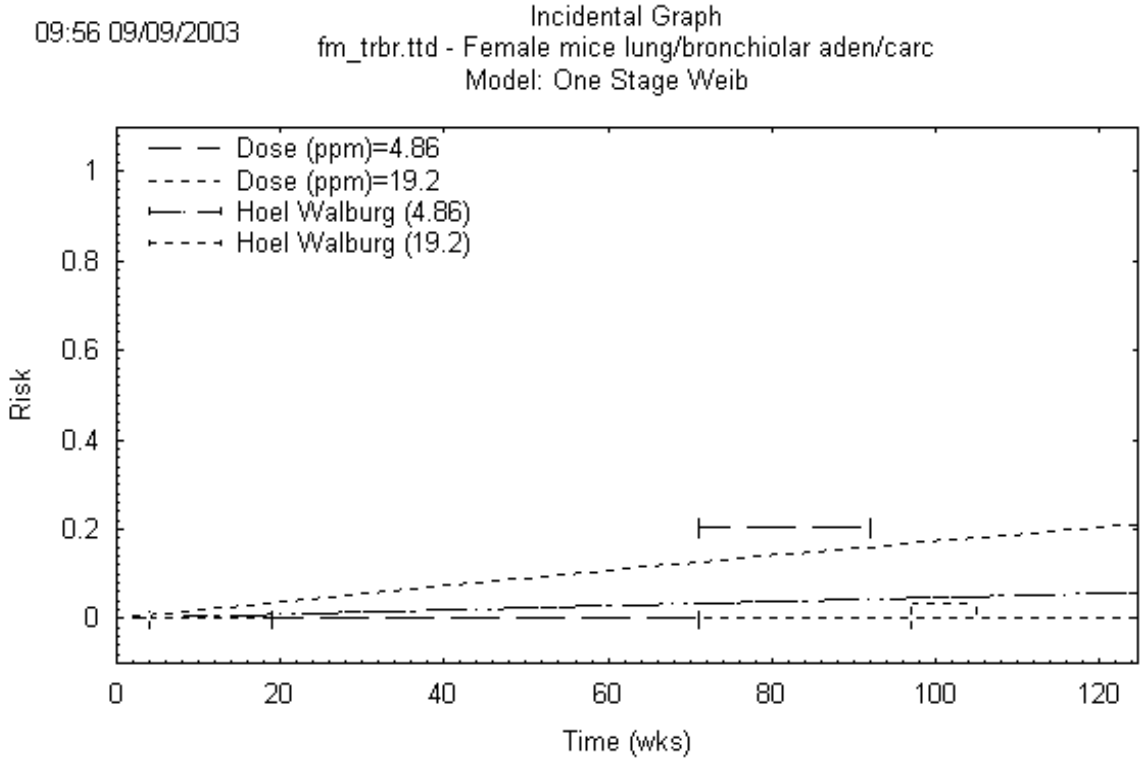
Output C-27. Multistage analysis of lung/bronchial adenomas, carcinomas in female mice, 1,2-dibromoethane inhalation exposure

```
BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = lungbr
   Independent variable = tb_ppm

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 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
                     Background =            0
                        Beta(1) =    0.0299027


           Asymptotic Correlation Matrix of Parameter Estimates

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

                Beta(1)

   Beta(1)            1



                           Parameter Estimates

       Variable           Estimate             Std. Err.
     Background                  0                   NA
        Beta(1)          0.0194024           0.0142568

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


                         Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model         -20.6726
   Fitted model         -22.4636       3.58204      2          0.1668
  Reduced model         -31.1506       20.9561      2         <.0001

           AIC:          46.9272


                      Goodness  of  Fit

     Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
  ----------------------------------------------------------------------
i: 1
    0.0000     0.0000         0.000         0          46       0.000
i: 2
```

```
    4.8600      0.0900          3.419          1           38       -0.778
i: 3
   12.9000      0.2214          5.757          8           26        0.500

 Chi-square =       3.00     DF = 2        P-value = 0.2227


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        5.43029

            BMDL =        3.28056
```



Output C-28. Multistage-Weibull analysis of lung/bronchial adenomas, carcinomas in female mice, 1,2-dibromoethane inhalation exposure



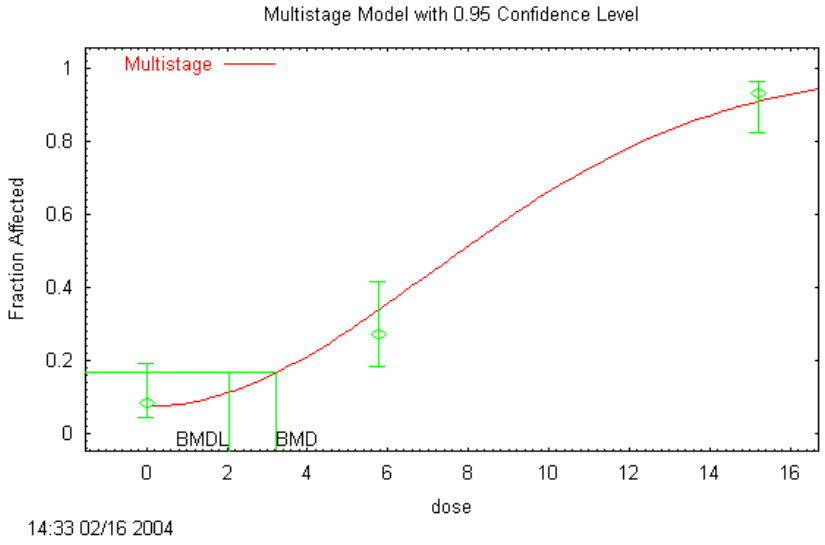

```
Model: One Stage Weib
Dataset: C:\Program Files\TOX_RISK\edb_inh\fm_trbr.ttd
Functional form: 1 - EXP[( -Q0 - Q1 * D ) * (T - T0)^Z]
         Maximum Log-Likelihood =  -2.704645e+001

       Parameter Estimates :
                             Q 0 = 0.000000E+000
                             Q 1 = 9.896876E-005
                             Z   = 1.000000E+000
                             T0  = 0.000000E+000


      Avg. Doses          -------------------- Number --------------------
        (ppm)               of animals       with fatal    with incidental
                                               tumors          tumors
          0                    49                0              0
          4.86                 50                0              1
         19.20                 50                0              8


                                              Exposure Pattern
              Model: One Stage Weib     Age Begins: 0     Age Ends: 70
     Target Species: Human              Weeks/Year: 52   Days/Week:  7
              Route: Air                                 Hours/Day : 24
    Animal to human conversion method: PPM IN AIR

         Unit Potency [ per mg/kg-day ] (computed for Risk of 1.0E-6)
Lower Bound = Not Reqstd   MLE = 5.0781E-003   Upper Bound(q1*) = 1.0765E-002

                                 Dose Estimates (ppb)
                               95.00 %                          95.00 %
  Incid Extra Risk   Time     Lower Bound          MLE          Upper Bound
     1.0000E-006      70.00   4.1524E-002      8.8023E-002     Not Reqstd
     1.0000E-005      70.00   4.1524E-001      8.8024E-001     Not Reqstd
     0.0001           70.00   4.1526E+000      8.8028E+000     Not Reqstd
     0.0010           70.00   4.1545E+001      8.8067E+001     Not Reqstd
```

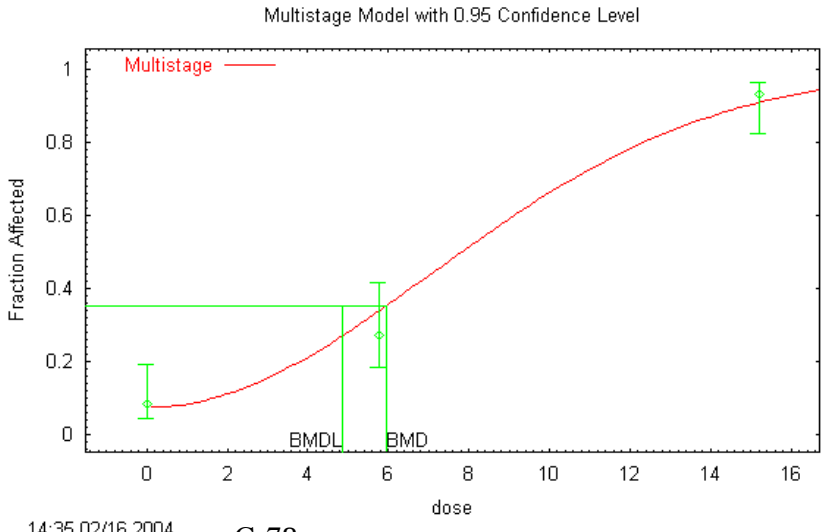
0.01	70.00	4.1733E+002	8.8466E+002	Not Reqstd
0.10	70.00	4.3750E+003	9.2742E+003	Not Reqstd

Output C-29. Multistage analysis of alveolar/bronchiolar adenomas, carcinomas in female mice, 1,2-dibromoethane inhalation exposure

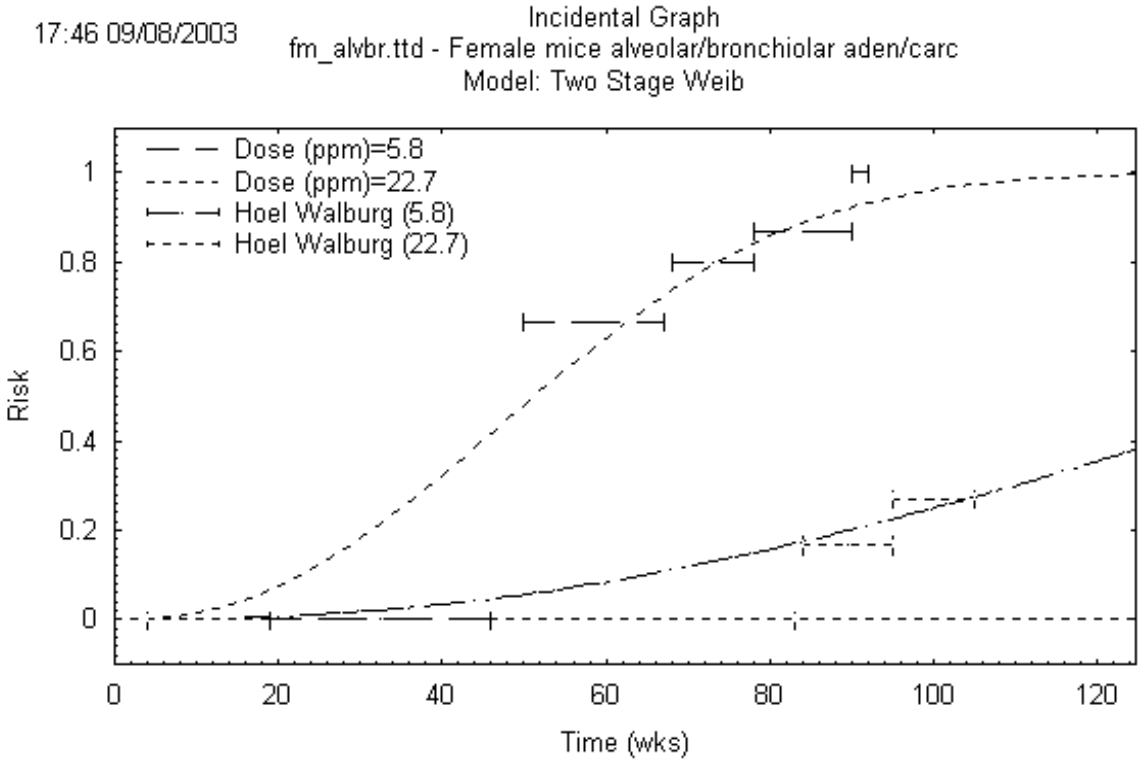
```
BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = alv_br
   Independent variable = pulm_ppm

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 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
                     Background =      0.02142
                        Beta(1) =            0
                        Beta(2) =    0.0114798


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Beta(1)
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

             Background      Beta(2)

Background            1        -0.39

   Beta(2)        -0.39            1



                          Parameter Estimates

      Variable           Estimate             Std. Err.
    Background          0.0763105             0.115724
       Beta(1)                  0                   NA
       Beta(2)          0.0100582          0.00220996

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



                       Analysis of Deviance Table

      Model      Log(likelihood)  Deviance  Test DF     P-value
    Full model          -48.069
   Fitted model        -48.6198       1.10154      1          0.2939
  Reduced model         -88.859       81.5799      2         <.0001

           AIC:          101.24


                     Goodness  of  Fit

    Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
```

```
  ------------------------------------------------------------------------
i: 1
    0.0000      0.0763          3.510          4           46        0.151
i: 2
    5.7600      0.3384         13.536         11           40       -0.283
i: 3
   15.2000      0.9096         40.021         41           44        0.270

 Chi-square =       1.06     DF = 1        P-value = 0.3040

   Benchmark Dose Computation

 Specified effect =            0.1          Specified effect =            0.3

 Risk Type        =      Extra risk          Risk Type        =      Extra risk

 Confidence level =           0.95          Confidence level =           0.95

              BMD =        3.23653                       BMD =        5.95493

             BMDL =        2.04555                      BMDL =        4.84281
```





Output C-30. Multistage-Weibull analysis of alveolar/bronchiolar adenomas, carcinomas in female mice, 1,2-dibromoethane inhalation exposure




```
Model: Two Stage Weib
Dataset: C:\Program Files\TOX_RISK\edb_inh\fm_alvbr.ttd
Functional form: 1 - EXP[( -Q0 - Q1 * D - Q2 * D^2) * (T - T0)^Z]
         Maximum Log-Likelihood =  -5.951707e+001
       Parameter Estimates :
                              Q 0 = 1.853318E-006
                              Q 1 = 0.000000E+000
                              Q 2 = 1.448222E-007
                              Z   = 2.314668E+000
                              T0  = 0.000000E+000

      Avg. Doses          -------------------- Number --------------------
        (ppm)               of animals       with fatal    with incidental
                                               tumors          tumors
         0                    49                 0              4
         5.80                 50                 0             11
        22.70                 50                 0             41


                                                 Exposure Pattern
              Model: Two Stage Weib     Age Begins: 0     Age Ends: 70
      Target Species: Human             Weeks/Year: 52   Days/Week:  7
              Route: Air                                 Hours/Day : 24
     Animal to human conversion method: PPM IN AIR

          Unit Potency [ per mg/kg-day ] (computed for Risk of 1.0E-6)
Lower Bound = Not Reqstd   MLE = 3.9741E-005   Upper Bound(q1*) = 1.6248E-002

                                  Dose Estimates (ppb)
                                95.00 %                          95.00 %
  Incid Extra Risk   Time     Lower Bound          MLE          Upper Bound
     1.0000E-006      70.00   2.7511E-002      1.1247E+001     Not Reqstd
     1.0000E-005      70.00   2.7510E-001      3.5567E+001     Not Reqstd
     0.0001           70.00   2.7502E+000      1.1248E+002     Not Reqstd
     0.0010           70.00   2.7419E+001      3.5576E+002     Not Reqstd
```

0.01	70.00	2.6643E+002	1.1276E+003	Not Reqstd
0.10	70.00	2.1863E+003	3.6508E+003	Not Reqstd

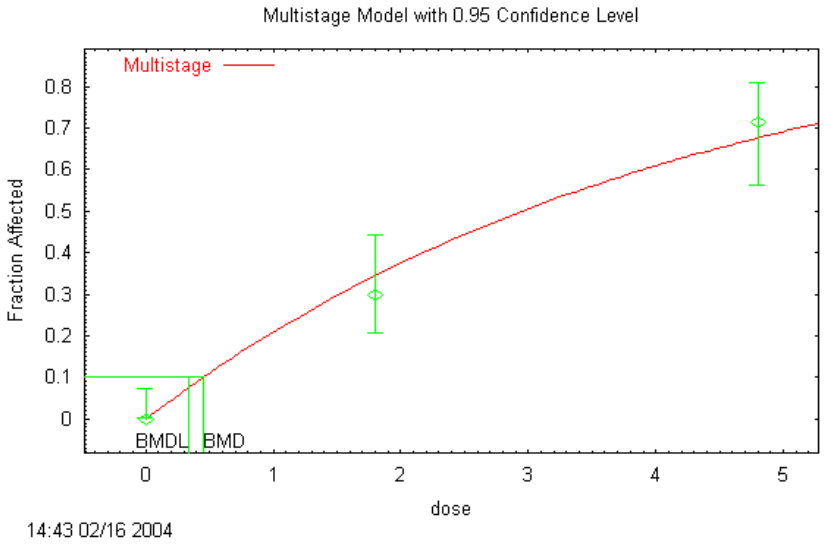
Output C-31. Multistage analysis of hemangiosarcomas in female mice, 1,2-dibromoethane inhalation exposure

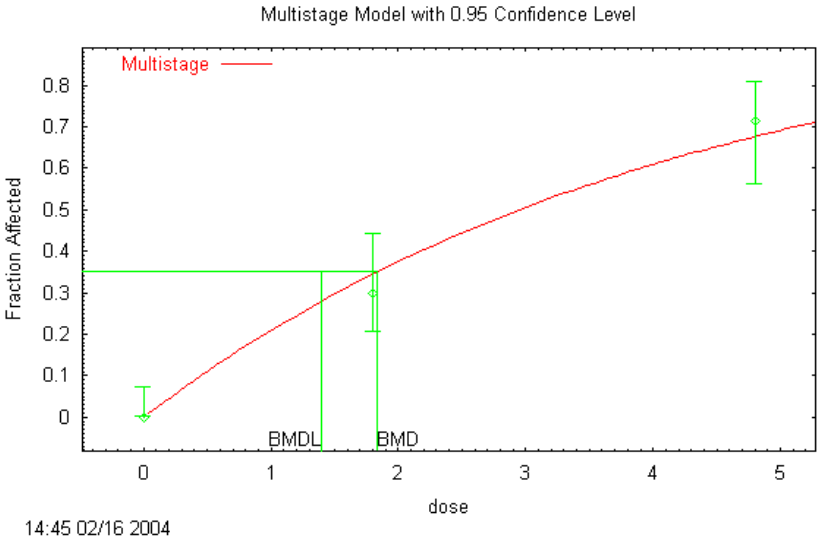
```
BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = hemang
   Independent variable = ppm

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 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
                     Background =            0
                        Beta(1) =      0.26484


           Asymptotic Correlation Matrix of Parameter Estimates

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

                Beta(1)

   Beta(1)            1



                           Parameter Estimates

       Variable           Estimate             Std. Err.
     Background                  0                   NA
        Beta(1)           0.235085            0.0535051

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

                        Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model         -45.374
   Fitted model        -45.6745      0.600956      2          0.7405
  Reduced model        -74.4981       58.2481      2         <.0001

           AIC:          93.349

                     Goodness  of  Fit

     Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
  ----------------------------------------------------------------------
i: 1
    0.0000     0.0000         0.000         0          46       0.000
i: 2
    1.8000     0.3450        13.801        12          40      -0.199
i: 3
    4.8000     0.6765        23.676        25          35       0.173
```

Chi-square = 0.59 DF = 2 P-value = 0.7454

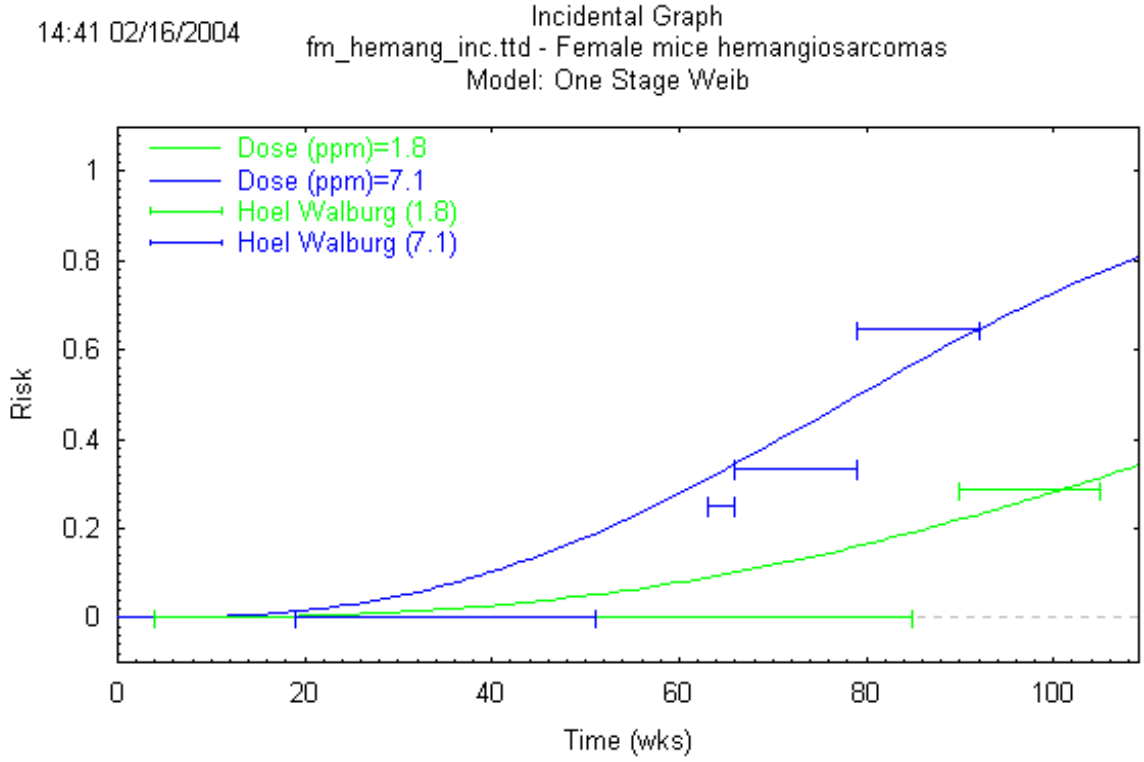
Benchmark Dose Computation

Specified effect =	0.1	Specified effect =	0.35
Risk Type =	Extra risk	Risk Type =	Extra risk
Confidence level =	0.95	Confidence level =	0.95
BMD =	0.44818	BMD =	1.83245
BMDL =	0.342107	BMDL =	1.39876





Output C-32. Multistage-Weibull analysis of hemangiosarcomas in female mice, 1,2-dibromoethane inhalation exposure




```
Generating Model Fit Table ---
TITLE: Female mice hemangiosarcomas

              Model: One Stage Weib         Dataset: C:\Program
Files\TOX_RISK\edb_inh\fm_hemang_inc.ttd
Functional form: 1 - EXP[( -Q0 - Q1 * D ) * (T - T0)^Z]
         Maximum Log-Likelihood =  -5.867227e+001

       Parameter Estimates :
                            Q 0 = 0.000000E+000
                            Q 1 = 7.001441E-007
                            Z   = 2.709143E+000
                            T0  = 0.000000E+000   Set by User


      Avg. Doses          -------------------- Number --------------------
        (ppm)               of animals       with fatal     with incidental
                                               tumors          tumors
         0                    50                 0              0
         1.80                 50                 0             12
         7.10                 50                 0             25



Generating Extrapolated Doses Table ---
TITLE: Female mice hemangiosarcomas

             Dataset: C:\Program Files\TOX_RISK\edb_inh\fm_hemang_inc.ttd
                                          Exposure Pattern
               Model: One Stage Weib     Age Begins: 0     Age Ends: 70
      Target Species: Human              Weeks/Year: 52   Days/Week:  7
               Route: Air                                 Hours/Day : 24
     Animal to human conversion method: PPM IN AIR

          Unit Potency [ per mg/kg/day ] (computed for Risk of 1.0E-6)
Lower Bound = Not Reqstd   MLE = 6.8278E-002   Upper Bound(q1*) = 8.9891E-002
```

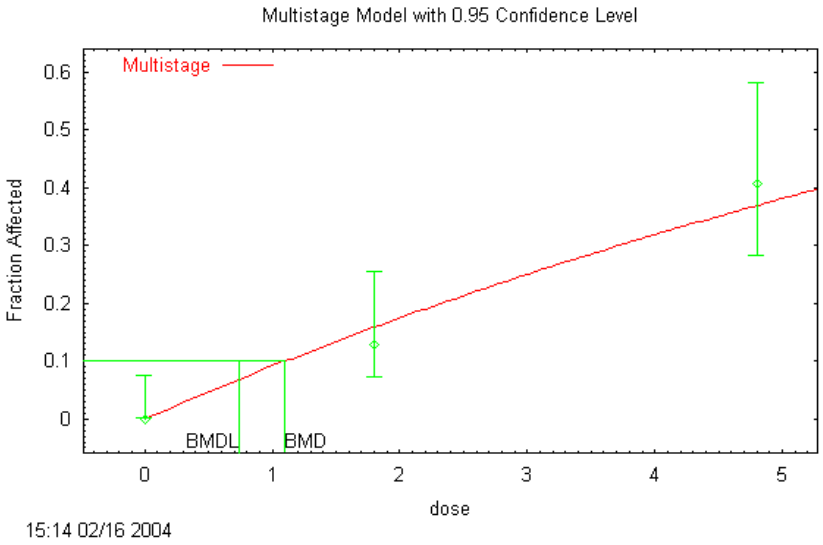
Induction Time (T0) Set by User to 0

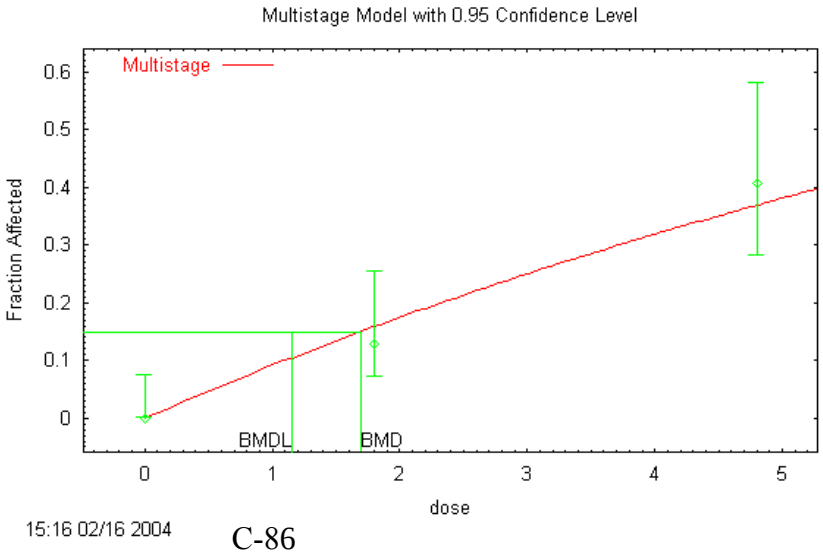
		Dose Estimates (ppb)		
		95.00 %		95.00 %
Incid Extra Risk	Time	Lower Bound	MLE	Upper Bound
1.0000E-006	70.00	4.9725E-003	6.5466E-003	Not Reqstd
1.0000E-005	70.00	4.9726E-002	6.5466E-002	Not Reqstd
0.0001	70.00	4.9728E-001	6.5469E-001	Not Reqstd
0.0010	70.00	4.9750E+000	6.5498E+000	Not Reqstd
0.01	70.00	4.9976E+001	6.5795E+001	Not Reqstd
0.10	70.00	5.2391E+002	6.8975E+002	Not Reqstd

Output C-33. Multistage analysis of fibrosarcomas in female mice, 1,2-dibromoethane inhalation exposure

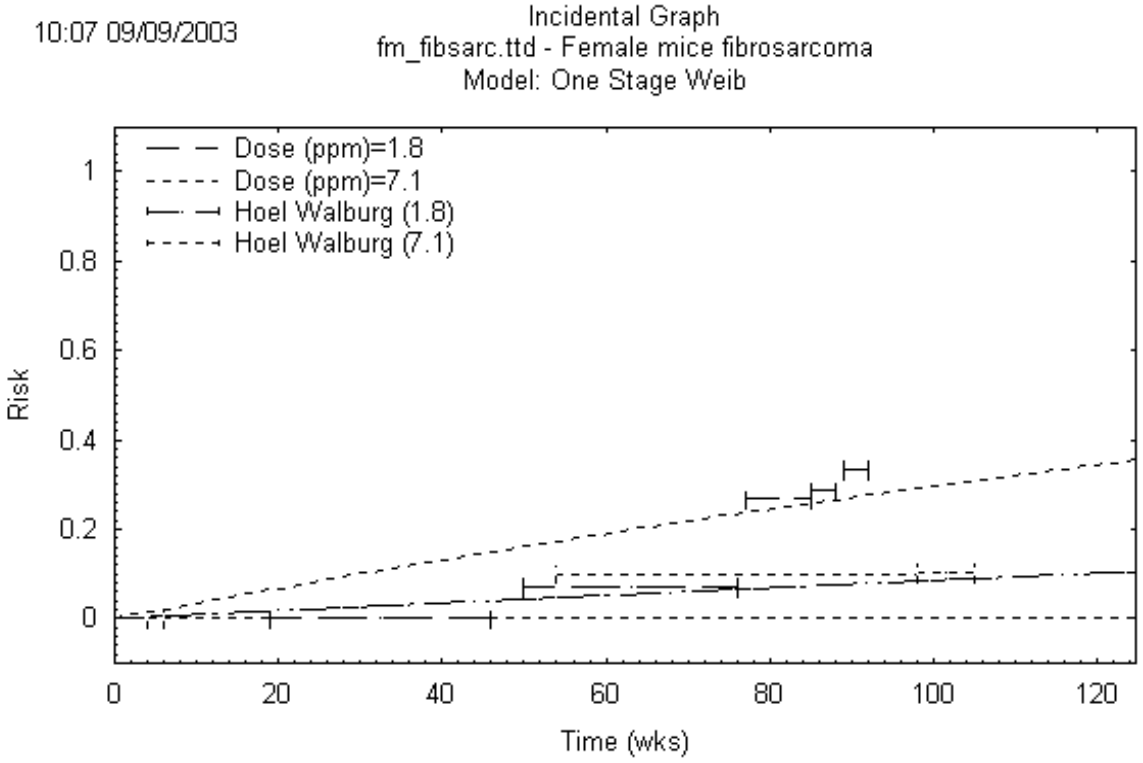
```
BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = fibro_inc
   Independent variable = ppm

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 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
                     Background =           0
                        Beta(1) =     0.111017


           Asymptotic Correlation Matrix of Parameter Estimates

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

                Beta(1)

   Beta(1)            1



                           Parameter Estimates

       Variable           Estimate             Std. Err.
     Background                  0                   NA
        Beta(1)          0.0959514            0.0438874

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



                         Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model         -33.1848
    Fitted model        -33.4118     0.454099      2          0.7969
  Reduced model          -45.933      25.4965      2         <.0001

           AIC:          68.8237


                      Goodness  of  Fit

     Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
  ----------------------------------------------------------------------
i: 1
    0.0000     0.0000         0.000         0          46       0.000
i: 2
```

```
    1.8000      0.1586          6.186          5           39       -0.228
i: 3
    4.8000      0.3691          9.965         11           27        0.165

 Chi-square =        0.44     DF = 2        P-value = 0.8022

   Benchmark Dose Computation

 Specified effect =            0.1          Specified effect =           0.15

 Risk Type        =      Extra risk          Risk Type        =      Extra risk

 Confidence level =           0.95          Confidence level =           0.95

               BMD =        1.09806                        BMD =        1.69376

              BMDL =       0.745016                       BMDL =        1.14919
```





Output C-34. Multistage-Weibull analysis of fibrosarcomas in female mice, 1,2-dibromoethane inhalation exposure




```
Model: One Stage Weib
Dataset: C:\Program Files\TOX_RISK\edb_inh\fm_fibsarc.ttd
Functional form: 1 - EXP[( -Q0 - Q1 * D ) * (T - T0)^Z]
         Maximum Log-Likelihood =  -4.280865e+001

       Parameter Estimates :
                            Q 0 = 0.000000E+000
                            Q 1 = 4.944679E-004
                            Z   = 1.000000E+000
                            T0  = 0.000000E+000


      Avg. Doses          -------------------- Number --------------------
        (ppm)               of animals       with fatal    with incidental
                                               tumors          tumors
          0                    50                0              0
          1.80                 50                0              5
          7.10                 50                0             11

                                             Exposure Pattern
              Model: One Stage Weib     Age Begins: 0     Age Ends: 70
      Target Species: Human             Weeks/Year: 52   Days/Week:  7
              Route: Air                                Hours/Day : 24
     Animal to human conversion method: PPM IN AIR

          Unit Potency [ per mg/kg-day ] (computed for Risk of 1.0E-6)
Lower Bound = Not Reqstd   MLE = 2.5367E-002   Upper Bound(q1*) = 4.3105E-002

                                  Dose Estimates (ppb)
                                95.00 %                              95.00 %
  Incid Extra Risk   Time     Lower Bound          MLE             Upper Bound
     1.0000E-006      70.00   1.0370E-002      1.7621E-002     Not Reqstd
     1.0000E-005      70.00   1.0370E-001      1.7621E-001     Not Reqstd
     0.0001           70.00   1.0370E+000      1.7622E+000     Not Reqstd
     0.0010           70.00   1.0375E+001      1.7630E+001     Not Reqstd
     0.01             70.00   1.0422E+002      1.7709E+002     Not Reqstd
     0.10             70.00   1.0926E+003      1.8565E+003     Not Reqstd
```

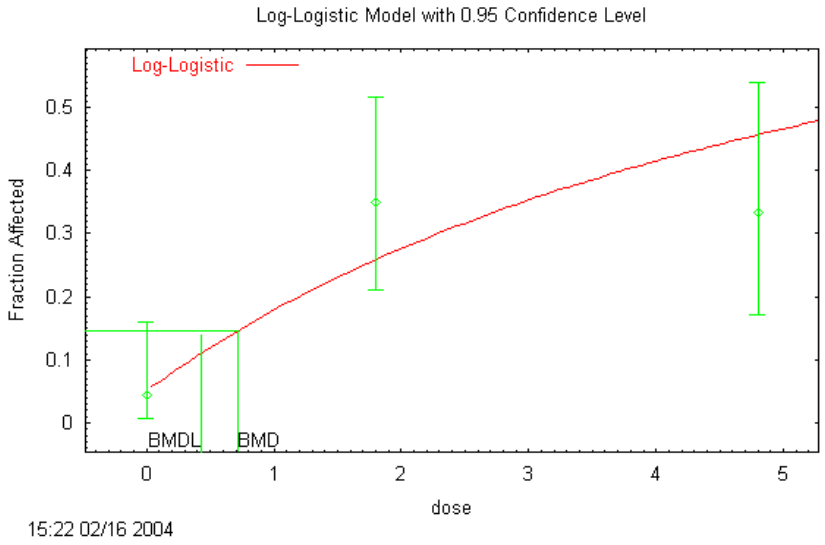
Output C-35. Multistage-Weibull analysis of mammary adenocarcinomas in female mice, 1,2-dibromothane inhalation exposure

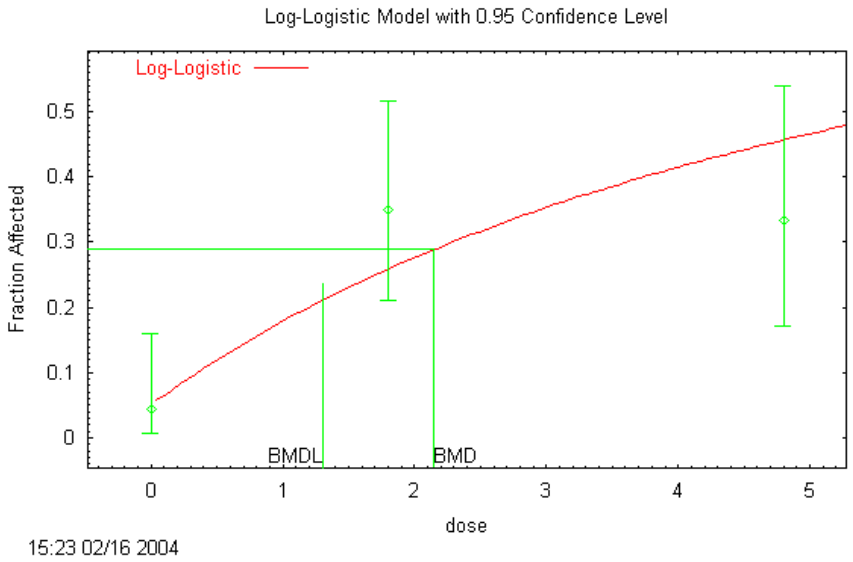
```
BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

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


   Dependent variable = m_aden
   Independent variable = ppm
   Slope parameter is restricted as slope >= 1

   Total number of observations = 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



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =    0.0434783
                     intercept =     -1.65098
                         slope =            1


          Asymptotic Correlation Matrix of Parameter Estimates

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

            background    intercept

background            1        -0.44

 intercept        -0.44            1


                         Parameter Estimates

      Variable           Estimate             Std. Err.
    background            0.051207           0.0351732
     intercept            -1.86383             0.33506
         slope                   1                  NA

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


                       Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
    Full model         -51.3106
   Fitted model        -53.0044       3.38748      1         0.06569
  Reduced model        -59.7173       16.8133      2       0.0002234

          AIC:          110.009


                     Goodness  of  Fit

                                                                 Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
  ----------------------------------------------------------------------
   0.0000      0.0512          2.356          2           46      -0.2378
   1.8000      0.2583         10.330         14           40        1.326
   4.8000      0.4561         12.314          9           27       -1.281
```

Chi-square = 3.45 DF = 1 P-value = 0.0631

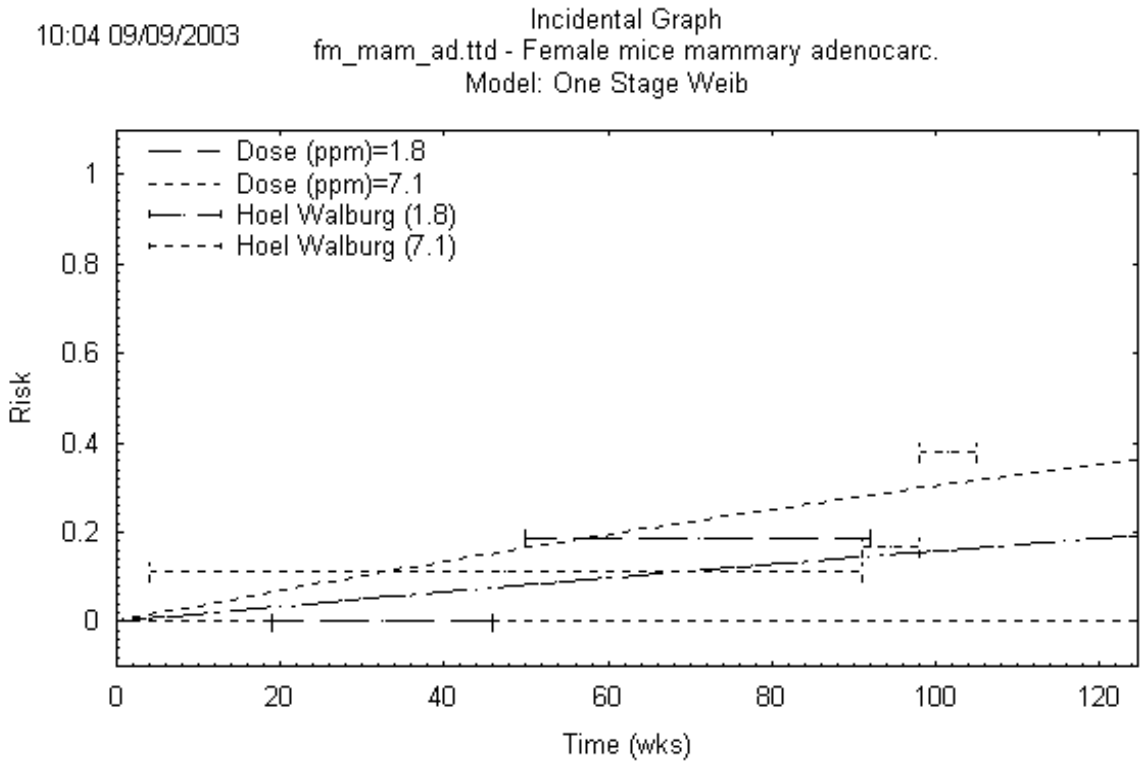
Benchmark Dose Computation

Specified effect =	0.1	Specified effect =	0.25
Risk Type =	Extra risk	Risk Type =	Extra risk
Confidence level =	0.95	Confidence level =	0.95
BMD =	0.716491	BMD =	2.14947
BMDL =	0.433751	BMDL =	1.30125





Output C-36. Multistage-Weibull analysis of mammary adenocarcinomas in female mice, 1,2-dibromothane inhalation exposure




```
Model: One Stage Weib
Dataset: C:\Program Files\TOX_RISK\edb_inh\fm_mam_ad.ttd
Functional form: 1 - EXP[( -Q0 - Q1 * D ) * (T - T0)^Z]
         Maximum Log-Likelihood =  -6.928667e+001

       Parameter Estimates :
                            Q 0 = 1.069724E-003
                            Q 1 = 3.577742E-004
                            Z   = 1.000000E+000
                            T0  = 0.000000E+000


      Avg. Doses          -------------------- Number --------------------
        (ppm)               of animals       with fatal    with incidental
                                               tumors          tumors
          0                   50                 0              2
          1.80                50                 0             14
          7.10                50                 0              9

                                            Exposure Pattern
              Model: One Stage Weib     Age Begins: 0     Age Ends: 70
      Target Species: Human             Weeks/Year: 52   Days/Week:  7
              Route: Air                                 Hours/Day : 24
     Animal to human conversion method: PPM IN AIR

          Unit Potency [ per mg/kg-day ] (computed for Risk of 1.0E-6)
Lower Bound = Not Reqstd   MLE = 2.1170E-002   Upper Bound(q1*) = 3.8976E-002

                                  Dose Estimates (ppb)
                                95.00 %                              95.00 %
  Incid Extra Risk   Time     Lower Bound          MLE             Upper Bound
     1.0000E-006      70.00   1.1468E-002      2.1114E-002     Not Reqstd
     1.0000E-005      70.00   1.1468E-001      2.1114E-001     Not Reqstd
     0.0001           70.00   1.1469E+000      2.1115E+000     Not Reqstd
     0.0010           70.00   1.1474E+001      2.1125E+001     Not Reqstd
     0.01             70.00   1.1526E+002      2.1221E+002     Not Reqstd
     0.10             70.00   1.2083E+003      2.2246E+003     Not Reqstd
```