

Provisional Peer-Reviewed Toxicity Values for

Hydroquinone
(CASRN 123-31-9)

Superfund Health Risk Technical Support Center
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COMMONLY USED ABBREVIATIONS

BMD	Benchmark Dose
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
LOAEL _{ADJ}	LOAEL adjusted to continuous exposure duration
LOAEL _{HEC}	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
NOAEL _{ADJ}	NOAEL adjusted to continuous exposure duration
NOAEL _{HEC}	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
RfC	inhalation reference concentration
RfD	oral reference dose
UF	uncertainty factor
UF _A	animal to human uncertainty factor
UF _C	composite uncertainty factor
UF _D	incomplete to complete database uncertainty factor
UF _H	interhuman uncertainty factor
UF _L	LOAEL to NOAEL uncertainty factor
UF _S	subchronic to chronic uncertainty factor

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Background

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

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

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

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

Disclaimers

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

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV document and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the U.S. EPA

Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVS

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

INTRODUCTION

There is no RfD for hydroquinone on IRIS (U.S. EPA, 2007) or in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006). A subchronic RfD of 0.4 mg/kg-day and a chronic RfD of 0.04 mg/kg-day are listed in the HEAST (U.S. EPA, 1997) for hydroquinone. These RfD values were derived using a NOAEL of 4.29 mg/kg-day for hematological effects from a 3–5 month study in humans (Carlson and Brewer, 1953) and an uncertainty factor of 10 (subchronic RfD) or 100 (chronic RfD). The source document for these derivations is a 1987 Health and Environmental Effects Document (HEED) (U.S. EPA, 1987). This HEED and a Reportable Quantity document (U.S. EPA, 1988a) are the only U.S. EPA reports on hydroquinone in the Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991a, 1994). ATSDR (2006) has not produced a Toxicological Profile for hydroquinone. An Environmental Health Criteria Document (WHO, 1994) is available, but it does not derive any risk assessment values.

There are no RfC values for hydroquinone on IRIS or in the HEAST, and both include messages stating that an RfC for hydroquinone is not verifiable (U.S. EPA, 2007, 1997). Occupational exposure limits are available for hydroquinone that include a threshold limit value-time weighted average (TLV-TWA) of 2 mg/m³, recommended by the American Conference of Governmental Industrial Hygienists (ACGIH, 2005), and a permissible exposure limit-time weighted average (PEL-TWA) of 2 mg/m³ promulgated by the Occupational Safety and Health Administration (OSHA, 2007). The National Institute of Occupational Safety and Health (NIOSH, 1978, 2005) has established a recommended exposure limit (REL) of 2 mg/m³ as a 15-minute ceiling for hydroquinone. These limits are intended to protect against eye injury (irritation or corneal changes), dermatitis, and CNS effects potentially associated with occupational exposure.

No carcinogenicity assessment is available on IRIS (U.S. EPA, 2008), and hydroquinone is not listed in the HEAST cancer table (U.S. EPA, 1997) or indicated in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006). The Office of Pesticide Programs (OPP) does not list a cancer classification for hydroquinone, but it does report an oral slope factor (OSF) of 5.6×10^{-2} per mg/kg-day for this chemical (basis not reported). The carcinogenicity of hydroquinone was tested by the National Toxicology Program (NTP, 1989) and evaluated by the International Agency for Research on Cancer (IARC, 1999), who categorized hydroquinone in Group 3 (*Not classifiable as to its carcinogenicity to humans*) based on inadequate evidence in

humans and limited evidence in experimental animals. The Environmental Health Criteria Document (WHO, 1994) on hydroquinone concluded that insufficient data are available for a thorough assessment of the carcinogenic potential for humans due to limited evidence in animals and the lack of adequate epidemiological studies.

Literature searches for studies relevant to the derivation of provisional toxicity values for hydroquinone (CASRN 123-31-9) were conducted in MEDLINE, TOXLINE special, and DART/ETIC (1960's–January 2007); BIOSIS (2000–January 2007); TSCATS/TSCATS2, RTECS, CCRIS, HSDB, and GENETOX (not date limited); and Current Contents (previous 6 months). A final search in PubMed was conducted (January 2007–July 2008).

REVIEW OF PERTINENT DATA

Human Studies

The oral toxicity of hydroquinone was assessed in two men who ingested 500 mg/day for 5 months and 17 men and women (numbers/sex not reported) who ingested 300 mg/day for 3–5 months (Carlson and Brewer, 1953). Total daily chemical intake was consumed with meals in three divided doses. Assuming an average human body weight of 70 kg (U.S. EPA, 1987), the estimated daily doses on a per-kg basis were 7.1 and 4.3 mg/kg-day. Hematology indices (red blood cell [RBC] count, hematocrit, percent hemoglobin, differential white blood cell count, sedimentation rate, platelet count, coagulation time, and iteric index) and urine indices (albumin, reducing sugars, white and red cell counts, casts, and urobilinogen) were evaluated during a control period for 1 month prior to exposure and again while the experiment was in progress, enabling each subject to serve as his/her own control. Results of the blood analyses and urinalyses revealed no abnormal findings. No additional information was reported on the design or results of this study. Because the high dose was administered to only two subjects, the low dose is used to identify a NOAEL of 4.3 mg/kg-day for hematological and renal effects in humans.

Corneal alterations with loss of visual acuity have been reported in workers with years of prolonged exposure to hydroquinone dust and quinone vapor (Anderson, 1947; Anderson and Oglesby, 1958; Miller, 1954; Naumann, 1966; Sterner et al., 1947). The eye lesions generally increased in severity with the length of exposure and progressed in some individuals even after exposure had ended. All studies describing eye lesions involved exposure to both hydroquinone dust and quinone vapor. The relative contributions of the two chemicals, as well as the relative roles of direct contact and systemic toxicity in causing corneal injury, are uncertain (DeCaprio, 1999; U.S. EPA, 1987).

Mortality from cancer and noncancer causes was not increased in a cohort of 879 workers (858 men and 21 women) who had worked for at least 6 months between January 1930 and December 1990 in a Tennessee plant in which hydroquinone was manufactured and used (Pifer et al., 1995). Average hydroquinone dust levels ranged from 0.1–6.0 mg/m² from 1949–1990. Mean employment duration was 13.7 years and mean follow-up from first exposure was 6.8 years; follow-up was essentially complete. Standardized mortality ratios (SMRs) were determined by comparing observed deaths with those expected in the general population of Tennessee, as well as in an occupational cohort from an out-of-state plant not exposed to hydroquinone. The SMRs for all causes of death combined ($n = 168$), all cancers combined

($n = 33$), and most site-specific cancers and noncancer diseases were significantly below 1.0 (less than expected) within both comparison populations. No SMRs were significantly greater than 1.0 within either population of referents. Only two sites, the colon (5 cases) and the lungs (14 cases), had more than three observed cancer cases; this indicates that the power of the study to detect site-specific effects was weak (IARC, 1999). There were no significant mortality excesses from the endpoints suggested by the animal studies of hydroquinone, including kidney cancer, liver cancer, leukemia, and nephrotoxicity. Dose-response analyses of deaths from selected cancers and other diseases did not show any significant heterogeneities or linear trends according to estimated career exposure (mg/m^3 -years) or latency (time from first exposure).

Animal Studies

Oral Exposure

Subchronic Studies—The systemic effects of oral exposure to hydroquinone have been investigated in numerous animal studies. Studies have been performed using drinking water, dietary, and gavage exposure.

Drinking water studies were conducted by Christian et al. (1980, as cited by U.S. EPA, 1987). In one study, groups of 6 male and 6 female Carworth Farm adult rats were exposed to 0, 2500, 5000, or 10,000 ppm of hydroquinone (purity not reported) in the drinking water for 8 weeks (Christian et al., 1980). The estimated doses based on measured water consumption were 0, 230, 390, or 700 mg/kg-day for males and 0, 270, 470, or 810 mg/kg-day for females. The effects included dose-related decreased water intake throughout the study in both males and females, decreased body weight gain in the females at ≥ 470 mg/kg-day and males at 700 mg/kg-day, and increased relative liver and kidney weights in males at ≥ 390 and females at ≥ 470 mg/kg-day. Blood analysis (hematocrit, hemoglobin content, and leukocyte count after 5 weeks of exposure) and comprehensive histological examinations (23 tissues at the end of the study) revealed no compound-related abnormalities. Additional information on the experimental design and results were not provided in the available U.S. EPA (1987) summary of this study. The low dose (230–270 mg/kg-day) is a NOAEL and the mid dose (390–470 mg/kg-day) a minimal LOAEL for effects on body and organ weights in this study.

Weanling rats were used in a second study by Christian et al. (1980, as summarized by U.S. EPA, 1987). Groups of 15 male and 15 female Carworth Farm weanling rats were exposed to 0, 1000, 2000, or 4000 ppm of hydroquinone (purity not reported) in the drinking water for 15 weeks. Estimated doses based on measured water consumption were 0, 110, 200, or 360 mg/kg-day for males and 0, 140, 240, or 430 mg/kg-day for females. Effects included dose-related decreased water intake throughout the study in both sexes, slightly decreased body weight gain in males at 360 mg/kg-day, highly significant increases in relative liver weight in males at ≥ 110 mg/kg-day and females at ≥ 140 mg/kg-day, and significant increases in relative kidney weight in males at ≥ 110 mg/kg-day and females at ≥ 240 mg/kg-day. Hemoglobin levels were slightly reduced in males at ≥ 200 mg/kg-day after 5 and 10 weeks of exposure, but they were normal after 14 weeks of exposure. No changes in total or differential leukocyte counts in the males or any hematological effects in the females were reported. Measurements of spontaneous locomotor activity and comprehensive histological examinations (23 tissues) revealed no compound-related abnormalities. Additional information on the experimental design and results was not provided in the available U.S. EPA (1987) summary of this study. The low dose of 110 mg/kg-day in males is identified as a minimal LOAEL for increased liver and kidney weights.

Feeding studies with hydroquinone were conducted in rats, hamsters, and dogs. Sprague-Dawley rats (groups of 14 adults of unspecified sex) were exposed to diets containing 0 or 5% (0 or 50,000 ppm) hydroquinone (purity not reported) for 9 weeks (Carlson and Brewer, 1953). Using reference values for food consumption and body weight in adult Sprague-Dawley rats (U.S. EPA, 1988b), the 50,000 ppm diet provided an estimated dose of 3333 mg/kg-day of hydroquinone in males and 4000 mg/kg-day in females. The exposed rats experienced a 46% loss in weight and developed aplastic anemia (incidence rate not reported). Examination of the bone marrow showed a 66% average decrease in cellularity relative to controls, with marked atrophy of the hematopoietic elements. Other effects included atrophy of the liver cord cells, splenic lymphoid tissue, adipose tissue and striated muscle, as well as superficial ulceration and hemorrhage of the stomach mucosa. The authors indicated that the effects were partly due to reduced food intake. The observed reduction in food consumption and weight loss introduces uncertainty into the dose estimate. No additional information on the design and results of this study were reported. The severity of the body weight and the hematological and histopathological changes indicate that the 5% dietary level (estimated as 3333 mg/kg-day in males and 4000 mg/kg-day in females) is a FEL for subchronic exposure in rats.

Hamsters (groups of 15 male 6-week-old Syrian strain) were exposed to 0 or 0.5% (5000 ppm) hydroquinone (>99% pure) in the diet for 20 weeks (Hirose et al., 1986). Using reference values for food consumption and body weight in male Syrian hamsters with subchronic exposure (U.S. EPA, 1988b), the 5000 ppm diet provided an estimated dose of 474 mg/kg-day. Evaluation of body, liver, and kidney weights and histology of seven tissues (cheek pouch, esophagus, stomach, liver, kidneys, bladder, pancreas, and lung) showed no effects other than an equivocal increase in mild hyperplasia of the forestomach. The lack of any clear exposure-related changes indicates that 474 mg/kg-day is a NOAEL for subchronic histopathology in hamsters.

For 80 weeks, 4-month old mongrel dogs from two litters were fed diets containing hydroquinone (purity not reported) in tablets (Carlson and Brewer, 1953). A single pup was exposed to 16 mg/kg-day, two pups were exposed to 1.6 mg/kg-day for 31 weeks followed by 40 mg/kg-day for 49 weeks (TWA dose 25.1 mg/kg-day), and two pups were maintained as controls. The sex of the treated and control dogs was not reported. In a second experiment, 5 adult male dogs were fed 100 mg/kg-day in tablets for 26 weeks. Routine analyses of the blood and urine were performed during the study (indices not specified) and limited histological examinations (liver, kidney, spleen, bone marrow, and 8 other tissues) were performed at necropsy. No further evaluations were reported. No exposure-related effects were observed in any exposed dogs, indicating that 100 mg/kg-day is a subchronic NOAEL for systemic toxicity in dogs.

Gavage studies reported high mortality in rats exposed to hydroquinone at doses of 500 mg/kg-day and above. High mortality was observed in groups of 20–48 rats (age not stated) that were treated with gavage doses ranging from 500 to 1750 mg/kg for up to 9 times in 12 days (Carlson and Brewer, 1953). Almost 75% of the deaths in this study occurred within 24 hours of the first dosing. More than 50% of the rats died within the first 2 months of exposure in a group of 16 Sprague-Dawley rats given hydroquinone by gavage (vehicle not specified; sex not specified) at a dose of 500 mg/kg for up to 101 times in 151 days (5 months) (Carlson and Brewer, 1953). Gross and histological examinations on the survivors at the end of the study showed no remarkable effects. No additional information was provided on the results and no

other endpoints were evaluated. The mortality data indicate that 500 mg/kg-day is a FEL for subchronic gavage exposure.

In a 40-day study, groups of 25 rats were dosed 6 days/week with hydroquinone by gavage in water at doses of 7.5 or 15 mg/kg-day (Delcambre et al., 1962, as summarized by U.S. EPA, 1987). A group of 20 rats dosed with 5% glucose served as controls. Hematological examinations were performed on 2 rats per dose on Exposure Days 8, 15, 26, and 36 and on 7 rats per dose on Day 40. No changes in total red, total white or differential white blood cell counts were observed on Days 8 and 15. On Day 26, one rat in the 7.5 mg/kg-day dosing group developed anisocytosis (considerable variation in the size of erythrocytes) with polychromatophilia (young or degenerating erythrocytes with unusual staining characteristics); these effects were not observed at 15 mg/kg-day on Day 26. No abnormalities were observed at 7.5 mg/kg-day on Day 36, although one rat in the 15 mg/kg-day dosing group developed slight anemia with decreased neutrophils, anisocytosis, severe polychromatophilia, and numerous erythroblasts in peripheral blood. On Day 40, one control rat had anisocytosis and erythroblastosis, one rat in the 7.5 mg/kg-day dosing group had erythroblastosis and several rats in the 15 mg/kg-day rats had anisocytosis (4 rats), definite polychromatophilia (5 rats), and erythroblasts in peripheral blood (4 rats). No additional information on the experimental design or results was reported in the U.S. EPA (1987) summary of this study. A NOAEL of 7.5 mg/kg-day and a LOAEL of 15 mg/kg-day are identified on the basis of the hematological effects. The LOAEL is considered by the U.S. EPA (1987) to be of minimal toxicological significance because the anisocytosis, polychromatophilia, and erythroblastosis were not accompanied by reduced numbers of circulating erythrocytes.

In a longer-term study by the same researchers, groups of 15 rats were treated with hydroquinone by gavage in water at doses of 5 or 10 mg/kg-day for 6 days/week for 4 months (Delcambre et al., 1962, as summarized by U.S. EPA, 1987). A group of 15 rats dosed with 5% glucose was used as controls. During the study, 1, 1, and 7 rats in the 0, 5, and 10 mg/kg-day groups died; causes of death were not reported, although 3 of the 7 high-dose rats died during a scabies epidemic. A decrease in body weight gain was observed at 10 mg/kg-day during the 3rd month, when mortality was greatest. No exposure-related changes in blood parameters were reported. Additional information on the experimental design and results was not provided in the U.S. EPA (1987) summary of this study. Identification of a reliable effect level is precluded by the insufficient information on the cause of death and by the lack of mortality in rats that were exposed to a higher dose of 15 mg/kg-day for 40 days by the same investigators, as summarized above.

A 13-week gavage study was performed in rats by Topping et al. (2007). Groups of Sprague-Dawley rats (10/sex/group) were given hydroquinone (99% purity) in degassed distilled water via gavage doses of 0, 20, 64, or 200 mg/kg-day, 5 days/week, for 13 weeks. Clinical observations were made daily and measurements of body weight and food consumption were made weekly. To assess nervous system impairment, a functional observational battery (FOB) was administered 3 days prior to first dose, after dosing on Day 1 (1 and 6 hours after dosing) and prior to dosing on Days 2, 7, 14, 30, 60 and 91. At necropsy, the brain and kidney were weighed and subjected to histopathological examination.

Increased incidences of depression (reduced locomotor and home cage activity) and tremors were statistically significant in the 64- and 200-mg/kg-day dose groups. Both male and female rats were affected at 1 and 6 hours after the first dosing (Topping et al., 2007). These

neurological effects appear to be acute, as recovery occurred prior to subsequent FOB observations. Body weights of 200 mg/kg-day males were decreased by 7% ($p < 0.05$) compared with controls at necropsy. Food consumption in the 200 mg/kg-day males was significantly lower than in controls for the first 5 days of the study, but it was increased to controls levels thereafter. No significant pathological findings were observed. Based on acute neurological effects, this study identified a LOAEL of 64 mg/kg-day and a NOAEL of 20 mg/kg-day in rats.

The NTP (1989) conducted 13-week toxicity studies in F344/N rats and B6C3F1 mice to determine the doses to be used in subsequent two-year studies (summarized below). Groups of 10 males and 10 females of each species were administered 0, 25, 50, 100, 200, or 400 mg/kg-day doses of hydroquinone (>99% pure) by gavage in corn oil on a 5 days/week regimen for 13 weeks. Clinical signs and body weight were evaluated throughout the study. Necropsies and liver weight measurements were performed on all animals. Comprehensive histological examinations were performed on all vehicle controls, animals receiving 200 or 400 mg/kg-day, and animals dying before the end of the study. Tissues examined in the 100 mg/kg-day dose groups were limited to the liver, kidneys, and stomach of male rats and kidneys of female rats.

All rats receiving 400 mg/kg-day and 3/10 female rats receiving 200 mg/kg-day died before the end of the study. Tremors and convulsions occurred after dosing in most males and females at 400 mg/kg-day and in some females at 200 mg/kg-day. There were also signs of lethargy in both sexes at ≥ 200 mg/kg-day. Other effects in the 400 mg/kg-day rats included red-to-brown perioral staining in 4/10 males and 5/10 females, reddened stomach mucosa in 1/10 males and 2/10 females, and meningeal hemorrhage in 1/10 males. The 200 mg/kg-day males exhibited intra-abdominal bleeding in 2/10 rats, while 1/10 females exhibited blood in the stomach and 2/10 had perioral bleeding. Also in the 200 mg/kg-day group, inflammation and/or epithelial hyperplasia (acanthosis) of the forestomach (4/10 males and 1/10 females) and toxic nephropathy (tubular cell degeneration in the renal cortex) (7/10 males and 6/10 females) were seen. Tubular cell degeneration in the renal cortex was observed in 1/10 females at 100 mg/kg-day. Significant 8–9% reductions in body weight, compared to controls, were seen in males at ≥ 100 mg/kg-day (with a smaller, but still statistically significant 5% decrease at 50 mg/kg-day). Increased absolute and relative liver weights were observed in females at ≥ 50 mg/kg-day. Decreases in absolute and relative liver weight in males were probably secondary to the reduced body weight in males. The kidney lesions in males were judged by NTP (1989) to be of moderate-to-marked severity and consisted of tubular cell degeneration and regeneration in the renal cortex. Kidney lesions in the females were similar to those in males but of lesser (minimal-to-mild) severity. The changes in liver weight (without corresponding histopathology at any dose) and the small decrease in body weight at 50 mg/kg-day are not considered adverse. Therefore, a NOAEL of 50 mg/kg-day and a LOAEL of 100 mg/kg-day are identified based on kidney lesions in females and 8–9% decreased body weight in males. Overt toxic effects and death were observed at 200 mg/kg-day.

The mice exposed to hydroquinone for 13 weeks experienced the following effects: mortality (8/10 males and 8/10 females at 400 mg/kg-day and 2/10 males at 200 mg/kg-day with one death in this group attributed by the study authors to gavage error); forestomach histopathology with ulceration, inflammation or epithelial hyperplasia (3/10 males and 2/10 females at 400 mg/kg-day and 1/10 females at 200 mg/kg-day); tremors after dosing (females at 400 mg/kg-day and males at ≥ 200 mg/kg-day); lethargy (females at ≥ 100 mg/kg-day

and males at ≥ 25 mg/kg-day); and increased absolute and relative liver weights (males at ≥ 25 mg/kg-day with no clear relationship to dose). There were no consistent dose-related changes in body weight and no hepatic histopathology (NTP, 1989). Although lethargy was the most common clinical sign and was observed in all dosed males, NTP (1989) concluded that doses of 100 mg/kg-day and below resulted in no discernible indices of toxicity that would preclude long-term growth and survival in mice. Additionally, the significance of the lethargy is questionable because there was no lethargy or any other signs of toxicity in mice exposed to 50 or 100 mg/kg-day for up to 103 weeks in the chronic experiment, as summarized below. The dose of 200 mg/kg-day is a FEL for marked gastric histopathology, tremors, and death. The NOAEL is 100 mg/kg-day.

Chronic Studies—Chronic toxicology/carcinogenesis studies were performed in which groups of 65 F344/N rats of each sex were treated with 0, 25, or 50 mg/kg-day doses of hydroquinone (>99% pure) by gavage in deionized water for 5 days/week for up to 103 weeks (NTP, 1989). Groups of 64 or 65 B6C3F1 mice of each sex were similarly exposed to doses of 0, 50, or 100 mg/kg-day. Clinical signs and body weight were evaluated throughout the studies. Hematology exams (total red and white blood cell counts, differential white cell counts, hematocrit, hemoglobin concentration, and reticulocyte counts) and clinical chemistry exams (6 indices including blood urea nitrogen) were performed on 10 animals from each group after 65 weeks of exposure. Necropsies, organ weight measurements (liver, kidney, brain), and histological examinations were performed on all rats after 65 or 103 weeks of exposure. The histological exams were comprehensive in all rats (except that preputial gland and thyroid were not examined in low-dose males) and vehicle control and high-dose mice; tissues examined in low-dose mice were limited to gross lesions, liver, spleen, thyroid, and adrenal glands in males, and gross lesions, liver, lungs, ovaries, salivary glands, and thyroid in females.

No compound-related clinical signs were observed in the rats (NTP, 1989). Survival in treated rats was similar to controls. Males treated with 50 mg/kg-day had reduced body weight (up to 13% lower than controls) throughout the second year of the study. Body weight was also reduced in males treated with 25 mg/kg-day, but the difference from controls was small (less than 10%) and the effect was only seen late in the study (Weeks 89–103). There was no effect on body weight in female rats. Increases in relative brain, kidney, and liver weights in the 50 mg/kg-day males appeared to be secondary to decreased body weight in this group. The relative weights of these organs were not different from controls in the female rats. Spontaneous nephropathy occurred in nearly all male and most female rats of all dosed groups and vehicle controls. The nephropathic changes occurred at both 15-month and 2-year sacrifices, were consistent with age-related advanced renal disease and were more severe in the 50 mg/kg-day males than in controls. No hyaline droplet formation was seen in the kidneys. Other effects in the rats included significantly ($p < 0.05$) decreased RBC count, hematocrit percent, and hemoglobin concentration in females at 50 mg/kg-day (evaluated at 15 months). Based on the hematological changes in females and the increased severity of toxic nephropathy and the reduced body weight in males, 50 mg/kg-day is a LOAEL and 25 mg/kg-day a NOAEL for nonneoplastic effects in rats in this study.

The NTP (1989) concluded that there was some evidence of carcinogenic activity of hydroquinone in male and female rats based on increases in renal tubular adenomas in male rats and mononuclear cell leukemia in females. The incidences of renal tubule cell adenomas in male rats are shown in Table 1. There was a statistically significant trend for increased renal tumors with dose and the incidence in the high dose-group was statistically increased in pairwise

comparison to concurrent controls. The incidence in both dose groups exceeded the highest historical incidence of this tumor in either untreated (3/50 = 6%) or water gavage (1/50 = 2%) controls, and it is markedly higher than the overall historical incidence of less than 0.5% in both types of controls. A reanalysis of the histology data from this study found that the adenomas were located in areas of severe chronic progressive nephropathy (Hard et al., 1997). The incidences of mononuclear cell leukemia are also given in Table 1. There was a statistically significant trend for increased mononuclear cell leukemia with dose and the incidence in the high-dose group was statistically increased in pair-wise comparison to concurrent controls. The historical incidence of mononuclear cell leukemia for water gavage vehicle control female F344/N rats was 25 ± 15% (*n* = 299), while that for untreated controls was 19% ± 7% (*n* = 1983). The incidence of leukemia in the high-dose females was just within the historical control range.

The researchers graded the severity of the observed leukemia as three stages. Features of Stage 1 include limited distortion of splenic architecture, no infiltration of other organs that are not likely to cause death. Stage 2 effects include an effacement of splenic architecture, limited infiltration of the liver, and possibly other organs that may contributed to mortality. Stage 3 effects include a marked effacement of splenic architecture and advanced infiltration of the liver and other organs that were the most probable cause of death in affected animals. The severity of the observed leukemia was increased in the high-dose group relative to controls. Of the leukemias observed in each group, 5/9 (56%), 8/15 (53%), and 14/22 (64%) were classified as Stage 3 in the control, low-, and high-dose groups, respectively.

Table 1. Incidences of Neoplastic Lesions in Male and Female F344/N Rats Given Gavage Doses of Hydroquinone for 103 Weeks^a			
Tumor Type	0 mg/kg-d	25 mg/kg-d	50 mg/kg-d
<i>Males</i>			
Renal tubule cell adenoma	0/55 ^b (0%)	4/55 (7%)	8/55 ^c (14%)
<i>Females</i>			
Mononuclear cell leukemia	9/55 ^b (16%)	15/55 (27%)	22/55 ^d (40%)

^aNTP, 1989

^b*p* ≤ 0.005 by logistic regression trend test

^c*p* ≤ 0.005 by logistic regression pairwise test

^d*p* ≤ 0.01 by logistic regression pairwise test

No compound-related clinical signs or effects on survival were observed in the mice (NTP, 1989). Body weight was slightly reduced (less than 10% reduction from controls) in 100 mg/kg-day males over the last 10 weeks of the study. Body weight was reduced 10–15% throughout the second year of the study in 100 mg/kg-day females. Small increases in relative liver weight in the 100 mg/kg-day males and females are consistent with the reduced body weight in these groups. An increased incidence of nonneoplastic hepatic lesions was observed after 103 weeks in males at 100 mg/kg-day (anisokaryosis, syncytial alterations, basophilic foci). Follicular cell hyperplasia of the thyroid gland was significantly increased in male and particularly female mice at both dose levels. Incidences of thyroid follicular cell hyperplasia in the control, low-, and high-dose groups were 5/55, 15/53, and 19/54 in the males and 13/55, 47/55, and 45/55 in the females, indicating that the low dose of 50 mg/kg-day is a LOAEL in this mouse study.

The NTP (1989) concluded that there was some evidence of carcinogenic activity of hydroquinone in the female mice, as shown by increases in liver hepatocellular neoplasms, mainly adenomas (Table 2). Incidences of hepatocellular adenomas and combined incidences of hepatocellular adenomas or carcinomas in the female mice were significantly elevated in both treated groups. The incidence of combined liver tumors in both dose groups exceeded the historical range for untreated ($9.1 \pm 4.7\%$, max = 20%) or water gavage ($8.3 \pm 5.0\%$, max = 14%) controls. The incidence of hepatocellular adenomas was also increased in treated male mice, but this increase was offset by a decrease in hepatocellular carcinoma in the treated males (Table 2) so that the combined incidence of hepatocellular adenoma or carcinoma was not increased in the treated males. Historical incidences for combined liver tumors in untreated and water gavage controls averaged 30%, but ranged as high as 58%, for male mice. The NTP concluded that there was no evidence of carcinogenicity in exposed male mice.

Table 2. Incidences of Neoplastic Lesions in Male and Female B6C3F1 Mice Given Gavage Doses of Hydroquinone for 103 Weeks^a			
Tumor Type	0 mg/kg-d	50 mg/kg-d	100 mg/kg-d
<i>Males</i>			
Hepatocellular adenoma	9/55 ^b	21/54 ^c	20/55 ^d
Hepatocellular carcinoma	13/55	11/54	7/55
Hepatocellular adenoma or carcinoma	20/55 (36%)	29/54 (54%)	25/55 (45%)
<i>Females</i>			
Hepatocellular adenoma	2/55 ^e	15/55 ^f	12/55 ^f
Hepatocellular carcinoma	1/55	2/55	2/55
Hepatocellular adenoma or carcinoma	3/55 ^d (5%)	16/55 ^e (29%)	13/55 ^e (24%)

^aNTP, 1989

^b $p \leq 0.05$ by logistic regression trend test

^c $p \leq 0.01$ by logistic regression pairwise test

^d $p \leq 0.05$ by logistic regression pairwise test

^e $p \leq 0.01$ by logistic regression trend test

^f $p \leq 0.005$ by logistic regression pairwise test

A chronic feeding study in rats was conducted by Carlson and Brewer (1953). Groups of 10 male and 10 female weanling Sprague-Dawley rats were exposed to 0, 0.1, 0.5, or 1.0% (0, 1000, 5000, or 10,000 ppm) hydroquinone (purity not reported) in the diet for 103 weeks (Carlson and Brewer, 1953). Using chronic reference values for food consumption and body weight in Sprague-Dawley rats (U.S. EPA, 1988b), the diets provided estimated doses of 0, 69, 344, or 688 mg/kg-day in males and 0, 80, 399, or 799 mg/kg-day in females. Endpoints included body weight, limited hematology (RBC counts, percent hemoglobin, and differential white blood cell counts; other indices not reported) at unspecified times during the study, and limited histology (liver, kidney, spleen, bone marrow, and 8 other tissues) at the end of the study. Terminal body weights in the treated rats were not significantly different from the controls, although rats in the mid- and high-dose groups reportedly gained weight more slowly than controls during the first month of the study (e.g., 10 g per week in high-dose rats versus 22–27 g per week in controls). No hematological or histopathological changes were found. Some of the exposed males and females were mated with each other after 6 months of exposure and two successive litters were produced. The average number of offspring in control and treated groups

were almost identical (data not presented). The offspring (16–23/sex) were fed hydroquinone that had been heated with lard at 190°C for 30 minutes before being incorporated into the diet in concentrations of 0, 0.1, 0.25, or 0.5% for 103 weeks. The offspring showed normal growth rates; no other details were reported. The transient effect on body weight gain in the mid- and high-dose groups is not considered adverse; the high-dose (688 mg/kg-day in males and 799 mg/kg-day in females) is a NOAEL in this study.

Effects from chronic dietary exposure were studied in rats and mice by Shibata et al. (1991). Groups of F344 rats (30/sex/group) and B6C3F1 mice (30/sex/group) were exposed to 0 or 0.8% hydroquinone in the diet for 104 or 96 weeks, respectively. Reported average hydroquinone intakes were 351 and 368 mg/kg-day in the male and female rats and 1046 and 1486 mg/kg-day in the male and female mice, respectively. Clinical signs, food and water intake, and body weight were assessed throughout the study. Evaluations performed at the end of the exposure period included gross necropsy, liver and kidney weights, and comprehensive histopathology. Effects in the exposed rats included reduced body weight gain in females (final weight 7.5% less than controls, $p < 0.05$), increased absolute and relative liver (49% absolute, 55% relative, $p < 0.01$) and kidney (69% absolute, 74% relative, $p < 0.01$) weights in males, increased relative kidney weights in females (10%, $p < 0.01$), and increased severity of age-related chronic nephropathy in males (13/30 treated rats with moderate or severe lesions vs. 0 controls, $p < 0.01$) and females (8/30 treated rats with slight lesions vs. 1/30 controls, $p < 0.05$). The prevalence and severity of the nephropathy was more severe in the males than females; the nephropathy was not of the alpha 2-u-globulin type, as determined by the study authors. Other renal changes in the male rats included increased incidences of renal hyperplasia (100% compared to 3% in controls) and adenomas. The treatment level in rats of 351 mg/kg-day is a LOAEL based on increased severity of age-related nephropathy and increased liver and kidney weights. A 47% increased incidence of renal adenomas in the male rats (14/30 vs. 0/30 in controls, $p < 0.01$) was observed.

Effects in the exposed mice included reduced body weight gain in females (final weight 27.6% less than controls, $p < 0.01$) and increased relative liver (46%, $p < 0.01$) and kidney (41%, $p < 0.01$) weights in females, hepatic centrilobular hypertrophy (26/30 treated mice vs. 0/30 controls, $p < 0.01$), and renal tubular hyperplasia (9/30 treated mice vs. 0/30 controls, $p < 0.01$) in the males, and forestomach hyperplasia in both males (11/30 treated mice vs. 1/30 controls, $p < 0.01$) and females (14/30 treated mice vs. 3/30 controls, $p < 0.01$) (Shibata et al., 1991). The treatment level in mice of 1046 mg/kg-day is a LOAEL based on pathology and increased liver and kidney weights. No statistically significant neoplastic changes in the kidneys were found in mice of either sex, although the incidences of hepatocellular adenomas were increased 25% in the exposed males (14/30 vs. 6/28 in controls, $p < 0.05$). No statistically significant increased incidences of tumors of any type were observed in the female rats or mice.

A long-term study in dogs was performed by Woodard (1951, as summarized by U.S. EPA, 1987). There were 4 mongrel dogs (2 males and 2 females) that were treated with a single 100 mg/kg dose of hydroquinone by stomach tube. Treatment was interrupted because this initial dose caused swelling of the eyes. The dogs were divided into two groups of one male and one female 10 days after the initial dose and administered daily capsules containing 25 or 50 mg/kg on a 6 days/week regimen for 809 days; 2 untreated dogs served as controls. Body weight measurements and blood counts were performed during the study and gross and histological examinations were performed at the end of the experiment. Treatment was suspended on Days 20–73 in one 25 mg/kg-day dog due to weight loss and on Days 238–309 for

all dogs to assess body weight gain effects. No significant changes in weight gain or blood counts were observed overall. Bone marrow hyperplasia and excessive pigment deposits in the spleen were observed in all exposed dogs, but it is not clear if these lesions were also observed in the controls (U.S. EPA, 1987), precluding reliable identification of a LOAEL.

Reproductive and Developmental Toxicity Studies—The effect of hydroquinone on rat teratogenicity was reported by Eastman Kodak Co. (1984). Groups of 10 pregnant COBS-CD BR rats were given gavage doses of hydroquinone (purity unspecified) of 0, 50, 100, or 200 mg/kg-day in water on Gestational Days 6 through 15. Clinical observations were made twice daily, while body weights and food consumption were measured on Days 1, 6, 9, 12, and 15. On Day 16, the rats were anesthetized, exsanguinated, and subjected to necropsy and gross pathology examinations. Maternal blood samples underwent hematological (hematocrit, hemoglobin concentration, total white and red blood cell, nucleated RBC and platelet counts, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and RBC morphology) and clinical chemistry (serum levels of alanine aminotransferase, alkaline phosphatase, urea nitrogen, glucose, creatinine, and sorbitol dehydrogenase) measurements. Liver and kidney weights were recorded. Implantation sites and *corpora lutea* were counted. Individual fetuses were weighed.

Brownish, dose-related urine discoloration was noted (Eastman Kodak Co., 1984). Body weights were not significantly affected by treatment, but food consumption was significantly lower on Gestational Days 6–9. Hematological and clinical chemistry parameters were not affected by treatment. Although sorbitol dehydrogenase levels in the 50 mg/kg-day dose group were significantly higher than controls, this finding was not considered treatment-related by the U.S. EPA, because the higher dose groups were not similarly affected. Gross and histological pathology were unremarkable. Relative kidney weights in the 50 and 200 mg/kg-day groups were slightly, but significantly, increased (6–7%) over controls. Since the increase was small and not dose-related, the toxicological significance of this finding is unknown. No treatment-related effects were seen on pregnancy rate, number of *corpora lutea*, implantations per dam, viable fetuses, fetal resorptions per litter, or fetal weight. This study identified a NOAEL of 200 mg/kg-day for maternal and fetal toxicity.

Groups of 30 pregnant COBS-CD BR rats were administered hydroquinone (>99% pure) in aqueous solution by gavage in doses of 0, 30, 100, or 300 mg/kg-day on Days 6–15 of gestation (Krasavage et al., 1992). The maternal rats were euthanized on Gestation Day 20. Maternal endpoints included food consumption, body weight, clinical signs, gross appearance of the thoracic and abdominal viscera, and liver and kidney weights and histology. Developmental endpoints included implantation and resorption indices, *corpora lutea* per dam, viable and dead fetuses per litter, pre- and postimplantation losses, gravid uterine and fetal weights, sex ratio, external abnormalities, internal soft tissue abnormalities (approximately half the fetuses in each litter examined), and skeletal malformations and variations (remaining half of the fetuses). No compound-related effects on reproductive or teratogenicity indices were observed. The 300 mg/kg-day dose level produced a slight reduction in maternal body weight gain and feed intake with a concomitant slight reduction in mean fetal body weight (6.3% less than controls, $p < 0.05$). The total number of fetuses with vertebral variations was slightly, but significantly, increased at 300 mg/kg-day (6.7% greater than controls, $p < 0.05$), but the study authors did not consider this finding to be toxicologically significant. The incidence of vertebral variations was not statistically increased on a litter basis. There is no evidence indicating that hydroquinone was selectively toxic to the developing rats; based on this study, 300 mg/kg-day is a minimal

LOAEL and 100 mg/kg-day a NOAEL for both maternal and developmental toxicity, respectively (slight reductions in maternal and fetal body weight).

A range-finding developmental toxicity study was conducted in which groups of 5 mated New Zealand White rabbits were administered 0, 50, 100, 200, 300, 400, or 500 mg/kg-day by gavage on Gestation Days 6–18 (Murphy et al., 1992). The range-finding study found slight-to-moderate decreases in the mean maternal weight gain and feed consumption at 50 and 100 mg/kg-day and effects clearly indicative of maternal toxicity at the higher doses, including weight loss at ≥ 200 mg/kg-day, tremors at ≥ 300 mg/kg-day and mortality at 500 mg/kg-day. There was no developmental toxicity at 50 or 100 mg/kg-day, although results suggestive (but not statistically significant) of fetotoxicity (reduced fetal body weight and slightly increased resorptions with no effect on litter size) were observed at 200 mg/kg-day.

In the definitive study (Murphy et al., 1992), groups of 18 mated New Zealand White rabbits were administered hydroquinone (100% pure) in aqueous solution by gavage at doses of 0, 25, 75, or 150 mg/kg-day on Days 6–18 of gestation (Murphy et al., 1992). The maternal rabbits were euthanized on Gestation Day 30. Maternal endpoints included food consumption, body weight, clinical signs, gross postmortem condition, and liver and kidney weights. Developmental endpoints included implantation and resorption indices, *corpora lutea* per dam, viable and dead fetuses per litter, pre- and postimplantation losses, gravid uterine and fetal weights, and sex ratio; all fetuses were examined for external abnormalities, visceral malformations/variations, and skeletal malformations/variations. No adverse maternal or developmental effects were observed at 25 mg/kg-day. Significantly reduced feed consumption on Gestation Days 12 and 13 (26 and 36% less than controls, $p \leq 0.05$), but no effects on body weight of the dams or developmental toxicity, occurred at 75 mg/kg-day. Effects at 150 mg/kg-day included significantly reduced maternal body weight gain and food consumption and slight, nonsignificant increases in the incidences of ocular and minor skeletal malformations (microphthalmia, vertebral/rib defects, angulated hyoid arch) on a per-fetus and a per-litter basis. The dose of 150 mg/kg-day is identified as a maternal and developmental LOAEL for reduced maternal body weight gain and slight increases in fetal ocular and skeletal malformations, respectively. The dose of 75 mg/kg-day is a NOAEL for both maternal and developmental toxicity.

A two-generation study was performed in which groups of 30 Sprague-Dawley F₀ and F₁ rats of each sex were treated with 0, 15, 50, or 150 mg/kg-day of hydroquinone by gavage in water on 7 days/week for at least 70 days prior to cohabitation and subsequently throughout mating, gestation, and lactation until scheduled termination (3–4 weeks after the mating period in males and following weaning in females) (Blacker et al., 1993). Gavage exposure of the F₁ generation was initiated at 25 days of age. Evaluations included clinical signs, body weight and feed consumption in parental animals throughout the study, as well as fertility, number of live pups/litter, sex ratio, pup weights, and gross external abnormalities in pups during the lactation period. All parental animals were necropsied, and histological examinations were performed on the reproductive tissues and the pituitary gland in all F₀ and F₁ control and high-dose animals, as well as in all F₀ and F₁ parents in the low- and mid-dose groups that failed to produce a litter. Gross external and internal examinations were performed on all pups culled on Day 4 of lactation, F₁ pups not selected as parental animals, and F₂ pups and intact pups found dead at birth or during lactation. No adverse effects on feed consumption, survival, or reproduction parameters were found in the F₀ or F₁ parental animals. Mild transient tremors occurred shortly, but infrequently, after dosing at 50 mg/kg-day in 1 F₀ male and at 150 mg/kg-day in a number of

F₀ rats (11 males, 13 females) and F₁ rats (5 males, 16 females). The tremors were considered to reflect an acute effect on the nervous system. Body weight gain was reduced slightly in F₁ males at 50 and 150 mg/kg-day (approximately 6% less than controls in both dose groups, $p \leq 0.05$) exposures, but body weight was unaffected in F₀ males or females of either generation. This study identified a LOAEL of 150 mg/kg-day and a NOAEL of 50 mg/kg-day based on acute neurological effects (mild transient tremors in a number of parental animals in both the F₀ and F₁ generations). There was no evidence for reproductive toxicity of hydroquinone at doses up to 150 mg/kg-day.

Inhalation Exposure

No information was located regarding effects of inhaled hydroquinone in animals.

Other Studies

Toxicokinetics

The metabolism of hydroquinone appears to be very similar in humans and rodents (IARC, 1999). The compound is metabolized mainly to sulfate and glucuronide conjugates, with glucuronidation in human liver microsomes being somewhat less than in mouse but greater than in rat microsomes (IARC, 1999). A small percentage can be converted to 1,4-benzoquinone by several cellular enzymes, particularly macrophage peroxidases. In rats receiving gavage doses of up to 350 mg/kg, the majority of hydroquinone was recovered as glucuronides (45–53%) and O-sulfate conjugates (19–33%) in the urine, with a small fraction metabolized to 1,4-benzoquinone and then to the hydroquinone mercapturate (<5%) (English and Deisinger, 2005). 1,4-Benzoquinone is a very reactive metabolite that can be conjugated with glutathione or form DNA adducts (IARC, 1999). Such adducts have been identified in promyelocytic HL-60 cell cultures. Similar macrophage peroxidase-mediated formation of 1,4-benzoquinone seems to be important in the myelotoxicity of benzene (IARC, 1999).

Genotoxicity

The genotoxicity of hydroquinone has been extensively tested. As evaluated by IARC (1999) and summarized below, hydroquinone is genotoxic in many in vitro systems using a variety of endpoints. Hydroquinone caused gene mutations in *Salmonella typhimurium* strains TA104 and TA102 (strains sensitive to oxidative mutagens) and induced gene conversion and mutations in *Saccharomyces cerevisiae*, although it did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster*. In cultured rodent and human cells, hydroquinone induced DNA strand breaks, gene mutations, chromosomal aberrations, sister chromatid exchanges, and micronuclei formation; and hydroquinone inhibits intercellular communication. Hydroquinone also caused micronuclei and chromosomal aberrations in mouse bone marrow cells and chromosomal aberrations and hyperploidy in mouse spermatocytes, after intraperitoneal injection (IARC, 1999). Hydroquinone-derived DNA adducts were not observed in F344 rat kidney cells (English et al., 1994) following 6 weeks of oral (gavage) dosing at nephrotoxic levels.

More recent genotoxicity literature corroborates the genotoxic effects summarized by IARC (1999). Genotoxic effects were detected in human (*supF* forward mutation via DNA adduction or gene deletion in embryonic adenovirus-transformed kidney cells) and animal (micronucleus formation in Chinese hamster V79 cells) in vitro assay systems (von der Hude et al., 2000; Silva et al., 2003; Nakayama et al., 2004; Gaskell et al., 2004, 2005a,b). The effects on meiotic segregation, exhibited as meiotic nondisjunction, were observed in treated oocytes of *Drosophila melanogaster* (Munoz and Barnett, 2000). Roza et al.

(2003) reported that hydroquinone treatment of cultured human lymphocytes did not result in clastogenic effects, while Silva et al. (2004) identified the expression of the polymorphism GSTM1 as protective against hydroquinone-induced micronuclei in the same cell type. Hydroquinone treatment of human whole blood cultures resulted in a particular form of aneuploidy (loss of chromosomes 5 and 7) associated with development of acute myeloid leukemia (Zhang et al., 2005).

Initiation/Promotion

A number of studies were performed in which oral administration of hydroquinone was predominantly inactive in promoting neoplasms initiated by other chemicals (IARC, 1999). Administration of 0.2% hydroquinone in the diet for 22 weeks caused no increase in bladder lesions in rats when given alone or following initiation by 0.05% *N*-nitrosobutyl-*N*-(4-hydroxybutyl)amine in the drinking water for 2 weeks (Miyata et al., 1985). Likewise, administration of 0.8% hydroquinone in the diet for 36 weeks did not induce bladder tumors in rats when given alone, nor did it increase the incidence or multiplicity of bladder tumors initiated by 0.05% *N*-nitrosobutyl-*N*-(4-hydroxybutyl)amine in the drinking water for 4 weeks (Kurata et al., 1990).

Administration of 0.8% hydroquinone in the diet for 49 weeks caused no increase in the incidence of upper digestive tract tumors when given alone or following initiation by 6 intraperitoneal injections of 25 mg/kg of *N*-nitrosomethyl-*n*-amylamine, although the multiplicity of esophageal carcinomas was increased in rats given the initiator (Yamaguchi et al., 1989). Administration of 0.8% hydroquinone in the diet for 51 weeks caused no increase in forestomach or glandular stomach lesions in rats when given alone or following initiation by a single 150 mg/kg gavage dose of *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine (Hirose et al., 1989).

Administration of hydroquinone in dietary doses of 100 or 200 mg/kg for 6 weeks following initiation by partial hepatectomy and intraperitoneal injection of 300 mg/kg of *N*-nitrosodiethylamine caused an increase in the multiplicity of liver enzyme-altered (γ -glutamyltranspeptidase) foci in rats, but the response was not dose-related (Stenius et al., 1989). Rats that underwent the same hepatectomy/*N*-nitrosodiethylamine regimen to initiate liver carcinogenesis, but were promoted with 1 mg/kg of hydroquinone by oral gavage on a 5 days/week regimen for 7 weeks, had no increase in the multiplicity of enzyme-altered foci, although the area and volume of the foci were increased (Stenius et al., 1989). Dietary administration of 0.8% hydroquinone for 36 weeks did not induce preneoplastic or neoplastic liver or kidney lesions in rats when given alone, although this exposure did increase the multiplicity of renal cell tumors and microadenomas that were initiated by 0.1% *N*-nitrosoethyl-*N*-hydroxyethylamine in their drinking water for 3 weeks (Kurata et al., 1990). Dietary administration of 1.5% hydroquinone for 16 weeks did not induce neoplastic lesions in the pancreas or liver of hamsters when administered alone or following initiation by two 70 mg/kg subcutaneous injections of *N*-nitrosobis(2-oxopropyl)amine, although administration of hydroquinone after the initiator reduced the multiplicity of pancreatic lesions (Maruyama et al., 1991). Finally, dietary administration of 0.8% hydroquinone for 30 weeks did not induce tumors in rats when given alone, nor did it promote thyroid, lung, kidney, or bladder tumors that were initiated by 0.1% *N*-nitroso-bis(2-hydroxypropyl)amine in their drinking water for 2 weeks (Hasegawa et al., 1990).

Dermal application and bladder implantation studies of hydroquinone are reviewed by IARC (1977), NTP (1989), and U.S. EPA (1987). Hydroquinone was inactive as a complete

dermal carcinogen, skin cocarcinogen, or initiator of skin carcinogenesis in dermal application studies in mice (Roe and Salaman, 1955; Van Duuren and Goldschmidt, 1976). Bladder implantation of hydroquinone in cholesterol pellets increased the incidence of bladder carcinomas in mice (Boyland et al., 1964).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR HYDROQUINONE

The systemic toxicity of repeated oral exposures to hydroquinone has been evaluated in one subchronic human study (Carlson and Brewer, 1953); several subchronic and chronic studies in rats (Carlson and Brewer, 1953; Delcambre et al., 1962; Christian et al., 1980; NTP, 1989; Shibata et al., 1991); subchronic and chronic studies in mice (NTP, 1989; Shibata et al., 1991), hamsters (Hirose et al., 1986), and dogs (Carlson and Brewer, 1953); and reproductive and developmental toxicity studies in rats and rabbits (Eastman Kodak Co., 1984; Krasavage et al., 1992; Murphy et al., 1992; Blacker et al., 1993) (Table 3). The human study identifies a NOAEL of 4.3 mg/kg-day for lack of hematological and renal effects in 17 subjects who ingested hydroquinone in 3 divided doses with meals for 3–5 months. The human NOAEL reflects normal results in blood analyses (RBC count, hematocrit, percent hemoglobin, differential white blood cell count, sedimentation rate, platelet count, coagulation time, and iteric index) and urinalyses (albumin, reducing sugars, white and red cell counts, casts, and urobilinogen), as determined by comparison of each subject with preexposure values.

The erythrocyte, kidney, and thyroid gland are the most sensitive targets of hydroquinone toxicity in the animal studies. Studies showing hematologic effects, including RBC changes in rats, identified a NOAEL of 7.5 mg/kg-day and minimal LOAEL of 15 mg/kg-day (for anisocytosis, polychromatophilia, and erythroblastosis) following gavage exposure on a 6 days/week regimen for 40 days (Delcambre et al., 1962). A NOAEL of 25 mg/kg-day and LOAEL of 50 mg/kg-day (for decreased hematocrit value, hemoglobin concentration, and erythrocyte count) was also identified following gavage exposure on a 5 days/week regimen for 15 months (NTP, 1989). These findings are consistent with the known toxicity of hydroquinone toward bone marrow, as illustrated by the development of aplastic anemia in rats exposed to 3333 mg/kg-day in the diet for 9 weeks (Carlson and Brewer, 1953), as well as mononuclear cell leukemia in rats exposed to 50 mg/kg-day by gavage on a 5 days/week regimen for 103 weeks (NTP, 1989). Hydroquinone is a metabolite of benzene and is suspected of playing a role in the myelodepressive and leukemogenic activity of benzene (IARC, 1999). Effects of hydroquinone on bone marrow have been demonstrated in mechanistic studies performed *in vitro* or by acute parenteral administration (IARC, 1999).

Table 3. Noncancer Effects and Effect Levels Identified from Studies of Oral (drinking water, dietary, and gavage dosing) Hydroquinone Exposure to Humans and Animals

Source	Species	Exposure duration / sub-route	NOAEL mg/kg-day	LOAEL mg/kg-day	Effect
<i>Subchronic Studies</i>					
Carlson and Brewer, 1953	Human	3–5 months, diet	4.3	ND	No dose-related hematological or renal effects
Christian et al., 1980	Rat	8 weeks, drinking water	230	390	Decreased body weight gain, increased relative liver and kidney weight
Christian et al., 1980	Rat	15 weeks, drinking water	ND	110	Increased relative liver and kidney weight
Carlson and Brewer, 1953	Rat	9 weeks, diet	ND	3333	FEL: decreased body weight, multitissue atrophy, aplastic anemia, stomach mucosa hemorrhage
Hirose et al., 1986	Hamster	20 weeks, diet	474	ND	No dose-related histopathology
Carlson and Brewer, 1953	Dog	26 weeks, diet	100	ND	No dose-related effects
Carlson and Brewer, 1953	Rat	12 days, gavage	ND	500	FEL: Death
Carlson and Brewer, 1953	Rat	22 weeks, gavage	ND	500	FEL: Death
Delcambre et al., 1962	Rat	40 days, gavage	7.5	15	Anisocytosis, polychromatophilia, erythroblastosis
Topping et al., 2007	Rat	13 weeks, gavage	20	64	Acute neurological effects (tremors, reduced activity)
NTP, 1989	Rat	13 weeks, gavage	50	100	Decreased body weight (8–9%), renal tubule degeneration
NTP, 1989	Mouse	13 weeks, gavage	100	200	FEL: tremors, forestomach hyperplasia and ulceration, death
<i>Chronic Studies</i>					
NTP, 1989	Rat	103 weeks, gavage	25	50	Hematological changes, increased severity of age-related nephropathy, decreased body weight
NTP, 1989	Mouse	103 weeks, gavage	ND	50	Thyroid follicular cell hyperplasia
Carlson and Brewer, 1953	Rat	103 weeks, diet	688	ND	No dose-related effects

Table 3. Noncancer Effects and Effect Levels Identified from Studies of Oral (drinking water, dietary, and gavage dosing) Hydroquinone Exposure to Humans and Animals

Source	Species	Exposure duration / sub-route	NOAEL mg/kg-day	LOAEL mg/kg-day	Effect
Shibata et al., 1991	Rat	104 weeks, diet	ND	351	Increased relative liver and kidney weights, increased severity of age-related nephropathy
Shibata et al., 1991	Mouse	96 weeks, diet	ND	1046	Increased relative liver and kidney weight, forestomach hyperplasia, renal tubular hyperplasia
<i>Reproductive and developmental effects</i>					
Blacker et al., 1993	Rat	Two generations, gavage	50	150	Acute neurological effects (tremors). No repro/developmental effects observed at any dose
Eastman Kodak Co., 1984	Rat	Gestational Days 6–15 (terminated at Day 15), gavage	200	ND	No repro/developmental effects observed
Krasavage et al., 1992	Rat	Gestational Days 6–15 (terminated at Day 20), gavage	100	300	Decreased fetal weight
Murphy et al., 1992	Rabbit	Gestational Days 6–18 (terminated at Day 30), gavage	75	150	Increased fetal ocular and skeletal malformations

ND = Not determined

Kidney lesions included tubular cell degeneration in rats with subchronic gavage exposure at a LOAEL of 100 mg/kg-day (NTP, 1989), an increased severity of age-related toxic nephropathy in rats with chronic exposure at a LOAEL of 50 mg/kg-day for gavage exposure (NTP, 1989), and a LOAEL of 351 mg/kg-day for dietary exposure (Shibata et al., 1991). The nephropathic changes were more severe in male rats than female rats, but they were not associated with hyaline droplet formation. Increases in renal tubular cell hyperplasia and adenomas were also observed (NTP, 1989; Shibata et al., 1991).

Follicular cell hyperplasia of the thyroid gland was increased in male and female mice that were exposed to hydroquinone by gavage on a 5 days/week regimen for 103 weeks (NTP, 1989); the LOAEL is 50 mg/kg-day and no NOAEL was identified. The toxicological significance of this effect is unclear because thyroid and pituitary hormone levels were not assessed, thyroid hyperplasia was not observed in the only other chronic study of hydroquinone (Shibata et al., 1991), and incidences of follicular cell neoplasia were not increased (NTP, 1989; Shibata et al., 1991).

A two-generation study found no effects on fertility and reproduction in rats exposed to hydroquinone at doses ≤ 150 mg/kg-day (Blacker et al., 1993). Developmental toxicity studies found no evidence indicating that hydroquinone was selectively toxic to the developing organism. In rats treated during gestation, 300 mg/kg-day was a LOAEL of minimal

toxicological significance and 100 mg/kg-day a NOAEL for both maternal and developmental toxicity (slight reductions in maternal and fetal body weight) (Krasavage et al., 1992). In rabbits, 150 mg/kg-day was a LOAEL and 75 mg/kg-day a NOAEL for reduced maternal body weight gain and slightly increased fetal ocular and skeletal malformations (Murphy et al., 1992). These data indicate that reproductive and developmental toxicity are not critical effects of concern for hydroquinone.

Studies, summarized above, yielded several potential points of departure (POD) for comparison. The human study identified a NOAEL of 4.3 mg/kg-day for lack of hematological and renal effects in subjects who ingested hydroquinone for 3–5 months (Carlson and Brewer, 1953). A LOAEL of minimal toxicological significance (15 mg/kg-day) for RBC changes (Delcambre et al., 1962) and a NOAEL and LOAEL (50 and 100 mg/kg-day, respectively) for kidney toxicity were identified for subchronic exposure to hydroquinone in rats (NTP, 1989). The reliability of the 15 mg/kg-day subchronic hematological LOAEL is questionable due to limited information in the available summary of the study and a lack of corroborating effects on RBCs in rats chronically exposed to a higher (25 mg/kg-day) dose level of hydroquinone (NTP, 1989). The chronic LOAEL for hematological effects in rats, kidney toxicity in rats, and thyroid follicular cell hyperplasia in mice is 50 mg/kg-day (NTP, 1989; Shibata et al., 1991).

The Carlson and Brewer (1953) study was selected as the basis for the POD because it reflects a human assessment of the two main targets of hydroquinone, as observed in animals, and is supported by the 50 mg/kg-day subchronic NOAEL for kidney effects (NTP, 1989) and the 25 mg/kg-day chronic NOAEL for hematologic effects in animals (NTP, 1989; Shibata et al., 1991). The subchronic NOAEL for hematological and renal effects in humans (4.3 mg/kg-day) is also the highest NOAEL below all identified LOAELs (Carlson and Brewer, 1953). Because of a lack of sufficient data for benchmark dose (BMD) modeling, the human NOAEL is the most appropriate basis for subchronic and chronic p-RfD derivation.

A **subchronic p-RfD** is derived by applying a composite Uncertainty Factor (UF) of 10 to the POD, the subchronic human NOAEL of 4.3 mg/kg-day. UFs are applied to the POD for low-dose extrapolation when specific data are lacking or insufficient. The composite UF of 10 is composed of an UF of 10 that is applied to account for variation in human sensitivity. An UF for extrapolation from animals to humans is not applied because a human study is available; an UF for extrapolating from a LOAEL to a NOAEL is not applied because a NOAEL is available; and an UF for database deficiencies is not applied because numerous well designed subchronic and chronic studies in animals are available, including developmental studies in multiple species and a multigeneration reproduction study.

$$\begin{aligned}\text{Subchronic p-RfD} &= \text{NOAEL} \div \text{composite UF} \\ &= 4.3 \text{ mg/kg-day} \div 10 \\ &= \mathbf{0.4 \text{ mg/kg-day or } 4 \times 10^{-1} \text{ mg/kg-day}}\end{aligned}$$

A **chronic p-RfD** is similarly derived by applying a composite UF of 100 to the subchronic human NOAEL. The composite UF is composed of the following two component factors: An UF of 10 is applied to account for variation in human sensitivity; and an UF of 10 is applied for extrapolation from subchronic to chronic exposure. An UF for animal-to-human extrapolation is not applied because a human study is available; an UF for extrapolation from a LOAEL is not applied because a NOAEL is available; and an UF for database deficiencies is not applied due to the robust database of available studies.

$$\begin{aligned}\text{Chronic p-RfD} &= \text{NOAEL} \div \text{composite UF} \\ &= 4.3 \text{ mg/kg-day} \div 100 \\ &= \mathbf{0.04 \text{ mg/kg-day or } 4 \times 10^{-2} \text{ mg/kg-day}}\end{aligned}$$

Confidence in the key study (Carlson and Brewer, 1953) is low. Although blood analyses and urinalyses were performed and showed no indications of adverse hematological and renal effects in humans, the study is poorly reported with minimal details, only a limited number of relevant indices were tested, the number of subjects is marginal, and only one dose level was adequately tested. Confidence in the database is high because subchronic, chronic, and developmental toxicity have been adequately tested in two species and reproductive toxicity has been evaluated in a multigeneration study. Medium confidence in the subchronic and chronic p-RfD values follows.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR HYDROQUINONE

The derivation of p-RfC values for hydroquinone is precluded by inadequate information on inhalation toxicity. Human data were limited to case reports of corneal lesions in workers with unquantified exposure to mixtures of hydroquinone dust and quinone vapor and a cohort mortality study that showed no increase in mortality from noncancer causes in a cohort of workers exposed to hydroquinone for a mean duration of 13.7 years (Pifer et al., 1995). No subchronic or chronic duration inhalation studies of hydroquinone in animals were located.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR HYDROQUINONE

Weight-of-Evidence Descriptor

Inadequate information is available on the carcinogenicity of hydroquinone in humans from two occupational studies. Standardized mortality ratios for total cancer and site-specific cancers were not elevated in a cohort of 879 workers who were exposed in a plant in which hydroquinone was manufactured and used (Pifer et al., 1995). This study is limited by a weak power to detect effects, due to the relatively small cohort size and small numbers of deaths from site-specific cancers. An increased number of malignant melanoma cases was observed in a cohort of 836 lithographers—about 200 of whom had worked regularly by hand with photographic chemicals and were exposed to hydroquinone (Nielsen et al., 1996). This study is limited by a small number of cases (the excess of malignant melanoma was based on 5 cases, only 2 of which had reported exposure to hydroquinone), as well as mixed chemical exposures to various pigments, dyes, and organic solvents used in lithography printing processes.

Chronic oral carcinogenicity tests of hydroquinone were conducted in two-dose-level studies in rats and mice (NTP, 1989) and in single-dose-level studies in rats and mice (Shibata et al., 1991). Hydroquinone induced significantly increased incidences of renal tubule adenomas in male rats in both studies, hepatocellular adenomas in female mice in the NTP (1989) study, and hepatocellular adenomas in male mice in the Shibata et al. (1991) study.

Incidences of mononuclear cell leukemia were significantly greater than controls in female rats in the NTP (1989) study, although the incidences in the exposed groups were just within the historical control range.

Orally-administered hydroquinone was predominantly inactive in promoting neoplasms initiated by other chemicals (Hasegawa et al., 1990; Hirose et al., 1989; Kurata et al., 1990; Miyata et al., 1985; Maruyama et al., 1991; Stenius et al., 1989; Yamaguchi et al., 1989). Hydroquinone was inactive as a complete dermal carcinogen, skin cocarcinogen, or initiator of skin carcinogenesis in dermal application studies in mice (Roe and Salaman, 1955; Van Duuren and Goldschmidt, 1976), although bladder implantation of hydroquinone in cholesterol pellets increased the incidence of bladder carcinomas in mice (Boyland et al., 1964).

Hydroquinone was genotoxic in many in vitro systems using a variety of endpoints (IARC, 1999). Hydroquinone induced gene mutations in some strains of *Salmonella typhimurium*, gene conversion and mutations in *Saccharomyces cerevisiae*; and DNA strand breaks, gene mutations, chromosomal aberrations, sister chromatid exchanges, and micronuclei in cultured rodent and human cells. In vivo effects induced by hydroquinone included micronuclei and chromosomal aberrations in mouse bone marrow cells and spermatocytes. In addition, structurally similar DNA adducts have been observed in bone marrow following either in vitro hydroquinone or in vivo benzene exposure in mice (Pathak et al., 1995). No hydroquinone-related DNA adducts were detected in the kidneys of rats gavaged with up to 50 mg/kg-day for up to six weeks (English et al., 1994).

Although the positive findings of carcinogenicity in animals were not unequivocally treatment-related (leukemia) or indicated development of benign tumors (renal tubular and hepatocellular adenomas), evidence of hydroquinone-induced cancer was identified in male and female mice and rats in two separate studies. Further, mutagenicity was clearly exhibited in in vitro studies of bacterial and mammalian cell cultures, including human kidney cells. Under the U.S. EPA (2005) cancer guidelines, these data provide evidence that hydroquinone is “*Likely to be Carcinogenic in Humans.*”

Mode-of-Action Discussion

There are no data for hydroquinone carcinogenicity in humans. Available evidence in animals shows that oral exposure to hydroquinone is carcinogenic, producing significant increases in the incidence of kidney tumors in male rats, liver tumors in male and female mice, and mononuclear cell leukemia in female rats. The MOA for these tumor types in animals is not known. However, hydroquinone has consistently given positive results in standard prokaryotic and eukaryotic tests of mutagenicity and other types of genotoxicity in animals and human cell cultures. Consequently, a mutagenic MOA is plausible for both renal cancer and mononuclear cell leukemia in rats and liver cancer in mice but data are inadequate to make such a determination.

Renal Cancer

Based on the available data, the MOA for hydroquinone-induced renal adenomas in male rats cannot currently be determined. While a single study failed to find hydroquinone-DNA adducts in the kidneys of rats (English et al., 1994), the genotoxicity database for this chemical is consistently positive for mutagenicity (IARC, 1999). Therefore, a mutagenic MOA is possible but a determination cannot be made given the available data.

Key Events—The available cancer bioassay data show that high doses of hydroquinone produce statistically significant increases in renal adenomas in male rats, but not in females or in mice (NTP, 1989; Shibata et al., 1991). This sex and species specificity suggests the possibility of alpha 2u-globulin-induced cancer as the MOA. As summarized in the Risk Assessment Forum Review of alpha 2u-globulin renal toxicity and neoplasia (U.S. EPA, 1991b), the first step in a sequence of events leading to the alpha 2u-globulin-mediated renal tumor formation in male rats is excessive accumulation of hyaline droplets containing alpha 2u-globulin in renal proximal tubules. Both the NTP (1989) gavage study and the Shibata et al. (1991) feeding study reported the lack of hyaline droplet accumulation in the renal tubules. Thus, renal adenomas in male rats resulting from different doses (50 and 351 mg/kg-day) and sub-routes of exposure (gavage and diet) do not appear to be alpha 2u-globulin-mediated. No other data identifying key events for renal tumor development are available.

Strength, Consistency, Specificity of Association—Information to support a genotoxic MOA for hydroquinone includes hydroquinone-induced mutagenicity in several in vitro assays using bacterial strains and animal and human cell cultures.

Dose-Response Concordance—Although dose-response concordance for tumor development was observed in mice and rats (NTP, 1989), there are no dose-response data for precursor events, precluding an assessment of dose-response concordance for a mutagenic MOA. In the studies of NTP (1989) and Shibata et al. (1991), the extent of age-related nephropathy is exacerbated by hydroquinone treatment. A reanalysis of the histology data from the NTP (1989) study found that renal tubular adenomas were located in areas of severe chronic progressive nephropathy (Hard et al., 1997). However, the increase in nephropathy-severity across the dose groups (dose-related incidence of moderate or marked severity: 69%, 71%, and 85%) did not show high concordance with renal adenoma incidence (0%, 7%, and 15%).

Biological Plausibility and Coherence—The plausibility and coherence of a mutagenic MOA for hydroquinone-induced renal adenomas in rats is provided by several positive in vitro genotoxicity assays in bacterial, animal, and human culture systems. The basis for the observed sex-specific difference in tumorigenic response is not currently known. Based on the positive mutagenic response to cell culture systems across species, the human relevance of hydroquinone-induced renal adenomas in male rats is assumed.

Conclusions—The available data on the increased incidences of renal adenomas in hydroquinone-exposed male rats are considered suitable for quantitative cancer assessment. The available data do not support a definitive MOA, but the largely positive results from the mutagenicity assays suggest that a mutagenic MOA is plausible.

Liver Cancer

The MOA for hydroquinone-induced liver adenomas and/or carcinomas in mice is not known. However, the genotoxicity database for this chemical is consistently positive for mutagenicity (IARC, 1999). Therefore, a mutagenic MOA is possible but data are not available to make such a determination.

Key Events—No key events have been identified leading to the development of hydroquinone-induced hepatic tumors in mice. The nonneoplastic lesions observed in mice by NTP (1989) and Shibata et al. (1991) are indicative of nuclear alterations, but not cytotoxicity. Shibata et al. (1991) reported significant increases in the incidence of hepatocyte hypertrophy

and foci of cellular alterations occurring with hepatic adenoma and carcinoma. Nonneoplastic lesions reported by NTP (1989) in male mice included anisokaryosis and syncytial alteration (more than 5 nuclei per cell). Basophilic foci, lesions that are considered to be a precursor to adenomas, have been observed in male and female mice. The observed nuclear alterations and preneoplastic lesions and the lack of observable cytotoxicity support a mutagenic MOA for liver carcinogenicity in mice.

Strength, Consistency, Specificity of Association—As with renal tumor development in rats, information to support a genotoxic MOA for hydroquinone includes hydroquinone-induced mutagenicity in several in vitro assays using bacterial strains and animal and human cell cultures.

Dose-Response Concordance—There are currently no dose-response data for key events for hydroquinone-induced liver tumors in mice, precluding an assessment of dose-response concordance. The available tumor data did not show an increase in incidence at the high-dose group in comparison to the low-dose group; response rates were similar in both groups (NTP, 1989).

Biological Plausibility and Coherence—The plausibility and coherence of a mutagenic MOA for liver adenomas or carcinomas in hydroquinone-exposed mice is based on several positive in vitro genotoxicity assays and lack of observable hepatic cytotoxicity. The basis for the observed species-specific difference in tumor development is not currently known. Based on the positive mutagenic response to cell culture systems across species, the human relevance of hydroquinone-induced liver cancer in mice is assumed.

Conclusions—The available data for increased incidences of liver adenomas or carcinomas in hydroquinone-exposed female mice (NTP, 1989, based on positive effects at two dose levels) are considered suitable for quantitative cancer assessment. The available data do not support a definitive MOA, but the consistently positive results from mutagenicity assays suggest that a mutagenic MOA is possible.

Mononuclear Cell Leukemia

The NTP (1989) reported that chronic gavage exposure to hydroquinone significantly increased the incidence of mononuclear cell leukemia in female F344 rats relative to concurrent (but not historical) controls. Development of mononuclear cell leukemia was not observed in other species exposed to hydroquinone. Mononuclear cell leukemia (also called “large granular lymphocytic [LGL] leukemia” or “T γ leukemia”) is a spontaneous, rapidly fatal neoplasm that is common in aged, untreated F344 rats (Haseman et al., 1998). The MOA for induction of mononuclear cell leukemia in rats is unknown. Hence, the MOA analysis in this case is applied in an attempt to address the question of human relevance of rat tumor responses.

Key Events—The MOA of development of mononuclear cell leukemia in rats is currently unknown, precluding review and discussion of key events.

Strength, Consistency, Specificity of Association—Mononuclear cell leukemia is a spontaneous, rapidly fatal neoplasm that is common (average incidence of 28.1%) in aged, untreated F344 rats in 2-year carcinogenicity studies conducted by NTP (Haseman et al., 1998); it is, uncommon in other strains of laboratory rats and unknown in mice. For this reason, some pathologists regard it as a unique cancer that is not relevant to humans. In the case of phthalates, Caldwell (1999) argued that the increased incidences of mononuclear cell leukemia in F344 rats

treated with phthalates are not relevant to humans because 1) the equivalent cell type (based on morphological criteria) does not exist in humans or other animals, 2) the course of disease differs between species, and 3) phthalates are not genotoxic and induce leukemia only at high dose levels. However, the species-dependent arguments are weakened by a reliance on relatively old literature (largely predating 1990) and an overly strict definition of the apparently related LGL leukemia in humans. Hydroquinone differs from the phthalates in that the results of mutagenicity and other genotoxicity assays have largely been positive.

Dose-Response Concordance—Dose-response data for key events in development of mononuclear cell leukemia in hydroquinone-exposed rats do not currently exist, precluding an assessment of dose-response concordance. However, the severity of observed leukemia (stages 1, 2, or 3) increased with increasing dose thus making the data suitable for modeling.

Biological Plausibility and Coherence—In a brief discussion of mononuclear cell leukemia, CHAPDP (2001) noted that the human correlate to rat mononuclear cell leukemia is chronic T γ lymphoproliferative disease, which is characterized by abnormal expansion of large granular lymphocytes (LGL). Patients with this disease are predominately older males, who exhibit disease-related changes in lymphocytes; bone marrow and the spleen that are reported to be morphologically, functionally, and clinically similar to mononuclear cell leukemia in rats. Other reviews of human LGL leukemia have concluded that the disease has a diverse origin (NK- or T-cells) and a wide spectrum of acute or chronic clinical presentations (Lamy and Loughran, 1998). Canine LGL leukemias also may present as acute or chronic diseases—either of which may be caused by NK- or T-cells (Vernau and Moore, 1999). The mode(s) of action for induction of mononuclear cell leukemia in rats and LGL leukemia in humans and canines are currently unknown, preventing an assessment of relevance to human cancer on this basis.

Conclusions—Based on the clinical and pathological similarities between chronic T γ lymphoproliferative disease in humans and mononuclear cell leukemia in rats, increases in the incidence of mononuclear cell leukemia in treated rats were considered relevant to human health and suitable for quantitative cancer assessment of hydroquinone.

Quantitative Estimates of Carcinogenic Risk

Oral Exposure

Data for hydroquinone are sufficient to perform benchmark dose (BMD) modeling (U.S. EPA, 2000). Modeling was performed based on the incidences of renal tubule adenomas in male rats, mononuclear cell leukemia in female rats, and hepatocellular tumors (adenomas and carcinomas combined) in female mice in the NTP (1989) study. The Shibata et al. (1991) data are not amenable to dose-response modeling because the study included only a single dose level in each species. Dose-response modeling of the NTP (1989) data (Table 4) was performed using the methodologies in the U.S. EPA (2005) Guidelines for Carcinogen Risk Assessment. A linear extrapolation is appropriate for all three tumor types as indicated above as the MOA(s) for these tumors is generally unknown. In accordance with the 2005 cancer guidelines, the BMDL₁₀ (lower bound on dose estimated to produce a 10% increase in tumor incidence over background) for each tumor site was estimated using the U.S. EPA (2000) benchmark dose methodology.

The incidence data were analyzed using all available models for dichotomous data in the benchmark dose software (BMDS) program (version 1.3.2) developed by U.S. EPA. Risk was calculated as extra risk. Confidence bounds were automatically calculated by the BMDS using a maximum likelihood profile method.

Output from the BMDS program was evaluated using the criteria described in U.S. EPA (2000). Goodness-of-fit was evaluated using the chi-square statistic calculated by the BMDS program. Acceptable global goodness-of-fit is indicated by a *p*-value greater than or equal to 0.1. Models that did not meet these criteria were eliminated from consideration. Local fit is evaluated visually on the graphic output by comparing the observed and estimated results at each data point. BMDL₁₀ estimates that are within a factor of three are considered to show no model dependence and are ranked using the AIC reported by the BMDS program. The model with the lowest AIC is considered to provide a superior fit.

Table 4. Data Selected for BMD Modeling of Cancer Incidence in Rats and Mice Given Gavage Doses of Hydroquinone for 103 Weeks^a

Tumor Type	Species	Sex	0 mg/kg-d	18 mg/kg-d	36 mg/kg-d
Renal tubule adenoma	rat	male	0/55	4/55	8/55
Mononuclear cell leukemia	rat	female	9/55	15/55	22/55
			0 mg/kg-d	36 mg/kg-d	71 mg/kg-d
Hepatocellular adenoma or carcinoma	mouse	female	3/55	16/55	13/55

Doses listed are daily average doses (gavage dose × 5days/7 days)

^aNTP, 1989

Modeling results are shown in Table 5 and Figures A-1 and A-2. For mononuclear cell leukemia, fits of the gamma, log logistic, and Weibull models to the data could not be evaluated due to the availability of only three dose groups—these models each have three estimable parameters and the inability of the BMD software to provide an initial specification for one of the three model parameters. Thus, too few degrees of freedom were available for calculation of a *p*-value with which to evaluate model fit. This did not occur for the renal or liver tumor data. None of the available models resulted in an adequate fit to the hepatocellular tumor data in mice (Table 5).

Table 5. Multistage Benchmark Dose Modeling Results for Rats and Mice Exposed to Hydroquinone by Gavage for 2 Years^{a,b}

Incidence	Species	Strain	Sex	AIC	<i>p</i> -Value ^c	BMD ₁₀ (mg/kg-day)	BMDL ₁₀ (mg/kg-day)
Renal Tubule Adenomas^d	Rats	F344/N	M	76.2961	0.9979	24.4596	15.7456
Mononuclear Cell Leukemia ^d	Rats	F344/N	F	191.571	0.8016	11.7719	7.3221
Hepatocellular Adenoma or Carcinoma (Combined) ^e	Mice	B6C3F ₁	F	157.99	0.0358	25.3683	16.4603

^aNTP, 1989

^bBest fitting model(s) in bold text

^cValues <0.1 fail to meet conventional goodness-of-fit criteria

^dBetas restricted to ≥0; polydegree = 1 (lowest degree polynomial with adequate fit)

^eBetas restricted to ≥0; polydegree = 1 (no adequate fit at any polydegree; higher polydegrees default to 1 degree)

Abbreviations: AIC = Akaike Information Criterion; BMD₁₀ = maximum likelihood estimate of the dose producing a 10% extra risk of effect; BMDL₁₀ = 95% lower confidence limit on the BMD₁₀

Human equivalent doses (BMDL_{10 HED}) were calculated for each animal BMDL₁₀ using U.S. EPA's cross-species scaling factor of body weight raised to the 3/4 power (U.S. EPA, 2005). Adjustment from animal-to-human administered dose is performed by multiplying the animal BMDL₁₀ by the ratio of animal-to-human body weight raised to the 1/4 power. The BMDL_{10 HED} represents the chronic daily dose (mg/kg-d) expected to result in 10% extra risk for tumor development extrapolated from the animal bioassay data. The BMDL_{10 HED} values for renal tumors in male rats and mononuclear cell leukemia in female rats are shown in Table 6.

Comparison of the BMDL_{10 HED} values in Table 6 shows that mononuclear cell leukemia in female rats is a more sensitive endpoint than renal tubule adenoma in male rats because it occurs at a lower dose.

Table 6. BMDL₁₀s and Human Equivalent Doses from Models Adequately Fit to Incidence Data for Tumors in Animals Chronically Treated with Hydroquinone				
Test Group	Tumor Location & Type	p-value	BMDL₁₀ (mg/kg-day)	BMDL_{10 HED}^a (mg/kg-day)
Male Rats	renal tubule adenoma	0.9979	15.8	4.4
Female Rats	mononuclear cell leukemia	0.8016	7.3	1.8
Female Mice	Hepatocellular adenoma or carcinoma (combined)	0.035 (failed)	16.46	2.5

^aHuman cancer equivalent dose of the BMDL₁₀ calculated as animal BMDL₁₀ × (W_{animal}/W_{human})^{1/4} where W_{human} = 70 kg (human reference body weight) and W_{animal} = 0.416 kg for male rats and 0.273 kg for female rats (time weighted average body weights in the study).

In order to linearly extrapolate cancer risks from the BMDL_{10 HED} to the origin, a cancer oral slope factor (OSF) was calculated as the ratio 0.1/BMDL_{10 HED}. Taking the BMDL_{10 HED} of 1.8 mg/kg-day for mononuclear cell leukemia in female rats as the POD, a provisional **OSF of 0.06 (mg/kg-day)⁻¹** is calculated as follows:

$$\begin{aligned}
 \text{p-OSF} &= 0.1 \div \text{BMDL}_{10 \text{ HED}} \\
 &= 0.1 \div 1.8 \text{ mg/kg-day} \\
 &= \mathbf{0.06 \text{ (mg/kg-day)}^{-1}}
 \end{aligned}$$

The OSF for hydroquinone should not be used with exposures exceeding the POD (BMDL_{10 HED} = 1.8 mg/kg-day) because above this level the fitted dose-response model better characterizes what is known about the carcinogenicity of hydroquinone.

Inhalation Exposure

No data are currently available for the quantitative estimate of cancer risk following inhalation exposure to hydroquinone.

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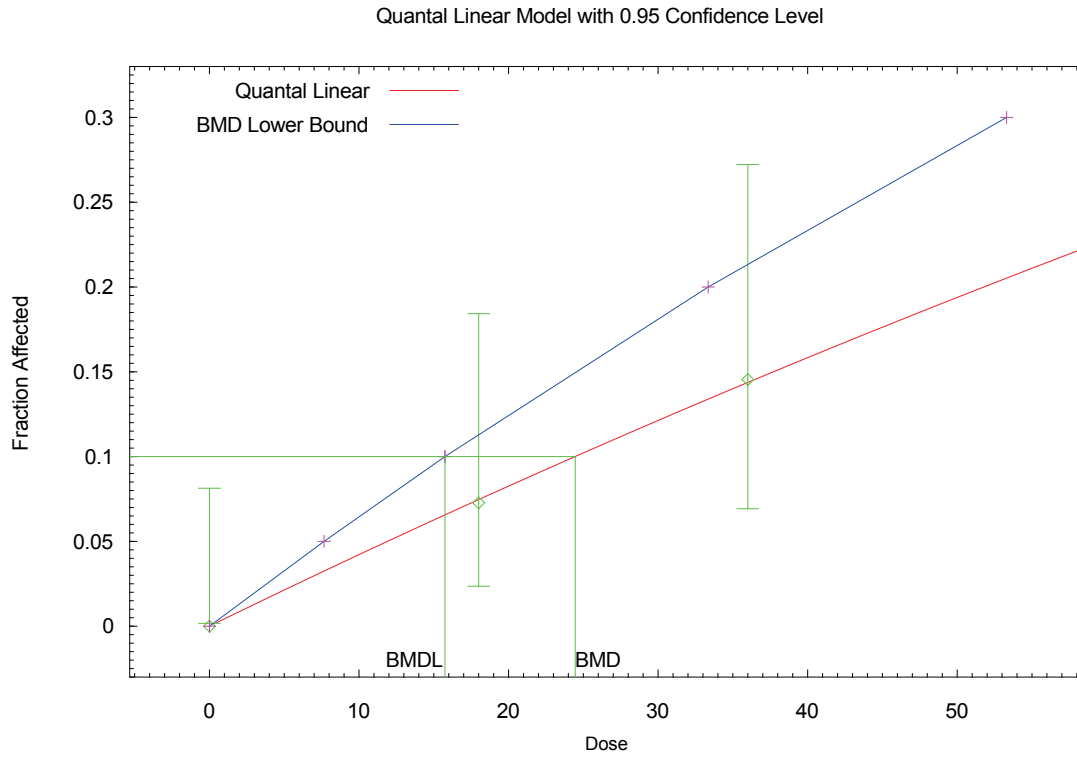
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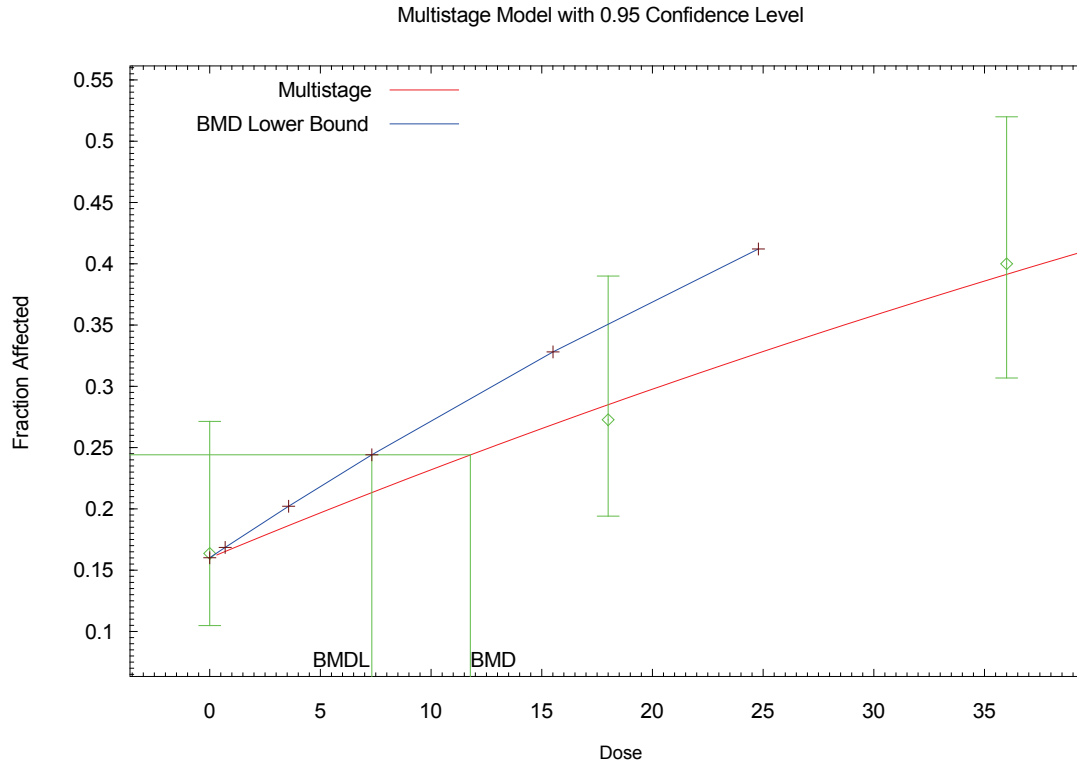
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APPENDIX A. DETAILS OF BENCHMARK DOSE MODELING FOR HYDROQUINONE



16:42 02/19 2007

Figure A-1. Observed and Predicted Incidences of Renal Tubule Adenomas in Male Rats Gavaged with Hydroquinone for 2 Years by NTP (1989)



11:41 02/22 2007

Figure A-2. Observed and Predicted Incidences of Mononuclear Cell Leukemia in Female Rats Gavaged with Hydroquinone for 2 Years by NTP (1989)

BMD Modeling of Rat and Mouse Tumor Data from 2-year Oral Hydroquinone Exposure (NTP 1989)

Part I. Male Rats: Renal Tubule Adenoma

Gamma model

```
=====
$Revision: 2.2 $ $Date: 2001/03/14 01:17:00 $
Input Data File: C:\BMDS\HYDROQUINONE\RENAL_ADENOMA_GAMMA.(d)
Gnuplot Plotting File: C:\BMDS\HYDROQUINONE\RENAL_ADENOMA_GAMMA.plt
Mon Feb 19 16:24:04 2007
=====
```

BMDS MODEL RUN

~~~~~

The form of the probability function is:

$P[\text{response}] = \text{background} + (1 - \text{background}) * \text{CumGamma}[\text{slope} * \text{dose}, \text{power}]$ ,  
where CumGamma(.) is the cumulative Gamma distribution function

Dependent variable = renal\_adenoma  
Independent variable = Dose  
Power parameter is restricted as power >=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

Default Initial (and Specified) Parameter Values  
Background = 0.00892857  
Slope = 0.00618629  
Power = 1.18252

Asymptotic Correlation Matrix of Parameter Estimates

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

|       | Slope | Power |
|-------|-------|-------|
| Slope | 1     | 0.99  |
| Power | 0.99  | 1     |

Parameter Estimates

| Variable   | Estimate   | Std. Err. |
|------------|------------|-----------|
| Background | 0          | NA        |
| Slope      | 0.00512205 | 0.0130769 |
| Power      | 1.06717    | 1.03886   |

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    | -37.1459        |             |         |          |
| Fitted model  | -37.1459        | 2.2952e-010 | 1       | 1        |
| Reduced model | -43.0051        | 11.7185     | 2       | 0.002853 |

AIC: 78.2918

Goodness of Fit

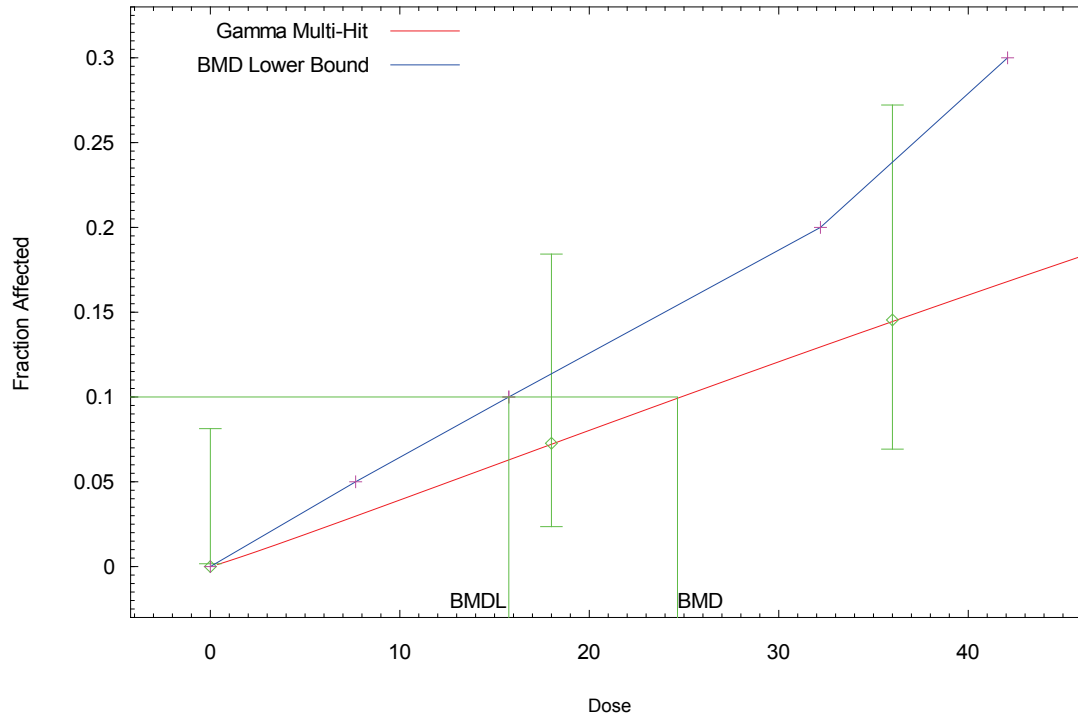
| Dose    | Est._Prob. | Expected | Observed | Size | Scaled Residual |
|---------|------------|----------|----------|------|-----------------|
| 0.0000  | 0.0000     | 0.000    | 0        | 55   | 0               |
| 18.0000 | 0.0727     | 4.000    | 4        | 55   | -5.573e-006     |
| 36.0000 | 0.1455     | 8.000    | 8        | 55   | -1.409e-005     |

Chi-square = 0.00 DF = 1 P-value = 1.0000

Benchmark Dose Computation

Specified effect = 0.1  
 Risk Type = Extra risk  
 Confidence level = 0.95  
 BMD = 24.6551  
 BMDL = 15.7507

Gamma Multi-Hit Model with 0.95 Confidence Level



16:24 02/19 2007

Log Logistic model

```
=====
Logistic Model. (Version: 2.9; Date: 02/20/2007)
Input Data File: C:\BMDS\DATA\HYDROQUINONE_CARC.(d)
Gnuplot Plotting File: C:\BMDS\DATA\HYDROQUINONE_CARC.plt
Wed Apr 18 14:14:51 2007
=====
```

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1 - \text{background}) / [1 + \text{EXP}(-\text{intercept} - \text{slope} * \text{Log}(\text{dose}))]$$

Dependent variable = renal\_M\_resp  
Independent variable = rat\_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 =    -5.77649
slope =          1.11784
```

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         | -1    |
| slope     | -1        | 1     |

Parameter Estimates

| Interval<br>Limit | Variable   | Estimate | Std. Err. | 95.0% Wald Confidence |             |
|-------------------|------------|----------|-----------|-----------------------|-------------|
|                   |            |          |           | Lower Conf. Limit     | Upper Conf. |
|                   | background | 0        | *         | *                     | *           |
|                   | intercept  | -5.77649 | *         | *                     | *           |
|                   | slope      | 1.11784  | *         | *                     | *           |

\* - Indicates that this value is not calculated.

Warning: Likelihood for the fitted model larger than the Likelihood for the full model.



Analysis of Deviance Table

| Model         | Log(likelihood) | # Param's | Deviance      | Test d.f. | P-value  |
|---------------|-----------------|-----------|---------------|-----------|----------|
| Full model    | -37.1459        | 3         |               |           |          |
| Fitted model  | -37.1459        | 2         | -1.42109e-014 | 1         |          |
| Reduced model | -43.0051        | 1         | 11.7185       | 2         | 0.002853 |

AIC: 78.2918

Goodness of Fit

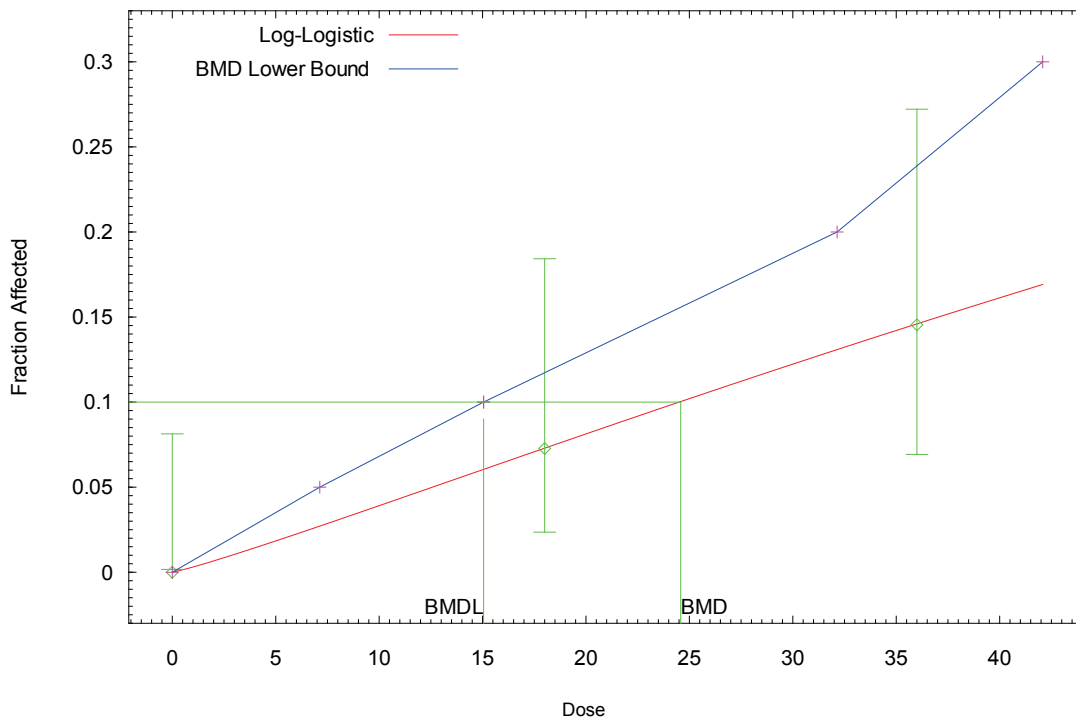
| Dose    | Est._Prob. | Expected | Observed | Size | Scaled Residual |
|---------|------------|----------|----------|------|-----------------|
| 0.0000  | 0.0000     | 0.000    | 0        | 55   | 0.000           |
| 18.0000 | 0.0727     | 4.000    | 4        | 55   | -0.000          |
| 36.0000 | 0.1455     | 8.000    | 8        | 55   | -0.000          |

Chi^2 = 0.00      d.f. = 1      P-value = 1.0000

Benchmark Dose Computation

Specified effect = 0.1  
 Risk Type = Extra risk  
 Confidence level = 0.95  
 BMD = 24.5807  
 BMDL = 15.0507

Log-Logistic Model with 0.95 Confidence Level



14:19 04/18 2007

Logistic model

```
=====
Logistic Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:20 $
Input Data File: C:\BMDS\HYDROQUINONE\RENAL_ADENOMA_LOGISTIC.(d)
Gnuplot Plotting File: C:\BMDS\HYDROQUINONE\RENAL_ADENOMA_LOGISTIC.plt
Mon Feb 19 16:31:37 2007
=====
```

BMDS MODEL RUN

~~~~~

The form of the probability function is:

$$P[\text{response}] = 1/[1+\text{EXP}(-\text{intercept}-\text{slope}*\text{dose})]$$

Dependent variable = renal_adenoma
Independent variable = Dose
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 Parameter Values
background =          0   Specified
intercept =    -4.45033
slope =         0.0830241
```

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	-0.94
slope	-0.94	1

Parameter Estimates

Variable	Estimate	Std. Err.
intercept	-4.34388	0.889063
slope	0.0742432	0.0283803

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-37.1459			
Fitted model	-38.238	2.18422	1	0.1394
Reduced model	-43.0051	11.7185	2	0.002853
AIC:	80.476			

Goodness of Fit

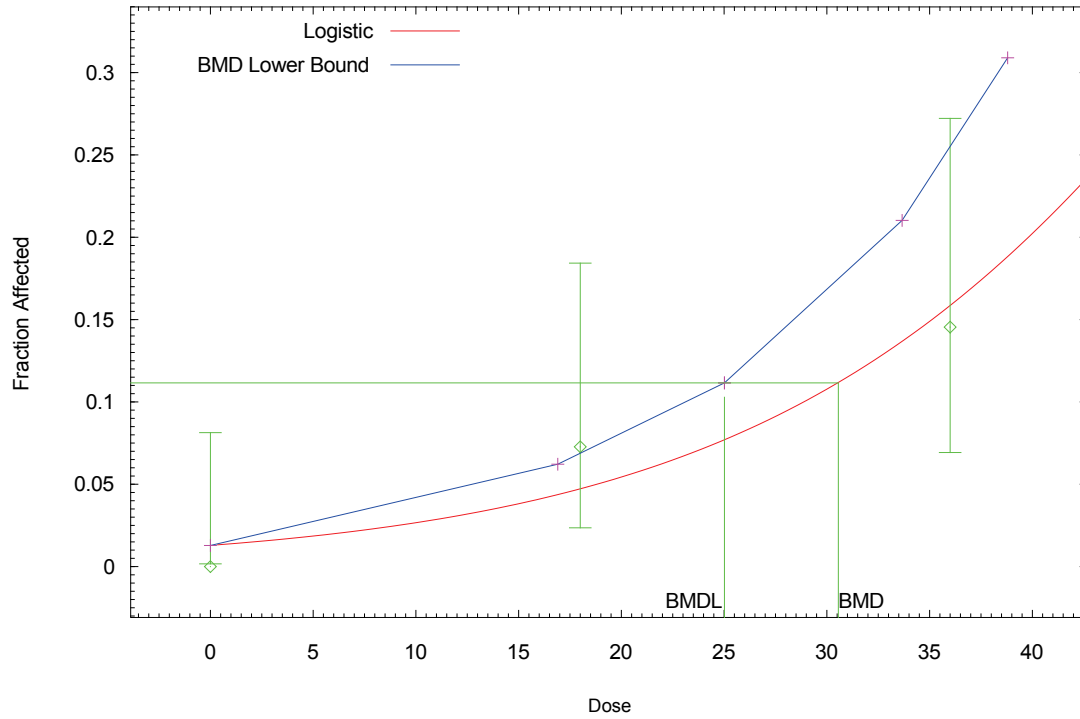
Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0128	0.705	0	55	-0.8451
18.0000	0.0471	2.590	4	55	0.8976
36.0000	0.1583	8.705	8	55	-0.2605

Chi-square = 1.59 DF = 1 P-value = 0.2076

Benchmark Dose Computation

Specified effect = 0.1
Risk Type = Extra risk
Confidence level = 0.95
BMD = 30.5583
BMDL = 25.0151

Logistic Model with 0.95 Confidence Level



16:31 02/19 2007

Multistage model: 2 degree polynomial

=====
Multistage Model. \$Revision: 2.1 \$ \$Date: 2000/08/21 03:38:21 \$
Input Data File: C:\BMDS\HYDROQUINONE\RENAL_ADENOMA_MS.(d)
Gnuplot Plotting File: C:\BMDS\HYDROQUINONE\RENAL_ADENOMA_MS.plt
Mon Feb 19 16:35:48 2007
=====

BMDS MODEL RUN

~~~~~

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose}^1 - \text{beta2} * \text{dose}^2)]$$

The parameter betas are restricted to be positive

Dependent variable = renal\_adenoma  
Independent variable = Dose

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 = 5.55112e-017  
Beta(1) = 0.00402346  
Beta(2) = 9.52234e-006

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(2) |
|---------|---------|---------|
| Beta(1) | 1       | -0.97   |
| Beta(2) | -0.97   | 1       |

Parameter Estimates

| Variable   | Estimate     | Std. Err.   |
|------------|--------------|-------------|
| Background | 0            | NA          |
| Beta(1)    | 0.00402346   | 0.0160776   |
| Beta(2)    | 9.52238e-006 | 0.000487293 |

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    | -37.1459        |              |         |          |
| Fitted model  | -37.1459        | 6.39488e-013 | 1       | 1        |
| Reduced model | -43.0051        | 11.7185      | 2       | 0.002853 |
| AIC:          | 78.2918         |              |         |          |

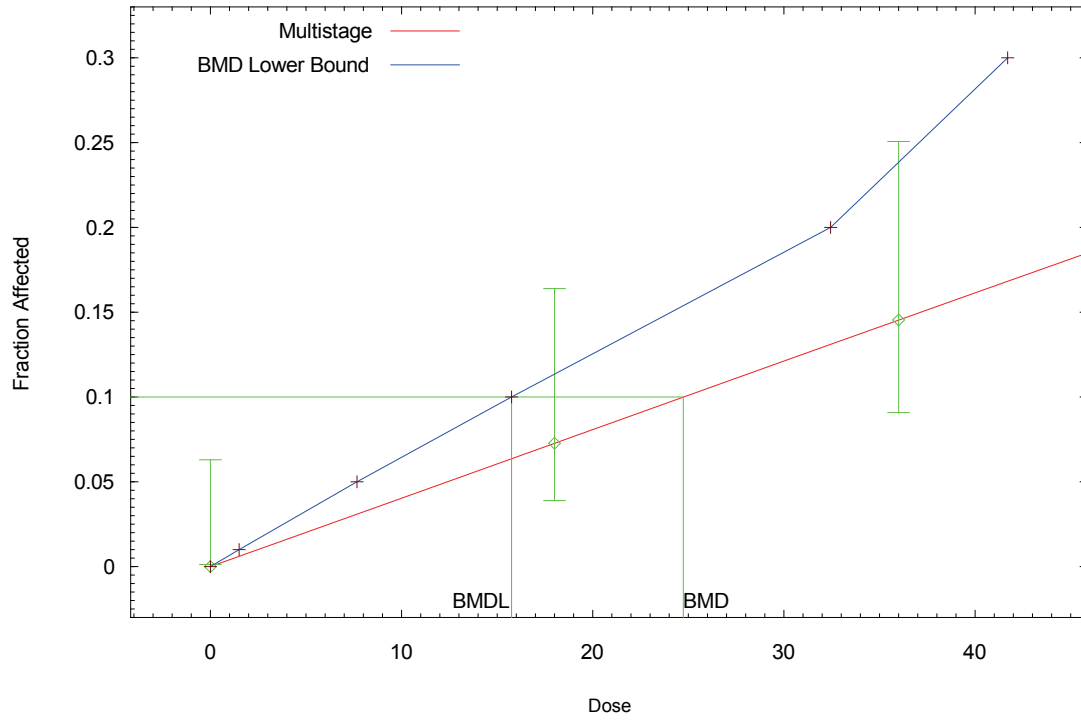
Goodness of Fit

|              | Dose    | Est._Prob. | Expected | Observed         | Size | Chi^2 Res. |
|--------------|---------|------------|----------|------------------|------|------------|
| i: 1         | 0.0000  | 0.0000     | 0.000    | 0                | 55   | 0.000      |
| i: 2         | 18.0000 | 0.0727     | 4.000    | 4                | 55   | -0.000     |
| i: 3         | 36.0000 | 0.1455     | 8.000    | 8                | 55   | -0.000     |
| Chi-square = | 0.00    | DF = 1     |          | P-value = 1.0000 |      |            |

Benchmark Dose Computation

Specified effect = 0.1  
 Risk Type = Extra risk  
 Confidence level = 0.95  
 BMD = 24.7382  
 BMDL = 15.7507

Multistage Model with 0.95 Confidence Level



16:35 02/19 2007

Multistage model: 1 degree polynomial

```
=====
Multistage Model. (Version: 2.8; Date: 02/20/2007)
Input Data File: C:\BMDS\DATA\HYDROQUINONE_CARC.(d)
Gnuplot Plotting File: C:\BMDS\DATA\HYDROQUINONE_CARC.plt
Wed Apr 18 14:24:26 2007
=====
```

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1-\text{EXP}(-\text{beta1} * \text{dose}^1)]$$

The parameter betas are restricted to be positive

Dependent variable = renal\_M\_resp  
Independent variable = rat\_dose

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) = 0.00436627

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

| Interval<br>Limit | Variable   | Estimate   | Std. Err. | 95.0% Wald Confidence |                   |
|-------------------|------------|------------|-----------|-----------------------|-------------------|
|                   |            |            |           | Lower Conf. Limit     | Upper Conf. Limit |
|                   | Background | 0          | *         | *                     | *                 |
|                   | Beta(1)    | 0.00430754 | *         | *                     | *                 |

\* - Indicates that this value is not calculated.



Analysis of Deviance Table

| Model         | Log(likelihood) | # Param's | Deviance   | Test d.f. | P-value  |
|---------------|-----------------|-----------|------------|-----------|----------|
| Full model    | -37.1459        | 3         |            |           |          |
| Fitted model  | -37.148         | 1         | 0.00429126 | 2         | 0.9979   |
| Reduced model | -43.0051        | 1         | 11.7185    | 2         | 0.002853 |
| AIC:          | 76.2961         |           |            |           |          |

Goodness of Fit

| Dose    | Est._Prob. | Expected | Observed | Size | Scaled Residual |
|---------|------------|----------|----------|------|-----------------|
| 0.0000  | 0.0000     | 0.000    | 0        | 55   | 0.000           |
| 18.0000 | 0.0746     | 4.103    | 4        | 55   | -0.053          |
| 36.0000 | 0.1436     | 7.901    | 8        | 55   | 0.038           |

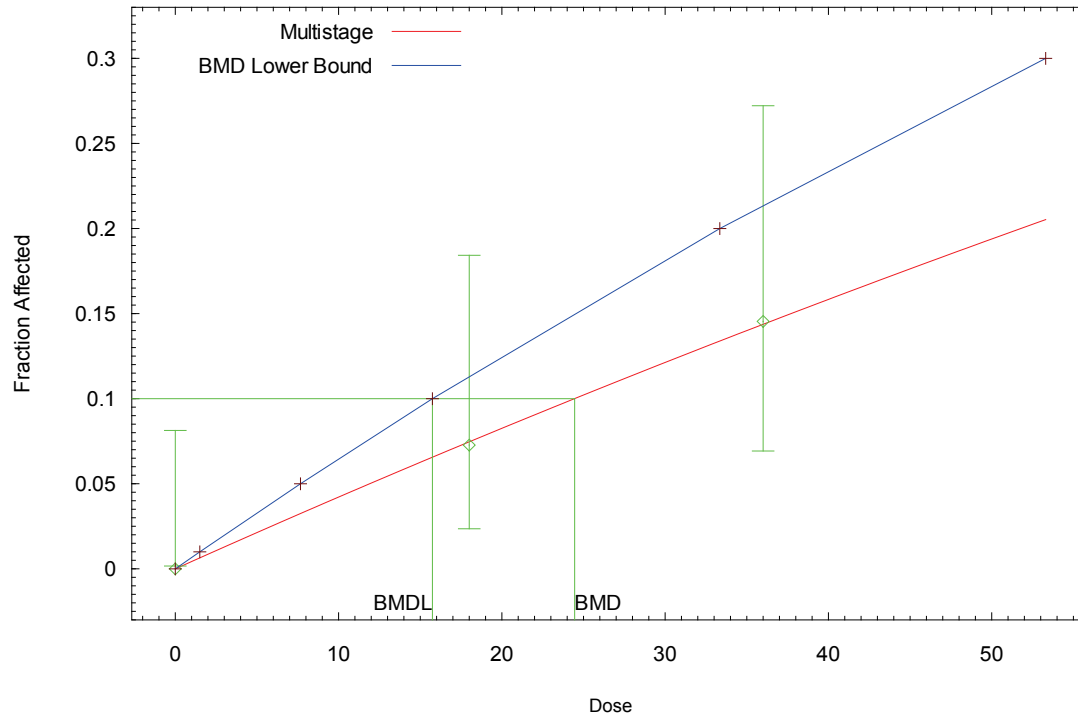
Chi^2 = 0.00      d.f. = 2      P-value = 0.9979

Benchmark Dose Computation

Specified effect = 0.1  
 Risk Type = Extra risk  
 Confidence level = 0.95  
 BMD = 24.4596  
 BMDL = 15.7456  
 BMDU = 41.3552

Taken together, (15.7456, 41.3552) is a 90 % two-sided confidence interval for the BMD

Multistage Model with 0.95 Confidence Level



14:24 04/18 2007

Log Probit model

```
=====
Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
Input Data File: C:\BMDS\HYDROQUINONE\RENAL_ADENOMA_LOGPROBIT.(d)
Gnuplot Plotting File: C:\BMDS\HYDROQUINONE\RENAL_ADENOMA_LOGPROBIT.plt
Mon Feb 19 16:41:07 2007
=====
```

BMDS MODEL RUN

~~~~~

The form of the probability function is:

$$P[\text{response}] = \text{Background} + (1 - \text{Background}) * \text{CumNorm}(\text{Intercept} + \text{Slope} * \text{Log}(\text{Dose})),$$

where CumNorm(.) is the cumulative normal distribution function

Dependent variable = renal_adenoma
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 =	-4.34615
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	-4.52904	0.162761
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	-37.1459			
Fitted model	-37.5373	0.782885	2	0.6761
Reduced model	-43.0051	11.7185	2	0.002853
AIC:	77.0747			

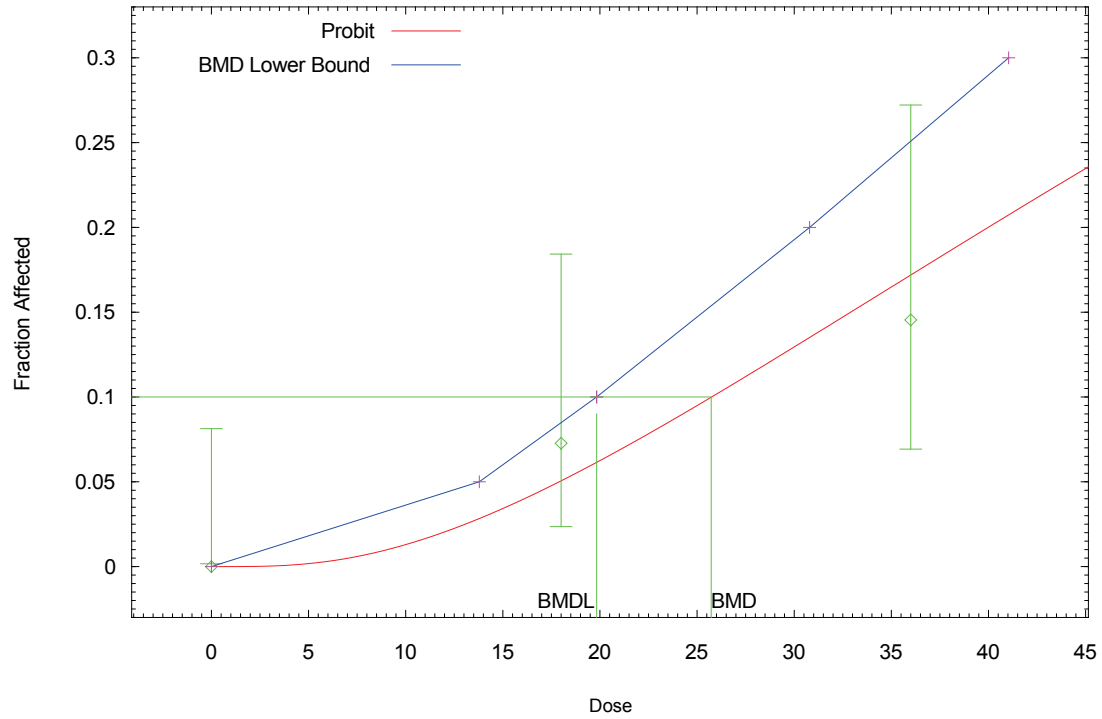
Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	55	0
18.0000	0.0506	2.785	4	55	0.747
36.0000	0.1722	9.471	8	55	-0.5253
Chi-square =	0.83	DF = 2	P-value =	0.6590	

Benchmark Dose Computation

Specified effect = 0.1
 Risk Type = Extra risk
 Confidence level = 0.95
 BMD = 25.7257
 BMDL = 19.8319

Probit Model with 0.95 Confidence Level



16:41 02/19 2007

Probit model

```
=====
Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
Input Data File: C:\BMDS\HYDROQUINONE\RENAL_ADENOMA_PROBIT.(d)
Gnuplot Plotting File: C:\BMDS\HYDROQUINONE\RENAL_ADENOMA_PROBIT.plt
Mon Feb 19 16:39:37 2007
=====
```

BMDS MODEL RUN

The form of the probability function is:

$P[\text{response}] = \text{CumNorm}(\text{Intercept} + \text{Slope} * \text{Dose}),$

where CumNorm(.) is the cumulative normal distribution function

Dependent variable = renal_adenoma

Independent variable = Dose

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 =      -2.61578
slope =          0.047858
```

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	-0.92
slope	-0.92	1

Parameter Estimates

Variable	Estimate	Std. Err.
intercept	-2.33003	0.398082
slope	0.0371221	0.0134772

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-37.1459			
Fitted model	-38.0507	1.80952	1	0.1786
Reduced model	-43.0051	11.7185	2	0.002853

AIC: 80.1013

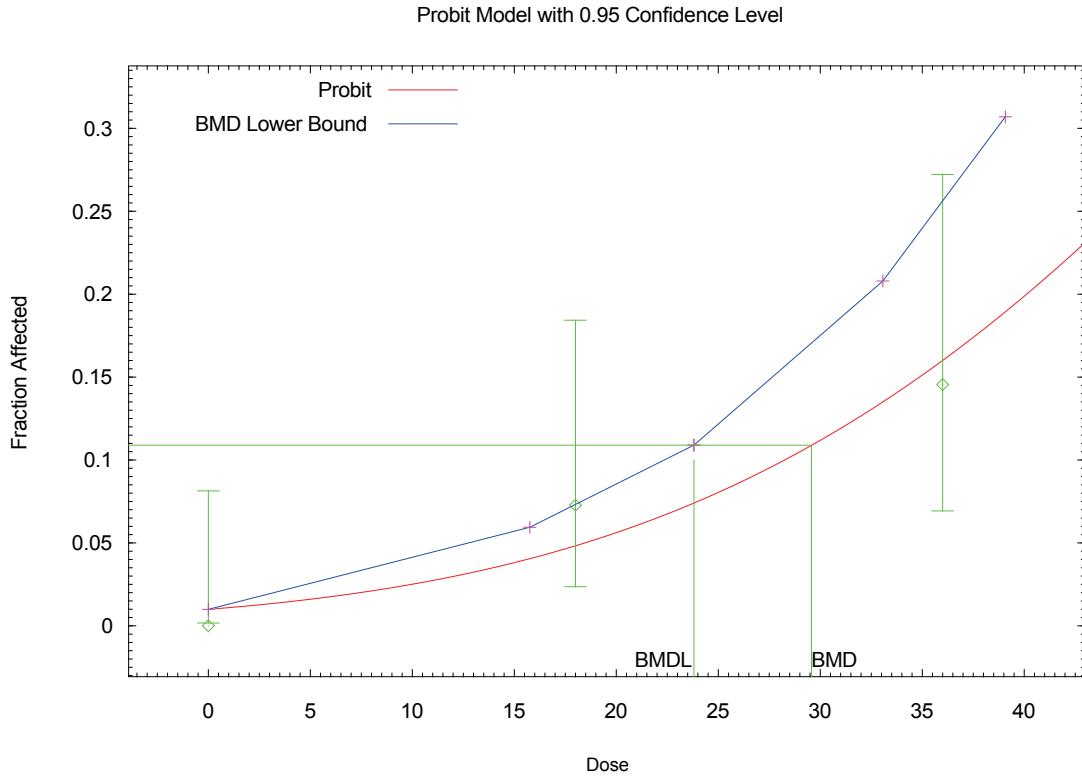
Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0099	0.545	0	55	-0.7417
18.0000	0.0483	2.655	4	55	0.8461
36.0000	0.1602	8.811	8	55	-0.2981

Chi-square = 1.35 DF = 1 P-value = 0.2444

Benchmark Dose Computation

Specified effect = 0.1
Risk Type = Extra risk
Confidence level = 0.95
BMD = 29.5699
BMDL = 23.8061



16:39 02/19 2007

Quantal Linear model

```
=====
Quantal Linear Model $Revision: 2.2 $ $Date: 2000/03/17 22:27:16 $
Input Data File: C:\BMDS\HYDROQUINONE\RENAL_ADENOMA_QL.(d)
Gnuplot Plotting File: C:\BMDS\HYDROQUINONE\RENAL_ADENOMA_QL.plt
Mon Feb 19 16:42:30 2007
=====
```

BMDS MODEL RUN

~~~~~

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1-\text{EXP}(-\text{slope} * \text{dose})]$$

Dependent variable = renal\_adenoma  
Independent variable = Dose

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 = 0.00892857  
Slope = 0.0043237  
Power = 1 Specified

Asymptotic Correlation Matrix of Parameter Estimates

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

Slope  
Slope 1

Parameter Estimates

| Variable   | Estimate   | Std. Err.  |
|------------|------------|------------|
| Background | 0          | NA         |
| Slope      | 0.00430754 | 0.00124441 |

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    | -37.1459        |            |         |          |
| Fitted model  | -37.148         | 0.00429126 | 2       | 0.9979   |
| Reduced model | -43.0051        | 11.7185    | 2       | 0.002853 |
| AIC:          | 76.2961         |            |         |          |

Goodness of Fit

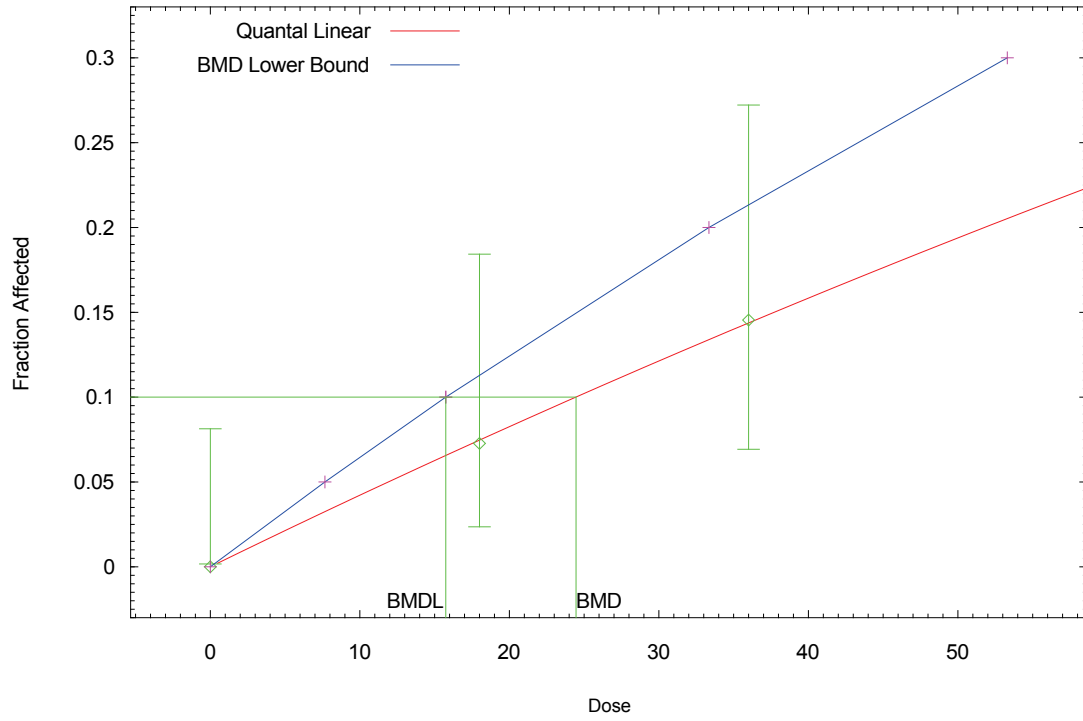
| Dose    | Est._Prob. | Expected | Observed | Size | Scaled Residual |
|---------|------------|----------|----------|------|-----------------|
| 0.0000  | 0.0000     | 0.000    | 0        | 55   | 0               |
| 18.0000 | 0.0746     | 4.103    | 4        | 55   | -0.05303        |
| 36.0000 | 0.1436     | 7.901    | 8        | 55   | 0.03824         |

Chi-square = 0.00      DF = 2      P-value = 0.9979

Benchmark Dose Computation

Specified effect = 0.1  
Risk Type = Extra risk  
Confidence level = 0.95  
BMD = 24.4596  
BMDL = 15.7456

Quantal Linear Model with 0.95 Confidence Level



16:42 02/19 2007

Quantal Quadratic model

```
=====
Quantal Quadratic Model $Revision: 2.2 $ $Date: 2000/03/17 22:27:16 $
Input Data File: C:\BMDS\HYDROQUINONE\RENAL_ADENOMA_QQ.(d)
Gnuplot Plotting File: C:\BMDS\HYDROQUINONE\RENAL_ADENOMA_QQ.plt
Mon Feb 19 16:43:51 2007
=====
```

BMDS MODEL RUN

~~~~~

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1-\text{EXP}(-\text{slope} * \text{dose}^2)]$$

Dependent variable = renal_adenoma
Independent variable = Dose

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 = 0.00892857
Slope = 0.000120103
Power = 2 Specified

Asymptotic Correlation Matrix of Parameter Estimates

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

Slope
Slope 1

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0	NA
Slope	0.000144402	4.17271e-005

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	-37.1459			
Fitted model	-37.6677	1.04354	2	0.5935
Reduced model	-43.0051	11.7185	2	0.002853
AIC:	77.3353			

Goodness of Fit

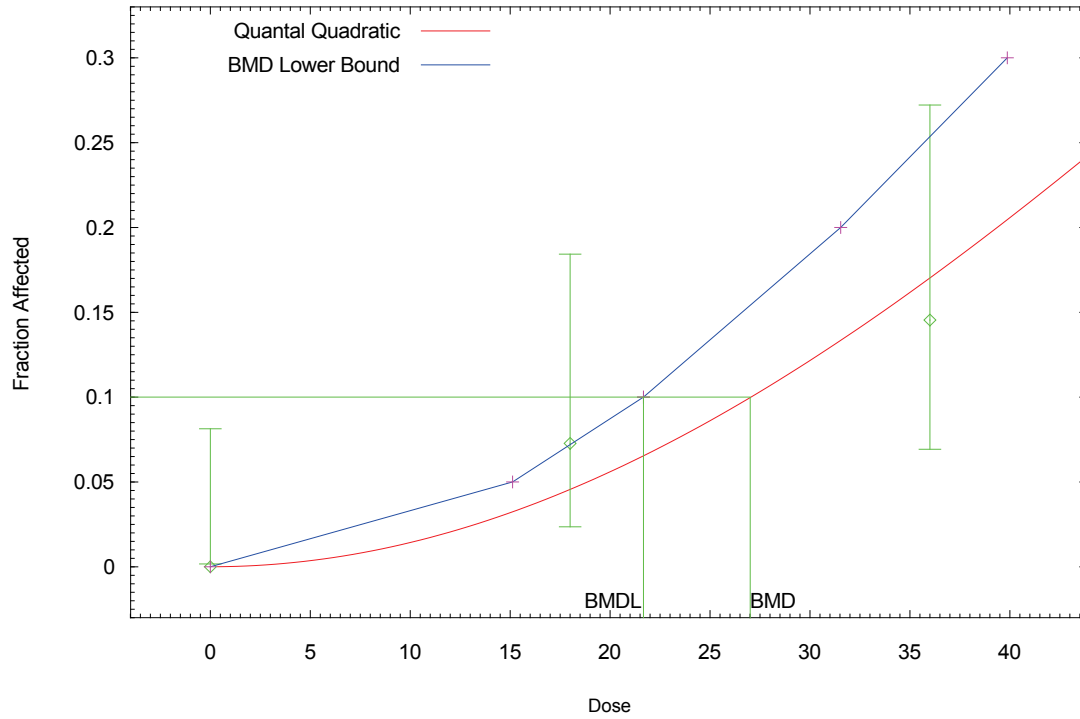
Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	55	0
18.0000	0.0457	2.514	4	55	0.9594
36.0000	0.1707	9.387	8	55	-0.4972

Chi-square = 1.17 DF = 2 P-value = 0.5578

Benchmark Dose Computation

Specified effect = 0.1
Risk Type = Extra risk
Confidence level = 0.95
BMD = 27.0117
BMDL = 21.6709

Quantal Quadratic Model with 0.95 Confidence Level



16:43 02/19 2007

Weibull model

```
=====
Weibull Model $Revision: 2.2 $ $Date: 2000/03/17 22:27:16 $
Input Data File: C:\BMDS\HYDROQUINONE\RENAL_ADENOMA_WEIBULL.(d)
Gnuplot Plotting File: C:\BMDS\HYDROQUINONE\RENAL_ADENOMA_WEIBULL.plt
Mon Feb 19 16:46:28 2007
=====
```

BMDS MODEL RUN

~~~~~

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1-\text{EXP}(-\text{slope} * \text{dose}^{\text{power}})]$$

Dependent variable = renal\_adenoma  
Independent variable = Dose  
Power parameter is restricted as power >=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

Default Initial (and Specified) Parameter Values

Background = 0.00892857  
Slope = 0.00192321  
Power = 1.22607

Asymptotic Correlation Matrix of Parameter Estimates

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

|       | Slope | Power |
|-------|-------|-------|
| Slope | 1     | -1    |
| Power | -1    | 1     |

Parameter Estimates

| Variable   | Estimate   | Std. Err. |
|------------|------------|-----------|
| Background | 0          | NA        |
| Slope      | 0.00354973 | 0.0105672 |
| Power      | 1.05777    | 0.88385   |

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 | -37.1459        |          |         |         |

|               |          |              |   |          |
|---------------|----------|--------------|---|----------|
| Fitted model  | -37.1459 | 2.31637e-011 | 1 | 1        |
| Reduced model | -43.0051 | 11.7185      | 2 | 0.002853 |

AIC: 78.2918

Goodness of Fit

| Dose    | Est._Prob. | Expected | Observed | Size | Scaled Residual |
|---------|------------|----------|----------|------|-----------------|
| 0.0000  | 0.0000     | 0.000    | 0        | 55   | 0               |
| 18.0000 | 0.0727     | 4.000    | 4        | 55   | 1.236e-006      |
| 36.0000 | 0.1455     | 8.000    | 8        | 55   | 4.652e-006      |

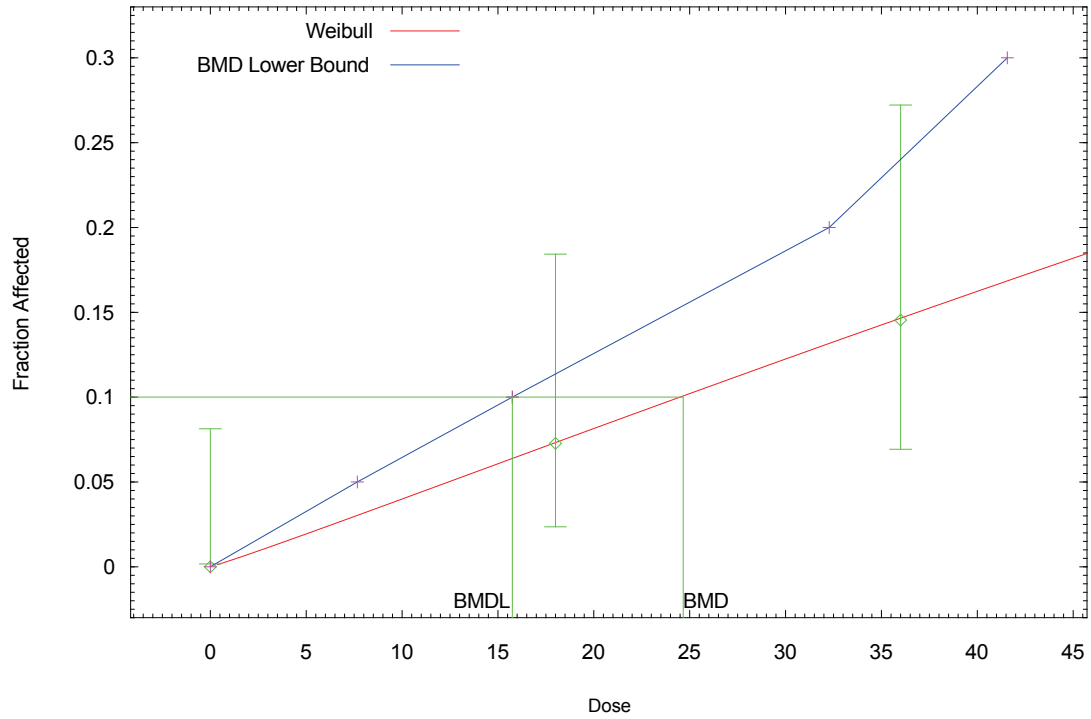
Chi-square = 0.00      DF = 1      P-value = 1.0000

Benchmark Dose Computation

Specified effect = 0.1  
Risk Type = Extra risk  
Confidence level = 0.95  
BMD = 24.6637  
BMDL = 15.7507



Weibull Model with 0.95 Confidence Level



16:46 02/19 2007

Part II. Female Rats: Mononuclear Cell Leukemia

Gamma model

```
=====
$Revision: 2.2 $ $Date: 2001/03/14 01:17:00 $
Input Data File: C:\BMDS\HYDROQUINONE\MNCL_GAMMA.(d)
Gnuplot Plotting File: C:\BMDS\HYDROQUINONE\MNCL_GAMMA.plt
                               Mon Feb 19 16:51:11 2007
=====
```

BMDS MODEL RUN

~~~~~

The form of the probability function is:

$P[\text{response}] = \text{background} + (1 - \text{background}) * \text{CumGamma}[\text{slope} * \text{dose}, \text{power}]$,
where CumGamma(.) is the cumulative Gamma distribution function

Dependent variable = MNCL
Independent variable = Dose
Power parameter is restricted as power >=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

Default Initial (and Specified) Parameter Values

Background = 0.169643
Slope = 0.0163268
Power = 1.39303

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Slope	Power
Background	1	0.24	0.33
Slope	0.24	1	0.99
Power	0.33	0.99	1

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.163636	0.0498785
Slope	0.015406	0.0300769
Power	1.33159	1.46377

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-93.7538			
Fitted model	-93.7538	4.80355e-010	0	NA
Reduced model	-97.6478	7.78794	2	0.02036
AIC:	193.508			

Goodness of Fit

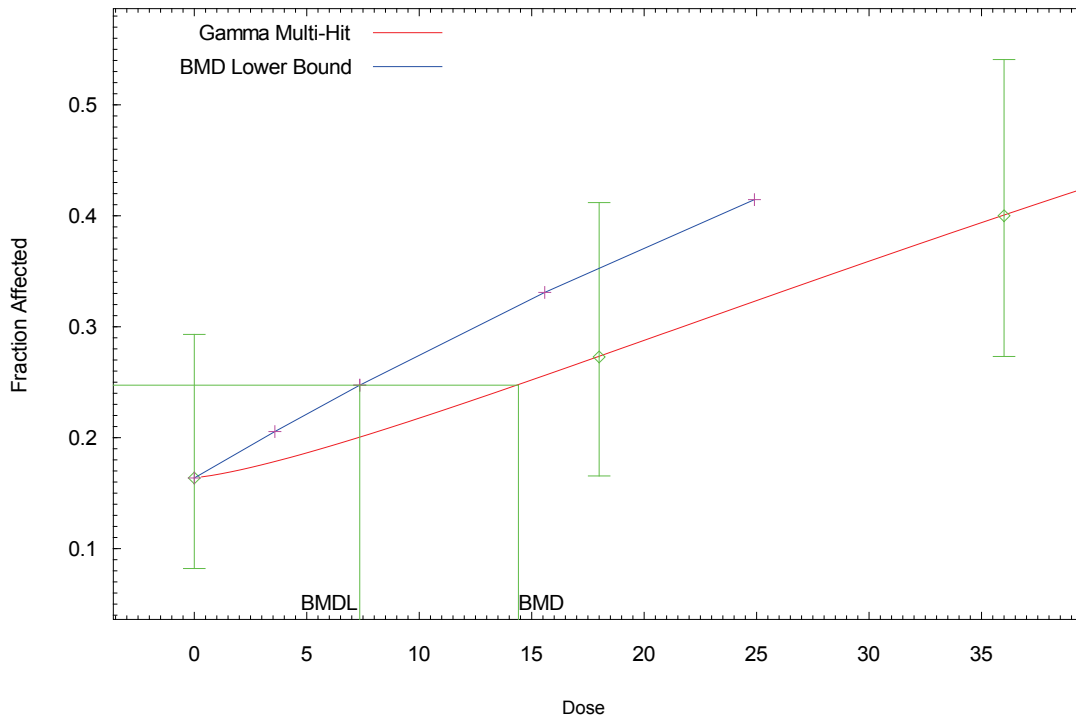
Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1636	9.000	9	55	2.448e-006
18.0000	0.2727	15.000	15	55	1.149e-006
36.0000	0.4000	22.000	22	55	-2.175e-005

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

Benchmark Dose Computation

Specified effect = 0.1
 Risk Type = Extra risk
 Confidence level = 0.95
 BMD = 14.4093
 BMDL = 7.35611

Gamma Multi-Hit Model with 0.95 Confidence Level



16:51 02/19 2007

Log Logistic model

```
=====
Logistic Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:20 $
Input Data File: C:\BMDS\HYDROQUINONE\MNCL_LOGLOGISTIC.(d)
Gnuplot Plotting File: C:\BMDS\HYDROQUINONE\MNCL_LOGLOGISTIC.plt
Mon Feb 19 16:57:16 2007
=====
```

BMDS MODEL RUN

~~~~~

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1 - \text{background}) / [1 + \text{EXP}(-\text{intercept} - \text{slope} * \text{Log}(\text{dose}))]$$

Dependent variable = MNCL  
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 = 0.163636
intercept = -5.92344
slope = 1.39301
```

Asymptotic Correlation Matrix of Parameter Estimates

|            | background | intercept | slope |
|------------|------------|-----------|-------|
| background | 1          | -0.38     | 0.31  |
| intercept  | -0.38      | 1         | -0.99 |
| slope      | 0.31       | -0.99     | 1     |

Parameter Estimates

| Variable   | Estimate | Std. Err. |
|------------|----------|-----------|
| background | 0.163636 | 0.0498825 |
| intercept  | -5.92344 | 3.94306   |
| slope      | 1.39301  | 1.12951   |

Analysis of Deviance Table

| Model         | Log(likelihood) | Deviance | Test DF | P-value |
|---------------|-----------------|----------|---------|---------|
| Full model    | -93.7538        |          |         |         |
| Fitted model  | -93.7538        | 0        | 0       | NA      |
| Reduced model | -97.6478        | 7.78794  | 2       | 0.02036 |
| AIC:          | 193.508         |          |         |         |

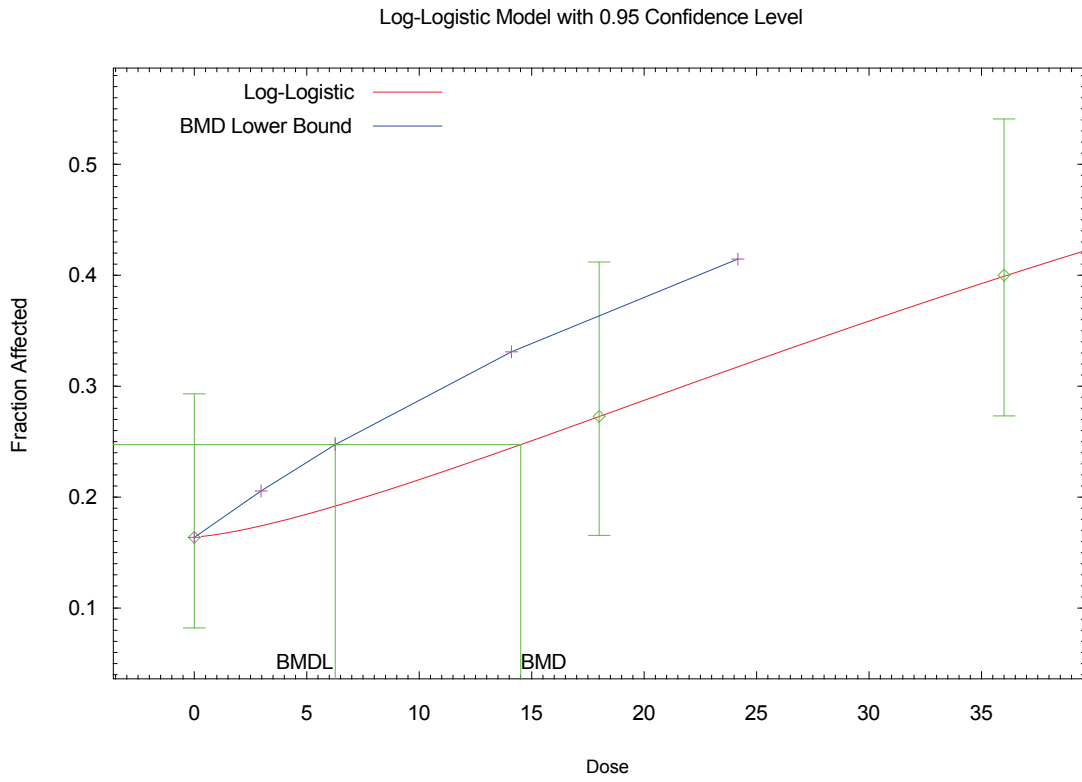
Goodness of Fit

| Dose    | Est._Prob. | Expected | Observed | Size | Scaled Residual |
|---------|------------|----------|----------|------|-----------------|
| 0.0000  | 0.1636     | 9.000    | 9        | 55   | 0               |
| 18.0000 | 0.2727     | 15.000   | 15       | 55   | -1.721e-014     |
| 36.0000 | 0.4000     | 22.000   | 22       | 55   | 1.076e-014      |

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

Benchmark Dose Computation

Specified effect = 0.1  
Risk Type = Extra risk  
Confidence level = 0.95  
BMD = 14.5114  
BMDL = 6.26573



16:57 02/19 2007

Logistic model

```
=====
Logistic Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:20 $
Input Data File: C:\BMDS\HYDROQUINONE\MNCL_LOGISTIC.(d)
Gnuplot Plotting File: C:\BMDS\HYDROQUINONE\MNCL_LOGISTIC.plt
                               Mon Feb 19 16:55:35 2007
=====
```

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = 1/[1+\text{EXP}(-\text{intercept}-\text{slope}*\text{dose})]$$

Dependent variable = MNCL  
Independent variable = Dose  
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 Parameter Values
background =          0   Specified
intercept =       -1.57728
slope =           0.0330592
```

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         | -0.83 |
| slope     | -0.83     | 1     |

Parameter Estimates

| Variable  | Estimate  | Std. Err. |
|-----------|-----------|-----------|
| intercept | -1.61418  | 0.318545  |
| slope     | 0.0338498 | 0.012471  |

Analysis of Deviance Table

| Model         | Log(likelihood) | Deviance   | Test DF | P-value |
|---------------|-----------------|------------|---------|---------|
| Full model    | -93.7538        |            |         |         |
| Fitted model  | -93.7587        | 0.00982294 | 1       | 0.9211  |
| Reduced model | -97.6478        | 7.78794    | 2       | 0.02036 |
| AIC:          | 191.517         |            |         |         |

Goodness of Fit

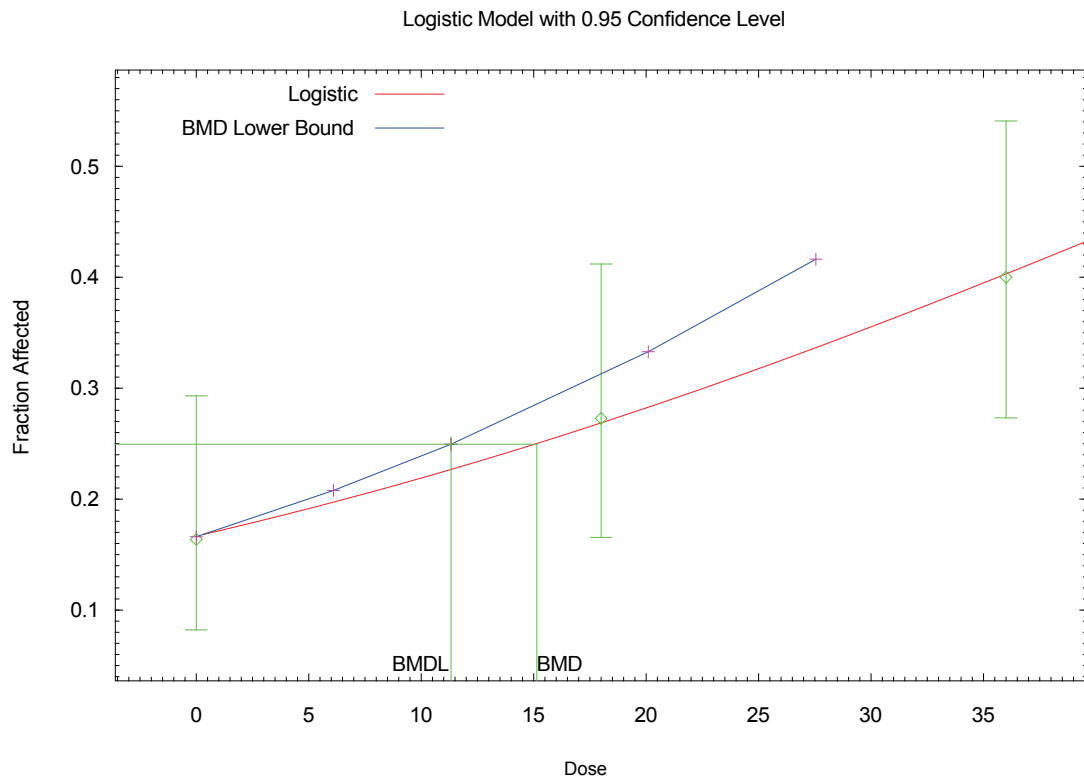
| Dose    | Est._Prob. | Expected | Observed | Size | Scaled Residual |
|---------|------------|----------|----------|------|-----------------|
| 0.0000  | 0.1660     | 9.130    | 9        | 55   | -0.04729        |
| 18.0000 | 0.2680     | 14.739   | 15       | 55   | 0.07946         |
| 36.0000 | 0.4024     | 22.130   | 22       | 55   | -0.03588        |

Chi-square = 0.01      DF = 1      P-value = 0.9210

Benchmark Dose Computation

Specified effect = 0.1  
Risk Type = Extra risk  
Confidence level = 0.95  
BMD = 15.1377  
BMDL = 11.3236





16:55 02/19 2007

Multistage model: 2 degree polynomial

```
=====
Multistage Model. (Version: 2.8; Date: 02/20/2007)
Input Data File: C:\BMDS\DATA\HYDROQUINONE_CARC.(d)
Gnuplot Plotting File: C:\BMDS\DATA\HYDROQUINONE_CARC.plt
Wed Apr 18 15:10:46 2007
=====
```

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1-\text{EXP}(-\text{beta1} * \text{dose}^{\text{1-beta2} * \text{dose}^2})]$$

The parameter betas are restricted to be positive

Dependent variable = mcl\_F\_resp  
Independent variable = rat\_dose

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 = 0.163636  
Beta(1) = 0.00630316  
Beta(2) = 8.11882e-005

Asymptotic Correlation Matrix of Parameter Estimates

|            | Background | Beta(1) | Beta(2) |
|------------|------------|---------|---------|
| Background | 1          | -0.56   | 0.38    |
| Beta(1)    | -0.56      | 1       | -0.96   |
| Beta(2)    | 0.38       | -0.96   | 1       |

Parameter Estimates

| Interval<br>Limit | Variable   | Estimate     | Std. Err. | 95.0% Wald Confidence |                   |
|-------------------|------------|--------------|-----------|-----------------------|-------------------|
|                   |            |              |           | Lower Conf. Limit     | Upper Conf. Limit |
|                   | Background | 0.163636     | *         | *                     | *                 |
|                   | Beta(1)    | 0.00630316   | *         | *                     | *                 |
|                   | Beta(2)    | 8.11882e-005 | *         | *                     | *                 |

\* - Indicates that this value is not calculated.

Error in computing chi-square; returning 2

Analysis of Deviance Table

| Model         | Log(likelihood) | # Param's | Deviance | Test d.f. | P-value |
|---------------|-----------------|-----------|----------|-----------|---------|
| Full model    | -93.7538        | 3         |          |           |         |
| Fitted model  | -93.7538        | 3         | 0        | 0         | NA      |
| Reduced model | -97.6478        | 1         | 7.78794  | 2         | 0.02036 |

AIC: 193.508

Goodness of Fit

| Dose    | Est._Prob. | Expected | Observed | Size | Scaled Residual |
|---------|------------|----------|----------|------|-----------------|
| 0.0000  | 0.1636     | 9.000    | 9        | 55   | -0.000          |
| 18.0000 | 0.2727     | 15.000   | 15       | 55   | 0.000           |
| 36.0000 | 0.4000     | 22.000   | 22       | 55   | 0.000           |

Chi^2 = 0.00      d.f. = 0      P-value =      NA

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

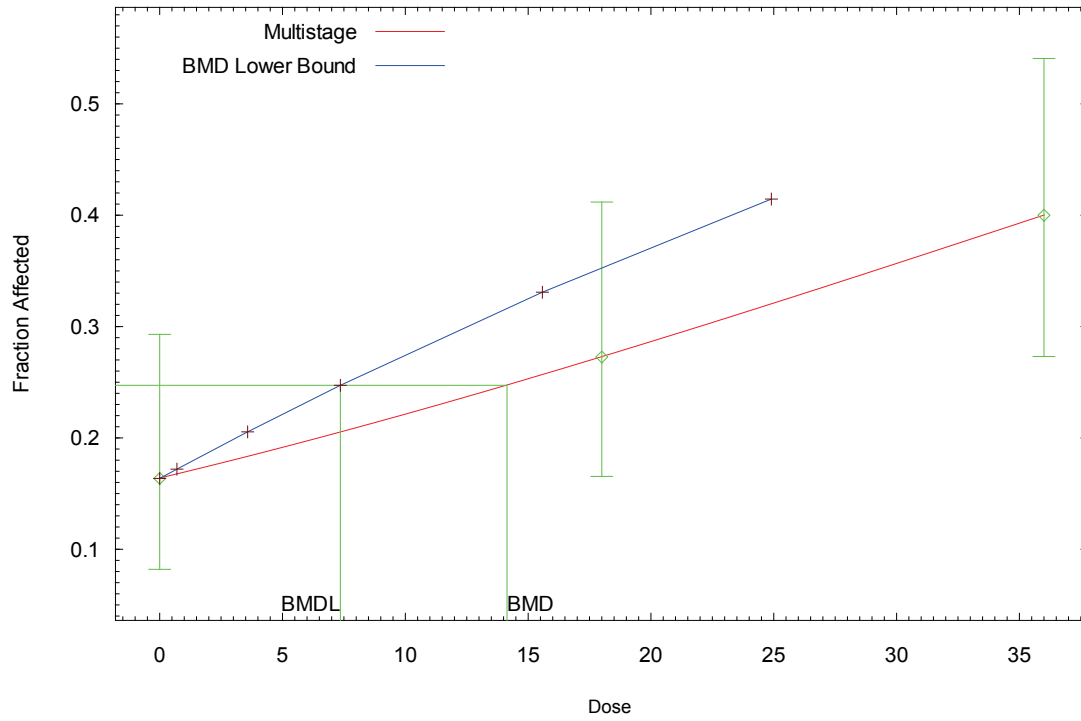
BMD = 14.1401

BMDL = 7.35611

BMDU = 31.2005

Taken together, (7.35611, 31.2005) is a 90 % two-sided confidence interval for the BMD

Multistage Model with 0.95 Confidence Level



15:12 04/18 2007

Multistage model: 1 degree polynomial

```
=====
Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
Input Data File: C:\BMDS\HYDROQUINONE\MNCL_MSC.(d)
Gnuplot Plotting File: C:\BMDS\HYDROQUINONE\MNCL_MSC.plt
Thu Feb 22 11:41:43 2007
=====
```

BMDS MODEL RUN

~~~~~

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta}1 * \text{dose}^1)]$$

The parameter betas are restricted to be positive

Dependent variable = MNCL
Independent variable = Dose

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 = 0.156271
Beta(1) = 0.00922594

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.74
Beta(1)	-0.74	1

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.160156	0.113667
Beta(1)	0.00895016	0.00621176

Analysis of Deviance Table

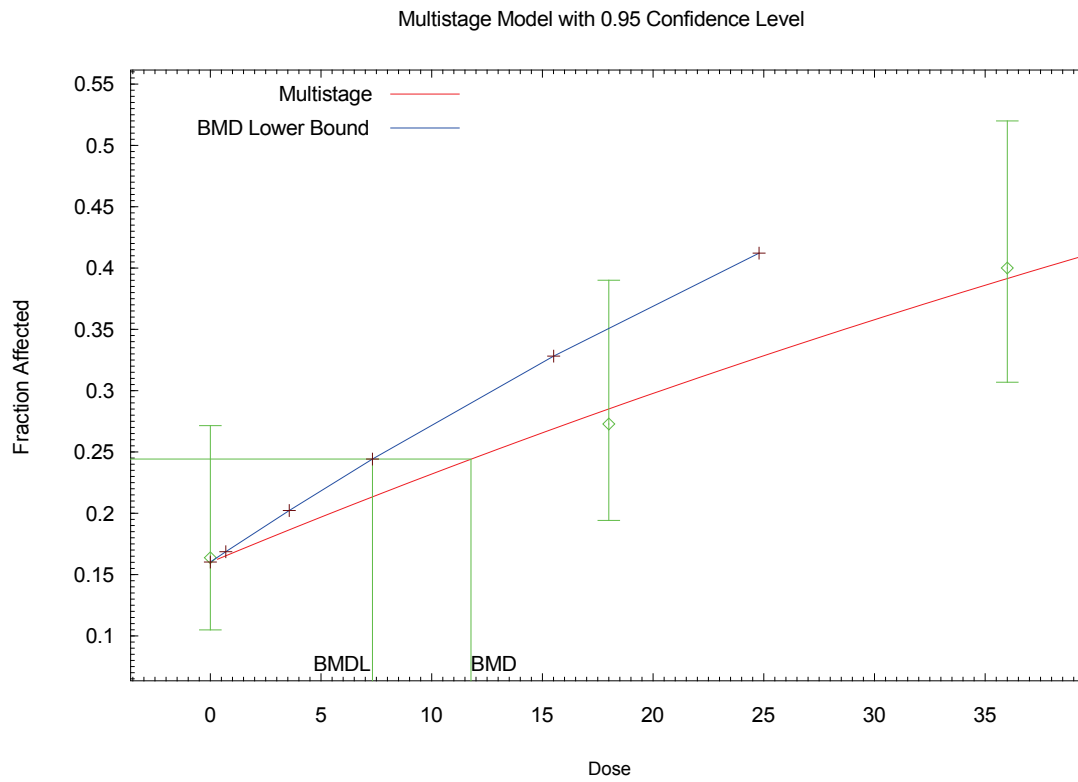
Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-93.7538			
Fitted model	-93.7855	0.0634144	1	0.8012
Reduced model	-97.6478	7.78794	2	0.02036
AIC:	191.571			

Goodness of Fit

	Dose	Est._Prob.	Expected	Observed	Size	Chi^2 Res.
i: 1	0.0000	0.1602	8.809	9	55	0.026
i: 2	18.0000	0.2851	15.682	15	55	-0.061
i: 3	36.0000	0.3915	21.532	22	55	0.036
Chi-square =		0.06	DF = 1	P-value = 0.8016		

Benchmark Dose Computation

Specified effect = 0.1
Risk Type = Extra risk
Confidence level = 0.95
BMD = 11.7719
BMDL = 7.32213



11:41 02/22 2007

Log Probit model

```
=====
Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
Input Data File: C:\BMDS\HYDROQUINONE\MNCL_LOGPROBIT.(d)
Gnuplot Plotting File: C:\BMDS\HYDROQUINONE\MNCL_LOGPROBIT.plt
Mon Feb 19 17:00:30 2007
=====
```

BMDS MODEL RUN

~~~~~

The form of the probability function is:

$$P[\text{response}] = \text{Background} + (1 - \text{Background}) * \text{CumNorm}(\text{Intercept} + \text{Slope} * \text{Log}(\text{Dose})),$$

where CumNorm(.) is the cumulative normal distribution function

Dependent variable = MNCL  
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 = 0.163636  
intercept = -4.01471  
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          | -0.64     |
| intercept  | -0.64      | 1         |

Parameter Estimates

| Variable   | Estimate | Std. Err. |
|------------|----------|-----------|
| background | 0.169336 | 0.0481103 |
| intercept  | -4.13687 | 0.26196   |
| 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    | -93.7538        |          |         |         |
| Fitted model  | -93.8046        | 0.101464 | 1       | 0.7501  |
| Reduced model | -97.6478        | 7.78794  | 2       | 0.02036 |

AIC: 191.609

Goodness of Fit

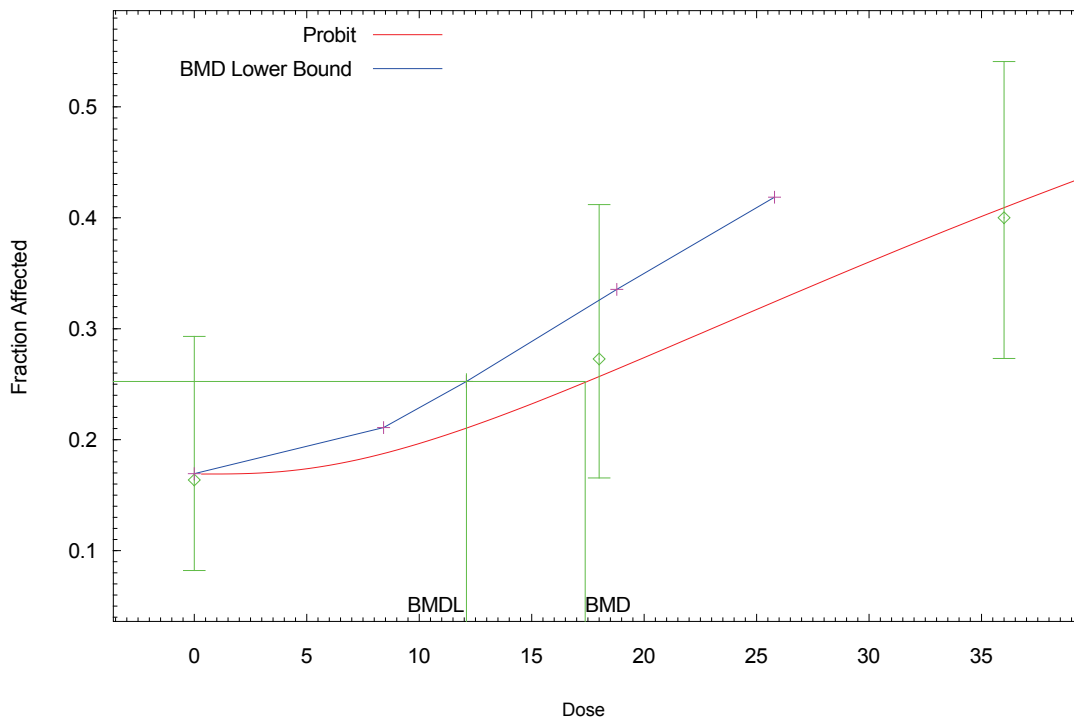
| Dose    | Est._Prob. | Expected | Observed | Size | Scaled Residual |
|---------|------------|----------|----------|------|-----------------|
| 0.0000  | 0.1693     | 9.313    | 9        | 55   | -0.1127         |
| 18.0000 | 0.2576     | 14.170   | 15       | 55   | 0.2561          |
| 36.0000 | 0.4102     | 22.563   | 22       | 55   | -0.1543         |

Chi-square = 0.10      DF = 1      P-value = 0.7493

Benchmark Dose Computation

Specified effect = 0.1  
 Risk Type = Extra risk  
 Confidence level = 0.95  
 BMD = 17.3801  
 BMDL = 12.0988

Probit Model with 0.95 Confidence Level



17:00 02/19 2007

Probit model

```
=====
Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
Input Data File: C:\BMDS\HYDROQUINONE\MNCL_PROBIT.(d)
Gnuplot Plotting File: C:\BMDS\HYDROQUINONE\MNCL_PROBIT.plt
Mon Feb 19 16:59:41 2007
=====
```

BMDS MODEL RUN  
~~~~~

The form of the probability function is:

$$P[\text{response}] = \text{CumNorm}(\text{Intercept} + \text{Slope} * \text{Dose}),$$

where CumNorm(.) is the cumulative normal distribution function

Dependent variable = MNCL
Independent variable = Dose
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 = -0.968445
slope = 0.0200245
```

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	-0.97479	0.180177
slope	0.0201363	0.00731154

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-93.7538			
Fitted model	-93.7552	0.0028213	1	0.9576
Reduced model	-97.6478	7.78794	2	0.02036

AIC: 191.51

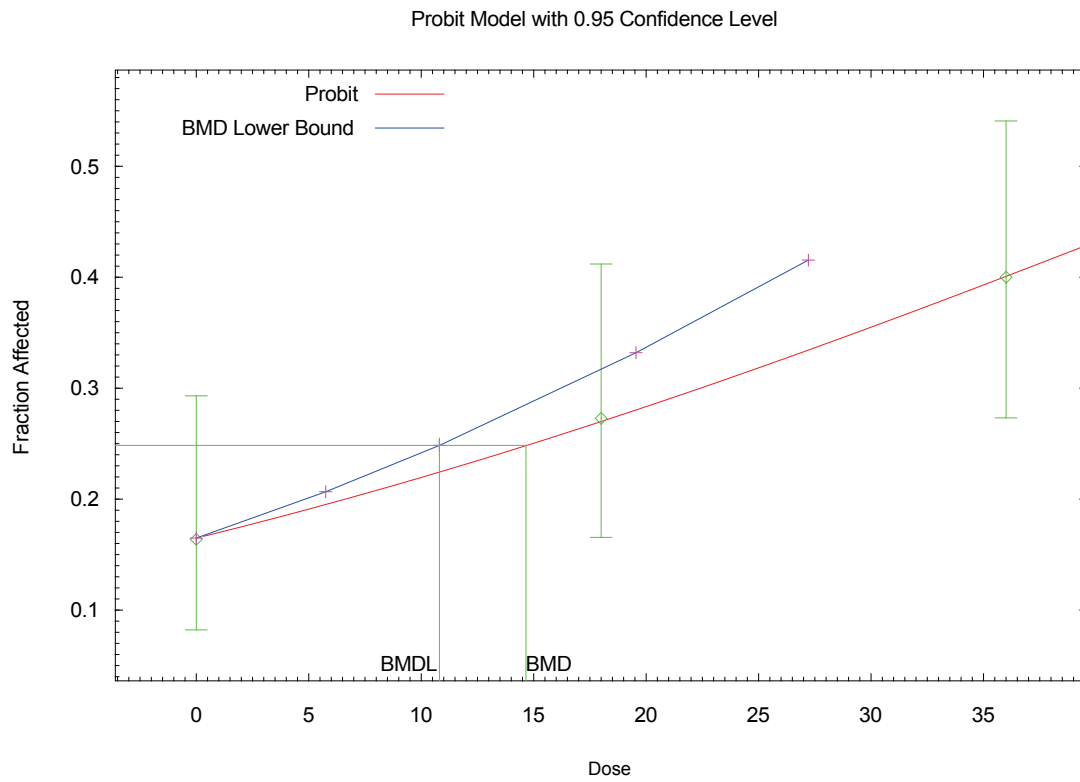
Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1648	9.066	9	55	-0.0239
18.0000	0.2702	14.859	15	55	0.04292
36.0000	0.4013	22.074	22	55	-0.02026

Chi-square = 0.00 DF = 1 P-value = 0.9576

Benchmark Dose Computation

Specified effect = 0.1
Risk Type = Extra risk
Confidence level = 0.95
BMD = 14.6549
BMDL = 10.8081



16:59 02/19 2007

Quantal Linear model

```
=====
Quantal Linear Model $Revision: 2.2 $ $Date: 2000/03/17 22:27:16 $
Input Data File: C:\BMDS\HYDROQUINONE\MNCL_QL.(d)
Gnuplot Plotting File: C:\BMDS\HYDROQUINONE\MNCL_QL.plt
Mon Feb 19 17:01:36 2007
=====
```

BMDS MODEL RUN

~~~~~

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1-\text{EXP}(-\text{slope} * \text{dose})]$$

Dependent variable = MNCL  
Independent variable = Dose

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 = 0.169643  
Slope = 0.00910852  
Power = 1 Specified

Asymptotic Correlation Matrix of Parameter Estimates

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

|            | Background | Slope |
|------------|------------|-------|
| Background | 1          | -0.62 |
| Slope      | -0.62      | 1     |

Parameter Estimates

| Variable   | Estimate   | Std. Err.  |
|------------|------------|------------|
| Background | 0.160154   | 0.0470496  |
| Slope      | 0.00895032 | 0.00321617 |

Analysis of Deviance Table

| Model         | Log(likelihood) | Deviance  | Test DF | P-value |
|---------------|-----------------|-----------|---------|---------|
| Full model    | -93.7538        |           |         |         |
| Fitted model  | -93.7855        | 0.0634144 | 1       | 0.8012  |
| Reduced model | -97.6478        | 7.78794   | 2       | 0.02036 |
| AIC:          | 191.571         |           |         |         |

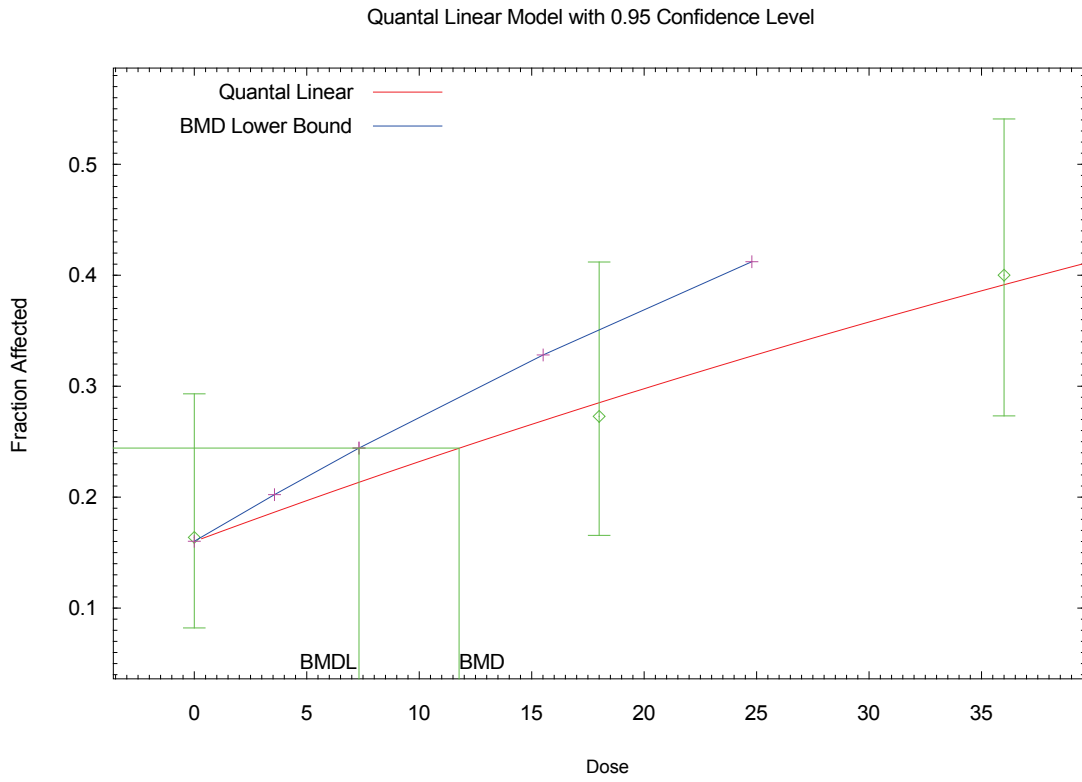
Goodness of Fit

| Dose    | Est._Prob. | Expected | Observed | Size | Scaled Residual |
|---------|------------|----------|----------|------|-----------------|
| 0.0000  | 0.1602     | 8.808    | 9        | 55   | 0.07043         |
| 18.0000 | 0.2851     | 15.682   | 15       | 55   | -0.2036         |
| 36.0000 | 0.3915     | 21.532   | 22       | 55   | 0.1293          |

Chi-square = 0.06      DF = 1      P-value = 0.8016

Benchmark Dose Computation

Specified effect = 0.1  
Risk Type = Extra risk  
Confidence level = 0.95  
BMD = 11.7717  
BMDL = 7.32213



17:01 02/19 2007

Quantal Quadratic model

```
=====
Quantal Quadratic Model $Revision: 2.2 $ $Date: 2000/03/17 22:27:16 $
Input Data File: C:\BMDS\HYDROQUINONE\MNCL_QQ.(d)
Gnuplot Plotting File: C:\BMDS\HYDROQUINONE\MNCL_QQ.plt
                               Mon Feb 19 17:02:50 2007
=====
```

BMDS MODEL RUN

~~~~~

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1-\text{EXP}(-\text{slope} * \text{dose}^2)]$$

Dependent variable = MNCL
Independent variable = Dose

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 = 0.169643
Slope = 0.000253015
Power = 2 Specified

Asymptotic Correlation Matrix of Parameter Estimates

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

	Background	Slope
Background	1	-0.59
Slope	-0.59	1

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.179025	0.0457014
Slope	0.000257272	0.000101905

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-93.7538			
Fitted model	-93.9292	0.350778	1	0.5537
Reduced model	-97.6478	7.78794	2	0.02036

AIC: 191.858

Goodness of Fit

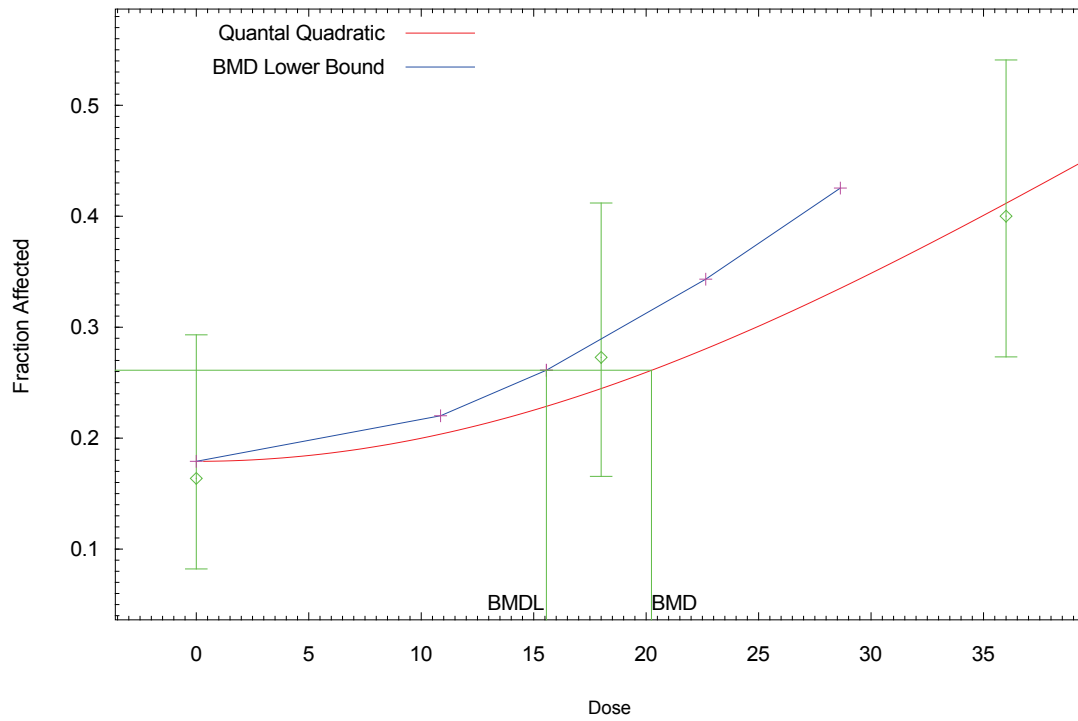
Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1790	9.846	9	55	-0.2977
18.0000	0.2447	13.458	15	55	0.4838
36.0000	0.4118	22.649	22	55	-0.1778

Chi-square = 0.35 DF = 1 P-value = 0.5517

Benchmark Dose Computation

Specified effect = 0.1
Risk Type = Extra risk
Confidence level = 0.95
BMD = 20.2368
BMDL = 15.5633

Quantal Quadratic Model with 0.95 Confidence Level



17:02 02/19 2007

Weibull model

```
=====
Weibull Model $Revision: 2.2 $ $Date: 2000/03/17 22:27:16 $
Input Data File: C:\BMDS\HYDROQUINONE\MNCL WEIBULL.(d)
Gnuplot Plotting File: C:\BMDS\HYDROQUINONE\MNCL WEIBULL.plt
                               Mon Feb 19 17:03:52 2007
=====
```

BMDS MODEL RUN

~~~~~

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1-\text{EXP}(-\text{slope} * \text{dose}^{\text{power}})]$$

Dependent variable = MNCL  
Independent variable = Dose  
Power parameter is restricted as power >=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

Default Initial (and Specified) Parameter Values

Background = 0.169643  
Slope = 0.0030436  
Power = 1.30589

Asymptotic Correlation Matrix of Parameter Estimates

|            | Background | Slope | Power |
|------------|------------|-------|-------|
| Background | 1          | -0.4  | 0.34  |
| Slope      | -0.4       | 1     | -0.99 |
| Power      | 0.34       | -0.99 | 1     |

Parameter Estimates

| Variable   | Estimate   | Std. Err. |
|------------|------------|-----------|
| Background | 0.163636   | 0.0498834 |
| Slope      | 0.00378274 | 0.0138287 |
| Power      | 1.2488     | 1.04037   |

Analysis of Deviance Table

| Model         | Log(likelihood) | Deviance     | Test DF | P-value |
|---------------|-----------------|--------------|---------|---------|
| Full model    | -93.7538        |              |         |         |
| Fitted model  | -93.7538        | 1.55467e-011 | 0       | NA      |
| Reduced model | -97.6478        | 7.78794      | 2       | 0.02036 |

AIC: 193.508

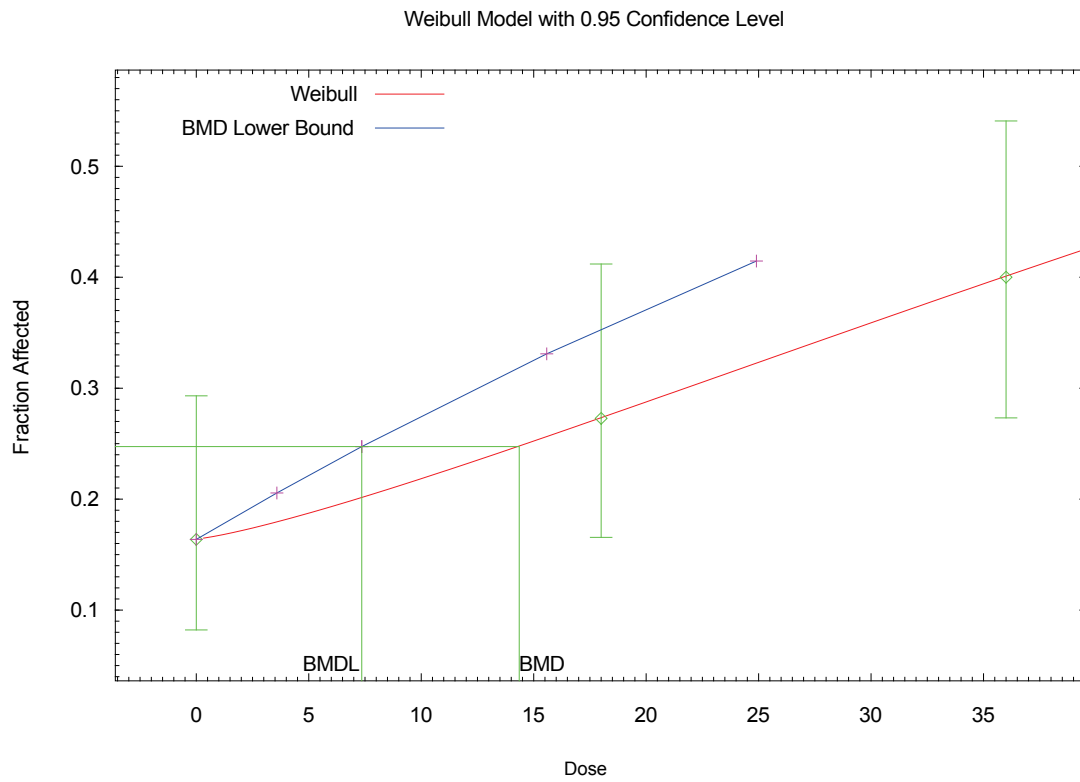
Goodness of Fit

| Dose    | Est._Prob. | Expected | Observed | Size | Scaled Residual |
|---------|------------|----------|----------|------|-----------------|
| 0.0000  | 0.1636     | 9.000    | 9        | 55   | -1.558e-006     |
| 18.0000 | 0.2727     | 15.000   | 15       | 55   | 3.215e-006      |
| 36.0000 | 0.4000     | 22.000   | 22       | 55   | -1.667e-006     |

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

Benchmark Dose Computation

Specified effect = 0.1  
Risk Type = Extra risk  
Confidence level = 0.95  
BMD = 14.3552  
BMDL = 7.35611



17:03 02/19 2007

Part III. Female Mice: Hepatocellular Adenoma or Carcinoma

Gamma model

```
=====
Gamma Model. (Version: 2.8; Date: 02/20/2007)
Input Data File: C:\BMDS\DATA\HYDROQUINONE_CARC.(d)
Gnuplot Plotting File: C:\BMDS\DATA\HYDROQUINONE_CARC.plt
                                Wed Apr 18 15:54:48 2007
=====
```

BMDS MODEL RUN

~~~~~

The form of the probability function is:

$P[\text{response}] = \text{background} + (1 - \text{background}) * \text{CumGamma}[\text{slope} * \text{dose}, \text{power}]$,
where CumGamma(.) is the cumulative Gamma distribution function

Dependent variable = liver_F_resp
Independent variable = mouse_dose
Power parameter is restricted as power >=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

```
Default Initial (and Specified) Parameter Values
Background =      0.0625
Slope =         0.0136565
Power =         1.3
```

Asymptotic Correlation Matrix of Parameter Estimates

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

	Background	Slope
Background	1	-0.62
Slope	-0.62	1

Parameter Estimates

Interval Limit	Variable	Estimate	Std. Err.	95.0% Wald Confidence	
				Lower Conf. Limit	Upper Conf.
0.144596	Background	0.0704472	0.0378316	-0.00370129	
0.00679	Slope	0.00415324	0.00134531	0.00151648	
	Power	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)	# Param's	Deviance	Test d.f.	P-value
Full model	-74.8827	3			
Fitted model	-76.995	2	4.22464	1	0.03984
Reduced model	-81.161	1	12.5567	2	0.001877
AIC:	157.99				

Goodness of Fit

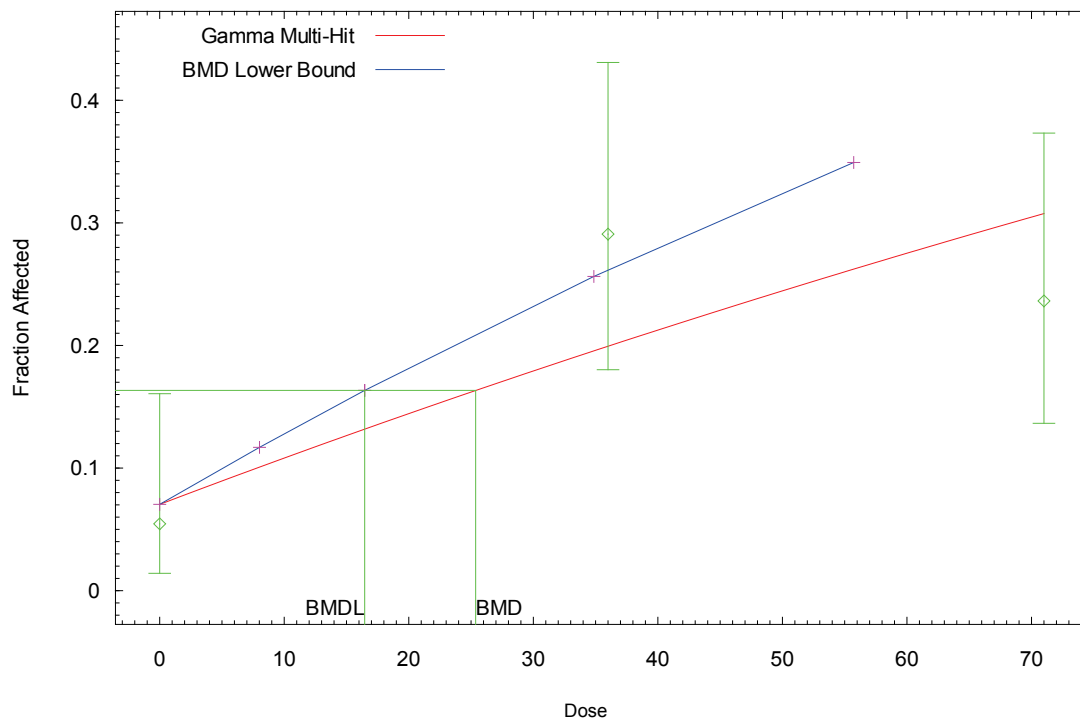
Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0704	3.875	3	55	-0.461
36.0000	0.1995	10.975	16	55	1.696
71.0000	0.3078	16.931	13	55	-1.148

Chi^2 = 4.41 d.f. = 1 P-value = 0.0358

Benchmark Dose Computation

Specified effect = 0.1
 Risk Type = Extra risk
 Confidence level = 0.95
 BMD = 25.3683
 BMDL = 16.4603

Gamma Multi-Hit Model with 0.95 Confidence Level



15:54 04/18 2007

Log Logistic model

```
=====
Logistic Model. (Version: 2.9; Date: 02/20/2007)
Input Data File: C:\BMDS\DATA\HYDROQUINONE_CARC.(d)
Gnuplot Plotting File: C:\BMDS\DATA\HYDROQUINONE_CARC.plt
                        Wed Apr 18 15:55:49 2007
=====
```

BMDS MODEL RUN

~~~~~

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1 - \text{background}) / [1 + \text{EXP}(-\text{intercept} - \text{slope} * \text{Log}(\text{dose}))]$$

Dependent variable = liver\_F\_resp  
Independent variable = mouse\_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 = 0.0545455
intercept = -4.66122
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          | -0.6      |
| intercept  | -0.6       | 1         |

Parameter Estimates

| Interval<br>Limit | Variable   | Estimate  | Std. Err. | 95.0% Wald Confidence |                   |
|-------------------|------------|-----------|-----------|-----------------------|-------------------|
|                   |            |           |           | Lower Conf. Limit     | Upper Conf. Limit |
|                   | background | 0.0656374 | *         | *                     | *                 |
|                   | intercept  | -5.30636  | *         | *                     | *                 |
|                   | slope      | 1         | *         | *                     | *                 |

\* - Indicates that this value is not calculated.

Analysis of Deviance Table

| Model         | Log(likelihood) | # Param's | Deviance | Test d.f. | P-value  |
|---------------|-----------------|-----------|----------|-----------|----------|
| Full model    | -74.8827        | 3         |          |           |          |
| Fitted model  | -76.7324        | 2         | 3.6995   | 1         | 0.05443  |
| Reduced model | -81.161         | 1         | 12.5567  | 2         | 0.001877 |

AIC: 157.465

Goodness of Fit

| Dose    | Est._Prob. | Expected | Observed | Size | Scaled Residual |
|---------|------------|----------|----------|------|-----------------|
| 0.0000  | 0.0656     | 3.610    | 3        | 55   | -0.332          |
| 36.0000 | 0.2072     | 11.396   | 16       | 55   | 1.532           |
| 71.0000 | 0.3090     | 16.994   | 13       | 55   | -1.166          |

Chi^2 = 3.82      d.f. = 1      P-value = 0.0508

Benchmark Dose Computation

Specified effect = 0.1

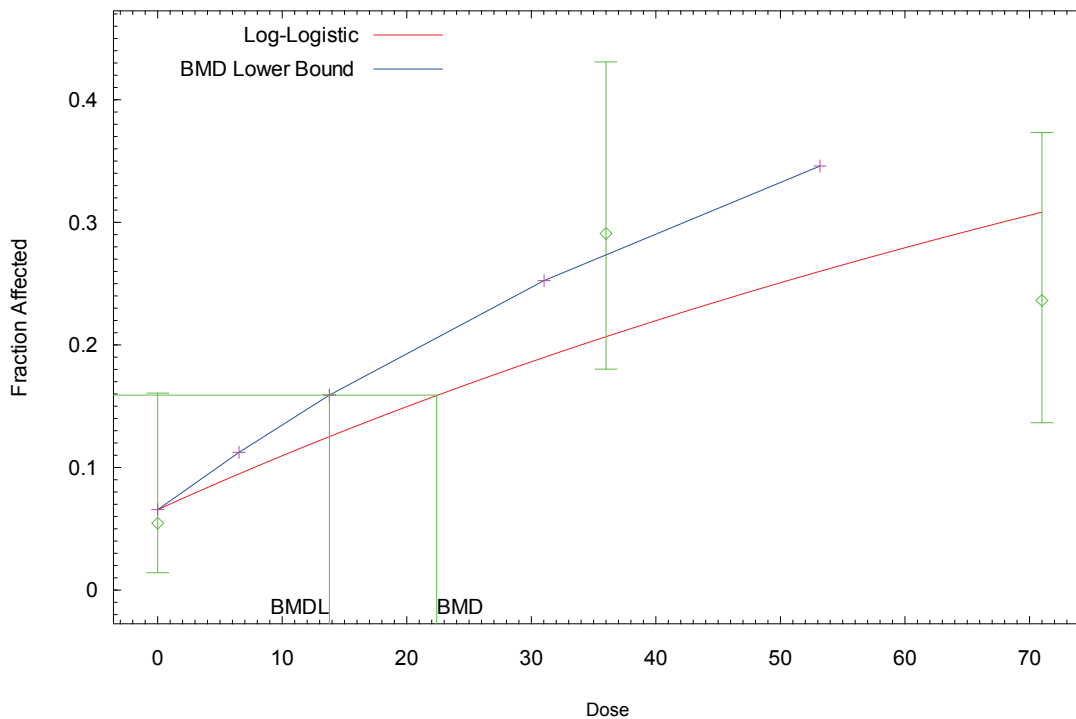
Risk Type = Extra risk

Confidence level = 0.95

BMD = 22.4017

BMDL = 13.7873

Log-Logistic Model with 0.95 Confidence Level



15:55 04/18 2007

Logistic model

```
=====
Logistic Model. (Version: 2.9; Date: 02/20/2007)
Input Data File: C:\BMDS\DATA\HYDROQUINONE_CAR.C.(d)
Gnuplot Plotting File: C:\BMDS\DATA\HYDROQUINONE_CAR.C.plt
                        Wed Apr 18 15:56:29 2007
=====
```

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = 1/[1+\text{EXP}(-\text{intercept}-\text{slope}*\text{dose})]$$

Dependent variable = liver\_F\_resp  
Independent variable = mouse\_dose  
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 Parameter Values
background =          0 Specified
intercept =        -2.36514
slope =           0.0221272
```

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         | -0.85 |
| slope     | -0.85     | 1     |

Parameter Estimates

| Interval<br>Limit | Variable  | Estimate  | Std. Err.  | 95.0% Wald Confidence |             |
|-------------------|-----------|-----------|------------|-----------------------|-------------|
|                   |           |           |            | Lower Conf. Limit     | Upper Conf. |
| -1.37287          | intercept | -2.11535  | 0.378823   | -2.85783              |             |
| 0.0314579         | slope     | 0.0172474 | 0.00725038 | 0.00303693            |             |

Analysis of Deviance Table

| Model         | Log(likelihood) | # Param's | Deviance | Test d.f. | P-value  |
|---------------|-----------------|-----------|----------|-----------|----------|
| Full model    | -74.8827        | 3         |          |           |          |
| Fitted model  | -78.1435        | 2         | 6.52164  | 1         | 0.01066  |
| Reduced model | -81.161         | 1         | 12.5567  | 2         | 0.001877 |

AIC: 160.287

Goodness of Fit

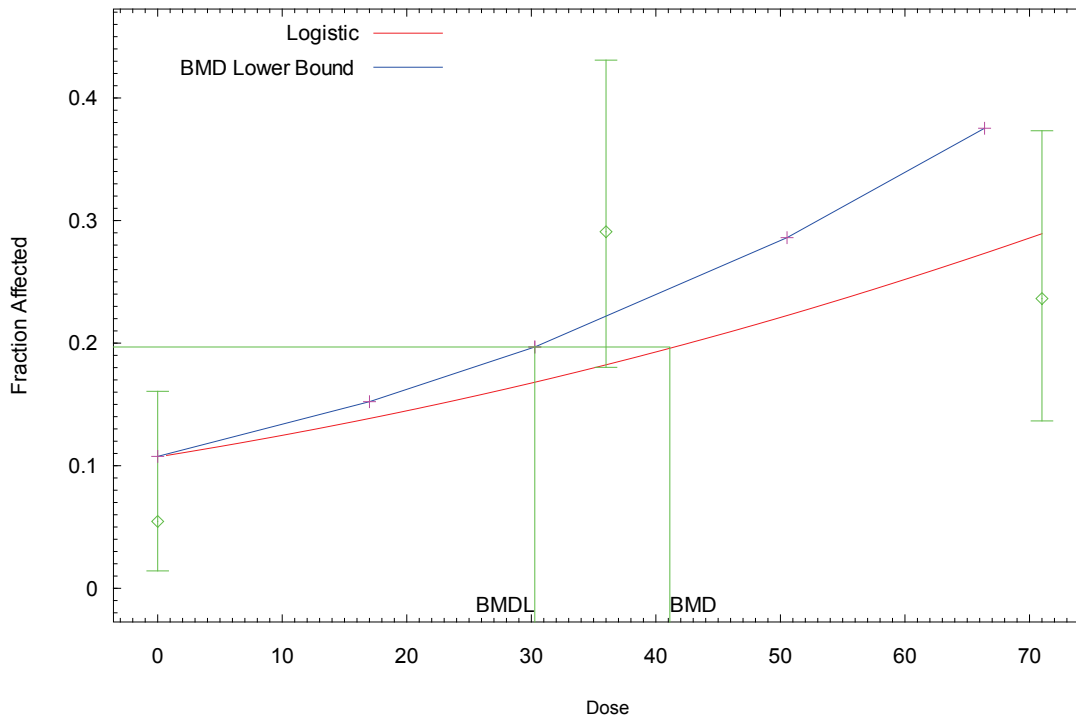
| Dose    | Est._Prob. | Expected | Observed | Size | Scaled Residual |
|---------|------------|----------|----------|------|-----------------|
| 0.0000  | 0.1076     | 5.919    | 3        | 55   | -1.270          |
| 36.0000 | 0.1833     | 10.079   | 16       | 55   | 2.064           |
| 71.0000 | 0.2909     | 16.002   | 13       | 55   | -0.891          |

Chi^2 = 6.67      d.f. = 1      P-value = 0.0098

Benchmark Dose Computation

Specified effect = 0.1  
 Risk Type = Extra risk  
 Confidence level = 0.95  
 BMD = 41.123  
 BMDL = 30.2749

Logistic Model with 0.95 Confidence Level



15:56 04/18 2007

Multistage model: 2 degree polynomial

```
=====
Multistage Model. (Version: 2.8; Date: 02/20/2007)
Input Data File: C:\BMDS\DATA\HYDROQUINONE_CARC.(d)
Gnuplot Plotting File: C:\BMDS\DATA\HYDROQUINONE_CARC.plt
Wed Apr 18 15:57:20 2007
=====
```

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose}^1 - \text{beta2} * \text{dose}^2)]$$

The parameter betas are restricted to be positive

Dependent variable = liver\_F\_resp  
Independent variable = mouse\_dose

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 = 0.10867  
Beta(1) = 0.00303181  
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          | -0.79   |
| Beta(1)    | -0.79      | 1       |

Parameter Estimates

| Interval    | Variable   | Estimate   | Std. Err. | 95.0% Wald Confidence |       |
|-------------|------------|------------|-----------|-----------------------|-------|
|             |            |            |           | Lower Conf. Limit     | Upper |
| Conf. Limit | Background | 0.0704472  | *         | *                     |       |
| *           | Beta(1)    | 0.00415324 | *         | *                     |       |
| *           |            |            |           |                       |       |

\*                      Beta(2)                      0                      \*                      \*

\* - Indicates that this value is not calculated.

Analysis of Deviance Table

| Model         | Log(likelihood) | # Param's | Deviance | Test d.f. | P-value  |
|---------------|-----------------|-----------|----------|-----------|----------|
| Full model    | -74.8827        | 3         |          |           |          |
| Fitted model  | -76.995         | 2         | 4.22464  | 1         | 0.03984  |
| Reduced model | -81.161         | 1         | 12.5567  | 2         | 0.001877 |
| AIC:          | 157.99          |           |          |           |          |

Goodness of Fit

| Dose    | Est._Prob. | Expected | Observed | Size | Scaled Residual |
|---------|------------|----------|----------|------|-----------------|
| 0.0000  | 0.0704     | 3.875    | 3        | 55   | -0.461          |
| 36.0000 | 0.1995     | 10.975   | 16       | 55   | 1.696           |
| 71.0000 | 0.3078     | 16.931   | 13       | 55   | -1.148          |

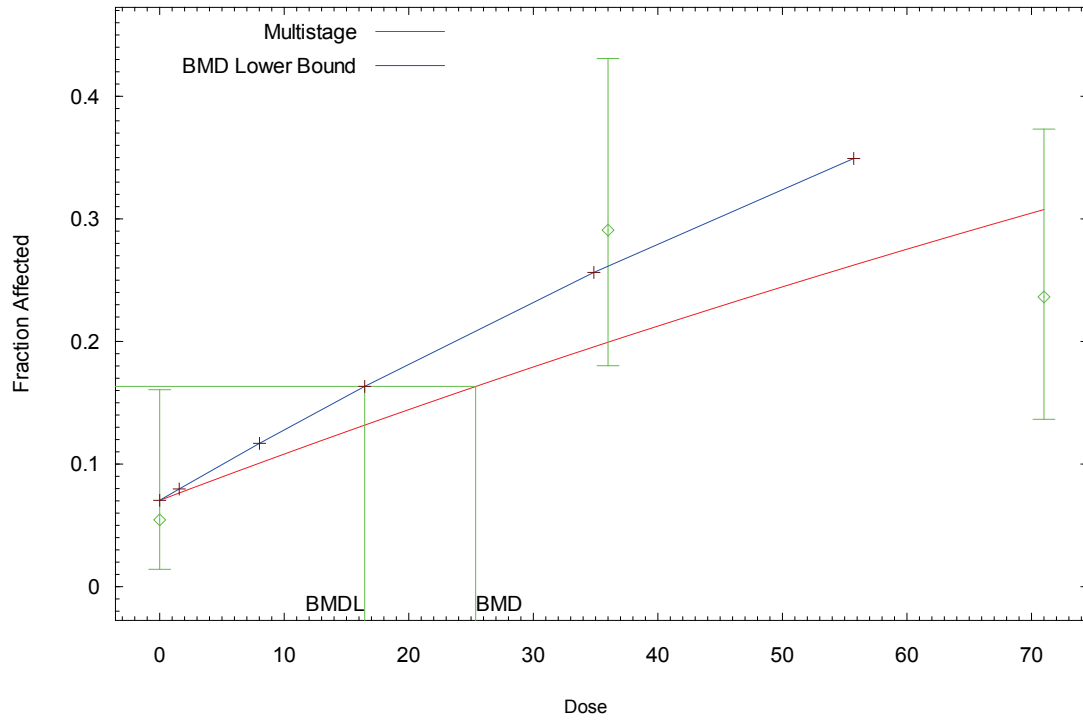
Chi^2 = 4.41              d.f. = 1              P-value = 0.0358

Benchmark Dose Computation

Specified effect =              0.1  
 Risk Type              =              Extra risk  
 Confidence level =              0.95  
                                          BMD =              25.3683  
                                          BMDL =              16.4603  
                                          BMDU =              56.2399

Taken together, (16.4603, 56.2399) is a 90              % two-sided confidence interval for the BMD

Multistage Model with 0.95 Confidence Level



15:57 04/18 2007

Multistage model: 1 degree polynomial

```
=====
Multistage Model. (Version: 2.8; Date: 02/20/2007)
Input Data File: C:\BMDS\DATA\HYDROQUINONE_CARC.(d)
Gnuplot Plotting File: C:\BMDS\DATA\HYDROQUINONE_CARC.plt
Wed Apr 18 15:58:11 2007
=====
```

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1-\text{EXP}(-\text{beta}1 * \text{dose}^1)]$$

The parameter betas are restricted to be positive

Dependent variable = liver\_F\_resp  
Independent variable = mouse\_dose

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 = 0.10867  
Beta(1) = 0.00303181

Asymptotic Correlation Matrix of Parameter Estimates

|            | Background | Beta(1) |
|------------|------------|---------|
| Background | 1          | -0.79   |
| Beta(1)    | -0.79      | 1       |

Parameter Estimates

| Interval<br>Variable | Estimate   | Std. Err. | 95.0% Wald Confidence |                   |
|----------------------|------------|-----------|-----------------------|-------------------|
|                      |            |           | Lower Conf. Limit     | Upper Conf. Limit |
| Background           | 0.0704472  | *         | *                     | *                 |
| Beta(1)              | 0.00415324 | *         | *                     | *                 |

\* - Indicates that this value is not calculated.

Analysis of Deviance Table

| Model | Log(likelihood) | # Param's | Deviance | Test d.f. | P-value |
|-------|-----------------|-----------|----------|-----------|---------|
|-------|-----------------|-----------|----------|-----------|---------|



|               |          |   |         |   |          |
|---------------|----------|---|---------|---|----------|
| Full model    | -74.8827 | 3 |         |   |          |
| Fitted model  | -76.995  | 2 | 4.22464 | 1 | 0.03984  |
| Reduced model | -81.161  | 1 | 12.5567 | 2 | 0.001877 |
| AIC:          | 157.99   |   |         |   |          |

Goodness of Fit

| Dose    | Est._Prob. | Expected | Observed | Size | Scaled Residual |
|---------|------------|----------|----------|------|-----------------|
| 0.0000  | 0.0704     | 3.875    | 3        | 55   | -0.461          |
| 36.0000 | 0.1995     | 10.975   | 16       | 55   | 1.696           |
| 71.0000 | 0.3078     | 16.931   | 13       | 55   | -1.148          |

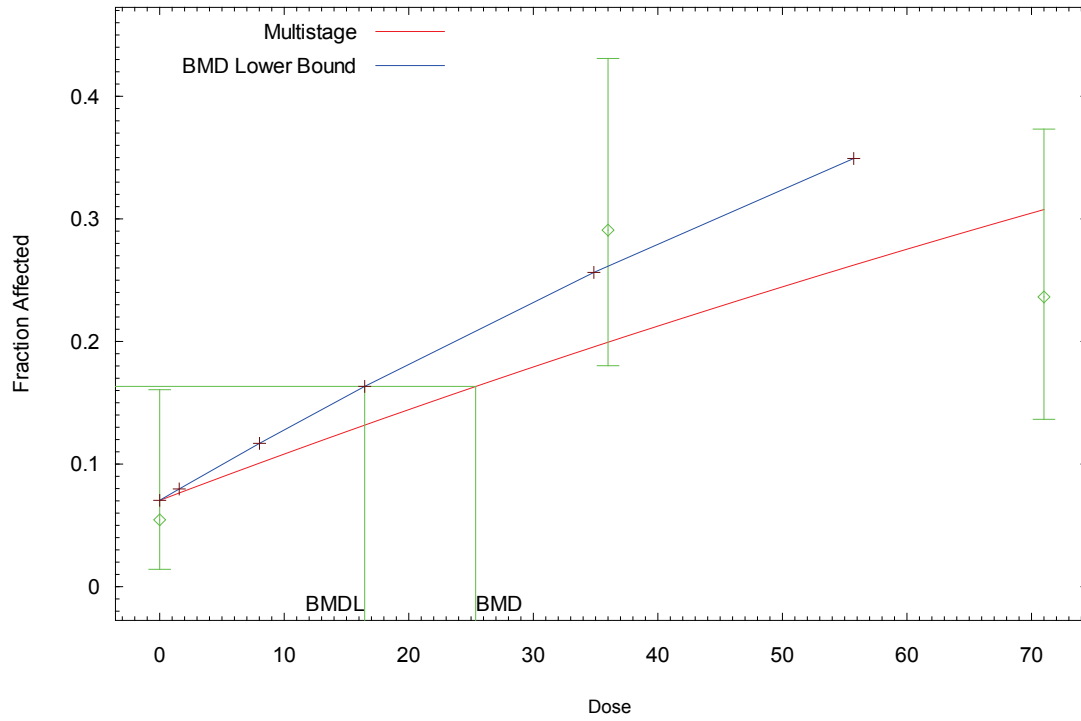
Chi<sup>2</sup> = 4.41      d.f. = 1      P-value = 0.0358

Benchmark Dose Computation

Specified effect = 0.1  
 Risk Type = Extra risk  
 Confidence level = 0.95  
 BMD = 25.3683  
 BMDL = 16.4603  
 BMDU = 56.2399

Taken together, (16.4603, 56.2399) is a 90 % two-sided confidence interval for the BMD

Multistage Model with 0.95 Confidence Level



15:58 04/18 2007

Log Probit model

```
=====
Probit Model. (Version: 2.8; Date: 02/20/2007)
Input Data File: C:\BMDS\DATA\HYDROQUINONE_CARC.(d)
Gnuplot Plotting File: C:\BMDS\DATA\HYDROQUINONE_CARC.plt
Wed Apr 18 15:59:00 2007
=====
```

BMDS MODEL RUN

~~~~~

The form of the probability function is:

$$P[\text{response}] = \text{Background} + (1 - \text{Background}) * \text{CumNorm}(\text{Intercept} + \text{Slope} * \text{Log}(\text{Dose})),$$

where CumNorm(.) is the cumulative normal distribution function

Dependent variable = liver_F_resp
Independent variable = mouse_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 = 0.0545455
intercept = -4.24001
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	-0.75
intercept	-0.75	1

Parameter Estimates

Interval Limit	Variable	Estimate	Std. Err.	95.0% Wald Confidence	
				Lower Conf. Limit	Upper Conf.
0.180869	background	0.0888211	0.046964	-0.00322662	
-4.3374	intercept	-4.89853	0.2863	-5.45967	
	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)	# Param's	Deviance	Test d.f.	P-value
Full model	-74.8827	3			
Fitted model	-78.6887	2	7.61211	1	0.005798
Reduced model	-81.161	1	12.5567	2	0.001877
AIC:	161.377				

Goodness of Fit

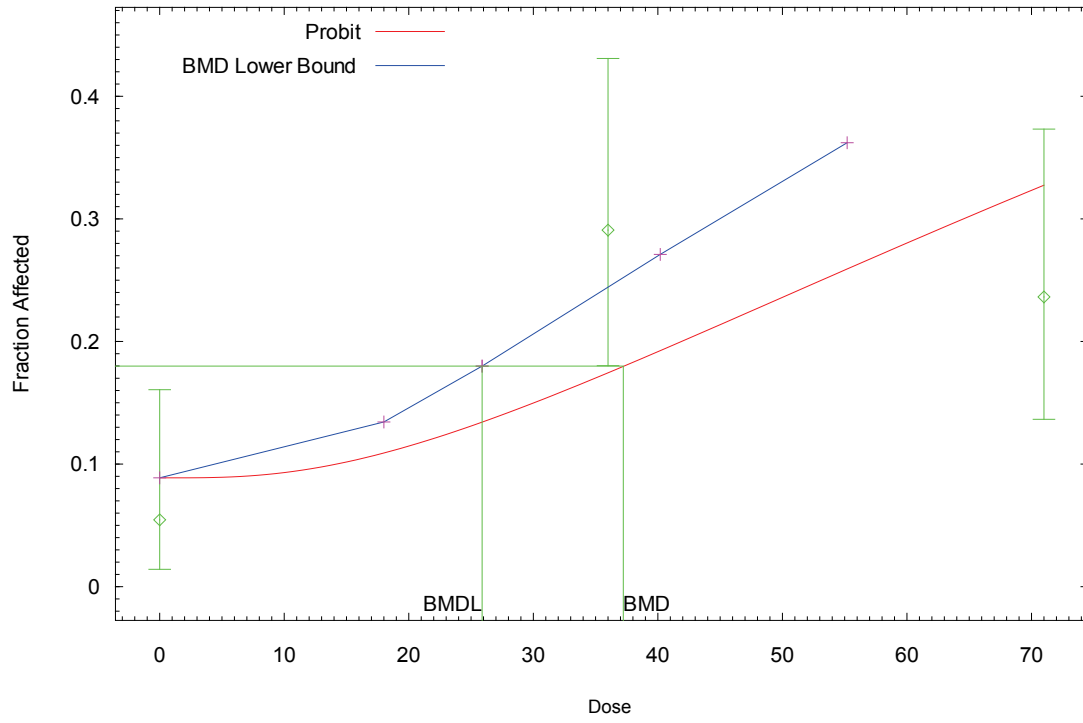
Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0888	4.885	3	55	-0.894
36.0000	0.1747	9.609	16	55	2.270
71.0000	0.3279	18.037	13	55	-1.447

Chi^2 = 8.04 d.f. = 1 P-value = 0.0046

Benchmark Dose Computation

Specified effect = 0.1
 Risk Type = Extra risk
 Confidence level = 0.95
 BMD = 37.225
 BMDL = 25.8879

Probit Model with 0.95 Confidence Level



15:59 04/18 2007

Probit model

```
=====
Probit Model. (Version: 2.8; Date: 02/20/2007)
Input Data File: C:\BMDS\DATA\HYDROQUINONE_CARC.(d)
Gnuplot Plotting File: C:\BMDS\DATA\HYDROQUINONE_CARC.plt
Wed Apr 18 15:59:36 2007
=====
```

BMDS MODEL RUN

~~~~~

The form of the probability function is:

$$P[\text{response}] = \text{CumNorm}(\text{Intercept} + \text{Slope} * \text{Dose}),$$

where CumNorm(.) is the cumulative normal distribution function

Dependent variable = liver\_F\_resp  
Independent variable = mouse\_dose  
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 =      -1.39179
slope =          0.0124078
```

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         | -0.83 |
| slope     | -0.83     | 1     |

Parameter Estimates

| Interval<br>Limit | Variable  | Estimate  | Std. Err.  | 95.0% Wald Confidence |             |
|-------------------|-----------|-----------|------------|-----------------------|-------------|
|                   |           |           |            | Lower Conf. Limit     | Upper Conf. |
| -0.860662         | intercept | -1.26742  | 0.207531   | -1.67417              |             |
| 0.0183628         | slope     | 0.0102247 | 0.00415216 | 0.00208665            |             |

Analysis of Deviance Table

| Model         | Log(likelihood) | # Param's | Deviance | Test d.f. | P-value  |
|---------------|-----------------|-----------|----------|-----------|----------|
| Full model    | -74.8827        | 3         |          |           |          |
| Fitted model  | -78.0008        | 2         | 6.23629  | 1         | 0.01252  |
| Reduced model | -81.161         | 1         | 12.5567  | 2         | 0.001877 |

AIC: 160.002

Goodness of Fit

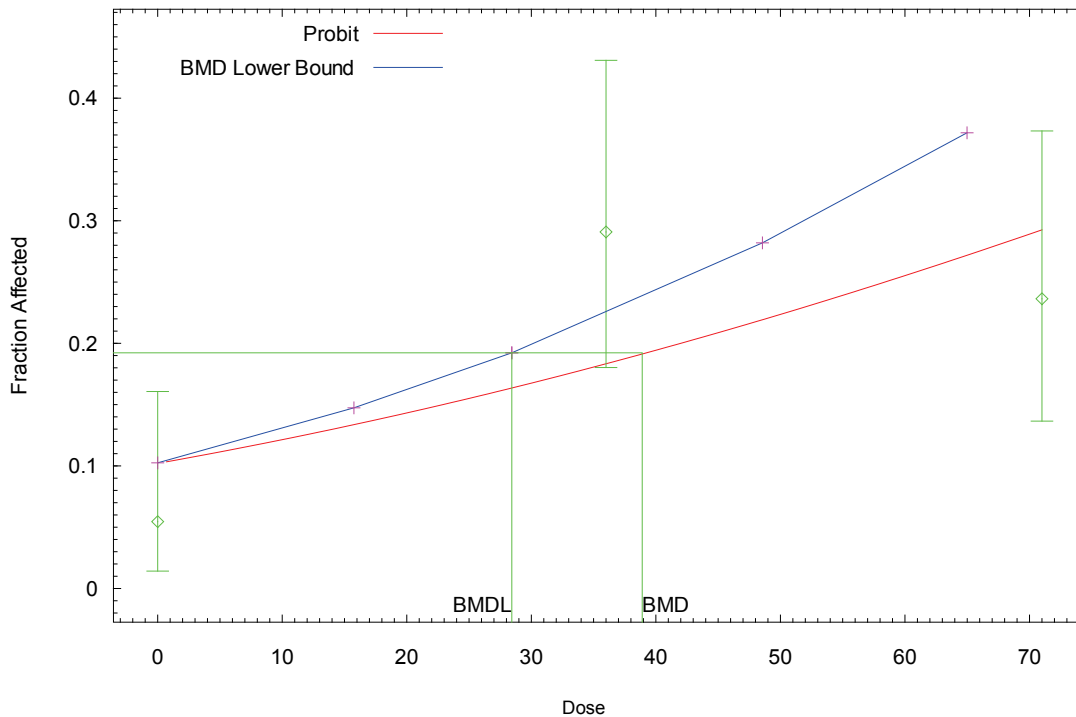
| Dose    | Est._Prob. | Expected | Observed | Size | Scaled Residual |
|---------|------------|----------|----------|------|-----------------|
| 0.0000  | 0.1025     | 5.638    | 3        | 55   | -1.173          |
| 36.0000 | 0.1842     | 10.133   | 16       | 55   | 2.041           |
| 71.0000 | 0.2941     | 16.175   | 13       | 55   | -0.940          |

Chi^2 = 6.42      d.f. = 1      P-value = 0.0113

Benchmark Dose Computation

Specified effect = 0.1  
 Risk Type = Extra risk  
 Confidence level = 0.95  
 BMD = 38.9049  
 BMDL = 28.4317

Probit Model with 0.95 Confidence Level



15:59 04/18 2007

Quantal Linear model

```
=====
Quantal Linear Model using Weibull Model (Version: 2.7; Date: 2/20/2007)
Input Data File: C:\BMDS\DATA\HYDROQUINONE_CARC.(d)
Gnuplot Plotting File: C:\BMDS\DATA\HYDROQUINONE_CARC.plt
Wed Apr 18 16:00:28 2007
=====
```

BMDS MODEL RUN

~~~~~

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1-\text{EXP}(-\text{slope} * \text{dose})]$$

Dependent variable = liver_F_resp
Independent variable = mouse_dose

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 = 0.0625
Slope = 0.00297618
Power = 1 Specified

Asymptotic Correlation Matrix of Parameter Estimates

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

	Background	Slope
Background	1	-0.62
Slope	-0.62	1

Parameter Estimates

Interval Limit	Variable	Estimate	Std. Err.	95.0% Wald Confidence	
				Lower Conf. Limit	Upper Conf.
0.144598	Background	0.0704471	0.0378326	-0.00370342	
0.00679008	Slope	0.00415323	0.00134535	0.00151639	

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-74.8827	3			
Fitted model	-76.995	2	4.22464	1	0.03984

Reduced model -81.161 1 12.5567 2 0.001877

AIC: 157.99

Goodness of Fit

Dose	Est. Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0704	3.875	3	55	-0.461
36.0000	0.1995	10.975	16	55	1.696
71.0000	0.3078	16.931	13	55	-1.148

Chi² = 4.41 d.f. = 1 P-value = 0.0358

Benchmark Dose Computation

Specified effect = 0.1

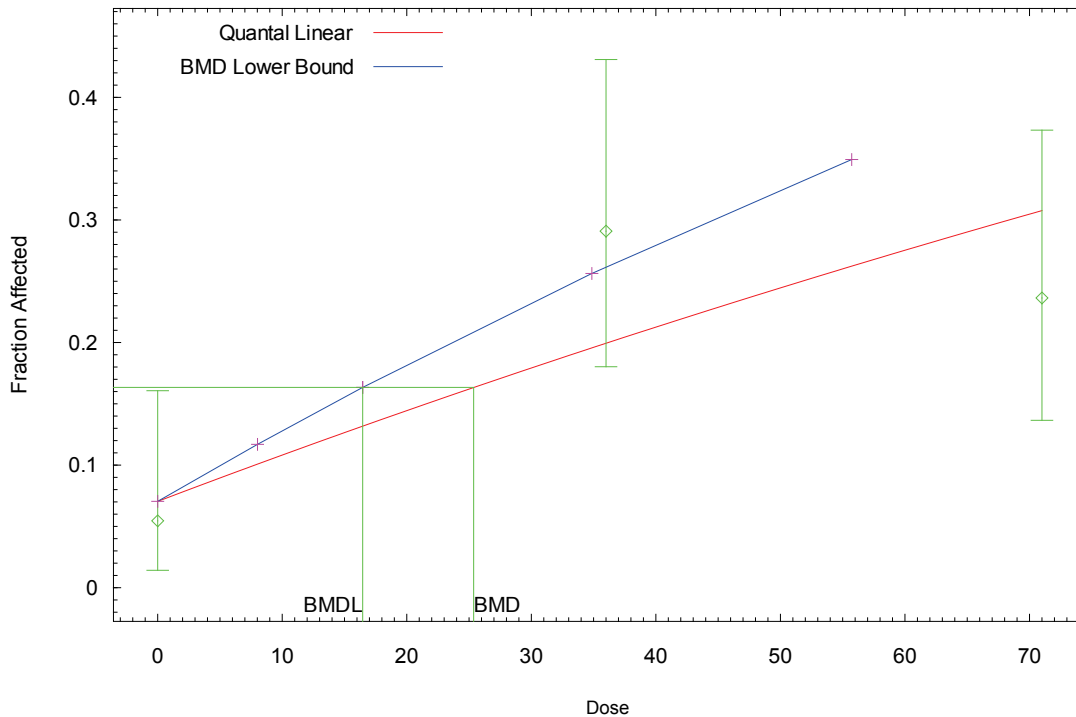
Risk Type = Extra risk

Confidence level = 0.95

BMD = 25.3683

BMDL = 16.4603

Quantal Linear Model with 0.95 Confidence Level



16:00 04/18 2007

Quantal Quadratic model

```
=====
Quantal Quadratic Model $Revision: 2.2 $ $Date: 2000/03/17 22:27:16 $
Input Data File: C:\BMDS\HYDROQUINONE\LIVER_TUMOR_QQ.(d)
Gnuplot Plotting File: C:\BMDS\HYDROQUINONE\LIVER_TUMOR_QQ.plt
Wed Apr 18 16:33:32 2007
=====
```

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1-\text{EXP}(-\text{slope} * \text{dose}^2)]$$

Dependent variable = COLUMN3
Independent variable = COLUMN1

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 = 0.0625
Slope = 5.64397e-005
Power = 2 Specified

Asymptotic Correlation Matrix of Parameter Estimates

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

	Background	Slope
Background	1	-0.62
Slope	-0.62	1

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.0866145	0.0388928
Slope	6.25592e-005	2.26923e-005

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-74.8827			
Fitted model	-76.6626	3.55985	1	0.05919
Reduced model	-81.161	12.5567	2	0.001877
AIC:	157.325			

Goodness of Fit

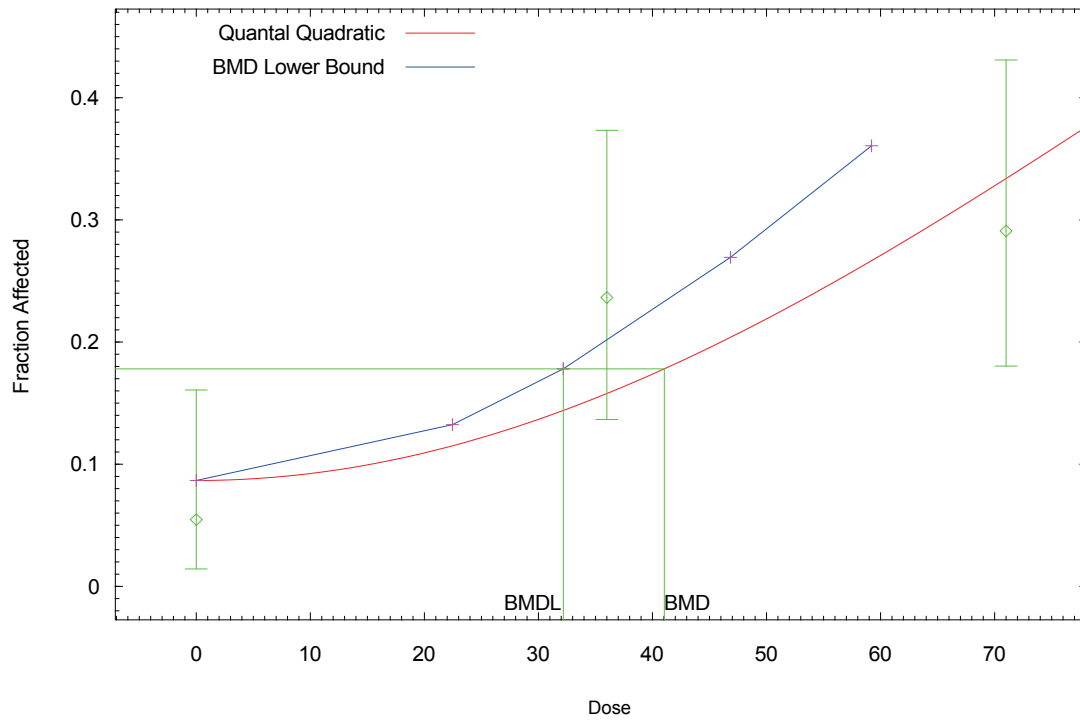
Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0866	4.764	3	55	-0.8456
36.0000	0.1577	8.676	13	55	1.6
71.0000	0.3337	18.351	16	55	-0.6724

Chi-square = 3.73 DF = 1 P-value = 0.0536

Benchmark Dose Computation

Specified effect = 0.1
Risk Type = Extra risk
Confidence level = 0.95
BMD = 41.0387
BMDL = 32.1823

Quantal Quadratic Model with 0.95 Confidence Level



16:33 04/18 2007

Weibull model

```
=====
Weibull Model using Weibull Model (Version: 2.7; Date: 2/20/2007)
Input Data File: C:\BMDS\DATA\HYDROQUINONE_CARC.(d)
Gnuplot Plotting File: C:\BMDS\DATA\HYDROQUINONE_CARC.plt
Wed Apr 18 16:01:36 2007
=====
```

BMDS MODEL RUN

~~~~~

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1-\text{EXP}(-\text{slope} * \text{dose}^{\text{power}})]$$

Dependent variable = liver\_F\_resp  
Independent variable = mouse\_dose  
Power parameter is restricted as power >=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

Default Initial (and Specified) Parameter Values

Background = 0.0625  
Slope = 0.00297618  
Power = 1

Asymptotic Correlation Matrix of Parameter Estimates

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

|            | Background | Slope |
|------------|------------|-------|
| Background | 1          | -0.62 |
| Slope      | -0.62      | 1     |

Parameter Estimates

| Interval<br>Limit | Variable   | Estimate   | Std. Err.  | 95.0% Wald Confidence |             |
|-------------------|------------|------------|------------|-----------------------|-------------|
|                   |            |            |            | Lower Conf. Limit     | Upper Conf. |
| 0.144598          | Background | 0.0704471  | 0.0378326  | -0.00370342           |             |
| 0.00679008        | Slope      | 0.00415323 | 0.00134535 | 0.00151639            |             |
|                   | Power      | 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) | # Param's | Deviance | Test d.f. | P-value  |
|---------------|-----------------|-----------|----------|-----------|----------|
| Full model    | -74.8827        | 3         |          |           |          |
| Fitted model  | -76.995         | 2         | 4.22464  | 1         | 0.03984  |
| Reduced model | -81.161         | 1         | 12.5567  | 2         | 0.001877 |
| AIC:          | 157.99          |           |          |           |          |

Goodness of Fit

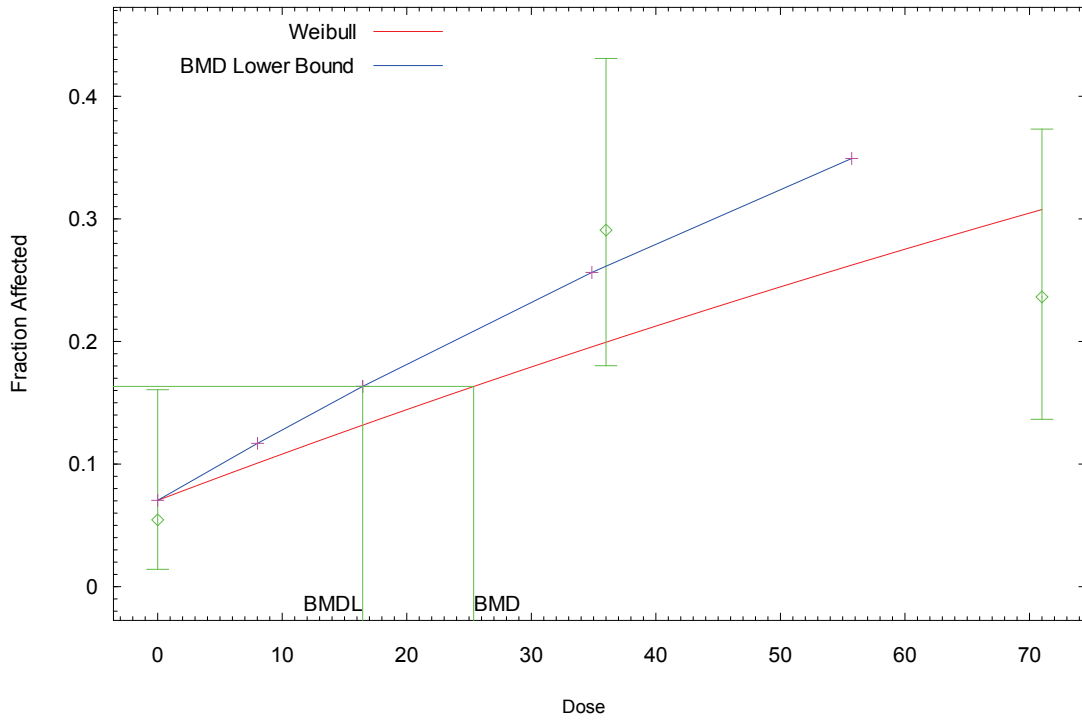
| Dose    | Est._Prob. | Expected | Observed | Size | Scaled Residual |
|---------|------------|----------|----------|------|-----------------|
| 0.0000  | 0.0704     | 3.875    | 3        | 55   | -0.461          |
| 36.0000 | 0.1995     | 10.975   | 16       | 55   | 1.696           |
| 71.0000 | 0.3078     | 16.931   | 13       | 55   | -1.148          |

Chi^2 = 4.41      d.f. = 1      P-value = 0.0358

Benchmark Dose Computation

Specified effect = 0.1  
 Risk Type = Extra risk  
 Confidence level = 0.95  
 BMD = 25.3683  
 BMDL = 16.4603

Weibull Model with 0.95 Confidence Level



16:01 04/18 2007