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Provisional Peer-Reviewed Toxicity Values for

Fluoranthene
(CASRN 206-44-0)

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Questions regarding the contents of this document 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).

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COMMONLY USED ABBREVIATIONS

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

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR FLUORANTHENE (CASRN 206-44-0)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (http://hhpprtv.ornl.gov) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (www.epa.gov/iris), the respective PPRTVs are removed from the database.

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. Environmental Protection Agency (EPA) programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

QUESTIONS REGARDING PPRTVS

Questions regarding the contents and appropriate use of this PPRTV assessment should be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

Fluoranthene occurs as pale yellow needles or crystals (Hazardous Substance Database, HSDB, 2005) and is a polycyclic aromatic hydrocarbon (PAH) of nonalternant type. An alternant PAH is a conjugated hydrocarbon that has only 6-membered (hexagonal) rings (e.g., benzo[a]pyrene), while nonalternant PAHs are those that have a mixture of 6- (hexagonal) and lower-membered rings. Fluoranthene is a 4-ring (tetracyclic) structure wherein a benzene and a naphthalene unit (both are hexagonal) are conjugated to a five-membered (pentagonal) ring. Fluoranthene occurs in a number of products including (i) as a natural constituent of coal tar and petroleum-derived asphalt, which can be used as lining material for the interior of steel and ductile-iron potable water pipes and storage tanks; (ii) in research; (iii) in the production of fluorescent dyes; (iv) as a stabilizer in epoxy resin adhesives; (v) in electrical insulating oils; and (vi) as a parent compound for pharmaceutical drugs. Fluoranthene is found in polluted urban air, water, diesel and gasoline engine exhaust, cigarette smoke, and other products of incomplete combustion of organic matter (International Agency for Research on Cancer, IARC, 1983; Grimmer and Pott, 1983). Its presence is an indicator of less efficient or lower-temperature combustion, as nonalternant PAHs are less preferred in formation than alternant PAHs. It is one of the most prevalent dietary PAHs; a dietary intake of 1−2 µg/day was estimated in one study (de Vos et al., 1990). The empirical formula for fluoranthene is $C_{16}H_{10}$, and the molecular structure of fluoranthene is presented in Figure 1. Some physicochemical properties of fluoranthene are provided in Table 1.

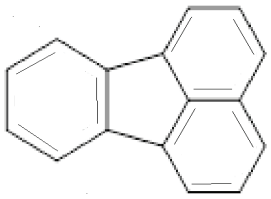


Figure 1. Fluoranthene Structure

Table 1. Physicochemical Properties Table for Fluoranthene (CASRN 206-44-0)[a]

Property (unit)	Value
Boiling point (ºC)	384
Melting point (ºC)	111
Density (g/cm^3 at 0ºC)	1.252
Vapor pressure (mm Hg at 20ºC)	0.01
pH (unitless)	NA
Solubility in water (mg/L at 25ºC)	0.20−0.26
Relative vapor density (air = 1)	NA
Molecular weight (g/mol)	202.26
Octanol/water partition coefficient (log K_{ow}, unitless)	5.16

[a]Values were obtained from HSDB (2005).

NA = Not available.

A noncancer oral RfD of 0.04 mg/kg-day for fluoranthene is included in the U.S. EPA IRIS database (U.S. EPA, 1990). The study used to derive this value is an EPA subchronic-toxicity study (U.S. EPA, 1988), in which CD-1 mice (20/sex/group) were administered gavage doses of fluoranthene at 0, 125, 250, or 500 mg/kg-day for 13 weeks. An additional group of 30 mice/sex was used for baseline blood evaluations. The lowest-observed-adverse-effect-level (LOAEL) was selected based on nephropathy, increased liver weights, hematological alterations, increased liver enzymes, and clinical signs in the mid- and high-dose groups. An uncertainty factor (UF) of 3000 was applied to the no-observed-adverse-effect-level (NOAEL) value of 125 mg/kg-day from this study to derive the RfD value. When values were developed by other regulatory agencies, this study was also cited as the principal study. No data were available to allow for the calculation of a RfC for IRIS (U.S. EPA, 1990). No RfD, RfC, or cancer assessment for fluoranthene is included in the Drinking Water Standards and Health Advisories List (U.S. EPA, 2009). A subchronic RfD value of 0.4 mg/kg-day is reported in the HEAST (U.S. EPA, 2010). This RfD value is based on nephropathy, liver-weight changes, and hematological changes. The Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1994) does not include a Health and Environmental Effects Profile (HEEP) for fluoranthene. The toxicity of fluoranthene has not been reviewed by the ATSDR (2010), but it is included in the review of PAHs (ATSDR, 1995). The ATSDR specifies a recommended oral minimum risk level (MRL) of 0.4 mg/kg-day for intermediate-duration exposure (15 to 364 days); no inhalation MRL values are reported for any PAHs. A World Health Organization (IPCS, 1998) Environmental Health Criteria (EHC) document on PAHs reports the NOAEL and LOAEL values cited by IRIS (125 and 250 mg/kg-day, respectively); no separate EHC document exists for fluoranthene. The CalEPA (2008) has not derived toxicity values for exposure to fluoranthene. No occupational exposure limits for fluoranthene have been derived by the American Conference of Governmental Industrial Hygienists (ACGIH, 2010), the National Institute of Occupational Safety and Health (NIOSH, 2010), or the Occupational Safety and Health Administration (OSHA, 2010). OSHA does provide standards for coal tar pitch volatiles; however, those regulations apply to a mixture of compounds.

A PPRTV document for fluoranthene also exists (i.e., U.S. EPA, 2002), which states that no OSF can be derived for fluoranthene due to inadequate human and animal data. In a previous IRIS assessment (U.S. EPA, 1990), fluoranthene was categorized in Group D ("*Not Classifiable as to Human Carcinogenicity*"). The HEAST (U.S. EPA, 2010) does not report a U.S. EPA (1986) cancer weight-of-evidence (WOE) classification for fluoranthene. The IARC (2010) determined that there is "limited evidence in animals" and that fluoranthene is "not classifiable" with respect to carcinogenicity in humans (Group 3). Fluoranthene is not included in the *12th Report on Carcinogens* (NTP, 2011). CalEPA (2008) has not prepared a quantitative estimate of carcinogenic potential for fluoranthene.

Literature searches were conducted on sources published from 1900 through April 2012 for studies relevant to the derivation of provisional toxicity values for fluoranthene (CAS No. 206-44-0). Searches were conducted using EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: AGRICOLA; American Chemical Society; BioOne; Cochrane Library; DOE: Energy Information Administration, Information Bridge, and Energy Citations Database; EBSCO: Academic Search Complete; GeoRef Preview; GPO: Government Printing Office; Informaworld; IngentaConnect; J-STAGE: Japan Science & Technology; JSTOR: Mathematics & Statistics and Life Sciences; NSCEP/NEPIS (EPA publications available through the National

Service Center for Environmental Publications [NSCEP] and National Environmental Publications Internet Site [NEPIS] database); PubMed: MEDLINE and CANCERLIT databases; SAGE; Science Direct; Scirus; Scitopia; SpringerLink; TOXNET (Toxicology Data Network): ANEUPL, CCRIS, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HEEP, HMTC, HSDB, IRIS, ITER, LactMed, Multi-Database Search, NIOSH, NTIS, PESTAB, PPBIB, RISKLINE, TRI; and TSCATS; Virtual Health Library; Web of Science (searches Current Content database among others); World Health Organization; and Worldwide Science. The following databases outside of HERO were searched for relevant health information: ACGIH, ATSDR, CalEPA, EPA IRIS, EPA HEAST, EPA HEEP, EPA OW, EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 2 provides an overview of the relevant database for fluoranthene and includes all potentially relevant repeated short-term-, subchronic-, and chronic-duration studies. The entry for the principal study is bolded.

Table 2. Summary of Potentially Relevant Data for Fluoranthene (CASRN 206-44-0)

Category	Number of Male/Female, Species, Strain, Study Type, Study Duration	Dosimetry[a]	Critical Effects at LOAEL	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference	Notes[b]
Human								
1. Oral (mg/kg-day)[a]								
None								
2. Inhalation (mg/m^3)[a]								
None								
Animal								
1. Oral (mg/kg-day)[a]								
Subchronic	40/40, rat, F344, dietary, 7 days/week, up to 90 days	0, 150, 750, 1500	Renal tubular casts (male)	NA[c]	Not performed	NA[c]	Knuckles et al. (2004)	PR
	20/20 mouse, CD-1, gavage, 13 weeks	**0, 125, 250, 500**	**Nephropathy, increased liver weights, hematological alterations, and clinical effects**	**125**	**124**	**250**	**U.S. EPA (1988)**	**PS, PR, IRIS**
Chronic	None							
Developmental	None							
Reproductive	None							
Carcinogenic	None							
2. Inhalation (mg/m^3)[a]								
None								

[a]Dosimetry: NOAEL, BMDL/BMCL, and LOAEL values are converted to an adjusted daily dose (ADD in mg/kg-day) for oral noncancer effects. All long-term exposure values (4 weeks and longer) are converted from a discontinuous to a continuous (weekly) exposure.
[b]IRIS = utilized by IRIS, date of last update, PS = principal study, NPR = not peer reviewed, PR = peer reviewed.
[c]The study authors stated that the NOAEL was 150 mg/kg-day, based upon renal tubular casts and hematological changes observed at 750 mg/kg-day; however, due to numerous deficiencies in this study, a NOAEL and LOAEL cannot be established.

HUMAN STUDIES

Oral Exposures

No oral studies on the subchronic, chronic, developmental, or reproductive toxicity or on the carcinogenicity of fluoranthene in humans were identified.

Inhalation Exposures

No inhalation studies on the subchronic, chronic, developmental, or reproductive toxicity or on the carcinogenicity of fluoranthene in humans were identified.

ANIMAL STUDIES

Oral Exposure

The effects of oral exposure of animals to fluoranthene have been evaluated in two subchronic studies: U.S. EPA (1988) and Knuckles et al. (2004).

Subchronic Studies

In the study by Knuckles et al. (2004), fluoranthene (98% purity) was administered in the diet at doses of 0, 150, 750, or 1500 mg/kg-day to male and female F344 rats for approximately 90 days. Although not explicitly stated in the study report, 40 rats/sex were apparently used for each dose group. Stability of the test compound in the diet and homogeneity was stated to be acceptable. Animal husbandry was adequate, conforming with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals. Animals were weighed twice weekly, and food consumption was recorded. Hematology and clinical chemistry were performed on blood samples obtained at sacrifice, and the following parameters were determined: erythrocyte count, total leukocyte count, hematocrit, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, alanine aminotransferase, aspartate aminotransferase, and blood urea nitrogen (BUN). During Days 29, 59, and 89, urine was collected over approximately 24 hours from 10 rats/sex/group, and urinalysis was determined for following parameters: urinary glucose, bilirubin, ketone, specific gravity, pH, protein, urobilinogen, nitrite, blood, and leukocytes.

Animals were euthanized on Day 30, 60, or 90, with 10 rats/sex/dose group sacrificed at each time point (Knuckles et al., 2004). The number of animals examined for renal tubular casts were apparently 6−8 rats/sex/dose group; two 1500-mg/kg-day males and one 750-mg/kg-day female died (Ramesh, personal communication, July 27, 2010). The methods did not report which organs were weighed and examined grossly and histologically. Based on the results, the stomach, liver, kidney, testes, prostate, and ovaries were excised and prepared routinely for histological examination; it is assumed that organs from all animals were examined, and that these organs were also weighed and examined grossly. (It is noted that the study authors used the words "such as" in their listing of organs examined histologically; therefore, it cannot be confirmed that this is a complete listing.) It is also unknown whether a full necropsy was performed. An acute study was also performed, but it is not pertinent to this assessment.

Organ-weight and toxicity data were initially analyzed by analysis of variance (ANOVA), followed by the Bonferroni multiple-range test (Knuckles et al., 2004). Pathology data were reportedly analyzed with Fisher's Exact Test and the Cochran-Armitage test for linear trends. A two-way ANOVA was used for the determination of statistical differences in toxicity on the basis of duration of dose and dose level and to assess the interactions among these variables. The criterion for statistical significance was $p < 0.05$.

Considering the various toxicological endpoints noted in the study (Knuckles et al., 2004), the occurrence of renal tubular casts in males provided the most sensitive endpoint. The incidences of renal tubular casts for the subchronic study were presented graphically in Figure 9 in the study; however, the study did not adequately describe the methodology used in obtaining the data presented in Figure 9. The study also did not explain whether the data in Figure 9 were dichotomous or continuous in nature. Figure 9 of the study depicts "percent tubular casts" (y-axis label) as a bar graph with mean and standard deviation (as specified in the caption), suggesting that the data are continuous, but the data seem to be dichotomous. Although the Figure 9 caption specifies that the "percentage incidence of renal casts in F344 rats" was measured, it is unclear if the authors were referring to percentage incidence of casts on multiple slides (inappropriate methodology) or the percentage incidence in the groups of animals. This confusion was continued in the report's text, which stated that "tubular casts were observed in 40%, 80%, and 100% of kidney tissues of male rats…" The very next sentence stated "only 10% of the female rats at the two highest dose levels showed significant kidney tubular casts," and further in the text it was stated that "this was especially true in the kidney, where 80% and 100% of the male rats at dosages of 750 or 1500 mg/kg/day developed abnormal tubular casts after 90 days." These latter statements suggest that analysis was conducted on dichotomous data.

The report also did not clearly explain how the data in Figure 9 were statistically analyzed (Knuckles et al., 2004). In the figure, all male dose groups were denoted as increased ($p < 0.05$) compared to controls; however, the abstract specified that only the two highest dose groups were significantly ($p < 0.05$) affected at 90 days. The methods indicated that histology data were analyzed by Fisher's Exact Test and the Cochran-Armitage test for linear trends. Fisher's Exact Test is not appropriate for the analysis of multiple dose groups of continuous data. A "step-down" approach using the Cochran-Armitage trend test can be used to indicate significance in particular groups, but the methods did not indicate that technique was used.

Additionally, there was a lack of corroborating evidence of an adverse effect in the kidney (Knuckles et al., 2004). Aside from the renal tubular casts, the only other mention of an adverse effect in the male kidney was noted in the report's abstract: "Only BUN in males was significantly increased in the high-dose group (1500-mg FLA/kg BW/day) at the 90-day time point." The data were not presented, and the magnitude difference between treatment groups was not reported. Because of the confusion related to the renal casts, independent verification (via BUN) was desirable, but not possible, and without the data on the magnitude of change, it is unknown if the effect is biologically significant by EPA definitions. Except for a possible negative effect at the high dose due to increased BUN, the gross and histological pathology, organ weight-, and clinical chemistry data provided no additional evidence of a negative effect on the kidney.

Food consumption and body weights were each decreased ($p < 0.05$) by 15% in the 1500-mg/kg-day males; however, neither summary data nor individual animal data were reported for independent verification (Knuckles et al., 2004). Despite some uncertainties with the data analysis, 1500 mg/kg-day is an appropriate adverse effect level in this study. It was also stated that the liver/body-weight ratios were significantly increased by 20% in the 1500-mg/kg-day males, but data were not reported for independent verification. Although these data are sufficient to establish an adverse effect, according to NCEA policy, there was no corroborative evidence of an adverse effect on the liver, which suggests that increased liver weight was an adaptive response.

Other possible toxicological endpoints presented in this study do not clearly establish an adverse effect level (Knuckles et al., 2004). Two high-dose males and one mid-dose female were sacrificed moribund; however, cause-of-death was not determined, and it is unclear if the deaths were treatment related. Erythrocyte and leukocyte counts, hematocrit percentages, and hemoglobin concentrations were reported graphically (x-y plots). However, the standard deviation associated with each mean was often unclear. In the findings reported in these plots, the variation was often large in magnitude, a clear trend in response with time was not apparent (transient effects), the mean values at Day 0 often differed considerably (significantly decreased erythrocyte count in the 150-mg/kg-day females, $p < 0.05$), and it is uncertain if the effects were dose dependent. Therefore, interpretation of these findings is problematic. The one finding that is possibly treatment related and adverse, by EPA definitions, was the decrease in leukocyte counts in the 1500-mg/kg-day male and female rats. However, due to the large numbers of deficiencies noted in this study, no LOAEL is established.

A chronic RfD value is available in the IRIS database (U.S. EPA, 1990) based on data from the study by the U.S. EPA (1988). This study is also selected as the principal study for deriving the subchronic p-RfD herein. This study is unpublished but is considered peer reviewed and was conducted according to Good Laboratory Practices (GLP). It was conducted by a contract laboratory, Toxic Research Laboratories, Ltd for the Dynamac Corporation and is dated 1987.

Fluoranthene (>97% purity) was administered once each day in corn oil by gavage to 20 CD-1 mice/sex/dose group at doses of 0, 125, 250, or 500 mg/kg-day for 13 weeks (U.S. EPA, 1988). A group of 30 mice/sex was used to assess clinical chemistry and hematology parameters prior to treatment. Mice were obtained from Charles River Laboratories (Portage, MI), and animal husbandry was performed appropriately. The mice were observed twice daily for mortality and signs of adverse effects. Body weights and food consumption were recorded weekly. The eyes of all mice were examined prior to treatment and during Week 13. Blood was collected from the treated groups at sacrifice, but urine was not collected. The following hematology and clinical chemistry parameters were measured or calculated: erythrocyte count, total and differential leukocyte count, hemoglobin, erythrocyte packed cell volume, mean corpuscular volume, mean corpuscular hemoglobin and hemoglobin concentration, glucose, urea nitrogen, cholesterol, total bilirubin, albumin, globulin, albumin/globulin ratio, alkaline phosphatase, serum glutamate oxalacetate and pyruvate transaminase, lactate dehydrogenase, sodium, potassium, chloride, and total carbon dioxide.

On Days 91−93, all surviving mice were euthanized. All mice—including decedents—were subjected to necropsy (U.S. EPA, 1988). Tissue samples were prepared routinely and examined microscopically. The following tissues were collected and examined microscopically: salivary glands, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, gall bladder, pancreas, trachea, lungs, aorta, heart, bone marrow, mesenteric lymph node, spleen, thymus, kidneys, urinary bladder, testes, epididymides, prostate, seminal vesicles, ovaries, uterus, mammary gland, brain, peripheral nerve (sciatic), spinal cord, pituitary, eyes with optic nerve, adrenal gland, parathyroids, thyroids, sternum, skeletal muscle, skin, femur bone with marrow and joint, and all gross lesions and masses. Additionally, liver, heart, spleen, kidneys, testes, and brain were weighed (paired organs were weighed together).

All tissues were processed routinely, and samples of the following tissues were examined microscopically: (i) all tissues from the control and 500-mg/kg-day groups and all decedents; (ii) liver, lungs, and kidneys from all groups; and (iii) all gross lesions (U.S. EPA, 1988). The severity grades of the histological lesions were not reported but may have been included in Appendix J (P.A.I. Histopathology Report; unavailable). The data were tested for homogeneity of variance by using Bartlett's Test. If the data were homogeneous, Dunnett's test was performed; otherwise, a modified Dunnett's test was used. Significance at $p \leq 0.05$ and 0.01 was reported. No treatment-related effects were noted on mortality, clinical signs, body weights, body-weight gains, food consumption, food efficiency, ophthalmology, hematology, clinical chemistry, or gross pathology (U.S. EPA, 1988).

Increased incidences of nephropathy were observed in the 500-mg/kg-day males (55%) and 250- and 500-mg/kg-day females (25−55%) compared to controls (5%, each sex; U.S. EPA, 1988). Severity of the histological lesions was minimal to mild except for one high-dose male that exhibited nephropathy with moderate severity.

The significant hematology and clinical chemistry findings are presented in Table B.1 and included the following: (i) decreases of 7−8% in packed cell volume in the 250- and 500-mg/kg-day females; (ii) decrease of 28% in absolute lymphocytes in the 500-mg/kg-day males; (iii) decreased percentage of eosinophils in the 500-mg/kg-day females (0.6% decrease in treated group vs. 2.0% in controls); (iv) increase of 11% in globulin in the 500-mg/kg-day males; (v) decrease of 10% in albumin/globulin ratio in the 250- and 500-mg/kg-day males; and (vi) increase of 40−54% in serum glutamate pyruvate transaminase at 250 and 500 mg/kg-day in both sexes (U.S. EPA, 1988). These findings are not considered significantly harmful to the animals' health due to the low magnitude of change (not considered biologically significant) and because a toxicological syndrome could not be identified to support a WOE approach.

Liver weights relative to body weights were increased ($p \leq 0.01$) by 7−32% in all treated male groups and by 12−26% in the 250- and 500-mg/kg-day females (see Table B.2; U.S. EPA, 1988). According to NCEA policy, a change in liver organ weight of at least 10% is considered adverse; therefore, an adverse effect was observed at 250 mg/kg-day and is determined to be a LOAEL. Also, increased incidences of liver pigment accumulation were noted in the 250- and 500-mg/kg-day males and females (55−100% of mice in treated groups vs. 0% in controls; see Table B.3). The brown, granular, anisotropic pigment was generally found in a centrilobular distribution primarily contained within Kupffer cells; however, the composition of the pigment was not determined.

This study (U.S. EPA, 1988) was conducted in compliance with the EPA Pesticide Assessment Guidelines, Subdivision F, Section 158.82-1 and the EPA Toxic Substance Control Act Testing Guidelines for Ninety Day Subchronic Toxicity Studies (40 CFR 798.2650).

IRIS stated that the LOAEL was 250 mg/kg-day for the study (U.S. EPA, 1988) based on nephropathy, increased liver weights, hematological alterations, and clinical effects and selected the 125-mg/kg-day dose as the NOAEL.

Chronic Studies

No studies regarding the effects of chronic oral exposure to fluoranthene in animals were identified.

Developmental and Reproductive Studies

No studies regarding the effects of oral exposure to fluoranthene in animals on developmental and reproductive parameters were identified.

Carcinogenic Studies

No studies regarding the effects of oral exposure to fluoranthene on carcinogenicity in animals were identified.

Inhalation Exposure

No inhalation studies on the subchronic, chronic, developmental, or reproductive toxicity or carcinogenicity of fluoranthene in animals were identified.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Other studies that are not appropriate for selection of a POD for fluoranthene and the determination of p-RfD, p-RfC, p-OSF, or p-IUR values may provide supportive data that supplement a WOE approach to risk assessment. These studies include carcinogenicity study designs other than standard 18-month or 24-month chronic studies in the mouse and rat, respectively, as well as genotoxicity, immunotoxicity, neurobehavioral toxicity, metabolism, and mechanistic studies. These studies are summarized briefly in Table 3, and further details and discussion are presented in the accompanying text.

Table 3. Other Fluoranthene Studies

Tests	Materials and Methods	Results	Conclusions	References
Tests evaluating carcinogenicity and genotoxicity				
Carcinogenicity	Twenty female CD rats/dose group were treated by subcutaneous injection with FDE (fluoranthene metabolite, 10 µmol), FDE (2 µmol), BcPDE (positive control, 2 µmol), or DMSO (negative control) under each of 3 nipples on the left, and DMSO was injected under 3 nipples on the right.[a] The procedure was repeated on the second day. Palpation for mammary tumors was conducted weekly. Termination occurred after 41 weeks.	Mammary adenomas were increased with FDE treatment at both doses, and adenocarcinomas were increased at the high FDE dose.	FDE, a metabolite of fluoranthene, may result in mammary tumors.	Hecht et al. (1995)
Carcinogenicity	Newborn CD-1 mice were treated by intraperitoneal injection of fluoranthene on Days 1, 8, and 15 (total doses of 0, 0.7, 1.75, or 3.5 mg), and 18−23 or 14−24 mice/sex/dose were euthanized at 6 or 9 months, respectively. Lung and liver tumors were counted.	The incidence of lung tumors was increased in both sexes at 6 and 9 months at both doses, and liver tumors were increased at 9 months in males at both doses.	Fluoranthene treatment in the newborn mouse assay results in lung and liver tumors.	Wang and Busby (1993)
Carcinogenicity	DNA was isolated from the tissues of animals in the study above (Wang and Busby, 1993). DNA adducts were isolated and quantified from various tissues.	A positive correlation was noted between DNA adduct level and persistence in relation to target organ specificity for tumor formation.	Fluoranthene treatment in the newborn mouse assay results in DNA adducts.	Wang et al. (1995)
Carcinogenicity	Newborn CD-1 mice were treated by intraperitoneal injection of fluoranthene on Days 1, 8, and 15 (total doses of 0, 3.46 µmol (approx. 70 mg/kg), or 17.3 µmol (approx. 350 mg/kg), and 16−34 mice/sex/dose were euthanized at 52 weeks. Lung and liver tumors were counted.	At both doses of fluoranthene, the incidence of lung tumors was increased in both sexes, and liver tumors were increased in males.	Fluoranthene treatment in the newborn mouse assay results in lung and liver tumors.	LaVoie et al. (1994)
Carcinogenicity	Fluoranthene was applied with benzo[*a*]pyrene (B[*a*]P) to mouse skin, and tumor yield was compared to application of B[*a*]P or fluoranthene alone. The tumor promoter potential of fluoranthene was also tested using B[*a*]P as an initiator.	The cocarcinogenic response was an approximate 3-fold increase in tumor yield and a reduction in the tumor latency period by at least half. Fluoranthene alone was not carcinogenic.	Fluoranthene was a cocarcinogen in this study.	Van Duuren and Goldschmidt (1976)
Carcinogenicity	Various studies are discussed that were performed prior to 1990 in animals. Six studies involved dermal application of fluoranthene to mice, and an additional study involved subcutaneous injection of fluoranthene in mice.	No increase in tumor incidence was noted in the fluoranthene-treated groups.	Fluoranthene was not carcinogenic in these studies.	U.S. EPA (1990)

Table 3. Other Fluoranthene Studies

Tests	Materials and Methods	Results	Conclusions	References
Genotoxicity	Male S-D rats were treated with radiolabeled fluoranthene by intraperitoneal injection or were treated with unlabeled fluoranthene by dietary administration. DNA adducts were isolated in the blood and organ tissues.	Hemoglobin adducts and DNA adducts in many organs were isolated, and the major DNA adduct was identified.	Fluoranthene administration resulted in DNA adducts.	Gorelick et al. (1989)
Genotoxicity	Fluoranthene (110 nmol [22 ug]) was applied with (or without) [^{3}H]B[*a*]P (11 nmol) to CD-1 mouse skin, and DNA adduct level and metabolite profile in skin were compared to application of [^{3}H]B[*a*]P alone.	The presence of fluoranthene increased the levels of B[*a*]P-DNA binding but did not affect the B[*a*]P metabolite profile.	Fluoranthene was a cocarcinogen in this study.	Rice et al. (1988)
Genotoxicity	In vivo mouse bone marrow micronucleus and rat liver unscheduled DNA synthesis tests were performed.	No evidence of genotoxicity was noted.	Fluoranthene was not genotoxic in this study	Stocker et al. (1996)
Genotoxicity	Various mutagenicity tests were reviewed.	Positive and negative results were observed in several of the same types of tests.	IRIS concluded that the evidence for mutagenicity is equivocal	U.S. EPA (1990)
Other toxicity tests				
Immunotoxicity	A series of experiments were performed using murine bone marrow cultures obtained from C57BL/6 mice.	Fluoranthene treatment can result in apoptosis in the pre-B cells or alter their growth and survival characteristics.	Fluoranthene treatment can suppress B-cell lymphopoiesis.	Hinoshita et al. (1992)
Immunotoxicity	BDF1 mice were immunized with Japanese cedar pollen antigen (JCPA). Various chemicals were used as adjuvants, including fluoranthene, and the mice were challenged with JCPA. IgE antibody levels and antibody response were measured. Intraperitoneal macrophages obtained from unimmunized mice were incubated with fluoranthene or other chemicals, and the chemiluminescence response and interleukin-1α (IL-1α) production to JCPA were measured.	Fluoranthene increased the production of IgE antibody to JCPA and IgE antibody response, and modulated the secretion of IL-1α.	Exposure to fluoranthene can increase the immune system response.	Kanoh et al. (1996)
Developmental	S-D rat embryos were incubated with fluoranthene and rat hepatic S-9. C57/B6 mice were injected intraperitoneally with fluoranthene on one of GDs 6-9.	Adverse effects were noted on embryos in vitro, and embryo resorption occurred in vivo.	Fluoranthene can be a developmental toxicant.	Irvin and Martin (1987)

Table 3. Other Fluoranthene Studies

Tests	Materials and Methods	Results	Conclusions	References
Neurobehavioral toxicity	F344 rats were treated with a single gavage dose of fluoranthene at doses of 0, 100, 200, or 400 mg/kg. Motor activity assessment and the functional observational battery (FOB) were performed.	At 200 and 400 mg/kg, activity was decreased after treatment, and abnormal findings were observed in the FOB, such as increased urination, decreased grip strength, etc.	Fluoranthene can affect neurobehavior adversely.	Saunders et al. (2003)
Metabolism studies				
Metabolism	Microsomes isolated from the small intestine and liver of various animals and humans were each incubated with fluoranthene in order to compare the metabolic rates and profiles.	Metabolic rate and metabolite profile for fluoranthene varied with species. The metabolic rate in humans was much higher than in rodents, and a greater amount of the parent was converted to a detoxification product in humans.	Fluoranthene toxicity studies in rodents may lead to conservative estimates of toxicity in humans.	Walker et al. (2006)
Metabolism	Radiolabeled fluoranthene was incubated with DNA. The DNA adducts were isolated and characterized using high-performance liquid chromatography (HPLC) and mass spectroscopy (MS).	DNA adducts were isolated and characterized. It was determined that a single DNA adduct accounted for approximately 70% of the total modified deoxyribonucleosides.	The primary DNA adduct was determined, providing insight into an important metabolic pathway.	Babson et al. (1986)
Mechanistic studies				
Mechanistic	The effects of six PAHs on gene expression in rat liver were examined.	PAHs generally induce a compound-specific response on gene expression. Carcinogenic PAHs induce the oxidative stress pathway. Fluoranthene does not induce oxidative stress.	Discrimination of carcinogenic potential may be possible by evaluating gene expression.	Staal et al. (2007)
Mechanistic	The effects of four PAHs on estrogenic activity in in vivo uterine assays in Wistar rats were examined.	Three of the four (including fluoranthene) exhibited estrogenic activity. Fluoranthene did not induce P450 monooxidases at the doses used.	Fluoranthene possess estrogenic activity	Kummer et al. (2008)
Mechanistic	The effects of 12 PAHs on gap junctional intracellular communication (GJIC) in WB-F344 rat liver epithelial cells were assayed.	PAHs containing bay or bay-like regions (including fluoranthene) inhibited GJIC more than linear PAHs.	This finding suggests that fluoranthene may act as a tumor promoter.	Weis et al. (1998)

Table 3. Other Fluoranthene Studies

Tests	Materials and Methods	Results	Conclusions	References
Mechanistic	The effects of 14 PAHs on the induction of CYP1A1 and 1B1 mRNA were examined using genetically engineered C57BL/6J mice.	Activation of the PAHs to mutagenic species correlated with induction of CYP1A1 and 1B1. Fluoranthene induction of these P450s was very low or nonexistent.	Carcinogenicity potency may relate to the potential of the PAHs to induce CYP1A1 and 1B1.	Shimada et al. (2002)

[a]FDE (*anti*-2,3-dihydroxy-1,10b-eopxy-10b,1,2,3-tetrahydrofluoranthene), BcPDE (*anti*-3,4-dihydroxy-1,2-epoxy-1,2,3,4-tetrahydrobenzo[c]phenanthrene; used as a positive control), DMSO (dimethyl sulfoxide; used as a negative control).

Tests Evaluating Carcinogenicity and Genotoxicity

Although a long-term study has not been performed in animals to evaluate the carcinogenic potential of fluoranthene, the results from several studies suggest that fluoranthene may be carcinogenic. Three of these studies (Hecht et al., 1995; Wang and Busby, 1993 and Wang et al., 1995; and LaVoie et al., 1994) were performed after the last carcinogenicity assessment for fluoranthene by IRIS. The IRIS document for fluoranthene (U.S. EPA, 1990) summarized the carcinogenicity and mutagenicity data available up to 12/01/1990. The cocarcinogenic potential of fluoranthene was evaluated in vivo by Van Duuren and Goldschmidt (1976) and by Rice et al. (1988). Gorelick et al. (1989) performed studies that demonstrate the formation of fluoranthene-DNA adducts in vivo and characterized the major DNA adduct. Stocker et al. (1996) performed two in vivo genotoxicity tests.

Hecht et al. (1995) evaluated the potential of a diol epoxide metabolite of fluoranthene (FDE; *anti*-2,3-dihydroxy-1,10b-epoxy-10b,1,2,3-tetrahydrofluoranthene) to induce mammary carcinogenicity. FDE is a metabolite of fluoranthene produced by human liver microsomes. FDE was previously shown to be a mutagen in *S. typhimurium* and to form DNA adducts in in vivo and in vitro tests. The DNA adduct was shown to be stable enough to be transported to other tissues after formation in human liver. Twenty female CD rats/dose group were treated with FDE, BcPDE (*anti*-3,4-dihydroxy-1,2-epoxy-1,2,3,4-tetrahydrobenzo[*c*]-phenanthrene; positive control), or DMSO (negative control). The animals were treated by subcutaneous injection with FDE (10 µmol; >99% purity), FDE (2 µmol), BcPDE (2 µmol; >99% purity), or DMSO under each of 3 nipples on the left, and DMSO was injected under 3 nipples on the right. The procedure was repeated on the second day. Palpation for mammary tumors was conducted weekly. Termination occurred after 41 weeks, and gross and histological examinations of the mammary glands were performed. Mammary adenomas were increased ($p \leq 0.05$) with FDE treatment (39−42 tumors in treated vs. 2 tumors in controls) at both doses, and adenocarcinomas were increased (not statistically significant) at the high dose of FDE (10 tumors in treated vs. 2 tumors in controls). Findings of this study indicate that treatment with FDE may result in mammary tumors.

Another carcinogenicity study was performed and was reported in two parts: the initial report presented the tumorigenicity data from this study (Wang and Busby, 1993), and the second report presented data regarding the formation and persistence of DNA adducts (Wang et al., 1995). Newborn VAF/Plus CD-1 mice were treated by intraperitoneal injection of fluoranthene (>99% purity). The total dosages were 0-, 0.7-, 1.75-, or 3.5-mg fluoranthene. The newborn mice were injected on Day 1 with 1/7 of the dose, Day 8 with 2/7 of the dose, and Day 15 with 4/7 of the dose. Mice were euthanized by CO_2 asphyxiation at 6 or 9 months of age and necropsied. Tissues for DNA adduct analysis were collected from animals euthanized at 2 hours, 1, 3, 7, 14, 30, 75, or 165 days after the last injection. Lungs, heart, liver, kidneys, spleen, and thymus were excised, rinsed, flash frozen in liquid nitrogen, and stored at −100°C. DNA from the tissue samples was isolated, hydrolyzed to nucleotides, enriched for modified nucleotides, ^{32}P-postlabeled, and chromatographed using a high-performance liquid chromatography (HPLC) system with a C18 column. At 6 months, 18−23 mice/sex/dose were examined, and 14−24 mice/sex/dose were examined at 9 months. Tumors in lung and liver were quantified. At 6 months, total lung tumor (adenoma and adenocarcinoma) incidences were increased ($p < 0.03$) in the combined sexes at 1.75 and 3.5 mg (10−44% in treated vs. 0% in controls), and the number of lung tumors/mouse was increased at 3.5 mg/kg (0.56 in treated vs. 0 in controls). The following increases in the incidences of tumors ($p < 0.03$) were observed at

9 months: incidences of liver tumors in all treated male groups (22−57% in treated vs. 0% in control); total lung tumors in the combined sexes of all dose groups (24−42% in treated vs. 5% in controls); and number of lung tumors/mouse in the combined sexes of all dose groups (0.27−0.68 in treated vs. 0.05 in controls). The study authors stated,

> *When FA was activated in vitro by rat liver microsomes in the presence of calf thymus DNA, the major DNA adduct formed was identified as anti-10b-N^2-deoxyguanosin-l,2,3-trihydroxy-1,2,3,10b-tetrahydrofluoranthene (anti-FADE adduct)* (Babson et al., 1986). *Subsequently, anti-FADE adduct was identified by an HPLC-^{32}P-postlabeling method as the major FA-DNA adduct in tissues of Sprague-Dawley rats chronically fed FA in the diet* (Gorelick et al., 1989). *We also demonstrated that anti-FADE adduct was the major FA-DNA adduct in tissues of Blu:Ha mice and further that the highest level of adduct formation was in the lung 24 h after a tumorigenic dose of FA* (Wang et al., 1995).

The study authors also concluded that,

> *Lung, the target organ for FA tumorigenicity, contained higher levels of anti-FADE adduct than other tissues from 1−165 days after treatment. The anti-FADE adduct level decreased in a biphasic manner after reaching maximum values at 2 h in heart and spleen plus thymus and 3 days in lungs, liver, and kidneys. About 10% of the maximum amount of anti-FADE adduct remained in lung, liver, and heart 165 days after final FA treatment, at which time 44% of animals had developed lung adenomas. Significant inter-litter variations, but no sex differences in adduct levels, were observed. These results indicated a positive correlation between anti-FADE adduct level and persistence in relation to target organ specificity for tumor formation.*

Busby et al. (1984) also noted lung tumors in a similarly performed newborn-mouse assay in the BLU:Ha (ICR) strain. Wang and Busby (1993) stated that this mouse strain is no longer commercially available.

LaVoie et al. (1994) also investigated fluoranthene tumorigenicity in the newborn-mouse assay. Newborn CD-1 mice (64−79 pups/sex/dose group) were treated by intraperitoneal injection of fluoranthene (>99.5% purity) on Days 1, 8, and 15, receiving total doses of 3.46 or 17.3 µmol (approximately70 and 350 mg/kg). 2-Methylfluoranthene (2MeFA) and 3-methylfluoranthene (3MeFA) were tested at the same doses. B[*a*]P was included as the positive control at a dose of 1.10 µmol, and DMSO was included as the vehicle control. Mice (16−34 mice/sex/dose group) were euthanized at 52 weeks of age. The percentages of mice with lung tumors were increased in all fluoranthene-treated animals (35−86%) and the high-dose 2MeFA group (69−96%) compared to vehicle control (12−17%). The percentages of mice with hepatic tumors were increased in all treated males in the fluoranthene, 2MeFA, and 3MeFA groups (33−100%) compared to vehicle control (17%), and increased in the high-dose 2MeFA and 3MeFA females (11−31%) compared to vehicle control (6%).

Van Duuren and Goldschmidt (1976) observed that fluoranthene was a potent cocarcinogen when applied together with B[*a*]P to mouse skin. Fluoranthene (40-µg/application) was applied to mouse skin (50 female ICR/Ha Swiss mice/group) three times weekly with B[*a*]P

(5-µg/application). Animals were euthanized after 440 days. The cocarcinogenic response resulted in an approximate 3-fold increase in tumor yield and reduced the tumor latency period by at least half. Fluoranthene, when applied alone to the backs of mice at the same dose, was not tumorigenic. Fluoranthene's potential as a tumor promoter was also evaluated. B[*a*]P (150-µg/application) was applied to mouse skin (50 animals). Fourteen days after the primary treatment, animals were given applications of fluoranthene (40-µg/application) three times weekly and were euthanized on Day 448. This treatment resulted in only one mouse having a single papilloma, indicating that fluoranthene had weak or no promoter ability in this test.

IRIS (U.S. EPA, 1990) summarized the animal carcinogenicity data that was observed prior to December 1, 1990, as follows:

> *Suntzeff et al. (1957) administered a 10% solution of fluoranthene in acetone by topical application 3 times/week to unspecified numbers of CAF, Jackson, Swiss and Millerton mice. No tumors were found by 13 months. Wynder and Hoffmann (1959) administered a 0.1% solution of fluoranthene in acetone onto the backs of 20 female Swiss (Millerton) mice 3 times/week for life. No tumors were found. Hoffmann et al. (1972) administered 50 µL of a 1% fluoranthene solution to the backs of 20 female Swiss-albino Ha/ICR/Mill mice 3 times/week for 12 months. All treated mice survived and no tumors were observed. As part of the same study, 30 mice received 0.1 mg fluoranthene in 50 µL acetone every second day for a total of 10 doses. Promotion by dermal application of 2.5% croton oil in acetone was initiated 10 days later and continued for 20 weeks. A single papilloma was noted in 29 surviving mice. Horton and Christian (1974) administered 50 mg fluoranthene in decalin or in decalin:n-dodecane (50:50) to the backs of 15 male C3H mice. The mice were treated 2 times/week for 82 weeks. No skin tumors were observed. Barry et al. (1935) administered 300 mg fluoranthene in benzene by dermal application (number of applications not stated) to 20 mice (type unspecified). The survival rate was 35% after 6 months and 20% at 1 year. No tumors were found by 501 days. Shear (1938) administered four doses of 10 mg fluoranthene in glycerol by subcutaneous injection to strain A mice. Six out of 14 mice survived for 18 months; no tumors were found by 19 months. In a skin-painting assay fluoranthene (100 ug) was administered to 20 Swiss albino Ha/ICR mice, 3 times/week for 1 year; 3.3% of the mice in both this group and in a similar acetone-control group tumors were observed in 3.3% of the mice in both the treated and acetone-control groups (LaVoie et al., 1979).*

Gorelick et al. (1989) performed experiments that suggest the fluoranthene-hemoglobin adducts may be useful as biomarkers. Male S-D rats (2−3/dose) were treated with one dose of [8-^{3}H] fluoranthene by intraperitoneal injection at doses of 2−177,000 nmol/kg. In a separate experiment, male S-D rats (n = 21) were treated with fluoranthene in the diet for 37 days to achieve an average daily intake of 80 mg/kg. Animals were fed uncontaminated diets 3 days before termination. In addition to the fluoranthene-containing diet, 6 of the 21 animals were also treated with [8-^{3}H] fluoranthene by intraperitoneal injection as a tracer (total of 8 doses). Blood and tissue samples were collected at sacrifice from all animals. The authors stated "Fluoranthene binding to globin was proportional to dose over the range of 2 nmol/kg to 177 µmol/kg, and the adducted protein was cleared at the same rate as unmodified hemoglobin, indicating that the

adducts are stable in vivo." Fluoranthene-DNA adduct formation was found in most tissues after chronic administration. The major DNA adduct was identified as the product of *anti*-2,3-dihydroxy-1,10*b*-epoxy-l,2,3-trihydro-fluoranthene and N^2-deoxyguanosine. This diol epoxide exhibited an unusual stability at physiological pH, suggesting that hemoglobin adducts could be useful for biomonitoring exposure to fluoranthene.

Rice et al. (1988) treated female CD-1 mice (9/time point/dose group) by applying 11 nmol [^{3}H]B[*a*]P (99.4% radiochemical purity) or 11 nmol [^{3}H]B[*a*]P with 110-nmol fluoranthene (>99% purity) in acetone to their shaved backs. The mice were euthanized at 4, 8, 24, or 48 hours post-treatment, and their skin was removed, frozen, and powdered. DNA was isolated from the skin and quantified. DNA hydrolysis and adduct isolation was accomplished by HPLC or Affi-Gel 601 column chromatography. Additionally, two groups of 35 female CD-1 mice were treated with 12 nmol [^{3}H]B[*a*]P or 12 nmol [^{3}H]B[*a*]P with 120-nmol fluoranthene in acetone to their shaved backs and animals (5/time point/dose group) were euthanized at 0.5, 1, 2, 4, 8, 24, or 48 hours. The skin was removed, frozen, powdered, homogenized in phosphate-buffered saline, and extracted with acetone and ethyl acetate. Aliquots were treated with β-glucuronidase or arylsulfatase, and B[*a*]P metabolites were isolated and quantified by HPLC. The level of B[*a*]P-DNA binding increased in the presence of fluoranthene at each time interval (36−76%). The B[*a*]P metabolite profile, including β-glucuronide and sulfate conjugates, was similar in the ethyl acetate skin extracts in the presence or absence of fluoranthene cotreatment. This finding suggests that fluoranthene affects B[*a*]P carcinogenicity at some point after B[*a*]P has been activated to an ultimate carcinogen.

Babson et al. (1986) incubated 3-[3H] fluoranthene with calf thymus DNA in the presence of rat liver microsomes and isolated and characterized the major DNA adducts using HPLC and mass spectrometry. Identity of the DNA adduct was further established by comparison with the DNA adduct formed by incubating a synthesized reactive metabolite with DNA. It was determined that *anti*-2,3-dihydroxy-l,10*b*-epoxy-1,2,3-trihydrofluoranthene binding to the N-2 position of deoxyguanosine is responsible for approximately 70% of the total modified deoxyribonucleosides.

Stocker et al. (1996) performed mouse bone marrow micronucleus and rat liver unscheduled DNA synthesis in vivo mutagenicity test systems. Fluoranthene did not show any evidence of genotoxicity in either of these assays following acute oral administration at levels of up to 2000 mg/kg.

IRIS (U.S. EPA, 1990) summarized the evidence for mutagenicity of fluoranthene as equivocal:

> *The results of mutagenicity assays of fluoranthene in several strains of Salmonella typhimurium have been positive and not positive. Evidence for mutagenicity in mammalian cells is also equivocal: results of tests for chromosomal effects in Chinese hamster cells have been both positive and not positive. A test for gene mutations in human lymphoblast cells was not positive, whereas results of tests in different mutant Chinese hamster ovary cell lines have been both positive and not positive.*

Other Toxicity Tests

Other toxicity studies were located, including immunotoxicity studies (Hinoshita et al., 1992; Kanoh et al., 1996), a developmental toxicity study (Irvin and Martin, 1987), and a neurobehavioral toxicity study (Saunders et al, 2003).

Hinoshita et al. (1992) conducted a series of in vitro experiments using murine bone marrow cultures obtained from C57BL/6 mice. It was stated that

> *Data presented herein indicate that: (i) fluoranthene suppresses B lymphopoiesis within 2 days in bone marrow cultures; (ii) fluoranthene suppresses lymphopoiesis at least in part by direct interactions with preB cells; (iii) fluoranthene lymphotoxicity is mediated by rapid induction of DNA fragmentation characteristic of programmed cell death (apoptosis), and (iv) preB cell populations surviving the initial death signal or preB cell populations exposed to lower doses of fluoranthene (0.5−5 µg/mL) exhibit altered growth and survival characteristics. These data suggest several levels at which fluoranthene could compromise B lymphopoiesis.*

Kanoh et al. (1996) immunized five female BDF1 mice seven times at 2-week intervals by the intranasal route with Japanese cedar pollen antigen (JCPA, 10 µg; containing 0.05 µg of the major allergen, Cry j 1) with 400-µg fluoranthene dissolved in 10-µL DMSO. The animals were boosted with JCPA alone at 9 weeks after the final immunization. Anthracene and B[*a*]P were also tested, as well as a JCPA-only control. Passive cutaneous anaphylaxis (PCA) titers were measured in the mice. Additionally, the intraperitoneal macrophages obtained from unimmunized mice were incubated with fluoranthene in vitro, and the chemiluminescence response profiles and interleukin (IL)-1α production of the macrophages were measured. Fluoranthene increased the production of IgE antibody to JCPA and IgE antibody response, but this increase was weak compared to the increase produced by alum or diesel exhaust particles. The authors concluded that fluoranthene also modulated the secretion of IL-1α.

Irvin and Martin (1987) incubated S-D rat embryos (Day 10) with fluoranthene in the presence of rodent hepatic S-9 fractions and reported the following findings: "decreased crown-rump length and somite development, deformities of the telencephalon, and absence of red blood cell circulation through the yolk sac." Administration of fluoranthene via intraperitoneal injection to C57/BL-6 mice on one of GDs 6−9 resulted in increased rates of embryo resorption. The data were reported in an abstract, but a complete report was not located.

Saunders et al. (2003) treated F344 rats with a single gavage dose of fluoranthene in peanut oil at doses of 0, 100, 200, or 400 mg/kg. The animals were subjected to a motor activity assessment and a functional observational battery (FOB). Activity (horizontal, vertical, total distance, and stereotypic) was decreased at doses of 200 and 400 mg/kg. The following findings were reported at 400 mg/kg, and many of these findings were also observed at 200 mg/kg: "dysfunction, including ataxia, decreased grip strengths, increased landing foot splay, loss of aerial righting, increased urination and defecation, and decreased responses to sensory stimuli in both sexes. Neurological deficits in the FOB peaked at 6 hours and lasted for 48 hours posttreatment." Males were more sensitive to these effects than females.

Metabolism Studies

The metabolism of fluoranthene is briefly described in the following study by Walker et al. (2006).

Walker et al. (2006) isolated microsomes from the small intestine and liver of rat, mouse, hamster, goat, sheep, pig, dog, cow, monkey, and humans (obtained commercially), and incubated these microsomes with fluoranthene in order to compare the metabolic rates and profiles. Postincubation, samples were extracted with ethyl acetate and analyzed for the parent and metabolites by reverse-phase HPLC with fluorescent detection. The results demonstrated that the metabolic rates and profiles varied greatly with species. Parent compound was not present in any sample after incubation. The mean concentration of total metabolites formed in liver microsomes was lowest in the rat and mouse (approximately 0.25−0.4 pmoles/mL/mg protein) and highest in human (approximately 2.6 pmoles/mL/mg protein). Similar results were observed in intestinal microsomes, but concentrations were approximately a tenth of the concentrations observed in liver microsomes. The fluoranthene metabolites generated in intestinal and liver microsomes were identified as fluoranthene 2,3-diol, trans-2,3-dihydroxy-1,10*b*-epoxy-1,2,3,10*b* tetrahydro fluoranthene (2,3D fluoranthene), 3-hydroxy fluoranthene, and 8-hydroxy fluoranthene. The rodent intestinal and hepatic microsomes produced a considerably higher proportion of 2,3D fluoranthene than human microsomes. Conversely, intestinal and hepatic microsomes from humans converted a greater proportion of fluoranthene to 3-hydroxy fluoranthene, the detoxification product.

Mechanistic Studies

Possible mechanisms or modes of action of fluoranthene as a carcinogen or cocarcinogen are briefly described in the following three studies: Staal et al. (2007), Weis et al. (1998), and Shimada et al. (2002).

Staal et al. (2007) examined the effects of six PAHs (including fluoranthene) on gene expression in precision-cut liver slices from male Wistar rats using DNA microarray technology. The results indicated that PAHs generally induce a compound-specific response on gene expression and that discrimination of carcinogenic from noncarcinogenic compounds is partly feasible with the oxidative stress response pathway. Fluoranthene induced the expression of 77 genes including those involved in mitochondrial fatty acid beta-oxidation and formed DNA adducts above background level. Only carcinogenic PAHs (which did not include fluoranthene) induced the oxidative stress pathway.

Kummer et al. (2008) examined the effects of four PAHs on estrogenic activity in in vivo uterine assays in Wistar rats. Three of the four (including fluoranthene) exhibited estrogenic activity. Fluoranthene did not induce P450 monooxidases at the doses used. The authors concluded that fluoranthene possessed estrogenic activity

Weis et al. (1998) assayed the effects of 12 PAHs on gap junctional intracellular communication (GJIC) in WB-F344 rat liver epithelial cells. GJIC was used as an epigenetic biomarker for structure-activity (tumor promotion) relationships of the 12 PAHs. Previous research indicates that epigenetic events play a part in tumor promotion, and that down-regulation of GJIC contributes to the uncontrolled cellular growth that leads to tumor development. Results indicated that PAHs containing bay or bay-like regions (like fluoranthene) inhibited GJIC more than did linear PAHs.

Shimada et al. (2002) evaluated the effects of 14 PAHs (including fluoranthene) on the induction of CYP1A1 and 1B1 mRNA. The effects were evaluated in genetically-engineered C57BL/6J arylhydrocarbon receptor knock-out mice, AhR (-/-), compared to wild-type, AhR (+/+). The authors concluded that, "Liver microsomal activities of 7-ethoxyresorufin and 7-ethoxycoumarin *O*-deethylations and of mutagenic activation of (±)-trans-7,8-dihydroxy-7,8-dihydro-B[*a*]P to DNA-damaging products were found to correlate with levels of CYP1A1 and 1B1 mRNAs in the liver." The authors stated that their findings suggest that the carcinogenicity potencies of PAHs may relate to their potential to induce CYP1A1 and 1B1. Fluoranthene induction of these P450 isozymes was very low or nonexistent.

DERIVATION OF PROVISIONAL VALUES

Table 4 presents a summary of noncancer reference values. Table 5 presents a summary of cancer values. No cancer values could be derived. For the oral subchronic studies, the average daily dose was provided.

Table 4. Summary of Noncancer Reference Values for Fluoranthene (CASRN 206-44-0)

Toxicity Type (Units)	Species/ Sex	Critical Effect	Reference Value	POD Method	POD	UF_C	Principal Study
Subchronic p-RfD (mg/kg-day)	Mouse/M+F	Renal nephropathy	1×10^{-1}	BMDL	124	1000	U.S. EPA (1988)
Chronic RfD (IRIS) (mg/kg-day)	Mouse/M+F	Nephropathy, increased liver weights, hematological alterations, and clinical effects	4×10^{-2}	NOAEL	125	3000	U.S. EPA (1988)
Subchronic p-RfC (mg/m^3)	None						
Chronic p-RfC (mg/m^3)	None						

Table 5. Summary of Cancer Reference Values for Fluoranthene (CASRN 206-44-0)

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF	None			
p-IUR	None			

DERIVATION OF ORAL REFERENCE DOSE

Derivation of Subchronic Provisional RfD (Subchronic p-RfD)

IRIS (U.S. EPA, 1990) based its chronic RfD on a mouse subchronic toxicity study, where the critical effects were nephropathy, increased liver weights, hematological alterations, and clinical effects (U.S. EPA, 1988).

Since 1990, an additional subchronic toxicity study using rats was performed with fluoranthene by Knuckles et al. (2004). Although, this study used dietary exposure, which is more relevant to human exposure than gavage dosing, it has numerous deficiencies which are noted in the study summary. The deficiencies in the study preclude its consideration for the derivation of the subchronic p-RfD.

Consequently, the subchronic toxicity study (U.S. EPA, 1988) used by IRIS was selected as the principal study to derive the subchronic p-RfD. The standard deviations for group organ weights were not reported in the available documentation nor were the individual data. Therefore, liver organ-weight data could not be modeled. The nephropathy endpoint is, however, the most sensitive of the two organ endpoints. A $BMDL_{10}$ of 124 mg/kg-day, based on nephropathy, was determined for the female mouse (more sensitive sex). Results from these modeling efforts are presented in Appendix C.

Adjusted for daily exposure:

The following dosimetric adjustments were made for each dose in the principal study for dietary treatment.

$$\begin{aligned} DOSE_{ADJ} &= DOSE \times [\text{conversion to daily dose}] \\ &= 125 \text{ mg/kg-day} \times (\text{days of week dosed} \div 7 \text{ days in week}) \\ &= 125 \text{ mg/kg-day} \times 7 \div 7 \\ &= 125 \text{ mg/kg-day} \end{aligned}$$

Among the dichotomous models for incidence of nephropathy (see Table 6), the Probit model was chosen as it had the lowest AIC, resulting in a $BMDL_{10}$ of 124 mg/kg-day for a POD. Visual inspection of the curves for each model did not result in the rejection of any model for problems such as supralinearity or compromised low-dose fitting due to modeling of the high-dose range. The range of the BMDL values from models meeting the goodness-of-fit criteria is <3-fold.

Table 6. Goodness-of-Fit Statistics, BMD_{10}, and $BMDL_{10}$ Values for Dichotomous Models for Nephropathy in Female Mice Dosed with Fluoranthene[a]

Model (in order of lowest BMDL)	Goodness-of-Fit *p*-Value[b]	AIC	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)
Probit	**0.94**	**75.078[c]**	**164**	**124**
Quantal Linear	0.49	76.492	87.8	58.2
Multistage	0.81	77.018	164	66.0
Gamma	0.92	76.974	166	66.3
Logistic	0.91	75.156	177	133
Log-Logistic	0.94	76.968	167	63.4
Log-Probit	0.96	76.966	168	103
Weibull	0.86	76.996	163	66.1

[a]U.S. EPA (1988).
[b]Values >0.1 meet conventional goodness-of-fit criteria.
[c]Lowest AIC.

After considering all treatment-related endpoints, the subchronic p-RfD for fluoranthene, based on the $BMDL_{10}$ of 124 mg/kg-day from the incidences of renal nephropathy in female mice (U.S. EPA, 1988), is derived as follows:

$$\textbf{Subchronic p-RfD} = BMDL_{10} \div UF_C$$
$$= 124 \text{ mg/kg-day} \div 1000$$
$$= \mathbf{1 \times 10^{-1} \text{ mg/kg-day}}$$

Table 7 summarizes the UFs for the subchronic p-RfD for fluoranthene, and the confidence descriptors for the subchronic p-RfD are provided in Table 8.

Table 7. Uncertainty Factors for Subchronic p-RfD for Fluoranthene[a]

UF	Value	Justification
UF_A	10	A UF_A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between mice and humans. There are no data to determine whether humans are more or less sensitive than mice to the nephrotoxicity of fluoranthene.
UF_D	10	A UF_D of 10 is applied because there are no acceptable two-generation reproduction studies or developmental studies.
UF_H	10	A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response in humans.
UF_L	1	A UF_L of 1 is applied for using a POD based on a BMDL.
UF_S	1	A UF_S of 1 is applied because a subchronic study was utilized as the principal study.
UF_C	1000	

[a]U.S. EPA (1988).

Table 8. Confidence Descriptor for Subchronic p-RfD for Fluoranthene[a]

Confidence Categories	Designation[b]	Rationale
Confidence in Study	M	The study was given a medium confidence level, as it is a well-designed study that identified both a LOAEL and a NOAEL for several sensitive endpoints using an adequate number of animals. The data from this study, such as histological severity data for each finding, were not available for independent review.
Confidence in Database	L	The database was given a low confidence level because only two subchronic studies were located; no reproductive or developmental studies were located.
Confidence in Subchronic p-RfD[c]	L	The overall confidence in the subchronic p-RfD is low due to a lack of confidence in the database.

[a]U.S. EPA (1988).
[b]L = Low, M = Medium, H = High.
[c]The overall confidence cannot be greater than the lowest entry in table.

Derivation of Chronic RfD (Chronic RfD)

A chronic RfD of 4×10^{-2} mg/kg-day is available on IRIS (U.S. EPA, 1990) based on the same mouse subchronic study that is used as the principal study for the subchronic p-RfD above, where the critical effects were nephropathy, increased liver weights, hematological alterations, and clinical effects (U.S. EPA, 1988). The UF_C was reported as 3000. The confidence factors were reported as follows: study (medium), database (low), and RfD (low). The IRIS database should be checked to determine if any changes have been made.

DERIVATION OF INHALATION REFERENCE CONCENTRATION

No published studies investigating the effects of subchronic or chronic inhalation exposure to fluoranthene in humans or animals were identified that were acceptable for use in risk assessment.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Table 9 identifies the cancer WOE descriptor for fluoranthene. IRIS (U.S. EPA, 1990) evaluated the overall WOE for carcinogenicity to humans using the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986) and designated fluoranthene under the category of "Group D—*Not Classifiable as to its Human Carcinogenicity*." The IRIS document stated that there are no human data and only inadequate data from animal bioassays.

As of April 2012, it is concluded that there is "inadequate information to assess carcinogenic potential" of fluoranthene. No studies could be located regarding the effects of chronic oral, inhalation, or dermal exposure to fluoranthene in animals. No epidemiological study was located that evaluates the effect of fluoranthene in humans.

Many studies, summarized above, suggest that fluoranthene is a cocarcinogen and may be a weak complete carcinogen (Hecht et al., 1995; Wang and Busby, 1993; Wang et al, 1995; LaVoie et al., 1994; Van Duuren and Goldschmidt, 1976; U.S. EPA, 1990; Rice et al., 1988; Gorelick et al., 1989; Stocker et al., 1996).

Newborn mice assays suggest that fluoranthene may be a complete carcinogen, although a weak carcinogen compared to B[*a*]P. DNA adducts were isolated in rat tissues, which suggests the possibility that fluoranthene may be involved in carcinogenic initiation. Conversely, skin painting tests were routinely negative, and four subcutaneous injections in mice did not induce tumors. Also, it was found that fluoranthene did not induce oxidative stress, in contrast to known PAH carcinogens. Fluoranthene does not induce CYP1A1 and 1B1; whereas, one study suggested that the carcinogenic potential of PAHs may correlate with the induction of these isozymes. Fluoranthene was not genotoxic in the mouse bone marrow micronucleus and rat liver unscheduled DNA synthesis in vivo mutagenicity test systems. IRIS concluded that evidence for mutagenicity of fluoranthene was equivocal.

There is more substantial evidence that fluoranthene is a cocarcinogen. When applied with B[*a*]P to mouse skin, the cocarcinogenic response resulted in an approximate 3-fold increase in tumor yield and reduced the tumor latency period by at least half. B[*a*]P-DNA binding was increased in the presence of fluoranthene by 36−76%. Fluoranthene was found to inhibit GJIC, which can lead to tumor promotion. However, in a mouse skin initiator-promoter test, fluoranthene had weak or no promoter ability. Exposure to other PAHs (such as B[*a*]P) may also occur when a person is exposed to fluoranthene. Human exposure to both fluoranthene and B[*a*]P occurs primarily through the smoking of tobacco, inhalation of polluted air, and by ingestion of food and water contaminated by combustion effluents (IARC, 1983). Consequently, the possibility of concurrent exposure to B[*a*]P is important if fluoranthene acts as a cocarcinogen.

Table 9. Cancer WOE Descriptor for Fluoranthene (CASRN 206-44-0)

Possible WOE Descriptor	Designation	Route of Entry (Oral, Inhalation, or Both)	Comments
"Carcinogenic to Humans"	N/A	N/A	There is no acceptable carcinogenicity study in animals or human studies.
"Likely to be Carcinogenic to Humans"	N/A	N/A	There is no acceptable carcinogenicity study in animals or human studies.
"Suggestive Evidence of Carcinogenic Potential"	N/A	N/A	There is no acceptable carcinogenicity study in animals or human studies.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**There is inadequate human and animal evidence of carcinogenicity. An acceptable chronic toxicity/carcinogenicity study has not been performed by either oral or inhalation routes of exposure.**
"Not Likely to be Carcinogenic to Humans"	N/A	N/A	No strong evidence of noncarcinogenicity in humans is available.

MUTAGENICITY INFORMATION

Fluoranthene was not genotoxic in the mouse bone marrow micronucleus and rat liver unscheduled DNA synthesis in vivo mutagenicity test systems. IRIS (U.S. EPA, 1990) concluded that evidence for mutagenicity of fluoranthene was equivocal. There are no adequate studies on the carcinogenic potential of fluoranthene in humans or animals.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of Provisional Oral Slope Factor (p-OSF)

No human or animal studies examining the carcinogenicity of fluoranthene following oral exposure were identified. Therefore, derivation of a p-OSF is precluded.

Derivation of Provisional Inhalation Unit Risk (p-IUR)

No human or animal studies examining the carcinogenicity of fluoranthene following inhalation exposure were identified. Therefore, derivation of a p-IUR is precluded.

APPENDIX A. PROVISIONAL SCREENING VALUES

There are no provisional screening values for fluoranthene.

APPENDIX B. DATA TABLES

Table B.1. Means ± SD of Selected Hematology and Clinical Chemistry Findings in Mice Administered Fluoranthene by Gavage for 13 Weeks[a,b]

Parameter	Dose group (mg/kg-day)			
	0	125	250	500
Males				
Absolute lymphocytes ($\times 10^3/\mu L$)	6.1 ± 1.70	5.7 ± 1.12	6.9 ± 1.64	4.4 ± 1.20[c] (↓28)
Globulin (g/dL)	2.62 ± 0.18	2.73 ± 0.16	2.74 ± 0.21	2.90 ± 0.29[c] (↑11)
Albumin/globulin ratio	1.20 ± 0.11	1.11 ± 0.10	1.08 ± 0.11[c] (↓10)	1.08 ± 0.10[c] (↓10)
Serum glutamate pyruvate transaminase (U/L)	21.9 ± 5.79	24.4 ± 4.65	30.7 ± 9.20[c] (↑40)	33.6 ± 9.22[d] (↑53)
Females				
Packed cell volume (%)	47.9 ± 2.73	46.9 ± 3.30	44.3 ± 2.55[c] (↓8)	44.6 ± 1.98[c] (↓7)
Eosinophils (%)	2.0 ± 0.82	1.5 ± 1.08	1.2 ± 1.03	0.6 ± 0.70[d] (↓70%)
Serum glutamate pyruvate transaminase (U/L)	20.2 ± 4.62	22.6 ± 4.62	31.1 ± 10.06[d] (↑54)	28.2 ± 5.03[c] (↑40)

[a]U.S. EPA (1988). Data were obtained from Tables 3−4 on pages 49−60 of the cited publication.
[b]Percent difference from control, calculated from the cited data, is listed in parentheses.
[c]Significantly different ($p \leq 0.05$) from the control group.
[d]Significantly different ($p \leq 0.01$) from the control group.

Table B.2. Mean of Selected Organ Weights in Mice Administered Fluoranthene by Gavage for 13 Weeks[a,b]

Parameter	Dose group (mg/kg-day)			
	0	125	250	500
Males				
Terminal body weight (g)	33.9	33.3	33.9	34.7
Absolute liver weight (g)	1.74	1.84	1.99[c] (↑14)	2.36[c] (↑35)
Liver weight relative to body weight (%)	5.14	5.52[d] (↑7)	5.88[c] (↑14)	6.78[c] (↑32)
Females				
Terminal body weight (g)	27.7	27.9	27.4	28.9
Absolute liver weight (g)	1.44	1.53	1.60[c] (↑11)	1.91[c] (↑32)
Liver weight relative to body weight (%)	5.22	5.48	5.83[c] (↑12)	6.59[c] (↑26)

[a]U.S. EPA (1988). Data were obtained from Table 8 on pages 103−104 of the cited publication.
[b]Percent difference from control, calculated from the cited data, is listed in parentheses. Standard deviation was not reported.
[c]Significantly different ($p \leq 0.01$) from the control group.

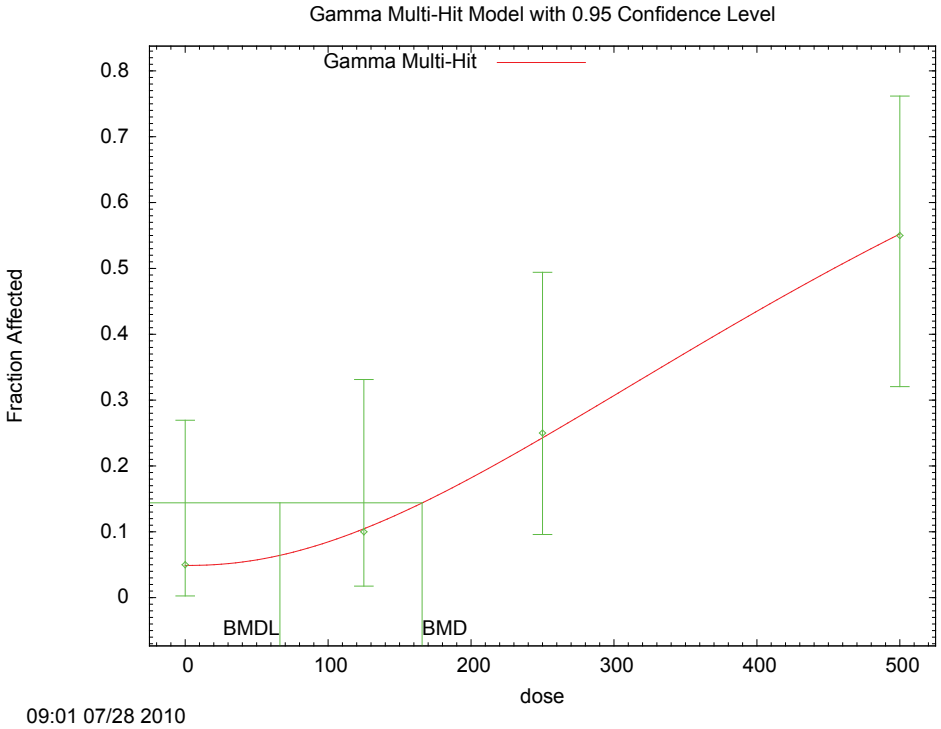
Table B.3. Selected Nonneoplastic Lesions (# Affected/20) in C57/BL-6 Mice Administered Fluoranthene by Gavage for 13 Weeks[a]

Parameter	Dose group (mg/kg-day)			
	0	125	250	500
Males				
Nephropathy	1	2	1	11
Liver pigment	0	1	15	20
Females				
Nephropathy	1	2	5	11
Liver pigment	0	2	11	15

[a]U.S. EPA (1988). Data were obtained from Table 9 on pages 105−110 of the cited publication.

APPENDIX C. BMD MODELING OUTPUTS FOR FLUORANTHENE

627575_Nephropathy_F_Gamma_1




```
 ======================================================================
        Gamma Model. (Version: 2.15;  Date: 10/28/2009)
        Input Data File: C:/BMDS/627575_Nephropathy_F_Gamma_1.(d)
        Gnuplot Plotting File: C:/BMDS/627575_Nephropathy_F_Gamma_1.plt
                                            Wed Jul 28 09:01:22 2010
 ======================================================================

 [add_notes_here]
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   The form of the probability function is:

   P[response]= background+(1-background)*CumGamma[slope*dose,power],
   where CumGamma(.) is the cummulative Gamma distribution function


   Dependent variable = DichPerc
   Independent variable = Dose
   Power parameter is restricted as power >=1

   Total number of observations = 4
   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 =    0.0909091
                          Slope =   0.00357867
```

Power = 2.11169

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Slope	Power
Background	1	0.36	0.45
Slope	0.36	1	0.98
Power	0.45	0.98	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0489334	0.0464776	-0.042161	0.140028
Slope	0.00414311	0.00353766	-0.00279057	0.0110768
Power	2.28944	1.52152	-0.692686	5.27156

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-35.4814	4			
Fitted model	-35.487	3	0.0110862	1	0.9161
Reduced model	-43.8545	1	16.7461	3	0.000797

AIC: 76.974

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0489	0.979	1.000	20	0.022
125.0000	0.1047	2.094	2.000	20	-0.069
250.0000	0.2431	4.862	5.000	20	0.072
500.0000	0.5529	11.058	11.000	20	-0.026

Chi^2 = 0.01 d.f. = 1 P-value = 0.9162

Benchmark Dose Computation

Specified effect = 0.1

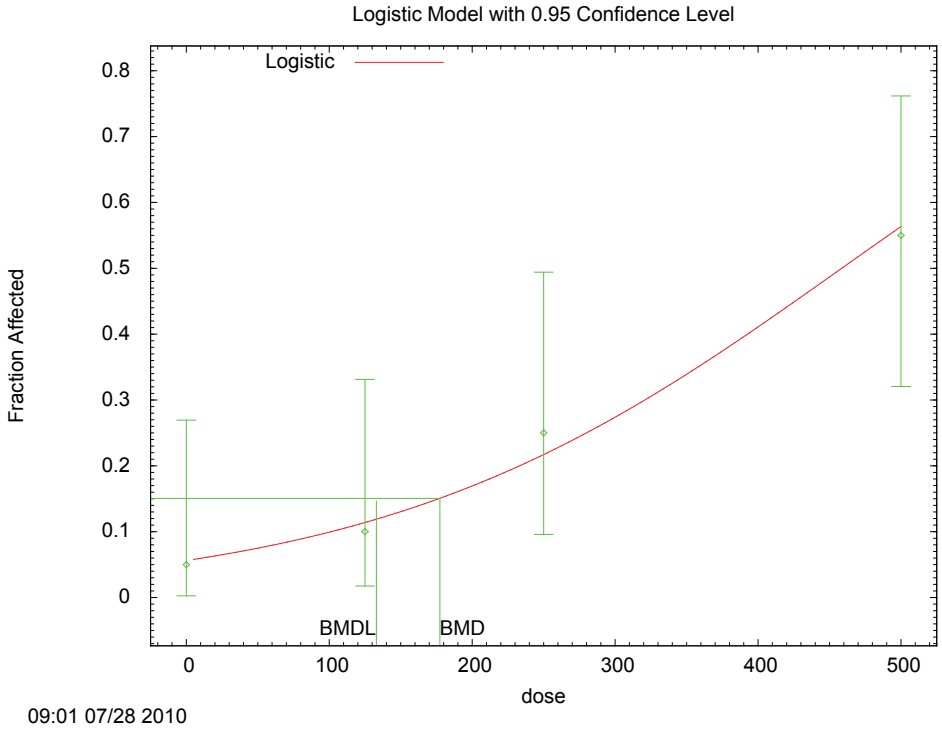
Risk Type = Extra risk

Confidence level = 0.95

BMD = 165.748

BMDL = 66.296

627575_Nephropathy_F_Logistic_1

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 ================================================================
        Logistic Model. (Version: 2.13; Date: 10/28/2009)
        Input Data File: C:/BMDS/627575_Nephropathy_F_Logistic_1.(d)
        Gnuplot Plotting File: C:/BMDS/627575_Nephropathy_F_Logistic_1.plt
                                            Wed Jul 28 09:01:22 2010
 ================================================================

 [add_notes_here]
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   The form of the probability function is:

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


   Dependent variable = DichPerc
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 4
   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 =     -2.58499
                          slope =   0.00563257


           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        -0.87

     slope        -0.87            1
```

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
intercept	-2.82119	0.598794	-3.9948	-1.64758
slope	0.00614982	0.00166495	0.00288658	0.00941306

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-35.4814	4			
Fitted model	-35.5777	2	0.1926	2	0.9082
Reduced model	-43.8545	1	16.7461	3	0.000797

AIC: 75.1555

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0562	1.124	1.000	20	-0.120
125.0000	0.1138	2.276	2.000	20	-0.194
250.0000	0.2169	4.338	5.000	20	0.359
500.0000	0.5631	11.262	11.000	20	-0.118

Chi^2 = 0.20 d.f. = 2 P-value = 0.9071

Benchmark Dose Computation

```
Specified effect =           0.1

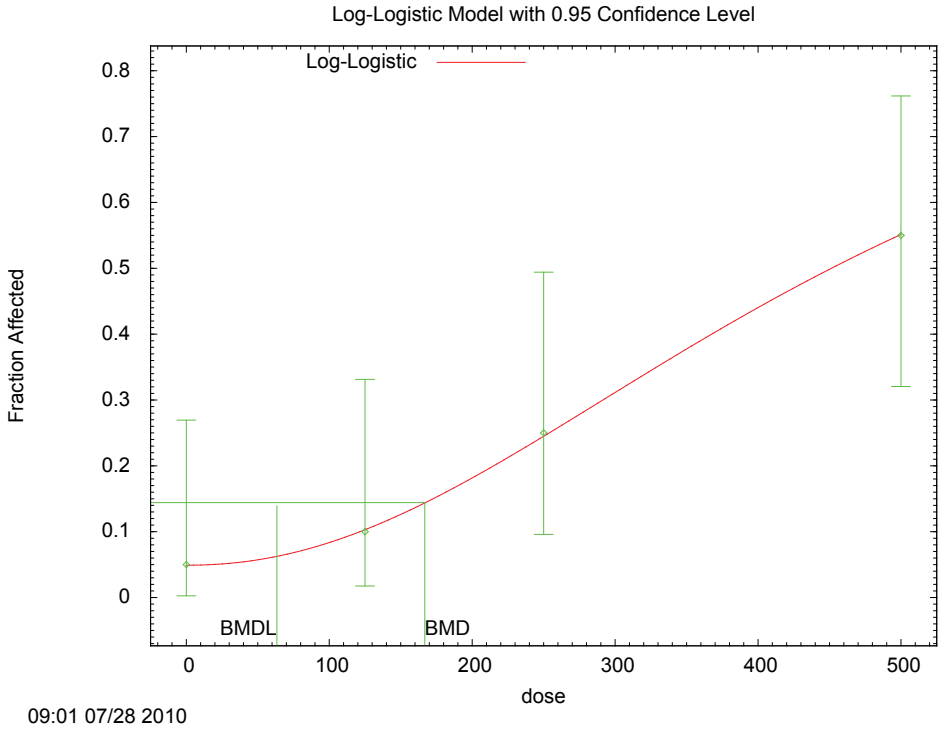
Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =       177.413

            BMDL =       132.974
```

627575_Nephropathy_F_LogLogistic_1

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 ================================================================
        Logistic Model. (Version: 2.13; Date: 10/28/2009)
        Input Data File: C:/BMDS/627575_Nephropathy_F_LogLogistic_1.(d)
        Gnuplot Plotting File: C:/BMDS/627575_Nephropathy_F_LogLogistic_1.plt
                                              Wed Jul 28 09:01:22 2010
 ================================================================

 [add_notes_here]
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   The form of the probability function is:

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


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

   Total number of observations = 4
   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 =         0.05
                     intercept =     -13.3006
                         slope =      2.16096
```

Asymptotic Correlation Matrix of Parameter Estimates

	background	intercept	slope
background	1	-0.45	0.42
intercept	-0.45	1	-1
slope	0.42	-1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0491162	*	*	*
intercept	-12.9785	*	*	*
slope	2.10694	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-35.4814	4			
Fitted model	-35.484	3	0.00511695	1	0.943
Reduced model	-43.8545	1	16.7461	3	0.000797

AIC: 76.968

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0491	0.982	1.000	20	0.018
125.0000	0.1033	2.067	2.000	20	-0.049
250.0000	0.2456	4.913	5.000	20	0.045
500.0000	0.5519	11.038	11.000	20	-0.017

Chi^2 = 0.01 d.f. = 1 P-value = 0.9430

Benchmark Dose Computation

Specified effect = 0.1

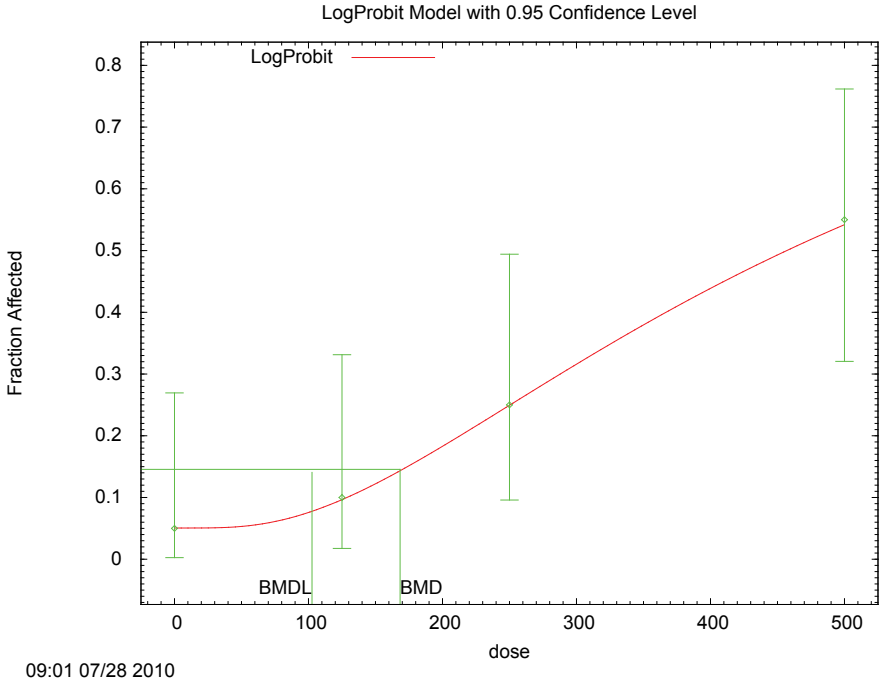
Risk Type = Extra risk

Confidence level = 0.95

BMD = 166.844

BMDL = 63.3727

627575_Nephropathy_F_LogProbit_1




```
 ================================================================
        Probit Model. (Version: 3.2;  Date: 10/28/2009)
        Input Data File: C:/BMDS/627575_Nephropathy_F_LogProbit_1.(d)
        Gnuplot Plotting File: C:/BMDS/627575_Nephropathy_F_LogProbit_1.plt
                                            Wed Jul 28 09:01:22 2010
 ================================================================

 [add_notes_here]
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   The form of the probability function is:

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

   where CumNorm(.) is the cumulative normal distribution function


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

   Total number of observations = 4
   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 =         0.05
                     intercept =     -7.50078
```

slope = 1.2161

Asymptotic Correlation Matrix of Parameter Estimates

	background	intercept	slope
background	1	-0.48	0.45
intercept	-0.48	1	-1
slope	0.45	-1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0506433	0.0479481	-0.0433333	0.14462
intercept	-7.60328	3.10857	-13.696	-1.51059
slope	1.23325	0.522285	0.209586	2.25691

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-35.4814	4			
Fitted model	-35.4828	3	0.00280448	1	0.9578
Reduced model	-43.8545	1	16.7461	3	0.000797

AIC: 76.9657

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0506	1.013	1.000	20	-0.013
125.0000	0.0977	1.955	2.000	20	0.034
250.0000	0.2534	5.069	5.000	20	-0.035
500.0000	0.5484	10.967	11.000	20	0.015

Chi^2 = 0.00 d.f. = 1 P-value = 0.9577

Benchmark Dose Computation

Specified effect = 0.1

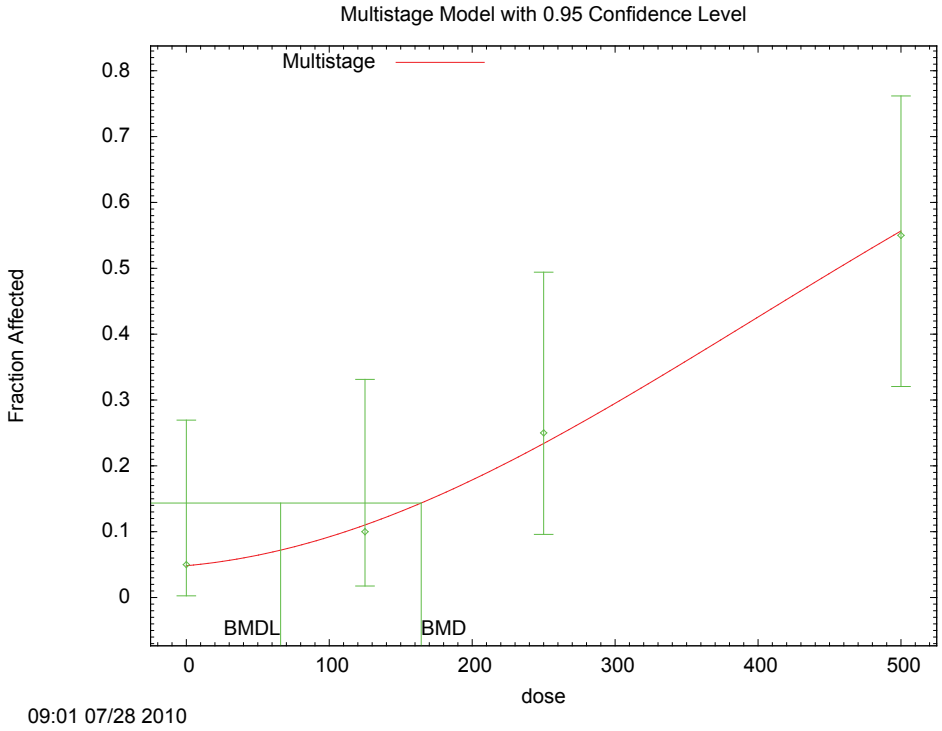
Risk Type = Extra risk

Confidence level = 0.95

BMD = 168.358

BMDL = 102.629

627575_Nephropathy_F_Multi_1

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 ======================================================================
        Multistage Model. (Version: 3.2;  Date: 05/26/2010)
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        Gnuplot Plotting File: C:/BMDS/627575_Nephropathy_F_Multi_1.plt
                                              Wed Jul 28 09:01:22 2010
 ======================================================================

 [add_notes_here]
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   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = DichPerc
   Independent variable = Dose

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


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values
Background = 0.0437984
Beta(1) = 0.000327276
Beta(2) = 2.36901e-006
Beta(3) = 0

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Beta(3)
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)	Beta(2)
Background	1	-0.7	0.53
Beta(1)	-0.7	1	-0.94
Beta(2)	0.53	-0.94	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0483278	*	*	*
Beta(1)	0.000207744	*	*	*
Beta(2)	2.63786e-006	*	*	*
Beta(3)	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	-35.4814	4			
Fitted model	-35.5089	3	0.0549934	1	0.8146
Reduced model	-43.8545	1	16.7461	3	0.000797

AIC: 77.0179

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0483	0.967	1.000	20	0.035
125.0000	0.1102	2.203	2.000	20	-0.145
250.0000	0.2338	4.676	5.000	20	0.171
500.0000	0.5564	11.128	11.000	20	-0.058

Chi^2 = 0.05 d.f. = 1 P-value = 0.8148

Benchmark Dose Computation

Specified effect = 0.1

```
Risk Type        =      Extra risk

Confidence level =           0.95

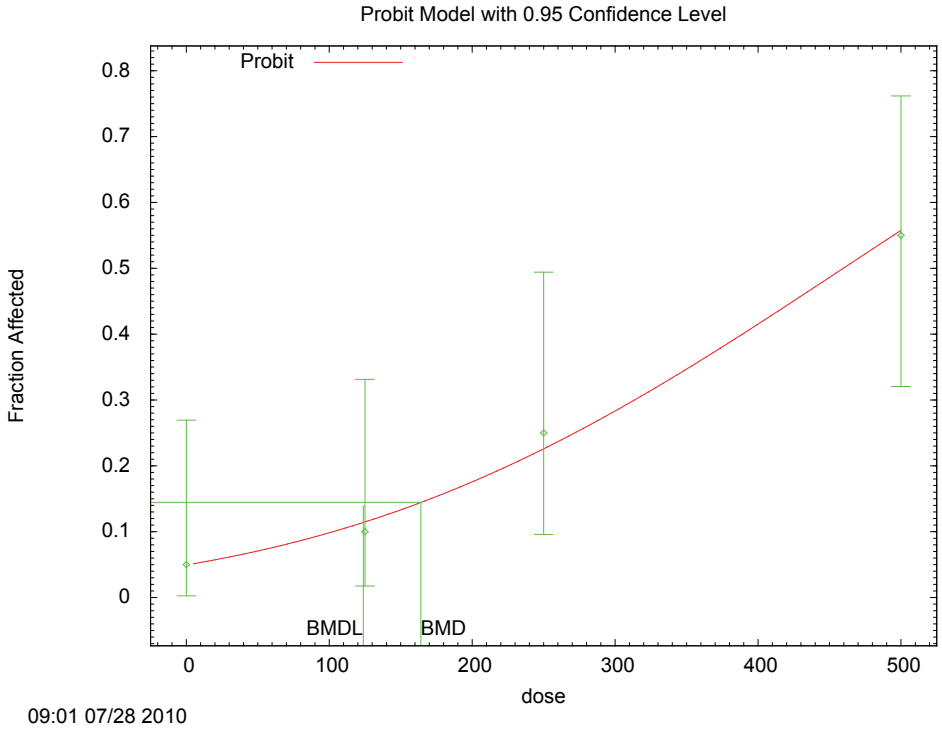
             BMD =        164.319

            BMDL =        65.9789

            BMDU =        301.233

Taken together, (65.9789, 301.233) is a 90     % two-sided confidence
interval for the BMD
```

627575_Nephropathy_F_Probit_1




```
 ===============================================================
        Probit Model. (Version: 3.2;  Date: 10/28/2009)
        Input Data File: C:/BMDS/627575_Nephropathy_F_Probit_1.(d)
        Gnuplot Plotting File: C:/BMDS/627575_Nephropathy_F_Probit_1.plt
                                          Wed Jul 28 09:01:22 2010
 ===============================================================

 [add_notes_here]
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   The form of the probability function is:

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

   where CumNorm(.) is the cumulative normal distribution function


   Dependent variable = DichPerc
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 4
   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 =     -1.61379
                          slope =   0.00351017
```

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	-0.84
slope	-0.84	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
intercept	-1.64939	0.31387	-2.26457	-1.03422
slope	0.00359211	0.000934601	0.00176033	0.0054239

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-35.4814	4			
Fitted model	-35.5388	2	0.114776	2	0.9442
Reduced model	-43.8545	1	16.7461	3	0.000797

AIC: 75.0777

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0495	0.991	1.000	20	0.010
125.0000	0.1150	2.300	2.000	20	-0.210
250.0000	0.2262	4.524	5.000	20	0.254
500.0000	0.5583	11.166	11.000	20	-0.075

Chi^2 = 0.11 d.f. = 2 P-value = 0.9444

Benchmark Dose Computation

Specified effect = 0.1

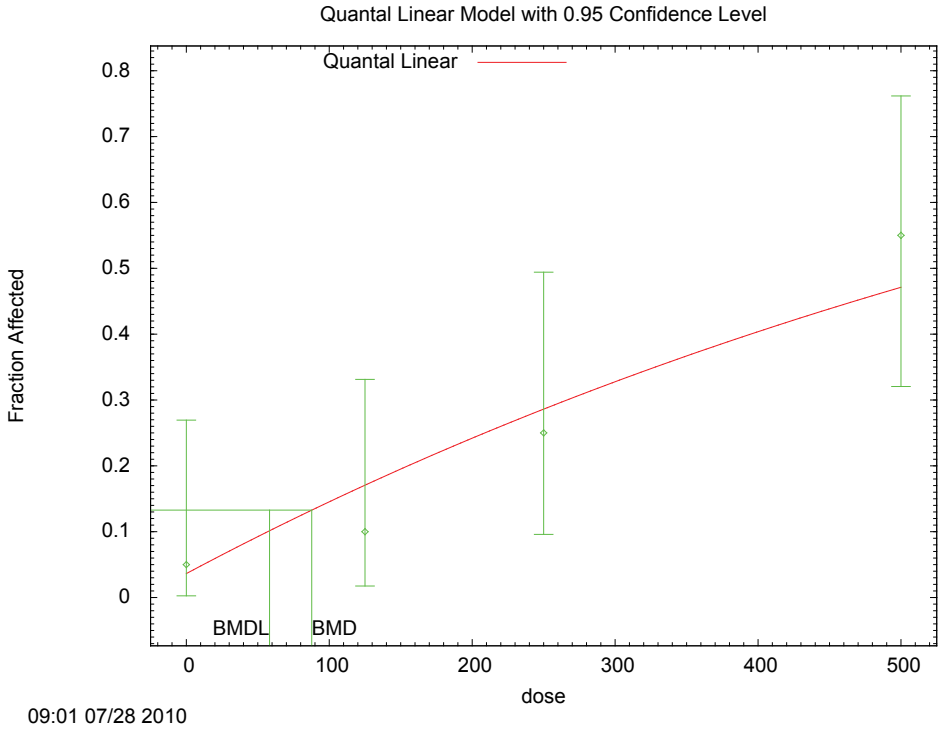
Risk Type = Extra risk

Confidence level = 0.95

BMD = 164.089

BMDL = 123.818

627575_Nephropathy_F_Quantal_1




```
 ================================================================
        Quantal Linear Model using Weibull Model (Version: 2.15;  Date: 10/28/2009)
        Input Data File: C:/BMDS/627575_Nephropathy_F_Quantal_1.(d)
        Gnuplot Plotting File: C:/BMDS/627575_Nephropathy_F_Quantal_1.plt
                                          Wed Jul 28 09:01:22 2010
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 [add_notes_here]
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   The form of the probability function is:

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


   Dependent variable = DichPerc
   Independent variable = Dose

   Total number of observations = 4
   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 =    0.0909091
                          Slope =   0.00138629
                          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	-0.33
Slope	-0.33	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0363917	0.0349751	-0.0321583	0.104942
Slope	0.0012007	0.000332899	0.000548226	0.00185316

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-35.4814	4			
Fitted model	-36.2459	2	1.52885	2	0.4656
Reduced model	-43.8545	1	16.7461	3	0.000797

AIC: 76.4917

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0364	0.728	1.000	20	0.325
125.0000	0.1707	3.414	2.000	20	-0.840
250.0000	0.2863	5.725	5.000	20	-0.359
500.0000	0.4713	9.427	11.000	20	0.705

Chi^2 = 1.44 d.f. = 2 P-value = 0.4875

Benchmark Dose Computation

Specified effect = 0.1

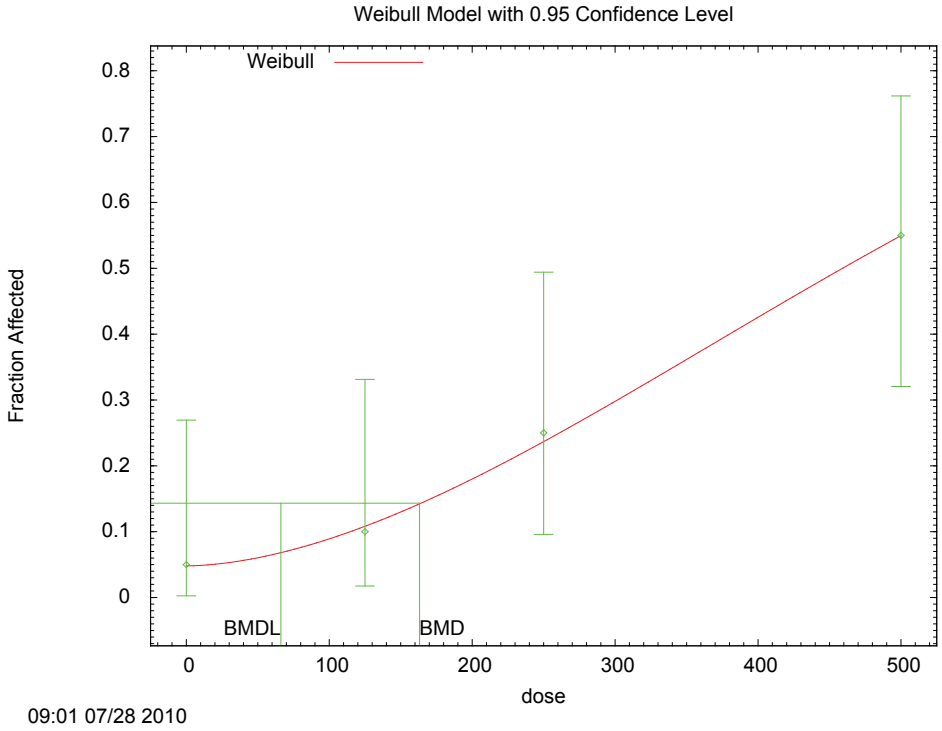
Risk Type = Extra risk

Confidence level = 0.95

BMD = 87.7496

BMDL = 58.235

627575_Nephropathy_F_Weibull_1




```
 ================================================================
        Weibull Model using Weibull Model (Version: 2.15;  Date: 10/28/2009)
        Input Data File: C:/BMDS/627575_Nephropathy_F_Weibull_1.(d)
        Gnuplot Plotting File: C:/BMDS/627575_Nephropathy_F_Weibull_1.plt
                                          Wed Jul 28 09:01:22 2010
 ================================================================

 [add_notes_here]
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   The form of the probability function is:

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


   Dependent variable = DichPerc
   Independent variable = Dose
   Power parameter is restricted as power >= 1.000000

   Total number of observations = 4
   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 =    0.0909091
                          Slope = 2.73771e-005
                          Power =      1.63153


           Asymptotic Correlation Matrix of Parameter Estimates
```

	Background	Slope	Power
Background	1	-0.46	0.44
Slope	-0.46	1	-1
Power	0.44	-1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0480752	0.0455308	-0.0411635	0.137314
Slope	1.32888e-005	6.07955e-005	-0.000105868	0.000132446
Power	1.7622	0.75474	0.282933	3.24146

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-35.4814	4			
Fitted model	-35.4979	3	0.0329838	1	0.8559
Reduced model	-43.8545	1	16.7461	3	0.000797

AIC: 76.9959

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0481	0.962	1.000	20	0.040
125.0000	0.1088	2.175	2.000	20	-0.126
250.0000	0.2387	4.773	5.000	20	0.119
500.0000	0.5539	11.077	11.000	20	-0.035

Chi^2 = 0.03 d.f. = 1 P-value = 0.8564

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 163.188

BMDL = 66.1369

APPENDIX D. REFERENCES

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