Report for the Hawaii Department of Health on Aldrin/Dieldrin Concentrations in Soil at the Hickam Air Force Base

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EXECUTIVE SUMMARY

U.S. EPA (1987) considered aldrin and dieldrin to be probable human carcinogens based on liver tumors in mice, but the mode of action for liver tumors in mice may not be applicable to humans. The National Toxicology Program (2010) does not consider aldrin or dieldrin to be human carcinogens or to be reasonably anticipated to be human carcinogens. The International Agency for Research on Cancer (1987) concluded that aldrin and dieldrin could not be classified as to their carcinogenicity in humans. Studies published since the U.S. EPA (1987) and IARC (1987) reports provide no evidence of a causal association between aldrin and dieldrin and an excess risk of cancer in humans.

U.S. EPA (1987) estimated Cancer Slope Factors for aldrin and dieldrin of 17 and 16 $(mg/kg\text{-}day)^{-1}$, respectively. The current EPA approach to deriving Cancer Slope Factors is different than it was when the U.S. EPA (1987) document was published. U.S. EPA would currently use a benchmark dose approach to estimate the cancer risk and would derive the human equivalent dose differently than it did in 1987. These differences would cause the cancer slope factors for aldrin and dieldrin to be estimated at 3.4 and 7.0 $(mg/kg\text{-}day)^{-1}$, respectively (i.e., about 5 and 2.3 fold lower risk). From knowledge of the soil concentrations of aldrin and dieldrin, the duration of exposure, and the cancer slope factors, one can estimate the excess cancer risks that one might incur from living at Hickam. To detect a risk of 10^{-5} or even 10^{-4} would require a larger population than currently exists in Hawaii.

U.S. EPA (1988, 1990) derived Reference Doses (RfDs) for noncancer endpoints (liver lesions) for aldrin and dieldrin of 0.00003 and 0.00005 mg/kg-day. Again, the method that EPA would currently use to derive the RfDs is different than that which was used in 1988 and 1990. The current approach would estimate RfDs of 0.0001 and 0.00008 mg/kg-day for aldrin and dieldrin, respectively. These are higher (i.e., less risk) than the RfDs estimated by EPA (1988, 1990) and close to the Allowable Daily Intake (ADI) of 0.0001 mg/kg-day, developed by the Joint Meeting on Pesticide Residues (JMPR) (1967). The ADI is similar to the RfD as a guidance value for noncancer risk. The JMPR is an international expert scientific group jointly administered by the Food and Agricultural Organization of the United Nations and the World Health Organization. The JMPR ADI for aldrin and dieldrin has been cited by Health Canada (1994), the World Health Organization (WHO) (1989), WHO (2008) and New Zealand (2010). Studies published since 1987 provide no evidence that would change the updated Reference Dose or ADI estimates described above.

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INTRODUCTION

This report is organized into two sections – cancer and noncancer. The cancer and noncancer sections include descriptions of hazard evaluations and dose response assessments on aldrin and dieldrin. The sections also include a review of the scientific literature that has been published since 1987 and that was not described in either the U.S. EPA (1987) or the ATSDR (2002b). 1987 was selected as the beginning date of the search since that was the year of the U.S. EPA and IARC assessments on aldrin and dieldrin. Each section concludes with a summary and discussion.

CANCER

HAZARD EVALUATIONS

U.S. EPA (1987)

U.S. EPA concluded that the evidence of a cancer risk in humans from exposure to aldrin and dieldrin was inadequate but that the animal evidence was sufficient leading to the overall evaluation that both aldrin and dieldrin were probable human carcinogens.

IARC (1987)

IARC (1987) concluded that the evidence of carcinogenicity in humans was inadequate and that the evidence of carcinogenicity in animals was limited for both aldrin and dieldrin. Aldrin and dieldrin were thus classified in Group 3 (cannot be classified as to its carcinogenicity in humans).

ATSDR (2002)

ATSDR does not classify substances as to their carcinogenic potential in the manner of U.S. EPA, IARC, or NTP but does state in its ToxFAQs (ATSDR 2002a) that, "There is no conclusive evidence that aldrin or dieldrin cause cancer in humans."

NTP (2005, 2010)

The NTP 11th Report on Carcinogens does not list aldrin or dieldrin as either "known to be human carcinogens" or "reasonably anticipated to be human carcinogens." Neither aldrin or dieldrin have been nominated as candidate substances for the 12th Report on Carcinogens.

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WHO (2008)

The 3rd edition of the World Health Organization Drinking Water Guidelines stated that while dieldrin produced tumors in mice, it did not produce tumors in rats and does not appear to be genotoxic. The document quoted the IARC (1987) classification of aldrin and dieldrin in Group 3 (cannot be classified as to its carcinogenicity in humans). The document stated, "It is considered that all the available information on aldrin and dieldrin taken together, including studies on humans, supports the view that, for practical purposes, these chemicals make very little contribution, if any, to the incidence of cancer in humans."

DOSE RESPONSE ASSESSMENT

The only cancer dose response assessment is that of the U.S. EPA (1987). The U.S. EPA (1987) assessment used a linearized multistage model to estimate risk which the Agency described as leading to an upper limit on risk. The current U.S. EPA approach to a cancer dose response assessment (assuming that the low dose response is linear) would be to use a benchmark dose (U.S. EPA 2000b). If mode of action data were available, the Agency would consider the effect of mode of action on the dose response.

The benchmark dose approach requires at least two dose groups and a control. The U.S. EPA (1987) dose response for aldrin was a geometric mean of three slope factors. Two slope factors were derived from male and female mice data from Davis (1965); the third slope factor was derived from an NCI study. The study by Davis (1965) had only one dose group. The benchmark dose approach requires at least two dose groups and a control. To arrive at a human equivalent dose from the animal studies, U.S. EPA (1987) multiplied the doses administered to the animals by the ratio of the animal to human weight to the 1/3 power. The current approach by U.S. EPA would be to multiply the doses administered to the animals by the ratio of animal to human weight to the ¼ power (U.S. EPA 1992, 2005).

Cancer slope factors for aldrin and dieldrin were developed using the same data used by U.S. EPA (1987) in its cancer risk estimates. Exceptions were that only data sets that had two or more dose groups were used and human equivalent doses were derived from animal doses by the ratio of the animal to human weight to the ¼ power. See Appendices A-1 and A-2 for explanations of how the benchmark dose results were derived. A comparison of the U.S. EPA (1987) cancer risk estimates for aldrin and dieldrin with the estimates for these substances derived from the benchmark dose approach are provided in Tables 1 and 2.

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Table 1. Comparison of U.S. EPA 1987 cancer slope factors for Aldrin with the Cancer Slope Factors Derived by Benchmark Dose and Human Equivalent Doses Derived by Scaling to the ¼ power.

Reference for Data Set (Subjects)	Dose levels in Human Equivalent Dose (mg/kg-day)	BMD	BMDL	BMD-Based CSF (mg/kg-day)$^{-1}$	U.S. EPA 1987 CSF[a] (mg/kg-day)$^{-1}$	U.S. EPA 1987 CSF[a] ¾ power BW scaling[b] (mg/kg-day)$^{-1}$
NCI 1978 (male B6C3F1 mice)	0 0.12273 0.24546	0.0426138	0.0294365	3.39715	17	5.54

a. Geometric mean of 3 slope factors
b. Scaling based on ratio of modern (¾ power) and historic Human Equivalent Dose methods

Table 2. Comparison of U.S. EPA 1987 cancer slope factors for Dieldrin with the Cancer Slope Factors Derived by Benchmark Dose and Human Equivalent Doses Derived by Scaling to the ¾ power.

Reference for Data Set (Subjects)	Dose levels in Human Equivalent Dose (mg/kg-day)	BMD	BMDL	BMD-Based CSF (mg/kg-day)$^{-1}$	U.S. EPA 1987 CSF[a] (mg/kg-day)$^{-1}$	U.S. EPA 1987 CSF[a] ¾ power BW scaling[b] (mg/kg-day)$^{-1}$
NCI 1978 (male B6C3F1 mice)	0 0.07674 0.1535	0.027485	0.0188779	5.29719	9.8	3.19
Walker et al. 1972 (male CF1 mice)	0 0.002607 0.02607 0.2607	0.0201651	0.0104576	9.56246	25	8.15
Walker et al. 1972 (male CF1 mice)	0 0.02579 0.065158 0.13032	0.0317161	0.0168577	5.932	15	4.89
Walker et al. 1972 (female CF1 mice)	0 0.03238 0.06476 0.12952	0.0218267	0.0125613	7.96094	26	8.47
Geometric mean of four BMD-based cancer slope factors				**6.99351**		
Geometric mean of 13 cancer slope factors reported by EPA 1987					**16**	
Geometric mean of 13 cancer slope factors reported by EPA 1987 with ¾ power BW scaling						**5.41**

a. Geometric mean of 3 slope factors
b. Scaling based on ratio of modern (¾ power) and historic Human Equivalent Dose methods

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DATA PUBLISHED SINCE 1987

The scientific literature since 1987 was searched utilizing PubMed for any articles related to exposure, cancer, mortality and disease and aldrin/dieldrin in humans. The following search terms were used: ((aldrin) OR dieldrin) AND ((epidemiological studies) OR cancer OR neoplasm OR carcinogenic OR tumor OR maternal OR diabetes). Two-hundred twenty five (225) potentially relevant references were identified. These references were further screened to identify studies of carcinogenicity related to exposure to aldrin and/or dieldrin in humans or animals. *In vitro* studies, environmental and wildlife monitoring reports, and studies of mixtures with other compounds in animals were excluded. Studies that have been reviewed by ATSDR (2002b) were also excluded. Of the remaining studies, thirty-seven references considered useful for further evaluation of both carcinogenic and non-cancer evidence for aldrin and dieldrin were identified.

Human Data

Twenty-three of the studies identified in the literature search were epidemiologic studies that assessed various cancer outcomes including any cancer, Non-Hodgkin's Lymphoma, pancreatic cancer, breast cancer, childhood cancers, prostate cancer, and carcinoma of the gallbladder. The cancer epidemiologic studies are described in more detail in Appendix B.

Two studies assessed cancer mortality among a cohort of 570 male employees at aldrin and dieldrin formulation and production plants at Pernis in the Netherlands (Swaen et al. 2002 and van Amelsvoort et al. 2009). Both studies were updates of de Jong et al. (1997) which is described in the ATSDR (2002b) review. Exposure assessment of aldrin and dieldrin among the Pernis workers included air and blood measurements that allowed for the calculation of chemical intake for each individual. These studies provide for the best assessment of exposure among the epidemiologic studies that have been conducted on aldrin and dieldrin. When stratified by job title, "operators" had significantly increased risks of both rectal and skin cancer mortality in the Swaen (2002) update, but only skin cancer mortality was significantly elevated in van Amelsvoort et al. (2009). In both Swaen et al. (2002) and van Amelsvoort et al. (2009), the rectal and skin cancer Standardized Mortality Ratios (SMRs) were based on only 4 and 3 deaths, respectively. When the cohort in both Swaen et al. (2002) and van Amelsvoort et al. (2009) was divided into low, moderate, and high intake, there was no evidence of a dose response for either skin or rectal cancer mortality. Sielken (1999), in an analysis of the de Jong et al. (1997) data, reported that there was no evidence of an increased cancer risk for a dose considerably above the dose for which the U.S. EPA dose response analysis would have predicted a 10^{-4} risk.

Three analyses of the Agricultural Health Study examined cancer outcomes and exposure to a variety of pesticides including aldrin and dieldrin (Engel et al. 2005; Flower et al. 2004; Purdue et al. 2007). Exposures were self reported. Engel et al. (2005) found an increased risk of breast cancer among wives of pesticide applicators who used aldrin and dieldrin, but the results were not consistent when stratified by state (Iowa vs. North Carolina), menopausal status at enrollment, and cumulative dose groups. No increase in breast cancer risk was found among

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female pesticide applicators that used aldrin and dieldrin. Flower et al. (2003) studied cancer risk among children of pesticide applicators who applied various pesticides including aldrin and dieldrin. A statistically significant increase in childhood cancer risk was associated with paternal application of aldrin prior to conception based on six cases which varied in site and morphology. Purdue et al. (2007) reported an increased risk of lung cancer following exposure to dieldrin and a decreased relative risk of rectal cancer following exposure to aldrin. The authors concluded that overall there was no clear relationship between organochlorine pesticide use and an increased risk of cancer.

Five case-control studies examined Non-Hodgkin's Lymphoma (NHL) and exposure to various pesticides including aldrin and dieldrin (Cantor et al. 2003; Cocco et al. 2008; McDuffie et al. 2001; Quintana et al. 2004; Schroeder et al. 2001). Exposure data were provided either by questionnaire, adipose or serum/plasma sample. Cantor et al. (2003) found no evidence of an association between NHL and serum levels of any of the chemicals that were evaluated. Cocco et al. (2008) found similar results and reported no increased risk of NHL or its subtypes was associated with any of the compounds examined, including aldrin and dieldrin. McDuffie et al. (2001) found a significant association of aldrin exposure and NHL, but exposure information was based on questionnaires and phone interviews. Quintana et al. (2004) found an association of organochlorine pesticide residue in adipose tissue and NHL. The authors also found that the highest quartile level of dieldrin exposure was significantly associated with NHL, and found a significant dose response trend for dieldrin. The exposure information was collected after diagnosis, however, and there was a lack of information on variables that could affect organochlorine levels in the body such as diet, occupation and BMI. Schroeder et al. (2001) examined t(14,18)-positive NHL and found that aldrin was not associated with this subtype or the negative subtype of NHL. Dieldrin was associated with t(14,18)-positive NHL when compared to controls. Exposure, however, was self-reported. Based on these five studies and their varying outcomes and limitations, there is inadequate evidence of a causal association between Non-Hodgkin's Lymphoma and either aldrin or dieldrin exposure.

Five case-control studies investigated the association between breast cancer and aldrin/dieldrin exposure (Gammon et al. 2002; Høyer et al. 2001; Høyer et al. 2002; Ibarluzea et al. 2004; Ward et al. 2000). Exposure status was ascertained through blood, serum or adipose samples. Gammon et al. (2002), conducted a study on Long Island, NY, and found no significant increased risk in breast cancer in association with the highest quintile of lipid-adjusted serum levels of dieldrin. A dose-response relationship was not apparent either. Regarding their results, the authors stated, "These findings, based on the largest number of samples analyzed to date among primarily white women, do not support the hypothesis that organochlorines increase breast cancer risk among Long Island women." Høyer et al. (2001 and 2002) conducted two studies on women who participated in the Copenhagen City Heart Study. In the first study, Høyer et al. (2001) found an increased breast cancer risk linked to exposure to dieldrin for women who developed estrogen receptor negative (ERN) breast tumors. Women with the highest dieldrin levels in their serum generally had tumors that were larger and more often spread at diagnosis when compared to estrogen receptor positive (ERP) tumors. The study,

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however, had limited statistical power and the authors state, "The results do not suggest that exposure to potential estrogenic organochlorines leads to development of an ERP breast cancer." Høyer et al. (2002) examined exposure to various organochlorine pesticides and breast cancer with respect to p53 mutation. A non-significant but slightly elevated risk was found in the highest level of exposure for dieldrin among women who developed a tumor with mutant p53. A significant dose response relationship was present for dieldrin in 'wild-type' p53 tumors. Ibarluzea et al. (2004) found that the geometric mean of aldrin in adipose tissue was higher (but not significantly) in breast cancer cases compared to controls. Ward et al. (2000) found no association between breast cancer and aldrin and dieldrin in serum. The breast cancer case-control studies have mixed results and provide unconvincing evidence of a causal association between breast cancer and aldrin/dieldrin exposure.

Additional studies including an ecologic study of pancreatic cancer, a cross-sectional study of prostate cancer, a study examining risk assessment of daily pesticide intake from drinking water and cancer risk, and a case-control study of carcinoma of the gallbladder did not yield any results indicating significantly increased risks associated with aldrin or dieldrin (Clary & Ritz 2003; Ritchie et al. 2003; Buczyńska & Szadkowska-Stanczyk 2005; Shukla et al. 2001). A cross-sectional study in India found increased blood levels of aldrin (and several other organochlorine pesticides) among breast cancer patients compared to women without breast cancer (Mathur et al. 2002). An ecological study examined the association between pesticide use and concentration in adipose tissue and prostate cancer (Belpomme et al. 2009). Ecological studies, however, are generally used to generate hypotheses and are subject to the ecological fallacy (an incorrect inference based on aggregate data). A cross-sectional study by Xu et al. (2010) examined serum concentrations of dieldrin and self-reported physician diagnosed breast and prostate cancer. The authors found a marginally significant trend in the odds ratios for prostate cancer when compared by tertiles of serum concentration. Due to the nature of the cross-sectional design of this study, causality between OC pesticide exposure and cancer risk cannot be concluded.

Collectively, these studies do not provide evidence of a causal association between aldrin and dieldrin and an increased risk of cancer. The results are inconsistent. There is no evidence of a dose response or specificity of cancer site. The study designs of several of the studies are limited (cross-sectional, ecological). The self-reported exposure and self-reported disease diagnosis of several of the studies limit their interpretation. The study with the best exposure data and the best design (and likely the greatest exposure to the study population) (Swaen et al. 2002; van Amelsvoort 2009) found no evidence of an increased risk of cancer.

Animal Data

One animal study related to the carcinogenicity of dieldrin was identified (Cameron et al. 2009). The authors found that perinatal exposure to dieldrin promotes tumors in genetically predisposed mice (i.e., mice that were genetically modified to be susceptible to the type of tumor expressed). The results are summarized in Table 3. No animal studies examining tumorigenic response to aldrin published since 1987 were identified.

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Table 3. Animal studies on Dieldrin published since 1987 that examined tumorigenic response.

Study	Type of study	Results	Comment
Cameron et al. 2009	Oral gavage of dieldrin to FVB-MMTV/neu female mice; 0.45, 2.25, and 4.5 µg/g daily for 5 days prior to mating and once weekly through gestation and lactation; pregnancy outcome with focus on mammary tumors in offspring.	No effect on litter size, birth weight or the number of pups surviving to weaning; significantly increased number and volume of total tumors of thoracic mammary glands at the 4.5 µg/g dose level but not at the lower dose levels; numbers of liver tumors increased dose-dependently in mice treated with 2.25, and 4.5 µg/g.	Dieldrin increased tumor burden in genetically predisposed mice.

DISCUSSION

There is a significant level of uncertainty in regard to whether aldrin and dieldrin should be classified as human carcinogens. IARC (1987) states that the evidence of carcinogenicity for aldrin and dieldrin cannot be classified (Group 3), and the National Toxicology Program did not include either aldrin or dieldrin in its 11th Report on Carcinogens or nominate these chemicals as candidate substances for the 12th Report on Carcinogens. Health Canada (1994) and WHO (2008) accepted the IARC classification of aldrin and dieldrin as Group 3. WHO (2008) went on to state that, "It is considered that all the available information on aldrin and dieldrin taken together, including studies on humans, supports the view that, for practical purposes, these chemicals make very little contribution, if any, to the incidence of cancer in humans."

Human studies on aldrin and dieldrin including studies conducted prior to and since 1987 do not provide evidence that either aldrin or dieldrin are causally associated with an increased risk of cancer. There is no new evidence from animal studies conducted since 1987 of an increased tumorigenic risk from exposure to aldrin and dieldrin. While the Cameron (2009) study showed an increase in mammary tumors in dieldrin exposed mice, the strain used, FVB-MMTV/neu, was genetically modified to be predisposed to express this type of tumor, and dieldrin was already known to be a tumor promoter in mice (ATSDR 2002b).

Furthermore, whether the tumorigenic response seen in mice is applicable to humans is questionable. Several assessments have concluded that aldrin and dieldrin are nongenotoxic (U.S. EPA 1987; WHO 1989; ATSDR 2002b; WHO 2008). The carcinogenic response has only been seen in mice and not in other laboratory species. Stevenson et al. (1999) theorized that dieldrin-induced oxidative stress or its sequelae result in modulation of gene expression that favors expansion of initiated mouse, but not rat liver cells.

Assuming that aldrin and dieldrin are carcinogens, the methods currently used by U.S. EPA to estimate cancer dose response would decrease the cancer slope factor for aldrin by 5-fold and

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the cancer slope factor for dieldrin by 2.3-fold. These decreases in potency are consistent with those observed when the U.S. EPA updated the toxicological review of chlordane in 1997 (U.S. EPA 1997a). Chlordane is an organochlorine pesticide chemically and toxicologically similar to aldrin and dieldrin that has also been detected in soil at Hickam. The updated CSFs for chlordane derived by U.S. EPA in 1997 are roughly 4-fold lower (i.e., less potent) than the previous CSFs, which were not derived based on current U.S. EPA guidelines for carcinogen risk assessment.

Finally, it is important for the reader to have a perspective on the meaning of a 10^{-5} or a 10^{-4} theoretical excess lifetime cancer risk. Theoretical excess lifetime risks are estimated from a high dose exposure and assume a lifetime of exposure. The theoretical relative risk can be expressed as the (excess lifetime risk + background risk) ÷ background risk. For argument's sake, we will assume that aldrin and dieldrin are associated with an increased risk of liver cancer in humans because they were found in some studies to increase liver tumors in the mouse. The lifetime (background) risk of liver cancer in the U.S. population (through age 85) is 6.6×10^{-3} (NCI 2010). If the theoretical excess lifetime risk is 10^{-4}, the relative risk is approximately 1.02 ($6.6 \times 10^{-3} + 1 \times 10^{-4}/6.6 \times 10^{-3}$). The population needed to detect such a risk would be 5,244,721. The population of Hawaii is only about 1.3 million. Thus it would take several times the population of Hawaii to even detect a theoretical excess lifetime cancer risk of 1×10^{-4} (if one actually exists).

NONCANCER

EXISTING GUIDANCE VALUES

U.S. EPA (1988, 1990)

An RfD for aldrin of 0.00003 mg/kg-day was derived based on a LOAEL (0.025 mg/kg/day) for liver toxicity in rats and an uncertainty factor of 1000. The study from which the RfD was derived is Fitzhugh et al. (1964).

An RfD for dieldrin of 0.00005 mg/kg-day was derived based on a NOAEL for liver toxicity in rats and an uncertainty factor of 100. The study from which the RfD was derived is Walker et al. (1969).

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Table 4. Oral MRLs derived by ATSDR (2002b) for aldrin and dieldrin

	Type of MRL	Study	Effect	Point of Departure	Uncertainty Factor	MRL (mg/kg/day)
Aldrin	Acute	Al Hachim (1971)	Decreased body weight and electroconvulsive shock threshold in offspring	LOAEL (2 mg/kg/day)	1000	0.002
	Chronic	Fitzhugh et al. (1964)	Enlarged hepatocyte, increase in cytplasmic eosinophia with peripheral migration of basophilic granules, and possible increases in vacuolation and bile duct proliferation	LOAEL (0.025 mg/kg/day)	1000	0.00003
Dieldrin	Intermediate	Smith et al. (1976)	Impaired learning of a successive discrimination task	NOAEL (0.01 mg/kg/day)	100	0.0001
	Chronic	Walker et al. (1969)	Liver weight was increased at the LOAEL with progression to parenchymal cell changes with progression to parenchymal cell changes including focal hyperplasia at 0.5 mg/kg/day	NOAEL (0.005 mg/kg/day)	100	0.00005

ATSDR (2002b)

ATSDR developed acute and chronic MRLs for aldrin and intermediate and chronic MRLs for dieldrin. These are described in Table 4.

JMPR (1967, 1971, 1977)

The Joint Meeting on Pesticide Residues (JMPR 1967) concluded that the Acceptable Daily Intake (ADI) for aldrin or dieldrin or the sum of both was 0.0001 mg/kg based on a NOAEL of 0.025 mg/kg-day and an uncertainty factor of 250. It is not clear on what factors JMPR based its uncertainty factor.

The NOAEL of 0.025 mg/kg-day was derived from NOAELs of 0.5 ppm in rats and 1 ppm in dogs. In the rat study (Fitzhugh et al. 1964), rats were given feed containing 0.5, 2, 10, 50, 100 and 150 ppm aldrin or dieldrin for up to 2 years. The liver weights and degree of microscopic lesions increased dose-dependently in all dose levels. The authors did not identify a NOAEL, because increased liver weight to body weight ratios were elevated and a minimal degree of microscopic lesions were reported at the lowest dose of 0.5 ppm. However, JMPR identified 0.5 ppm as the level causing no toxicological effect in rats.

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In the dog study (Treon and Cleveland 1955), groups of 4 dogs (2/sex) were given 1 or 3 ppm dieldrin in their diet for 68 weeks. The dogs in the 3 ppm group had increased liver/body-weight ratio, and one female in this group had renal damage. In the 1 ppm group, livers were enlarged but no histopathological changes were reported. JMPR identified 1 ppm as the level causing no toxicological effect in dogs.

JMPR re-evaluated the toxicity data for aldrin and dieldrin in 1970 and 1977, and the 1967 ADI of 0.0001 mg/kg-day was endorsed (JMPR 1971, 1977).

Health Canada (1994)

Health Canada adopted the JMPR (1967, 1971, 1977) ADI of 0.0001 mg/kg-day for both aldrin and dieldrin and has used it as the basis for deriving allowable levels of these compounds in drinking water.

New Zealand Ministry for the Environment (2010)

The New Zealand Ministry for the Environment adopted the JMPR (1977) ADI of 0.0001 mg/kg-day for dieldrin. The New Zealand assessment of dieldrin questioned the U.S. EPA and ATSDR description of the critical toxic effects of dieldrin. The U.S. EPA (1990) and ATSDR (2002) both state that they used liver cell changes "characteristic of exposure to organochlorine insecticides" reported by Walker et al. 1969 as the toxicological endpoint for defining the LOAEL of 1 ppm. However, the authors of Walker et al. (1969) state that "no changes in liver cell morphology that could be attributed specifically to chlorinated hydrocarbons occurred in rats receiving 1 ppm dieldrin." Therefore the New Zealand reviewers endorsed the Fitzhugh et al. (1964) study as providing the more sensitive endpoint.

DATA PUBLISHED SINCE 1987

As described earlier for cancer outcomes, the scientific literature since 1987 was searched utilizing PubMed for any articles related to exposure, cancer, mortality and disease and aldrin/dieldrin in humans. The following search terms were used: ((aldrin) OR dieldrin) AND ((epidemiological studies) OR cancer OR neoplasm OR carcinogenic OR tumor OR maternal OR diabetes). Two-hundred twenty five (225) potentially relevant references were identified. These references were further screened to identify studies of carcinogenicity related to exposure to aldrin and/or dieldrin in humans or animals. *In vitro* studies, environmental and wildlife monitoring reports, and studies of mixtures with other compounds in animals were excluded. Studies that have been reviewed by ATSDR (2002b) were also excluded. Of the remaining studies, thirty seven references considered useful for further evaluation of both carcinogenic and non-cancer evidence for aldrin and dieldrin were identified.

Human Data

Fourteen noncancer epidemiologic studies of aldrin and/or dieldrin were identified from the PubMed search of epidemiologic literature published since 1987 and not included in the ATSDR (2002b) review. The noncancer epidemiologic studies are described in more detail in Appendix B.

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Two studies (Weisskopf et al. 2010; Louis et al. 2006) and one review (Li et al. 2005) assessed the risk of Parkinson's Disease associated with exposure to pesticides. Weisskopf et al. (2010) found increased serum levels of dieldrin among cases compared to controls (serum levels of many other pesticides including aldrin were not significantly increased). This study relied on serum samples collected between 1968 and 1972 and analyzed in 2005-2007. The study also relies on a questionnaire administered to study participants at the time the serum samples were collected. The questionnaire included questions on smoking status, cholesterol, hypertension, etc. Both the samples and the baseline characteristics (e.g., smoking, hypertension, etc.) could have changed considerably over the 35-year period between collection and analysis. Furthermore the study did not control for risk factors known to be associated with Parkinson's Disease (e.g., family history, genetic factors, head trauma). Li et al. (2005), in a review of the literature on pesticides and Parkinson's Disease including 27 case-control studies, concluded that the epidemiologic data do not provide sufficient evidence to support a causal association. In a study of essential tremor and serum concentrations of six pesticides including dieldrin, the authors were unable to detect any increased risk from dieldrin exposure (Louis et al. 2006).

Risk of diabetes was assessed by two publications. Montgomery et al. (2008) found an increased risk of diagnosed diabetes among participants of the Agricultural Health Study. The odds ratios were elevated but were not statistically significant when stratified by age, state (North Carolina or Iowa), or weight group. The authors do not specify or delineate between type I and II diabetes, which are known to have different etiologies (CDC 2010). A cross sectional analysis using the National Health and Nutrition Examination Survey did not find an association between dieldrin in serum and diagnosed, undiagnosed, or pre-diabetes; aldrin was not evaluated (Everett & Matheson 2010).

A cohort study by Landgren et al. (2009) examined monoclonal gammopathy of undetermined significance (MGUS) and self-reported pesticide use and pesticide concentrations in serum. Among individuals ever reporting exposure to dieldrin, the relationship with MGUS was significant. However, excess risk of MGUS associated with dieldrin was not attenuated when adjustment was made for the use of other pesticides.

Additional studies including a cross sectional study regarding age at menopause, a cross sectional study examining levels of thyroid hormones, a case control study on cryptorchidism, a cohort study on infant's length of gestation, birth weight and crown-heel length, an experimental study on Leydig cell disruption, a cross sectional study on lymphocyte subsets and a cross sectional study on allergic immune response in women and infants all yielded insignificant results regarding aldrin/dieldrin exposure and their corresponding outcomes (Akkina et al. 2004; Asawasinsopon et al. 2006; Damgaard et al. 2006; Fenster et al. 2005; Fowler et al. 2007; Nagayama et al. 2007; Noakes et al. 2006).

The evidence is not sufficient to conclude that a causal association exists between aldrin and/or dieldrin and Parkinson's Disease, diabetes, or MGUS. The studies are not robust and what data

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exist are inconsistent. Studies examining other noncancer endpoints have not found evidence of an effect.

Animal Data

Five animal studies of dieldrin were identified. Three of these were oral gavage studies in mice, and two were intraperitoneal studies in rats. The results are summarized in Table 5.

Four of the five animal studies investigated the effects of dieldrin on perinatal development. Cameron et al (2009) and Foster (2008) each exposed mice to a range of dieldrin doses by oral gavage during gestation and lactation, and both studies showed no effects on birth outcomes. Although the offspring in the Cameron et al (2009) study developed mammary tumors, the strain of mice used was genetically predisposed to develop mammary tumors. The Richardson et al. (2006) study exposed mice to dieldrin perinatally and evaluated specific neurotoxic effects not measured in most developmental toxicity studies. Tarraf et al. (2003) gave rats a single intraperitoneal injection of dieldrin in late-gestation and found effects on dam mammary gland maturation and effects on litter size and pup weight gain. Neither U.S. EPA (1987) nor ATSDR (2002b) reported developmental effects of intraperitoneally-administered dieldrin.

The non-developmental study (Hallegue et al. 2010) investigated the hepatotoxic effects of dieldrin, and the results were consistent with the known hepatoxicity in studies previously reviewed by U.S. EPA (1987) and ATSDR (2002b).

Overall, none of the more recent studies are likely to impact the current hazard assessment of aldrin or dieldrin.

Table 5. Animal studies on Dieldrin published since 1987 that examined noncancer response.

Study	Type of study	Results	Comment
Hallegue et al. 2010	Single IP injection of dieldrin to male and female rats; 3 or 6 mg/kg bw; hepatic effects measured by serum enzymes and histopathological examination.	Dose-dependent increase in relative liver weight; elevated AST, ALT, bilirubin, and LDH; cytoplasmic vacuolation, focal necrosis and nuclear enlargement of hepatocytes.	Consistent with known hepatotoxic effects of dieldrin in rodents.
Cameron et al. 2009 (also described in Table 3).	Oral gavage of dieldrin to FVB-MMTV/neu female mice; 0.45, 2.25, and 4.5 µg/g daily for 5 days prior to mating and once weekly through gestation and lactation.	No effect on litter size, birth weight or the number of pups surviving to weaning.	Dieldrin caused increased tumor burden in genetically predisposed mice.

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Foster et al 2008	Oral gavage of dieldrin to BALB/c mice; 0.45, 2.25, 4.5, and 22.5 µg/g bw throughout mating, pregnancy, and lactation.	Treatments had no effect on fertility parameters in dams or mammary gland morphology at sexual maturity.	
Richardson et al. 2006	Oral gavage of dieldrin to C57BL/6J mice 0.3, 1, or 3 mg/kg every 3 days throughout mating, pregnancy, and lactation.	Altered dopaminergic neurochemistry in the offspring and exacerbated MPTP toxicity.	The authors suggested that perinatal exposure to dieldrin increases the risk of Parkinson's disease.
Tarraf et al. 2003	IP injection of dieldrin to female rats; 2.5 or 15 µM on gestation day 14.	Impaired mammary gland development of dams; reduced litter size; reduced pup weight gain.	

BENCHMARK DOSE

The U.S. EPA (1988, 1990) RfDs for aldrin and dieldrin were derived using a LOAEL and a NOAEL, respectively and uncertainty factors of 1000 and 100 for aldrin and dieldrin, respectively. The current EPA approach would be to use a Benchmark Dose model to determine point of departure. Using the U.S. EPA 's current version of the BMDS software, Tetra Tech derived BMDLs for aldrin and dieldrin of 0.0120675 and 0.00837329 mg/kg-day, respectively. See Appendices C and D for explanations of how the benchmark dose results were derived. Using uncertainty factors of 10 (human intraspecies variability) and 10 (interspecies variability), the RfDs for aldrin and dieldrin would be 0.0001 and 0.00008, respectively. A comparison of these RfDs with those of U.S. EPA (1988, 1990) is made in Table 6.

Table 6. Comparison of U.S. EPA (1988) RfD for Aldrin and U.S. EPA (1990) for Dieldrin with RfDs for Aldrin and Dieldrin derived using a benchmark dose approach

	U.S. EPA (1988, 1990) (mg/kg/day)	Benchmark Dose (mg/kg/day)
Aldrin	0.00003	0.0001
Dieldrin	0.00005	0.00008

DISCUSSION

The U.S. EPA (1988, 1990) RfDs for aldrin and dieldrin are 0.00003 mg/kg-day and 0.00005 mg/kg-day, respectively. The RfDs are based on liver toxicity in rats. The ATSDR chronic MRL values for aldrin and dieldrin are the same as the RfDs. The WHO Allowable Daily Intake (ADI) is roughly 3.3-fold and 2-fold higher than the RfDs for aldrin and dieldrin, respectively.

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The EPA RfD, the ATSDR chronic MRL (oral), and the JMPR ADI for aldrin are all based on the study by Fitzhugh et al. (1964). In this study, rats were fed diets containing 0.5 to 150 ppm for two years (estimated dose levels of 0.025 to 7.5 mg/kg-day). Fitzhugh et al. (1964) described the liver lesions that they observed as "characteristic of chlorinated insecticide poisoning." These lesions included enlarged centrilobular hepatic cells (hypertrophy), with increased cytoplasmic oxyphilia, and peripheral migration of basophilic granules. The U.S. EPA (1988) and ATSDR (2002) identified 0.5 ppm as a LOAEL for aldrin in rats, based on these characteristic organochlorine insecticide lesions. ATSDR (2002) noted that "the changes at 0.5 ppm are consistent with a marked hepatic adaptive response associated with induction of the hepatic mixed function oxidase system and proliferation of smooth endoplasmic reticulum. The observation of hepatocellular hypertrophy is consistent with adaption." Although ATSDR considered the changes to be "adaptive," they still considered the responses to be adverse because the enhanced metabolic activity induced by aldrin could potentiate or inhibit toxic responses to other exogenous substances. This reasoning contradicts interpretations by U.S. EPA (1997a, 1997b, 2000b) that adaptive induction of microsomal enzymes should not be considered adverse.

JMPR considered aldrin and dieldrin interchangeable, due to the rapid biotransformation of aldrin to dieldrin in mammalian systems. When JMPR (1967) reviewed the Fitzhugh et al. (1964) study, they identified 0.5 ppm dieldrin as the NOAEL, noting that the hepatic lesions reported at 0.5 ppm dieldrin were "minimal." The authors of Fitzhugh et al. (1966) classified the lesions seen at 0.5 ppm as "trace or minimal." JMPR (1967) affirmed this NOAEL with a dog study (Treon and Cleveland 1955) in which a diet including 1 ppm dieldrin produced enlarged livers with no histopathological changes. These nontoxic dose levels in the rat and dog studies were both determined by JMPR (1967) to be equivalent to 0.025 mg/kg-day, to which JMPR applied an uncertainty factor of 250 to derive an ADI of 0.0001 mg/kg-day for aldrin and dieldrin combined.

A study by Walker et al. (1969) is the basis of the EPA RfD and the ATSDR chronic MRL (oral) for dieldrin. In their reviews of Walker et al. (1969), the U.S. EPA (1990) and ATSDR (2002) identified 0.1 ppm (0.005 mg/kg-day) dieldrin as the NOAEL and 1 ppm (0.05 mg/kg-day) as the LOAEL. The critical effect was increased liver weight in female rats. The hepatic lesions observed at 1 ppm were not considered by the authors of Walker et al. (1969) to be associated with organochlorine insecticides. Therefore, the LOAEL of 1 ppm determined by U.S. EPA (1990) and ATSDR (2002) is apparently based solely on increased liver weights in female rats. However, increased liver weight without other signs of liver toxicity (e.g., histopathology or clinical chemistry) is an adaptive response to increased metabolism of the chemical and is generally not considered to be an adverse effect (Sipes and Gandolfi 1991; Amacher et al. 1998). The EPA has determined that increased liver weight and hepatoctyte hypertrophy were adaptive non-adverse effects in the IRIS toxicological reviews of chlordane, vinyl chloride, and cumene (U.S. EPA 1997a, 1997b, 2000b). Thus, the NOAEL of the Walker et al. (1969) study would more appropriately be 1 ppm (0.05 mg/kg-day), and the LOAEL should be 10 ppm (0.5 mg/kg-day) where increased liver weights were accompanied by histological changes

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(parenchymal cell changes including focal hyperplasia). Compared to the Walker et al. (1969) study, the study by Fitzhugh et al (1964) appears to provide the more sensitive endpoints for hepatic lesions associated with chronic dieldrin exposure.

Chlordane is an organochlorine pesticide chemically and toxicologically similar to aldrin and dieldrin. In its updated toxicological review of chlordane, U.S. EPA (1997a) did not consider increased liver cell volume (hypertrophy) to be an adverse effect. Hypertrophy is commonly associated with ultrastructural adaptive changes involving metabolic activity due to the presence of the toxicant (Sipes and Gandolfi 1991; Amacher et al. 1998). An adaptive increase in relative liver weight if moderate and transitory is not adverse, but if severe and sustained, leads to adverse effects (Williams and Latropoulos 2002). U.S. EPA (1997a) considered hepatic necrosis to be the most clearly adverse noncancerous lesion for chlordane. Hepatic necrosis was not reported in the chronic and intermediate studies of aldrin and dieldrin. The RfDs for chlordane based on U.S. EPA's updated toxicological review (U.S. EPA 1997), are roughly 8-fold higher (i.e., less toxic) than the previous U.S. EPA RfDs.

In considering how the U.S. EPA would calculate RfD values for aldrin and dieldrin if these compounds were reviewed today, one must take into account the complete data set available since the last reviews and changes in the hazard assessment methodology in common practice at the agency. A review of studies published since the previous U.S. EPA reviews raised no new concerns of systemic toxicity and introduced no endpoints more sensitive than those described in the Fitzhugh et al. (1964) study. In a developmental toxicity study by Richardson et al. (2006) mice exposed to dieldrin perinatally reported possible neurodevelopmental effects. While the Richardson et al. (2006) study raises concerns about potential effects in young children, the California EPA (2007) determined that liver toxicity in adult animals was a more sensitive endpoint when assessing non-cancer risk of dieldrin at school sites in California.

At the time of the previous U.S. EPA reviews of aldrin and dieldrin, the use of benchmark dose modeling to determine point of departure was not in common practice. Under the current U.S. EPA guidelines, benchmark dose modeling is preferred to the NOAEL/LOAEL approach if the data set supports appropriate use of the model. In the current review, liver lesion data for chronic dietary exposure to aldrin and dieldrin provided in the Fitzhugh et al. (1964) study were applied to benchmark dose modeling, using the current version of BMDS software provided by the U.S. EPA. The resulting BMDL values, with appropriate uncertainty factors applied, produced RfD values of 0.0001 mg/kg-day for aldrin and 0.00008 mg/kg-day for dieldrin. Interestingly, these benchmark dose-based RfD values are similar to the ADI of 0.0001 mg/kg-day endorsed by JMPR, Health Canada, and the New Zealand Ministry for the Environment.

SUMMARY

Only the U.S. EPA has classified aldrin and dieldrin as probable human carcinogens. Other U.S. agencies in more recent assessments have not classified aldrin or dieldrin as known or probable human carcinogens. The International Agency for Research on Cancer has determined that

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aldrin and dieldrin cannot be classified as to their carcinogenicity. The World Health Organization has determined that "these chemicals make very little contribution, if any, to the incidence of cancer in humans."

The only cancer dose response for aldrin and dieldrin is that done by the U.S. EPA in 1987 based on liver tumors in mice. It is questionable whether the tumors seen in the mouse are relevant for linear low dose extrapolation to humans. It has been generally agreed that aldrin and dieldrin are nongenotoxic. Furthermore, the carcinogenic response has only been seen in mice and not in other laboratory species.

Assuming that aldrin and dieldrin are carcinogens, the methods currently used by U.S. EPA to estimate cancer dose response would decrease the cancer slope factor for aldrin by 5 fold and the cancer slope factor for dieldrin by 2.3 fold. Although a number of cancer epidemiologic studies have been conducted since the U.S. EPA assessment, there is not enough evidence from these studies to conclude that there is a causal association between exposure to aldrin/dieldrin and an increased risk of cancer in humans.

The selection of the endpoints used for the noncancer assessment by U.S. EPA is controversial. U.S. EPA and ATSDR identified the dose of 0.5 ppm in Fitzhugh et al. (1964) as a Lowest Observed Adverse Effect Level (LOAEL) whereas JMPR considered 0.5 ppm to be a No Observed Adverse Effect Level (NOAEL). ATSDR noted that "the changes at 0.5 ppm are consistent with a marked hepatic adaptive response associated with induction of the hepatic mixed function oxidase system and proliferation of smooth endoplasmic reticulum. The observation of hepatocellular hypertrophy is consistent with adaption." ATSDR considered these changes adverse. U.S. EPA has concluded, however, that adaptive induction of microsomal enzymes should not be considered adverse. U.S. EPA and ATSDR used the increased liver weight in a study on dieldrin by Walker et al. (1969) as the basis to derive the RfD and oral MRL, respectively. U.S. EPA has more recently determined that increased liver weight and hepatoctyte hypertrophy were adaptive non-adverse effects in its assessments of chlordane, vinyl chloride, and cumene (U.S. EPA 1997a, 1997b, 2000b). JMPR considered aldrin and dieldrin to be interchangeable (aldrin is rapidly metabolized to dieldrin in the body) and used Fitzhugh et al. (1964) as the basis for the ADI on aldrin and dieldrin combined. The methods currently used by U.S. EPA to estimate non-cancer dose response would produce RfD values for aldrin and dieldrin that are roughly 3.3-fold and 2-fold higher, respectively, than the current USEPA RfDs. The RfDs that would be derived by the current EPA methodology would also be comparable to the ADI determined by JMPR. Table 7 summarizes the existing EPA Cancer Slope Factors and RfDs for aldrin and dieldrin with those that would be derived using current EPA methodology.

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TETRA TECH

Table 7. Comparison of existing U.S. EPA Cancer Slope Factors/RfDs for aldrin and dieldrin with Cancer Slope Factors/RfDs that would be derived using existing EPA methodology

	U.S. EPA (1987) (mg/kg-day)	Benchmark Dose (mg/kg-day)
	Cancer	
Aldrin	**17**	**3.38**
Dieldrin	**16**	**6.99**
	Non-cancer	
Aldrin	**0.00003**	**0.0001**
Dieldrin	**0.00005**	**0.00008**

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Appendix A-1: Benchmark Dose Derivation of a Cancer Slope Factor for Aldrin

Introduction

In the IRIS review of aldrin (CAS No. 309-00-2), the U.S. EPA calculated an oral cancer slope factor of 17 $(mg/kg\text{-}day)^{-1}$. This oral cancer slope factor was the geometric mean of two slope factors based on data published by Davis 1965 (re-evaluated by Reuber; cited in Epstein 1975) and NCI 1978. The Davis 1965 study exposed male and female C_3H mice to 0 or 10 ppm aldrin in diet for up to 104 weeks (2 years). IRIS calculated a cancer slope factor of 23 $(mg/kg\text{-}day)^{-1}$ for this study, based on increases in liver tumors in aldrin-exposed mice. The NCI 1978 study exposed male B6C3F1 mice to 0, 4, or 8 ppm aldrin in diet and female B6C3F1 mice to 0, 3, or 6 ppm aldrin, each sex for 80 weeks followed by 10 to 13 weeks of post-exposure observation. IRIS calculated a cancer slope factor of 12 $(mg/kg\text{-}day)^{-1}$ for this study, based on dose-dependent increases in liver tumors in aldrin-exposed male mice. Aldrin-exposed female mice did not show any increase in liver tumor incidence.

Methods

A benchmark dose (BMD) approach was used to derive a new cancer slope factor for aldrin. The US EPA's BMDS 2.1.2 software package was used. BMDS 2.1.2 is the latest version of the BMDS series, released by EPA in June 2010. Benchmark dose analysis requires a control and at least two treatment dose levels. Because the Davis 1965 study only used one treatment dose level, this data set is not appropriate for benchmark dose analysis. The NCI 1978 data set includes a control group and two treatment dose levels and can be applied to a benchmark dose model. The NCI 1978 data as presented in IRIS 1993 were as follows:

Dose (ppm in mouse diet)	Human Equivalent Dose (mg/kg-day)	Tumor Incidence
0	0	3/20
4	0.04	16/49
8	0.08	25/45

Recalculation of Human Equivalent Dose

To arrive at a human equivalent dose from the animal studies, U.S. EPA historically multiplied the doses administered to the animals by the ratio of the animal to human weight to the 1/3 power. The current approach by U.S. EPA is to apply the "3/4 power" assumption in which the human equivalent dose, in units of mg/kg-day, is equal to the animal dose × (animal weight in kg/70 kg) $^{1/4}$ (U.S. EPA 1992, 2005).

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Assumptions:

- Mouse BW = 0.03 kg (IRIS page for Aldrin)
- Food consumption rate = 6400 mg/day (based on EPA reference values, B6C3F1 mouse, male, chronic; EPA 1982)
- Human Equivalent Dose = Mouse Dose x $(0.03\ kg/70\ kg)^{1/4}$ = mouse dose x 0.143882

Calculations:

Mouse dose for 4 ppm = (4/1,000,000) x (6400 mg/0.03 kg-day) = 0.853 mg/kg-day

Human Equivalent Dose for 4 ppm = 0.853 mg/kg-day x 0.143882 = 0.12273 mg/kg-day

Mouse dose for 8 ppm = (8/1,000,000) x (6400 mg/0.03 kg-day) = 1.706 mg/kg-day

Human Equivalent Dose for 8 ppm = 1.706 mg/kg-day x 0.143882 = 0.24546 mg/kg-day

NCI 1978 data with Revised HED

Dose (ppm in mouse diet)	Human Equivalent Dose (mg/kg-day)	Tumor Incidence
0	0	3/20
4	0.12273	16/49
8	0.24546	25/45

Benchmark Dose Models

Tumor incidence data are quantal data that the EPA (2000a) recommends for use in a Dichotomous Multistage-Cancer Model. In the analyses for aldrin, dose levels in Human Equivalent Dose were entered with the sample size (N) and tumor incidence data were entered into the BMDS 2.1.2 spreadsheet. The Dichotomous Model Multistage-Cancer Model allows for variation of the Degree of Polynomial to find the best curve fit. In a data set containing two treatment dose levels, the Degree of Polynomial can be set to either 1 or 2. In the first run of the model, Degree of Polynomial was set to 1, and in the second run, this value was changed to 2.

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Results

A summary of the BMD analyses of the liver tumor incidence data is presented in the table below, and the BMDS input data, model parameters, and output are presented in subsequent pages. The first run (Degree of Polynomial =1) produced a curve with a good visual fit, and the mathematical tests for a good fit produced values within the acceptable ranges (see table footnotes). The second run, while providing a visually perfect for to the data points, the P-value of "NA" is difficult to interpret. Based on these factors, the first run is deemed to have the better curve fit, and the cancer slope factor for the NCI 1978 male mouse liver tumor incidence data is **3.39715 (mg/kg-day)$^{-1}$**.

Summary of Dichotomous Model Multistage-Cancer Model for Aldrin (NCI 1978 male liver tumor data)

Run	Degree of Polynomial	P-value[1]	Highest Scaled Residual[2]	AIC[2]	Visual Assessment of Curve to Data Points[4]	BMD	BMDL[5]	Cancer Slope Factor
1	1	0.5127	-0.501	145.072	Good	**0.0426138**	**0.0294365**	**3.39715**
2	2	NA	0.000	146.641	Excellent	0.0674753	0.0302286	3.30812

1 For the model to be acceptable, P-value must be > 0.1.
2 Scaled residuals report the gap between the curve line and the actual data points; for the model to be acceptable, all scaled residuals must have an absolute value of < 2.
3 The Akaike Information Coefficient (AIC) is used for comparison between models; generally, a lower AIC value indicates a better curve fit to the data.
4 Even when the numbers indicate a good curve fit, a visual inspection of the graph is important to ensure the curve is not wavy or contains other aberrations.
5 BMDL = Lower one-sided confidence limit on the BMD.

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BMDS Input Data:

Model Type: Dichotomous | Model Name: Multistage-Cancer

	Dose	N	Tumor_Incidence	Col4
1	0	20	3	
2	0.12273	49	16	
3	0.24546	45	25	
4				

BMDS Model Parameters – First Run:

<<Column Assignments>>

Dose	Dose
# Subjects in Dose Group	N
Incidence	
% Positive	

<<Optimizer Assignments>>

Iteration	250
Relative Function	1.00E-08
Parameter	1.00E-08

<<Parameter Assignments>>

Parameters	Options	Values
Background	Default	
Beta1	Default	
Beta2	Default	

<<Other Assignments>>

Risk Type	Extra
BMR	0.1000
Confidence Level	0.95
BMD Calculation	☑
BMDL Curve. Calc.	☐
Dose Groups	
Degree of Polynomial	1

User Notes:

Data File: Show

Out File Name: C:\USEPA\BMDS212\Data\msc_UntitledData_Setting.out Set

Run

Save | Save As ... | Set Values To Default | Optimize Initial Param. Values | Close

Multistage-Cancer->Dichotomous

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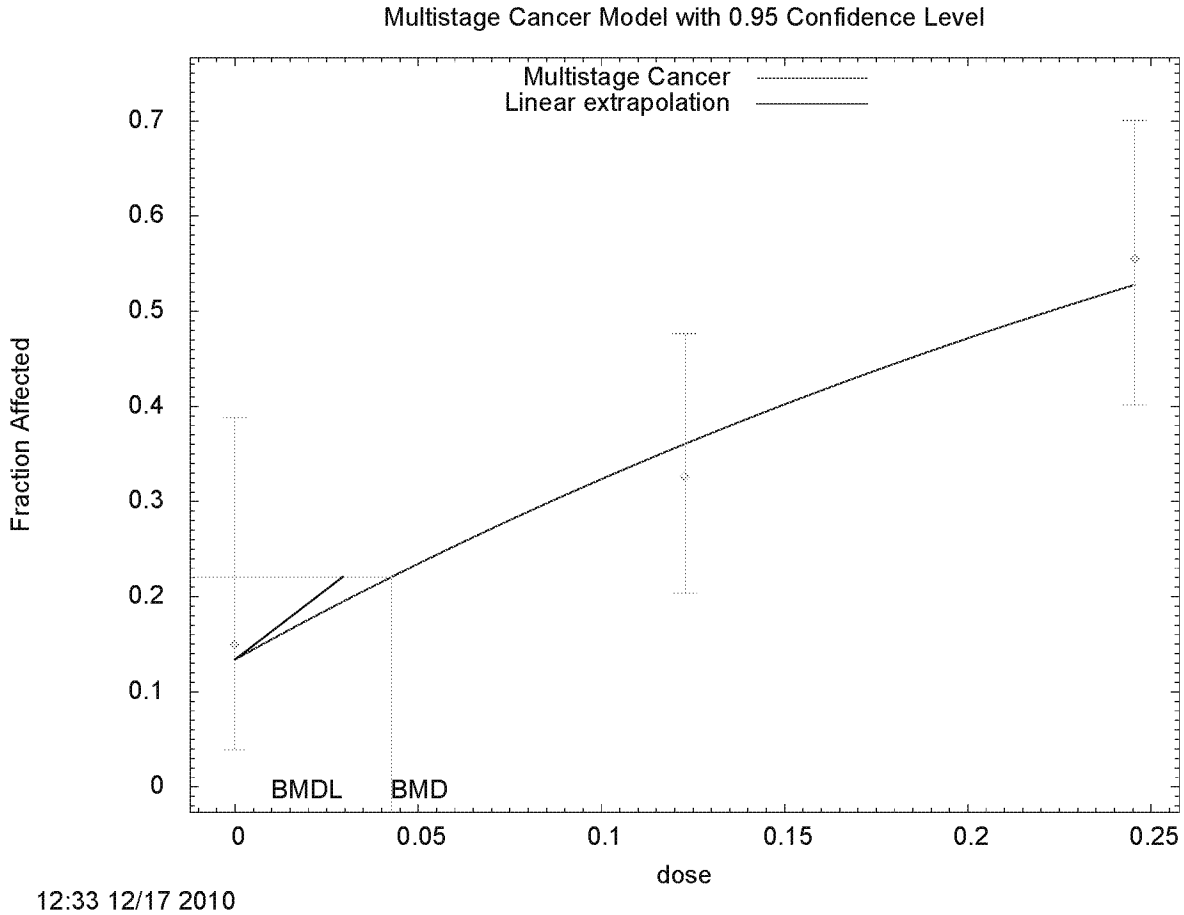
First Run Output (Degree of Polynomial = 1)




```
=====================================================================
        Multistage Cancer Model. (Version: 1.9;  Date: 05/26/2010)
        Input Data File: C:/USEPA/BMDS212/Data/msc_UntitledData_Setting.(d)
        Gnuplot Plotting File:  C:/USEPA/BMDS212/Data/msc_UntitledData_Setting.plt
                                                Fri Dec 17 12:33:28 2010
=====================================================================

BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the probability function is:

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

  The parameter betas are restricted to be positive


  Dependent variable = Tumor_Incidence
  Independent variable = Dose

Total number of observations = 3
Total number of records with missing values = 0
```

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Total number of parameters in model = 2
Total number of specified parameters = 0
Degree of polynomial = 1

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

Default Initial Parameter Values
Background = 0.123701
Beta(1) = 2.64162

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.8
Beta(1)	-0.8	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.134329	*	*	*
Beta(1)	2.47245	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-70.3205	3			
Fitted model	-70.5362	2	0.431408	1	0.5113
Reduced model	-76.0276	1	11.4143	2	0.003322

AIC: 145.072

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1343	2.687	3.000	20	0.206
0.1227	0.3609	17.684	16.000	49	-0.501
0.2455	0.5282	23.768	25.000	45	0.368

Chi^2 = 0.43 d.f. = 1 P-value = 0.5127

Benchmark Dose Computation

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Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.0426138

BMDL = 0.0294365

BMDU = 0.0797552

Taken together, (0.0294365, 0.0797552) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 3.39715

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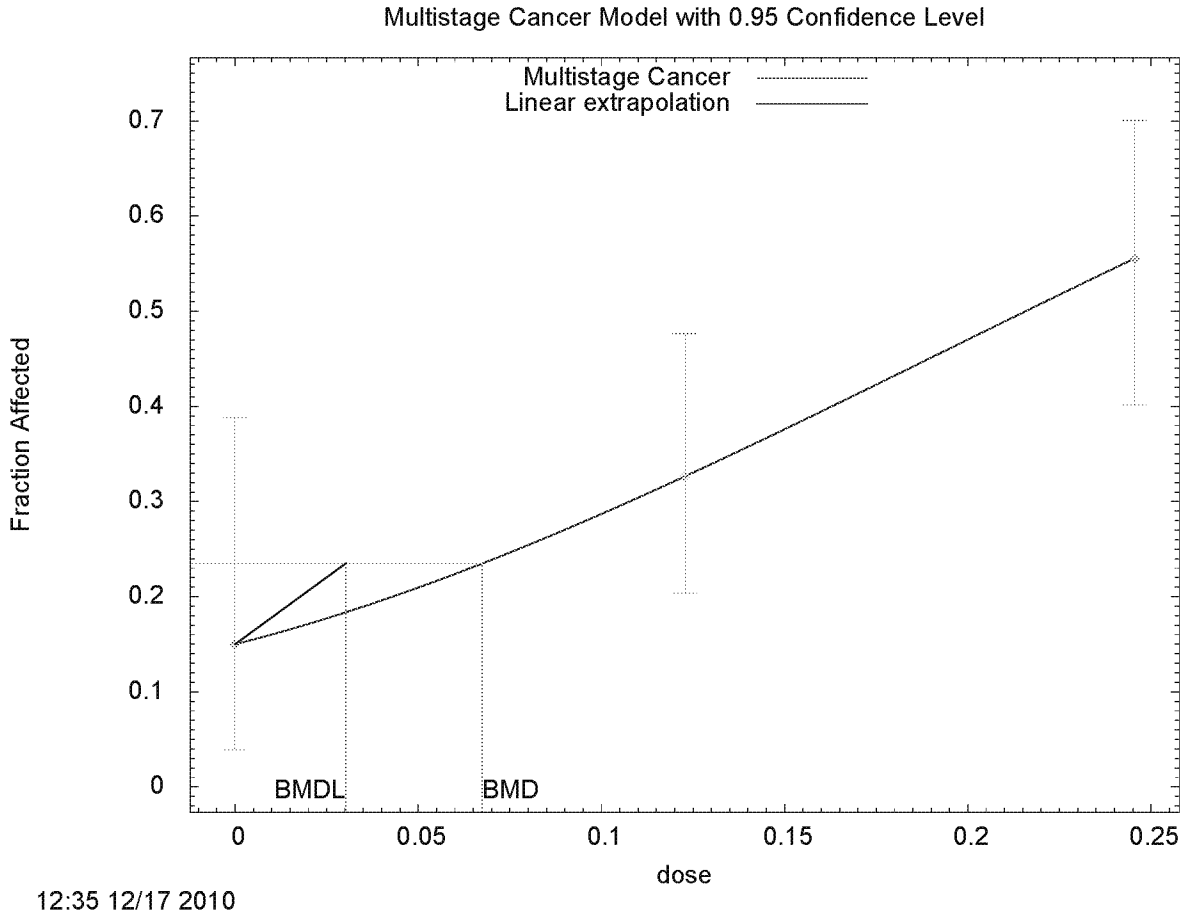
Second Run Output (Degree of Polynomial = 2)




```
=====================================================================
        Multistage Cancer Model. (Version: 1.9;  Date: 05/26/2010)
        Input Data File: C:/USEPA/BMDS212/Data/msc_UntitledData_Setting.(d)
        Gnuplot Plotting File:  C:/USEPA/BMDS212/Data/msc_UntitledData_Setting.plt
                                          Fri Dec 17 12:35:12 2010
=====================================================================

BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the probability function is:

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

  The parameter betas are restricted to be positive


  Dependent variable = Tumor_Incidence
  Independent variable = Dose

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

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Total number of specified parameters = 0
Degree of polynomial = 2

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

Default Initial Parameter Values

Background =	0.15
Beta(1) =	1.15198
Beta(2) =	6.06877

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)	Beta(2)
Background	1	-0.71	0.51
Beta(1)	-0.71	1	-0.95
Beta(2)	0.51	-0.95	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.15	*	*	*
Beta(1)	1.15198	*	*	*
Beta(2)	6.06877	*	*	*

* - Indicates that this value is not calculated.

Error in computing chi-square; returning 2

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-70.3205	3			
Fitted model	-70.3205	3	0	0	NA
Reduced model	-76.0276	1	11.4143	2	0.003322

AIC: 146.641

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1500	3.000	3.000	20	-0.000
0.1227	0.3265	16.000	16.000	49	0.000
0.2455	0.5556	25.000	25.000	45	0.000

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

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.0674753

BMDL = 0.0302286

BMDU = 0.137475

Taken together, (0.0302286, 0.137475) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 3.30812

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Appendix A-2: Benchmark Dose Derivation of a Cancer Slope Factor for Dieldrin

Introduction

In the IRIS 1993 review of dieldrin (CAS No. 60-57-1), the U.S. EPA calculated an oral cancer slope factor of 16 $(mg/kg\text{-}day)^{-1}$. This oral cancer slope factor was the geometric mean of 13 slope factors derived from studies of chronic oral (dietary) exposure to dieldrin in mice with dose-related increases in incidence of liver tumors. The table below lists the data sets that IRIS used to calculate its slope factor value. The data sets in bolded type within the table (Walker et al. 1972 and NCI 1978) had adequate study designs for analysis to recalculate slope factors based on benchmark dose modeling.

Sex, Strain	Dose Levels (ppm)	IRIS-calculated Slope Factor	Reference
Male, C3H	0, 10	22	Davis (1965), reevaluated by Reuber 1974 (cited in Epstein 1975)
Female, C3H	0, 10	25	Davis (1965), reevaluated by Reuber 1974 (cited in Epstein 1975)
Male, CF1	**0, 0.1, 1, 10**	**25**	**Walker et al 1972**
Female, CF1	**0, 0.1, 1, 10**	**28**	**Walker et al 1972**
Male, CF1	**0, 1.25, 2.5, 5, 10, 20**	**15**	**Walker et al 1972**
Female, CF1	**0, 1.25, 2.5, 5, 10, 20**	**7.1**	**Walker et al 1972**
Male, CF1	0, 10	55	Thorpe and Walker 1973
Female, CF1	0, 10	26	Thorpe and Walker 1973
Male, B6C3F1	**0, 2.5, 5**	**9.8**	**NCI (1978)**
Male, CF1	0, 10	18	Tennekes et al. 1981
Male, C57B1/6J	0, 10	7.4	Meierhenry et al. 1983
Male, C3H/He	0, 10	8.5	Meierhenry et al. 1983
Male, B6C3F1	0, 10	11	Meierhenry et al. 1983

Methods

A benchmark dose (BMD) approach was used to derive new cancer slope factor for dieldrin. The US EPA's BMDS 2.1.2 software package was used. BMDS 2.1.2 is the latest version of the BMDS series, released by EPA in June 2010. Benchmark dose analysis requires a control and at least two treatment dose levels. Because the studies by Davis 1965, Thorpe and Walker 1973, Tennekes et al 1981, and Meierhenry et al. 1983 each only used one treatment dose level, these data sets are not appropriate for benchmark dose analysis. Each of the Walker et al 1972 and NCI 1978 data sets includes a control group and two or more treatment dose levels and can be applied to a benchmark dose model.

Walker et al. 1972 presented results of two chronic dieldrin experiments in mice: in one experiment, mice of both sexes were exposed to dietary dieldrin for 132 weeks; in the other mice of both sexes were exposed for 128 weeks.

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132-Week Male Mouse Tumor Incidence Data from Walker 1973

Dose (ppm in mouse diet)	Human Equivalent Dose[1] (mg/kg-day)	N	% Mice with Tumors
0	0	288	20
0.1	0.002607	124	26
1.0	0.02607	111	31
10.0	0.2607	94	94

1 See *Calculation of Human Equivalent Dose* section below.

132-Week Female Mouse Tumor Incidence Data from Walker 1973

Dose (ppm in mouse diet)	Human Equivalent Dose[1] (mg/kg-day)	N	% Mice with Tumors
0	0	297	13
0.1	0.0025895	90	27
1.0	0.025895	87	37
10.0	0.25895	148	92

1 See *Calculation of Human Equivalent Dose* section below.

128-Week Male Mouse Tumor Incidence Data from Walker 1973

Dose (ppm in mouse diet)	Human Equivalent Dose[1] (mg/kg-day)	N	% Mice with Tumors
0	0	78	12
1.25	0.032579	30	20
2.5	0.065158	30	43
5.0	0.13032	30	87
10.0	0.26063	11	45
20.0	0.52127	17	71

1 See *Calculation of Human Equivalent Dose* section below.

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128-Week Female Mouse Tumor Incidence Data from Walker 1973

Dose (ppm in mouse diet)	Human Equivalent Dose[1] (mg/kg-day)	N	% Mice with Tumors
0	0	78	10
1.25	0.03238	30	17
2.5	0.06476	28	43
5.0	0.12952	30	60
10.0	0.25903	17	53
20.0	0.51807	21	38

1 See *Calculation of Human Equivalent Dose* section below.

The NCI 1978 study exposed male and female mice for 80 weeks. The female mice did not show a dose-related increase in liver tumor incidences, so only the data from exposure to male mice were analysed.

80-Week Male Mouse Tumor Incidence Data from NCI 1978

Dose (ppm in mouse diet)	Human Equivalent Dose[1] (mg/kg-day)	N	Number of Mice with Tumors
0	0	20	3
6.1	0.07674	49	16
13.8	0.1535	46	25

1 See *Calculation of Human Equivalent Dose* section below.

Calculation of Human Equivalent Dose

To arrive at a human equivalent dose from the animal studies, U.S. EPA historically multiplied the doses administered to the animals by the ratio of the animal to human weight to the 1/3 power. The current approach by U.S. EPA is to apply the "3/4 power" assumption in which the human equivalent dose, in units of mg/kg-day, is equal to the animal dose × (animal weight in kg/70 kg) $^{1/4}$ (US EPA 1992, 2005).

Assumptions:

- Male Mouse BW = 0.0373 kg (based on EPA reference values, B6C3F1 mouse, male, chronic; EPA 1982)
- Female mouse BW = 0.0353 kg (based on EPA reference values, B6C3F1 mouse, female, chronic; EPA 1982)

- Food consumption rate = 6400 mg/day (based on EPA reference values, B6C3F1 mouse, male, chronic; EPA 1982)

Benchmark Dose Models

Tumor incidence data are quantal data that the EPA (2000) recommends for use in a Dichotomous Multistage-Cancer Model. Each data set in the above tables was run separately. In the analyses for each data set, dose levels in Human Equivalent Dose were entered with the sample size (N) and tumor incidence data were entered into a BMDS 2.1.2 spreadsheet. The Dichotomous Model Multistage-Cancer Model allows for variation of the Degree of Polynomial to find the best curve fit. If an adequate curve fit cannot be created by manipulation of the Degrees of Polynomial, this may be because the program is trying to fit the curve to the higher dose groups, however the focus in BMDS modeling should be in the range of the lower dose levels. It is therefore sometimes appropriate to exclude data at the higher dose level(s) in order to get a better curve fit at the lower dose levels. However, at least two dose levels above control must remain in the data set.

Results

The BMDS output of the benchmark dose analyses for each of the data sets is presented after the References section. Below are summaries of the output used for comparison of output results to determine the best-fit curve and thus the best benchmark dose-derived cancer slope value for each data set. Explanations of the curve-fit evaluation criteria are in the table footnotes below. Within the tables, P-value and scaled residual values which are acceptable are identified in green text, and those which are not acceptable are identified in red text.

132-Week Male Mouse Tumor Incidence Data from Walker 1973

The 132-week male mouse tumor incidence data from Walker 1973 was analysed in the BMDS 2.1.2 program in two runs, with Degree of Polynomial respectively set to 2 or 3. Both runs produced acceptable curve-fit evaluation results. Based on the comparison of Akaike Information Coefficient (AIC) values, Run 2 indicated the better curve-fit. BMD-derived cancer slope factor is **9.56246** $(mg/kg\text{-}d)^{-1}$.

Run #	Data Set	Degree of Polynomial	Curve-Fit Acceptance			BMD	BMD-derived CSF
			P-value[1]	Highest Scaled Residual[2]	AIC[3]		
1	All	2	0.2477	1.040	648.896	0.0204274	9.60453
2	All	3	0.2557	1.022	648.85	0.0201651	**9.56246**

1 For the model to be acceptable, P-value must be > 0.1.
2 Scaled residuals report the gap between the curve line and the actual data points; for the model to be acceptable, all scaled residuals must have an absolute value of < 2.
3 The Akaike Information Coefficient (AIC) is used for comparison between models; a lower AIC value indicates a better curve fit to the data.

TETRA TECH

132-Week Female Mouse Tumor Incidence Data from Walker 1973

The 132-week female mouse tumor incidence data from Walker 1973 was analysed in the BMDS 2.1.2 program in five runs, with Degree of Polynomial set to 1, 2, or 3 with the full data set and 1 or 2 with the highest dose excluded. None of the runs produced a curve with an acceptable fit to the data set. A benchmark dose-derived cancer slope factor was not calculable for this data set.

Run	Data Set	Degree of Polynomial	Curve - Fit Acceptance			BMD	BMD-derived CSF
			P-value[1]	Highest Scaled Residual[2]	AIC[3]		
1	all	1	0.0235	2.333	534.514	0.0108277	11.1299
2	all	2	0.0235	2.333	534.514	0.0108277	11.1299
3	all	3	0.0235	2.333	534.514	0.0108277	11.1299
4	without top dose	1	0.0117	2.319	455.422	0.00826961	18.0876
5	without top dose	2	0.0117	2.319	455.422	0.00826961	18.0876

1 For the model to be acceptable, P-value must be > 0.1.
2 Scaled residuals report the gap between the curve line and the actual data points; for the model to be acceptable, all scaled residuals must have an absolute value of < 2.
3 The Akaike Information Coefficient (AIC) is used for comparison between models; a lower AIC value indicates a better curve fit to the data.

128-Week Male Mouse Tumor Incidence Data from Walker 1973

The 128-week male mouse tumor incidence data from Walker 1973 was analysed in the BMDS 2.1.2 program in 10 runs. Using the complete data set with Degree of Polynomial respectively set to 1, 2, 3, or 4 each produced the exact same curve, and the curve-fit acceptance criteria were not met. Removal of the highest dose level did not improve the curve fit with the full range of Degree of Polynomial (1-4). In order to improve the curve fit in the lower dose level range, the data set was run again with the top two dose levels excluded. Removal of the top two dose levels produced a curve with acceptable curve-fit results, and Degree of Polynomial values of 2 or 3 produced identical results. Removal of the highest dose levels is justifiable, because the tumor incidence dose-dependently increased up to 5 ppm and then decreased at 10 and 20 ppm. This decrease in tumor incidence at the higher dose levels is likely due to the higher mortality rates at these dose levels, thus the dose-response curve for tumor incidence had an irregular shape. Removal of these top two dose levels produced a more normal dose-response curve and a better curve fit. BMD-derived cancer slope factor is **5.932 (mg/kg-d)$^{-1}$**.

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Run	Data Set	Degree of Polynomial	Curve-Fit Acceptance			BMD	BMD-derived CSF
			P-value[1]	Highest Scaled Residual[2]	AIC[3]		
1	All	1/2/3/4	0.0000	-2.407	218.672	0.0265497	5.11612
2	Without top dose	1/2/3/4	0.0002	-3.050	190.494	0.0178307	7.55696
3	Without top 2 doses	2/3	0.9282	0.306	153.953	0.0317161	**5.932**

1 For the model to be acceptable, P-value must be > 0.1.
2 Scaled residuals report the gap between the curve line and the actual data points; for the model to be acceptable, all scaled residuals must have an absolute value of < 2.
3 The Akaike Information Coefficient (AIC) is used for comparison between models; a lower AIC value indicates a better curve fit to the data.

128-Week Female Mouse Tumor Incidence Data from Walker 1973

The 128-week female mouse tumor incidence data from Walker 1973 was analysed in the BMDS 2.1.2 program in eight runs. Using the complete data set with Degree of Polynomial respectively set to 1, 2, 3, or 4 each produced the exact same curve, and the curve-fit acceptance criteria were not met. Exclusion of the highest dose level improved the curve fit with Degree of Polynomial set to 2 or 3, with identical results. Exclusion of the top two dose levels produced a curve with acceptable curve-fit results, and Degree of Polynomial values of 2 or 3 produced identical results. Removal of the highest dose levels is justifiable, because the tumor incidence dose-dependently increased up to 5 ppm and then decreased at 10 and 20 ppm. This decrease in tumor incidence at the higher dose levels is likely due to the higher mortality rates at these dose levels, thus the dose-response curve for tumor incidence had an irregular shape. Removal of these top two dose levels produced a more normal dose-response curve and a better curve fit. Because exclusion of the top dose only and the top two doses each produced acceptable curve fit results, the comparison is decided by the AIC value, which indicated that the exclusion of the top two dose levels produced the better curve fit. BMD-derived cancer slope factor is **7.96094(mg/kg-d)$^{-1}$**.

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Run #	Data Set	Degree of Polynomial	Curve-Fit Acceptance			BMD	BMD-derived CSF
			P-value[1]	Highest Scaled Residual[2]	AIC[3]		
1	All	1/2/3/4	0.0001	3.243	233.07	0.063535	2.43635
2	Without top dose	2/3	0.1035	1.177	185.673	0.0231772	5.8833
3	Without top 2 doses	2/3	0.2667	0.729	159.398	0.0218267	**7.96094**

1 For the model to be acceptable, P-value must be > 0.1.
2 Scaled residuals report the gap between the curve line and the actual data points; for the model to be acceptable, all scaled residuals must have an absolute value of < 2.
3 The Akaike Information Coefficient (AIC) is used for comparison between models; a lower AIC value indicates a better curve fit to the data.

80-Week Male Mouse Tumor Incidence Data from NCI 1978

The 80-week male mouse tumor incidence data from Walker 1973 was analysed in the BMDS 2.1.2 program in eight runs. A summary of the BMD analyses of the liver tumor incidence data is presented in the table below, and the BMDS input data, model parameters, and output are presented in subsequent pages. The first run (Degree of Polynomial =1) produced a curve with a good visual fir, and the mathematical tests for a good fit produced values within the acceptable ranges (see table footnotes). The second run, while providing a visually perfect for to the data points, the P-value of "NA" is difficult to interpret. Based on these factors, the first run is deemed to have the better curve fit, and the cancer slope factor for the NCI 1978 male mouse liver tumor incidence data is **5.29719 (mg/kg-day)$^{-1}$**.

Run #	Data Set	Degree of Polynomial	Curve-Fit Acceptance			BMD	BMD-derived CSF
			P-value[1]	Highest Scaled Residual[2]	AIC[3]		
1	All	1	0.5714	-0.435	146.558	**0.027485**	**5.29719**
2	All	2	NA	0.000	148.236	0.0411225	5.19367

1 For the model to be acceptable, P-value must be > 0.1.
2 Scaled residuals report the gap between the curve line and the actual data points; for the model to be acceptable, all scaled residuals must have an absolute value of < 2.
3 The Akaike Information Coefficient (AIC) is used for comparison between models; a lower AIC value indicates a better curve fit to the data.

TETRA TECH

Conclusion

Below is a comparison of the EPA-IRIS 1993 cancer slope factors for dieldrin with the cancer slope factors derived by benchmark dose and adjusted to human equivalent doses derived by scaling to the ¾ power.

Reference for Data Set (Subjects)	Dose levels in Human Equivalent Dose (mg/kg-day)	Best Curve Fit Data		BMD	BMDL	BMD-Based Cancer Slope Factor (mg/kg-day)$^{-1}$	U.S. EPA 1987 Cancer Slope Factor (mg/kg-day)$^{-1}$
		P value	Highest scaled residual				
NCI 1978 (male B6C3F1 mice)	0 0.07674 0.1535	0.5714	-0.435	0.027485	0.0188779	5.29719	9.8
Walker et al. 1972 male CF1 mice)	0 0.002607 0.02607 0.2607	0.2557	1.022	0.0201651	0.0104576	9.56246	25
Walker et al. 1972 male CF1 mice)	0 0.02579 0.065158 0.13032	0.9282	0.306	0.0317161	0.0168577	5.932	15
Walker et al. 1972 female CF1 mice)	0 0.03238 0.06476 0.12952	0.2667	0.729	0.0218267	0.0125613	7.96094	26
Geometric mean of four BMD-based cancer slope factors						**6.99351**	
Geometric mean of 13 cancer slope factors reported by EPA 1987							**16**

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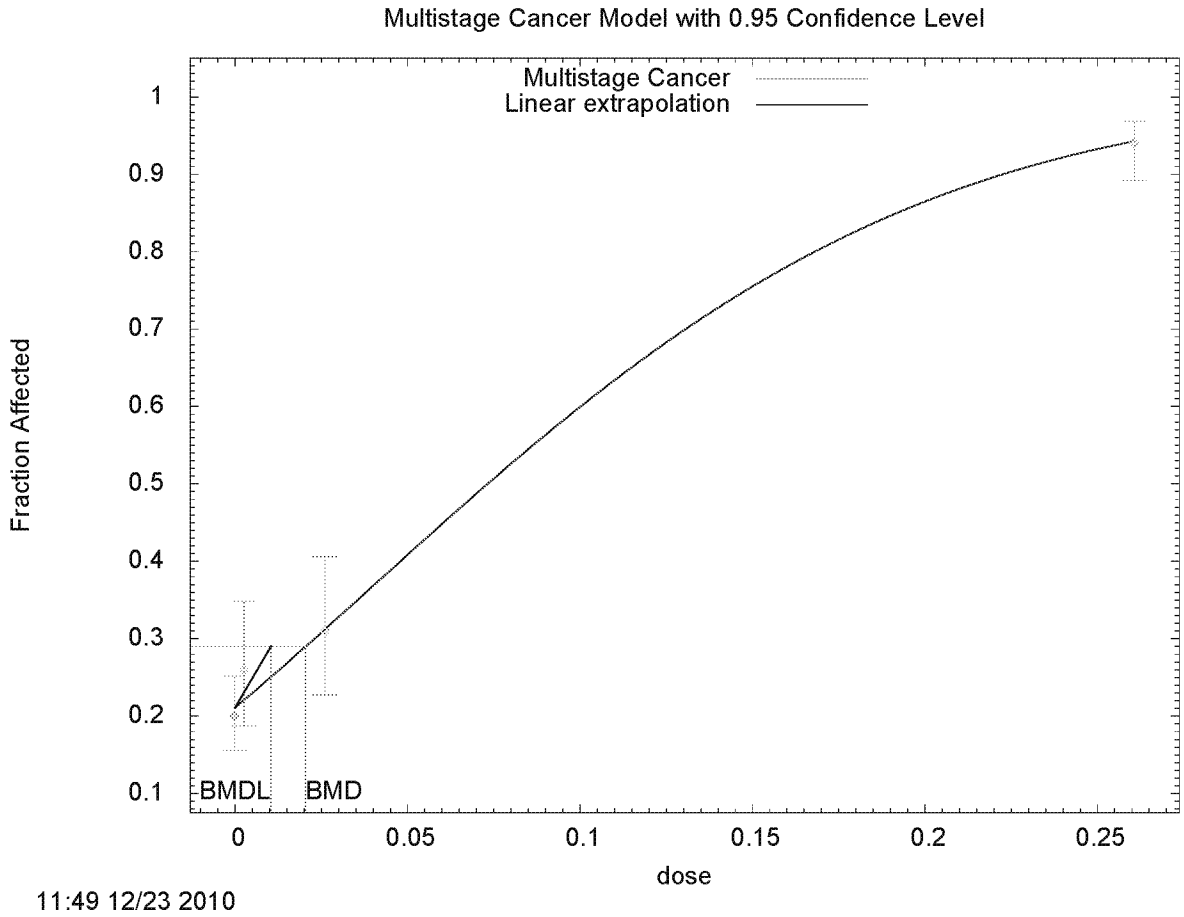
BMDS Output

132-Week Male Mouse Tumor Incidence Data from Walker 197 - First Run (Degree of Polyniomial = 2):




```
=====================================================================
        Multistage Cancer Model. (Version: 1.9;  Date: 05/26/2010)
        Input Data File: C:/USEPA/BMDS212/Data/msc_UntitledData_Setting.(d)
        Gnuplot Plotting File:  C:/USEPA/BMDS212/Data/msc_UntitledData_Setting.plt
                                                  Thu Dec 23 11:49:42 2010
=====================================================================

BMDS_Model_Run
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  The form of the probability function is:

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

  The parameter betas are restricted to be positive
```

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TETRATECH

Dependent variable = %_Tumors
Independent variable = Dose

Total number of observations = 4
Total number of records with missing values = 0
Total number of parameters in model = 3
Total number of specified parameters = 0
Degree of polynomial = 2

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

Default Initial Parameter Values

Background =	0.224973
Beta(1) =	4.02918
Beta(2) =	22.1897

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)	Beta(2)
Background	1	-0.5	0.45
Beta(1)	-0.5	1	-0.98
Beta(2)	0.45	-0.98	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.211425	*	*	*
Beta(1)	4.741	*	*	*
Beta(2)	20.404	*	*	*

* - Indicates that this value is not calculated.

Warning: Likelihood for the fitted model larger than the Likelihood for the full model.
Error in computing chi-square; returning 2

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-323.841	4			
Fitted model	-321.448	3	-4.78713	1	2
Reduced model	-474.224	1	300.765	3	<.0001

AIC: 648.896

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TETRATECH

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.2114	60.890	57.600	288	-0.475
0.0026	0.2212	27.431	32.240	124	1.040
0.0261	0.3127	34.710	34.410	111	-0.062
0.2607	0.9427	165.923	165.440	176	-0.157

Chi^2 = 1.34 d.f. = 1 P-value = 0.2477

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.0204274

BMDL = 0.0104118

BMDU = 0.0518688

Taken together, (0.0104118, 0.0518688) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 9.60453

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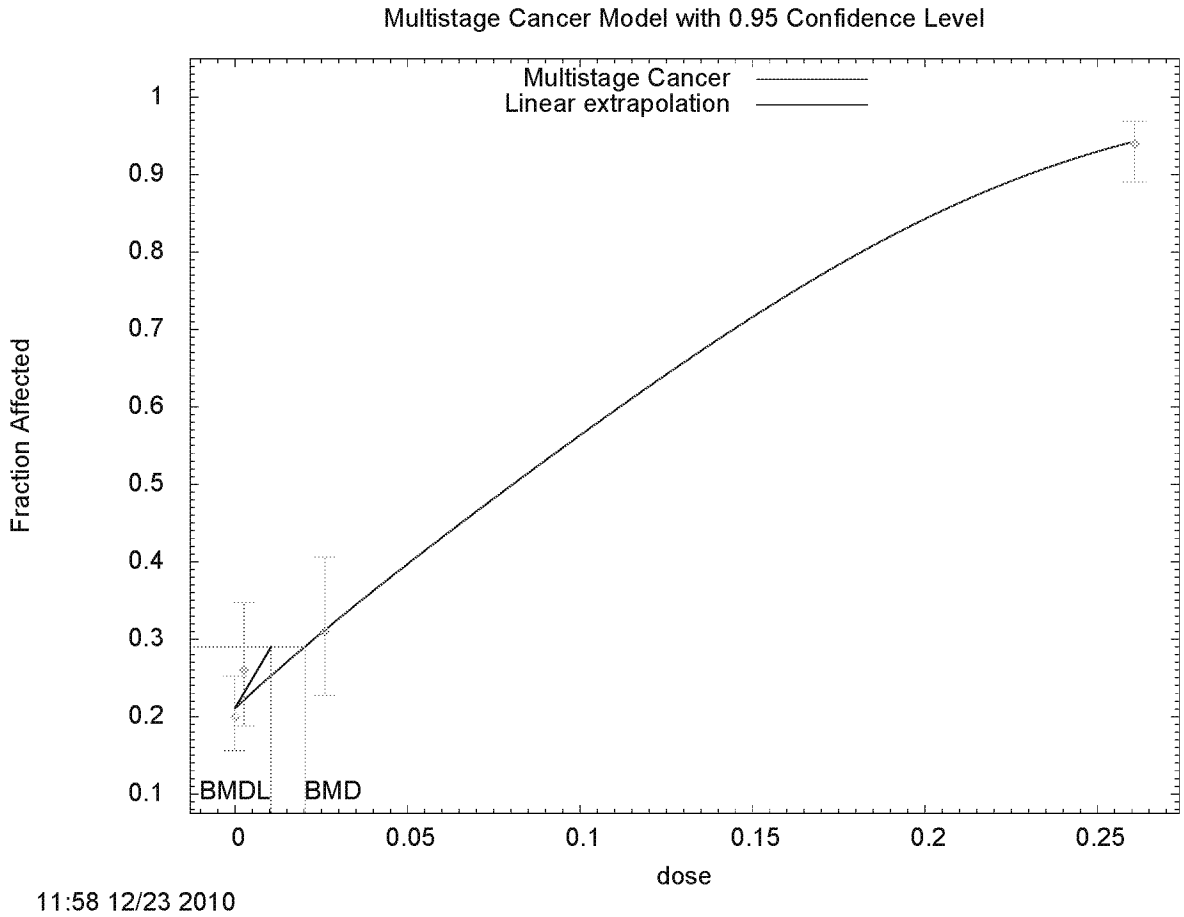
TETRA TECH

132-Week Male Mouse Tumor Incidence Data from Walker 197 - First Run (Degree of Polyniomial = 3):




```
=====================================================================
        Multistage Cancer Model. (Version: 1.9;  Date: 05/26/2010)
        Input Data File: C:/USEPA/BMDS212/Data/msc_UntitledData_Setting.(d)
        Gnuplot Plotting File:  C:/USEPA/BMDS212/Data/msc_UntitledData_Setting.plt
                                          Thu Dec 23 11:58:36 2010
=====================================================================

BMDS_Model_Run
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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 = %_Tumors
  Independent variable = Dose

Total number of observations = 4
```

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TETRA TECH

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 =	0.224641
Beta(1) =	4.55611
Beta(2) =	0
Beta(3) =	77.3888

Asymptotic Correlation Matrix of Parameter Estimates

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

	Background	Beta(1)	Beta(3)
Background	1	-0.49	0.45
Beta(1)	-0.49	1	-0.97
Beta(3)	0.45	-0.97	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.211258	*	*	*
Beta(1)	5.19575	*	*	*
Beta(2)	0	*	*	*
Beta(3)	71.6863	*	*	*

* - Indicates that this value is not calculated.

Warning: Likelihood for the fitted model larger than the Likelihood for the full model.
Error in computing chi-square; returning 2

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-323.841	4			
Fitted model	-321.425	3	-4.83323	1	2
Reduced model	-474.224	1	300.765	3	<.0001

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TETRATECH

AIC: 648.85

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.2113	60.842	57.600	288	-0.468
0.0026	0.2219	27.512	32.240	124	1.022
0.0261	0.3120	34.638	34.410	111	-0.047
0.2607	0.9428	165.941	165.440	176	-0.163

Chi^2 = 1.29 d.f. = 1 P-value = 0.2557

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.0201651

BMDL = 0.0104576

BMDU = 0.0675466

Taken together, (0.0104576, 0.0675466) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 9.56246

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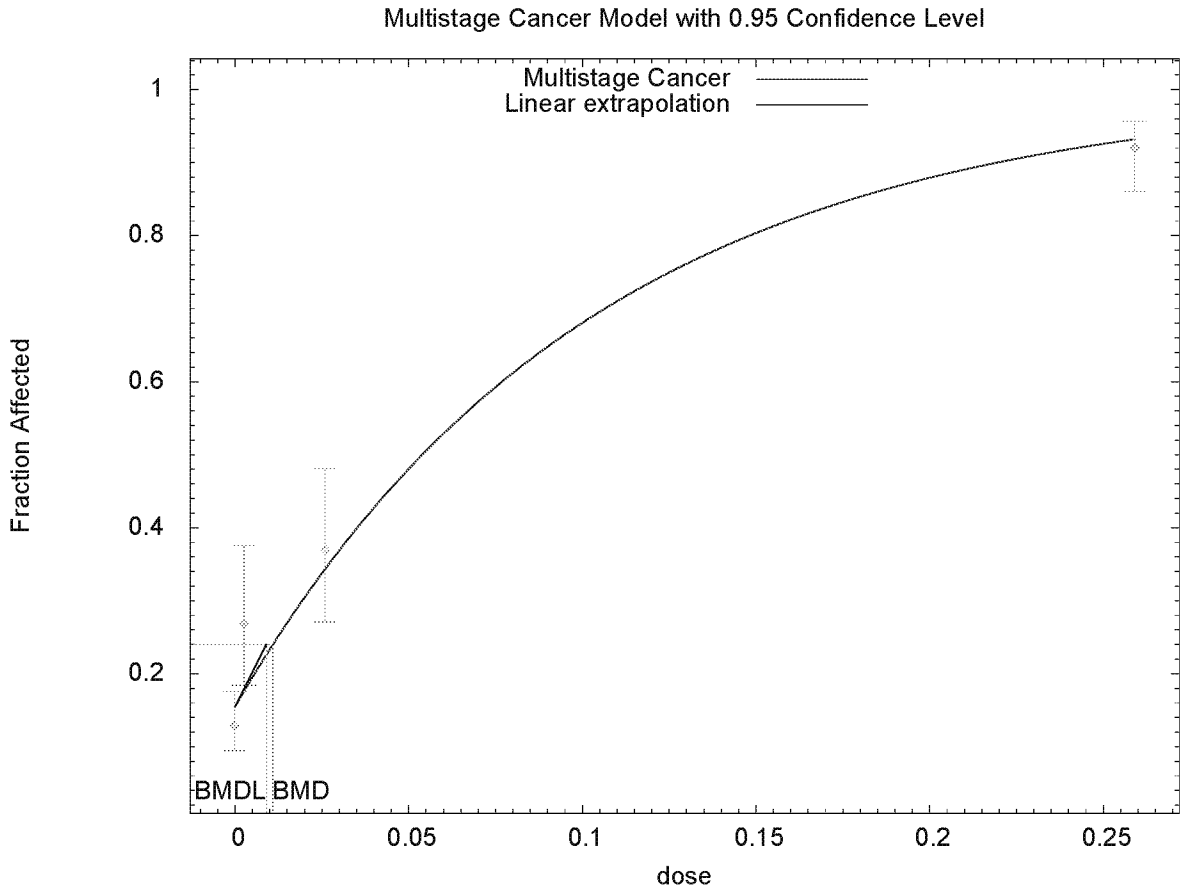
TETRA TECH

132-Week Female Mouse Tumor Incidence Data from Walker 197 - First Run (Degree of Polyniomial = 1):




```
=====================================================================
        Multistage Cancer Model. (Version: 1.9;  Date: 05/26/2010)
        Input Data File: C:/USEPA/BMDS212/Data/msc_UntitledData_Setting.(d)
        Gnuplot Plotting File:  C:/USEPA/BMDS212/Data/msc_UntitledData_Setting.plt
                                          Thu Dec 23 13:22:33 2010
=====================================================================

BMDS_Model_Run
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  The form of the probability function is:

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

  The parameter betas are restricted to be positive


  Dependent variable = %_Tumors
  Independent variable = Dose

Total number of observations = 4
```

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TETRA TECH

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

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

Default Initial Parameter Values
Background = 0.197577
Beta(1) = 8.91076

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.27
Beta(1)	-0.27	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.15526	*	*	*
Beta(1)	9.73064	*	*	*

* - Indicates that this value is not calculated.

Warning: Likelihood for the fitted model larger than the Likelihood for the full model.
Error in computing chi-square; returning 2

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-265.837	4			
Fitted model	-265.257	2	-1.16053	2	2
Reduced model	-410.462	1	289.25	3	<.0001

AIC: 534.514

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1553	46.112	38.610	297	-1.202
0.0026	0.1763	15.865	24.300	90	2.333
0.0259	0.3434	29.877	32.190	87	0.522
0.2590	0.9320	137.938	136.160	148	-0.581

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TETRATECH

Chi^2 = 7.50 d.f. = 2 P-value = 0.0235

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.0108277

BMDL = 0.00898478

BMDU = 0.01312

Taken together, (0.00898478, 0.01312) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 11.1299

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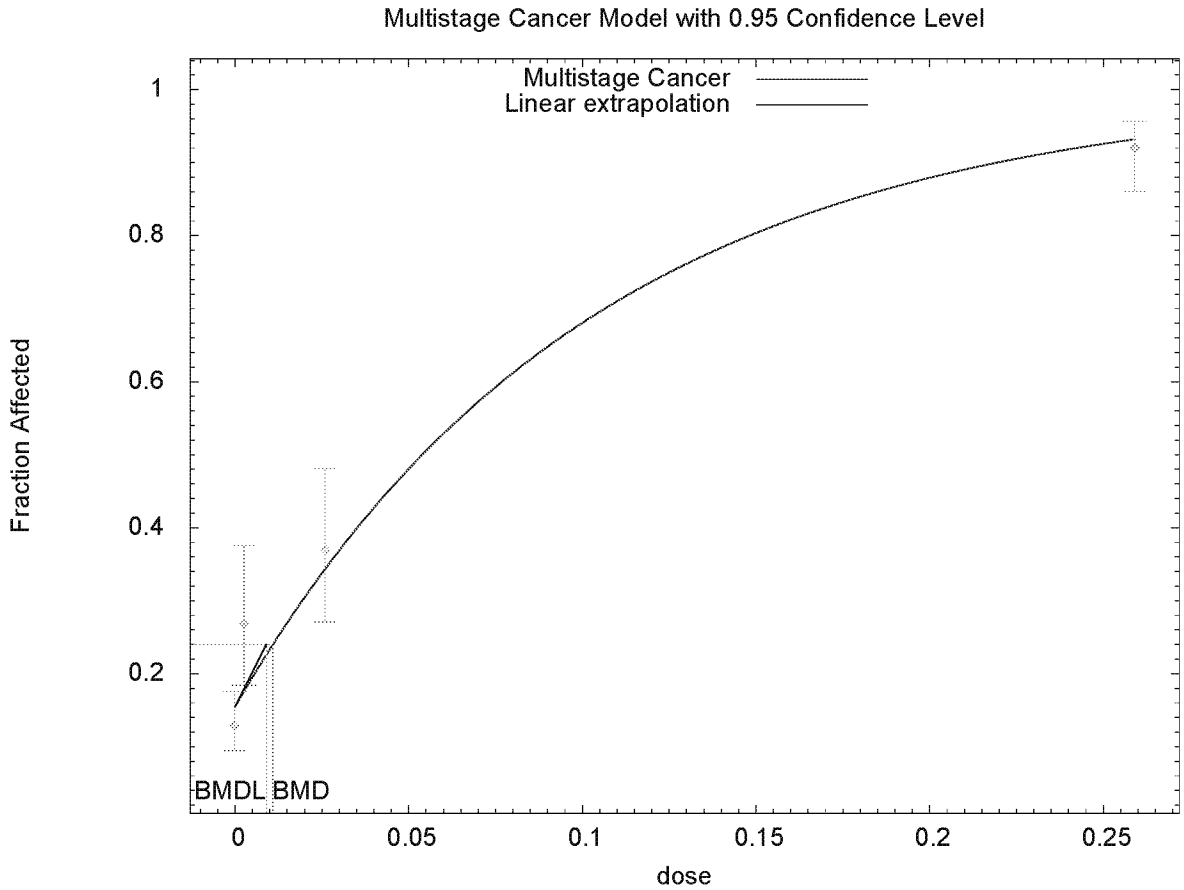
TETRA TECH

132-Week Female Mouse Tumor Incidence Data from Walker 197 - Second Run (Degree of Polyniomial = 2):




```
=====================================================================
        Multistage Cancer Model. (Version: 1.9;  Date: 05/26/2010)
        Input Data File: C:/USEPA/BMDS212/Data/msc_UntitledData_Setting.(d)
        Gnuplot Plotting File:  C:/USEPA/BMDS212/Data/msc_UntitledData_Setting.plt
                                          Thu Dec 23 13:16:20 2010
=====================================================================

BMDS_Model_Run
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  The form of the probability function is:

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

  The parameter betas are restricted to be positive


  Dependent variable = %_Tumors
  Independent variable = Dose

Total number of observations = 4
```

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TETRATECH

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

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

Default Initial Parameter Values

Background =	0.197577
Beta(1) =	8.91076
Beta(2) =	0

Asymptotic Correlation Matrix of Parameter Estimates

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

	Background	Beta(1)
Background	1	-0.27
Beta(1)	-0.27	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.15526	*	*	*
Beta(1)	9.73063	*	*	*
Beta(2)	0	*	*	*

* - Indicates that this value is not calculated.

Warning: Likelihood for the fitted model larger than the Likelihood for the full model.
Error in computing chi-square; returning 2

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-265.837	4			
Fitted model	-265.257	2	-1.16053	2	2
Reduced model	-410.462	1	289.25	3	<.0001

AIC: 534.514

Goodness of Fit

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TETRATECH

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1553	46.112	38.610	297	-1.202
0.0026	0.1763	15.865	24.300	90	2.333
0.0259	0.3434	29.877	32.190	87	0.522
0.2590	0.9320	137.938	136.160	148	-0.581

Chi^2 = 7.50 d.f. = 2 P-value = 0.0235

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.0108277

BMDL = 0.00898478

BMDU = 0.0160063

Taken together, (0.00898478, 0.0160063) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 11.1299

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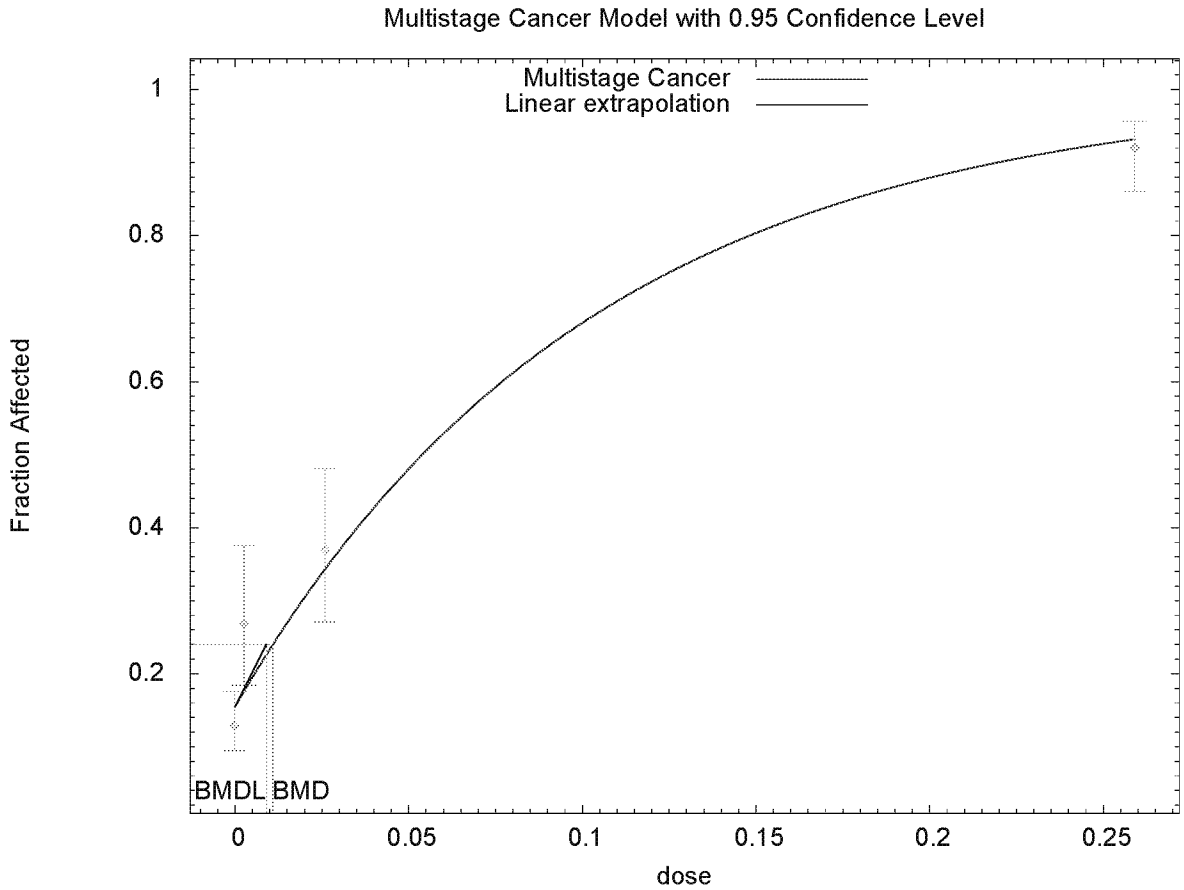
TETRA TECH

132-Week Female Mouse Tumor Incidence Data from Walker 197 - First Run (Degree of Polyniomial = 3):




```
=====================================================================
        Multistage Cancer Model. (Version: 1.9;  Date: 05/26/2010)
        Input Data File: C:/USEPA/BMDS212/Data/msc_UntitledData_Setting.(d)
        Gnuplot Plotting File:  C:/USEPA/BMDS212/Data/msc_UntitledData_Setting.plt
                                          Thu Dec 23 13:25:10 2010
=====================================================================

BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  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 = %_Tumors
  Independent variable = Dose

Total number of observations = 4
```

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TETRA TECH

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 =	0.197577
Beta(1) =	8.91076
Beta(2) =	0
Beta(3) =	0

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Beta(2) -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)
Background	1	-0.27
Beta(1)	-0.27	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.15526	*	*	*
Beta(1)	9.73064	*	*	*
Beta(2)	0	*	*	*
Beta(3)	0	*	*	*

* - Indicates that this value is not calculated.

Warning: Likelihood for the fitted model larger than the Likelihood for the full model.
Error in computing chi-square; returning 2

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-265.837	4			
Fitted model	-265.257	2	-1.16053	2	2
Reduced model	-410.462	1	289.25	3	<.0001

AIC: 534.514

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TETRATECH

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1553	46.112	38.610	297	-1.202
0.0026	0.1763	15.865	24.300	90	2.333
0.0259	0.3434	29.877	32.190	87	0.522
0.2590	0.9320	137.938	136.160	148	-0.581

Chi^2 = 7.50 d.f. = 2 P-value = 0.0235

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.0108277

BMDL = 0.00898478

BMDU = 0.0160063

Taken together, (0.00898478, 0.0160063) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 11.1299

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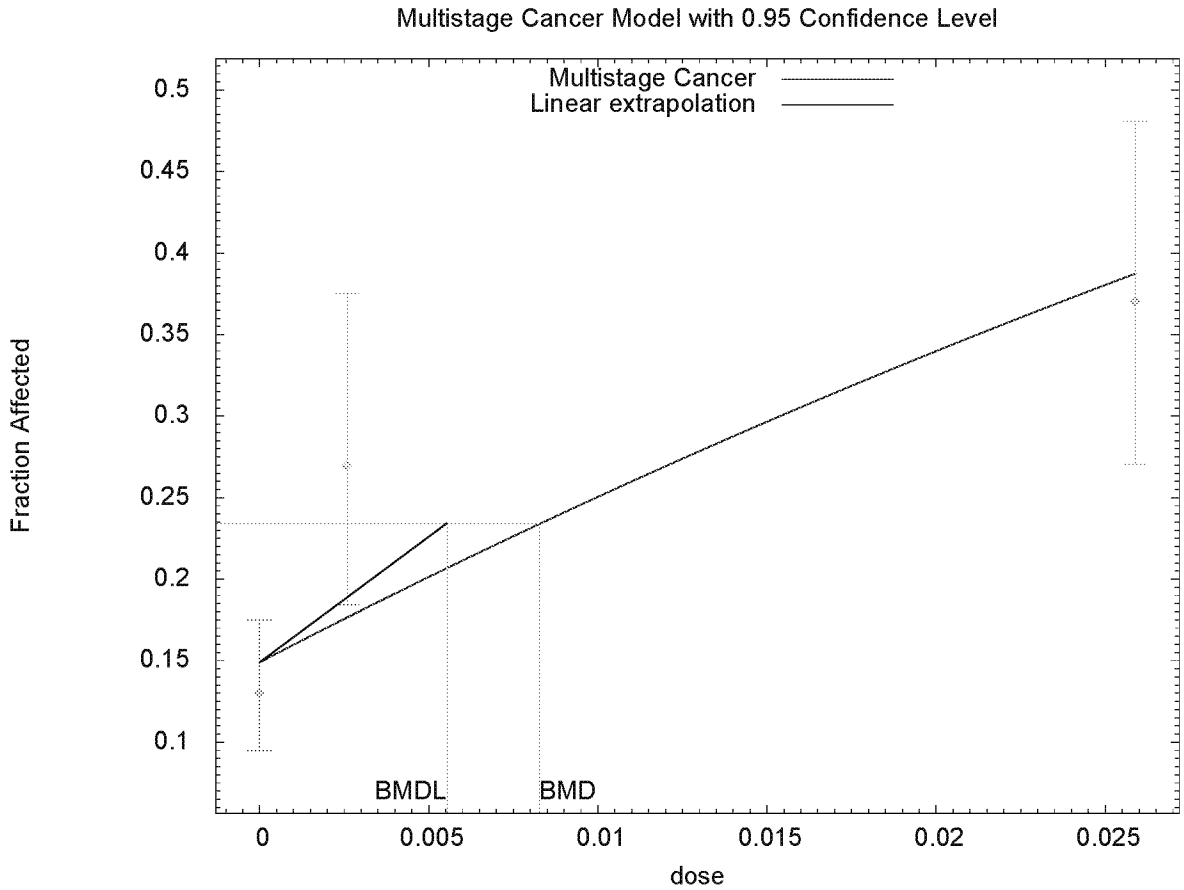
TETRA TECH

132-Week Female Mouse Tumor Incidence Data from Walker 197 - Fourth Run (High Dose Excluded, Degree of Polyniomial = 1):



13:26 12/23 2010

```
=====================================================================
        Multistage Cancer Model. (Version: 1.9;  Date: 05/26/2010)
        Input Data File: C:/USEPA/BMDS212/Data/msc_UntitledData_Setting.(d)
        Gnuplot Plotting File:  C:/USEPA/BMDS212/Data/msc_UntitledData_Setting.plt
                                          Thu Dec 23 13:26:16 2010
=====================================================================

BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the probability function is:

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

  The parameter betas are restricted to be positive


  Dependent variable = %_Tumors
  Independent variable = Dose
```

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TETRATECH

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

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

Default Initial Parameter Values
Background = 0.189465
Beta(1) = 10.0344

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.44
Beta(1)	-0.44	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.149139	*	*	*
Beta(1)	12.7407	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-224.579	3			
Fitted model	-225.711	2	2.2636	1	0.1324
Reduced model	-237.606	1	26.0535	2	<.0001

AIC: 455.422

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1491	44.294	38.610	297	-0.926
0.0026	0.1768	15.908	24.300	90	2.319
0.0259	0.3882	33.778	32.190	87	-0.349

Chi^2 = 6.36 d.f. = 1 P-value = 0.0117

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TETRA TECH

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.00826961

BMDL = 0.00552865

BMDU = 0.0142487

Taken together, (0.00552865, 0.0142487) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 18.0876

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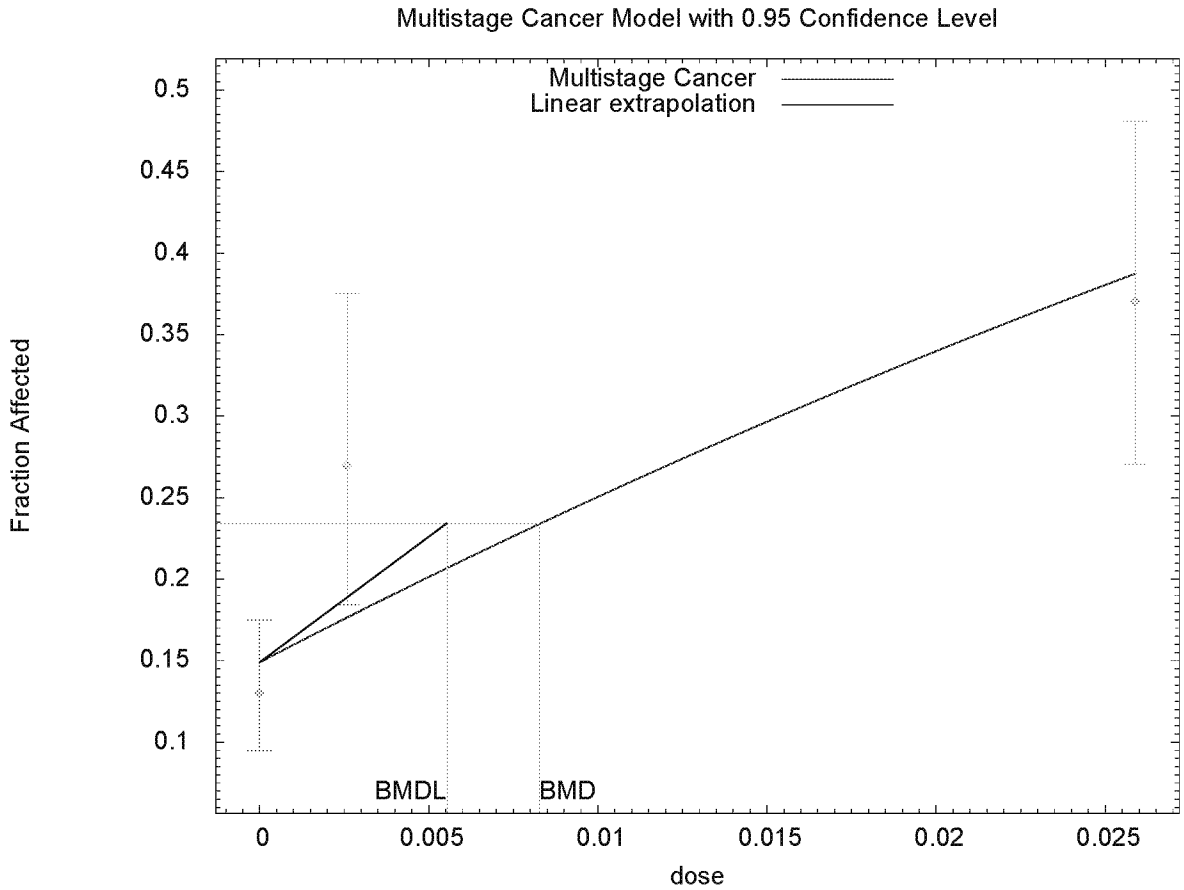
TETRA TECH

132-Week Female Mouse Tumor Incidence Data from Walker 197 - Fifth Run (High Dose Excluded, Degree of Polyniomial = 2):



13:27 12/23 2010

```
=====================================================================
        Multistage Cancer Model. (Version: 1.9;  Date: 05/26/2010)
        Input Data File: C:/USEPA/BMDS212/Data/msc_UntitledData_Setting.(d)
        Gnuplot Plotting File:  C:/USEPA/BMDS212/Data/msc_UntitledData_Setting.plt
                                          Thu Dec 23 13:27:01 2010
=====================================================================

BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the probability function is:

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

  The parameter betas are restricted to be positive


  Dependent variable = %_Tumors
  Independent variable = Dose
```

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TETRATECH

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

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

Default Initial Parameter Values

Background =	0.189465
Beta(1) =	10.0344
Beta(2) =	0

Asymptotic Correlation Matrix of Parameter Estimates

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

	Background	Beta(1)
Background	1	-0.44
Beta(1)	-0.44	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.149139	*	*	*
Beta(1)	12.7407	*	*	*
Beta(2)	0	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-224.579	3			
Fitted model	-225.711	2	2.2636	1	0.1324
Reduced model	-237.606	1	26.0535	2	<.0001

AIC: 455.422

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual

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TETRATECH

0.0000	0.1491	44.294	38.610	297	-0.926
0.0026	0.1768	15.908	24.300	90	2.319
0.0259	0.3882	33.778	32.190	87	-0.349

Chi^2 = 6.36 d.f. = 1 P-value = 0.0117

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.00826961

BMDL = 0.00552865

BMDU = 0.0160351

Taken together, (0.00552865, 0.0160351) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 18.0876

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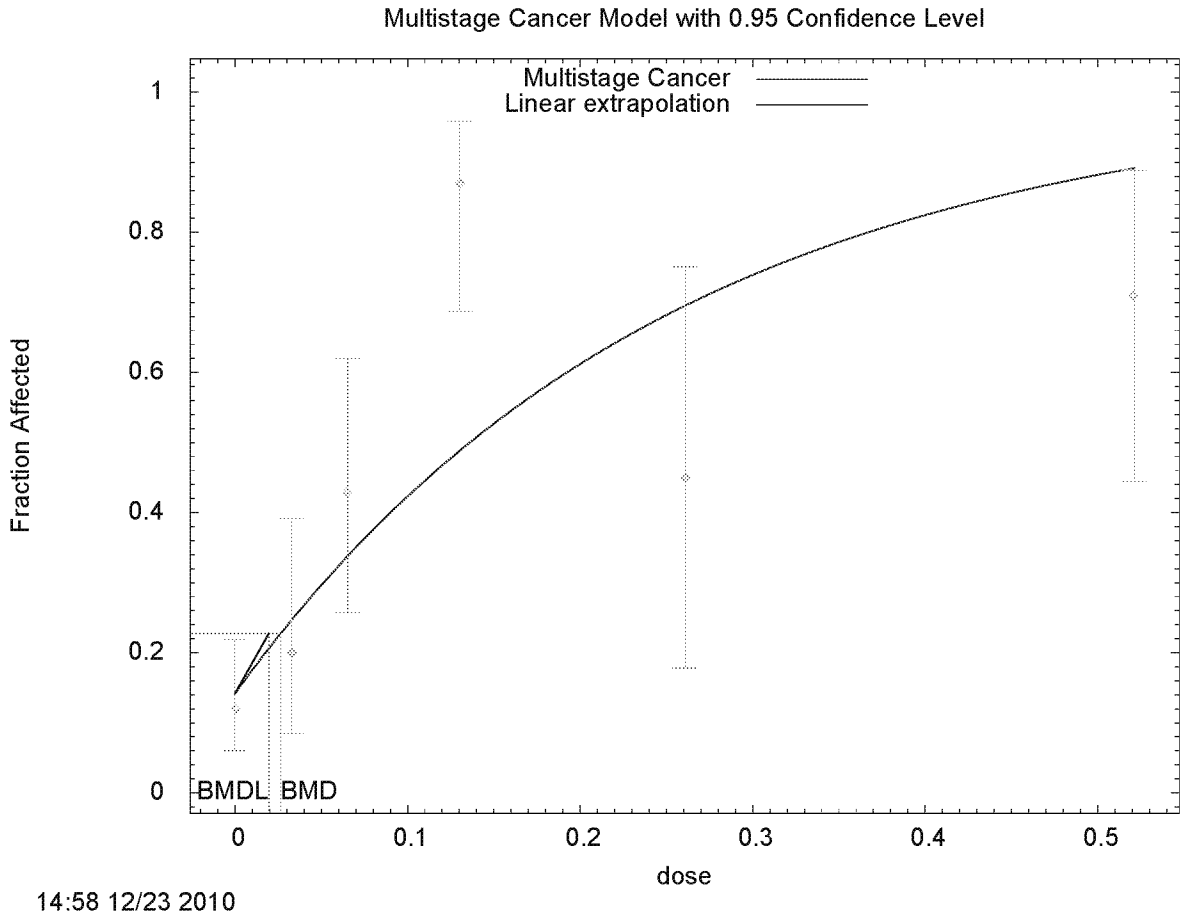
TETRA TECH

128-Week Male Mouse Tumor Incidence Data from Walker 1972 – First set of Runs (Degree of Polyniomial = 1, 2, 3, 4 produced exactly the same results):




```
=====================================================================
        Multistage Cancer Model. (Version: 1.9;  Date: 05/26/2010)
        Input Data File: C:/USEPA/BMDS212/Data/msc_UntitledData_Setting.(d)
        Gnuplot Plotting File:  C:/USEPA/BMDS212/Data/msc_UntitledData_Setting.plt
                                          Thu Dec 23 14:58:56 2010
=====================================================================

BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the probability function is:

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

  The parameter betas are restricted to be positive


  Dependent variable = Percent_Tumors
  Independent variable = Dose
```

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TETRATECH

Total number of observations = 6
Total number of records with missing values = 0
Total number of parameters in model = 3
Total number of specified parameters = 0
Degree of polynomial = 2

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

Default Initial Parameter Values

Background =	0.411936
Beta(1) =	1.5877
Beta(2) =	0

Asymptotic Correlation Matrix of Parameter Estimates

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

	Background	Beta(1)
Background	1	-0.6
Beta(1)	-0.6	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.141657	*	*	*
Beta(1)	3.96843	*	*	*
Beta(2)	0	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-93.5294	6			
Fitted model	-107.336	2	27.6131	4	1.4939647e-005
Reduced model	-128.534	1	70.0099	5	<.0001

AIC: 218.672

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual

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TETRA TECH

0.0000	0.1417	11.049	9.360	78	-0.549
0.0326	0.2458	7.373	6.000	30	-0.582
0.0652	0.3372	10.117	12.900	30	1.075
0.1303	0.4882	14.647	26.100	30	4.183
0.2606	0.6949	7.644	4.950	11	-1.764
0.5213	0.8915	15.156	12.070	17	-2.407

Chi^2 = 28.20 d.f. = 4 P-value = 0.0000

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.0265497

BMDL = 0.0195461

BMDU = 0.0388455

Taken together, (0.0195461, 0.0388455) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 5.11612

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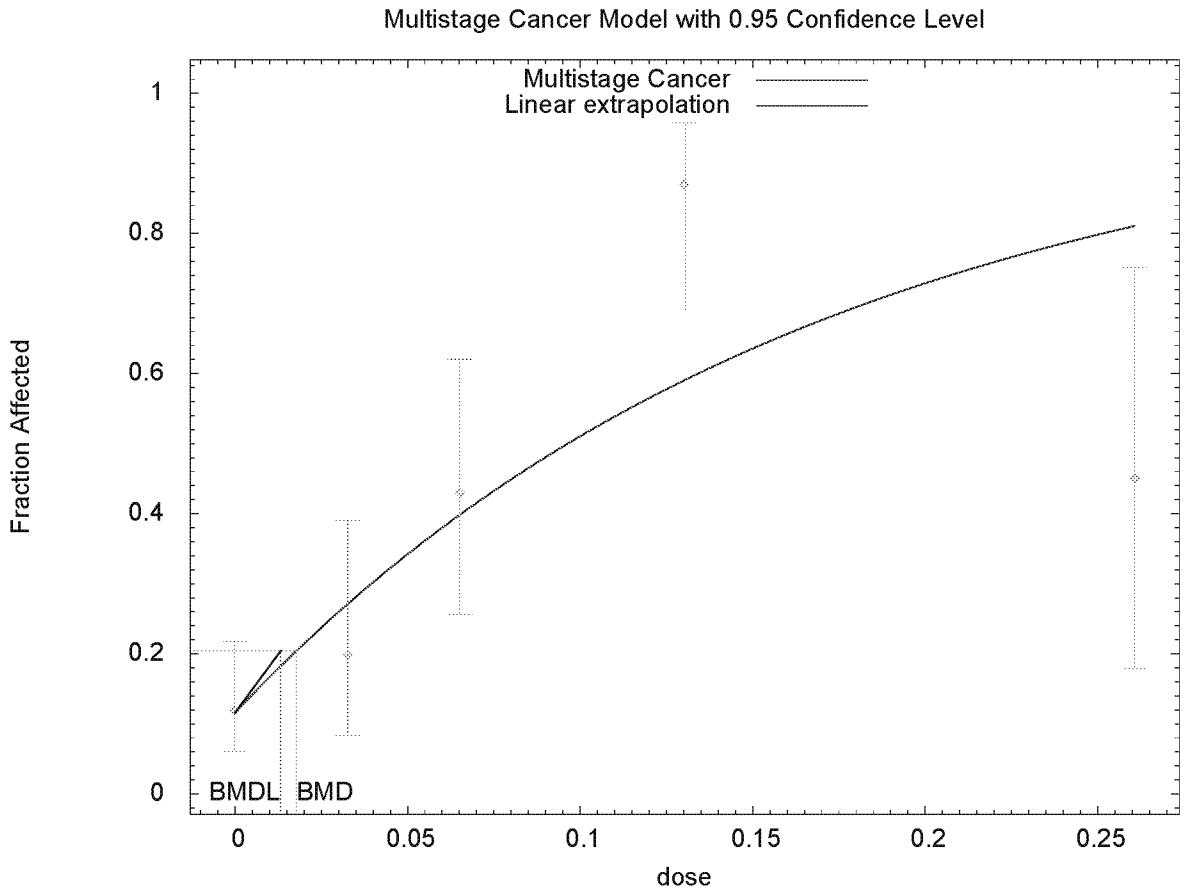
TETRA TECH

128-Week Male Mouse Tumor Incidence Data from Walker 1972 – Second Set of Runs (Excluded top dose level; Degree of Polyniomial = 1, 2, 3, 4 produced exactly the same results):




```
 ===================================================================
        Multistage Cancer Model. (Version: 1.9;  Date: 05/26/2010)
        Input Data File: C:/USEPA/BMDS212/Data/msc_Dieldrin Walker 73 male T2_Opt.(d)
        Gnuplot Plotting File:  C:/USEPA/BMDS212/Data/msc_Dieldrin Walker 73 male
T2_Opt.plt
                                                Thu Dec 23 15:03:14 2010
 ===================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = Percent_Tumors
   Independent variable = Dose
```

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TETRA TECH

Total number of observations = 5
Total number of records with missing values = 0
Total number of parameters in model = 3
Total number of specified parameters = 0
Degree of polynomial = 2

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

Default Initial Parameter Values

Background =	0.354288
Beta(1) =	2.79145
Beta(2) =	0

Asymptotic Correlation Matrix of Parameter Estimates

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

	Background	Beta(1)
Background	1	-0.58
Beta(1)	-0.58	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.115765	*	*	*
Beta(1)	5.90894	*	*	*
Beta(2)	0	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-83.2928	5			
Fitted model	-93.2472	2	19.9088	3	0.0001773
Reduced model	-113.687	1	60.7888	4	<.0001

AIC: 190.494

Goodness of Fit

Scaled

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TETRA TECH

Dose	Est._Prob.	Expected	Observed	Size	Residual
0.0000	0.1158	9.030	9.360	78	0.117
0.0326	0.2706	8.118	6.000	30	-0.870
0.0652	0.3983	11.950	12.900	30	0.354
0.1303	0.5906	17.718	26.100	30	3.112
0.2606	0.8104	8.915	4.950	11	-3.050

Chi^2 = 19.88 d.f. = 3 P-value = 0.0002

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.0178307

BMDL = 0.0132328

BMDU = 0.0256235

Taken together, (0.0132328, 0.0256235) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 7.55696

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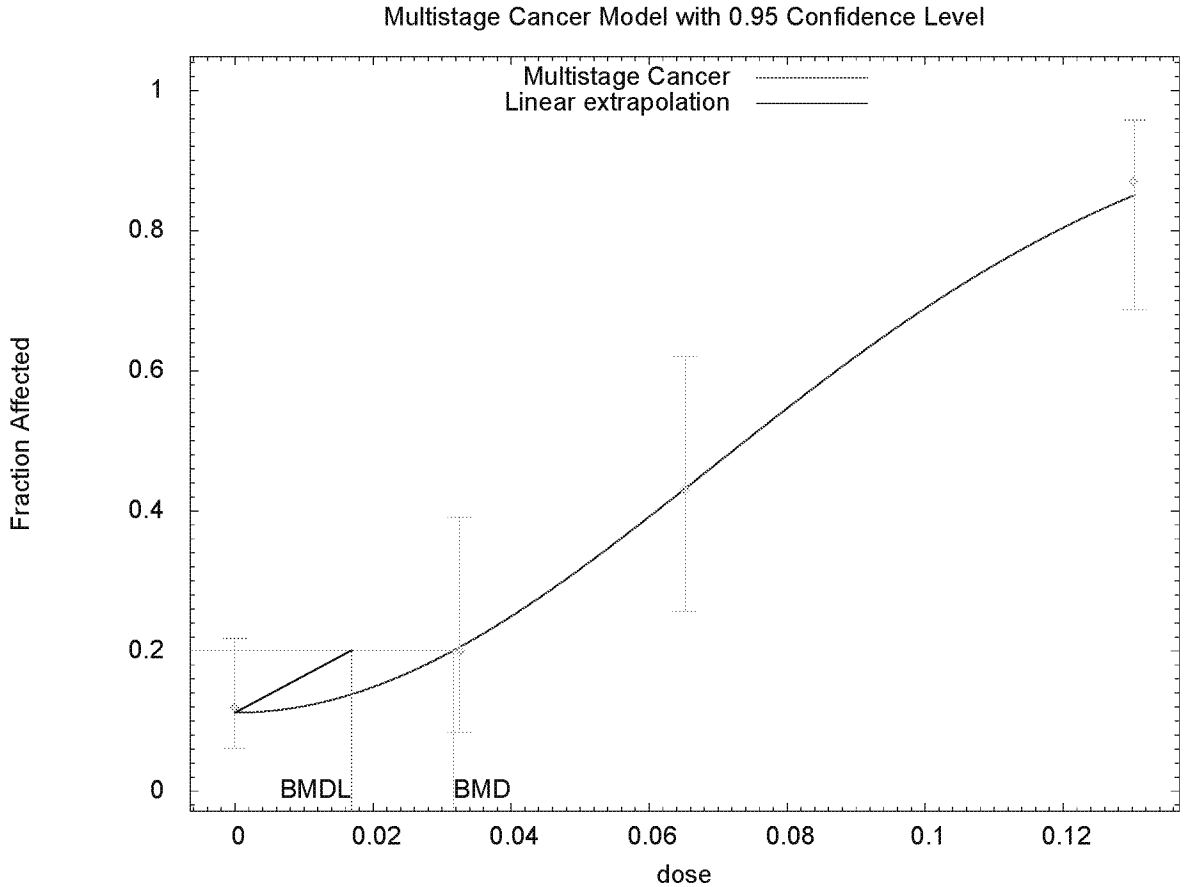
TETRA TECH

128-Week Male Mouse Tumor Incidence Data from Walker 1972 – Second Set of Runs (Excluded top two dose levels; Degree of Polyniomial = 2 or 3 produced exactly the same results):




```
 ======================================================================
        Multistage Cancer Model. (Version: 1.9;  Date: 05/26/2010)
        Input Data File: C:/USEPA/BMDS212/Data/msc_Dieldrin Walker 73 male T2_Opt.(d)
        Gnuplot Plotting File:  C:/USEPA/BMDS212/Data/msc_Dieldrin Walker 73 male
T2_Opt.plt
                                                Thu Dec 23 15:06:02 2010
 ======================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = Percent_Tumors
```

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TETRATECH

Independent variable = Dose

Total number of observations = 4
Total number of records with missing values = 0
Total number of parameters in model = 3
Total number of specified parameters = 0
Degree of polynomial = 2

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

Default Initial Parameter Values

Background =	0.100352
Beta(1) =	0
Beta(2) =	113.516

Asymptotic Correlation Matrix of Parameter Estimates

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

	Background	Beta(2)
Background	1	-0.4
Beta(2)	-0.4	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.112007	*	*	*
Beta(1)	0	*	*	*
Beta(2)	104.741	*	*	*

* - Indicates that this value is not calculated.

Warning: Likelihood for the fitted model larger than the Likelihood for the full model.
Error in computing chi-square; returning 2

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-75.7233	4			
Fitted model	-74.9765	2	-1.49357	2	2
Reduced model	-105.761	1	60.0763	3	<.0001

AIC: 153.953

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TETRATECH

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1120	8.737	9.360	78	0.224
0.0326	0.2054	6.163	6.000	30	-0.074
0.0652	0.4308	12.923	12.900	30	-0.009
0.1303	0.8501	25.502	26.100	30	0.306

Chi^2 = 0.15 d.f. = 2 P-value = 0.9282

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.0317161

BMDL = 0.0168577

BMDU = 0.0379934

Taken together, (0.0168577, 0.0379934) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 5.932

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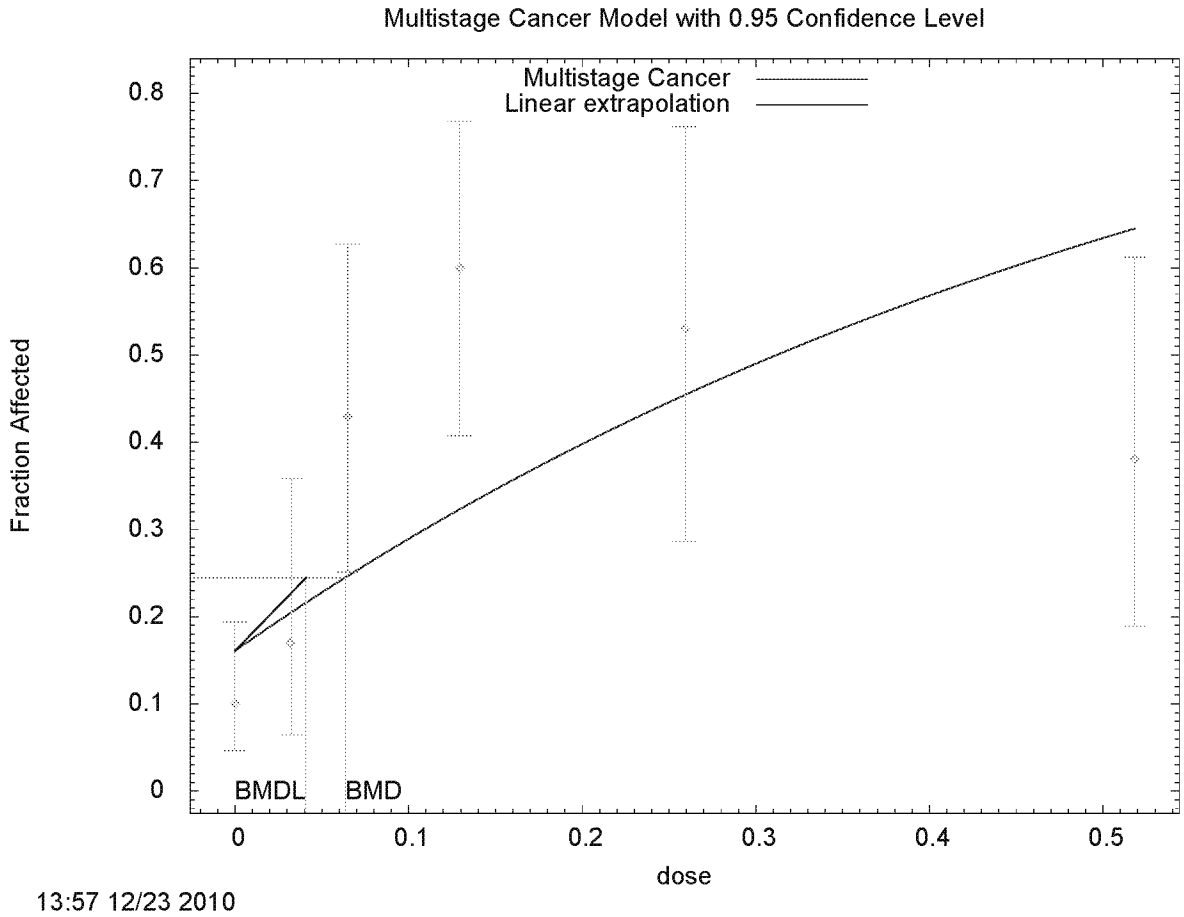
TETRA TECH

128-Week Female Mouse Tumor Incidence Data from Walker 1972 – First set of Runs (Degree of Polyniomial = 1, 2, 3, 4 produced exactly the same results):




```
=====================================================================
        Multistage Cancer Model. (Version: 1.9;  Date: 05/26/2010)
        Input Data File: C:/USEPA/BMDS212/Data/msc_UntitledData_Setting.(d)
        Gnuplot Plotting File:  C:/USEPA/BMDS212/Data/msc_UntitledData_Setting.plt
                                          Thu Dec 23 13:57:47 2010
=====================================================================

BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the probability function is:

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

  The parameter betas are restricted to be positive


  Dependent variable = %_Tumors
  Independent variable = Dose

Total number of observations = 6
```

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TETRATECH

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

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

Default Initial Parameter Values
Background = 0.336733
Beta(1) = 0.537666

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.65
Beta(1)	-0.65	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.160948	*	*	*
Beta(1)	1.65831	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-104.054	6			
Fitted model	-114.535	2	20.9616	4	0.0003223
Reduced model	-123.521	1	38.9338	5	<.0001

AIC: 233.07

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1609	12.554	7.800	78	-1.465
0.0324	0.2048	6.144	5.100	30	-0.472
0.0648	0.2464	6.899	12.040	28	2.255
0.1295	0.3231	9.694	18.000	30	3.243
0.2590	0.4539	7.717	9.010	17	0.630
0.5181	0.6446	13.537	7.980	21	-2.534

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TETRATECH

Chi^2 = 24.78 d.f. = 4 P-value = 0.0001

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.063535

BMDL = 0.041045

BMDU = 0.123955

Taken together, (0.041045, 0.123955) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 2.43635

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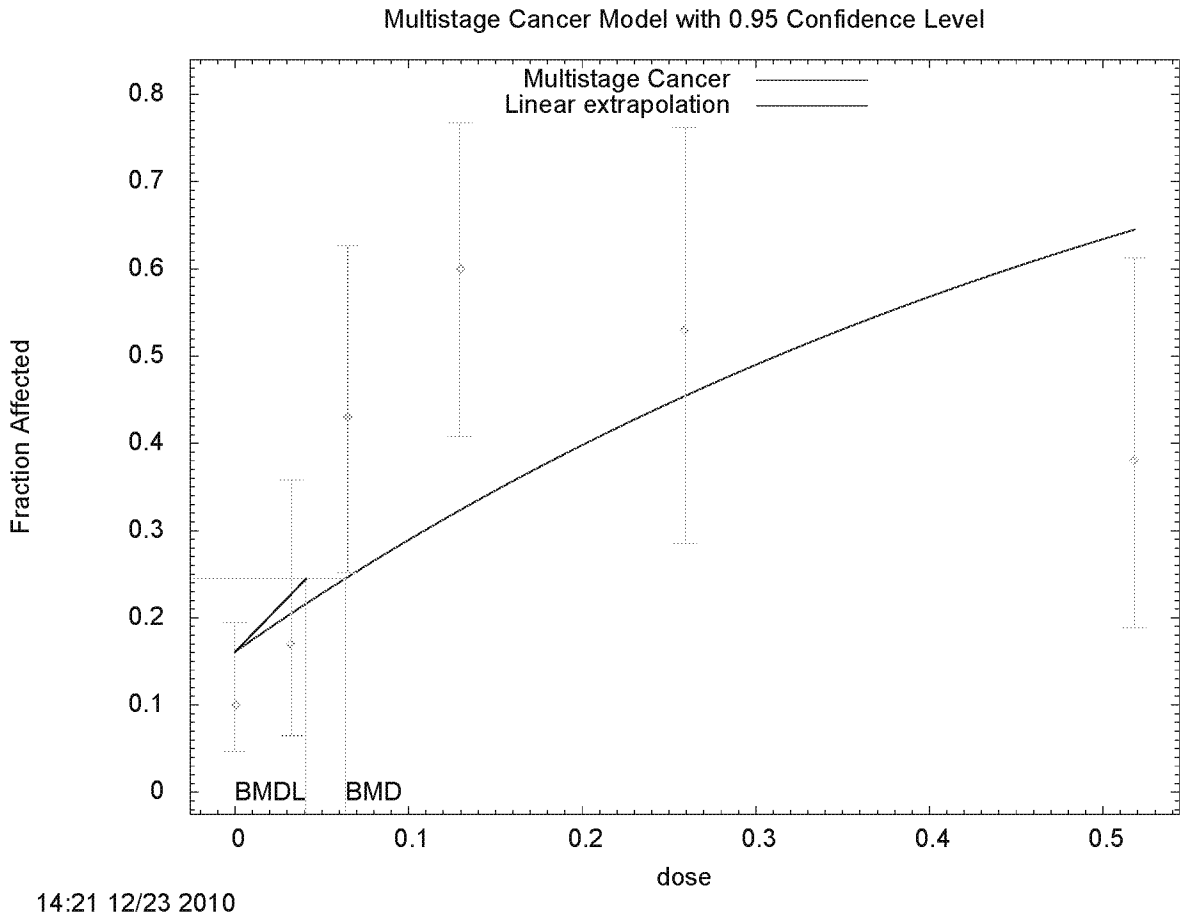
TETRA TECH

128-Week Female Mouse Tumor Incidence Data from Walker 1972 – Second set of Runs (Highest dose level excluded; Degree of Polyniomial = 2 or 3 produced exactly the same results):




```
 ======================================================================
        Multistage Cancer Model. (Version: 1.9;  Date: 05/26/2010)
        Input Data File: C:/USEPA/BMDS212/Data/msc_Dieldrin Walker 73 fem T2_Opt.(d)
        Gnuplot Plotting File:  C:/USEPA/BMDS212/Data/msc_Dieldrin Walker 73 fem
T2_Opt.plt
                                                Thu Dec 23 14:15:10 2010
 ======================================================================

 BMDS_Model_Run
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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 = Percent_Tumors
```

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TETRATECH

Independent variable = Dose

Total number of observations = 5
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 =	0.21884
Beta(1) =	2.65653
Beta(2) =	0
Beta(3) =	0

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Beta(2) -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)
Background	1	-0.57
Beta(1)	-0.57	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0950059	*	*	*
Beta(1)	4.54588	*	*	*
Beta(2)	0	*	*	*
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	-90.1091	5			
Fitted model	-90.8366	2	1.45505	3	0.6927
Reduced model	-109.174	1	38.1302	4	<.0001

AIC: 185.673

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TETRA TECH

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0950	7.410	7.800	78	0.150
0.0324	0.2189	6.566	5.100	30	-0.647
0.0648	0.3258	9.122	12.040	28	1.177
0.1295	0.4977	14.932	18.000	30	1.120
0.2590	0.7212	12.261	9.010	17	-1.758

Chi^2 = 6.17 d.f. = 3 P-value = 0.1035

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.0231772

BMDL = 0.0169973

BMDU = 0.034489

Taken together, (0.0169973, 0.034489) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 5.8833

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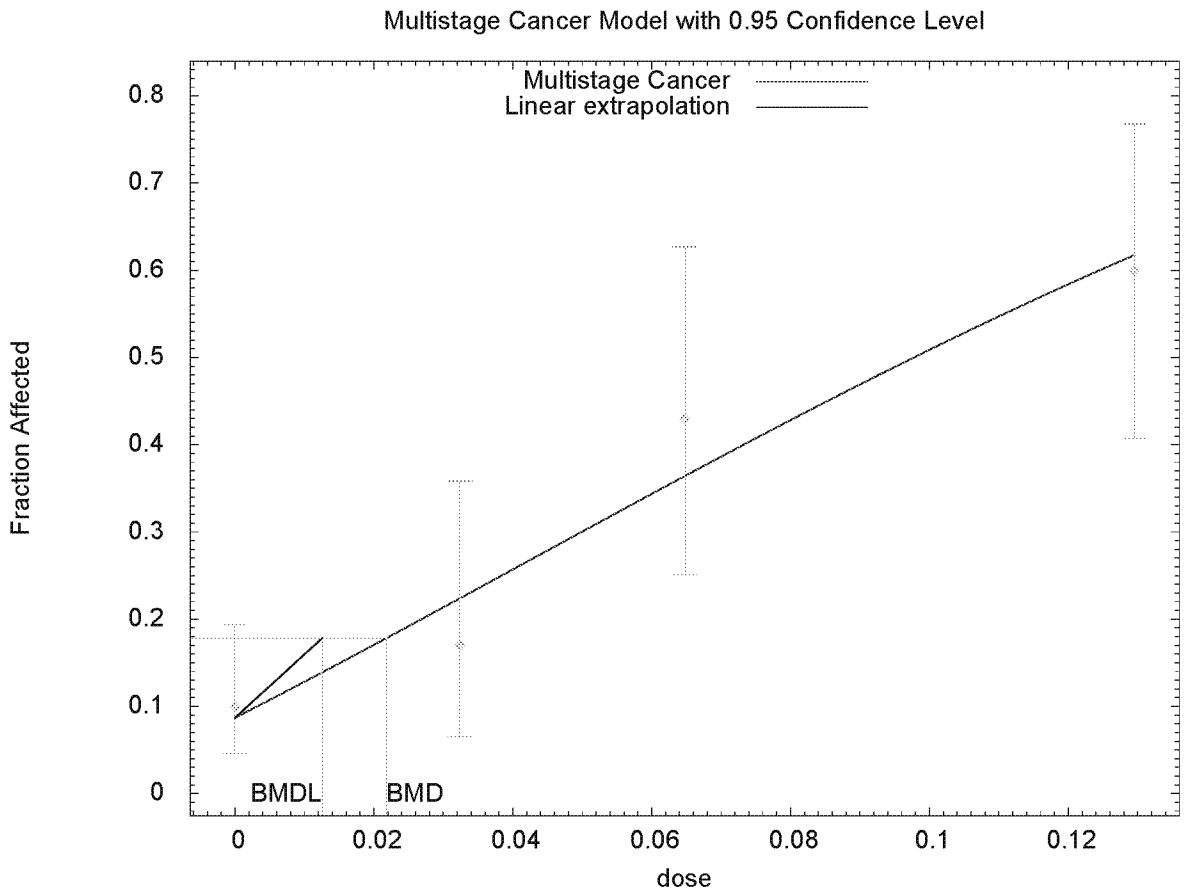
TETRA TECH

128-Week Female Mouse Tumor Incidence Data from Walker 1972 – Third set of Runs (Highest two dose levels excluded; Degree of Polyniomial = 2 or 3 produced exactly the same results):



14:32 12/23 2010

```
 ===================================================================
        Multistage Cancer Model. (Version: 1.9;  Date: 05/26/2010)
        Input Data File: C:/USEPA/BMDS212/Data/msc_Dieldrin Walker 73 fem T2_Opt.(d)
        Gnuplot Plotting File:  C:/USEPA/BMDS212/Data/msc_Dieldrin Walker 73 fem
T2_Opt.plt
                                                Thu Dec 23 14:10:14 2010
 ===================================================================

 BMDS_Model_Run
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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
```

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TETRATECH

Dependent variable = Percent_Tumors
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 =	0.0679795
Beta(1) =	6.40557
Beta(2) =	1.66277
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	-0.47	0.32
Beta(1)	-0.47	1	-0.94
Beta(2)	0.32	-0.94	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0869626	*	*	*
Beta(1)	4.44565	*	*	*
Beta(2)	17.4786	*	*	*
Beta(3)	0	*	*	*

* - Indicates that this value is not calculated.

Warning: Likelihood for the fitted model larger than the Likelihood for the full model.
Error in computing chi-square; returning 2

Analysis of Deviance Table

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

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TETRATECH

Full model	-78.3562	4			
Fitted model	-76.6989	3	-3.31463	1	2
Reduced model	-94.8966	1	33.0807	3	<.0001

AIC: 159.398

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0870	6.783	7.800	78	0.409
0.0324	0.2237	6.712	5.100	30	-0.706
0.0648	0.3638	10.185	12.040	28	0.729
0.1295	0.6171	18.513	18.000	30	-0.193

Chi^2 = 1.23 d.f. = 1 P-value = 0.2667

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.0218267

BMDL = 0.0125613

BMDU = 0.0477172

Taken together, (0.0125613, 0.0477172) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 7.96094

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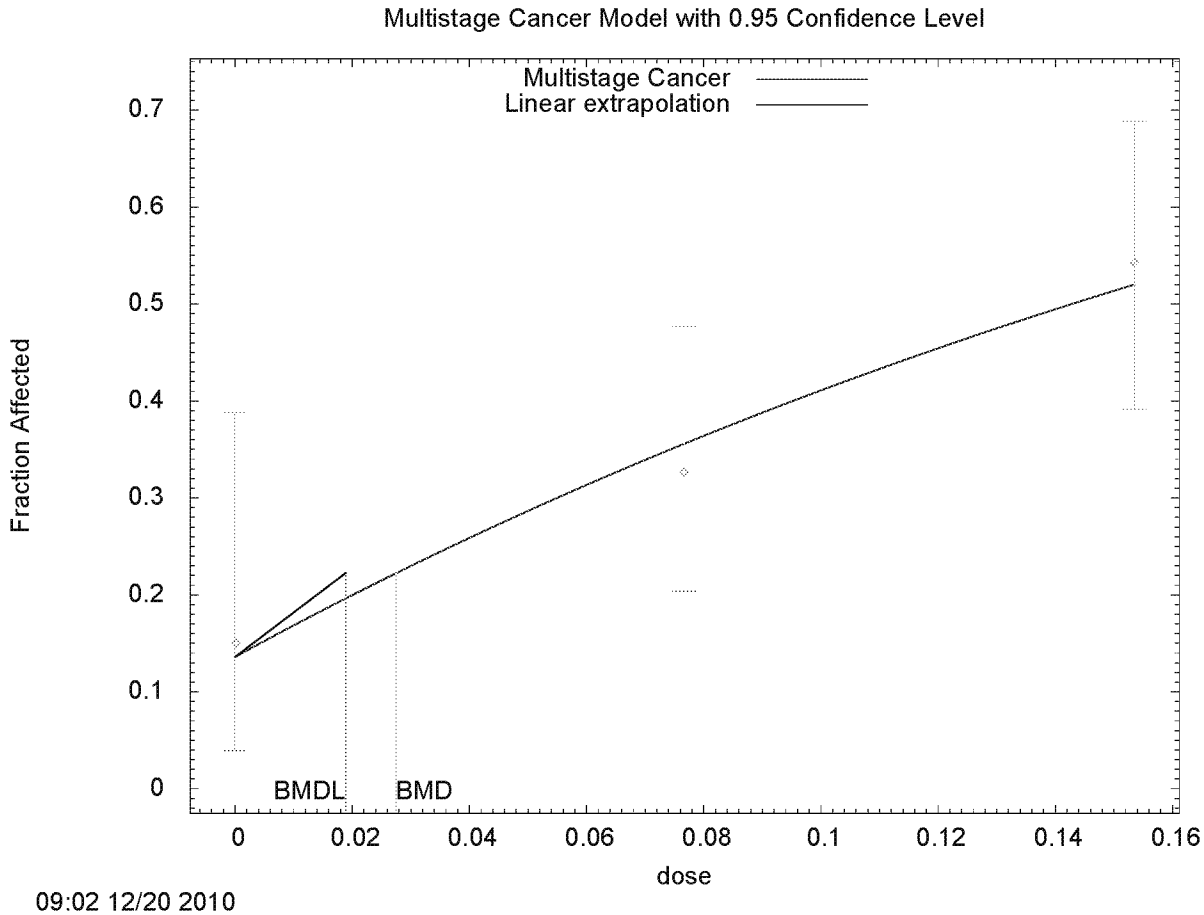
TETRA TECH

80-Week Male Mouse Tumor Incidence Data from NCI 1978 – First Run (Degree of Polyniomial = 1):




```
=====================================================================
        Multistage Cancer Model. (Version: 1.9;  Date: 05/26/2010)
        Input Data File: C:/USEPA/BMDS212/Data/msc_UntitledData_Setting.(d)
        Gnuplot Plotting File:  C:/USEPA/BMDS212/Data/msc_UntitledData_Setting.plt
                                          Mon Dec 20 09:02:20 2010
=====================================================================

BMDS_Model_Run
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  The form of the probability function is:

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

  The parameter betas are restricted to be positive


  Dependent variable = Tumor_Incidence
  Independent variable = Dose

Total number of observations = 3
```

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TETRA TECH

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

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

Default Initial Parameter Values
Background = 0.127617
Beta(1) = 4.04956

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.81
Beta(1)	-0.81	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.136087	*	*	*
Beta(1)	3.83339	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-71.1178	3			
Fitted model	-71.2789	2	0.322071	1	0.5704
Reduced model	-76.5126	1	10.7895	2	0.00454

AIC: 146.558

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1361	2.722	3.000	20	0.181
0.0767	0.3563	17.457	16.000	49	-0.435
0.1535	0.5204	23.936	25.000	46	0.314

Chi^2 = 0.32 d.f. = 1 P-value = 0.5714

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TETRA TECH

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.027485

BMDL = 0.0188779

BMDU = 0.0526374

Taken together, (0.0188779, 0.0526374) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 5.29719

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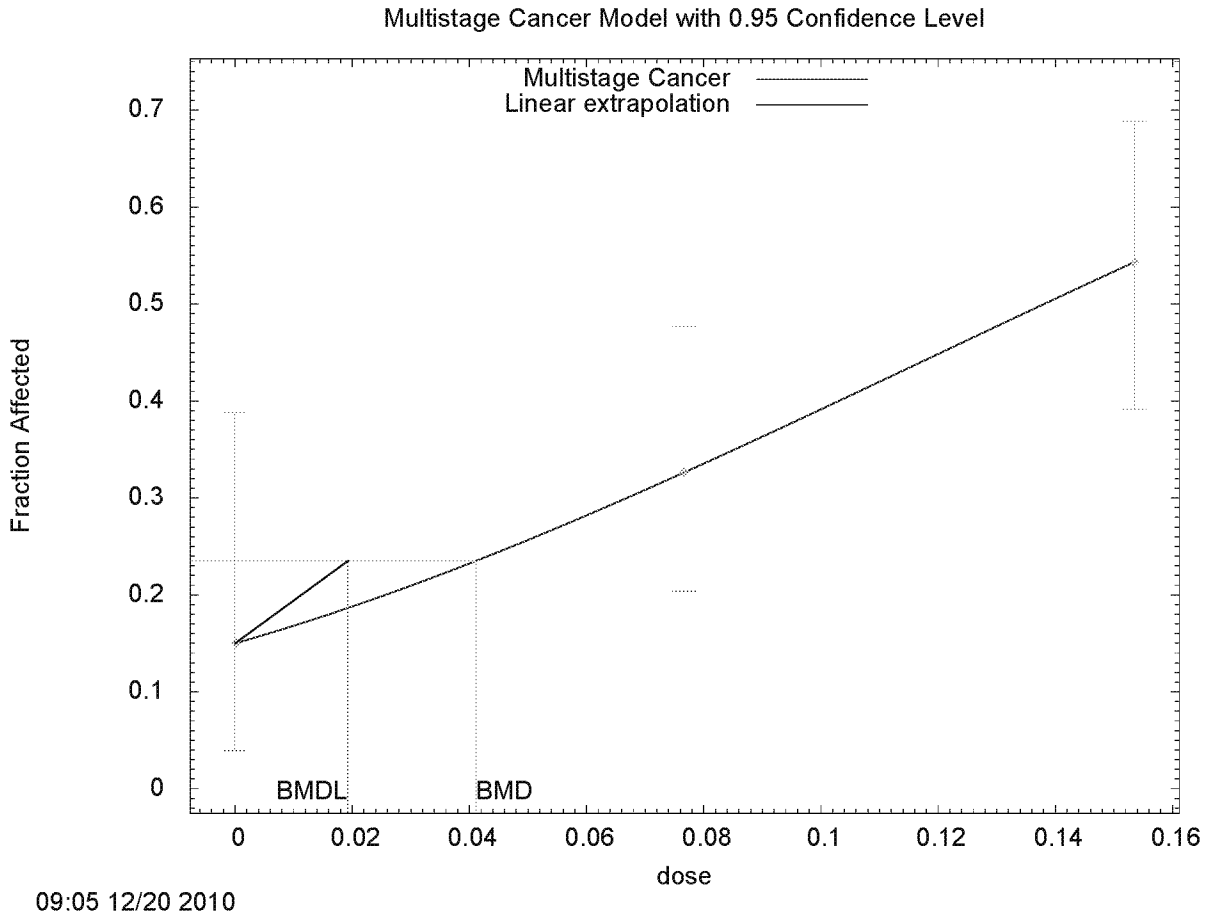
TETRA TECH

80-Week Male Mouse Tumor Incidence Data from NCI 1978 – Second Run (Degree of Polyniomial = 2):




```
=====================================================================
        Multistage Cancer Model. (Version: 1.9;  Date: 05/26/2010)
        Input Data File: C:/USEPA/BMDS212/Data/msc_UntitledData_Setting.(d)
        Gnuplot Plotting File:  C:/USEPA/BMDS212/Data/msc_UntitledData_Setting.plt
                                                Mon Dec 20 09:05:48 2010
=====================================================================

BMDS_Model_Run
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  The form of the probability function is:

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

  The parameter betas are restricted to be positive


  Dependent variable = Tumor_Incidence
  Independent variable = Dose
```

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TETRA TECH

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

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

Default Initial Parameter Values

Background =	0.15
Beta(1) =	2.01783
Beta(2) =	13.2357

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)	Beta(2)
Background	1	-0.71	0.51
Beta(1)	-0.71	1	-0.95
Beta(2)	0.51	-0.95	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.15	*	*	*
Beta(1)	2.01783	*	*	*
Beta(2)	13.2357	*	*	*

* - Indicates that this value is not calculated.

Error in computing chi-square; returning 2

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-71.1178	3			
Fitted model	-71.1178	3	0	0	NA
Reduced model	-76.5126	1	10.7895	2	0.00454

AIC: 148.236

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1500	3.000	3.000	20	0.000

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0.0767	0.3265	16.000	16.000	49	0.000
0.1535	0.5435	25.000	25.000	46	0.000

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

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.0411225

BMDL = 0.0192542

BMDU = 0.0887233

Taken together, (0.0192542, 0.0887233) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 5.19367

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TETRA TECH

Appendix B – Epidemiologic Studies

The following tables summarize the epidemiologic studies assessing health effects from exposure to aldrin and dieldrin. PubMed was searched for studies published after the 1987 EPA review and not included in the 2002 ATSDR review. Thirty seven studies were identified and assessed. Table 1 contains studies assessing cancer outcomes while Table 2 reviews non-cancer outcomes.

Table 1- Cancer Studies

Study	Type	Size/ Population	Methods	Exposure	Outcome	Results	Notes
Belpomme et al. 2009	Ecological Study	All prostate cancer cases diagnosed between 1995 and 2002 in Guadeloupe and between 1983 and 2002 in Martinique; 2104 cases and 4613 cases, respectively.	Data was collected from the Martinique cancer registry by the Martinique Association for Epidemiological Research on Cancer (AMREC) and data published by urologists at the University Hospital of Pointe-a-Pitre in Guadeloupe. Metropolitan France was used as a comparison by employing data from the French National Cancer Registry. For international comparison, incidence rates from Globocan 2002 (IARC) were used. Mapping was used to correlate the localization of prostate cancer with banana plantations on Martinique and Guadeloupe.	Pesticide use and concentration in adipose tissue	Prostate cancer	Through mapping analysis of soil contamination, the authors found that water contamination from pesticides comes from the banana plantations. The researchers retrospectively proved that a population of individuals examined in 1972 in Martinique for the presence of OC pesticides in their adipose tissue had been contaminated by very high amounts of DDT, DDE, alpha, beta and gamma HCH and aldrin and dieldrin.	Most of the banana plantations are located in the Northern part of the islands. However, the highest prostate cancer incidence rates were in the South-Western part of the island.

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Study	Type	Size/ Population	Methods	Exposure	Outcome	Results	Notes
Buczynska & Szadkowska -Stanczyk 2005	Risk Assess-ment	900 Inhabitants within 1.5km of 2 Polish dumpsites	286 Polish dumpsites were prioritized by their potential hazard, the amount of pesticides dumped there, proximity to residential areas and drinking water intake. The two sites selected had piezometric systems to allow for ground water sampling. 31 different pesticides were detected in ground water. Mean pesticide concentrations in ground water was used to calculate daily intake. Population data was collected from local administration units.	Daily pesticide intake from drinking water	Estimated cancer and non-cancer risks	Dieldrin was detected in water samples but not above the 0.1 ug/l drinking water standard and was not included in the risk estimates. Aldrin was not detected.	
Cantor et al. 2003	Case control	74 Non-Hodgkin's Lymphoma cases and 147 matched controls	Serum samples were collected from 25,802 individuals participating in Campaign Against Cancer and Stroke in Washington County, MD in 1974. The samples were cryopreserved so they could be studied in the future. Incident cases of NHL were identified using the Washington County Cancer Registry. Two controls were matched for every one case of NHL.	Pre-diagnostic levels of chlordane, lindane, beta-hexachlorocyclo-hexane, transnonachlor, heptachlor, heptachlor epoxide, oxychlorodane, dieldrin and hexachlorobenzene in serum samples	Non-Hodgkin's Lymph-oma	Researchers found no evidence of an association between NHL and serum levels of any of the chemicals that were evaluated.	
Clary & Ritz 2003	Ecological	950 pancreatic cancer death cases and	Cases were identified from computerized California Death Tape Files living within three selected counties and deaths	Exposure to 18 organochlorine pesticides was determined from usage	Death from pancreatic cancer	A total of 20.15 tons of dieldrin was applied in 48 of 102 zip codes. The highest quartile ranged from 0.32 to 4.43 tons.	No assessment of aldrin. Analysis controlled for age, race, education,

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Study	Type	Size/ Population	Methods	Exposure	Outcome	Results	Notes
		9,435 non-cancer death controls	occurring between 1989 and 1996. 10 non-cancer death controls, occurring during the same time period and in the same counties, for each case were randomly selected. Logistic regression was used to model total pesticide usage in each zip code for each chemical. To calculate MORs, the highest quartile of pesticide exposure was compared to the bottom three quartiles.	data between 1972-1989 for each zip code in the three counties.		The highest quartile of exposure to dieldrin compared to all lesser exposures resulted in a non-significant MOR of 1.52 among subjects having resided in the county for at least 20 years before death. A dose response patter was not observed for dieldrin exposure.	year of death, years living in county, and other pesticides. Study is unable to control for smoking. The latency that is able to be assessed here is only 1 to 12 years.
Cocco et al. 2008	Case Control	174 cases, 203 controls	Cases and controls were participants of the Epilymph study in France, Germany, and Spain. Information was collected by questionnaire and blood samples were taken. Covariates included in the final model included age, gender, education, and center.	Measurements of 17 organochlorine pesticides in plasma samples	Non-Hodgkin's Lymph-oma and subtypes	No increased risk of NHL or its subtypes was found to be associated with any of the compounds examined (including aldrin and dieldrin). There were no participants from France or Germany with aldrin or dieldrin plasma concentration levels above the detection limit; among Spanish participants there were 12 controls and 14 cases with detectable aldrin and dieldrin plasma concentrations.	Differences between countries were noted. Retrospective design limits the inferences that can be made about any associations.
Engel et al. 2005	Prospect-ive Cohort	30,454 women enrolled in the Ag Health Study (309 cases of breast	Participants enrolled between 1993 and 1997 in the Ag Health Study. Cases were identified from population-based cancer registries in Iowa and North Caroline. NDI was used to determine vital status of	Use and exposure to 50 specific pesticides was determined by questionnaires administered at enrollment by the women and their	Breast cancer diagnosis	There was no significantly increased risk among women having reported using aldrin and dieldrin. Among women who did not directly use aldrin and dieldrin but their husbands did, the RR for aldrin was 1.9 (1.3-	The authors classify the relationship between breast cancer and the husband's use of dieldrin as weak. Analysis controlled

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TETRA TECH

Study	Type	Size/ Population	Methods	Exposure	Outcome	Results	Notes
		cancer)	participants. Participants who had moved out of state were followed up using personal contacts, motor vehicle records, pesticide registration records, and IRS records. End of follow-up was 12/31/2000.	husbands.		2.7) and 2.0 (1.1-3.3) for dieldrin. RRs for 7 other pesticides were also significant among women whose husbands used pesticides. Results were not consistent when stratified by state. Risks were higher in postmenopausal women compared to premenopausal women: the RR for women whose husbands worked with aldrin was 1.7 (1.1-2.6), the RR for dieldrin still wasn't significant. Comparing low and high cumulative exposure groups of women whose husbands used dieldrin to husbands that did not use it, the respective RRs for breast cancer were 1.4 (0.6-3.5) and 3.2 (1.3-8.0).	for age, race, and state of residence.
Flower et al. 2004	Prospect-ive Cohort	17,357 children of Iowa pesticide applicators enrolled in the Ag Health Study (50 incident childhood cancer cases)	Information on exposure and other variables was provided by parents responding to questionnaires between 1993 and 1997. Cancer cases among children ages 0-19 years were identified from the Iowa Cancer registry for the period 1975-1998 (retro and prospective identification of cases). Cases from North Carolina were excluded based on small numbers. 50 specific pesticides	Use and exposure to 50 specific pesticides was determined by questionnaires administered at enrollment by the parents.	Childhood cancers	Parental use of organochlorine pesticides (including aldrin, DDT, dieldrin, heptachlor, chlordane, lindane, and toxaphene) were not significantly associated with childhood cancers while aldrin was associated with childhood cancers. There were 6 cases, OR= 2.66 (1.08-6.59).	Data for NC is not available, which may be a weakness based on the inconsistencies seen by Engel et al. Numbers were too small to look at specific types of tumors. Overall, the SIR for all childhood cancers was 1.36 (1.03-

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TETRA TECH

Study	Type	Size/ Population	Methods	Exposure	Outcome	Results	Notes
			were assessed.				1.79) but only lymphomas (9 cases) and more specifically, Hodgkin's lymphoma (5 cases) were significantly related to parental pesticide exposures. No dose-response relationship was detected.
Gammon et al. 2002	Case control	646 cases and 429 controls (women)	Cases included females residing in Nassau and Suffolk Counties on Long Island, NY who were 20 or older, spoke English and were recently diagnosed with in situ or invasive breast cancer between August 1, 1996 and July 31, 1997. They were identified through pathology labs in all of the hospitals in the Long Island region. Controls were residents of the same counties on Long Island and were frequency matched according to 5-year age group. Controls were identified through random digit dialing and Health Care Financing Administration rosters	Organochlorines (9 including dieldrin) in blood	Breast cancer	There was no significant increased risk in breast cancer in association with the highest quintile of lipid-adjusted serum levels of dieldrin and a dose-response relationship was not apparent either.	"These findings, based on the largest number of samples analyzed to date among primarily white women, do not support the hypothesis that organochlorines increase breast cancer risk among Long Island women."

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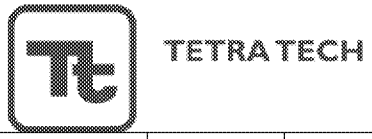

Study	Type	Size/ Population	Methods	Exposure	Outcome	Results	Notes
			depending on age. Questionnaires were administered in person by trained interviewers and samples were obtained through nonfasting blood samples.				
Høyer et al. 2001	Cohort nested case control	161 breast cancer cases and 536 controls	The breast cancer cases and matched controls participated in the Copenhagen City Heart Study (CCHS) between 1976 and 1978. Cases were identified through the Danish Cancer Registry. A random sample of 536 women matched on age and vital statistics served as controls. Information was collected on lifestyle factors, reproductive history and socioeconomic conditions using questionnaires. Serum was frozen and retrieved later for analysis.	Exposure to dieldrin	Breast cancer risk and survival according to estrogen receptor status	There was an increased breast cancer risk linked to exposure to dieldrin for women who developed estrogen receptor negative breast tumors. Women with the highest dieldrin levels in their serum generally had tumors that were larger and more often spread at diagnosis when compared to estrogen receptor positive (ERP) tumors.	"The results do not suggest that exposure to potential estrogenic organochlorines leads to development of an ERP breast cancer." This study had limited statistical power, in particular in the estrogen receptor negative tumors.
Høyer et al. 2002	Cohort nested case control	162 breast cancer cases and 316 matched controls	The breast cancer cases and matched controls participated in the Copenhagen City Heart Study (CCHS) between 1976 and 1978. Cases diagnosed between the start of the study and 1993 were found through the Danish Cancer Registry. Blood samples were taken without fasting and serum was frozen and stored.	Exposure to organochlorine pesticides	Breast Cancer and p53 mutation	A non-significant but slightly elevated risk was found in the highest level of exposure for dieldrin among women who developed a tumor with mutant p53. However, a significant dose-response relationship was present for dieldrin in 'wild-type' p53 tumors.	

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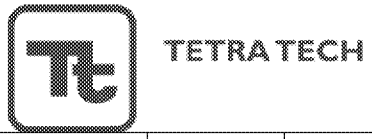

Study	Type	Size/ Population	Methods	Exposure	Outcome	Results	Notes
Ibarluzea et al. 2004	Case Control	198 cases, 260 controls	Cases and controls were selected from 3 hospitals in Southern Spain from April 1996-June 1998. Cases were women ages 35-70 undergoing surgery for newly diagnosed breast cancer. Controls were women without breast cancer, matched for age and hospital who were undergoing surgery not related to cancer. Interviews were conducted to collect data on sociodemographic factors, reproductive history, fertility, menopausal status, exogenous hormones, diet, tobacco and alcohol consumption, and family history of breast cancer.	16 Organochlorine pesticides in adipose tissue	Breast cancer	The geometric mean of aldrin in adipose was higher (but not significantly) among cases compared to controls. Overall, the OR for aldrin was 1.55 (1.0-2.4) and was 1.84 (1.06-3.18) among postmenopausal women. The only other significant risk of breast cancer was for lindane among postmenopausal women.	All women were Caucasian. Dieldrin was detected in <40% of the samples.
Mathur et al. 2002	Cross Sectional	135 cases and 50 controls	Breast cancer cases and controls were recruited from the Birla Cancer Institute, Jaipur, India. Blood samples were collected and questionnaires administered.	Questionnaire assessed age, diet, obstetrical and menstrual history, information regarding pesticide use, and geographic information.	Pesticide levels in blood breast cancer patients	Breast cancer patients had significantly higher average aldrin in blood samples than the controls (1.997 vs. 0.115 mg/L). This relationship continued to exist even after stratifying by age group for those aged 31-40 and 41-50 years old; and for all strata when stratified by urban vs. rural populations and for vegetation vs. non-vegetarian diets. Increased levels of DDT, DDE, DDD, HCH and its isomers, and heptachlor were also found.	There were no participants with any occupational or accidental exposure to pesticides.

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Study	Type	Size/ Population	Methods	Exposure	Outcome	Results	Notes
McDuffie et al. 2001	Case control	517 Non-Hodgkins's Lymophoma cases and 1506 controls in Canada	Pesticide exposure was obtained through initial postal questionnaires followed by a phone interview for individuals who reported pesticide exposure of 10 h/year or more and a 15% random sample of the remaining individuals. Cases were obtained through provincial cancer registries excluding Quebec where hospital ascertainment was employed. Controls were selected from provincial health insurance records, computerized telephone listings or voters' lists.	Exposure to herbicides	Non-Hodgkin's Lymph-oma	The odds ratios associating NHL with aldrin were statisicallly significant. Aldrin was a significant predictor in a multivariate model which included exposure to other major chemical classes or individual pesticides, personal antecedent cancer, a history of cancer among first-degree relatives.	
Purdue et al. 2007	Cohort	51,011 participants from the Ag Health Study	Questionnaires were completed at the time of enrollment (1993-1997) including information on occupation, and pesticide use and exposure. Follow-up through December 31, 2002 was conducted using Iowa and North Carolina State Cancer Registries, state death registries, and NDI. Cohort members out of state were identified using IRS records, Motor Vehicle registration databases, and pesticide license registries. Analyses adjusted for age, sex, state, education,	Ever/never use, cumulative exposure, lifetime exposure days, and intensity weighted lifetime exposure to 50 specific pesticides	Cancer	22,409 (48%) of participants ever used insecticides. Leukemia risk was greater than 1.5 (but not significant) with dieldrin use. When stratified by cumulative exposure categories, dieldrin use was significantly associated with an elevated risk of lung cancer among those with >9 days exposure [lifetime days of exposure: RR=2.8 (1.1-7.2) with p-trend=0.02; and intensity-weighted lifetime days of exposure: RR=3.5 (1.6-7.7) with p-trend=0.002]. Conversely, aldrin was associated with a	Insecticide applicators were primarily male and white.

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			smoking, alcohol use, cancer family history, and lifetime days of total pesticide application.			decreasing risk of colon cancer among those exposed to >9 intensity-weighted lifetime days of exposure [RR=0.4 (0.2-1.0) with p-trend=0.04].	
Quintana et al. 2004	Nested case control	175 Non-Hodgkin's Lymphoma cases and 481 controls taken from original cohort	A data set originally collected between 1969 and 1983 by the EPA for the U.S. EPA National Human Adipose Tissue Survey was utilized. Samples of adipose tissue were collected randomly from cadavers and surgery patients. Levels of organochlorine pesticide residues were determined through the collected samples.	Organochlorine pesticide residue in adipose tissue	Non-Hodgkin's Lymph-oma	The highest quartile level of dieldrin in adipose tissue was associated with increased risk of NHL (OR=2.70; 1.58-4.61). The p-value for trend was significant for dieldrin as well.	There are a few limitations to this study including the collection of exposure information after diagnosis as well as lack of information on variables that could affect organochlorine levels. These variables include diet, occupation and BMI.
Ritchie et al. 2003	Cross Sectional (pilot study)	58 cases, 99 controls	Incident prostate cancer cases were identified from 2 Iowa clinics. Cases were pathologically confirmed, newly diagnosed (May 2000 to May 2001), and all were adenocarcinomas. Questionnaires were administered to collect data on age, race, family history, tobacco and alcohol use, sexual partners, STDs, hormone usage. Blood samples were taken to	Blood levels of 48 organochlorine compounds	Prostate cancer	Aldrin was not detected in any of the study participants. Dieldrin was detected in 29.3% of cases and 38.4% of controls. For those with >0.024 ug/g dieldrin in serum, the adjusted OR for prostate cancer was 0.28 (0.09-0.88) and not significant at lower concentrations. Dieldrin did not remain in the multivariate model of prostate cancer risks (p=0.13).	Cases were more likely to have a history of prostatitis, be overweight, and be married. Other organochlorines were associated with increased risk of prostate cancer.

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Study	Type	Size/ Population	Methods	Exposure	Outcome	Results	Notes
			test for organochlorines.				
Schroeder et al. 2001	Case Control	182 cases and 1245 controls form the Factors Affecting Rural Men study	Authors investigated the role of agricultural risk factors for t(14,18) -positive non-Hodgkin's lymphoma (NHL), compared to t(14,18)-negative. Participants were from Iowa (identified thru the State Health Registry of Iowa) and Minnesota (identified thu active hospital surveillance). Tissues samples from male NHL cases collected by the Factors Affecting Rural Men study were assayed for t(14,18). Controls were recruited using random digit dialing. Controls were white men without hemolymphatic cancer, frequency mated on age, state, and vital status. Exposures were determined by interviews with participants or next-of-kin. Data collected included socio-demographic factors, tobacco	Self-reported exposure to 111 compounds	T(14,18)-positive non-Hodgkin's Lymph-oma	Aldrin was not associated with t(14,18) positive or negative NHL when comparing to control or positive to negative. Dieldrin was associated with t(14,18)-positive NHL when compared to controls (OR = 3.7, CI 1.9-7.0). Several other chemicals were also significantly associated with t(14,18)-positive NHL including Lindane, Toxaphene, Atrazine, and Phthalimides.	Comparisons of combinations of joint exposures between fumigants and other factors (farming, dairy cattle, chickens, pigs, soybeans, corn, fungicides, organophosphates) resulted in significantly elevated risks of t(14,18)-positive NHL among those exposed to both exposures compared to those without either exposure.

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Study	Type	Size/ Population	Methods	Exposure	Outcome	Results	Notes
			and alcohol use, hobbies, pets, medical history, occupational history, and non-occupational exposures.				
Shukla et al. 2001	Case Control	30 cases, 30 controls	Participants were patients at the surgical unit of a university hospital from March 1997 to Feb. 1999. Controls were cases of cholelithiasis. Bile and blood were collected at the time of surgery.	Organochlorines in bile	Carcinoma of the gall-bladder	Biliary and blood aldrin was higher in cases than controls but the difference was not significant.	Most participants were postmenopausal housewives (24 cases, 22 controls). All of the men worked in offices.
Sielken et al. 1999	Cohort	570 male employees who worked for at least 1 year in the production of aldrin and dieldrin between Jan. 1, 1954 and Jan. 1, 1970.	Workers were followed-up through Jan 1, 1993. Blood samples were available for 343 participants taken during the exposure period. Lifetime average daily dose was calculated for each participant as the worker's average daily dose in the period between birth and end of follow-up date. Analyses assumed no exposure to aldrin and dieldrin outside of work and that workers weighed 70 kg. Air measurements and biological samples were available for analysis. Dose response was modeled using multistage, multistage Weibull, and proportional hazards models.	Dieldrin and aldrin intake, air and biomonitoring data	Cancer Death	118 deaths including 37 cancer deaths as of Jan 1, 1993. 15% of workers had lifetime daily doses > 1ug/kg/day. Multistage and multistage Weibull dose response models showed that cancer risk was less than zero at 1ug/kg/day. Proportional hazards models resulted in estimated risks less than zero for lifetime average daily doses up to 2ug/kg/day.	"The cancer mortality data on these male workers suggest that low-dose exposures to aldrin and dieldrin do not significantly increase human cancer risk and may even decrease the human hazard rate for all types of cancer combined at low doses (e.g., 1ug/kg/day)."

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Study	Type	Size/ Population	Methods	Exposure	Outcome	Results	Notes
Swaen et al. 2002	Cohort	570 male employees who worked for at least 1 year in the production of aldrin and dieldrin between Jan. 1, 1954 and Jan. 1, 1970.	Workers were followed through Jan 1, 2001. Blood samples were available for 343 participants taken during the exposure period. Total intake of dieldrin was estimated for all participants. Air measurements and biological samples were available for analysis.	Dieldrin and aldrin intake, air and biomonitoring data	Cancer Death	Estimated dieldrin intake ranged from 11 to 7755 mg (average=737mg). There were 171 deaths and the overall SMR was 75.6 (64.6-87.7). The SMR for all neoplasms was not elevated (SMR=75.5). The only cause of death that was elevated was rectal cancer for the whole cohort and among those in the low intake group (first tertile, mean=270 mg dieldrin intake), SMR=3 (1.1-6.5) based on 6 cases and SMR=6 (1.2-17.2) based on 3 cases, respectively. When stratified by job title, only operators had any significant results, for rectal cancer SMR=5 (1.3-12.7) based on 4 cases and skin cancer SMR=7.5 (1.5-21.5) based on 3 cases.	Small numbers. "...no evidence of an increased risk for cancer of any particular type as a result of exposure to aldrin and dieldrin."
van Amelsvoort et al. 2009	Cohort	570 male employees who worked for at least 1 year in the production of aldrin and dieldrin between Jan. 1, 1954 and Jan. 1, 1970.	Workers were followed-up through April 30, 2006. Blood samples were available for 343 participants taken during the exposure period.	Dieldrin and aldrin intake, air and biomonitoring data	Cancer Death	Estimated dieldrin intake ranged from 11 to 7755 mg (average=737mg). There were 226 deaths, 82 from cancer, giving an SMR of 0.69 (0.60-0.79) for all causes of death and 0.76 (0.61-0.95) for cancer deaths. No specific cause of death or neoplasm was significantly elevated with exposure to aldrin and dieldrin at any level of exposure. However several	

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Study	Type	Size/ Population	Methods	Exposure	Outcome	Results	Notes
						causes were significantly lower than expected: For the total group, cardiovascular disease, other causes, and trachea and lung cancer; cardiovascular disease for the low and moderate intake groups; and among those experiencing high intake all neoplasms, cardiovascular disease, and trachea and lung cancer all had SMRs significantly less than 1. When stratified by job title other causes among assistant operators; all causes among maintenance workers; all causes, cardiovascular disease, respiratory disease, and trachea and lung cancer among operators were all significantly less than 1. Operators had a significantly elevated SMR of 5.76 (1.19-16.8) for skin cancer based on 3 cases.	

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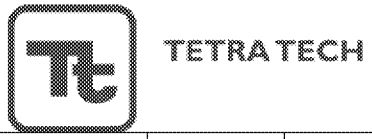

Study	Type	Size/ Population	Methods	Exposure	Outcome	Results	Notes
Ward et al. 2000	Case Control	150 cases, 150 controls	Among serum donors collected by the Janus Serum Bank in Norway between 1973 and 1991, women who worked outside the home or were resident farmers as of the 1970 or 1980 census. Of those women, breast cancer cases were determined from records of the Norwegian Cancer Registry though Dec. 31, 1993. Cancer-free controls from the same group were matched based on date of sample and date of birth. Additional data on potential confounders was collected from the Janus Serum Bank and Norwegian Cancer Registry.	71 organochlorine compounds in serum	Breast Cancer	Aldrin and Dieldrin were not associated with breast cancer.	
Xu et al. 2010	Cross-sectional	4,237 in the HANES survey including 4,109 individuals without cancer, 65 prostate cancer cases, 63 breast cancer cases	Participants provided blood samples and information about medical conditions and demographic variables.	Serum concentrations of thirteen organochlorine (OC) pesticides including dieldrin	Self-reported physician-diagnosed breast and prostate cancer	There was a marginally significant (p=0.04) trend in the Odds Ratios (OR) for prostate cancer when compared by tertiles of serum concentration of dieldrin. The OR for the second tertile was 1.06 (95% CI: 0.30-3.73), the OR for the 3rd tertile was 2.74 (95% CI: 1.01-7.49) as compared to the lowest quartile. No association was found between serum concentrations of any of the OC pesticides and breast cancer.	Due to the nature of the cross-sectional design of this study, causality between OC pesticides and cancer risk cannot be concluded.

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Table 2- Epidemiologic Studies of Non-Cancer Endpoints

Study	Type	Size/ Population	Methods	Exposure	Outcome	Results	Notes
Akkina et al. 2004	Cross Sectional	219 menopausal women in Hispanic Health NHANES	1982-1984 survey years of the Hispanic Health NHANES were used. Data on age at menopause, reproductive history, demographic variables, other potential confounders were collected as part of the survey. Serum samples were also collected. ANOVA was used to investigate the relationship between age at menopause and serum levels of pesticides.	18 organochlorine pesticides in serum	Age at menopause	Serum levels of dieldrin were above the detection limit (1ppb) in 19 individuals (8.7%). Dieldrin was not associated with age at menopause.	Serum levels of pesticides may not represent exposure at the time of menopause. Time from menopause to survey ranged from 0 to 37 years.
Asawasinsopon et al. 2006	Cross Sectional	39 mother-infant pairs Chian Pai province, Thailand	Participants were mother-infant pairs having normal, full term pregnancies. Women diagnosed with hypothyroid were ruled out. Questionnaires collected data on lifestyle, pesticide use/exposure, and delivery history. Maternal blood was collected 2-5 hours before delivery. Umbilical cord blood was collected when it was cut.	Organochlorines in maternal serum and in umbilical cord blood	Levels of thyroid hormones (total thyroxine, free thyroxine, thyroid stimulating hormone)	Level of dieldrin was positively correlated between material and umbilical cord blood. However, thyroid hormone levels did not vary with dieldrin levels. Significant decreases in total thyroxine were noted for 3 other pesticides.	This study is very small with only 39 births being analyzed. There is no indication of actual health effects among these children after birth.

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Damgaard et al. 2006	Case-Control	62 milk samples from mothers of cryptorchid boys and 68 milk samples from mothers of healthy boys	A joint longitudinal, prospective birth cohort study was performed by the authors in Finland and Denmark from 1997 to 2001. They examined regional prevalence rates and risk factors for cryptorchidism through questionnaires and biological samples including one breast milk sample per child. From the bank of breast milk samples, the researchers included 65 samples from each country (Denmark and Finland) to examine organochlorine pesticide exposures. Cases were defined as boys with cryptorchidism at birth and controls were defined as boys without cryptorchidism at birth or 3 months old. Breast milk was collected between 1 and 3 months postpartum and was analyzed for 27 OC pesticides.	Organochlorine pesticides in human breast milk	Crypt-orchidism	Eight of the OC pesticides were measurable in all samples (p,p'-DDE, β-HCH, HCB, α-endosulfan oxychlordane, p,p'-DDT, dieldrin, cis-HE). Five were measured in most samples. Seventeen of the 21 OC pesticides including dieldrin were measured in higher median concentrations in case breast milk compared to control breast milk. Except for trans-chlordane, there were no significant differences between cases and controls for individual pesticide chemicals. However, combined statistical analysis of the eight pesticides measured in all samples shows that the levels of pesticides in breast milk were significantly higher in cryptorchid boys.	This study cannot provide proof for a causal relationship because it cannot be proven that exposure preceded disease.
Everett & Matheson 2010	Cross Sectional	2341 NHANES participants used to examine exposure to dieldrin	Study of NHANES 1999-2004 survey years. Associations were tested using logistic regression adjusting for age, race, gender, education, poverty income ratio, BMI, waist circumference, physical activity, and family history of diabetes.	8 pesticides and their metabolites were measured in non-fasting blood samples	Diagnosed and undiagnosed diabetes and pre-diabetes (glycohemo-globin 5.7-6.54%) based on self-report and glycohema-globin measure-ments	Dieldrin was not associated with total diabetes (diagnosed, undiagnosed, and pre-diabetes) OR=1.19 (0.70-2.04), or to pre-diabetes OR=0.89 (0.61-1.29).	No assessment of aldrin, no environmental information, no occupational or residential information was used in the analysis.

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Fenster et al. 2005	Cohort	385 Latinas living in the Salinas Valley, CA, an agricultural community.	Participants were part of a longitudinal birth cohort study, the Center for the Health Assessment of Mothers and Children of Salina project of the Center for Children's Environmental Health Research. Eligible women were <20 weeks gestation, at least 18 years old, eligible for Medi-Cal, and planning on giving birth at the Natividad Medical Center. Data was collected from interviews and medical record abstraction. Serum was drawn from the mothers at approximately 26 weeks gestation and at the hospital before delivery. Models were adjusted for maternal age, parity, country of birth, family income, timing of entry into prenatal care, smoking, total dimethyls at 26 weeks, pregnancy weight gain, prepregnancy BMI, total DAPs in urine at 26 weeks, infant sex, gestational age and gestational age squared.	11 organochlorine pesticides in maternal serum	Infant's length of gestation, birth weight, and crown-heel length	Neither crude nor adjusted associations between health effects in infants and maternal serum dieldrin concentration during pregnancy were found.	Results are not generalizable as most women were Latina and born in Mexico, and selection was limited to low-income families.
Fowler et al. 2007	Experi-mental	In vitro exposure of fetal human testis from women undergoing medical termination of pregnancy.	Investigators collected fetal testes from medically terminated normal pregnancies between 13 and 19 weeks of gestation. An in vitro experiment was carried out by exposing testes explants to 0.4ppb, 0.0004ppb or no dieldrin. Investigators performed immunolocalization of marker proteins, 2-dimensional gel electrophoresis and mass spectroscopy, 1-dimensional gel electrophoresis and western blot, and hormone assays.	Dieldrin in vitro	Leydig cell disruption	Dieldrin blocked LH-induced testosterone secretion from fetal testis explants in vitro. Dieldrin also blocked tissue protein concentrations of LH receptor and steroid acute regulatory protein. Dieldrin had no direct toxicological effects on the testis explants and no effect on anti-Mullerian hormone.	There were 2 to 4 specimens available for each treatment group of each experiment.

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Landgren et al. 2009	Cohort	678 men participat-ing in the Ag Health Study - stratified random sample of 57,310 licensed pesticide applicators.	Age-adjusted prevalence of MGUS among the men in the Ag Health Study were compared to 9,469 men from MN. Exposure to pesticide was self-reported at time of study enrollment (1993-1997) and serum samples were collected between 2006 and 2008. Logistic regression was used to control for age, education.	Self-reported pesticide use and pesticide concentrations in serum	Mono-clonal gammo-pathy of undeter-mined significance (MGUS)	Among those ever reporting exposure to dieldrin, the OR for MGUS was 5.6 (1.9-16.6) based on 6 cases. Two other compounds were significantly associated with increased risk of MGUS out of 50 compounds tested.	Excess risk of MGUS associated with dieldrin was not attenuated when adjusted for the use of other pesticides. The comparison group from MN was chosen because the Mayo Clinic had the largest MGUS screening study available at the time this study was conducted.
Li et al. 2005	Review		Comprehensive review of toxicological and epidemiological studies of the association between pesticides and Parkinson's Disease (PD). Analytic epidemiology studies were required to examine pesticide exposure (not farm work or rural residence, and broad descriptions like 'agricultural chemicals') and an outcome based on the PD case definition (i.e., not just a tremor).	Any pesticide, insecticide or herbicide	Parkinson's Disease	"We conclude that the animal and epidemiological data reviewed do not provide sufficient evidence to support a causal association between pesticide exposure and Parkinson's disease." 27 case control studies were reviewed, 16 reported no significant association between pesticides, herbicides, and/or insecticides and PD. None of the studies reviewed included any biomarker or environmental data. Base on the epidemiology studies alone, the authors concluded that the evidence is mixed. Dieldrin exposure in animal models is discussed and the authors conclude that it does not cause effects consistent with an animal model of PD.	Only one person scored the studies discussed in the paper.

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Louis et al. 2006	Case Control	136 cases and 144 controls	Cases were treated at the Neurological Institute of New York and identified from a database at the Center for Parkinson's disease and other movement disorders. Those with physical signs/diagnoses of Parkinsonism, dystonia, spinocerebellar ataxia were excluded. Controls were ascertained from the same source and from the same zip codes as cases, matched by age-strata, gender, and race. Questionnaires administered by a trained tester; videotaped neurological evaluations; serum samples collected; occupational histories evaluated by an industrial hygienist were all analyzed using Chi-square and student's T-tests, and Pearson correlation coefficients.	Exposure to 6 organochlorine pesticides was assessed by serum concentrations and occupational histories.	Essential Tremor	No association between ET and any of the 6 pesticides tested in serum. Parity (in women) was the only variable significantly associated with log dieldrin.	The authors report that they needed 160 cases and 160 controls to have adequate statistical power to detect a 20% difference based on a pilot study.
Montgomery et al. 2008	Cohort	31,787 pesticide applicators in the Ag Health Study	All data was collected from questionnaires at the time of study enrollment and after 5 years. Participants having diabetes at enrollment and those missing information pertaining to diabetes or other covariates (age, state, BMI) were excluded. Lifetime exposure to pesticides was calculated from reported use at enrollment (1993-1997). Only pesticide applicators were included (not family members); 97% were non-Hispanic White and 97% were male.	Cumulative number of days and ever/never use of 50 specific pesticides	Diabetes	1,176 diagnosed diabetics and 30,611 non-diabetics were self-reported after a 5-year follow-up interview (conducted 1999-2003). The adjusted ORs (95% CI) found for exposure to aldrin are as follows: Ever use- 1.14 (0.97-1.33) compared to never users; 0.01-10 cumulative days of use: 0.84 (0.59-1.19), 10.01-100 days: 1.21(0.89-1.65), and over 100 days: 1.51 (0.88-2.58), with a p-value for trend of 0.08; additionally stratifying by age < and > 60 years and by state resulted in elevated but not significant ORs. When stratified by weight, under and normal, and overweight, individuals had elevated but not significant risks of diabetes with use of aldrin, however, obese individuals reporting ever use of aldrin had an OR=1.31 (1.05-1.63) for diabetes.	Not generalizable- the study was mostly white men, in rural areas. The study does not specify type I or type II diabetes, which are very different in etiology. Diabetes was only self-reported, not confirmed by a physician.

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Nagayama et al. 2007	Cross Sectional	92 Japanese mother-infant pairs living in or near Fukuoka, Japan.	Participants were recruited in the months of July and August of 1994-1996. Infants that were carried to term, without congenital abnormalities or disease, with normal pregnancies were included. Breast milk samples were collected 2-4 months after delivery. Peripheral venous blood was collected from infants at about 10 months of age. Lymphocyste subsets and ratio of CD4+ T cell to CD8+ T cell were investigated in vitro.	Pesticides in breast milk	Lymphocyte subsets (CD16+, HLA-DR+, CD4+, CD8+, CD3+,CD20+) percentage and ratio	While other pesticides were significantly associated with increases or decreases in lymphocyte subset percentages, dieldrin was not.	There is no consideration of other environmental, viral, bacterial, causes for changes in immune response. No attempt was made to measure exposure in utero.
Noakes et al. 2006	Cross Sectional	31 women in Western Australia	Participants were randomly selected among pregnant women undergoing caesarean section in 2001-2002, at a Hospital in an area of Western Australia where allergenic disease is epidemic. Maternal and neonate blood samples, maternal milk and adipose, and placental tissue was used to determine levels of persistent organic pollutants. Cord blood and maternal blood was collected for cytokine and lymphoproliferation response analyses. Immune responses were investigated in vitro. Data was analyzed by comparing medians and IQRs using Spearman rank correlation.	Persistent organic pollutants in maternal blood, adipose and breast milk, and in cord blood and placental tissue.	Allergenic immune response in women and infants	Aldrin was not present at detectable levels in any of the samples. While dieldrin was detected (in 1 adipose sample, 8 breast milk samples) it was not associated with any change in immune response.	All subjects had pollutant levels much less than has previously been associated with any subclinical effects.
Tomasallo et al. 2010	Cohort	3847 individuals and 1141 referents	Participants were originally recruited in 1993 and sport fish anglers studied in 1986 in the Great Lakes region. They included charter boat captains, their spouses, and sport fish anglers; referents were from the same communities but did not consume sport fish and less than 6 sport fish meals over the previous 10 years. Follow-up surveys were conducted in 1993-1995 by telephone. NDI was used to identify 342 deaths.	Total fish consumption, number of sport fish meals from the Great Lakes. The fish were expected to contain a variety of persistent bioaccumulative toxins.	Mortality	Fish consumption was not shown to be associated with any specific cause of death.	Dieldrin exposure was not specifically measured or tested.

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			Information on fish consumption and confounders (race, age, gender, BMI, education, annual income, and limited data for smoking and alcohol consumption) were collected from surveys. Analyses included Cox proportional hazards models and calculation of SMRs.				
Weisskopf et al. 2010	Case Control	101 cases, 349 controls	Incident Parkinson's disease cases and controls were identified from the Finnish Mobile Clinic Health Examination Survey. The survey collected serum samples between 1968 and 1972 (analyzed in 2005-2007 for organochlorine pesticides). Cases were identified in the Social Insurance Institution's registry and were confirmed by medical records. Controls were matched by age, sex, municipality, and vital status. Logistic Regression was used to analyze the dataset.	Organochlorine pesticides in serum.	Parkinson's Disease	Dieldrin was the only chemical with any association to Parkinson's disease in this analysis. The average serum concentration of dieldrin was 39.6ng/g lipid and the median was 40 ng/g lipid. Geometric mean serum concentrations of dieldrin differed significantly based on region, smoking, and increase in BMI units per year. Analyses restricted to confirmed cases of never smokers, the OR per IQR was 1.95 (1.26-3.02), and for never smokers over the age of 66 the OR per IQR was 2.55 (1.58-4.39). For all cases, including those not confirmed by medical records but restricted to never smokers, risks were elevated but not significantly. The IQR is 28.2 ng/g lipid of dieldrin.	Aldrin was detected in 11.5% of controls, and 12.9% of cases. Never smokers have a higher risk of PD than ever smokers. The amount of time from collection of the samples to when cases were diagnosed presents problems with interpretation. Other risk factors such as genetics, head trauma, declining estrogen level, and family history were not considered.

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Appendix C: Benchmark Dose Analysis of Non-Cancer Effects of Aldrin

Introduction

In the 1993 IRIS document for Aldrin (CAS No. 309-00-2), the U.S. EPA calculated an oral Reference Dose (RfD) of 0.00003 mg/kg/day. The study on which the RfD was based was Fitzhugh et al. 1964, a study in which 12 rats/sex were fed diet containing 0, 0.5, 2, 10, 50, 100, or 150 ppm Aldrin for 2 years. The critical effects in this study were signs of liver toxicity, including enlarged centrilobular hepatic cells, with increased cytoplasmic oxyphilia, and peripheral migration of basophilic granules in dose levels ≥ 0.5 ppm. The authors of the paper described these effects as characteristic "chlorinated insecticide" lesions. Liver-to-body weight ratios were statistically significantly higher than controls in all aldrin treatments. The lowest dose of 0.5 ppm in the diet was determined to be the lowest observed adverse effect level (LOAEL). Because 0.5 ppm was the lowest dose level tested, a no observed adverse effect level (NOAEL) was not established. IRIS converted the LOAEL to 0.025 mg/kg-day, using the conversion factor of 1 ppm = 0.05 mg/kg-day. The RfD was formulated by dividing the LOAEL by an uncertainty factor of 1000 rounding: (0.025 mg/kg-day)/1000 = 0.000025 ≈ 0.00003 mg/kg/day. The uncertainty factor was based on extrapolation from animal to human (10), range of human sensitivities (10), and use of a LOAEL rather than a NOAEL (10).

ATSDR (2002) also used the Fitzhugh et al. 1964 study to develop a Minimal Risk Level (MRL) of 0.00003 mg/kg/day for aldrin. The MRL was calculated based on the same reasoning and calculations as the IRIS RfD.

Method

A benchmark dose (BMD) approach was used to derive a new RfD for aldrin based on the data reported by Fitzhugh et al. 1964. The U.S. EPA's BMDS 2.1.2 software package was used. BMDS 2.1.2 is the latest version of the BMDS series, released by EPA in June 2010.

One of the strengths of the BMD method is that it uses quantitative data. Unfortunately this strength is also a limitation in that the types of data required are not always available in published studies. The Fitzhugh et al. 1964 paper includes two tables that provide data about the liver toxicity of aldrin. Table 2 provides mean liver weight to body weight ratios for male and female rats that had been treated with 0.5 to 150 ppm aldrin. These data would be good for a BMD analysis by use of a Continuous Data model, except that the Continuous Data model requires means to be accompanied by standard deviations. Table 2 of the Fitzhugh paper does not report standard deviations in its mean organ weights table, so these data cannot be applied in a BMD model.

Table 4 of the Fitzhugh paper (see next page) reports the incidences of "characteristic chlorinated pesticide changes" in the liver of aldrin-treated rats. These are quantal data and can be used in a Dichotomous Model in the BMDS 2.1.2 software. The authors divided the incidences of observed liver lesions into categories of severity (from Trace to Moderate and >

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Moderate). For simplicity, the total observations for all lesions were entered into the BMDS data input spreadsheet.

Table 4 from Fitzhugh et al. 1964 (Note, only Aldrin data were used in this modeling):

Table 4. *Characteristic "chlorinated insecticide" changes in livers of rats fed aldrin or dieldrin*

Compound and feeding level (ppm)	Degree of liver change*						Number microscopically sectioned
	N	T	VS	S	S–M & M	>M	
None	16	1	0	0	0	0	17
Aldrin							
0·5	15	4	0	0	0	0	19
2	10	8	0	1	0	0	19
10	11	3	7	1	0	0	22
50	0	0	0	6	10	2	18
100	0	0	0	0	5	6	11
150	0	0	0	0	2	7	9
Dieldrin							
0·5	17	4	0	1	0	0	22
2	12	5	5	1	0	0	23
10	7	7	3	1	0	0	18
50	0	0	3	8	6	3	20
100	0	0	1	1	8	8	18
150	0	0	0	1	5	5	11

*Among the symbols for the different grades of liver lesions, N=none, T=trace or minimal, VS=very slight, S=slight, and M=moderate. The figures for various degrees of liver lesions are based on the microscopic sections.

In order to make the BMD calculations more applicable to human risk from exposure to aldrin, the dose levels in ppm were converted into Human Equivalent Dose (HED) levels in units of mg/kg-day. The two steps in estimating the HED from the animal dose are: (1) converting the dietary concentrations to milligrams per kilograms per day in the animals; and (2) converting the animal dose to the equivalent human dose. ATSDR and IRIS used an assumption that 1 ppm = 0.05 mg/kg-day to convert the rat dose levels to units of mg/kg-day. The second step used the "¾ power" assumption where the human equivalent dose, in units of milligrams per kilograms body weight per day, is equal to the animal dose × (animal body weight/70)$^{1/4}$, where the rat body weight was estimated from Figure 1 of the Fitzhugh paper to be approximately 450 g, or 0.450 kg. The formulae and table below summarize the calculations to convert rat dose in ppm to HED in mg/kg/day.

Rat dose in mg/kg-day = (dose in ppm) x 0.05 mg/kg-day.

Rat dose to HED conversion factor = $(0.450/70)^{1/4}$ = 0.2831578

HED in mg/kg-day = (Rat dose in mg/kg-day) x 0.2831578

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Calculation of Human Equivalent Dose

PPM in Diet	Rat Dose (mg/kg-day)	Human Equivalent Dose (mg/kg-day)
0	0	0
0.5	0.025	0.0070789
2	0.1	0.028316
10	0.5	0.14158
50	2.5	0.07089
100	5	1.4158
150	7.5	2.1237

Results

The BMD analysis of the liver lesion data are presented in the table below, and the BMDS input data, model parameters, and output are presented in subsequent pages. The first model was run in the Dichotomous Multistage model, as this is the simplest model for quantal data. The first run results using the entire range of doses were acceptable. In BMDS modeling, the highest dose level is commonly removed to see if it improves the fit of the curve to the data points. In the liver lesion data set, both the full data set and removal of the highest dose produced curves with acceptable p-value and scaled residuals, and the Akaike Information Coefficient (AIC) values were identical.

Run	Data Set	P-value[1]	Highest Scaled Residual[2]	AIC[2]	Visual Assessment of Curve to Data Points[4]	BMD	BMDL[5]
1	All Data	0.1835	1.938	96.3408	Good	0.0233849	0.0120675
2	All Except High Dose	0.1015	1.938	96.3408	Good	0.0233849	0.0120675

1 For the model to be acceptable, P-value must be > 0.1.
2 Scaled residuals report the gap between the curve line and the actual data points; for the model to be acceptable, all scaled residuals must have an absolute value of < 2.
3 The Akaike Information Coefficient (AIC) is used for comparison between models; generally, a lower AIC value indicates a better curve fit to the data.
4 Even when the numbers indicate a good curve fit, a visual inspection of the graph is important to ensure the curve is not wavy or contains other aberrations.
5 BMDL = Lower one-sided confidence limit on the BMD.

Conclusion

In both runs of the liver lesion data, with and without the highest dose level, the reported BMD was identical, 0.0233849 mg/kg-d. The BMDL was 0.0120675 mg/kg-d.

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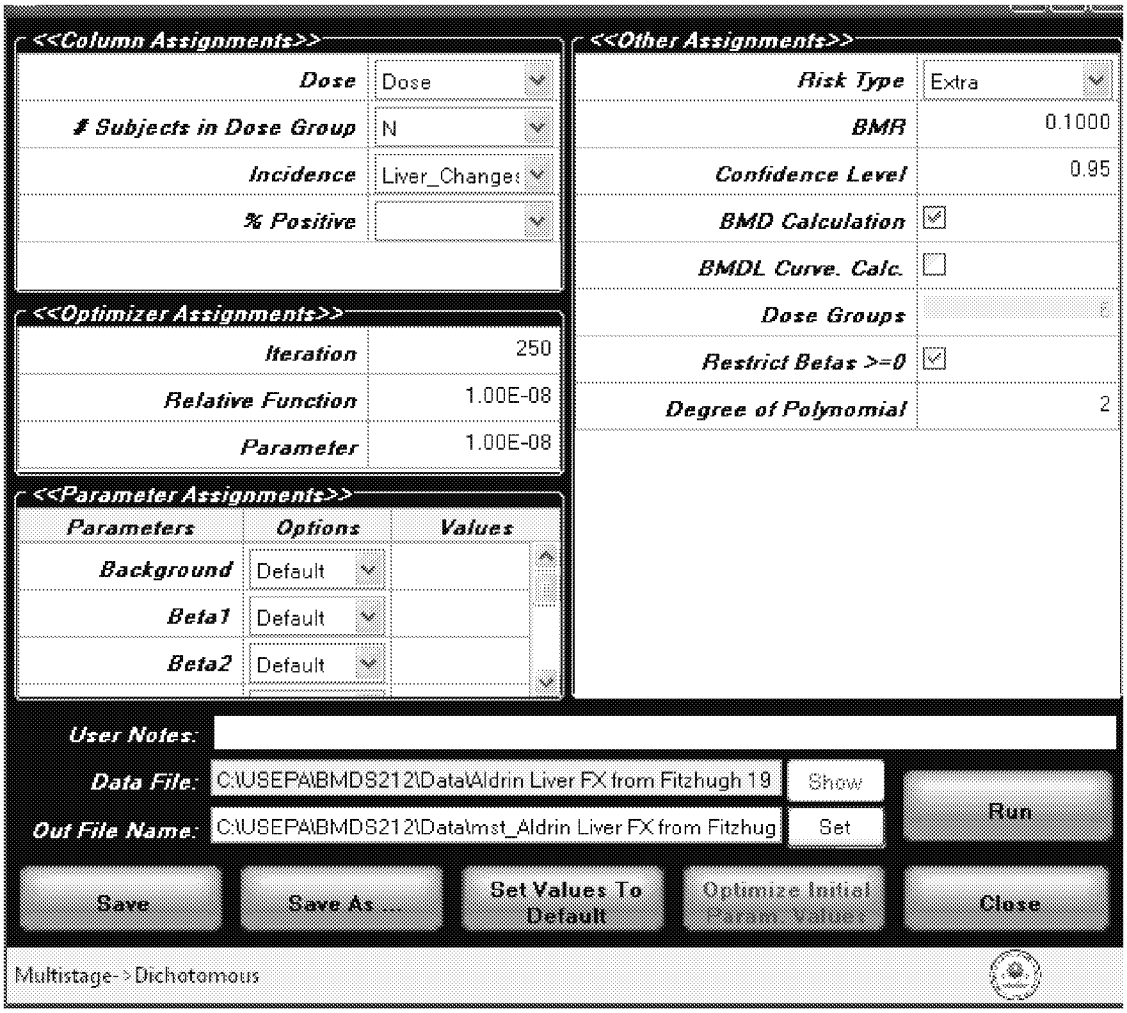
BMDS Input Data Set:

Model Type: Dichotomous Model Name: Multistage

	Dose	N	Liver_Changes	Col4	Col5
1	0	17	1		
2	0.007079	19	4		
3	0.02832	19	9		
4	0.1416	22	11		
5	0.7079	18	18		
6	1.416	11	11		
7	2.124	9	8		

Model Parameters:



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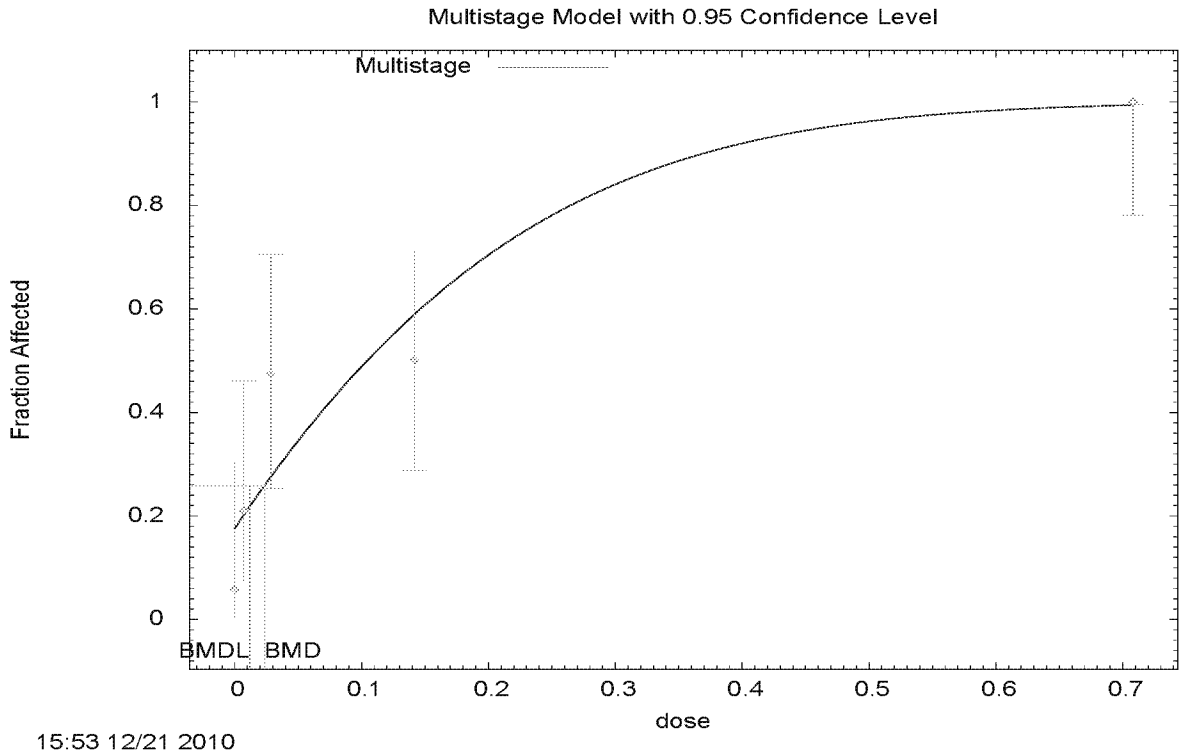
Output for Run 1, Complete Data Set (All Dose Levels):




```
 ===================================================================
        Multistage Model. (Version: 3.2;  Date: 05/26/2010)
        Input Data File: C:/USEPA/BMDS212/Data/mst_Aldrin Liver FX from Fitzhugh
1964_Opt.(d)
        Gnuplot Plotting File:  C:/USEPA/BMDS212/Data/mst_Aldrin Liver FX from
Fitzhugh 1964_Opt.plt
                                                Tue Dec 21 15:52:46 2010
 ===================================================================

 BMDS_Model_Run
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   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = Liver_Changes
   Independent variable = Dose

 Total number of observations = 7
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2
```

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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 = 1
Beta(1) = 5.54426e+019
Beta(2) = 0

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)	Beta(2)
Background	1	-0.65	0.41
Beta(1)	-0.65	1	-0.78
Beta(2)	0.41	-0.78	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.176075	*	*	*
Beta(1)	4.42317	*	*	*
Beta(2)	3.52018	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-41.9743	7			
Fitted model	-45.1704	3	6.39212	4	0.1717
Reduced model	-79.185	1	74.4214	6	<.0001

AIC: 96.3408

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1761	2.993	1.000	17	-1.269
0.0071	0.2016	3.831	4.000	19	0.097
0.0283	0.2751	5.227	9.000	19	1.938
0.1416	0.5896	12.971	11.000	22	-0.854
0.7079	0.9938	17.889	18.000	18	0.334
1.4160	1.0000	11.000	11.000	11	0.004
2.1240	1.0000	9.000	9.000	9	0.000

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Chi^2 = 6.22 d.f. = 4 P-value = 0.1835

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.0233849

BMDL = 0.0120675

BMDU = 0.0897018

Taken together, (0.0120675, 0.0897018) is a 90 % two-sided confidence interval for the BMD

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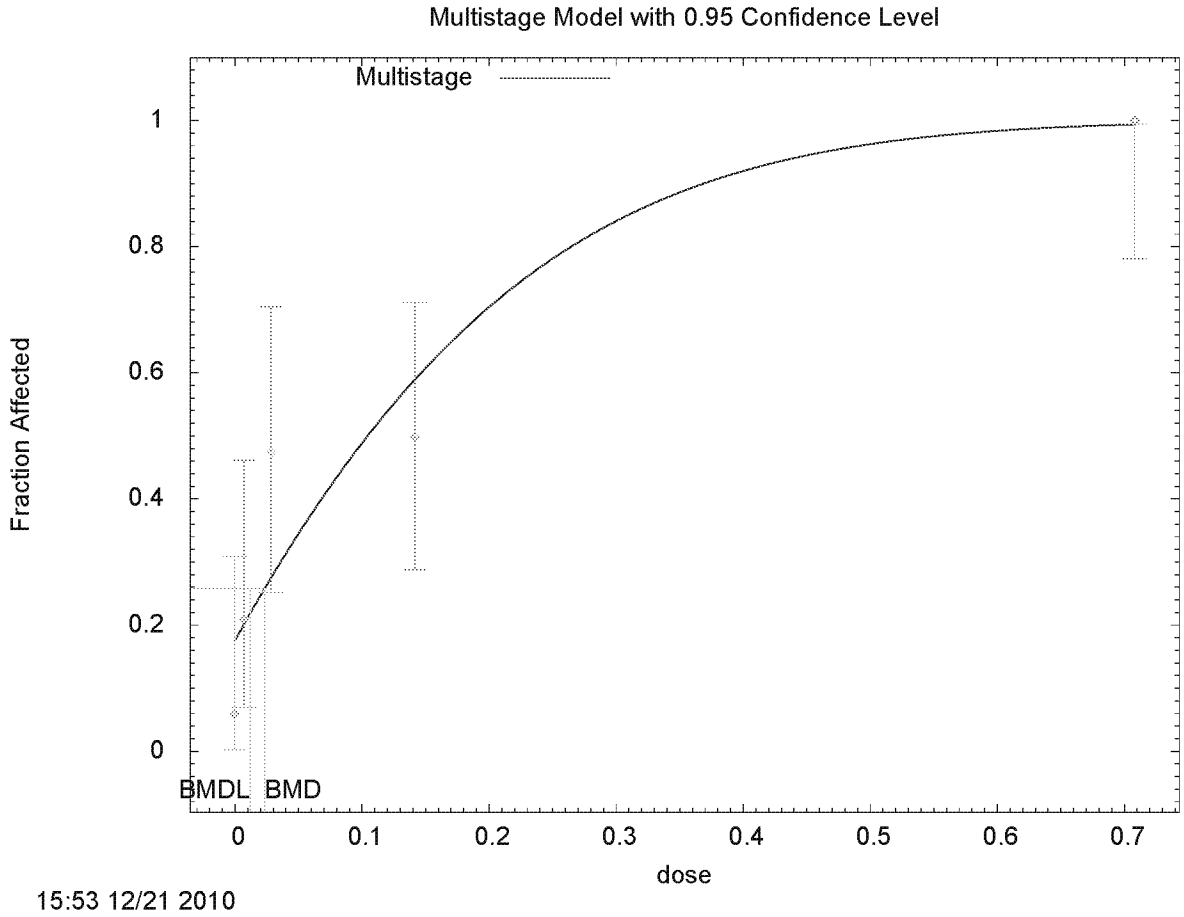
Output of Run 2, Data Set Excluding Highest Dose Group:




```
 ====================================================================
        Multistage Model. (Version: 3.2;  Date: 05/26/2010)
        Input Data File: C:/USEPA/BMDS212/Data/mst_Aldrin Liver FX from Fitzhugh
1964_Opt.(d)
        Gnuplot Plotting File:  C:/USEPA/BMDS212/Data/mst_Aldrin Liver FX from
Fitzhugh 1964_Opt.plt
                                                Tue Dec 21 15:51:33 2010
 ====================================================================

 BMDS_Model_Run
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   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = Liver_Changes
   Independent variable = Dose

 Total number of observations = 6
```

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

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

Default Initial Parameter Values

Background =	1
Beta(1) =	8.25022e+019
Beta(2) =	0

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)	Beta(2)
Background	1	-0.65	0.41
Beta(1)	-0.65	1	-0.78
Beta(2)	0.41	-0.78	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.176075	*	*	*
Beta(1)	4.42317	*	*	*
Beta(2)	3.52018	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-41.9743	6			
Fitted model	-45.1704	3	6.39212	3	0.09402
Reduced model	-73.4547	1	62.9608	5	<.0001

AIC: 96.3408

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1761	2.993	1.000	17	-1.269
0.0071	0.2016	3.831	4.000	19	0.097
0.0283	0.2751	5.227	9.000	19	1.938

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0.1416	0.5896	12.971	11.000	22	-0.854
0.7079	0.9938	17.889	18.000	18	0.334
1.4160	1.0000	11.000	11.000	11	0.004

Chi^2 = 6.22 d.f. = 3 P-value = 0.1015

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.0233849

BMDL = 0.0120675

BMDU = 0.0897018

Taken together, (0.0120675, 0.0897018) is a 90 % two-sided confidence interval for the BMD

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Appendix D: Benchmark Dose Analysis of Non-Cancer Effects of Dieldrin

Introduction

In the 1993 IRIS document for Dieldrin (CAS No. 60-57-1), the U.S. EPA calculated an oral Reference Dose (RfD) of 0.00005 mg/kg/day. The study on which the RfD was based was Walker et al. 1969, a study in which 12 rats/sex were fed diet containing 0, 0.1, 1.0, or 10.0 ppm Dieldrin for 2 years. IRIS converted the ppm dose levels to mg/kg-day, using the conversion factor of 1 ppm = 0.05 mg/kg-day. At the end of 2 years, females fed 1.0 and 10.0 ppm (0.05 and 0.5 mg/kg/day) had increased liver weights and liver-to-body weight ratios ($p<0.05$). Histopathological examinations revealed liver parenchymal cell changes including focal proliferation and focal hyperplasia at the 10 ppm dose level. These hepatic lesions were considered to be characteristic of exposure to an organochlorine insecticide. The LOAEL was identified by EPA as 1.0 ppm (0.005 mg/kg/day) and the NOAEL as 0.1 ppm (0.005 mg/kg/day). The RfD was formulated by dividing the LOAEL by an uncertainty factor of 100: (0.005 mg/kg-day)/100 = 0.00005 mg/kg/day. The uncertainty factor was based on extrapolation from animal to human (10) and range of human sensitivities (10).

ATSDR (2002) also used the Walker et al. 1969 study to develop a Minimal Risk Level (MRL) of 0.00005 mg/kg/day for dieldrin. The MRL was calculated based on the same reasoning and calculations as the IRIS RfD.

Method

A benchmark dose (BMD) approach was used to derive a new RfD for dieldrin. The U.S. EPA's BMDS 2.1.2 software package was used. BMDS 2.1.2 is the latest version of the BMDS series, released by EPA in June 2010.

One of the strengths of the BMD method is that it uses quantitative data. Unfortunately this strength is also a limitation in that the types of data required are not always available in published studies. The data presented in Walker et al. 1969 was not suitable for a BMD model, because the data displaying the sensitive endpoint (liver lesions, Table 5 of Walker et al. 1969) did not represent a clear dose-response, and the authors determined that the liver lesions reported in this table were deemed to not be associated with organochlorine insecticides. The liver weight data in Table 4 of Walker et al. 1969 were a suitable fit for BMD modeling, but liver weight increases in the absence of other signs of liver toxicity (e.g., histopathology or clinical chemistry) is an adaptive response to increased metabolism of the chemical and is generally not considered to be an adverse effect (Sipes and Gandolfi 1991; Amacher et al. 1998). Therefore, Walker et al. 1969 did not present any data set that could be applied to a BMD model .

When JMPR (1967) reviewed the chronic rat toxicity of dieldrin, they identified the liver lesions reported by Fitzhugh et al. 1964 to represent the sensitive endpoint for dieldrin-induced liver toxicity. A BMD model analysis was conducted based on the data reported by Fitzhugh et al. 1964. Table 4 of the Fitzhugh paper (see next page) reports the incidences of "characteristic chlorinated pesticide changes" in the liver of aldrin-treated rats. These are quantal data and

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can be used in a Dichotomous Model in the BMDS 2.1.2 software. The authors divided the incidences of observed liver lesions into categories of severity (from Trace to Moderate and > Moderate). For simplicity, the total observations for all lesions were entered into the BMDS data input spreadsheet.

Table 4 from Fitzhugh et al. 1964 (Note, only Dieldrin data were used in this modeling):

Table 4. *Characteristic "chlorinated insecticide" changes in livers of rats fed aldrin or dieldrin*

Compound and feeding level (ppm)	Degree of liver change*						Number microscopically sectioned
	N	T	VS	S	S–M & M	>M	
None	16	1	0	0	0	0	17
Aldrin							
0·5	15	4	0	0	0	0	19
2	10	8	0	1	0	0	19
10	11	3	7	1	0	0	22
50	0	0	0	6	10	2	18
100	0	0	0	0	5	6	11
150	0	0	0	0	2	7	9
Dieldrin							
0·5	17	4	0	1	0	0	22
2	12	5	5	1	0	0	23
10	7	7	3	1	0	0	18
50	0	0	3	8	6	3	20
100	0	0	1	1	8	8	18
150	0	0	0	1	5	5	11

*Among the symbols for the different grades of liver lesions, N=none, T=trace or minimal, VS=very slight, S=slight, and M=moderate. The figures for various degrees of liver lesions are based on the microscopic sections.

In order to make the BMD calculations more applicable to human risk from exposure to aldrin, the dose levels in ppm were converted into Human Equivalent Dose (HED) levels in units of mg/kg-day. The two steps in estimating the HED from the animal dose are: (1) converting the dietary concentrations to milligrams per kilograms per day in the animals; and (2) converting the animal dose to the equivalent human dose. ATSDR and IRIS used an assumption that 1 ppm = 0.05 mg/kg-day to convert the rat dose levels to units of mg/kg-day. The second step used the "¾ power" assumption where the human equivalent dose, in units of milligrams per kilograms body weight per day, is equal to the animal dose × (animal body weight/70)$^{1/4}$, where the rat body weight was estimated from Figure 1 of the Fitzhugh paper to be approximately 450 g, or 0.450 kg. The formulae and table below summarize the calculations to convert rat dose in ppm to HED in mg/kg/day.

Rat dose in mg/kg-day = (dose in ppm) x 0.05 mg/kg-day.

Rat dose to HED conversion factor = $(0.450/70)^{1/4}$ = 0.2831578

HED in mg/kg-day = (Rat dose in mg/kg-day) x 0.2831578

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Calculation of Human Equivalent Dose

PPM in Diet	Rat Dose (mg/kg-day)	Human Equivalent Dose (mg/kg-day)
0	0	0
0.5	0.10.025	0.0070789
2	0.50.1	0.028316
10	2.50.5	0.14158
50	52.5	0.07089
100	5	1.4158
150	7.5	2.1237

Results

The BMD analysis of the liver lesion data are presented in the table below, and the BMDS input data, model parameters, and output are presented in subsequent pages. The Dichotomous Multistage model was used, as this is the simplest model for quantal data. The first run results using the entire range of doses were acceptable. In BMDS modeling, the highest dose level is commonly removed to see if it improves the fit of the curve to the data points. In the liver lesion data set, both the full data set and removal of the highest dose produced curves with acceptable p-value and scaled residuals, and the Akaike Information Coefficient (AIC) values were identical.

Run	Data Set	P-value[1]	Highest Scaled Residual[2]	AIC[2]	Visual Assessment of Curve to Data Points[4]	BMD	BMDL[5]
1	All Data	0.2937	1.579	96.2317	Good	0.0136975	0.00837329
2	All Except High Dose	0.2937	1.579	96.2317	Good	0.0136975	0.00837329

1 For the model to be acceptable, P-value must be > 0.1.
2 Scaled residuals report the gap between the curve line and the actual data points; for the model to be acceptable, all scaled residuals must have an absolute value of < 2.
3 The Akaike Information Coefficient (AIC) is used for comparison between models; generally, a lower AIC value indicates a better curve fit to the data.
4 Even when the numbers indicate a good curve fit, a visual inspection of the graph is important to ensure the curve is not wavy or contains other aberrations.
5 BMDL = Lower one-sided confidence limit on the BMD.

Conclusion

In both runs of the liver lesion data, with and without the highest dose level, the reported BMD was identical, 0.0136975 mg/kg-d. The BMDL was 0.00837329 mg/kg-d.

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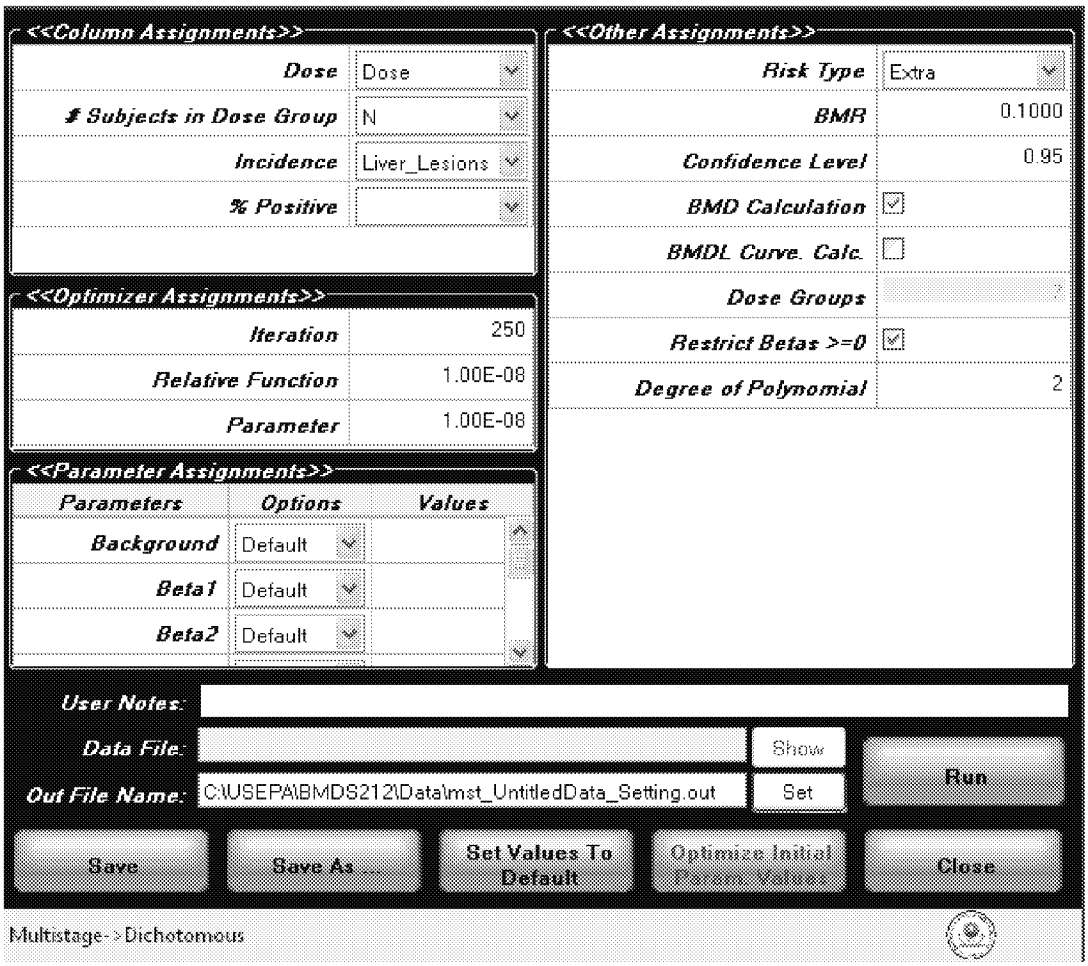
BMDS Input Data Set:

Model Type: Dichotomous | Model Name: Multistage

	Dose	N	Liver_Lesions	Col4
1	0	17	1	
2	0.007079	22	5	
3	0.02823	23	11	
4	0.1416	18	11	
5	0.7079	20	20	
6	1.416	18	18	
7	2.124	11	11	

Model Parameters:



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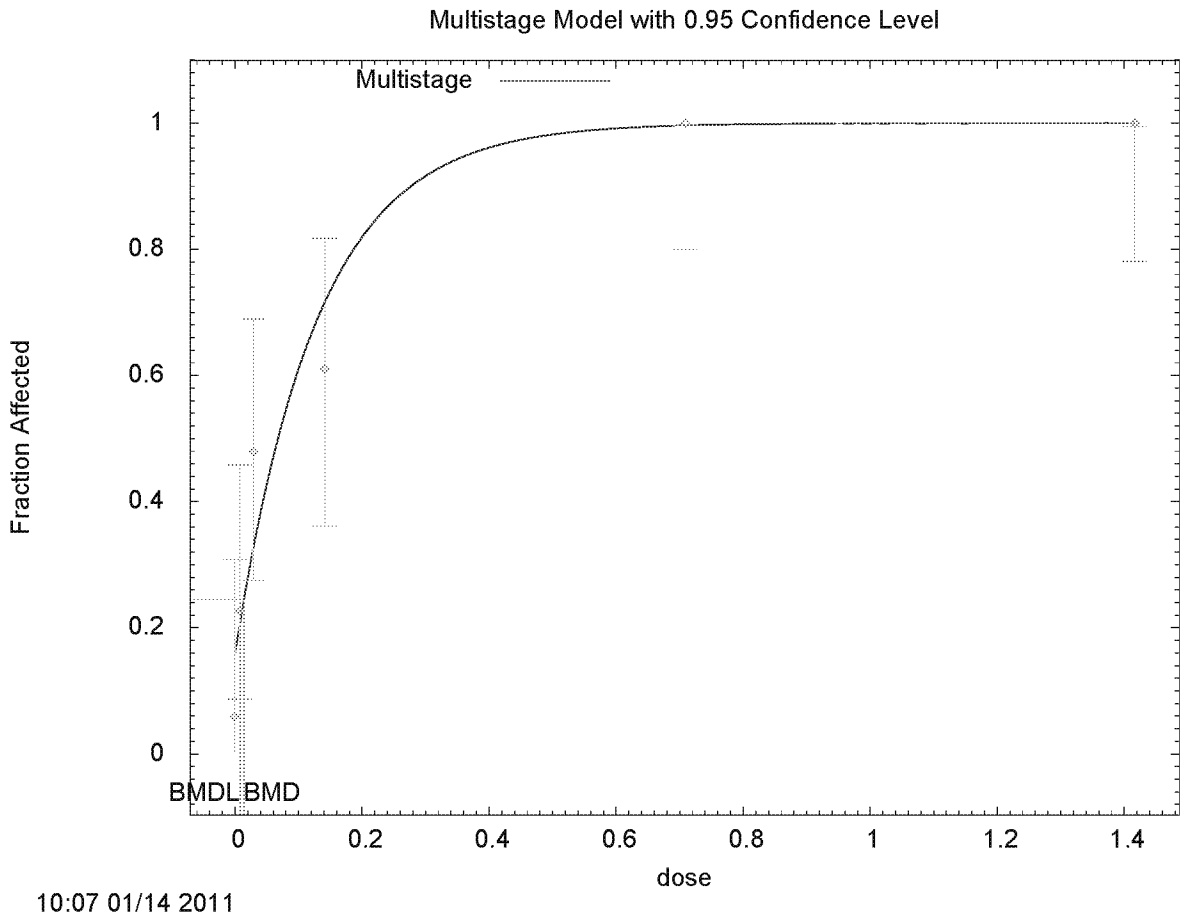
Output for Run 1, Complete Data Set (All Dose Levels):




```
=====================================================================
        Multistage Model. (Version: 3.2;  Date: 05/26/2010)
        Input Data File: C:/USEPA/BMDS212/Data/mst_UntitledData_Setting.(d)
        Gnuplot Plotting File:  C:/USEPA/BMDS212/Data/mst_UntitledData_Setting.plt
                                                Fri Jan 14 10:07:56 2011
=====================================================================

BMDS_Model_Run
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  The form of the probability function is:

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

  The parameter betas are restricted to be positive


  Dependent variable = Liver_Lesions
  Independent variable = Dose

Total number of observations = 7
Total number of records with missing values = 1
```

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Total number of parameters in model = 3
Total number of specified parameters = 0
Degree of polynomial = 2

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

Default Initial Parameter Values

Background =	1
Beta(1) =	8.25008e+019
Beta(2) =	0

Asymptotic Correlation Matrix of Parameter Estimates

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

	Background	Beta(1)
Background	1	-0.53
Beta(1)	-0.53	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.160248	*	*	*
Beta(1)	7.69196	*	*	*
Beta(2)	0	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-43.5434	6			
Fitted model	-46.1159	2	5.14488	4	0.2728
Reduced model	-80.9589	1	74.8309	5	<.0001

AIC: 96.2317

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1602	2.724	1.000	17	-1.140

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TETRATECH

0.0071	0.2048	4.505	5.000	22	0.262
0.0282	0.3242	7.456	11.000	23	1.579
0.1416	0.7174	12.914	11.000	18	-1.002
0.7079	0.9964	19.927	20.000	20	0.270
1.4160	1.0000	18.000	18.000	18	0.017

Chi^2 = 4.94 d.f. = 4 P-value = 0.2937

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.0136975

BMDL = 0.00837329

BMDU = 0.0418518

Taken together, (0.00837329, 0.0418518) is a 90 % two-sided confidence interval for the BMD

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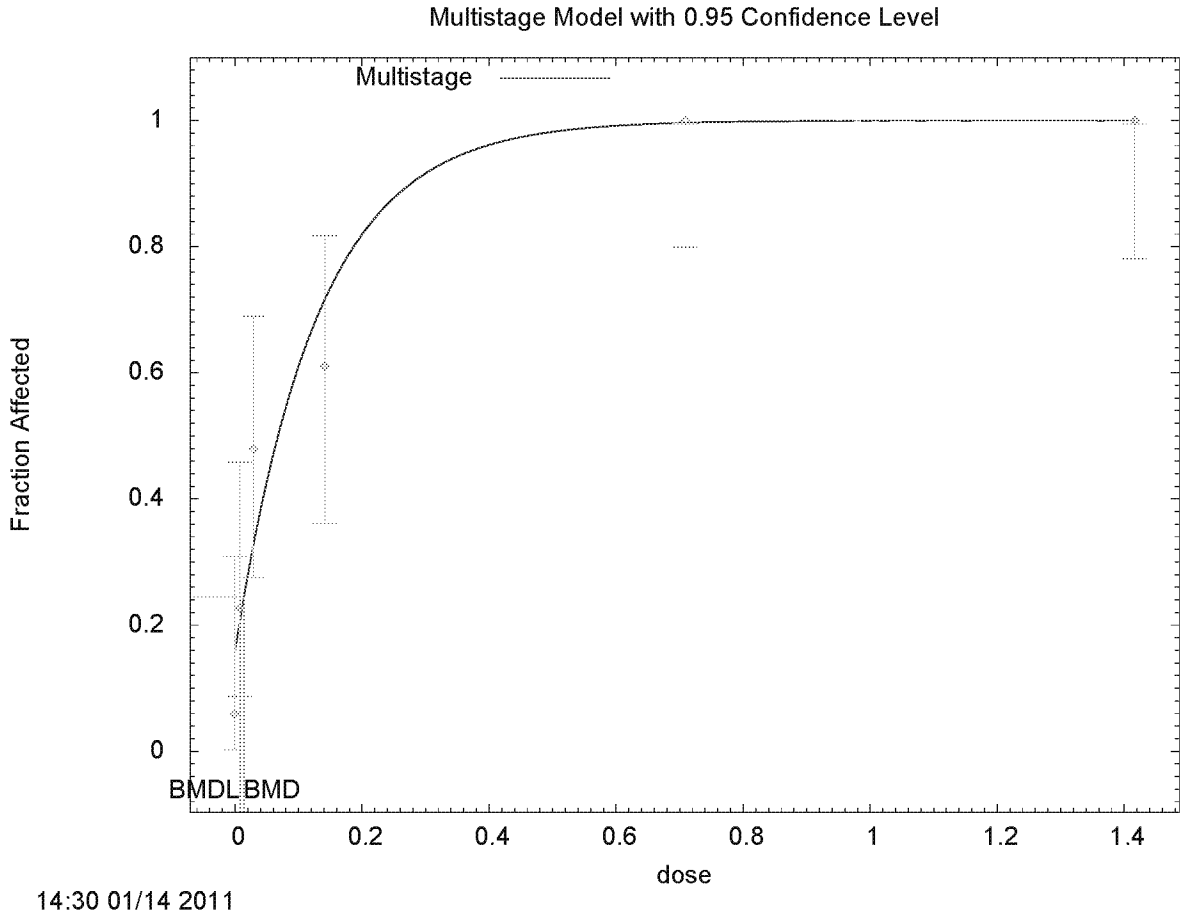
TETRA TECH

Output of Run 2, Data Set Excluding Highest Dose Group:




```
14:30 01/14 2011
=====================================================================
        Multistage Model. (Version: 3.2;  Date: 05/26/2010)
        Input Data File: C:/USEPA/BMDS212/Data/mst_UntitledData_Setting.(d)
        Gnuplot Plotting File:  C:/USEPA/BMDS212/Data/mst_UntitledData_Setting.plt
                                                Fri Jan 14 14:30:21 2011
 ====================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = Liver_Lesions
   Independent variable = Dose

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

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TETRATECH

Degree of polynomial = 2

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

Default Initial Parameter Values

Background =	1
Beta(1) =	8.25008e+019
Beta(2) =	0

Asymptotic Correlation Matrix of Parameter Estimates

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

	Background	Beta(1)
Background	1	-0.53
Beta(1)	-0.53	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.160248	*	*	*
Beta(1)	7.69196	*	*	*
Beta(2)	0	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

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