United States Environmental Protection Agency
Office of Chemical Safety and Pollution Prevention

Risk Evaluation for Methylene Chloride

Supplemental File: Methylene Chloride Benchmark Dose and PBPK Modeling Report

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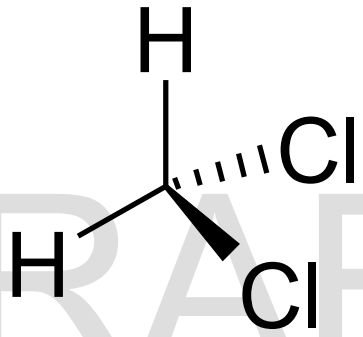

October 2019, DRAFT

This supplemental file includes both updated BMD and PBPK modeling results for cancer (and non-cancer liver toxicity endpoints from Aiso et al. (2014) (PART A, beginning on page 3) and an excerpt of the BMD and PBPK modeling results from the IRIS Assessment Document from 2011 (U.S. EPA, 2011) for non-cancer liver toxicity endpoints from Nitschke et al. (1988) (PART B, beginning on page 140).

PART A:
Methylene Chloride Benchmark Dose and PBPK Modeling Report

May 31, 2019
[Date submitted by ORD to OPPT]

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington, DC

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CONTENTS

1. Background

OCSPP requested that NCEA run PBPK and benchmark dose (BMD) models, including all dichotomous models that are available in BMDS 3.1, to estimate risk from methylene chloride (dichloromethane, DCM) for select endpoints from the Aiso et al (2014) and NTP (1986) cancer inhalation studies. The specific endpoints selected by OCSPP are identified in Appendix A, Tables 1 and 2 of the OCSPP request. The justifications provided by OCSPP for the exclusion of certain endpoints from the Aiso et al. (2014) study are provided in Appendix B.

Subsequently to the initial OCSPP request (Appendices A and B), OCSPP requested that ORD NCEA assess the combined risk of tumor when multiple tumors were observed in the same study. This was done by applying the BMDS 3.1 multi-tumor (MS_Combo) model to the tumors identified in Appendix A, Tables 1 and 2 that occurred in the same study, same sex. As described in the BMDS 3.1 User Guide, the multi-tumor (MS_Combo) model uses the individual Multistage models fits to the individual tumors to estimate the risk of getting one or more of the tumors being analyzed.

As noted in Section 6 of the BMDS 3.1 User Guide, the multi-tumor (MS_Combo) model assumes that the tumors are statistically independent of one another, and that this assumption is generally considered appropriate unless there is "substantial biological evidence to indicate that the tumor types are not independent—conditional on model parameter values." NCEA has not evaluated the appropriateness of this assumption specifically for the tumors evaluated in this report.

2. Summary of BMD Modeling Approach

As requested by OCSPP, all BMDS 3.1 dichotomous models that use likelihood optimization and profile likelihood-based confidence intervals were used in this analysis. Standard and non-standard forms of these models (defined below) were run separately in BMDS 3.1 so that auto-generated model selection recommendations accurately reflect current EPA model selection procedures (EPA, 2012, EPA, 2014) (See Appendix C). BMDS 3.1 models that use Bayesian fitting procedures and Bayesian model averaging were not applied in this work.

Standard BMDS 3.1 Models[1] Applied to All Individual Endpoints[2]:

- Gamma-restricted (gam-r)
- Log-Logistic-restricted (lnl-r)
- Multistage-restricted (mst-r); from degree = 1 to degree = # dose groups - 1
- Weibull-restricted (wei-r)
- Dichotomous Hill-unrestricted (dhl-ur)
- Logistic (log)
- Log-Probit-unrestricted (lnp-ur)
- Probit (pro)

Non-Standard BMDS 3.1 Models[1] Applied to All Individual Endpoints:

- Dichotomous Hill-restricted (dhl-r)
- LogProbit-restricted (lnp-r)
- Gamma-unrestricted (gam-ur)
- Log-Logistic-unrestricted (lnl-ur)
- Multistage-unrestricted (mst-ur)
- Weibull-unrestricted (wei-ur)

Models Applied by BMDS 3.1 Multi-tumor (MS_Combo) Model for Estimating Combined Risk

- Multistage (restricted); from degree = 1 to degree = # dose groups - 2

[1] The set of standard models are identified in accordance with EPA BMD technical guidance (EPA, 2012) and the default dichotomous models in BMDS 3.1. Non-standard models are the remaining (non-default) dichotomous models available in BMDS 3.1.

[2] Consistent with EPA cancer (EPA, 2005) and BMD (EPA, 2012) guidance, ORD NCEA prefers to only apply the Multistage model to cancer endpoints. In this case, all BMDS 3.1 dichotomous models were applied to both cancer and noncancer datasets at the request of OCSPP (see Appendix A).

General Model Options Used for Individual Endpoint and Combined Risk (MS_Combo) Analyses:

- Risk Type: Extra Risk
- BMR: 0.1 (10%)
- Confidence Level: 0.95
- Background: Estimated
- Model Restrictions: Restrictions for BMDS 3.1 models are defined in the BMDS 3.1 User Guide and are applied in accordance with EPA BMD Technical Guidance (EPA, 2012).

Model Selection

For each individual endpoint BMD analysis, a model was selected from among the preferred standard set of models (noting instances where consideration of non-standard models may be justified) in accordance with EPA BMD Technical Guidance (EPA, 2012) (see Appendix C). This model is hereafter referred to as "Selected, Full Model Suite." For cancer (tumor) endpoints,[3] a model was first chosen in accordance with EPA's technical guidance for choosing the appropriate stage of a multistage model for cancer modeling (EPA, 2014).[4] This model is hereafter referred to as "Selected, Multistage." EPA BMD Technical Guidance (EPA, 2012) was then used to compare the "Selected, Multistage" model to other standard dichotomous models that were applied to the cancer (tumor) endpoint to identify a "Selected, Full Model Suite" model for the cancer (tumor) endpoint. The "Selected, Multistage" models for the cancer (tumor) endpoints were the Multistage model forms used in the multi-tumor combined risk (MS_Combo) analyses.

Dose Metrics Used in Dose-response Analyses (see PBPK report for details on each dose metric)

Liver Glutathione S-Transferase dose (Li-GST) (mg DCM metabolized via GST pathway / Liter of liver tissue / day) for the analysis of liver tumor responses reported by Aiso et al. (2014) for male and female mice and by NTP (1986) for male mice.

Lung Glutathione S-Transferase dose (Lu-GST) (mg DCM metabolized via GST pathway /Liter of lung tissue /day) for the analysis of lung tumor responses reported by Aiso et al. (2014) for male and female mice and by NTP (1986) for male mice, and for the analysis of terminal bronchiole hyperplasia responses reported by Aiso et al. (2014) for male and female mice.

Whole Body Glutathione S-Transferase dose (WB-GST) (mg dichloromethane metabolized via GST pathway in lung and liver/kg-day) for multi-tumor (MS_Combo) analysis of combined risk

[3] Consistent with OCSPP instructions (Table 1), the Aiso et al. (2014) female rat acidophilic and basophilic cell foci endpoints have been treated as "Non-Neoplastic Foci" for the purposes of individual endpoint analysis and model selection (as was the lung hyperplasia endpoint) and were not evaluated for combined risk using the BMDS multi-tumor (MS_Combo) model. The Aiso et al (2014) paper treats these lesions as "preneoplastic."

[4] Consistent with this guidance, only Multistage degrees up to the number of dose groups (n) - 2 were considered for cancer (tumor) endpoints. For the noncancer endpoints (i.e., the cell foci and hyperplasia endpoints), results for Multistage models with degrees up to n -1 are considered (EPA, 2012).

of lung or liver tumors reported by Aiso et al. (2014) for male and female mice and by NTP (1986) for male mice.

Slowly perfused AUC(DCM) (SP-AUC) (mg DCM - hour / Liter of Slowly Perfused Tissue) for the analysis of tumors of the mammary gland region reported by Aiso et al. (2014) for male and female rats and for multi-tumor (MS_Combo) estimation of combined risk of mammary gland and subcutis (in mammary gland region) tumors reported by Aiso et al. (2014) for male rats.

Liver Cytochrome P450 dose (Li-CYP) (mg DCM metabolized via CYP pathway /Liter of lung tissue /day) for the analysis of liver acidophilic cell foci and basophilic cell foci reported by Aiso et al. (2014) for male and female rats.

Endpoint Selection for BMD Modeling

NCEA has modeled the endpoints chosen in accordance with the statistical justification provided by OCSPP (Appendix B) for the choice of endpoints to be modelled. There it is stated that some endpoints were not chosen, despite significant trend tests, because of no dose with a significant difference from controls based on a pairwise statistical comparison of treated to control. NCEA recommends that selection be based primarily on trend testing, noting that trend tests are to be particularly preferred over pairwise tests in the context of less common health effects.

3. Summary of BMD Modeling Results

Sec.	Endpoint	Dose Metric[1]	Selected, Full Model Suite/ Selected, Multistage[1]	Selected, Full Model Suite		Selected, Multistage/MS_Combo[2]	
				BMD_{10}	$BMDL_{10}$	BMD_{10}	$BMDL_{10}$
3	**Aiso et al. (2014) – Male Rats**						
3.1	Subcutis	SP-AUC	lnp-ur/mst2-r	142.3	27.626	156.13	106.730
3.2	Mammary Gland (F/A)	SP-AUC	log/mst1-r	352.95	266.06	373.53	205.35
3.3	Mammary Gland (F/A/AC)	SP-AUC	Log/mst1-r	374.83	267.16	440.28	222.31
3.4	Subcutis or Mammary Gland (F/A)	SP-AUC	MS_Combo (Subcutis: mst2-r; F/A: mst1-r)			110.11	78.802
3.5	Subcutis or Mammary Gland (F/A/AC)	SP-AUC	MS_Combo (Subcutis: mst2-r; F/A: mst1-r)			115.26	81.265
4	**Aiso et al. (2014) – Female Rats**						
4.1	Mammary Gland (F/A/AC)	SP-AUC	pro/mst1-r	271.35	166.68	247.23	123.70
4.2	Acidophilic Cell Foci	Li-CYP	gam-r	732.62	645.50		
4.3	Basophilic Cell Foci	Li-CYP	log	136.40	114.20		
5	**Aiso et al. (2014) – Male Mice**						
5.1	Liver	Li-GST	lnl-r/mst2-r	754.63	413.06	956.50	593.21
5.2	Lung	Lu-GST	pro/mst1-r	136.66	115.93	70.936	55.91
5.3	Liver or Lung Tumor	WB-GST	MS_Combo (Liver: mst2-r; Lung: mst1-r)			10.938	8.2167
5.4	TB Hyperplasia	Lu-GST	gam	487.13	324.61		
6	**Aiso et al. (2014) – Female Mice**						
6.1	Liver	Li-GST	Pro/mst2-r	1595.1	1332.8	1408.7	762.3
6.2	Lung	Lu-GST	mst2-r/mst2-r	371.9	223.47	371.9	223.47
6.3	Liver or Lung Tumor	WB-GST	MS_Combo (Liver: mst2-r; Lung: mst2-r)			44.901	25.302
6.4	TB Hyperplasia	Lu-GST	mst3-r/mst3-r	648.4247	411.2842	648.4247	411.2842
7	**NTP (1986) – Male Mice**						
7.1	Liver Tumor	Li-GST	pro-r/mst1-r	1072.4	740.82	914.22	544.51
7.2	Lung Tumor	Lu-GST	mst1-r/mst1-r	61.67445	48.6464	61.67445	48.6464
7.3	Liver or Lung Tumor	WB-GST	MS_Combo (Liver: mst1-r; Lung: mst1-r)			9.764454	7.752931

[1] See Section 2 for abbreviation definitions; As described in Section 2, BMDs were derived from the standard set of models as defined in the EPA BMD technical guidance and as identified in BMDS 3.1 as defaults. Since the standard approach gave adequate results for all endpoints, non-standard models were not considered for BMD derivations.

[2] As described Section 2, "Model Selection," the "Selected, Multistage" models were selected in accordance with EPA's guidance for choosing the appropriate stage of a multistage model for cancer modeling (EPA, 2014). These criteria are implemented automatically when MS_Combo is used with the "autoselect" option (MS_Combo also supports manual specification of multistage degree).

F=Fibroadenoma, A=Adenoma, AC=Adenocarcinoma, TB=Terminal Bronchiole

4. Summary of PBPK Analyses

The DCM PBPK model as adapted and applied in the 2011 IRIS Toxicological Review was used for the additional analyses of the NTP bioassay and the newer Aiso et al. (2104) bioassay. Briefly, with the model parameterized for mice or rats, internal doses were calculated for the inhalation exposures used in the bioassays. BW values for each species, sex, exposure, and study were set: for NTP the values used for the 2011 IRIS Toxicological Review were applied and the end-of-exposure values reported in Aiso et al. (2014) were used for that study. The dose metrics listed in the previous section for the various endpoints were calculated and used in the BMD modeling.

With the model parameterized for humans, the corresponding internal doses for a fixed exposure level (1 $\mu g/m^3$) were calculated to estimate human cancer risk. For non-cancer endpoints the inhalation concentration was calculated such that the human internal dose matched the human $BMDL_{10}$ (scaled from animal values); i.e., the human equivalent concentration (HEC). Further, the human parameter script allows the parameters to be sampled from distributions for the population being evaluated, in this case women and men 18-65 years of age. This population sampling includes the polymorphism known to occur for the enzyme glutathione S-transferase (GST) thetat-1 (GST-T1); individuals can either have two active GST-T1 alleles (referred to as "+/+"), one active and one inactive allele (+/-), or two inactive alleles (-/-). The activity distribution for the corresponding metabolic step in the +/- population is one half that of the +/+ population, and in GST-T1 -/- individuals the activity is zero.

For each individual in the simulated or virtual population, the internal dose was estimated and the mean of the resulting distribution calculated, allowing for the calculation of a population mean risk level (cancer evaluation). Similarly, a population sample of HEC values was estimated; in this case the 1st percentile of the distribution is selected to assure that the HEC (after application of other relevant uncertainty factors) is protective of the population as a whole. In particular, using the 1st percentile of the non-cancer HEC values obviates the need for an intra-human uncertainty factor for pharmacokinetics (PK), but a factor of 3 for pharmacodynamic (PD) variability should still be applied, along with a factor of 3 for animal-human PD differences.

Prior to model application, to check that the model code was still functioning as it did for the 2011 Toxicological Review, we attempted to reproduce rat and mouse internal doses for the NTP bioassay (i.e., using the same parameters and exposure levels). However, some numerical instability was found, particularly for the mouse simulations (integration warnings occurred). Although these only involved model variables becoming very slightly negative (~ 10^{-8}), they were corrected by restricting the integration step size to 10^{-4} h. Integration warnings still occurred with this correction, but blood and tissue concentrations did not become negative and restricting the step size further did not alter the dose metric calculations up to 4 significant figures.

The resulting rat and mouse internal doses differed slightly from those reported in the 2011 IRIS review, but differences were less than 0.1%, so this was considered a reasonable validation of the computational model.

Simulations with the human model parameters did not have numerical warnings and it was found that when the same random seed was used, Monte Carlo (MC) sampling for human distributions were reproducible across 3 separate computers/operators.

As outlined above, several modifications to the analysis of human dosimetry were made, from the analysis performed for the 2011 Toxicological Review, at OCSPP's request:

- The analyses were conducted for workplace exposures; hence the scripts were modified to sample from individuals 18-65 years of age and exposure was assumed to occur 8 h/d, 5 d/w.
- Analyses were primarily conducted for all GST-T1 genotypes in the population (i.e., using the estimated prevalence of the polymorphism in the U.S. population) but results for GST-T1 mediated cancer risks are also provided for the +/+ sub-population (which has the highest risk). The 20% of the population who are -/- are effectively at zero risk when a GST metric is used (liver-specific GST metabolism, lung-specific GST metabolism, or whole-body GST metabolism), since they produce no DCM-GST metabolites.
- For non-cancer endpoints the population PBPK approach calls for calculating the human equivalent concentration (HEC) for each person, then calculating the 1st percentile of that distribution to obtain a value expected to be protective of the whole population. This was done for acidophilic and basophilic cell foci in female rats, where liver-specific CYP metabolism is the dose metric.
- However, for non-cancer lung lesions in the mouse lung (terminal bronchiole hyperplasia), the GST pathway is thought to be causative, so is the preferred metric. However, the HEC for a GST-T1 -/- individual would be effectively infinite, since they produce none of the metabolite, making it impossible to obtain a meaningful result. GST -/- individuals are predicted to be 20% of the general population. Therefore, these HEC calculations will be restricted to GST-T1 +/+ and +/- individuals, but instead of calculating the 1st percentile of their HEC distribution, the percentile used will be 1%/(100% - 20%) = 1.25%. If 1.25% of the +/+ and +/- populations have internal doses below the BMDL¬10 at a given exposure level, then 99% of the overall population will be protected.

Other details of the risk calculations are provided in footnotes to the table of results, just below.

BMD modeling results and tumor risk factors/HECs determined for 10% extra risk, various endpoints and BMD models

Internal dose metric[a]	Sex, Species	Endpoint (Asio study, unless "(NTP)")	BMD model[b]	Animal $BMDL_{10}$[a,c]	Human $BMDL_{10}$[a,d]	Human tumor risk factor[c]	Mean human internal dose from 1 µg/m³ exposure[a]		Resulting human inhalation unit risk (g/m³)⁻¹ or *HEC (mg/m³)*[f]	
							Mixed population	GST +/+	Mixed population	GST +/+
Slowly perfused AUC (DCM)	Male rat	Subcutis	lnp-ur	27.626	27.626	3.62×10^{-3}	1.59×10^{-5}	Not significantly different from mixed population	5.76×10^{-8}	Not significantly different from mixed population
			mst2-r	106.73	106.73	9.37×10^{-4}			1.49×10^{-8}	
		Mammary Gland (F/A)	log	266.06	266.06	3.76×10^{-4}			5.98×10^{-9}	
			mst1-r	205.35	205.35	4.87×10^{-4}			7.74×10^{-9}	
		Mammary Gland (F/A/AC)	log	267.16	267.16	3.74×10^{-4}			5.95×10^{-9}	
			mst1-r	222.31	222.31	4.50×10^{-4}			7.15×10^{-9}	
		Subcutis or Mammary Gland (F/A)	multi-tumor	78.802	78.802	1.27×10^{-3}			2.02×10^{-8}	
		Subcutis or Mammary Gland (F/A/AC)	multi-tumor	81.265	81.265	1.23×10^{-3}			1.96×10^{-8}	
	Female rat	Subcutis or Mammary Gland (F/A/AC)	pro	166.68	166.68	6.00×10^{-4}			9.54×10^{-9}	
			mst1-r	123.7	123.7	8.08×10^{-4}			1.29×10^{-8}	
Liver CYP metabolism	Female rat	Acidophilic cell foci	gam-r	645.5	157.4	n/a	n/a		*98.2 mg/m³*	
		Basophilic cell foci	log	114.2	27.85	n/a			*17.3 mg/m³*	
Liver GST	Male mice	Liver tumor	lnl-r	413.06	59.01	1.70×10^{-3}	6.65×10^{-7}	1.17×10^{-6}	1.13×10^{-9}	1.98×10^{-9}
			mst2-r	593.21	84.74	1.18×10^{-3}			7.58×10^{-10}	1.38×10^{-9}
		Liver tumor (NTP)	lnl-r	***740.82***	105.8	9.45×10^{-4}			6.28×10^{-10}	1.11×10^{-9}
			mst1-r	***544.51***	77.79	1.29×10^{-3}			8.55×10^{-10}	1.50×10^{-9}
	Female mice	Liver tumor	**pro**	1332.8	190.40	5.25×10^{-4}			3.49×10^{-10}	6.14×10^{-10}
			mst2-r	762.31	108.90	9.18×10^{-4}			6.11×10^{-10}	1.07×10^{-9}

BMD modeling results and tumor risk factors/HECs determined for 10% extra risk, various endpoints and BMD models

Internal dose metric[a]	Sex, Species	Endpoint (Asio study, unless "(NTP)")	BMD model[b]	Animal $BMDL_{10}$[a, c]	Human $BMDL_{10}$[a, d]	Human tumor risk factor[e]	Mean human internal dose from 1 µg/m³ exposure[a]		Resulting human inhalation unit risk (g/m³)⁻¹ or *HEC (mg/m³)*[f]	
							Mixed population	GST +/+	Mixed population	GST +/+
Lung GST	Male mice	Lung tumor	pro	115.93	16.56	6.04×10^{-3}	4.39×10^{-8}	7.75×10^{-8}	2.65×10^{-10}	4.68×10^{-10}
			mst1-r	55.91	7.987	1.25×10^{-2}			5.50×10^{-10}	9.70×10^{-10}
		Lung tumor (NTP)	mst1-r	48.646	6.949	1.44×10^{-2}			6.32×10^{-10}	1.12×10^{-9}
	Female mice	Lung tumor	mst2-r	223.47	31.92	3.13×10^{-3}	4.39×10^{-8}	7.75×10^{-8}	1.38×10^{-10}	2.43×10^{-10}
		TB hyperplasia	mst3-r	411.28	58.75	n/a			7.75×10^{4} *mg/m³*	5.73×10^{4} *mg/m³*
Whole body GST	Male mice	Liver or lung tumor	multi-tumor	8.217	1.174	8.52×10^{-2}	1.53×10^{-8}	2.68×10^{-8}	1.30×10^{-9}	2.28×10^{-9}
		Liver or lung (NTP)		***7.753***	1.108	9.03×10^{-2}			1.38×10^{-9}	2.42×10^{-9}
	Female mice	Liver or lung tumor		25.302	3.615	2.77×10^{-2}			4.23×10^{-10}	7.41×10^{-10}

[a] Tissue-specific dose-units = mg dichloromethane metabolized via GST pathway/L tissue (liver or lung)/day; whole-body dose units = mg dichloromethane metabolized via GST pathway in lung and liver/kg-day; AUC(DCM) = mg-h/L tissue; all metrics are daily averages given a - week exposure per bioassay conditions (animal dosimetry) or 8 h/d, 5 d/w workplace exposure scenario (human dosimetry).

[b] See BMD modeling report for model definitions and details.

[c] Animal $BMDL_{10}$ refers to the BMD-model-predicted mouse or rat internal dose and its 95% lower confidence limit, associated with a 10% extra risk for the incidence of tumors; units are those for the identified dose metric, described in footnote "a".

[d] When the dose metric is the rate of production of the presumed toxic metabolite (mg/kg/d), allometric scaling is applied to adjust for the fact that humans are expected to detoxify the metabolite more slowly than mice and rats. A mouse $BMDL_{10}$ is divided by $(BW_{human}/BW_{mouse})^{0.25} = 7$ and a rat $BMDL_{10}$ divided by $(BW_{human}/BW_{rat})^{0.25} = 4.1$. When the metric is the concentration (AUC) of a chemical, no adjustment is made. Units are the same as for the Animal $BMDL_{10}$.

[e] Dichloromethane tumor risk factor (extra risk per unit internal dose) derived by dividing the BMR (0.1) by the allometric-scaled human $BMDL_{10}$. Units are $1/(BMDL_{10}$ units) for corresponding tissues/endpoints.

[f] Human inhalation risk is the product of the mean internal dose and the tumor risk factor. HEC is the 1st percentile of a distribution obtained by determining the exposure concentration for each individual in a simulated population that is predicted to yield an internal dose equal to the (internal) Human $BMDL_{10}$; with use of the 1st percentile the intra-human uncertainty factor can be reduced from a standard value of 10 to 3, to account for remaining variability in pharmacodynamic sensitivity.

5. BMD Modeling for Aiso et al. (2014) Male Rats

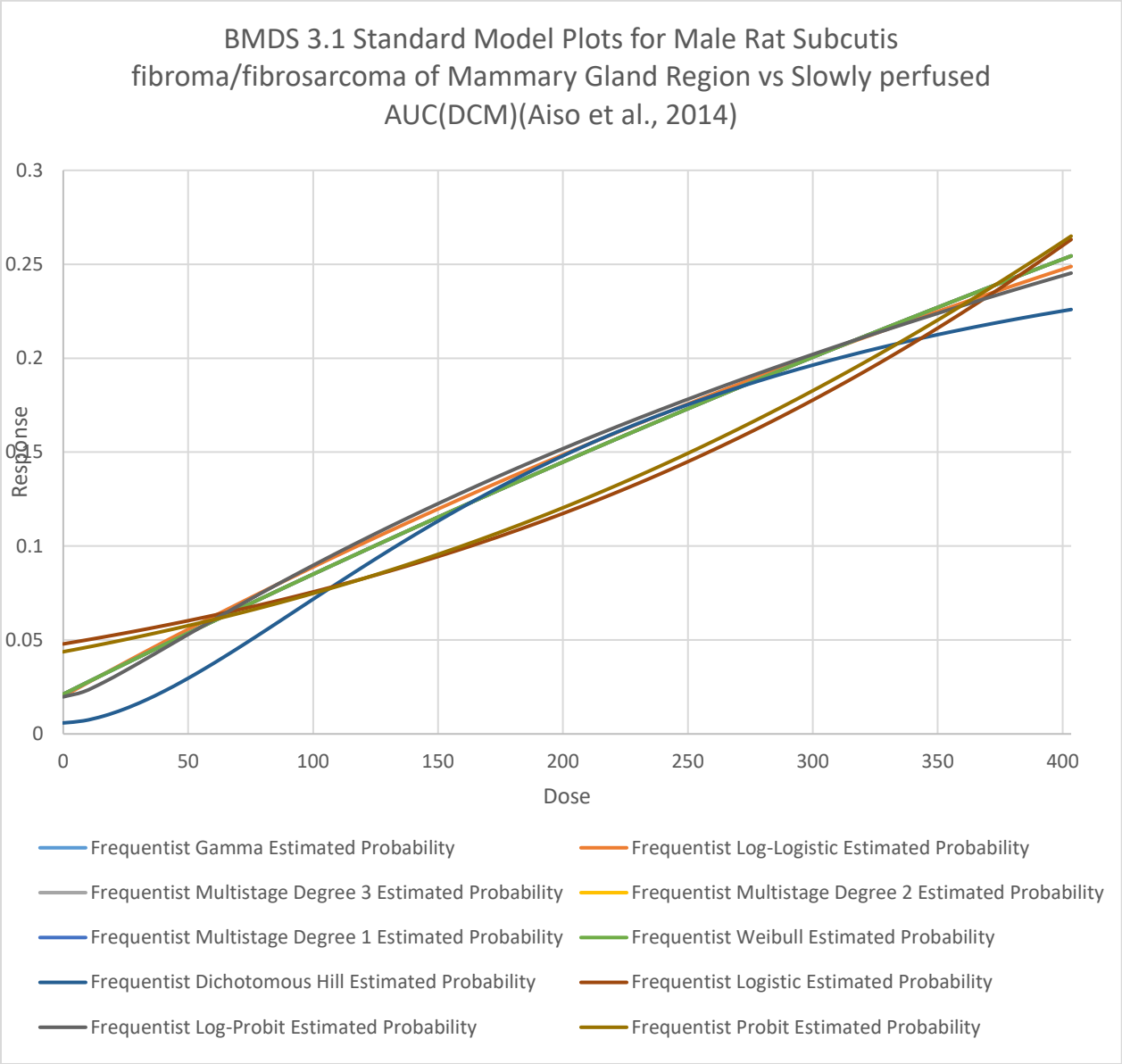
5.1. Subcutis (Fibroma/Fibrosarcoma)

Slowly perfused AUC(DCM)	N	Incidence
0	50	1
93.33	50	4
196.4	50	8
403.4	50	12

Summary of BMDS 3.1 Modeling Results for Male Rat Subcutis fibroma/fibrosarcoma of Mammary Gland Region vs Slowly Perfused AUC(DCM) (Aiso et al., 2014)

Standard Models	Restriction***	10% Extra Risk		P Value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL				
Gamma	Restricted	156.13	106.73	0.91319	140.9343	Viable - Alternate	
Log-Logistic	Restricted	147.17	96.484	0.94833	140.8606	Viable - Alternate	
Multistage Degree 2*	Restricted	156.13	106.730	0.91319	140.9343	Selected, Multistage	Multistage-cancer guidance (EPA, 2014)
Multistage Degree 1 (Quantal Linear)	Restricted	156.13	106.731	0.91319	140.9343	Viable - Alternate	
Weibull	Restricted	156.13	106.73	0.91319	140.9343	Viable - Alternate	
Dichotomous Hill	Unrestricted	138.03	27.686	NA	144.7558	Questionable	BMDL 3x lower than lowest non-zero dose d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Logistic	NA	246.95	197.55	0.36954	142.8886	Viable - Alternate	
Log-Probit**	Unrestricted	142.3	27.626	0.79923	142.8201	Selected, Full Model Suite	Lowest BMDL BMDL 3x lower than lowest non-zero dose
Probit	NA	233.52	184.66	0.42664	142.5548	Viable - Alternate	
Non-Standard Models							
Dichotomous Hill	Restricted	137.99	2.5892	NA	144.7558	Questionable	BMD/BMDL ratio > 20 BMD/BMDL ratio > 5 BMDL 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Log-Probit	Restricted	217.41	157.08	0.33052	143.036	Viable - Alternate	
Gamma	Unrestricted	144.28	22.716	0.72859	142.8754	Viable - Alternate	Lowest BMDL
Log-Logistic	Unrestricted	143.44	24.99	0.75334	142.854	Viable - Alternate	BMD/BMDL ratio > 5 BMDL 3x lower than lowest non-zero dose
Multistage Degree 3	Unrestricted	141.76	48.088	NA	144.7558	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Multistage Degree 2	Unrestricted	139.38	69.79	0.7815	142.8332	Viable - Alternate	
Multistage Degree 1	Unrestricted	156.13	106.73	0.91319	140.9343	Viable - Alternate	
Weibull	Unrestricted	143.85	23.673	0.73253	142.872	Viable - Alternate	BMD/BMDL ratio > 5 BMDL 3x lower than lowest non-zero dose

*Selected, Multistage (Yellow); residuals for doses 0, 93.33, 196.4, and 403.4 were -0.056061617, -0.023081873, 0.350885593, and -0.234147449, respectively.
**Selected, Full Model Suite (Green); residuals for doses 0, 93.33, 196.4, and 403.4 were 0.012874656, -0.128373844, 0.201154994, and -0.087060503, respectively.
***Restrictions defined in the BMDS 3.1 User Guide; CF = Computation failed; NA = Not Applicable


BMDS 3.1 Standard Model Plots for Male Rat Subcutis fibroma/fibrosarcoma of Mammary Gland Region vs Slowly perfused AUC(DCM)(Aiso et al., 2014)
Response
Dose
0.3
0.25
0.2
0.15
0.1
0.05
0
0
50
100
150
200
250
300
350
400
Frequentist Gamma Estimated Probability
Frequentist Log-Logistic Estimated Probability
Frequentist Multistage Degree 3 Estimated Probability
Frequentist Multistage Degree 2 Estimated Probability
Frequentist Multistage Degree 1 Estimated Probability
Frequentist Weibull Estimated Probability
Frequentist Dichotomous Hill Estimated Probability
Frequentist Logistic Estimated Probability
Frequentist Log-Probit Estimated Probability
Frequentist Probit Estimated Probability

Selected, Multistage - Multistage 2 Restricted; Extra Risk, BMR = 0.1

User Input

Info	
Model	Multistage degree 2 v1.0
Dataset Name	Aiso Male Rat Subcutis (fibroma/fibrosarcoma)
Formula	P[dose] = g + (1-g)*[1-exp(-b1*dose^1)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Slowly perfused AUC(DCM)
Independent Variable	[Tumor Incidence]
Total # of Observation	4

Model Results

Benchmark Dose	
BMD	156.1284704
BMDL	106.7298415
BMDU	285.6542832
AIC	140.9342972
P-value	0.913190507
D.O.F.	2
Chi^2	0.181621518
Slope Factor	0.000936945

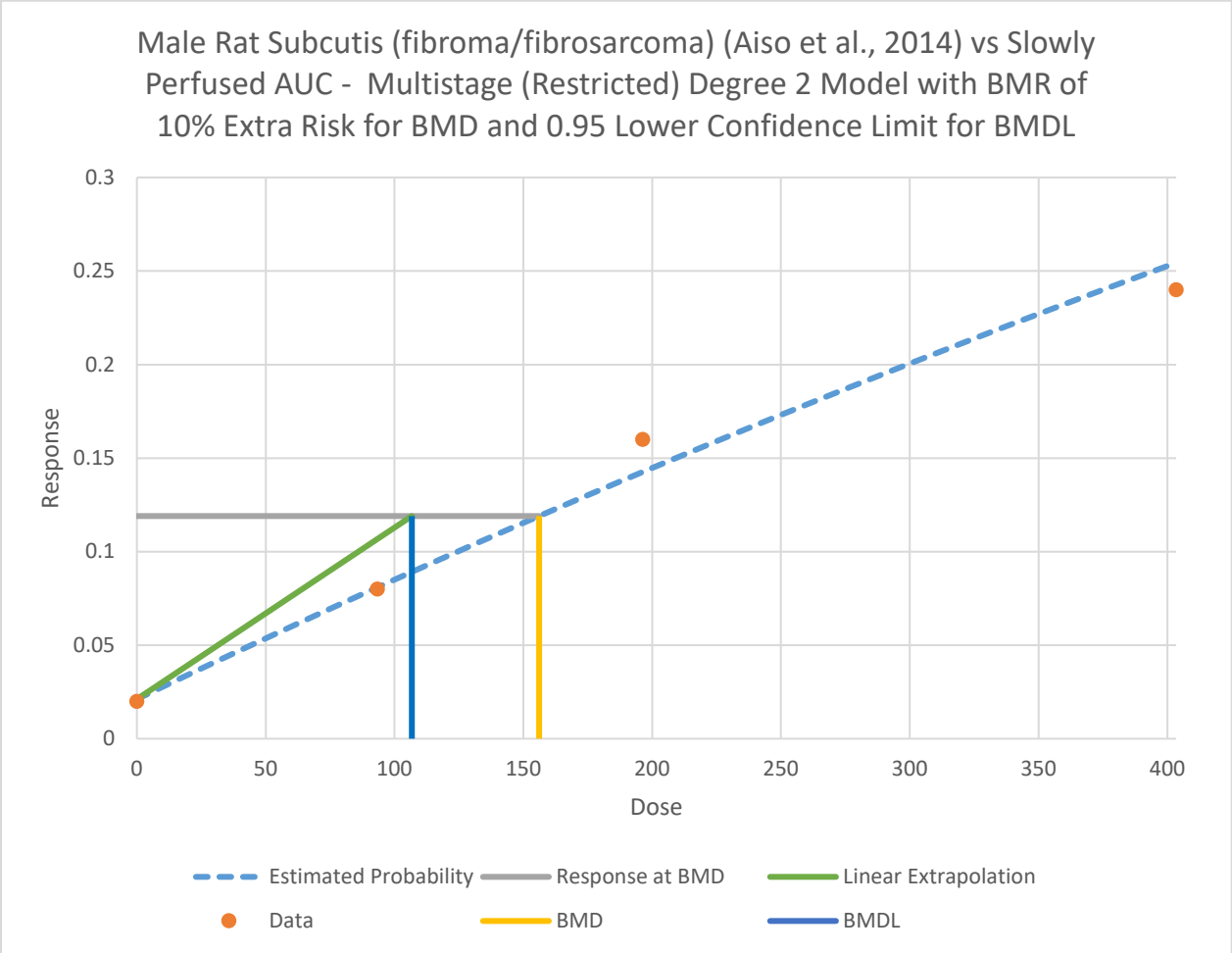
Model Parameters	
# of Parameters	3
Variable	Estimate
Background (g)	0.021140922
Beta1	0.000674832
Beta2	0

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.021140922	1.05704609	1	50	-0.0561
93.33	0.080890193	4.04450965	4	50	-0.0231
196.4	0.142646218	7.1323109	8	50	0.35089
403.4	0.25442153	12.7210765	12	50	-0.2341

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-68.3779146	0	-	-	-
Fitted Model	-68.4671486	2	0.178468	2	0.91463
Reduced Model	-75.3540323	1	13.95224	3	0.00297


Male Rat Subcutis (fibroma/fibrosarcoma) (Aiso et al., 2014) vs Slowly Perfused AUC - Multistage (Restricted) Degree 2 Model with BMR of 10% Extra Risk for BMD and 0.95 Lower Confidence Limit for BMDL
Response
0.3
0.25
0.2
0.15
0.1
0.05
0
0
50
100
150
200
250
300
350
400
Dose
Estimated Probability
Response at BMD
Linear Extrapolation
Data
BMD
BMDL

Selected, Full Model Suite - LogProbit (Unrestricted) - Extra Risk, BMR = 0.1

User Input

Info	
Model	Log-Probit v1.0
Dataset Name	Aiso Male Rat Subcutis (fibroma/fibrosarcoma)
Formula	P[dose] = g+(1-g) * CumNorm(a+b*Log(Dose))

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Slowly perfused AUC(DCM)
Independent Variable	[Tumor Incidence]
Total # of Observation	4

Model Results

Benchmark Dose	
BMD	142.2953605
BMDL	27.62612894
BMDU	272.2029592
AIC	142.8201328
P-value	0.799233465
D.O.F.	1
Chi^2	0.064688463
Slope Factor	0.00361976

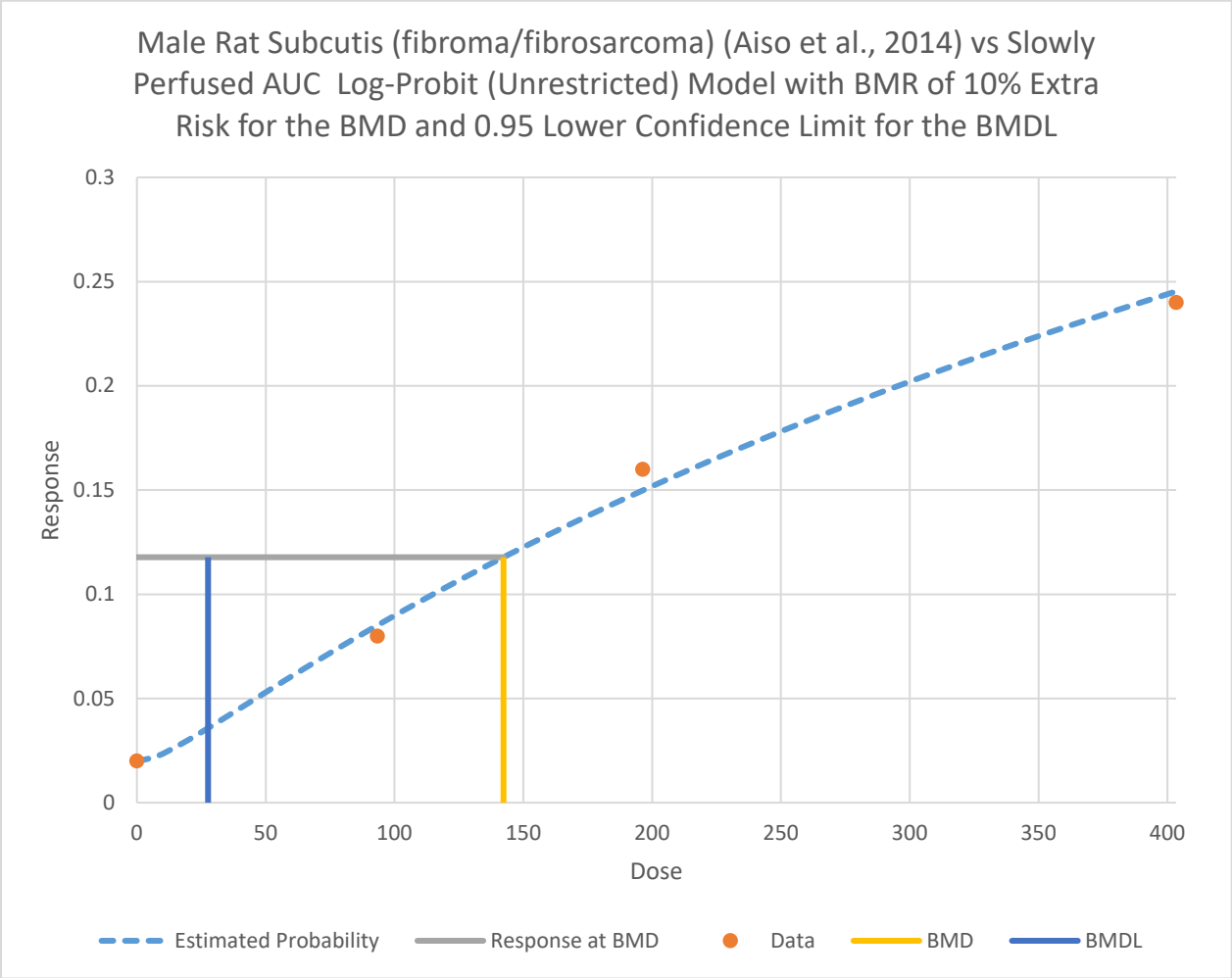
Model Parameters	
# of Parameters	3
Variable	Estimate
Background (g)	0.019746682
a	-3.86519696
b	0.521116367

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.019746682	0.98733408	1	50	0.01287
93.33	0.085064792	4.25323961	4	50	-0.1284
196.4	0.149846454	7.4923227	8	50	0.20115
403.4	0.245297496	12.2648748	12	50	-0.0871

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-68.3779146	0	-	-	-
Fitted Model	-68.4100664	3	0.064304	1	0.79982
Reduced Model	-75.3540323	1	13.95224	3	0.00297


Male Rat Subcutis (fibroma/fibrosarcoma) (Aiso et al., 2014) vs Slowly Perfused AUC Log-Probit (Unrestricted) Model with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
0.3
0.25
0.2
0.15
0.1
0.05
0
0
50
100
150
200
250
300
350
400
Dose
Estimated Probability
Response at BMD
Data
BMD
BMDL

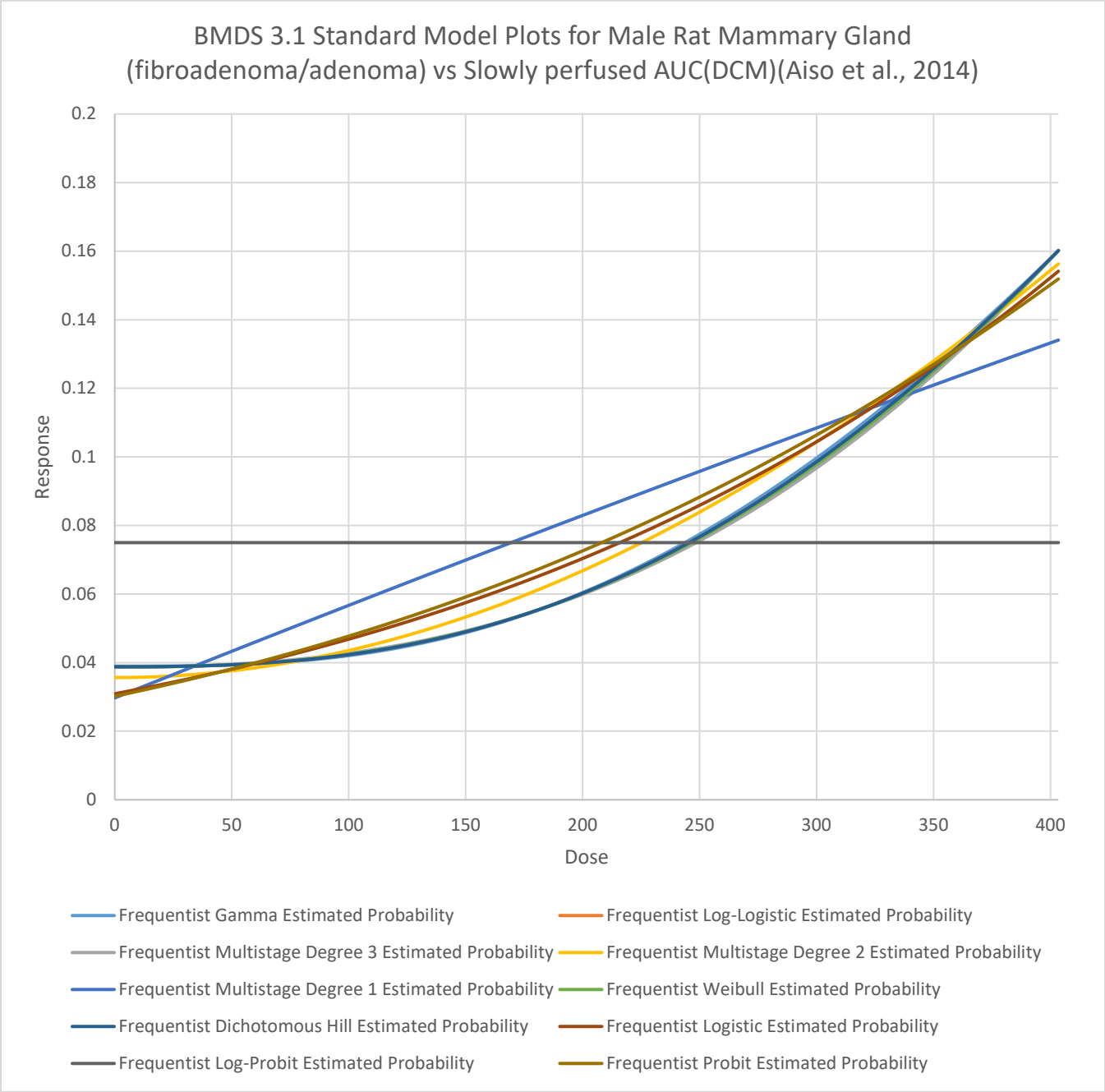
5.2. Mammary Gland (Fibroadenoma/Adenoma)

Slowly perfused AUC(DCM)	N	Incidence
0	50	2
93.33	50	2
196.4	50	3
403.4	50	8

Summary of BMDS 3.1 Modeling Results for Male Rat Mammary Gland (Fibroadenoma/Adenoma) vs Slowly Perfused AUC(DCM) (Aiso et al., 2014)

Standard Models	Restriction***	10% Extra Risk		P Value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL				
Gamma	Restricted	364.06	228.26	0.94651	106.2571	Viable - Alternate	
Log-Logistic	Restricted	365.05	226.8	0.9371	106.2588	Viable - Alternate	
Multistage Degree 2*	Restricted	358.17	227.01	0.96695	104.3196	Viable – Alternate	
Multistage Degree 1 (Quantal Linear)*	Restricted	373.53	205.35	0.60372	105.2816	Selected, Multistage	Multistage-cancer guidance (EPA, 2014)
Weibull	Restricted	366.05	228.37	0.9338	106.2595	Viable - Alternate	
Dichotomous Hill	Unrestricted	365.05	226.8	NA	108.2588	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Logistic**	NA	352.95	266.06	0.88061	104.4998	Selected, Full Model Suite	Lowest AIC****
Log-Probit	Unrestricted	7E+07	0	0.00756	112.5538	Unusable	BMD computation failed; lower limit includes zero BMDL not estimated Goodness of fit p-value < 0.1 Goodness of fit p-value < 0.05 |Residual for Dose Group Near BMD| > 2 BMD higher than maximum dose
Probit	NA	350.46	254.8	0.84549	104.5806	Viable - Alternate	
Non-Standard Models							
Dichotomous Hill	Restricted	288.9	196.59	NA	108.2526	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Log-Probit	Restricted	1E+08	0	0.00756	112.5538	Unusable	BMD computation failed; lower limit includes zero BMDL not estimated Goodness of fit p-value < 0.1 Goodness of fit p-value < 0.05 |Residual for Dose Group Near BMD| > 2 BMD higher than maximum dose
Gamma	Unrestricted	364.06	228.26	0.94651	106.2571	Viable - Alternate	
Log-Logistic	Unrestricted	365.05	226.8	0.9371	106.2588	Viable - Alternate	
Multistage Degree 3	Unrestricted	365.01	195.33	NA	108.2526	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Multistage Degree 2	Unrestricted	364.68	228.27	0.99225	106.2527	Viable - Alternate	
Multistage Degree 1	Unrestricted	373.53	205.35	0.60372	105.2816	Viable - Alternate	
Weibull	Unrestricted	366.06	228.38	0.9338	106.2595	Viable - Alternate	

*Selected, Multistage (Yellow); residuals for doses 0, 93.33, 196.4, and 403.4 were 0.428673711, -0.463013542, -0.56695839, and 0.538250382, respectively.
**Selected, Full Model Suite (Green); residuals for doses 0, 93.33, 196.4, and 403.4 were 0.371049352, -0.188859404, -0.260432602, and 0.114455242, respectively.
***Restrictions defined in the BMDS 3.1 User Guide
****Note that while Multistage 2 has a lower AIC, it was not the selected Multistage model in accordance with Multistage selection criteria (EPA, 2014)


BMDS 3.1 Standard Model Plots for Male Rat Mammary Gland
(fibroadenoma/adenoma) vs Slowly perfused AUC(DCM)(Aiso et al., 2014)
Response
Dose
0
0.02
0.04
0.06
0.08
0.1
0.12
0.14
0.16
0.18
0.2
0
50
100
150
200
250
300
350
400
Frequentist Gamma Estimated Probability
Frequentist Log-Logistic Estimated Probability
Frequentist Multistage Degree 3 Estimated Probability
Frequentist Multistage Degree 2 Estimated Probability
Frequentist Multistage Degree 1 Estimated Probability
Frequentist Weibull Estimated Probability
Frequentist Dichotomous Hill Estimated Probability
Frequentist Logistic Estimated Probability
Frequentist Log-Probit Estimated Probability
Frequentist Probit Estimated Probability

Selected, Multistage - Multistage 1 Restricted; Extra Risk, BMR = 0.1

User Input

Info	
Model	Multistage degree 1 v1.0
Dataset Name	Mammary Gland (Fibroadenoma/Adenoma)
Formula	P[dose] = g + (1-g)*[1-exp(-b1*dose^1)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Slowly perfused AUC(DCM)
Independent Variable	[Tumor Incidence]
Total # of Observation	4

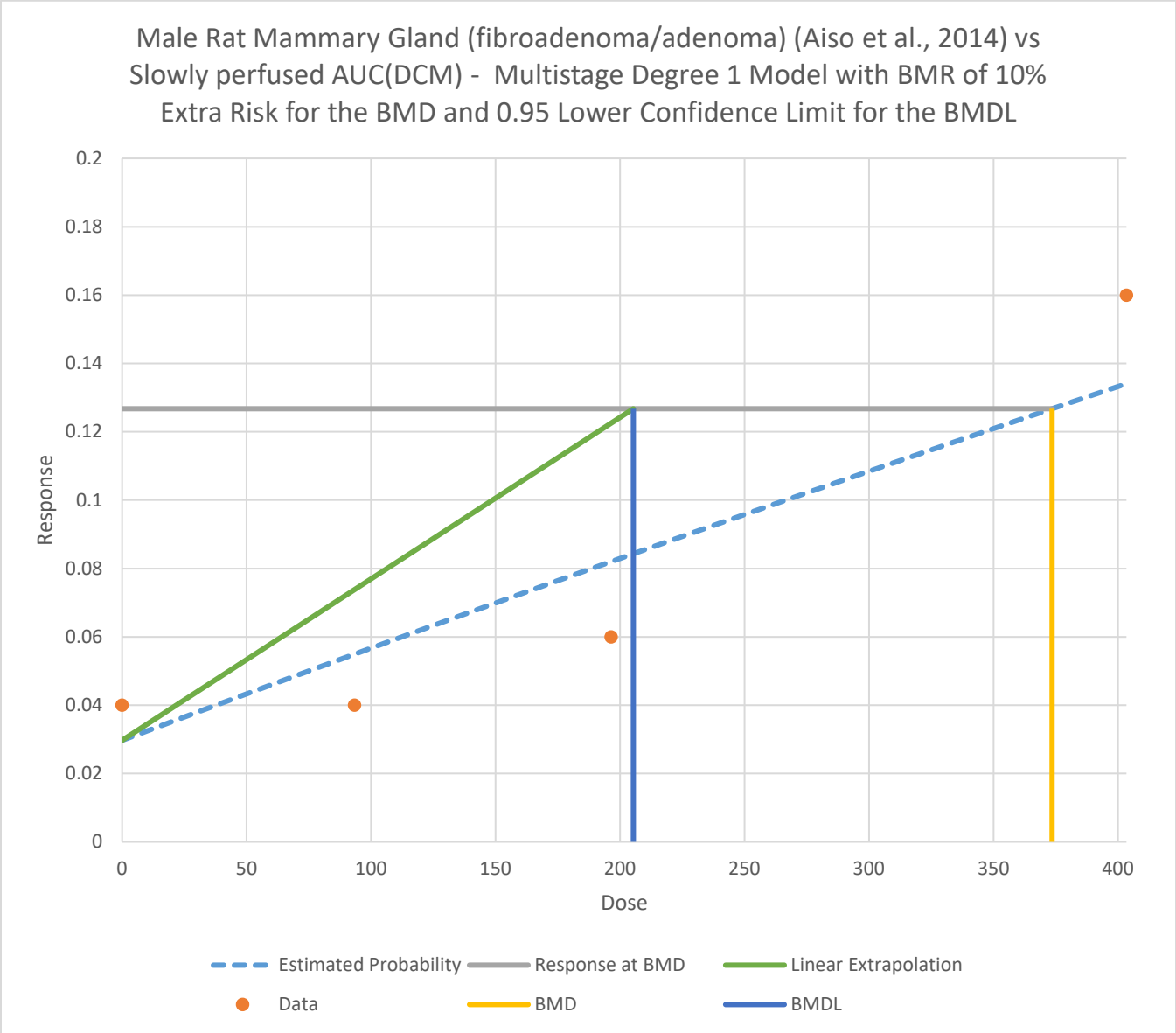
Model Results

Benchmark Dose	
BMD	373.526323
BMDL	205.347909
BMDU	Infinity
AIC	105.2815672
P-value	0.603717449
D.O.F.	2
Chi^2	1.00929798
Slope Factor	0.000486978

Model Parameters	
# of Parameters	2
Variable	Estimate
Background (g)	0.029707391
Beta1	0.00028207

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.029707391	1.48536956	2	50	0.42867
93.33	0.054917614	2.74588068	2	50	-0.463
196.4	0.081998371	4.09991855	3	50	-0.567
403.4	0.134064258	6.70321289	8	50	0.53825

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-50.1262849	0	-	-	-
Fitted Model	-50.6407836	2	1.028997	2	0.5978
Reduced Model	-53.2768927	1	6.301216	3	0.09784


Male Rat Mammary Gland (fibroadenoma/adenoma) (Aiso et al., 2014) vs Slowly perfused AUC(DCM) - Multistage Degree 1 Model with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
0.2
0.18
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
0
50
100
150
200
250
300
350
400
Dose
Estimated Probability
Response at BMD
Linear Extrapolation
Data
BMD
BMDL

Selected, Full Model Suite - Logistic - Extra Risk, BMR = 0.1

User Input

Info	
Model	Logistic v1.0
Dataset Name	Mammary Gland (Fibroadenoma/Adenoma)
Formula	P[dose] = 1/[1+exp(-a-b*dose)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	
Independent Variable	[Tumor Incidence]
Total # of Observation	4

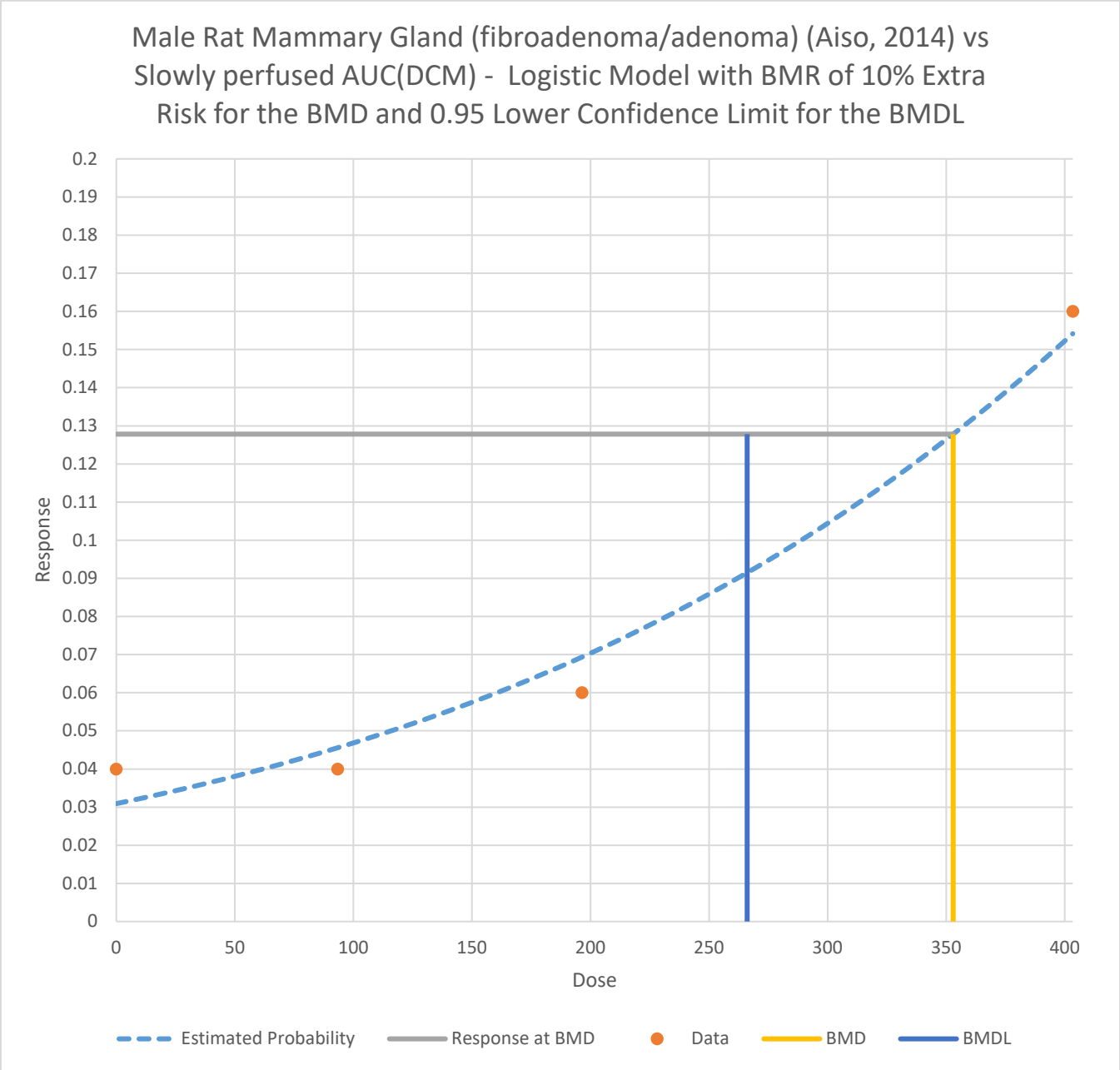
Model Results

Benchmark Dose	
BMD	352.9483762
BMDL	266.0600548
BMDU	763.0199094
AIC	104.499798
P-value	0.8806145
D.O.F.	2
Chi^2	0.254270639

Model Parameters	
# of Parameters	3
Variable	Estimate
a	-3.44504194
b	0.004319944

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.030917064	1.54585318	2	50	0.37105
93.33	0.045570136	2.27850679	2	50	-0.1889
196.4	0.06935724	3.46786198	3	50	-0.2604
403.4	0.154155128	7.70775638	8	50	0.11446

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-50.1262849	0	-	-	-
Fitted Model	-50.249899	2	0.247228	2	0.88372
Reduced Model	-53.2768927	1	6.301216	3	0.09784


Male Rat Mammary Gland (fibroadenoma/adenoma) (Aiso, 2014) vs Slowly perfused AUC(DCM) - Logistic Model with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
0.2
0.19
0.18
0.17
0.16
0.15
0.14
0.13
0.12
0.11
0.1
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
0
50
100
150
200
250
300
350
400
Dose
Estimated Probability
Response at BMD
Data
BMD
BMDL

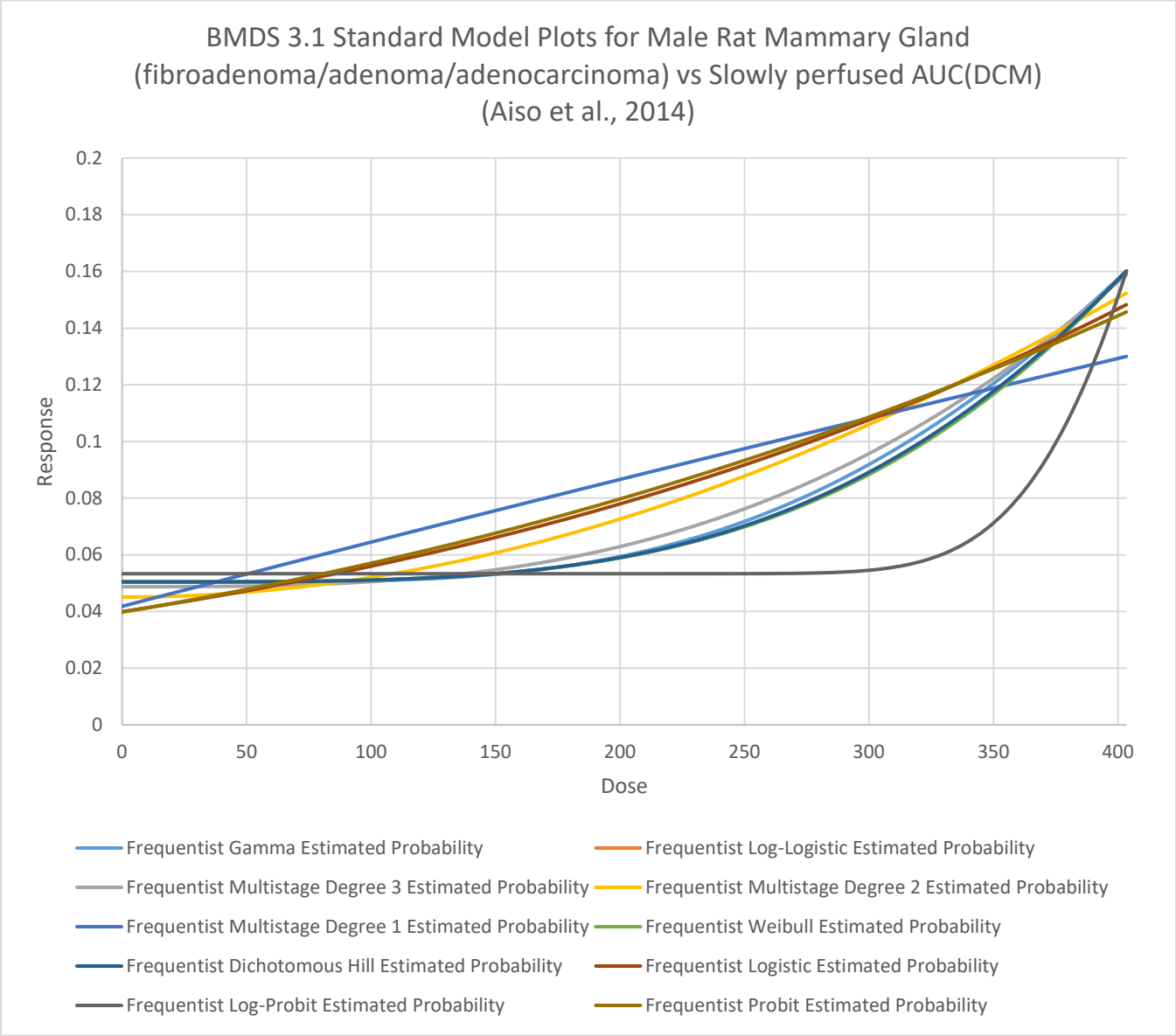
5.3. Mammary Gland (Fibroadenoma/Adenoma/Adenocarcinoma)

Slowly Perfused AUC(DCM)	N	Incidence
0	50	3
93.33	50	2
196.4	50	3
403.4	50	8

Summary of BMDS 3.1 Modeling Results for Male Rat Mammary Gland Fibroadenoma/Adenoma/Adenocarcinoma of Mammary Gland Region (Aiso et al., 2014)

Standard Models	Restriction***	10% Extra Risk		P Value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL				
Gamma	Restricted	384.84	256.66	0.64092	112.376	Viable - Alternate	
Log-Logistic	Restricted	386.6	255.7	0.63837	112.38	Viable - Alternate	
Multistage Degree 2	Restricted	379.36	255.01	0.77427	110.6585	Viable - Alternate	
Multistage Degree 1 (Quantal Linear)*	Restricted	440.28	222.31	0.43113	111.8755	Selected, Multistage	Multistage-cancer guidance (EPA, 2014) BMD higher than maximum dose
Weibull	Restricted	387.21	257.66	0.63796	112.3806	Viable - Alternate	
Dichotomous Hill	Unrestricted	386.55	255.7	NA	114.38	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Logistic**	NA	374.83	267.16	0.60803	111.117	Selected, Full Model Suite	Lowest AIC****
Log-Probit	Unrestricted	398.85	248.42	0.60733	112.4316	Viable - Alternate	
Probit	NA	377.87	257.81	0.57841	111.2227	Viable - Alternate	
Non-Standard Models							
Dichotomous Hill	Restricted	385.04	200.37	NA	114.3787	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Log-Probit	Restricted	382.52	259.78	0.6436	112.3716	Viable - Alternate	
Gamma	Unrestricted	384.68	256.66	0.64074	112.376	Viable - Alternate	
Log-Logistic	Unrestricted	386.58	255.71	0.63836	112.38	Viable - Alternate	
Multistage Degree 3	Unrestricted	391.45	210.95	NA	114.1549	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Multistage Degree 2	Unrestricted	389.98	267.91	0.84764	112.1921	Viable - Alternate	
Multistage Degree 1	Unrestricted	440.28	222.31	0.43113	111.8755	Viable - Alternate	BMD higher than maximum dose
Weibull	Unrestricted	387.21	257.66	0.63796	112.3806	Viable - Alternate	

*Selected, Multistage (Yellow); residuals for doses 0, 93.33, 196.4, and 403.4 were 0.642295022, -0.668909011, -0.65159258, and 0.63098188, respectively.
**Selected, Full Model Suite (Green); residuals for doses 0, 93.33, 196.4, and 403.4 were 0.725402568, -0.458166157, -0.452330816, and 0.233107389, respectively.
***Restrictions defined in the BMDS 3.1 User Guide
****Note that while Multistage 2 has a lower AIC, it was not the selected Multistage model in accordance with Multistage selection criteria (EPA, 2014)


BMDS 3.1 Standard Model Plots for Male Rat Mammary Gland
(fibroadenoma/adenoma/adenocarcinoma) vs Slowly perfused AUC(DCM)
(Aiso et al., 2014)
Response
Dose
0
0.02
0.04
0.06
0.08
0.1
0.12
0.14
0.16
0.18
0.2
0
50
100
150
200
250
300
350
400
Frequentist Gamma Estimated Probability
Frequentist Log-Logistic Estimated Probability
Frequentist Multistage Degree 3 Estimated Probability
Frequentist Multistage Degree 2 Estimated Probability
Frequentist Multistage Degree 1 Estimated Probability
Frequentist Weibull Estimated Probability
Frequentist Dichotomous Hill Estimated Probability
Frequentist Logistic Estimated Probability
Frequentist Log-Probit Estimated Probability
Frequentist Probit Estimated Probability

Selected, Multistage - Multistage 1 Restricted; Extra Risk, BMR = 0.1

User Input

Info	
Model	Multistage degree 1 v1.0
Dataset Name	Mammary Gland (Fibroadenoma/Adenoma/Adenocarcinoma)
Formula	P[dose] = g + (1-g)*[1-exp(-b1*dose^1)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Slowly Perfused AUC(DCM)
Independent Variable	[Tumor Incidence]
Total # of Observation	4

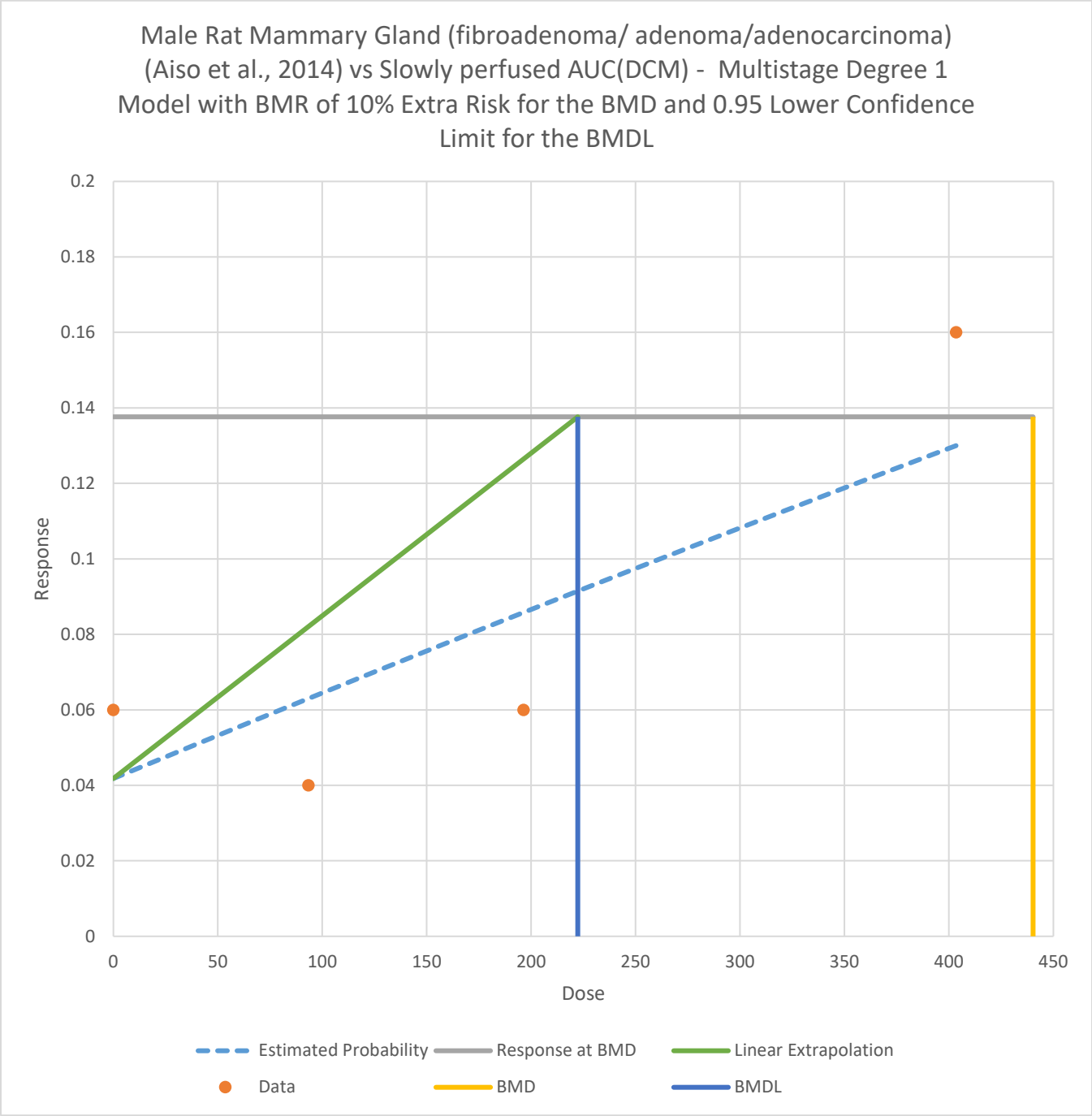
Model Results

Benchmark Dose	
BMD	440.2811477
BMDL	222.3136192
BMDU	Infinity
AIC	111.875539
P-value	0.431129577
D.O.F.	2
Chi^2	1.682693184
Slope Factor	0.000449815

Model Parameters	
# of Parameters	2
Variable	Estimate
Background (g)	0.041817531
Beta1	0.000239303

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.041817531	2.09087655	3	50	0.6423
93.33	0.062980496	3.1490248	2	50	-0.6689
196.4	0.085809333	4.29046666	3	50	-0.6516
403.4	0.129991071	6.49955353	8	50	0.63098

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-53.0774536	0	-	-	-
Fitted Model	-53.9377695	2	1.720632	2	0.42303
Reduced Model	-55.7538744	1	5.352841	3	0.14771


Male Rat Mammary Gland (fibroadenoma/ adenoma/adenocarcinoma) (Aiso et al., 2014) vs Slowly perfused AUC(DCM) - Multistage Degree 1 Model with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
0.2
0.18
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
0
50
100
150
200
250
300
350
400
450
Dose
Estimated Probability
Response at BMD
Linear Extrapolation
Data
BMD
BMDL

Selected, Full Model Suite - Logistic - Extra Risk, BMR = 0.1

User Input

Info	
Model	Logistic v1.0
Dataset Name	Mammary Gland (Fibroadenoma/Adenoma/Adenocarcinoma)
Formula	P[dose] = 1/[1+exp(-a-b*dose)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Slowly Perfused AUC(DCM)
Independent Variable	[Tumor Incidence]
Total # of Observation	4

Model Results

Benchmark Dose	
BMD	374.8279749
BMDL	267.1555314
BMDU	Infinity
AIC	111.1169774
P-value	0.608028412
D.O.F.	2
Chi^2	0.995067334

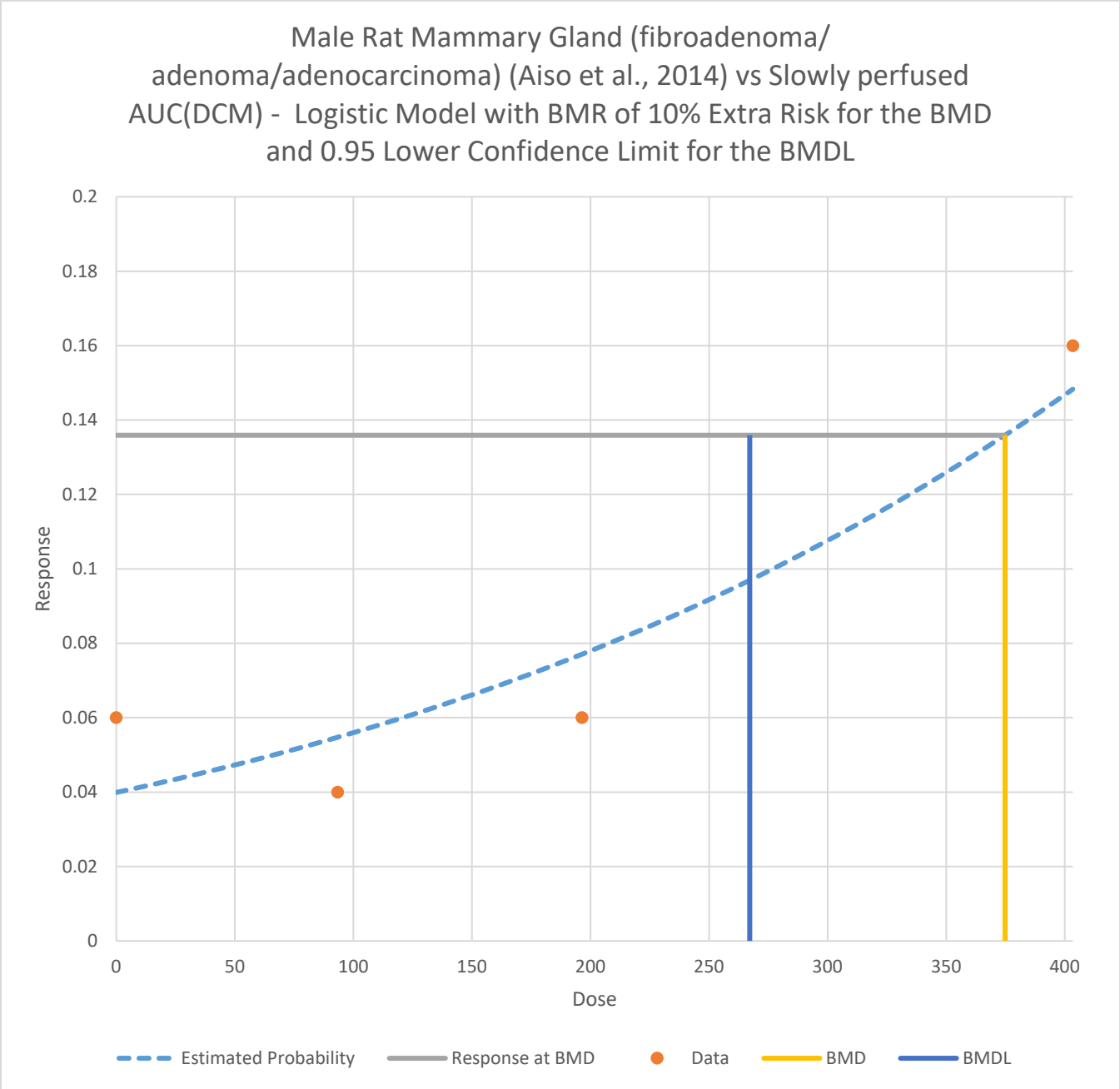
Model Parameters	
# of Parameters	2
Variable	Estimate
a	-3.18021631
b	0.003550063

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.039917043	1.99585217	3	50	0.7254
93.33	0.054738778	2.73693889	2	50	-0.4582
196.4	0.077059711	3.85298554	3	50	-0.4523
403.4	0.14828436	7.414218	8	50	0.23311

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-53.0774536	0	-	-	-
Fitted Model	-53.5584887	2	0.96207	2	0.61814
Reduced Model	-55.7538744	1	5.352841	3	0.14771


Male Rat Mammary Gland (fibroadenoma/ adenoma/adenocarcinoma) (Aiso et al., 2014) vs Slowly perfused AUC(DCM) - Logistic Model with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
0.2
0.18
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
0
50
100
150
200
250
300
350
400
Dose
Estimated Probability
Response at BMD
Data
BMD
BMDL

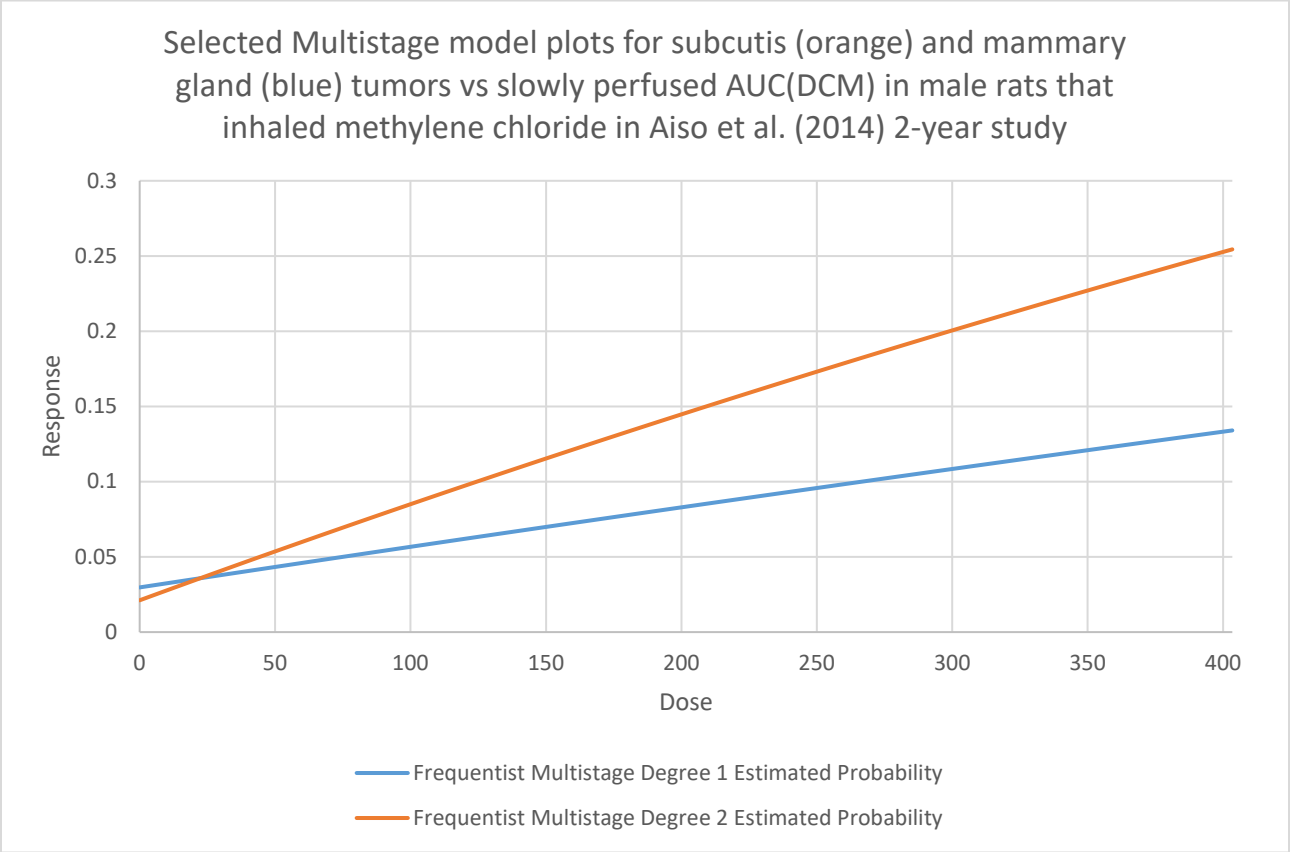
5.4. Subcutis (Fibroma/Fibrosarcoma) or Mammary Gland (Fibroadenoma/Adenoma)

Aiso Male Rat Subcutis (fibroma/fibrosarcoma of mammary gland region)		
Slowly perfused AUC(DCM)	N	Incidence
0	50	1
93.33	50	4
196.4	50	8
403.4	50	12
Aiso Male Rat Mammary Gland (fibroadenoma/adenoma)		
Slowly perfused AUC(DCM)	N	Incidence
0	50	2
93.33	50	2
196.4	50	3
403.4	50	8

Summary of BMDS 3.1 Multi-tumor (MS_Combo) Modeling Results for Male Rat Subcutis (fibroma/fibrosarcoma of mammary gland region) and Mammary Gland (fibroadenoma/adenoma) vs. Slowly perfused AUC(DCM) (Aiso et al., 2014)

Models*	Dataset	10% Extra Risk		Slope Factor	P Value	AIC	BMDS Recommendation Notes
		BMD	BMDL				
Multi-tumor (MS_Combo)	Combined Risk	110.11	78.802	$1.27e^{-3}$	NA	NA	-
Multistage Degree 1	Mammary Gland	373.53	205.35	$4.87e^{-4}$	0.60372	105.2816	Multistage-cancer guidance (EPA, 2014)
Multistage Degree 2	Subcutis	156.13	106.73	$9.37e^{-4}$	0.91319	140.9343	Multistage-cancer guidance (EPA, 2014)

*Multistage models used in the BMDS multi-tumor (MS_Combo) model are restricted as described in the BMDS 3.1 User Guide. The selected Multistage model was chosen from among all relevant model runs (see detailed results for all relevant Multistage degrees below) in accordance with EPA's technical guidance for choosing the appropriate stage of a multistage model for cancer modeling (EPA, 2014).



Multi-tumor (MS_Combo) Results for Male Rat Subcutis (fibroma/fibrosarcoma of mammary gland region) and Mammary Gland (fibroadenoma/adenoma) vs. Slowly perfused AUC(DCM) (Aiso et al., 2014)

User Input

Info	
Model	Multi-tumor v1.0

Model Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Results

Benchmark Dose	
BMD	110.10601
BMDL	78.801884
BMDU	198.32585
Slope Factor	0.001269
Combined Log-Likelihood	-119.1079322
Combined Log-Likelihood Constant	106.0887573

Male Rat Mammary Gland (fibroadenoma/adenoma) - Multistage 1 Restricted (Selected Multistage Degree); Extra Risk, BMR = 0.1

User Input

Info	
Model	Multistage degree 1 v1.0
Dataset Name	Mammary Gland (fibroadenoma/adenoma) – Male Rats
Formula	P[dose] = g + (1-g)*[1-exp(-b1*dose^1)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Slowly perfused AUC(DCM)
Independent Variable	[Tumor Incidence]
Total # of Observation	4

Model Results

Benchmark Dose	
BMD	373.526323
BMDL	205.347909
BMDU	Infinity
AIC	105.2815672
P-value	0.603717449
D.O.F.	2
Chi^2	1.00929798
Slope Factor	0.000486978

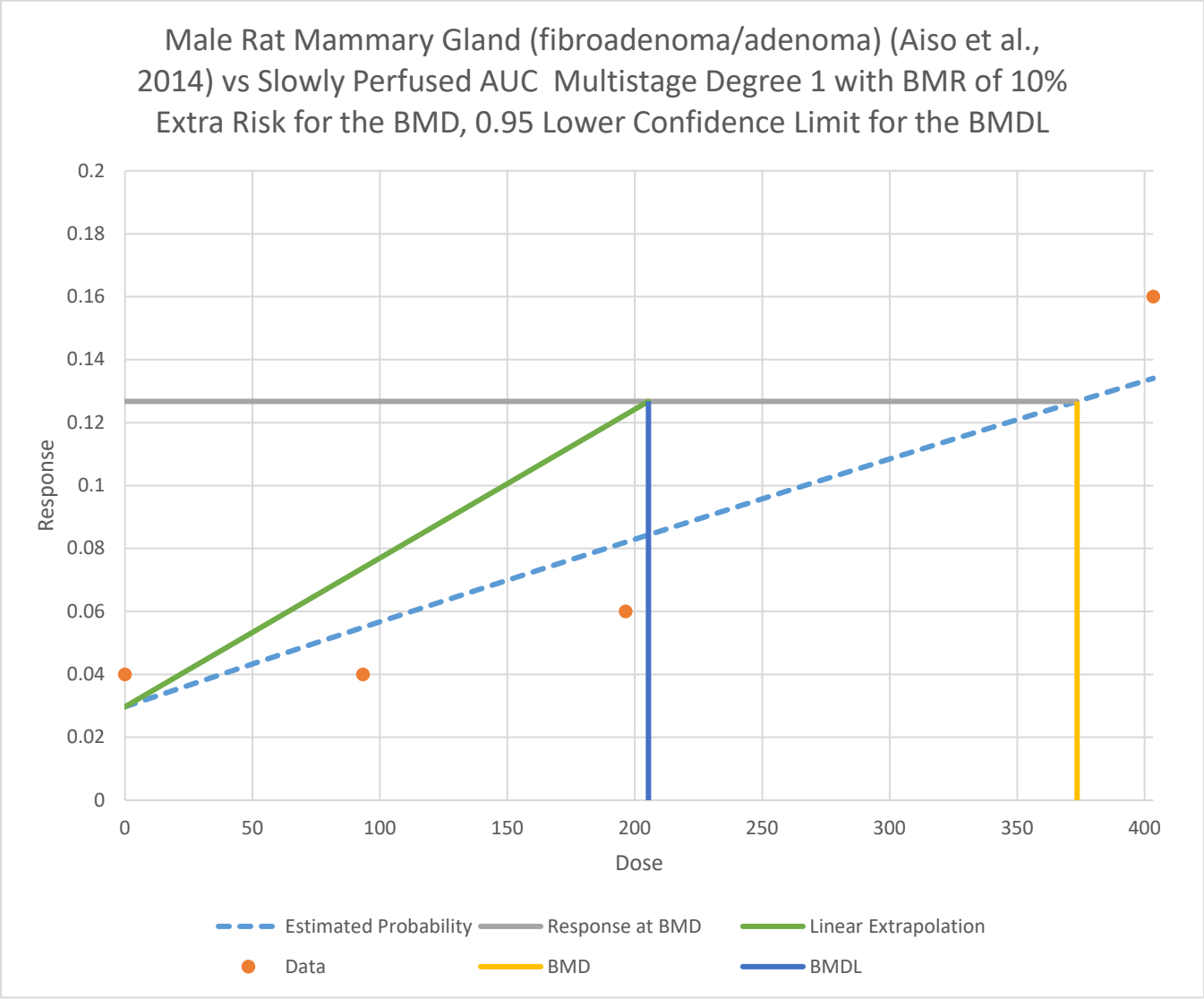
Model Parameters	
# of Parameters	2
Variable	Estimate
Background (g)	0.029707391
Beta1	0.00028207

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.029707391	1.48536956	2	50	0.42867
93.33	0.054917614	2.74588068	2	50	-0.463
196.4	0.081998371	4.09991855	3	50	-0.567
403.4	0.134064258	6.70321289	8	50	0.53825

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-50.1262849	0	-	-	-
Fitted Model	-50.6407836	2	1.028997	2	0.5978
Reduced Model	-53.2768927	1	6.301216	3	0.09784


Male Rat Mammary Gland (fibroadenoma/adenoma) (Aiso et al., 2014) vs Slowly Perfused AUC Multistage Degree 1 with BMR of 10% Extra Risk for the BMD, 0.95 Lower Confidence Limit for the BMDL
Response
0.2
0.18
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
0
50
100
150
200
250
300
350
400
Dose
Estimated Probability
Response at BMD
Linear Extrapolation
Data
BMD
BMDL

Male Rat Mammary Gland (fibroadenoma/adenoma) - Multistage 2 Restricted; Extra Risk, BMR = 0.1

User Input

Info	
Model	Multistage degree 2 v1.0
Dataset Name	Mammary Gland (fibroadenoma/adenoma) – Male Rat
Formula	P[dose] = g + (1-g)*[1-exp(-b1*dose^1-b2*dose^2)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Slowly perfused AUC(DCM)
Independent Variable	[Tumor Incidence]
Total # of Observation	4

Model Results

Benchmark Dose	
BMD	358.1716141
BMDL	227.0120986
BMDU	890.3526015
AIC	104.3196334
P-value	0.96694809
D.O.F.	2
Chi^2	0.067220934
Slope Factor	0.000440505

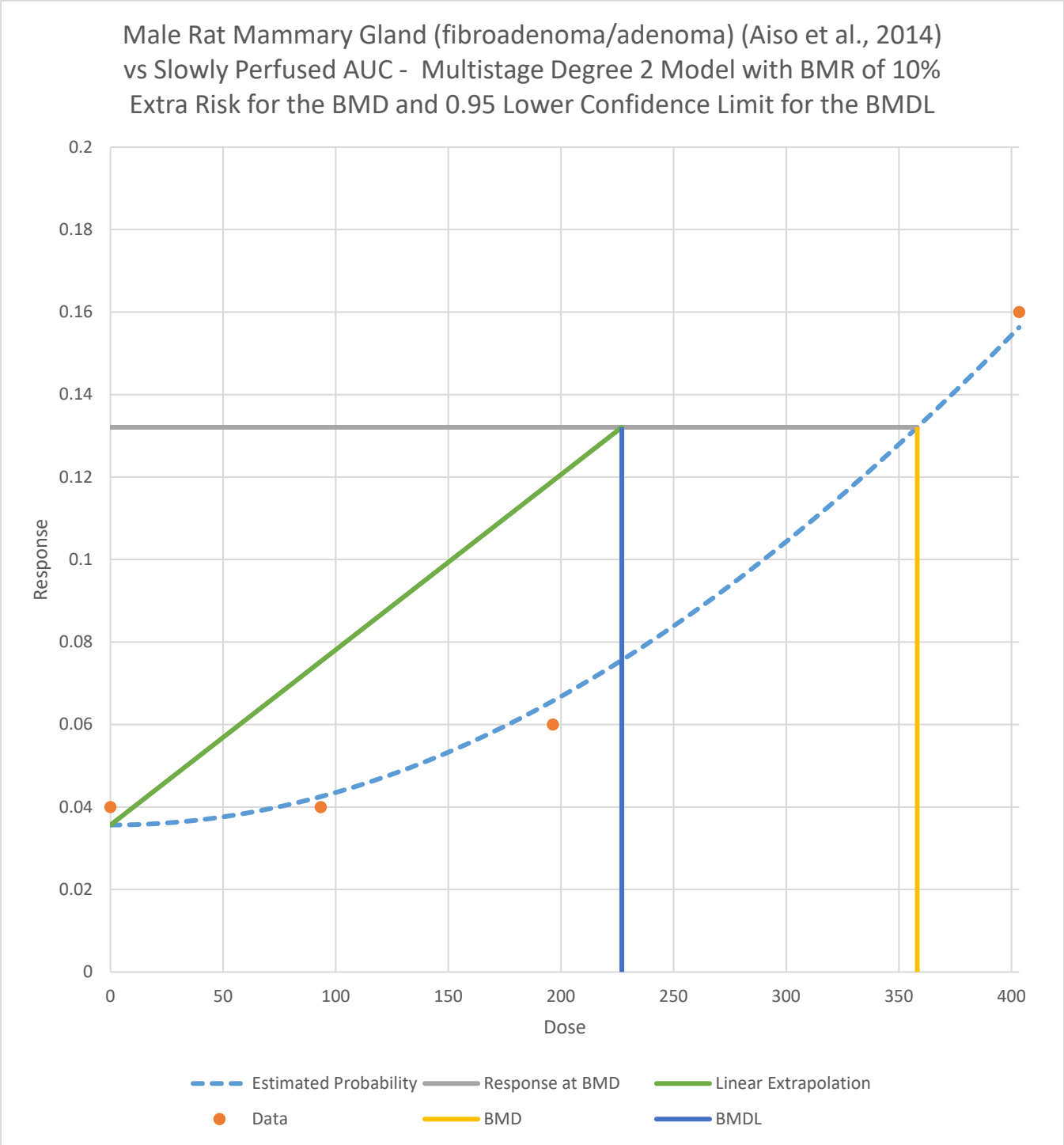
Model Parameters	
# of Parameters	3
Variable	Estimate
Background (g)	0.035640591
Beta1	0
Beta2	8.21288E-07

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.035640591	1.78202957	2	50	0.16627
93.33	0.042514829	2.12574143	2	50	-0.0881
196.4	0.065712188	3.28560941	3	50	-0.163
403.4	0.156285175	7.81425874	8	50	0.07234

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-50.1262849	0	-	-	-
Fitted Model	-50.1598167	2	0.067064	2	0.96702
Reduced Model	-53.2768927	1	6.301216	3	0.09784


Male Rat Mammary Gland (fibroadenoma/adenoma) (Aiso et al., 2014) vs Slowly Perfused AUC - Multistage Degree 2 Model with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
Dose
0.2
0.18
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
0
50
100
150
200
250
300
350
400
Estimated Probability
Response at BMD
Linear Extrapolation
Data
BMD
BMDL

Male Rat Subcutis (fibroma/fibrosarcoma) - Multistage 1 Restricted; Extra Risk, BMR = 0.1

User Input

Info	
Model	Multistage degree 1 v1.0
Dataset Name	Subcutis – Male Rats
Formula	P[dose] = g + (1-g)*[1-exp(-b1*dose^1)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Slowly perfused AUC(DCM)
Independent Variable	[Tumor Incidence]
Total # of Observation	4

Model Results

Benchmark Dose	
BMD	156.1277934
BMDL	106.7309355
BMDU	275.9726206
AIC	140.9342972
P-value	0.913190559
D.O.F.	2
Chi^2	0.181621405
Slope Factor	0.000936935

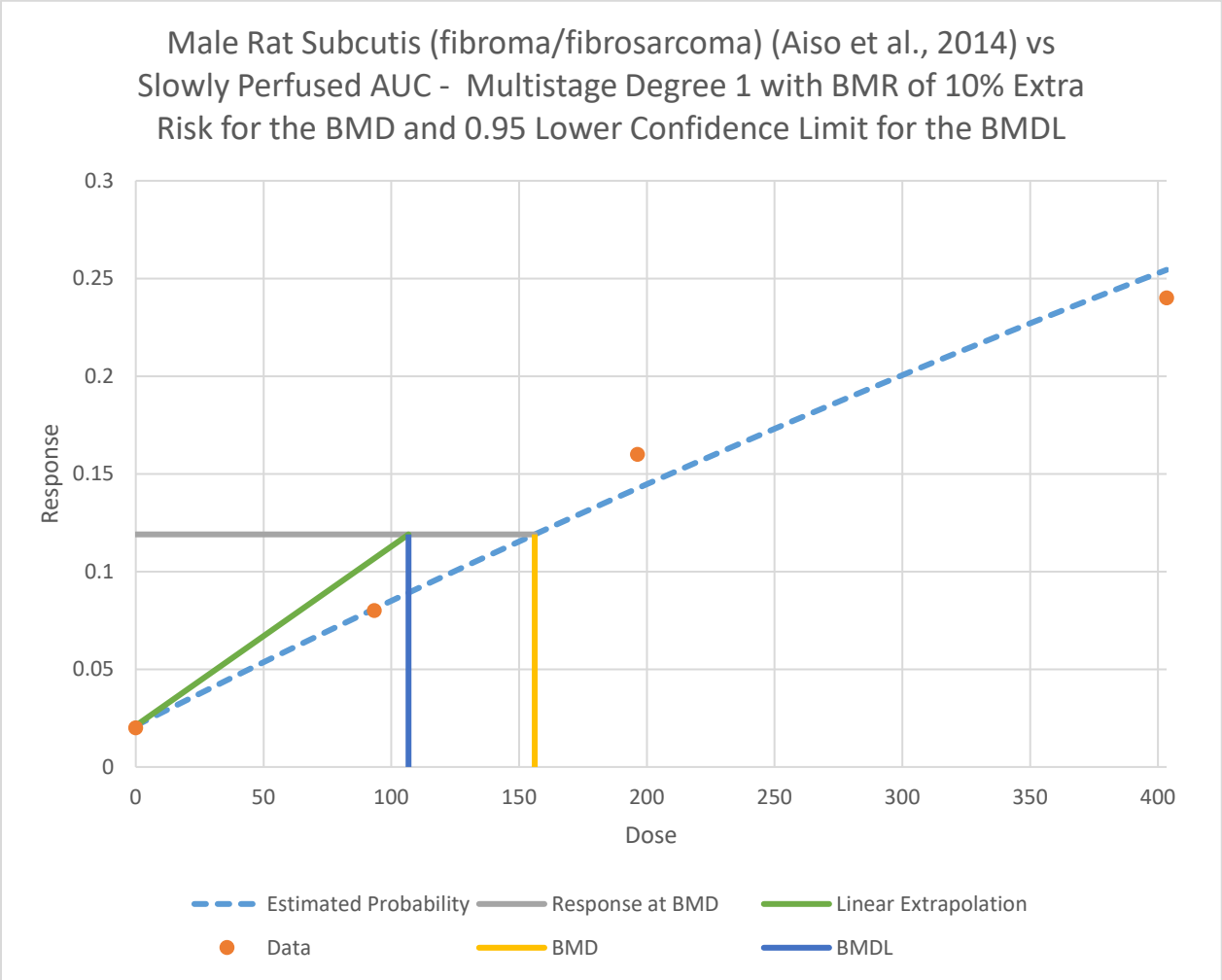
Model Parameters	
# of Parameters	3
Variable	Estimate
Background (g)	0.021140508
Beta1	0.000674835
Beta2	0

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.021140508	1.05702542	1	50	-0.0561
93.33	0.080890056	4.0445028	4	50	-0.0231
196.4	0.142646349	7.13231744	8	50	0.35089
403.4	0.254422095	12.7211048	12	50	-0.2341

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-68.3779146	0	-	-	-
Fitted Model	-68.4671486	2	0.178468	2	0.91463
Reduced Model	-75.3540323	1	13.95224	3	0.00297


Male Rat Subcutis (fibroma/fibrosarcoma) (Aiso et al., 2014) vs Slowly Perfused AUC - Multistage Degree 1 with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
0.3
0.25
0.2
0.15
0.1
0.05
0
0
50
100
150
200
250
300
350
400
Dose
Estimated Probability
Response at BMD
Linear Extrapolation
Data
BMD
BMDL

Male Rat Subcutis (fibroma/fibrosarcoma) - Multistage 2 Restricted (Selected Multistage Degree); Extra Risk, BMR = 0.1

User Input

Info	
Model	Multistage degree 2 v1.0
Dataset Name	Subcutis – Male Rats
Formula	P[dose] = g + (1-g)*[1-exp(-b1*dose^1-b2*dose^2)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Slowly perfused AUC(DCM)
Independent Variable	[Tumor Incidence]
Total # of Observation	4

Model Results

Benchmark Dose	
BMD	156.1284704
BMDL	106.7298415
BMDU	285.6542832
AIC	140.9342972
P-value	0.913190507
D.O.F.	2
Chi^2	0.181621518
Slope Factor	0.000936945

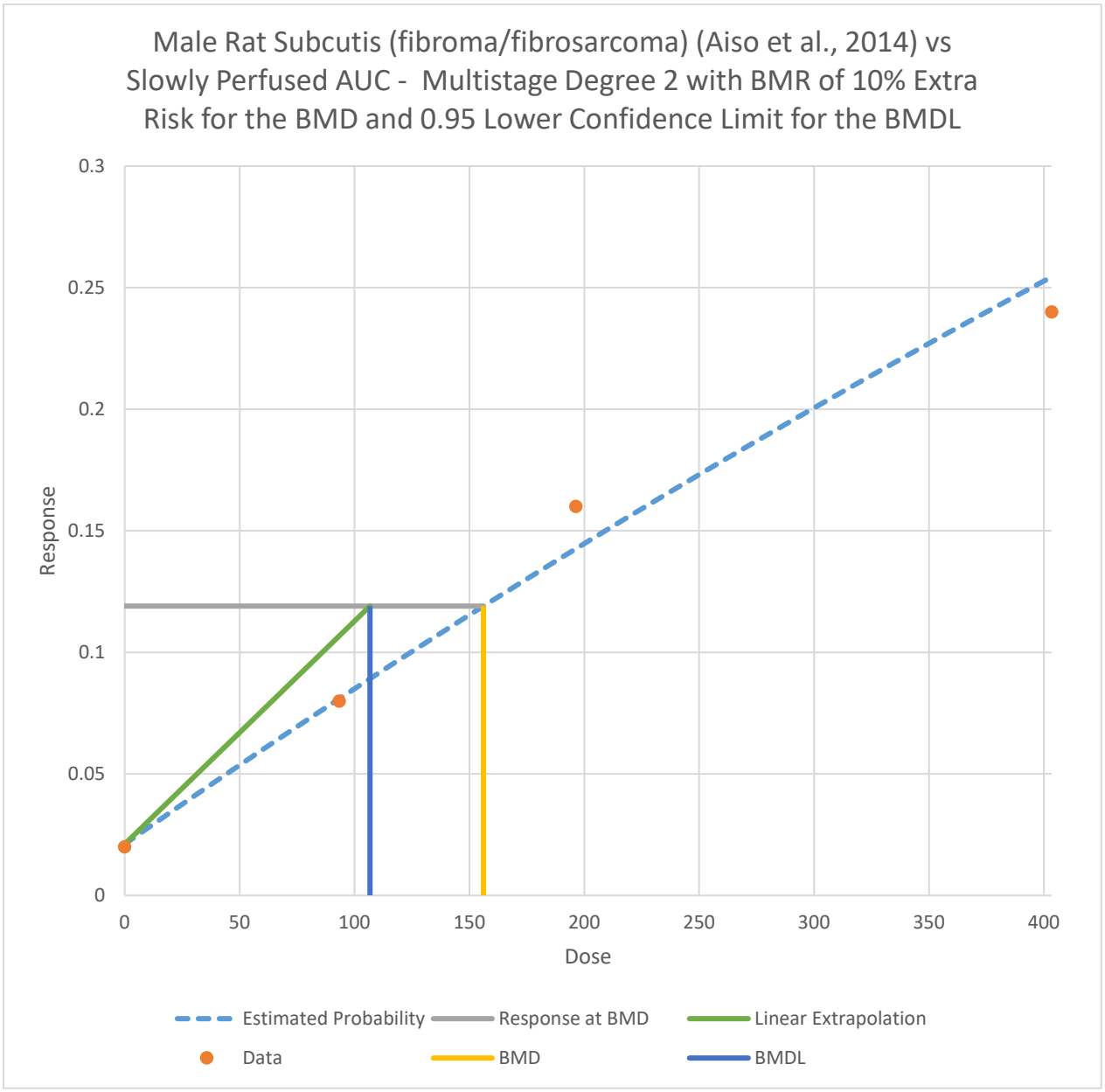
Model Parameters	
# of Parameters	3
Variable	Estimate
Background (g)	0.021140922
Beta1	0.000674832
Beta2	0

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.021140922	1.05704609	1	50	-0.0561
93.33	0.080890193	4.04450965	4	50	-0.0231
196.4	0.142646218	7.1323109	8	50	0.35089
403.4	0.25442153	12.7210765	12	50	-0.2341

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-68.3779146	0	-	-	-
Fitted Model	-68.4671486	2	0.178468	2	0.91463
Reduced Model	-75.3540323	1	13.95224	3	0.00297


Male Rat Subcutis (fibroma/fibrosarcoma) (Aiso et al., 2014) vs Slowly Perfused AUC - Multistage Degree 2 with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
0.3
0.25
0.2
0.15
0.1
0.05
0
0
50
100
150
200
250
300
350
400
Dose
Estimated Probability
Response at BMD
Linear Extrapolation
Data
BMD
BMDL

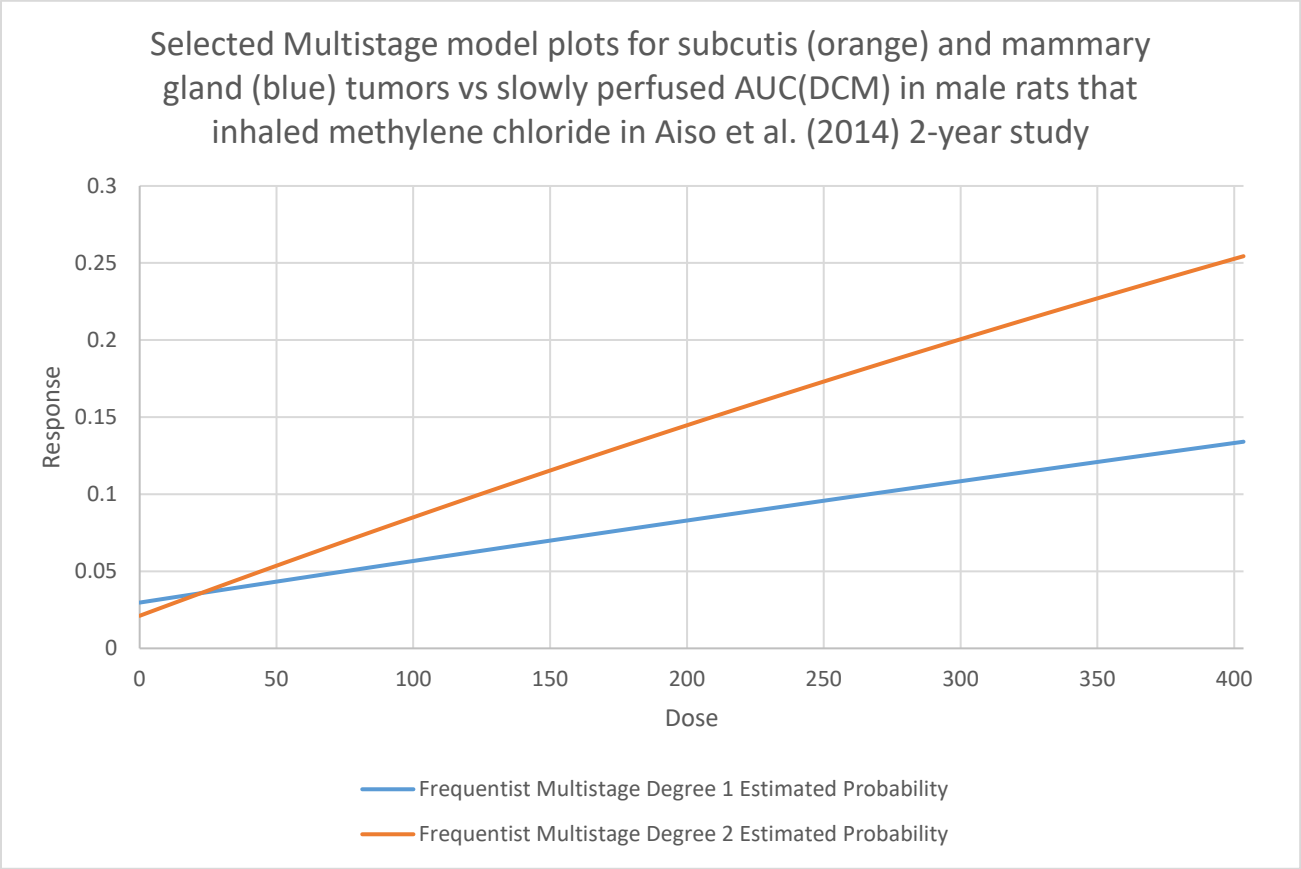
5.5. Subcutis or Mammary Gland (Fibroadenoma/Adenoma/Adenocarcinoma)

Aiso Male Rat Subcutis (fibroma/fibrosarcoma of mammary gland region)		
Slowly perfused AUC(DCM)	N	Incidence
0	50	1
93.33	50	4
196.4	50	8
403.4	50	12
Aiso Male Rat Mammary Gland (fibroadenoma/adenoma/adenocarcinoma)		
Slowly perfused AUC(DCM)	N	Incidence
0	50	3
93.33	50	2
196.4	50	3
403.4	50	8

Summary of BMDS 3.1 Multi-tumor (MS_Combo) Results for Male Rat Subcutis (fibroma/fibrosarcoma of mammary gland region) and Mammary Gland (fibroadenoma/adenoma/adenocarcinoma) vs. Slowly perfused AUC(DCM) (Aiso et al., 2014)

Models*	Dataset	10% Extra Risk		Slope Factor	P Value	AIC	BMDS Recommendation Notes
		BMD	BMDL				
Multi-tumor (MS_Combo)	Combined Risk	115.26	81.265	$1.23e^{-3}$	NA	NA	-
Multistage Degree 1	Mammary Gland	440.28	222.31	$4.50e^{-4}$	0.43113	111.8755	Multistage-cancer guidance (EPA, 2014) BMD higher than maximum dose
Multistage Degree 2	Subcutis	156.13	106.73	$9.37e^{-4}$	0.91319	140.9343	Multistage-cancer guidance (EPA, 2014)

*Multistage models used in the BMDS multi-tumor (MS_Combo) model are restricted as described in the BMDS 3.1 User Guide. The selected Multistage model was chosen from among all relevant model runs (see detailed results for all relevant Multistage degrees below) in accordance with EPA's technical guidance for choosing the appropriate stage of a multistage model for cancer modeling.



Multi-tumor (MS_Combo) Results for Male Rat Subcutis (fibroma/fibrosarcoma of mammary gland region) and Mammary Gland (fibroadenoma/adenoma/adenocarcinoma) vs. Slowly perfused AUC(DCM) (Aiso et al., 2014)

User Input

Info	
Model	Multi-tumor v1.0

Model Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Results

Benchmark Dose	
BMD	115.25711
BMDL	81.265248
BMDU	211.11693
Slope Factor	0.0012305
Combined Log-Likelihood	-122.4049181
Combined Log-Likelihood Constant	108.861346

Male Rat Mammary Gland (fibroadenoma/adenoma/adenocarcinoma) - Multistage 1 Restricted (Selected Multistage Degree); Extra Risk, BMR = 0.1

User Input

Info	
Model	Multistage degree 1 v1.0
Dataset Name	Mammary Gland (fibroadenoma/adenoma/adenocarcinoma) – Male Rats
Formula	P[dose] = g + (1-g)*[1-exp(-b1*dose^1)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Slowly perfused AUC(DCM)
Independent Variable	[Tumor Incidence]
Total # of Observation	4

Model Results

Benchmark Dose	
BMD	440.2811477
BMDL	222.3136192
BMDU	Infinity
AIC	111.875539
P-value	0.431129577
D.O.F.	2
Chi^2	1.682693184
Slope Factor	0.000449815

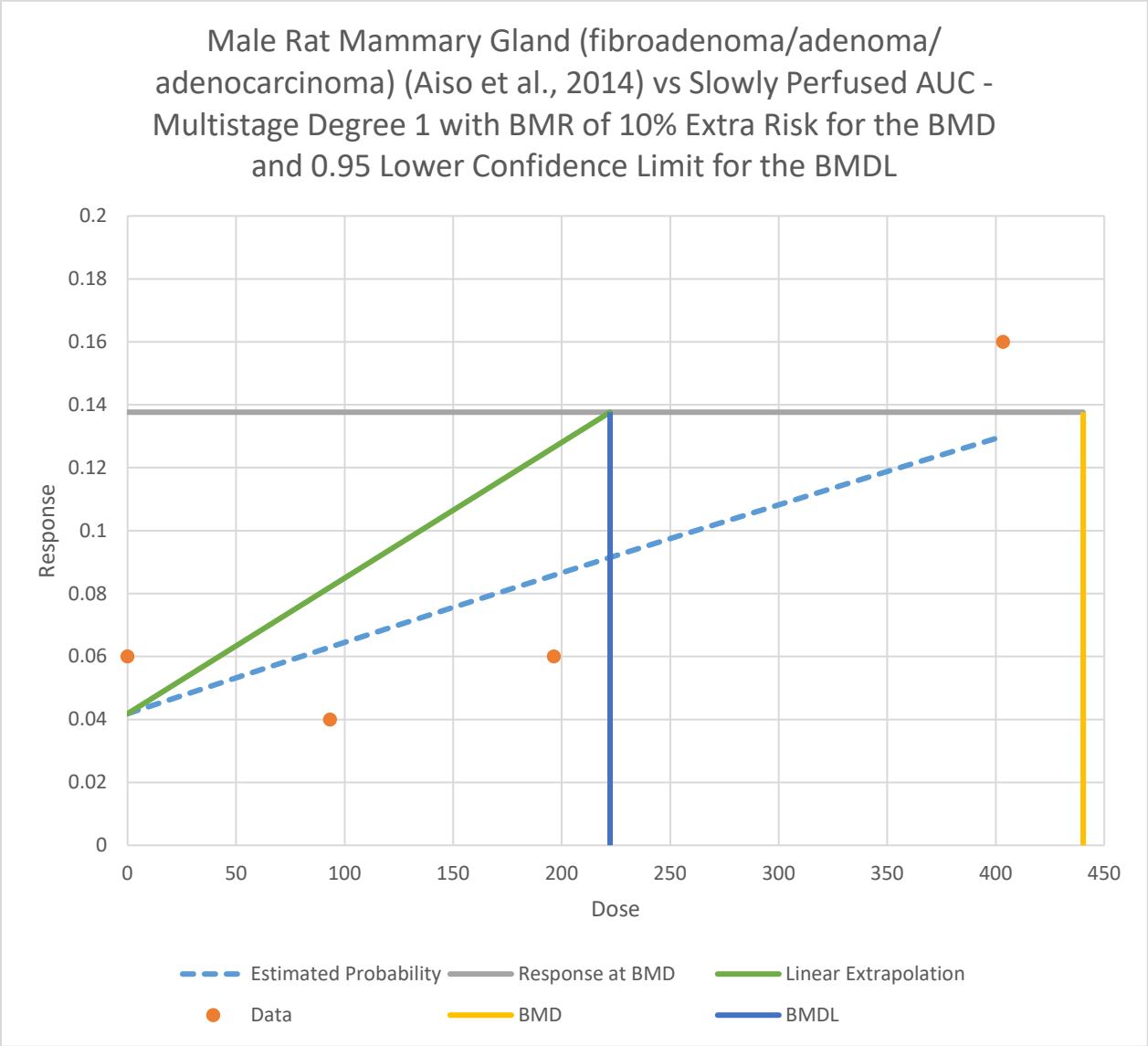
Model Parameters	
# of Parameters	3
Variable	Estimate
Background (g)	0.041817531
Beta1	0.000239303
Beta2	0

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.041817531	2.09087655	3	50	0.6423
93.33	0.062980496	3.1490248	2	50	-0.6689
196.4	0.085809333	4.29046666	3	50	-0.6516
403.4	0.129991071	6.49955353	8	50	0.63098

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-53.0774536	0	-	-	-
Fitted Model	-53.9377695	2	1.720632	2	0.42303
Reduced Model	-55.7538744	1	5.352841	3	0.14771


Male Rat Mammary Gland (fibroadenoma/adenoma/ adenocarcinoma) (Aiso et al., 2014) vs Slowly Perfused AUC - Multistage Degree 1 with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
0.2
0.18
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
0
50
100
150
200
250
300
350
400
450
Dose
Estimated Probability
Response at BMD
Linear Extrapolation
Data
BMD
BMDL

Male Rat Mammary Gland (fibroadenoma/adenoma/adenocarcinoma) - Multistage 2 Restricted; Extra Risk, BMR = 0.1

User Input

Info	
Model	Multistage degree 2 v1.0
Dataset Name	Mammary Gland (fibroadenoma/adenoma/adenocarcinoma) – Male Rat
Formula	P[dose] = g + (1-g)*[1-exp(-b1*dose^1-b2*dose^2)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Slowly perfused AUC(DCM)
Independent Variable	[Tumor Incidence]
Total # of Observation	4

Model Results

Benchmark Dose	
BMD	379.3582184
BMDL	255.0118006
BMDU	Infinity
AIC	110.6584528
P-value	0.774267398
D.O.F.	2
Chi^2	0.511675979
Slope Factor	0.000392139

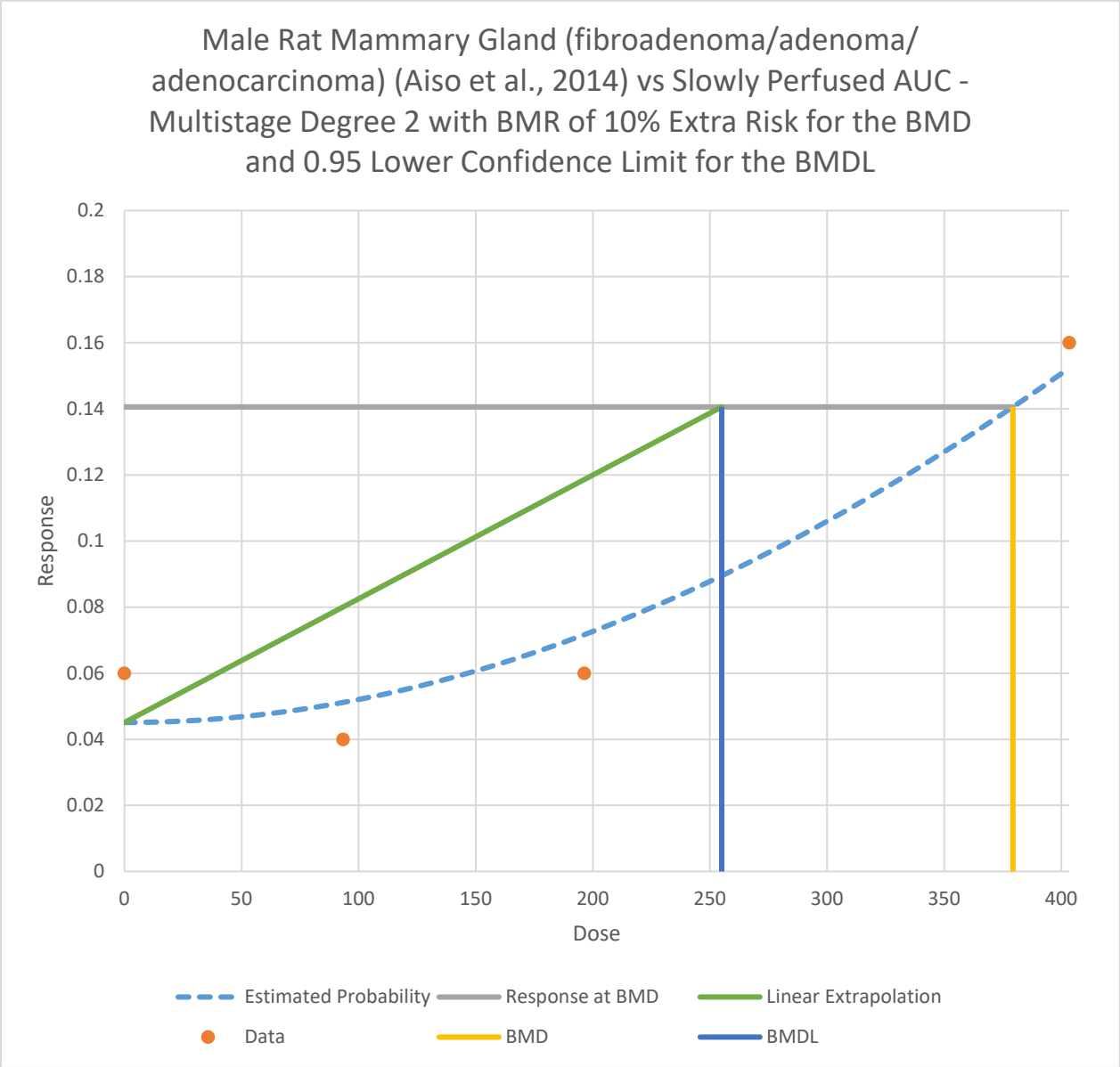
Model Parameters	
# of Parameters	3
Variable	Estimate
Background (g)	0.045087926
Beta1	0
Beta2	7.32114E-07

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.045087926	2.2543963	3	50	0.50817
93.33	0.051158095	2.55790475	2	50	-0.3581
196.4	0.071677261	3.58386305	3	50	-0.3201
403.4	0.152338684	7.61693422	8	50	0.15076

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-53.0774536	0	-	-	-
Fitted Model	-53.3292264	2	0.503546	2	0.77742
Reduced Model	-55.7538744	1	5.352841	3	0.14771


Male Rat Mammary Gland (fibroadenoma/adenoma/ adenocarcinoma) (Aiso et al., 2014) vs Slowly Perfused AUC - Multistage Degree 2 with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
0.2
0.18
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
0
50
100
150
200
250
300
350
400
Dose
Estimated Probability
Response at BMD
Linear Extrapolation
Data
BMD
BMDL

Male Rat Subcutis (fibroma/fibrosarcoma) - Multistage 1 Restricted; Extra Risk, BMR = 0.1

User Input

Info	
Model	Multistage degree 1 v1.0
Dataset Name	Subcutis – Male Rats
Formula	P[dose] = g + (1-g)*[1-exp(-b1*dose^1)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Slowly perfused AUC(DCM)
Independent Variable	[Tumor Incidence]
Total # of Observation	4

Model Results

Benchmark Dose	
BMD	156.1277934
BMDL	106.7309355
BMDU	275.9726206
AIC	140.9342972
P-value	0.913190559
D.O.F.	2
Chi^2	0.181621405
Slope Factor	0.000936935

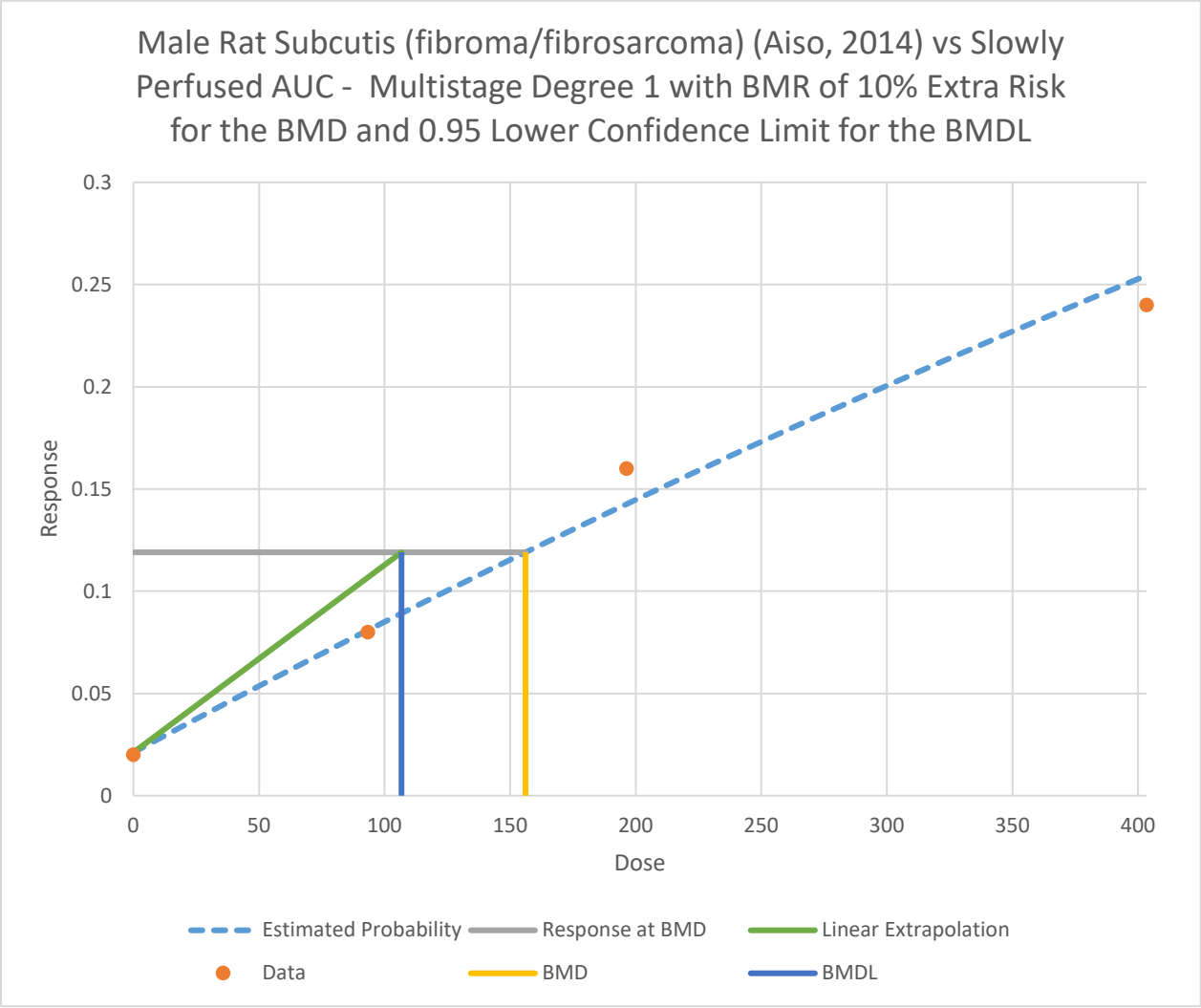
Model Parameters	
# of Parameters	3
Variable	Estimate
Background (g)	0.021140508
Beta1	0.000674835
Beta2	0

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.021140508	1.05702542	1	50	-0.0561
93.33	0.080890056	4.0445028	4	50	-0.0231
196.4	0.142646349	7.13231744	8	50	0.35089
403.4	0.254422095	12.7211048	12	50	-0.2341

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-68.3779146	0	-	-	-
Fitted Model	-68.4671486	2	0.178468	2	0.91463
Reduced Model	-75.3540323	1	13.95224	3	0.00297


Male Rat Subcutis (fibroma/fibrosarcoma) (Aiso, 2014) vs Slowly Perfused AUC - Multistage Degree 1 with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
0.3
0.25
0.2
0.15
0.1
0.05
0
0
50
100
150
200
250
300
350
400
Dose
Estimated Probability
Response at BMD
Linear Extrapolation
Data
BMD
BMDL

Male Rat Subcutis (fibroma/fibrosarcoma) - Multistage 2 Restricted (Selected Multistage Degree); Extra Risk, BMR = 0.1

User Input

Info	
Model	Multistage degree 2 v1.0
Dataset Name	Subcutis – Male Rats
Formula	P[dose] = g + (1-g)*[1-exp(-b1*dose^1-b2*dose^2)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Slowly perfused AUC(DCM)
Independent Variable	[Tumor Incidence]
Total # of Observation	4

Model Results

Benchmark Dose	
BMD	156.1284704
BMDL	106.7298415
BMDU	285.6542832
AIC	140.9342972
P-value	0.913190507
D.O.F.	2
Chi^2	0.181621518
Slope Factor	0.000936945

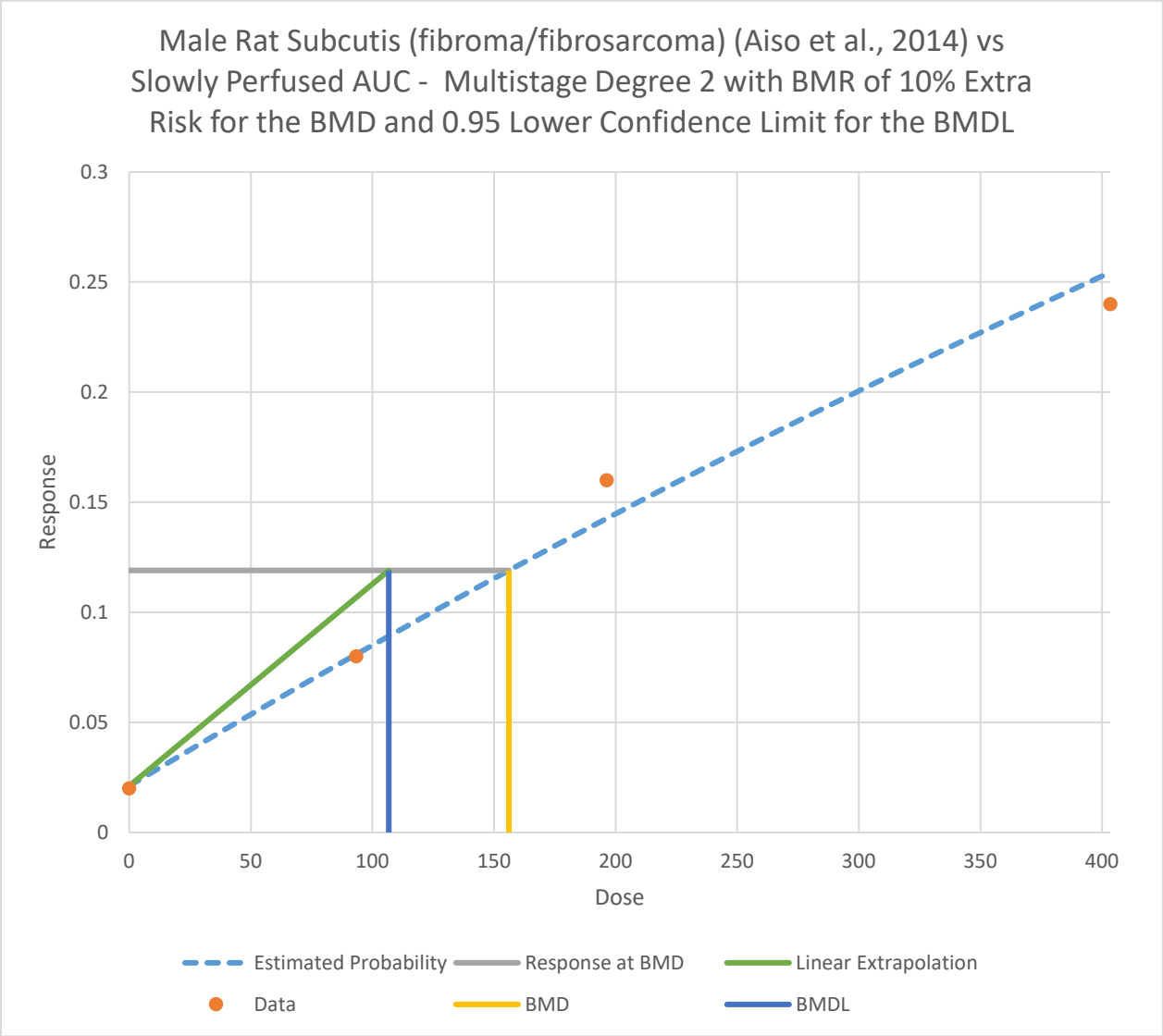
Model Parameters	
# of Parameters	3
Variable	Estimate
Background (g)	0.021140922
Beta1	0.000674832
Beta2	0

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.021140922	1.05704609	1	50	-0.0561
93.33	0.080890193	4.04450965	4	50	-0.0231
196.4	0.142646218	7.1323109	8	50	0.35089
403.4	0.25442153	12.7210765	12	50	-0.2341

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-68.3779146	0	-	-	-
Fitted Model	-68.4671486	2	0.178468	2	0.91463
Reduced Model	-75.3540323	1	13.95224	3	0.00297


Male Rat Subcutis (fibroma/fibrosarcoma) (Aiso et al., 2014) vs Slowly Perfused AUC - Multistage Degree 2 with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
0.3
0.25
0.2
0.15
0.1
0.05
0
0
50
100
150
200
250
300
350
400
Dose
Estimated Probability
Response at BMD
Linear Extrapolation
Data
BMD
BMDL

6. BMD Modeling for Aiso et al. (2014) Female Rats

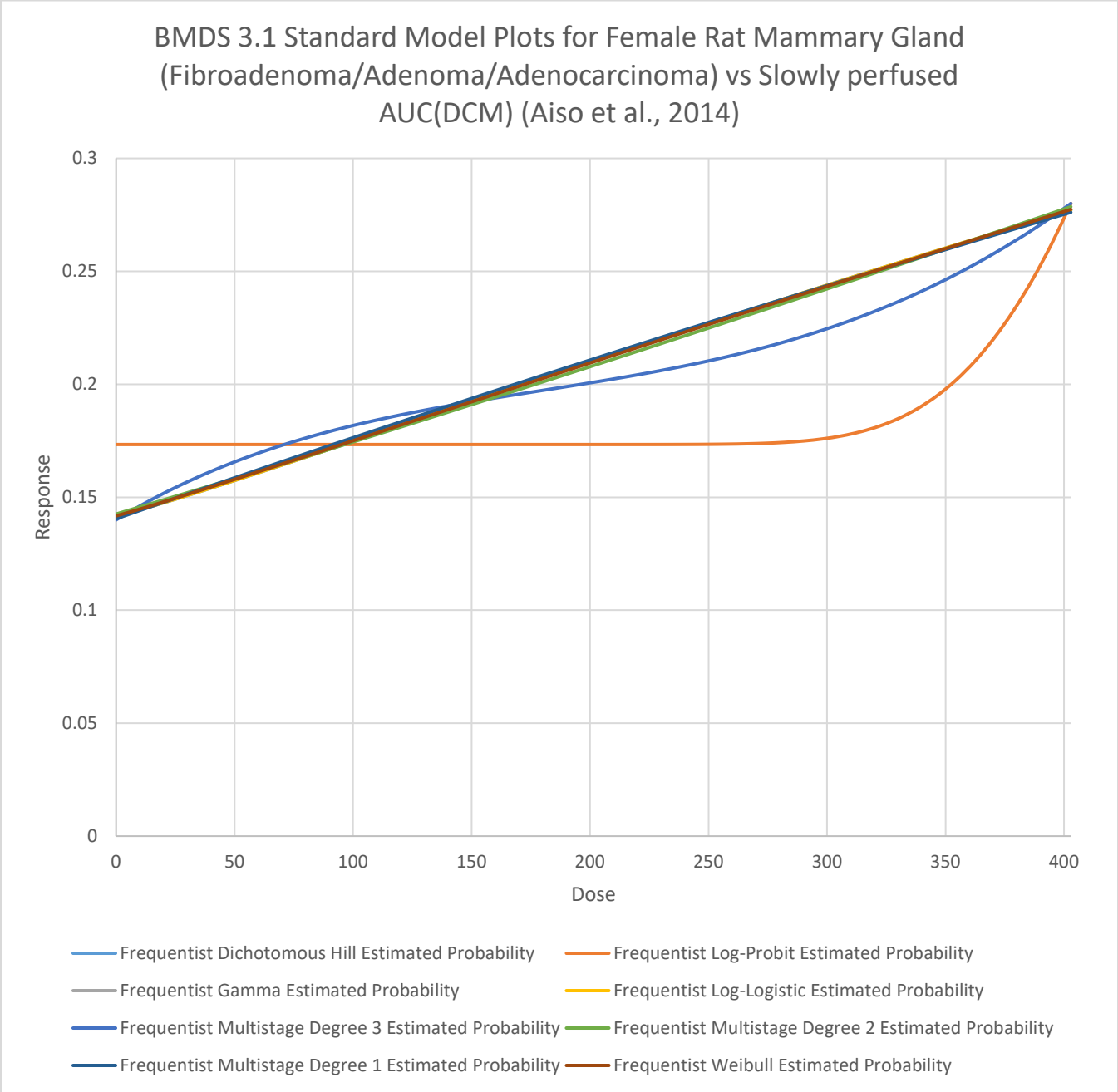
6.1. Mammary Gland (Fibroadenoma/Adenoma/Adenocarcinoma)

Slowly Perfused AUC(DCM)	N	Incidence
0	50	7
93.29	50	9
196.3	50	10
402.9	50	14

Summary of BMDS 3.1 Modeling Results for Female Rat Mammary Gland Fibroadenoma/Adenoma/Adenocarcinoma (Aiso et al., 2014)

Standard Models	Restriction***	10% Extra Risk		P Value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL				
Gamma	Restricted	252.38	123.73	0.83726	203.01348	Viable - Alternate	
Log-Logistic	Restricted	251.92	112.12	0.83049	203.01710	Viable - Alternate	
Multistage Degree 2	Restricted	259.85	123.79	0.84732	203.00822	Viable - Alternate	
Multistage Degree 1 (Quantal Linear)*	Restricted	247.23	123.70	0.97846	201.01500	Selected, Multistage	Multistage-cancer guidance (EPA, 2014)
Weibull	Restricted	253.00	123.74	0.83797	203.01308	Viable - Alternate	
Dichotomous Hill	Unrestricted	251.92	0	NA	205.01710	Unusable	BMD computation failed; lower limit includes zero; BMDL not estimated d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Logistic	NA	275.68	173.88	0.97832	201.01485	Viable - Alternate	
Log-Probit	Unrestricted	391.50	0	0.41963	203.63506	Unusable	BMD computation failed; lower limit includes zero; BMDL not estimated
Probit**	NA	271.35	166.68	0.97985	201.01173	**Selected, Full Model Suite**	**Lowest AIC**
Non-Standard Models							
Dichotomous Hill	Restricted	251.94	112.12	NA	205.01710	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Log-Probit	Restricted	391.75	186.71	0.41963	203.63507	Viable - Alternate	
Gamma	Unrestricted	251.76	11.125	0.83726	203.01350	Questionable	BMD/BMDL ratio > 20 BMD/BMDL ratio > 5 BMDL 3x lower than lowest non-zero dose
Log-Logistic	Unrestricted	251.92	0	0.83049	203.01710	Unusable	BMD computation failed; lower limit includes zero; BMDL not estimated
Multistage Degree 3	Unrestricted	303.92	28.637	NA	204.97127	Questionable	BMD/BMDL ratio > 5 BMDL 3x lower than lowest non-zero dose d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Multistage Degree 2	Unrestricted	259.90	70.927	0.84731	203.00822	Viable - Alternate	
Multistage Degree 1	Unrestricted	247.15	123.70	0.97846	201.01500	Viable - Alternate	
Weibull	Unrestricted	253.20	0	0.83798	203.01308	Unusable	BMD computation failed; lower limit includes zero; BMDL not estimated

*Selected, Multistage (Yellow); residuals for doses 0, 93.29, 196.3, and 402.9 were -0.010239177, 0.111846652, -0.164713519, and 0.061617456, respectively.
**Selected, Full Model Suite (Green); residuals for doses 0, 93.29, 196.3, and 402.9 were -0.092589223, 0.164652106-0.070902629, and -0.001870175, respectively.
***Restrictions defined in the BMDS 3.1 User Guide; NA = Not Applicable


BMDS 3.1 Standard Model Plots for Female Rat Mammary Gland (Fibroadenoma/Adenoma/Adenocarcinoma) vs Slowly perfused AUC(DCM) (Aiso et al., 2014)
Response
Dose
0.3
0.25
0.2
0.15
0.1
0.05
0
0
50
100
150
200
250
300
350
400
Frequentist Dichotomous Hill Estimated Probability
Frequentist Log-Probit Estimated Probability
Frequentist Gamma Estimated Probability
Frequentist Log-Logistic Estimated Probability
Frequentist Multistage Degree 3 Estimated Probability
Frequentist Multistage Degree 2 Estimated Probability
Frequentist Multistage Degree 1 Estimated Probability
Frequentist Weibull Estimated Probability

Selected, Multistage - Multistage 1 Restricted; Extra Risk, BMR = 0.1

User Input

Info	
Model	Multistage degree 1 v1.0
Dataset Name	Aiso Female Rat Mammary Gland (Fibroadenoma/Adenoma/ Adenocarcinoma)
Formula	P[dose] = g + (1-g)*[1-exp(-b1*dose^1)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Slowly perfused AUC(DCM)
Independent Variable	[Tumor Incidence]
Total # of Observation	4

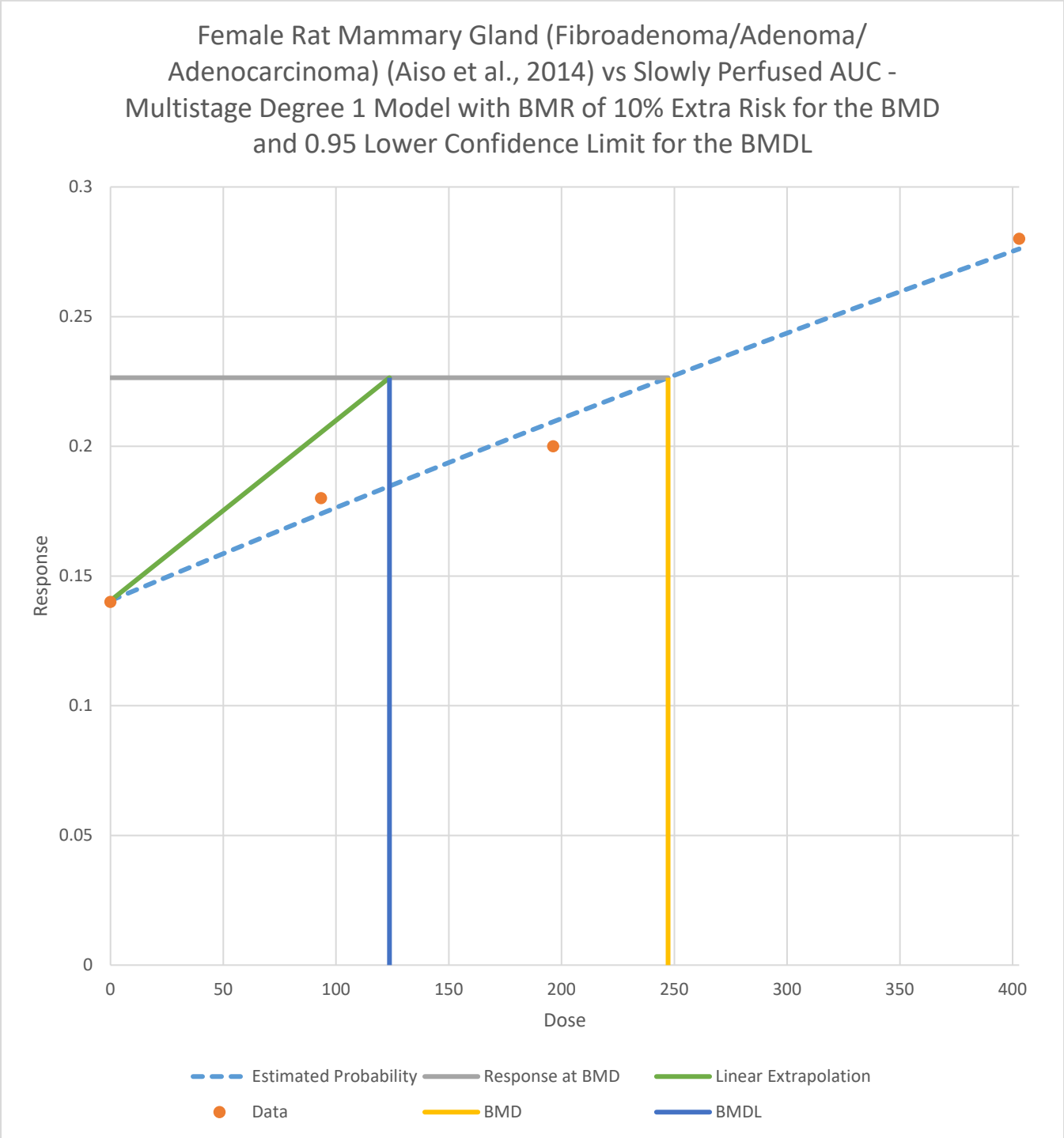
Model Results

Benchmark Dose	
BMD	247.2325655
BMDL	123.7009246
BMDU	Infinity
AIC	201.0149992
P-value	0.978464391
D.O.F.	2
Chi^2	0.043541769
Slope Factor	0.000808401

Model Parameters	
# of Parameters	3
Variable	Estimate
Background (g)	0.140503205
Beta1	0.00042616

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.140503205	7.025160271	7	50	-0.010239
93.29	0.174003388	8.700169384	9	50	0.1118467
196.3	0.209479192	10.47395962	10	50	-0.164714
402.9	0.27610423	13.8052115	14	50	0.0616175

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-98.48563564	0	-	-	-
Fitted Model	-98.50749962	2	0.04372796	2	0.9783733
Reduced Model	-100.0804847	1	3.18969813	3	0.363292


Female Rat Mammary Gland (Fibroadenoma/Adenoma/ Adenocarcinoma) (Aiso et al., 2014) vs Slowly Perfused AUC - Multistage Degree 1 Model with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
0.3
0.25
0.2
0.15
0.1
0.05
0
0
50
100
150
200
250
300
350
400
Dose
Estimated Probability
Response at BMD
Linear Extrapolation
Data
BMD
BMDL

Selected, Full Model Suite - Probit - Extra Risk, BMR = 0.1

User Input

Info	
Model	Probit v1.0
Dataset Name	Aiso Female Rat Mammary Gland (Fibroadenoma/Adenoma/ Adenocarcinoma)
Formula	P[dose] = CumNorm(a+b*Dose)

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Slowly perfused AUC(DCM)
Independent Variable	[Tumor Incidence]
Total # of Observation	4

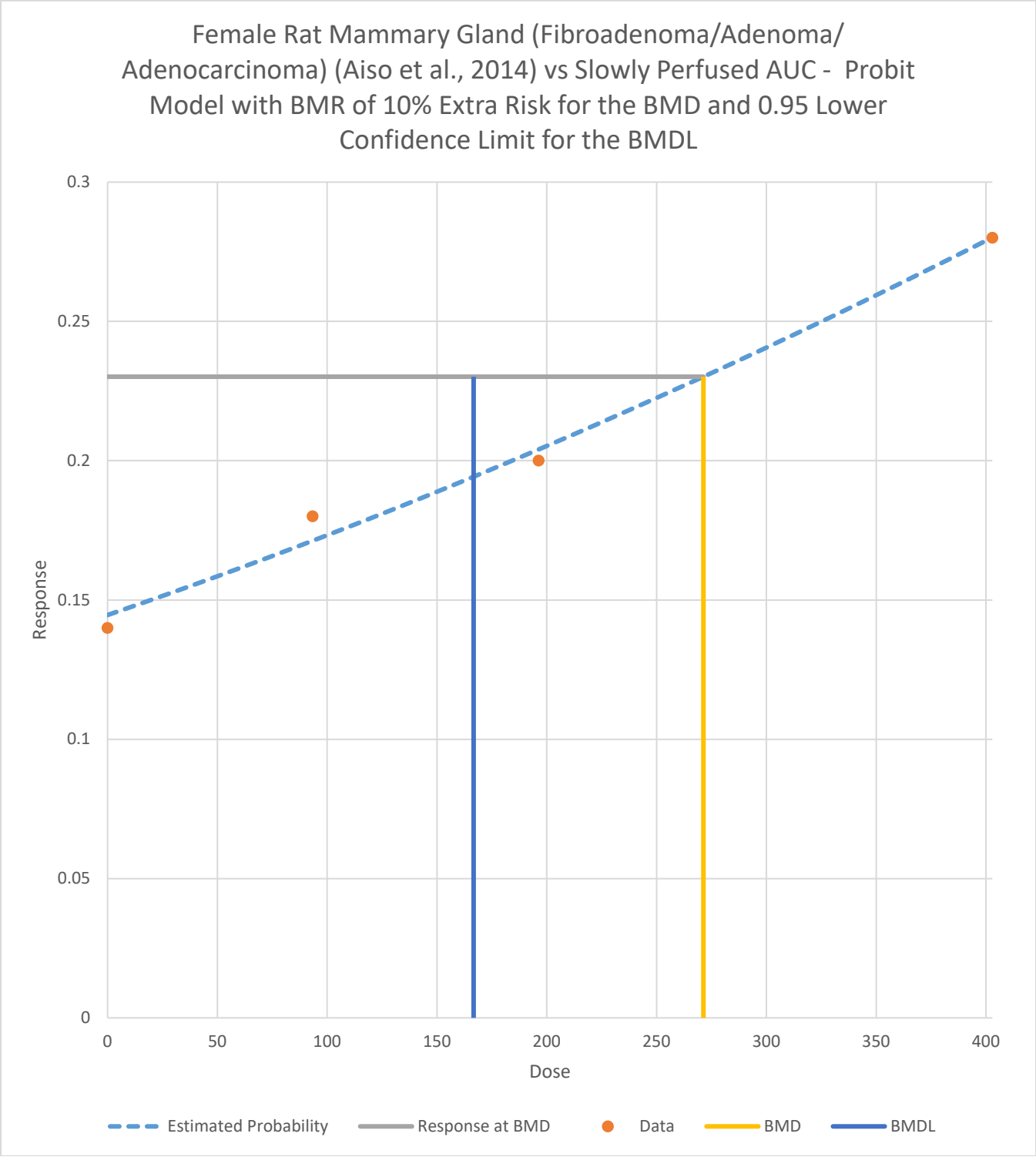
Model Results

Benchmark Dose	
BMD	271.3350125
BMDL	166.6839944
BMDU	Infinity
AIC	201.0117292
P-value	0.979848922
D.O.F.	2
Chi^2	0.04071376
Slope Factor	271.3350125

Model Parameters	
# of Parameters	3
Variable	Estimate
a	-1.059855271
b	0.001184826

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.144605224	7.230261182	7	50	-0.092589
93.29	0.171228226	8.561411293	9	50	0.1646521
196.3	0.20404093	10.20204651	10	50	-0.070903
402.9	0.280118768	14.00593839	14	50	-0.00187

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-98.48563564	0	-	-	-
Fitted Model	-98.50586461	2	0.04045793	2	0.9799743
Reduced Model	-100.0804847	1	3.18969813	3	0.363292


Female Rat Mammary Gland (Fibroadenoma/Adenoma/ Adenocarcinoma) (Aiso et al., 2014) vs Slowly Perfused AUC - Probit Model with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
0.3
0.25
0.2
0.15
0.1
0.05
0
0
50
100
150
200
250
300
350
400
Dose
Estimated Probability
Response at BMD
Data
BMD
BMDL

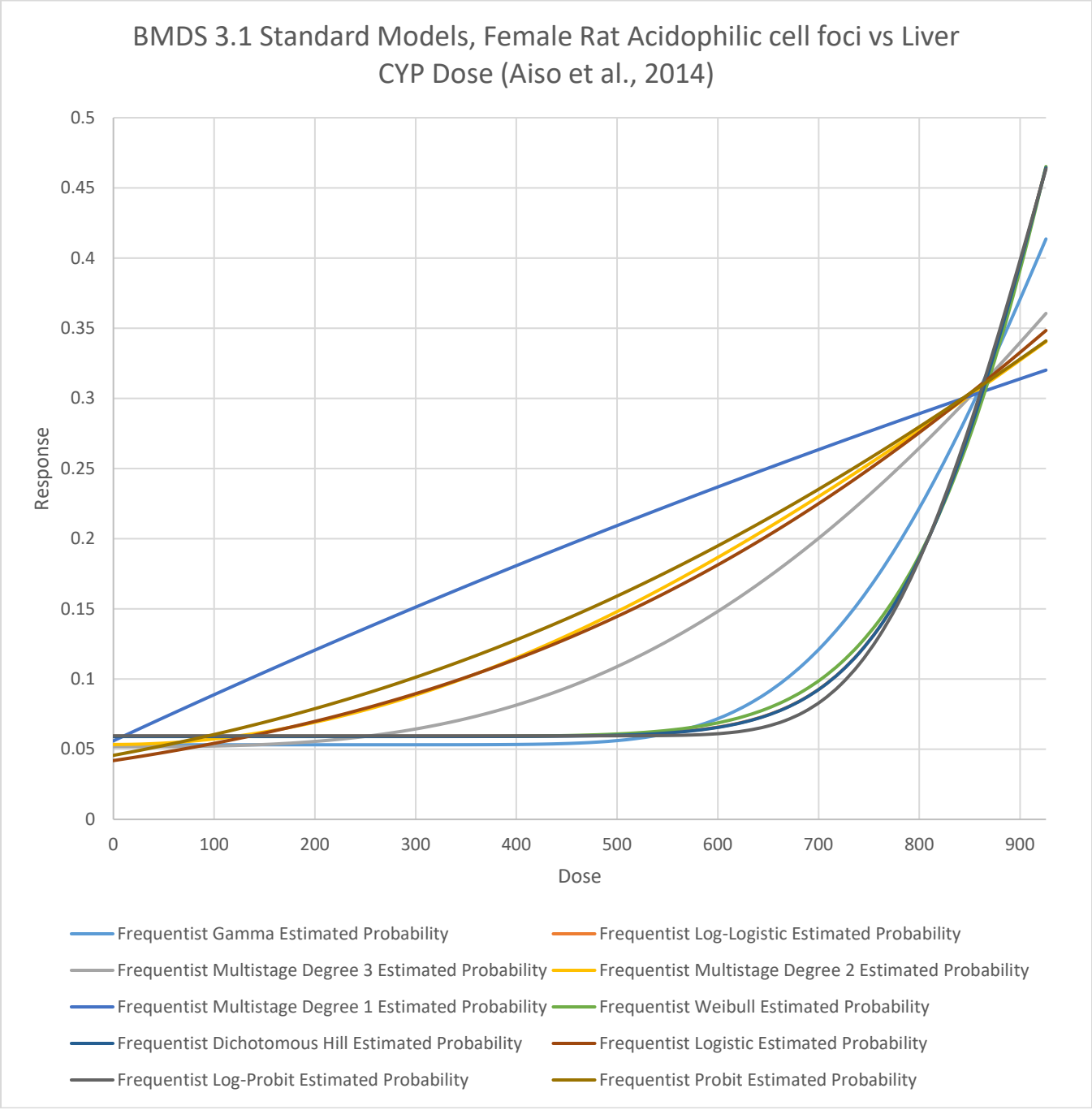
6.2. Liver Acidophilic Cell Foci

Liver CYP dose	N	Incidence
0	50	3
786.8	50	8
846	50	14
925.7	50	23

Summary of BMDS 3.1 Results for Female Rat Liver Acidophilic Cell Foci (Aiso et al., 2014)

Standard Models	Restrict.**	10% Extra Risk		P Value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL				
Gamma*	Restricted	732.62	645.50	0.56828	200.11723	Selected, Full Model Suite	Lowest AIC
Log-Logistic	Restricted	775.29	676.75	0.80528	201.01418	Viable - Alternate	
Multistage Degree 3	Restricted	596.40	362.39	0.09585	203.82564	Questionable	Goodness of fit p-value < 0.1
Multistage Degree 2	Restricted	499.87	254.05	0.04010	205.60272	Questionable	Goodness of fit p-value < 0.1 Goodness of fit p-value < 0.05 BMDL 3x lower than lowest non-zero dose
Multistage Degree 1 (Quantal Linear)	Restricted	297.12	219.94	0.01435	207.65468	Questionable	Goodness of fit p-value < 0.1 Goodness of fit p-value < 0.05 BMDL 3x lower than lowest non-zero dose
Weibull	Restricted	771.46	665.19	0.74279	201.06111	Viable - Alternate	
Dichotomous Hill	Unrestricted	775.15	676.82	NA	203.01388	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Logistic	NA	478.95	403.17	0.04372	205.40117	Questionable	Goodness of fit p-value < 0.1 Goodness of fit p-value < 0.05
Log-Probit	Unrestricted	778.75	687.49	0.86786	200.98110	Viable - Alternate	
Probit	NA	443.88	374.89	0.03421	205.92483	Questionable	Goodness of fit p-value < 0.1 Goodness of fit p-value < 0.05
Non-Standard Models							
Dichotomous Hill	Restricted	782.89	678.91	NA	202.95345	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Log-Probit	Restricted	778.75	687.49	0.86786	200.98110	Viable - Alternate	
Gamma	Unrestricted	732.62	645.49	0.56828	200.11723	Viable - Alternate	
Log-Logistic	Unrestricted	775.25	676.75	0.80529	201.01418	Viable - Alternate	
Multistage Degree 3	Unrestricted	783.55	12.570	NA	202.95345	Questionable	BMD/BMDL ratio > 20 BMD/BMDL ratio > 5 BMDL 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Multistage Degree 2	Unrestricted	785.48	706.31	0.86464	200.98261	Viable - Alternate	
Multistage Degree 1	Unrestricted	297.13	219.94	0.01435	207.65468	Questionable	Goodness of fit p-value < 0.1 Goodness of fit p-value < 0.05 BMDL 3x lower than lowest non-zero dose
Weibull	Unrestricted	771.45	665.18	0.74279	201.06111	Viable - Alternate	

*Selected, Full Model Suite (Green); residuals for doses 0, 786.8, 846, and 925.7 were 0.215521983, -0.795365045, -0.087537521, and 0.66601925, respectively.
**Restrictions defined in the BMDS 3.1 User Guide; NA = Not Applicable


BMDS 3.1 Standard Models, Female Rat Acidophilic cell foci vs Liver CYP Dose (Aiso et al., 2014)
Response
Dose
0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
0.4
0.45
0.5
0
100
200
300
400
500
600
700
800
900
Frequentist Gamma Estimated Probability
Frequentist Log-Logistic Estimated Probability
Frequentist Multistage Degree 3 Estimated Probability
Frequentist Multistage Degree 2 Estimated Probability
Frequentist Multistage Degree 1 Estimated Probability
Frequentist Weibull Estimated Probability
Frequentist Dichotomous Hill Estimated Probability
Frequentist Logistic Estimated Probability
Frequentist Log-Probit Estimated Probability
Frequentist Probit Estimated Probability

Selected, Full Model Suite - Gamma (Restricted) - Extra Risk, BMR = 0.1

User Input

Info	
Model	Gamma v1.0
Dataset Name	Aiso Female Rat Liver Acidophilic Cell Foci
Formula	P[dose]= g+(1-g)*CumGamma[b*dose,a]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Liver CYP Dose
Independent Variable	[Tumor Incidence]
Total # of Observation	4

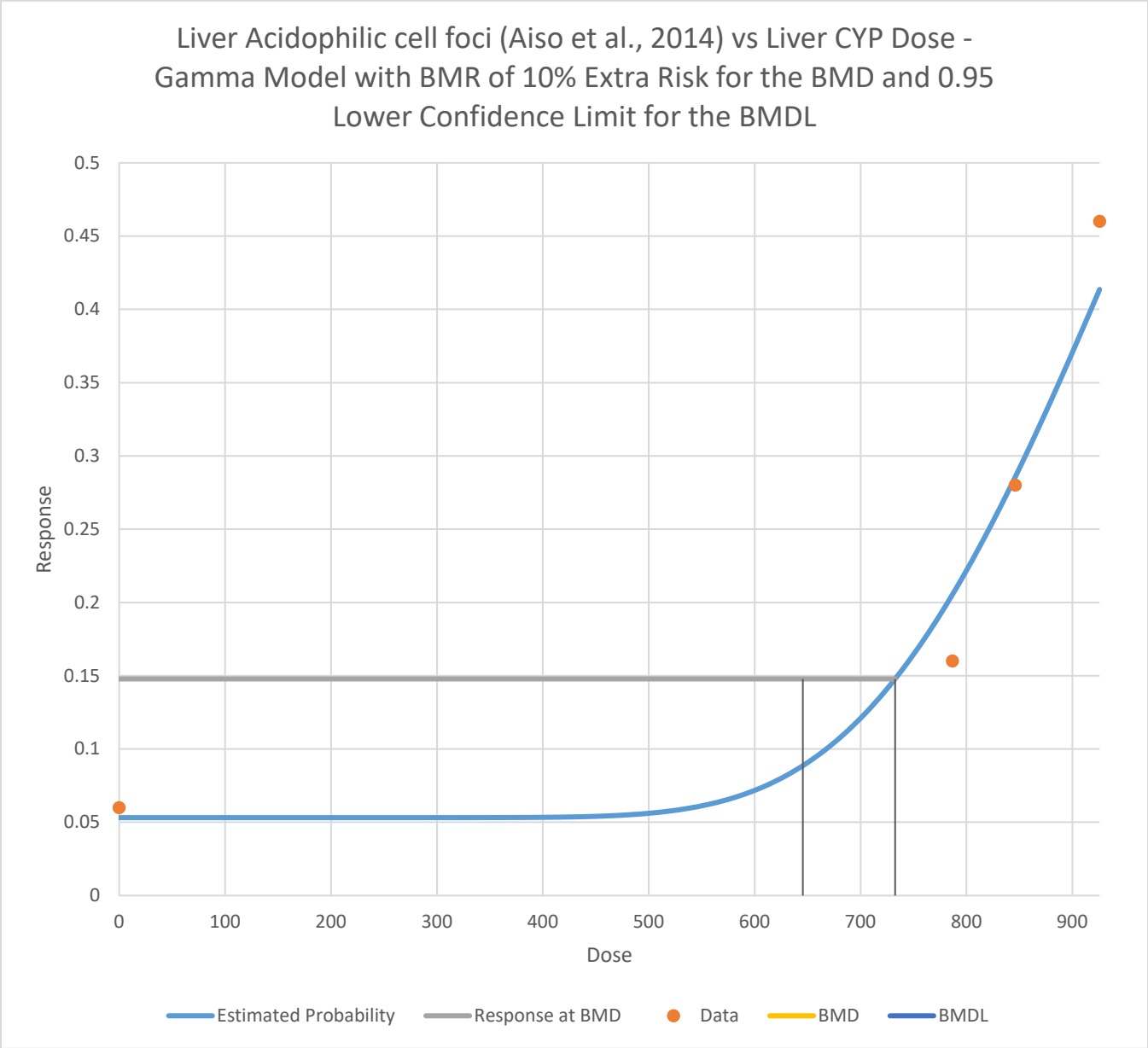
Model Results

Benchmark Dose	
BMD	732.6188725
BMDL	645.4953642
BMDU	780.2931446
AIC	200.1172284
P-value	0.568274974
D.O.F.	2
Chi^2	1.130299738

Model Parameters	
# of Parameters	3
Variable	Estimate
Background (g)	0.053161763
a	20
b	0.019826491

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.053161763	2.658088146	3	50	0.215522
786.8	0.205445588	10.27227941	8	50	-0.795365
846	0.285591848	14.27959239	14	50	-0.087538
925.7	0.413613552	20.68067758	23	50	0.6660192

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-97.47672389	0	-	-	-
Fitted Model	-98.05861422	2	1.16378066	2	0.558841
Reduced Model	-110.2159856	1	25.4785235	3	<0.0001


Liver Acidophilic cell foci (Aiso et al., 2014) vs Liver CYP Dose - Gamma Model with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
0
100
200
300
400
500
600
700
800
900
Dose
Estimated Probability
Response at BMD
Data
BMD
BMDL

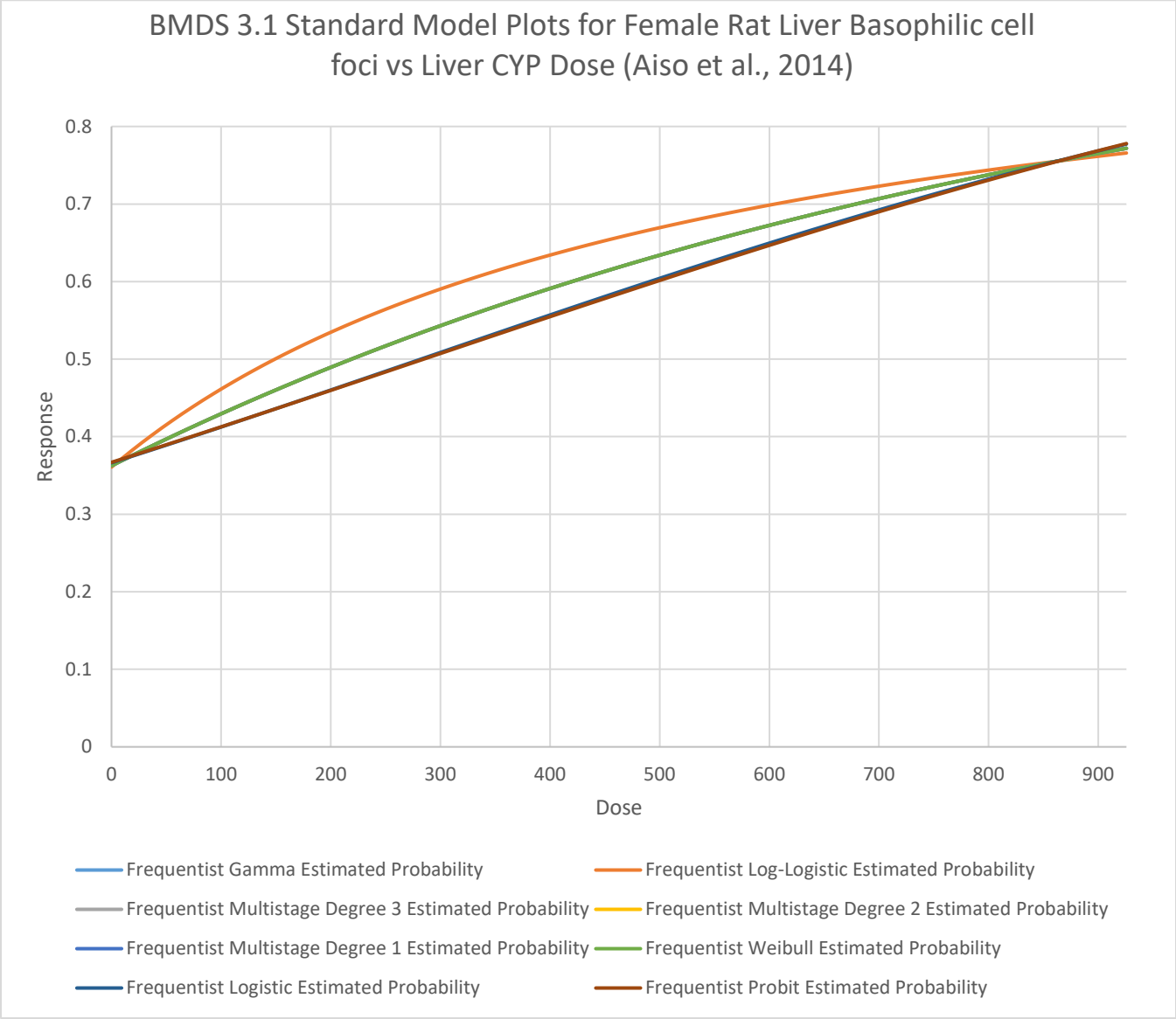
6.3. Liver Basophilic Cell Foci

Liver CYP dose	N	Incidence
0	50	18
786.8	50	37
846	50	40
925.7	50	36

Summary of BMDS 3.1 Results for Female Rat Liver Basophilic Cell Foci (Aiso et al., 2014)

Standard Models	Restriction**	10% Extra Risk		P Value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL				
Gamma	Restricted	94.924	72.238	0.49100	237.40193	Questionable	**BMD 3x lower than lowest non-zero dose BMDL 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose**
Log-Logistic	Restricted	59.469	38.027	0.54988	237.18500	Questionable	**BMD 3x lower than lowest non-zero dose BMDL 3x lower than lowest non-zero dose BMD 10x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose**
Multistage Degree 3	Restricted	94.925	72.238	0.49100	237.40193	Questionable	**BMD 3x lower than lowest non-zero dose BMDL 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose**
Multistage Degree 2	Restricted	94.925	72.237	0.49100	237.40193	Questionable	**BMD 3x lower than lowest non-zero dose BMDL 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose**
Multistage Degree 1 (Quantal Linear)	Restricted	94.925	72.235	0.49100	237.40193	Viable - Alternate	**BMD 3x lower than lowest non-zero dose BMDL 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose**
Weibull	Restricted	94.924	72.238	0.49100	237.40193	Questionable	**BMD 3x lower than lowest non-zero dose BMDL 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose**
Dichotomous Hill	Unrestricted	CF	CF	CF	CF		
Logistic*	NA	136.40	114.20	0.43147	237.6487	Selected, Full Model Suite	**Lowest AIC BMD 3x lower than lowest non-zero dose BMDL 3x lower than lowest non-zero dos**
Log-Probit	Unrestricted	CF	CF	CF	CF		
Probit	NA	137.52	116.44	0.41968	237.7033	Viable - Alternate	**BMD 3x lower than lowest non-zero dose BMDL 3x lower than lowest non-zero dose**
Non-Standard Models							
Dichotomous Hill	Restricted	3.37E-6	0	0.33414	238.93484	Unusable	**BMD lower limit includes 0; BMDL not estimated BMD 3x lower than lowest non-zero dose BMD 10x lower than lowest non-zero dose**
Log-Probit	Restricted	177.39	134.88	0.48467	237.42358	Viable - Alternate	**BMD 3x lower than lowest non-zero dose BMDL 3x lower than lowest non-zero dose**
Gamma	Unrestricted	0.0931	0.0415	0.59427	237.03875	Questionable	**BMD 3x lower than lowest non-zero dose BMDL 3x lower than lowest non-zero dose BMD 10x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose**
Log-Logistic	Unrestricted	591.91	8.1697	0.55116	238.34446	Questionable	**BMD/BMDL ratio > 20 BMD/BMDL ratio > 5 BMDL 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose**
Multistage Degree 3	Unrestricted	34.560	14.395	0.37934	238.77240	Questionable	**BMD 3x lower than lowest non-zero dose BMDL 3x lower than lowest non-zero dose BMD 10x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose**
Multistage Degree 2	Unrestricted	94.925	72.2360 7	0.49100	237.40193	Questionable	**BMD 3x lower than lowest non-zero dose BMDL 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose**
Multistage Degree 1	Unrestricted	-9999	0	0.62726	236.93484	Unusable	**BMD computation failed; BMDL not estimated**
Weibull	Unrestricted	3.37E-6	0	0.33414	238.93484	Unusable	**BMD lower limit includes 0; BMDL not estimated BMD 3x lower than lowest non-zero dose BMD 10x lower than lowest non-zero dose**

*Selected, Full Model Suite (Green); residuals for doses 0, 786.8, 846, and 925.7 were -0.092410996, 0.204561516, 0.826796158, and -0.973209778, respectively.
**Restrictions defined in the BMDS 3.1 User Guide; CF = Computation Failed; NA = Not Applicable


BMDS 3.1 Standard Model Plots for Female Rat Liver Basophilic cell foci vs Liver CYP Dose (Aiso et al., 2014)
Response
Dose
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0
100
200
300
400
500
600
700
800
900
Frequentist Gamma Estimated Probability
Frequentist Log-Logistic Estimated Probability
Frequentist Multistage Degree 3 Estimated Probability
Frequentist Multistage Degree 2 Estimated Probability
Frequentist Multistage Degree 1 Estimated Probability
Frequentist Weibull Estimated Probability
Frequentist Logistic Estimated Probability
Frequentist Probit Estimated Probability

Selected, Full Model Suite - Logistic - Extra Risk, BMR = 0.1

User Input

Info	
Model	Log-Probit v1.0
Dataset Name	Aiso Female Rat Liver Basophilic Cell Foci
Formula	P[dose] = 1/[1+exp(-a-b*dose)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Liver CYP Dose
Independent Variable	[Tumor Incidence]
Total # of Observation	4

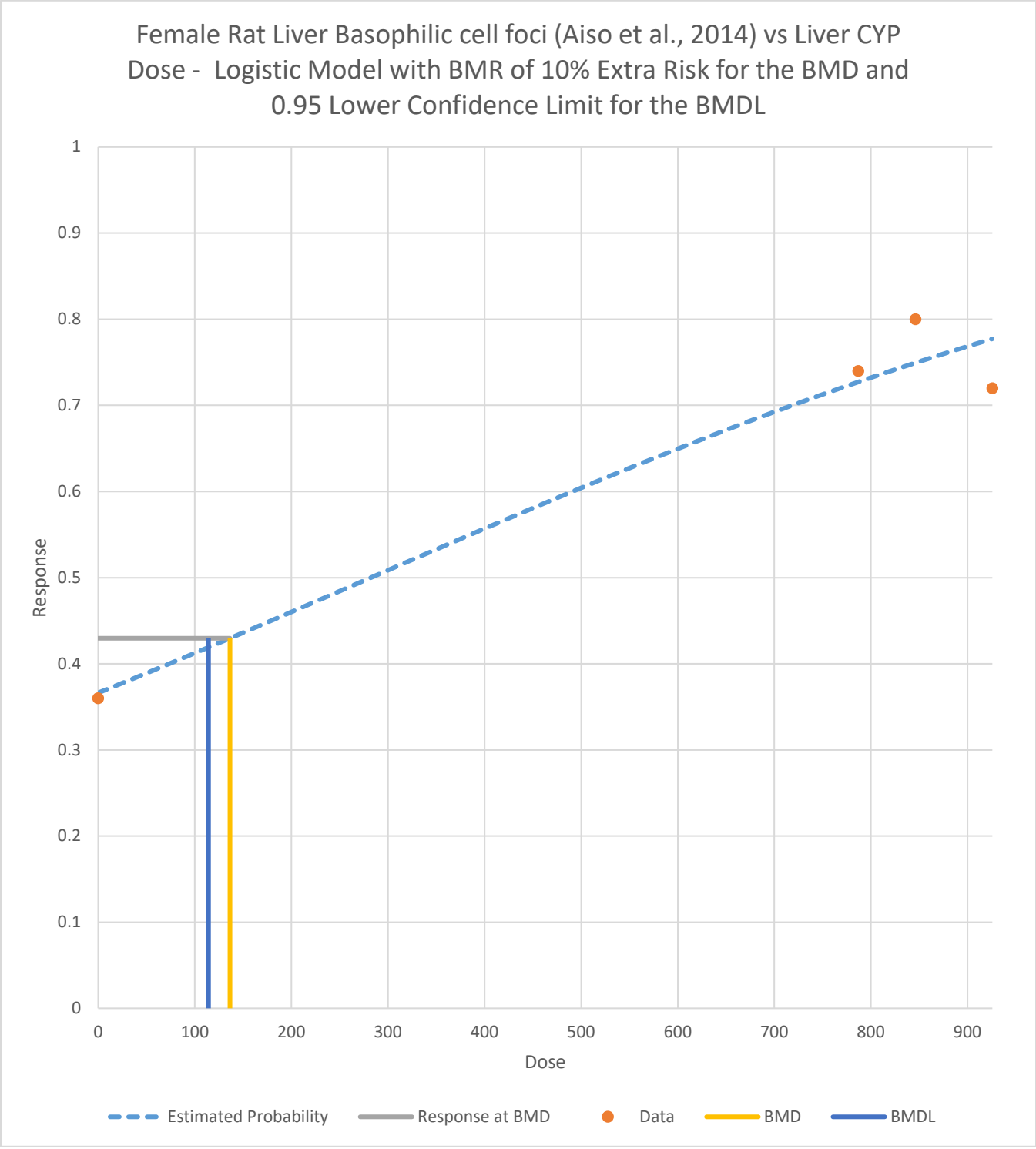
Model Results

Benchmark Dose	
BMD	136.4021223
BMDL	114.2007853
BMDU	172.2573305
AIC	237.6487326
P-value	0.431470049
D.O.F.	2
Chi^2	1.681114366

Model Parameters	
# of Parameters	2
Variable	Estimate
a	-0.548138135
b	0.001942254

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.366296484	18.31482418	18	50	-0.092411
786.8	0.727113618	36.3556809	37	50	0.2045615
846	0.74932371	37.46618549	40	50	0.8267962
925.7	0.777266327	38.86331634	36	50	-0.97321

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-115.9915426	0	-	-	-
Fitted Model	-116.8243663	2	1.66564729	2	0.4348198
Reduced Model	-128.8592752	1	25.735465	3	<0.0001


Female Rat Liver Basophilic cell foci (Aiso et al., 2014) vs Liver CYP
Dose - Logistic Model with BMR of 10% Extra Risk for the BMD and
0.95 Lower Confidence Limit for the BMDL
Response
Dose
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
100
200
300
400
500
600
700
800
900
Estimated Probability
Response at BMD
Data
BMD
BMDL

7. BMD Modeling for Aiso et al. (2014) Male Mice

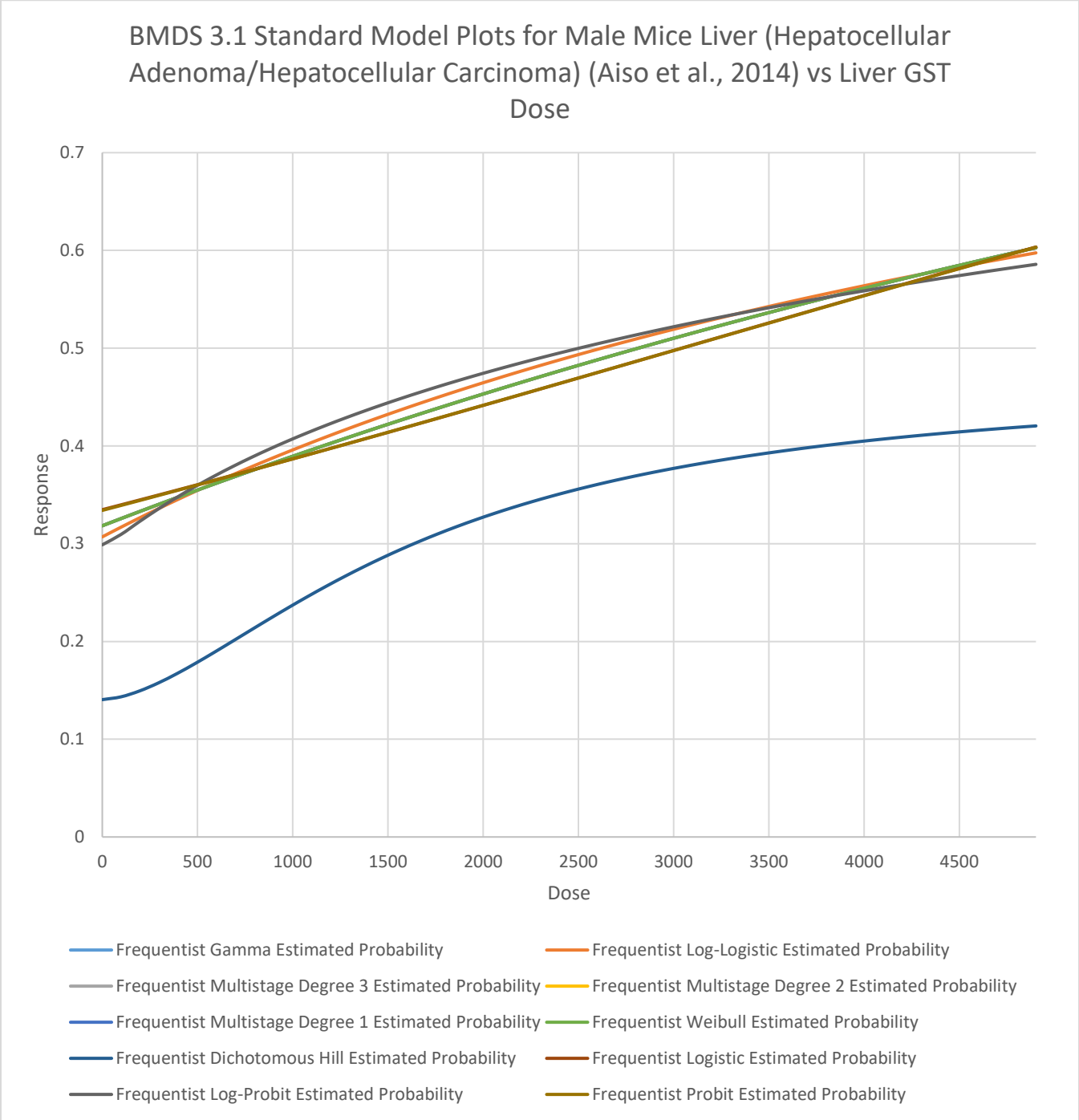
7.1. Liver (Hepatocellular Adenoma/Hepatocellular Carcinoma)

Liver GST dose	[N]	[Incidence]
0	50	15
1029	50	20
2213	50	25
4902	50	29

Summary of BMDS 3.1 Modeling Results for Male Mice Liver (Hepatocellular Adenoma/Hepatocellular Carcinoma) (Aiso et al., 2014)

Standard Models	Restrict.***	10% Extra Risk		P Value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL				
Gamma	Restricted	956.50	593.22	0.80407	270.16723	Viable - Alternate	
Log-Logistic*	Restricted	754.63	413.06	0.91435	269.91025	Selected, Full Model Suite	Lowest AIC
Multistage Degree 2**	Restricted	956.50	593.21	0.80407	270.16723	Selected, Multistage	Multistage-cancer guidance (EPA, 2014)
Multistage Degree 1 (Quantal Linear)	Restricted	956.58	593.21	0.80407	270.16723	Viable - Alternate	
Weibull	Restricted	956.50	593.22	0.80407	270.16723	Viable - Alternate	
Dichotomous Hill	Unrestricted	770.44	0	NA	273.73152	Unusable	BMD failed; lower limit includes zero; BMDL not estimated d.f.=0 (cannot apply Goodness of fit test)
Logistic	NA	1269.5	899.68	0.65243	270.58795	Viable - Alternate	
Log-Probit	Unrestricted	586.23	0	0.79534	271.79881	Unusable	BMD failed; lower limit includes zero BMDL not estimated
Probit	NA	1256.8	891.02	0.65701	270.57370	Viable - Alternate	
Non-Standard Models							
Dichotomous Hill	Restricted	770.40	0.0169	NA	273.73152	Questionable	BMD/BMDL ratio > 20 BMD/BMDL ratio > 5 BMDL 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose d.f.=0 (cannot apply Goodness of fit test)
Log-Probit	Restricted	1694.8	1086.6	0.47506	271.22362	Viable - Alternate	
Gamma	Unrestricted	462.72	2.6093	0.73184	271.84901	Questionable	BMD/BMDL ratio > 20 BMD/BMDL ratio > 5 BMDL 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose
Log-Logistic	Unrestricted	532.29	0	0.77261	271.81505	Unusable	BMD failed; lower limit includes zero BMDL not estimated
Multistage Degree 3	Unrestricted	719.61	163.72	NA	273.73152	Questionable	BMDL 3x lower than lowest non-zero dose d.f.=0 (cannot apply Goodness of fit test)
Multistage Degree 2	Unrestricted	609.60	287.19	0.87753	271.75529	Viable - Alternate	
Multistage Degree 1	Unrestricted	956.52	593.21	0.80407	270.16723	Viable - Alternate	
Weibull	Unrestricted	480.61	0	0.74356	271.83861	Unusable	BMD failed; lower limit includes zero BMDL not estimated

*Selected, Full Model Suite (Green); residuals for doses 0, 1029, 2213, and 4902 were -0.107305354, 0.026275785, 0.321177338, and -0.252428629, respectively.
**Selected, Multistage (Yellow); residuals for doses 0, 1029, 2213, and 4902 were -0.278519227, 0.124691166, 0.484655839, and -0.328825131, respectively.
***Restrictions defined in the BMDS 3.1 User Guide; NA = Not Applicable


BMDS 3.1 Standard Model Plots for Male Mice Liver (Hepatocellular Adenoma/Hepatocellular Carcinoma) (Aiso et al., 2014) vs Liver GST Dose
Response
Dose
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0
500
1000
1500
2000
2500
3000
3500
4000
4500
Frequentist Gamma Estimated Probability
Frequentist Log-Logistic Estimated Probability
Frequentist Multistage Degree 3 Estimated Probability
Frequentist Multistage Degree 2 Estimated Probability
Frequentist Multistage Degree 1 Estimated Probability
Frequentist Weibull Estimated Probability
Frequentist Dichotomous Hill Estimated Probability
Frequentist Logistic Estimated Probability
Frequentist Log-Probit Estimated Probability
Frequentist Probit Estimated Probability

Selected, Multistage - Multistage 2 Restricted; Extra Risk, BMR = 0.1

User Input

Info	
Model	Multistage degree 2 v1.0
Dataset Name	Aiso et al. (2014) Male Mice Liver (Hepatocellular Adenoma/ Carcinoma)
Formula	P[dose] = g + (1-g)*[1-exp(-b1*dose^1-b2*dose^2)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Liver GST Dose
Independent Variable	[Tumor Incidence]
Total # of Observation	4

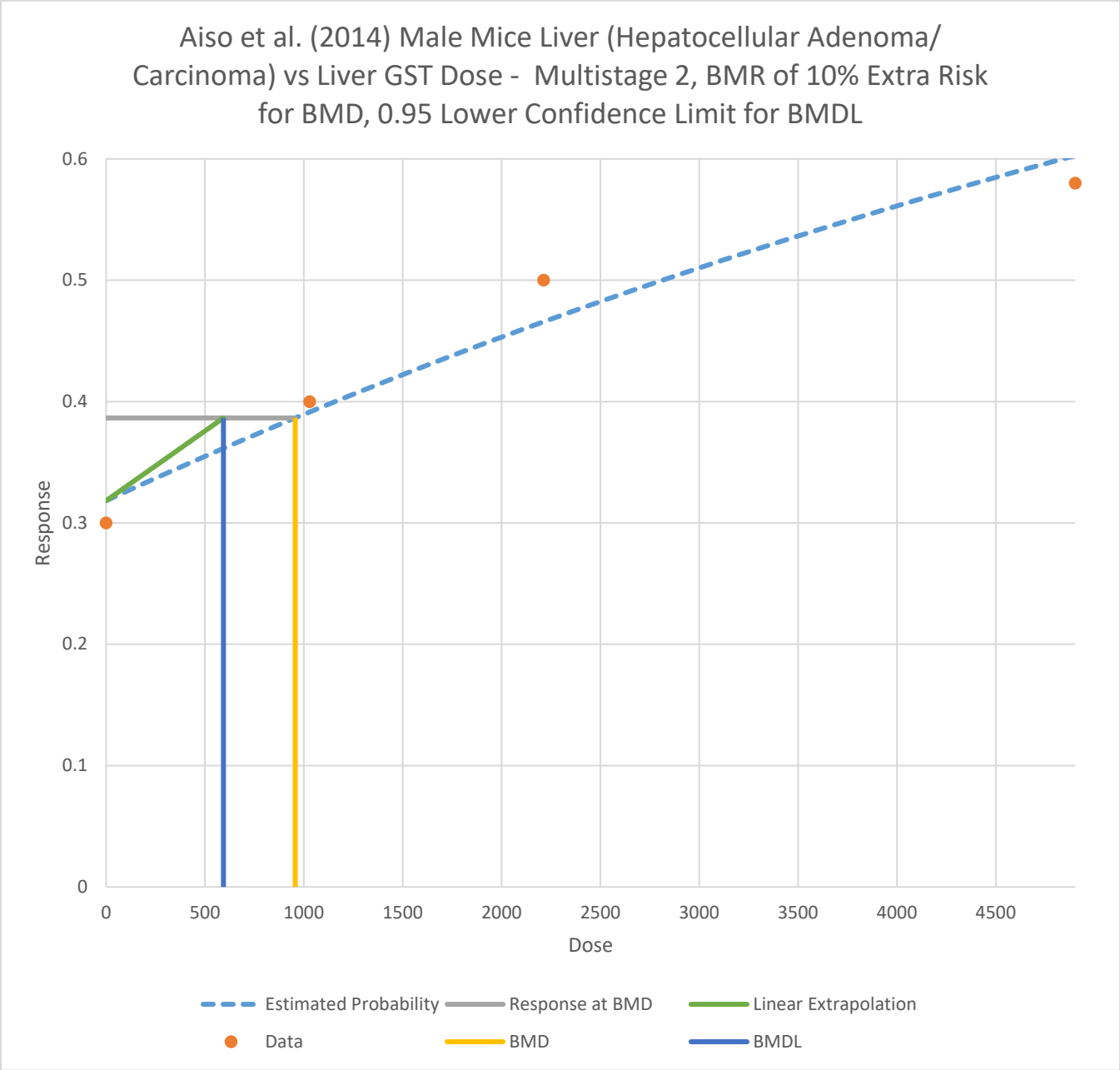
Model Results

Benchmark Dose	
BMD	956.5003924
BMDL	593.2107703
BMDU	2941.314946
AIC	270.1672319
P-value	0.804069921
D.O.F.	2
Chi^2	0.436138096
Slope Factor	0.000168574

Model Parameters	
# of Parameters	3
Variable	Estimate
Background (g)	0.318348595
Beta1	0.000110152
Beta2	0

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.318348595	15.9174297	15	50	-0.2785
1029	0.391393516	19.5696758	20	50	0.12469
2213	0.465809873	23.2904936	25	50	0.48466
4902	0.602755145	30.1377572	29	50	-0.3288

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-132.865757	0	-	-	-
Fitted Model	-133.083616	2	0.435717	2	0.80424
Reduced Model	-137.416984	1	9.102453	3	0.02796


Aiso et al. (2014) Male Mice Liver (Hepatocellular Adenoma/ Carcinoma) vs Liver GST Dose - Multistage 2, BMR of 10% Extra Risk for BMD, 0.95 Lower Confidence Limit for BMDL
Response
Dose
0
0.1
0.2
0.3
0.4
0.5
0.6
0
500
1000
1500
2000
2500
3000
3500
4000
4500
Estimated Probability
Response at BMD
Linear Extrapolation
Data
BMD
BMDL

Selected, Full Model Suite - Log-Logistic (Restricted) - Extra Risk, BMR = 0.1

User Input

Info	
Model	Log-Logistic v1.0
Dataset Name	Aiso et al. (2014) Male Mice Liver (Hepatocellular Adenoma/ Carcinoma)
Formula	P[dose] = g+(1-g)/[1+exp(-a-b*Log(dose))]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Liver GST Dose
Independent Variable	[Tumor Incidence]
Total # of Observation	4

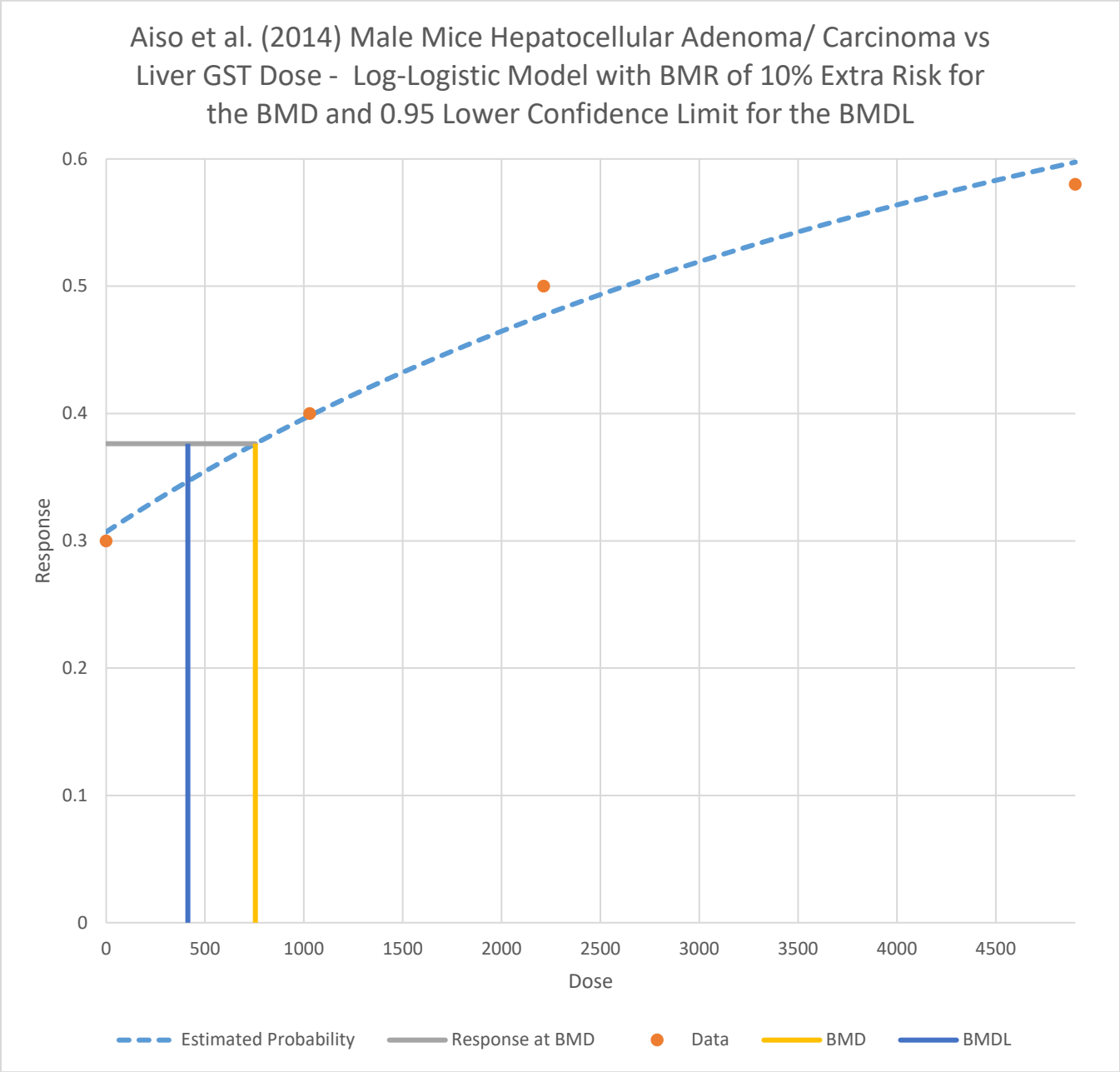
Model Results

Benchmark Dose	
BMD	754.627573
BMDL	413.0555392
BMDU	2812.916208
AIC	269.9102517
P-value	0.914351713
D.O.F.	2
Chi^2	0.179079951

Model Parameters	
# of Parameters	3
Variable	Estimate
Background (g)	0.306999581
a	-8.82344892
b	1

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.306999581	15.349979	15	50	-0.1073
1029	0.398180953	19.9090477	20	50	0.02628
2213	0.477312724	23.8656362	25	50	0.32118
4902	0.597506701	29.8753351	29	50	-0.2524

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-132.865757	0	-	-	-
Fitted Model	-132.955126	2	0.178737	2	0.91451
Reduced Model	-137.416984	1	9.102453	3	0.02796


Aiso et al. (2014) Male Mice Hepatocellular Adenoma/ Carcinoma vs Liver GST Dose - Log-Logistic Model with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
0.6
0.5
0.4
0.3
0.2
0.1
0
0
500
1000
1500
2000
2500
3000
3500
4000
4500
Dose
Estimated Probability
Response at BMD
Data
BMD
BMDL

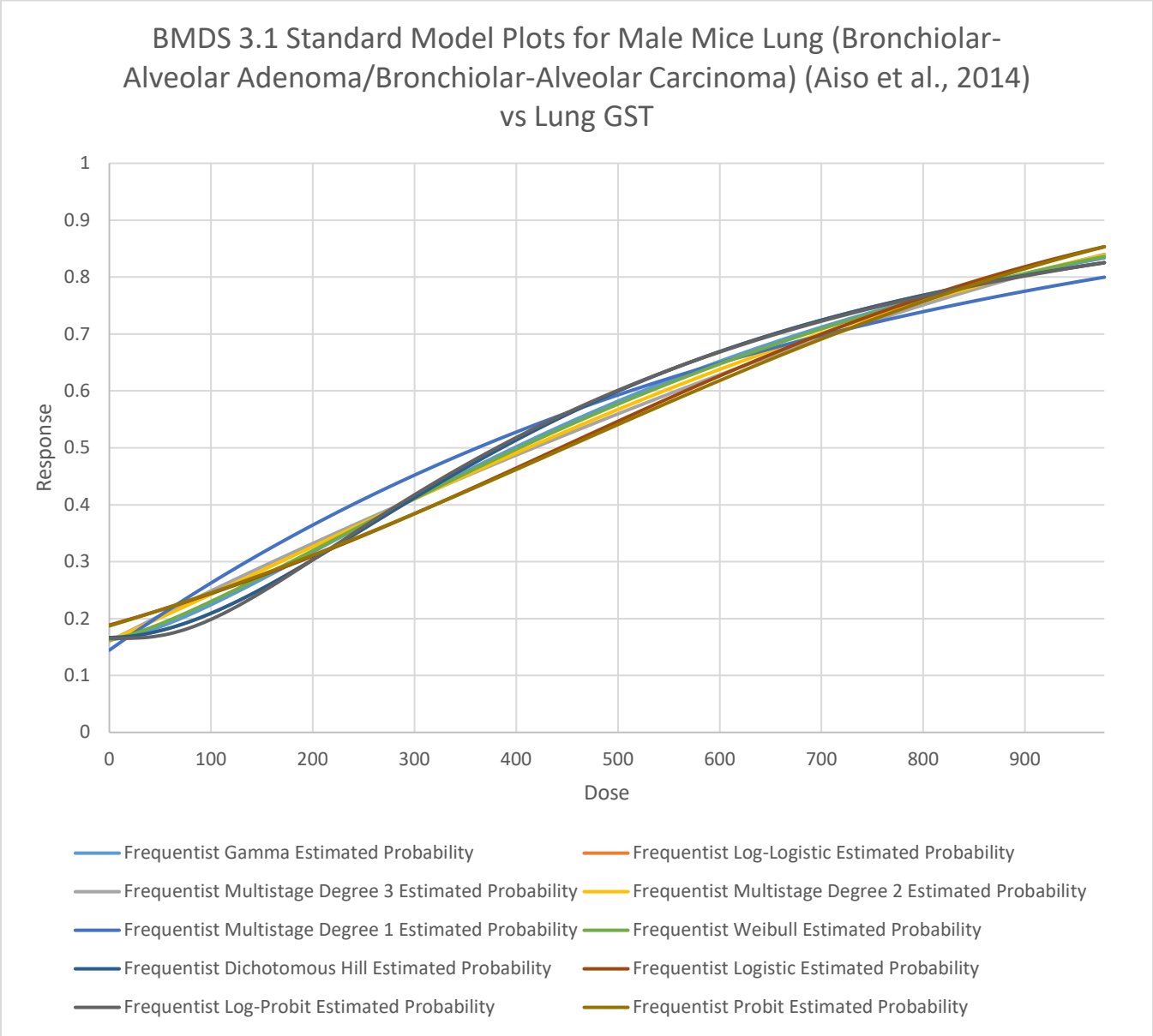
7.2. Lung (Bronchiolar-Alveolar Adenoma/Bronchiolar-Alveolar Carcinoma)

Lung GST dose	[N]	[Incidence]
0	50	8
209.8	50	17
444.6	50	26
978.1	50	42

Summary of BMDS 3.1 Modeling Results for Male Mice Lung (Bronchiolar-Alveolar Adenoma/Bronchiolar-Alveolar Carcinoma) vs Lung GST (Aiso et al., 2014)

Standard Models	Restriction***	10% Extra Risk		P Value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL				
Gamma	Restricted	124.71	58.666	0.7187	227.4017	Viable - Alternate	BMDL 3x lower than lowest non-zero dose
Log-Logistic	Restricted	147.21	67.859	0.48672	227.7546	Viable - Alternate	BMDL 3x lower than lowest non-zero dose
Multistage Degree 2	Restricted	102.86	59.031	0.90626	227.2861	Viable - Alternate	BMDL 3x lower than lowest non-zero dose
Multistage Degree 1 (Quantal Linear)*	Restricted	70.936	55.91	0.56748	226.4326	Selected, Multistage	Multistage-cancer guidance (EPA, 2014) BMDL 3x lower than lowest non-zero dose
Weibull	Restricted	118.56	58.831	0.78247	227.3483	Viable - Alternate	BMDL 3x lower than lowest non-zero dose
Dichotomous Hill	Unrestricted	147.22	67.858	0.48672	227.7546	Viable - Alternate	BMDL 3x lower than lowest non-zero dose
Logistic	NA	140.66	117.27	0.7658	225.8138	Viable - Alternate	
Log-Probit	Unrestricted	151.94	74.246	0.47274	227.7862	Viable - Alternate	
Probit**	NA	**136.66**	**115.93**	**0.76894**	**225.8046**	**Selected, Full Model Suite**	**Lowest AIC**
Non-Standard Models							
Dichotomous Hill	Restricted	147.22	67.858	0.48672	227.7546	Viable - Alternate	BMDL 3x lower than lowest non-zero dose
Log-Probit	Restricted	151.94	102.69	0.47274	227.7862	Viable - Alternate	
Gamma	Unrestricted	124.71	41.956	0.7187	227.4017	Viable - Alternate	BMDL 3x lower than lowest non-zero dose
Log-Logistic	Unrestricted	147.25	67.859	0.48672	227.7546	Viable - Alternate	BMDL 3x lower than lowest non-zero dose
Multistage Degree 3	Unrestricted	94.442	32.031	NA	229.2722	Questionable	BMDL 3x lower than lowest non-zero dose d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Multistage Degree 2	Unrestricted	102.86	56.921	0.90626	227.2861	Viable - Alternate	BMDL 3x lower than lowest non-zero dose
Multistage Degree 1	Unrestricted	70.936	55.91	0.56748	226.4326	Viable - Alternate	BMDL 3x lower than lowest non-zero dose
Weibull	Unrestricted	118.56	46.611	0.78247	227.3483	Viable - Alternate	BMDL 3x lower than lowest non-zero dose

*Selected, Multistage (Yellow); residuals for doses 0, 209.8, 444,6, and 978.1 were 0.312670191, -0.489892085, -0.54059179, and 0.709290841, respectively.
**Selected, Full Model Suite (Green); residuals for doses 0, 209.8, 444,6, and 978.1 were -0.492233766, 0.330089147, 0.323276987, and -0.264073236, respectively.
***Restrictions defined in the BMDS 3.1 User Guide; NA = Not Applicable


BMDS 3.1 Standard Model Plots for Male Mice Lung (Bronchiolar-Alveolar Adenoma/Bronchiolar-Alveolar Carcinoma) (Aiso et al., 2014) vs Lung GST
Response
Dose
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
100
200
300
400
500
600
700
800
900
Frequentist Gamma Estimated Probability
Frequentist Log-Logistic Estimated Probability
Frequentist Multistage Degree 3 Estimated Probability
Frequentist Multistage Degree 2 Estimated Probability
Frequentist Multistage Degree 1 Estimated Probability
Frequentist Weibull Estimated Probability
Frequentist Dichotomous Hill Estimated Probability
Frequentist Logistic Estimated Probability
Frequentist Log-Probit Estimated Probability
Frequentist Probit Estimated Probability

Selected, Multistage - Multistage 1 Restricted; Extra Risk, BMR = 0.1

User Input

Info	
Model	Multistage degree 1 v1.0
Dataset Name	Aiso et al. (2014) Male Mice Lung (Bronchiolar-Alveolar Adenoma/Bronchiolar-Alveolar Carcinoma)
Formula	P[dose] = g + (1-g)*[1-exp(-b1*dose^1)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Lung GST Dose
Independent Variable	[Tumor Incidence]
Total # of Observation	4

Model Results

Benchmark Dose	
BMD	70.93641143
BMDL	55.90961925
BMDU	94.01120627
AIC	226.4325854
P-value	0.567482742
D.O.F.	2
Chi^2	1.133089883
Slope Factor	0.001788601

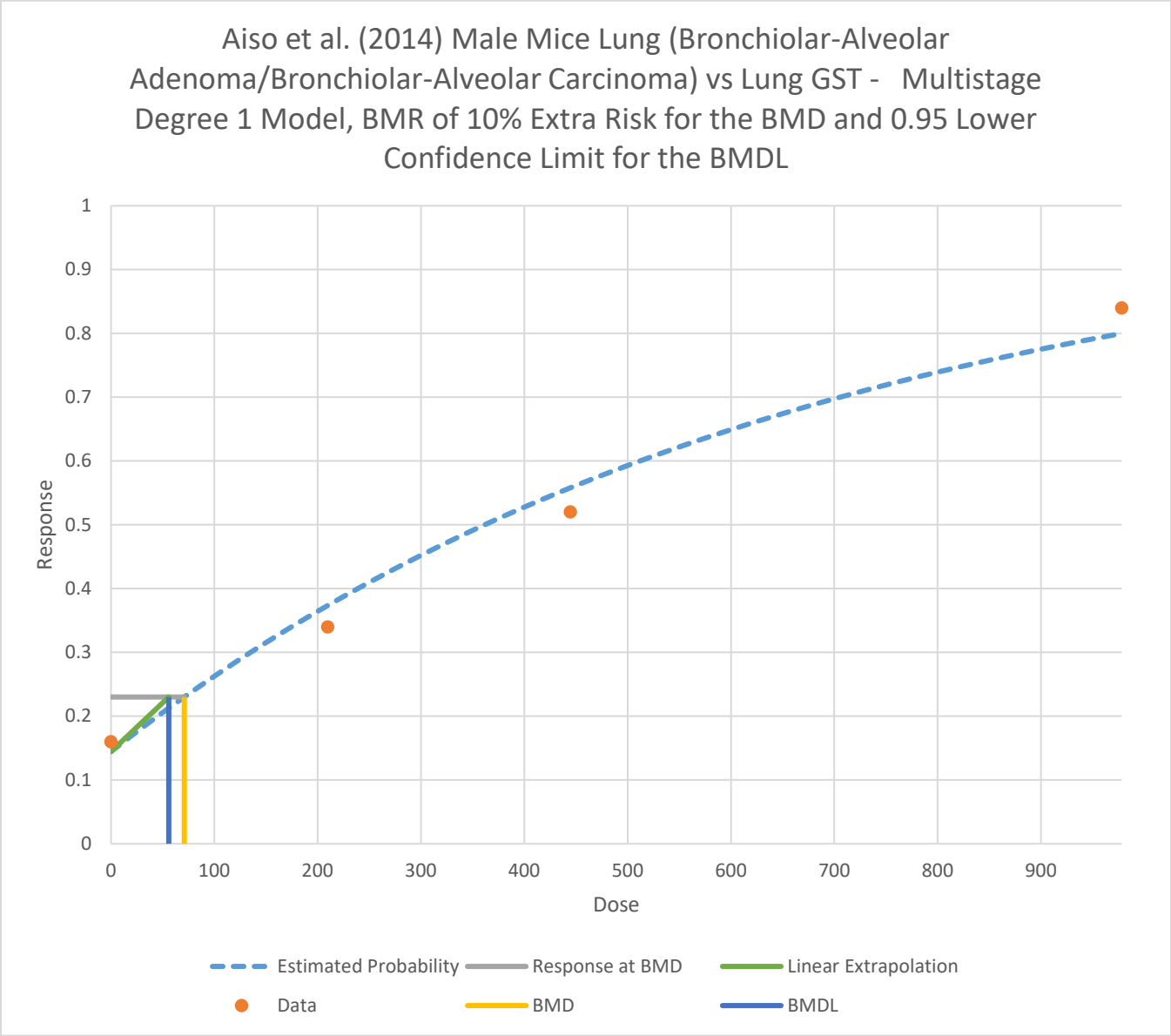
Model Parameters	
# of Parameters	2
Variable	Estimate
Background (g)	0.144455052
Beta1	0.001485281

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.144455052	7.22275262	8	50	0.31267
209.8	0.373513865	18.6756933	17	50	-0.4899
444.6	0.557967846	27.8983923	26	50	-0.5406
978.1	0.799866404	39.9933202	42	50	0.70929

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-110.63611	0	-	-	-
Fitted Model	-111.216293	2	1.160365	2	0.5598
Reduced Model	-138.139035	1	55.00585	3	<0.0001


Aiso et al. (2014) Male Mice Lung (Bronchiolar-Alveolar Adenoma/Bronchiolar-Alveolar Carcinoma) vs Lung GST - Multistage Degree 1 Model, BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
Dose
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
100
200
300
400
500
600
700
800
900
Estimated Probability
Response at BMD
Linear Extrapolation
Data
BMD
BMDL

Selected, Full Model Suite - Probit - Extra Risk, BMR = 0.1

User Input

Info	
Model	Log-Probit v1.0
Dataset Name	Aiso et al. (2014) Male Mice Lung (Bronchiolar-Alveolar Adenoma/Bronchiolar-Alveolar Carcinoma)
Formula	P[dose] = CumNorm(a+b*Dose)

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Lung GST Dose
Independent Variable	[Tumor Incidence]
Total # of Observation	4

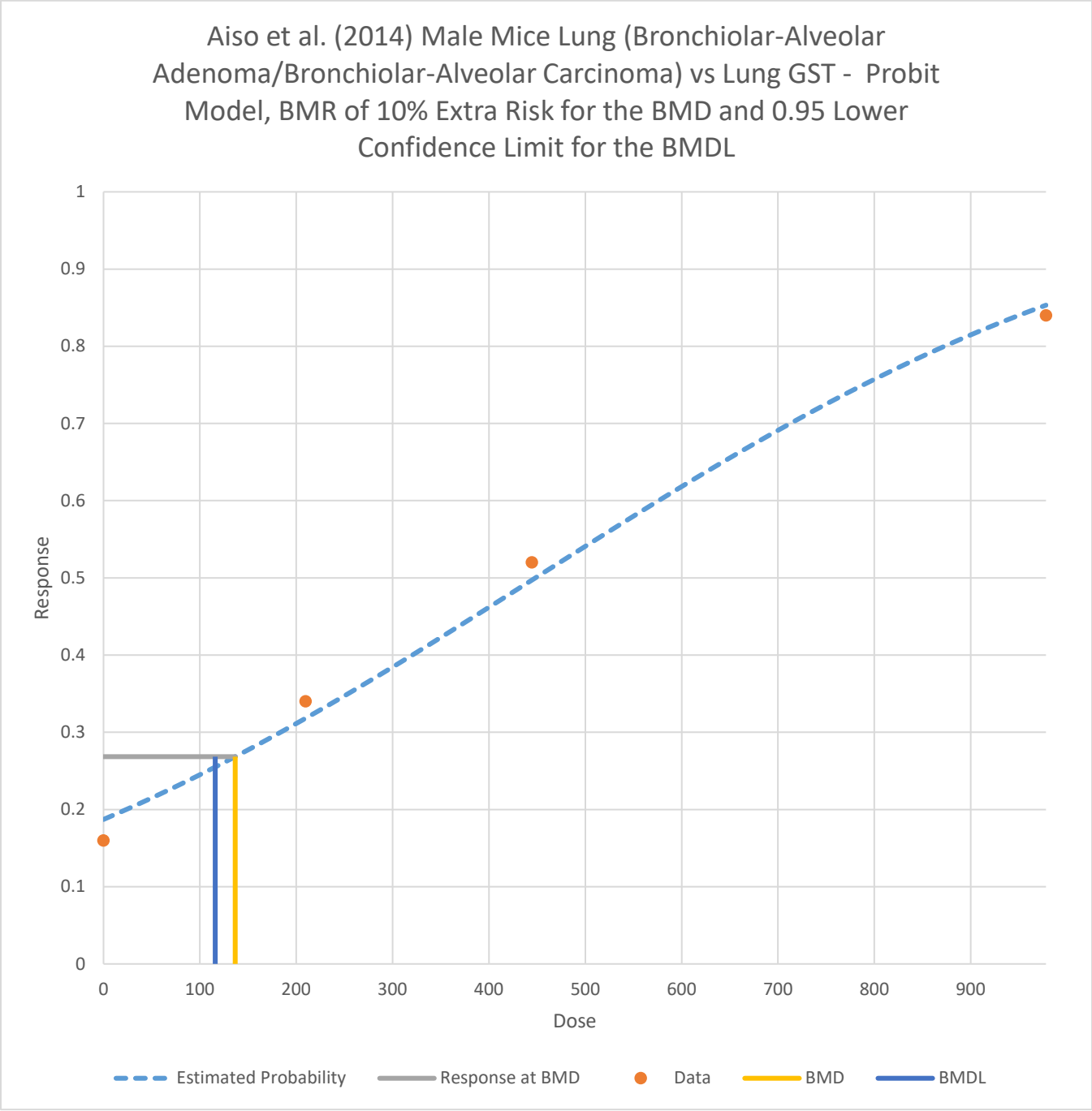
Model Results

Benchmark Dose	
BMD	136.6643728
BMDL	115.9251001
BMDU	162.0151938
AIC	225.8046015
P-value	0.768935795
D.O.F.	2
Chi^2	0.52549561

Model Parameters	
# of Parameters	2
Variable	Estimate
a	-0.88844355
b	0.001982181

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.187151105	9.35755524	8	50	-0.4922
209.8	0.318255716	15.9127858	17	50	0.33009
444.6	0.497141239	24.8570619	26	50	0.32328
978.1	0.853216241	42.660812	42	50	-0.2641

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-110.63611	0	-	-	-
Fitted Model	-110.902301	2	0.532381	2	0.76629
Reduced Model	-138.139035	1	55.00585	3	<0.0001


Aiso et al. (2014) Male Mice Lung (Bronchiolar-Alveolar Adenoma/Bronchiolar-Alveolar Carcinoma) vs Lung GST - Probit Model, BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
Dose
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
100
200
300
400
500
600
700
800
900
Estimated Probability
Response at BMD
Data
BMD
BMDL

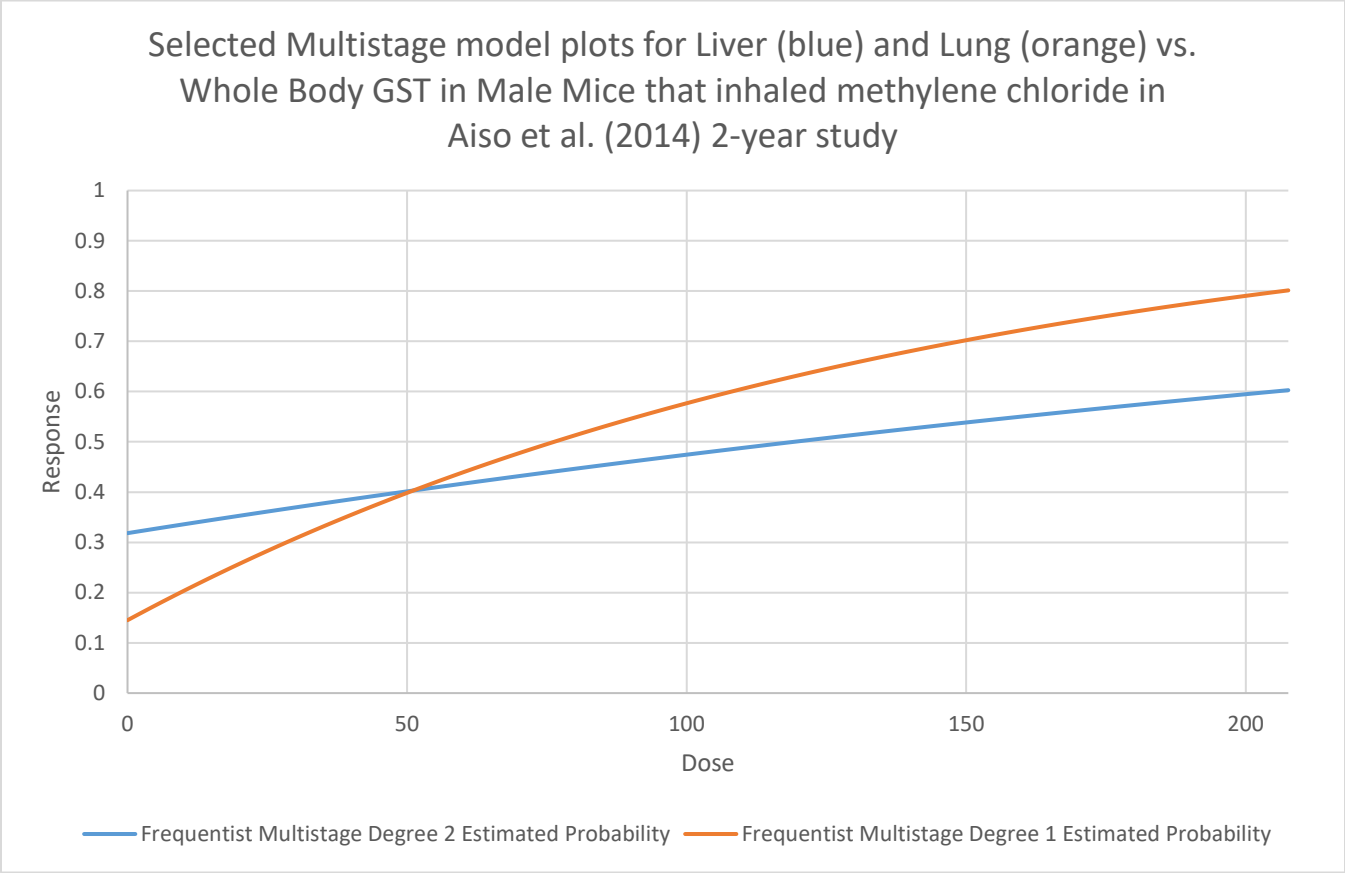
7.3. Liver or Lung Tumor

Aiso et al. (2014) Male Mouse Liver (Hepatocellular Adenoma/Carcinoma)		
Whole body GST dose	[N]	[Incidence]
0	50	15
43.65	50	20
93.77	50	25
207.6	50	29
Aiso et al. (2014) Male Mouse Lung (Bronchiolar-Alveolar Adenoma/Carcinoma)		
Whole body GST dose	[N]	[Incidence]
0	50	8
43.65	50	17
93.77	50	26
207.6	50	42

Summary of BMDS 3.1 Multi-tumor (MS_Combo) Modeling Results for Male Mouse Liver and Lung vs. Whole Body GST Dose (Aiso et al., 2014)

Models*	Dataset	10% Extra Risk		Slope Factor	P Value	AIC	BMDS Recommendation Notes
		BMD	BMDL				
Multi-tumor (MS_Combo)	Combined Risk	10.938	8.2167	1.22e-2	NA	NA	-
Multistage Degree 2	Liver Tumors	40.505	25.123	3.98e-3	0.80461	270.1659	Multistage-cancer guidance (EPA, 2014)
Multistage Degree 1	Lung Tumors	14.985	11.804	8.47e-3	0.59028	226.3507	Multistage-cancer guidance (EPA, 2014) BMDL 3x lower than lowest non-zero dose

*Multistage models used in the BMDS multi-tumor (MS_Combo) model are restricted as described in the BMDS 3.1 User Guide. The selected Multistage model was chosen from among all relevant model runs (see detailed results for all relevant Multistage degrees below) in accordance with EPA's technical guidance for choosing the appropriate stage of a multistage model for cancer modeling (Aiso, 2014).



Multi-tumor (MS_Combo) Results for Combined Risk of Male Mouse Liver (Hepatocellular Adenoma/Carcinoma) and Lung (Bronchiolar-Alveolar Adenoma/Carcinoma) vs. Whole Body GST Dose (Aiso et al., 2014)

User Input

Info	
Model	Multi-tumor v1.0

Model Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Results

Benchmark Dose	
BMD	10.93812
BMDL	8.2166986
BMDU	15.868682
Slope Factor	0.0121703
Combined Log-Likelihood	-244.2583144
Combined Log-Likelihood Constant	226.7895073

Male Mouse Liver (Hepatocellular Adenoma/Carcinoma)- Multistage 1 Restricted; Extra Risk, BMR = 0.1

User Input

Info	
Model	Multistage degree 1 v1.0
Dataset Name	Male Mouse Liver (Hepatocellular Adenoma/Carcinoma)
Formula	P[dose] = g + (1-g)*[1-exp(-b1*dose^1)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Whole Body GST
Independent Variable	[Tumor Incidence]
Total # of Observation	4

Model Results

Benchmark Dose	
BMD	40.51379621
BMDL	25.12342007
BMDU	94.63866854
AIC	270.1658827
P-value	0.804615103
D.O.F.	2
Chi^2	0.434782497
Slope Factor	0.00398035

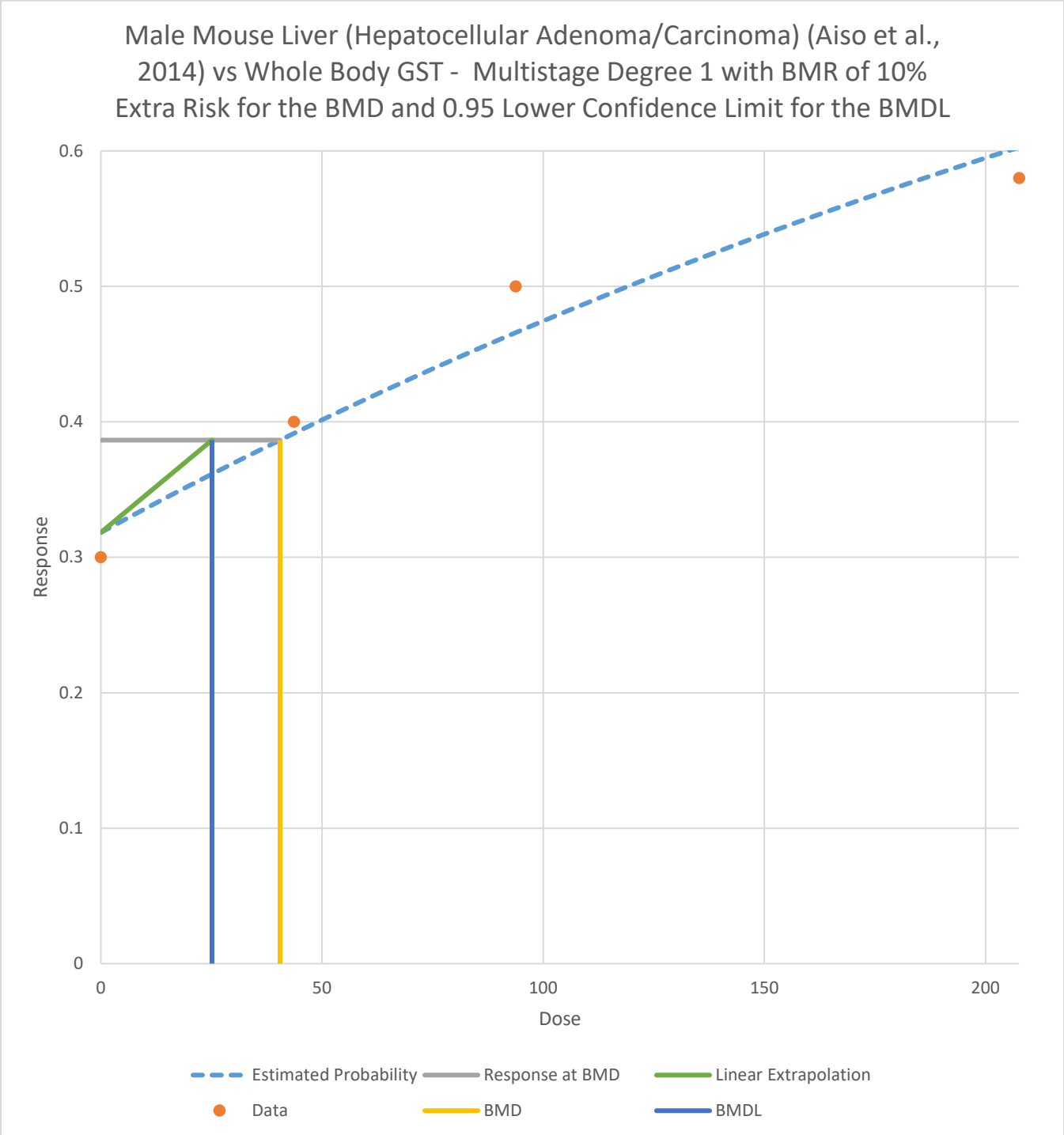
Model Parameters	
# of Parameters	2
Variable	Estimate
Background (g)	0.318340384
Beta1	0.002600608

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.318340384	15.91701921	15	50	-0.278397
43.65	0.391489673	19.57448367	20	50	0.1232926
93.77	0.465852833	23.29264167	25	50	0.484044
207.6	0.602718877	30.13594386	29	50	-0.328296

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-132.8657575	0	-	-	-
Fitted Model	-133.0829414	2	0.43436774	2	0.804782
Reduced Model	-137.4169841	1	9.10245313	3	0.0279593


Male Mouse Liver (Hepatocellular Adenoma/Carcinoma) (Aiso et al., 2014) vs Whole Body GST - Multistage Degree 1 with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
Dose
0
0.1
0.2
0.3
0.4
0.5
0.6
0
50
100
150
200
Estimated Probability
Response at BMD
Linear Extrapolation
Data
BMD
BMDL

Male Mouse Liver (Hepatocellular Adenoma/Carcinoma) - Multistage 2 Restricted (Selected Multistage Degree); Extra Risk, BMR = 0.1

User Input

Info	
Model	Multistage degree 2 v1.0
Dataset Name	Male Mouse Liver (Hepatocellular Adenoma/Carcinoma)
Formula	P[dose] = g + (1-g)*[1-exp(-b1*dose^1-b2*dose^2)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Whole Body GST Dose
Independent Variable	[Tumor Incidence]
Total # of Observation	4

Model Results

Benchmark Dose	
BMD	40.50540747
BMDL	25.12334901
BMDU	124.5617822
AIC	270.1658817
P-value	0.804611589
D.O.F.	2
Chi^2	0.434791233
Slope Factor	0.003980361

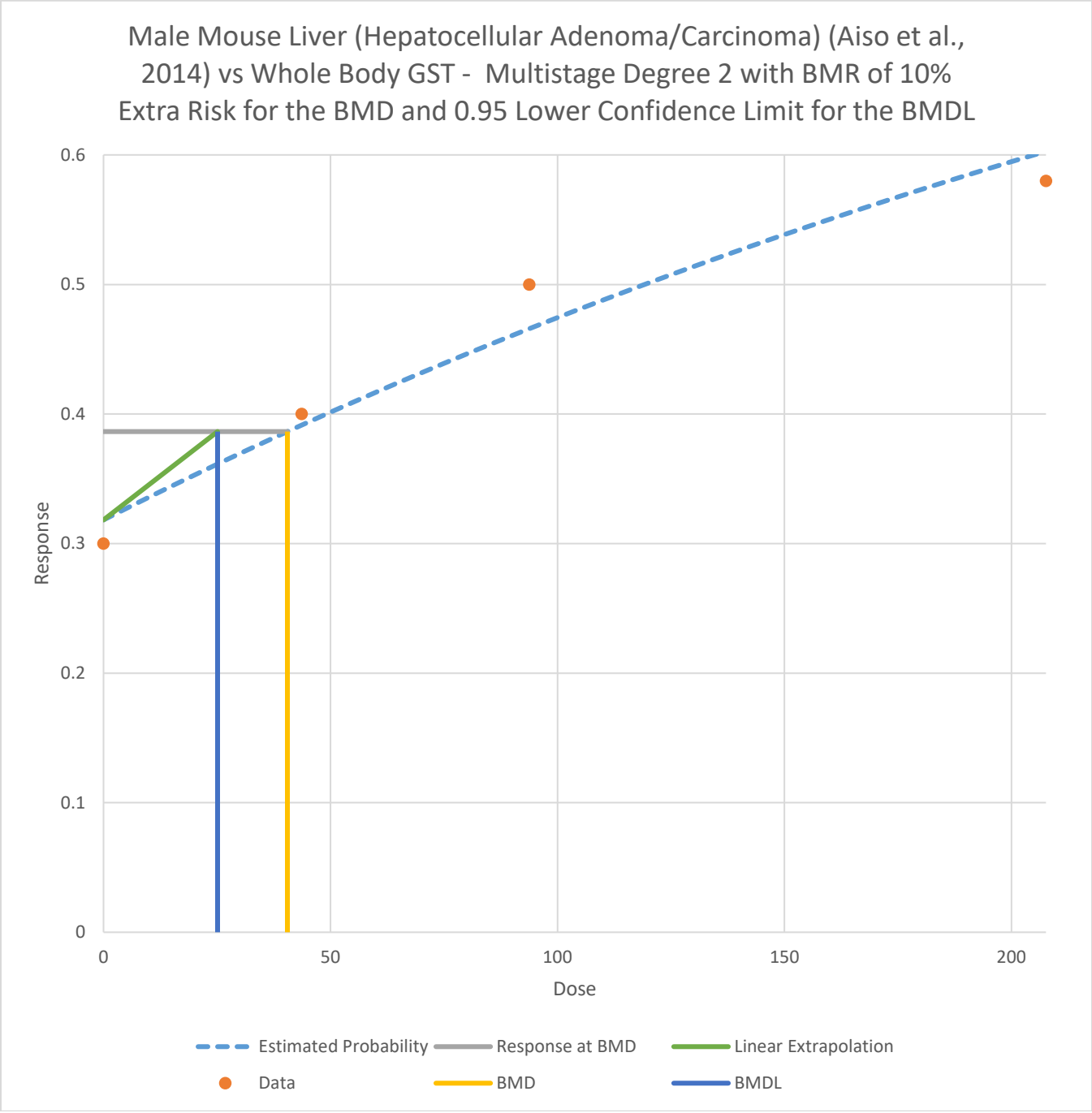
Model Parameters	
# of Parameters	3
Variable	Estimate
Background (g)	0.318285763
Beta1	0.002601147
Beta2	0

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.318285763	15.91428813	15	50	-0.27758
43.65	0.39145522	19.57276099	20	50	0.1237937
93.77	0.46583701	23.29185049	25	50	0.4842694
207.6	0.602731464	30.13657321	29	50	-0.32848

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-132.8657575	0	-	-	-
Fitted Model	-133.0829409	2	0.43436674	2	0.8047824
Reduced Model	-137.4169841	1	9.10245313	3	0.0279593


Male Mouse Liver (Hepatocellular Adenoma/Carcinoma) (Aiso et al., 2014) vs Whole Body GST - Multistage Degree 2 with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
Dose
0
0.1
0.2
0.3
0.4
0.5
0.6
0
50
100
150
200
Estimated Probability
Response at BMD
Linear Extrapolation
Data
BMD
BMDL

Male Mouse Lung (Bronchiolar-Alveolar Adenoma/Carcinoma) - Multistage 1 Restricted (Selected Multistage Degree); Extra Risk, BMR = 0.1

User Input

Info	
Model	Multistage degree 1 v1.0
Dataset Name	Aiso et al. (2014) Male Mouse Lung (Bronchiolar-Alveolar Adenoma/Carcinoma)
Formula	P[dose] = g + (1-g)*[1-exp(-b1*dose^1)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Whole Body GST Dose
Independent Variable	[Tumor Incidence]
Total # of Observation	4

Model Results

Benchmark Dose	
BMD	14.9845282
BMDL	11.80389197
BMDU	19.87149393
AIC	226.3507471
P-value	0.590282056
D.O.F.	2
Chi^2	1.054309591
Slope Factor	0.008471782

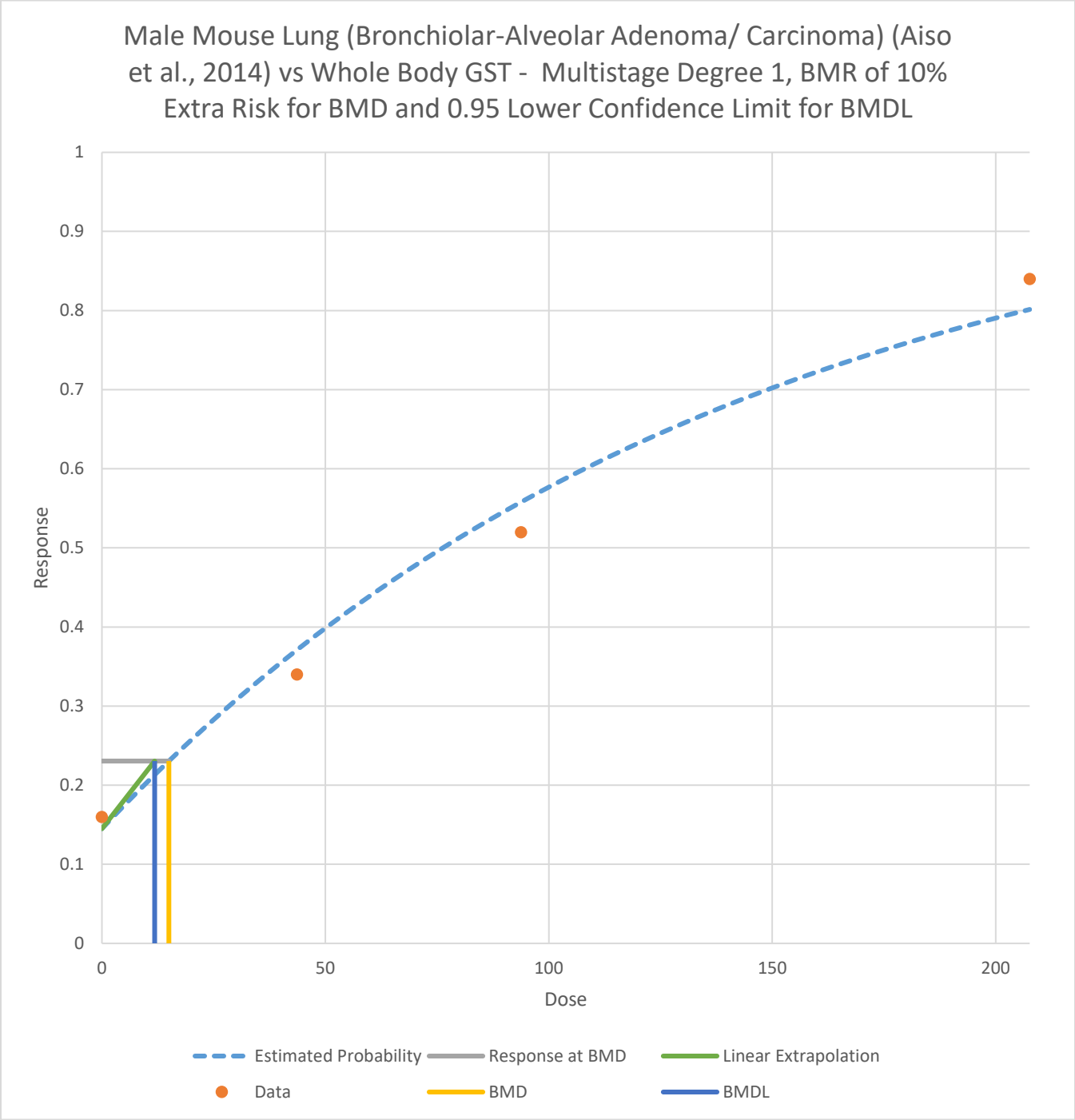
Model Parameters	
# of Parameters	2
Variable	Estimate
Background (g)	0.145037511
Beta1	0.007031287

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.145037511	7.251875556	8	50	0.300452
43.65	0.370993289	18.54966446	17	50	-0.453672
93.77	0.557812575	27.89062875	26	50	-0.538361
207.6	0.801386157	40.06930785	42	50	0.6843879

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-110.6361102	0	-	-	-
Fitted Model	-111.1753736	2	1.07852675	2	0.5831777
Reduced Model	-138.1390352	1	55.0058499	3	<0.0001


Male Mouse Lung (Bronchiolar-Alveolar Adenoma/ Carcinoma) (Aiso et al., 2014) vs Whole Body GST - Multistage Degree 1, BMR of 10% Extra Risk for BMD and 0.95 Lower Confidence Limit for BMDL
Response
Dose
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
50
100
150
200
Estimated Probability
Response at BMD
Linear Extrapolation
Data
BMD
BMDL

Male Mouse Lung (Bronchiolar-Alveolar Adenoma/Carcinoma) - Multistage 2 Restricted; Extra Risk, BMR = 0.1

User Input

Info	
Model	Multistage degree 2 v1.0
Dataset Name	Aiso et al. (2014) Male Mouse Lung (Bronchiolar-Alveolar Adenoma/Carcinoma)
Formula	P[dose] = g + (1-g)*[1-exp(-b1*dose^1-b2*dose^2)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Whole Body GST Dose
Independent Variable	[Tumor Incidence]
Total # of Observation	4

Model Results

Benchmark Dose	
BMD	21.4029062
BMDL	12.40675232
BMDU	48.5177516
AIC	227.2897899
P-value	0.894475331
D.O.F.	1
Chi^2	0.017594297
Slope Factor	0.008060127

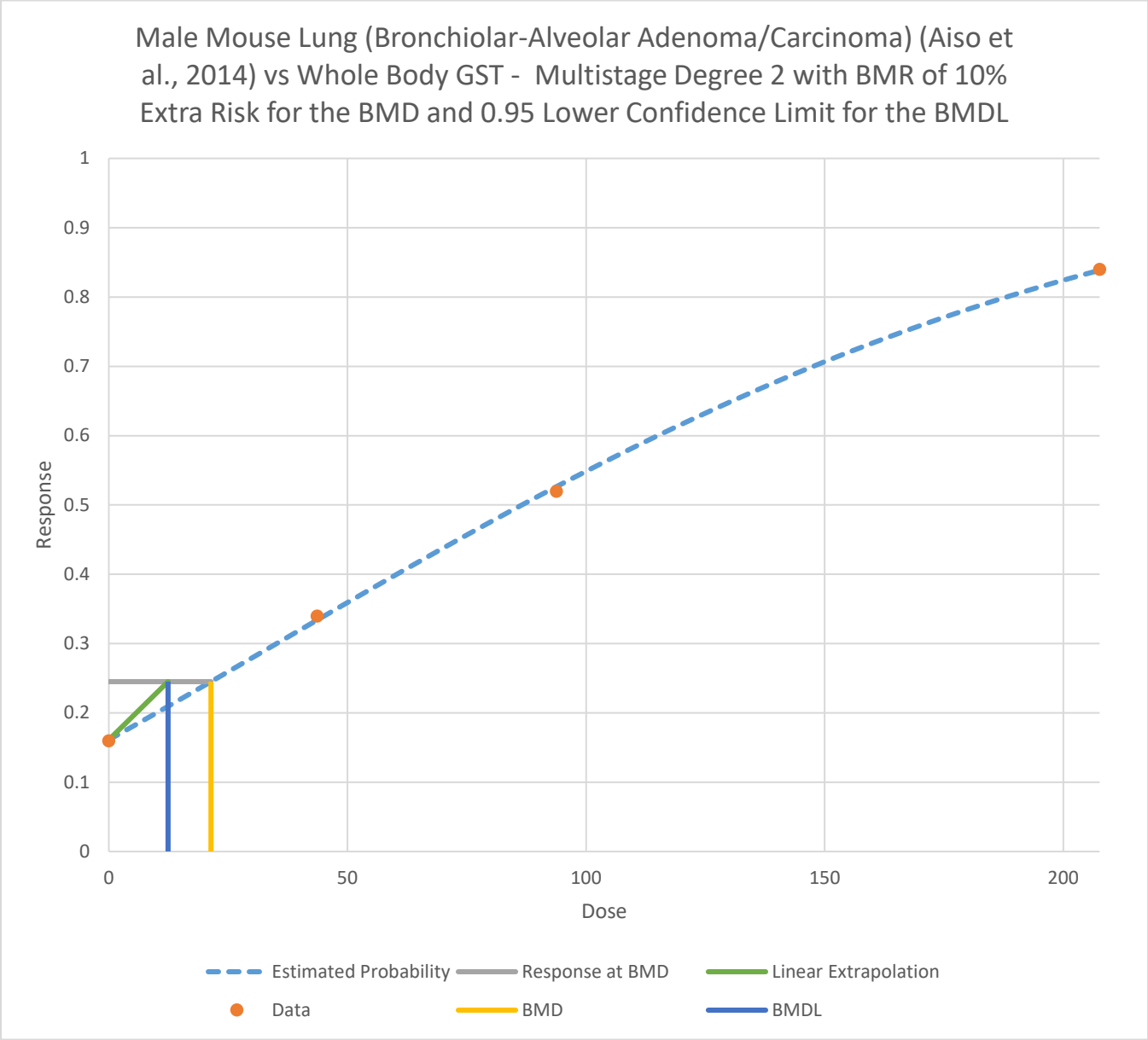
Model Parameters	
# of Parameters	3
Variable	Estimate
Background (g)	0.161228481
Beta1	0.004576058
Beta2	1.6197E-05

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.161228481	8.061424049	8	50	-0.023622
43.65	0.333971155	16.69855776	17	50	0.0903895
93.77	0.526370885	26.31854426	26	50	-0.090223
207.6	0.838598333	41.92991665	42	50	0.0269401

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-110.6361102	0	-	-	-
Fitted Model	-110.644895	3	0.01756954	1	0.8945492
Reduced Model	-138.1390352	1	55.0058499	3	<0.0001


Male Mouse Lung (Bronchiolar-Alveolar Adenoma/Carcinoma) (Aiso et al., 2014) vs Whole Body GST - Multistage Degree 2 with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
Dose
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
50
100
150
200
Estimated Probability
Response at BMD
Linear Extrapolation
Data
BMD
BMDL

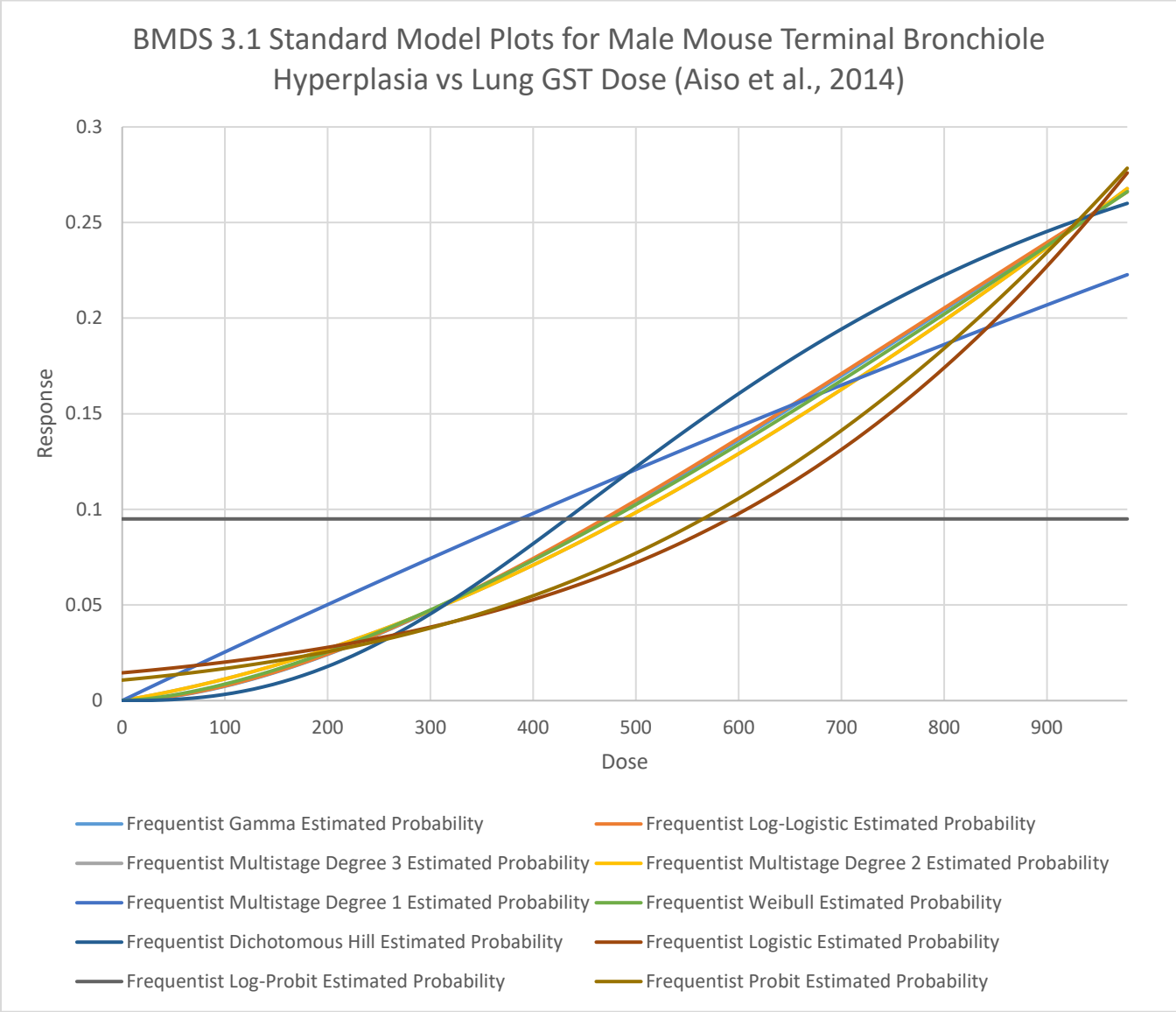
7.4. Lung Terminal Bronchiole Hyperplasia

Lung GST dose	[N]	[Incidence]
0	50	0
209.8	50	1
444.6	50	5
978.1	50	13

Summary of BMDS 3.1 Modeling Results for Male Mouse Terminal Bronchiole Hyperplasia vs Lung GST Dose (Aiso et al., 2014)

Standard Models	Restriction**	10% Extra Risk		P Value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL				
Gamma*	Restricted	487.13	324.61	0.90863	103.8117	Selected, Full Model Suite	Lowest AIC
Log-Logistic	Restricted	484.91	322.18	0.66742	105.8058	Viable - Alternate	
Multistage Degree 3	Restricted	505.45	319.43	0.83894	103.9745	Viable - Alternate	
Multistage Degree 2	Restricted	505.44	319.43	0.55341	105.9745	Viable - Alternate	
Multistage Degree 1 (Quantal Linear)	Restricted	409.03	286.57	0.47162	105.4225	Viable - Alternate	
Weibull	Restricted	491.72	323.09	0.62769	105.8579	Viable - Alternate	
Dichotomous Hill	Unrestricted	444.82	309.41	NA	107.6179	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Logistic	NA	648.76	543.11	0.31824	106.4429	Viable - Alternate	
Log-Probit	Unrestricted	2E+08	0	<0.0001	131.5823	Unusable	BMD failed; lower limit includes zero BMDL not estimated Goodness of fit p-value < 0.1 Goodness of fit p-value < 0.05 |Residual for Dose Group Near BMD| > 2 BMD higher than maximum dose |Residual at control| > 2
Probit	NA	612.08	507.25	0.40875	105.8043	Viable - Alternate	
Non-Standard Models							
Dichotomous Hill	Restricted	444.6	309.41	NA	107.61790	Questionable	d.f.=0 (Goodness of fit cannot be calculated)
Log-Probit	Restricted	937813	0	<0.0001	131.58234	Unusable	BMD failed; lower limit includes zero BMDL not estimated Goodness of fit p-value < 0.1 Goodness of fit p-value < 0.05 |Residual for Dose Group Near BMD| > 2 BMD higher than maximum dose |Residual at control| > 2
Gamma	Unrestricted	487.12	324.43	0.90863	103.81169	Viable - Alternate	
Log-Logistic	Unrestricted	484.91	322.18	0.66742	105.80578	Viable - Alternate	
Multistage Degree 3	Unrestricted	444.43	321.21	NA	107.61791	Questionable	d.f.=0 (Goodness of fit cannot be calculated)
Multistage Degree 2	Unrestricted	505.44	317.30	0.83894	103.97450	Viable - Alternate	
Multistage Degree 1	Unrestricted	409.03	286.57	0.47162	105.42253	Viable - Alternate	
Weibull	Unrestricted	491.70	322.73	0.62771	105.85787	Viable - Alternate	

*Selected, Full Model Suite (Green); residuals for doses 0, 209.8, 444,6, and 978.1 were -0.000872639, -0.273690741, 0.325572248, and -0.103637637, respectively.
**Restrictions defined in the BMDS 3.1 User Guide; NA = Not Applicable


BMDS 3.1 Standard Model Plots for Male Mouse Terminal Bronchiole Hyperplasia vs Lung GST Dose (Aiso et al., 2014)
Response
0.3
0.25
0.2
0.15
0.1
0.05
0
0
100
200
300
400
500
600
700
800
900
Dose
Frequentist Gamma Estimated Probability
Frequentist Log-Logistic Estimated Probability
Frequentist Multistage Degree 3 Estimated Probability
Frequentist Multistage Degree 2 Estimated Probability
Frequentist Multistage Degree 1 Estimated Probability
Frequentist Weibull Estimated Probability
Frequentist Dichotomous Hill Estimated Probability
Frequentist Logistic Estimated Probability
Frequentist Log-Probit Estimated Probability
Frequentist Probit Estimated Probability

Selected, Full Model Suite - Gamma (Restricted) - Extra Risk, BMR = 0.1

User Input

Info	
Model	Gamma v1.0
Dataset Name	Aiso et al. (2014) Male Mouse Terminal Bronchiole Hyperplasia
Formula	P[dose]= g+(1-g)*CumGamma[b*dose,a]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Lung GST Dose
Independent Variable	[Tumor Incidence]
Total # of Observation	4

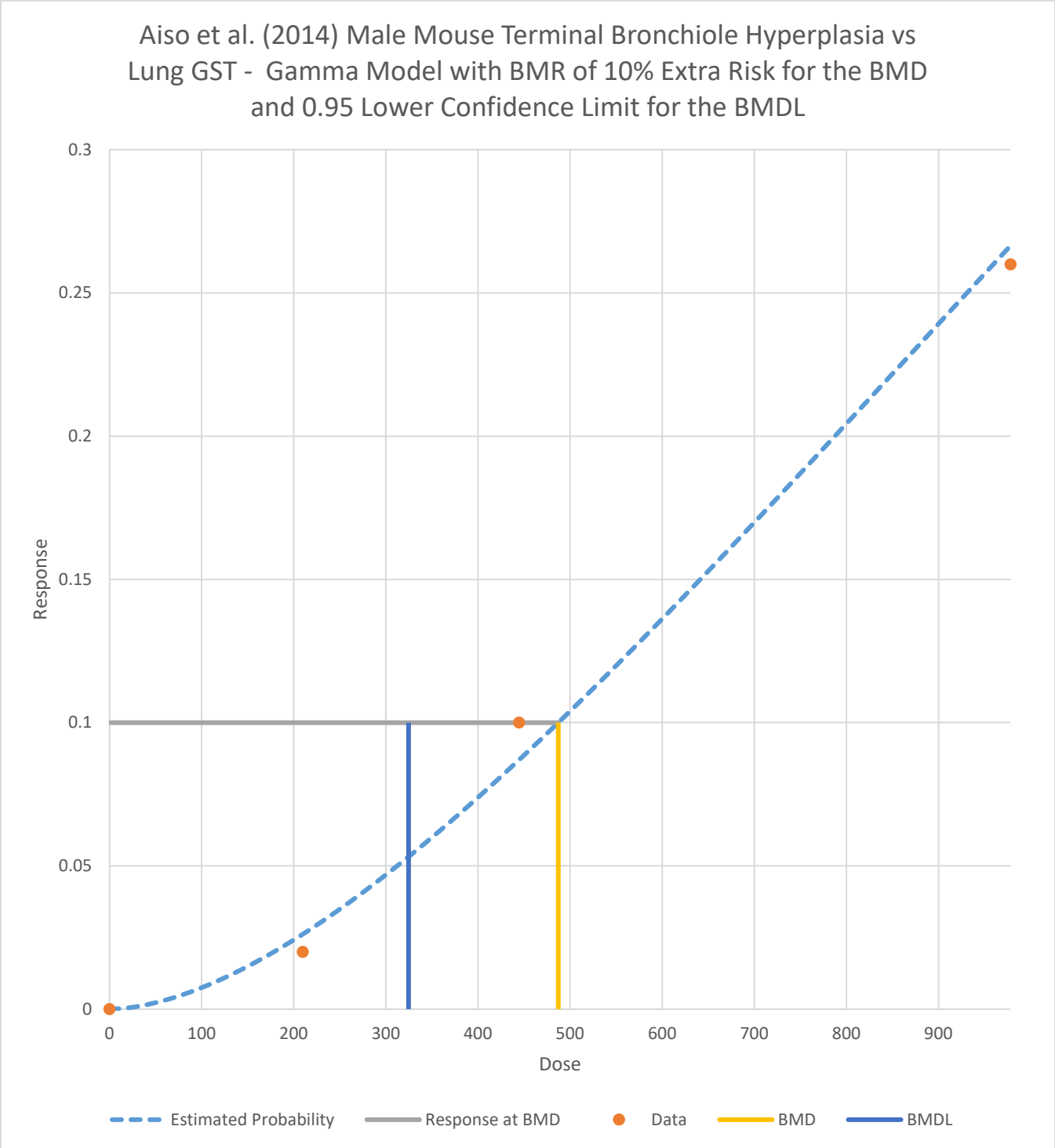
Model Results

Benchmark Dose	
BMD	487.1280354
BMDL	324.6110673
BMDU	634.974297
AIC	103.8116931
P-value	0.908625087
D.O.F.	2
Chi^2	0.191645431

Model Parameters	
# of Parameters	3
Variable	Estimate
Background (g)	1.523E-08
a	1.764256328
b	0.000849385

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	7.615E-07	0	50	-0.0009
209.8	0.026180174	1.30900868	1	50	-0.2737
444.6	0.08702202	4.35110099	5	50	0.32557
978.1	0.266479937	13.3239968	13	50	-0.1036

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-49.8089503	0	-	-	-
Fitted Model	-49.9058465	2	0.193792	2	0.90765
Reduced Model	-62.79117	1	25.96444	3	<0.0001


Aiso et al. (2014) Male Mouse Terminal Bronchiole Hyperplasia vs Lung GST - Gamma Model with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
0.3
0.25
0.2
0.15
0.1
0.05
0
0
100
200
300
400
500
600
700
800
900
Dose
Estimated Probability
Response at BMD
Data
BMD
BMDL

8. BMD Modeling for Aiso et al. (2014) Female Mice

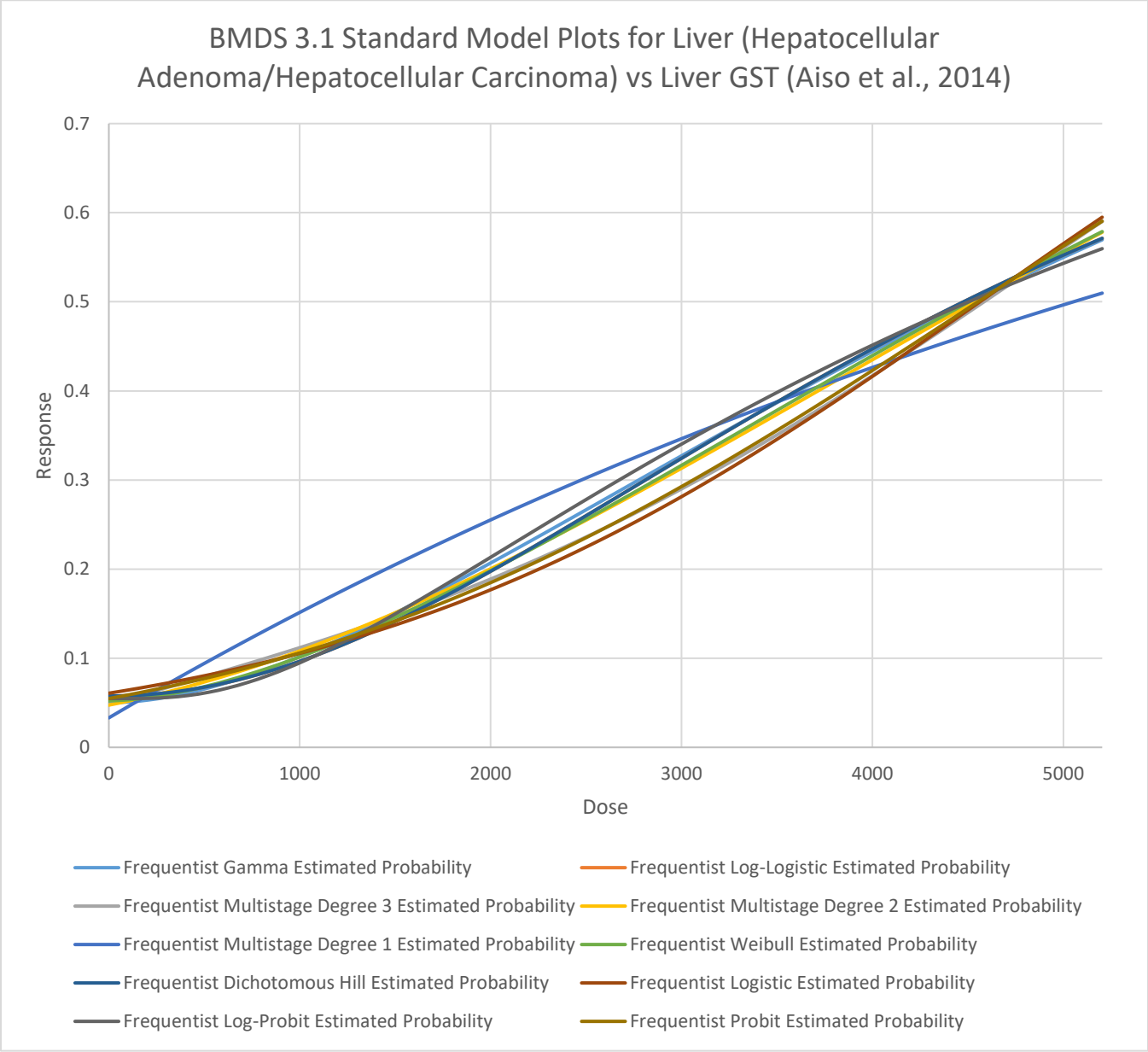
8.1. Liver (Hepatocellular Adenoma/Hepatocellular Carcinoma)

Liver GST dose	[N]	[Incidence]
0	50	2
1127	49	8
2435	49	9
5203	50	30

Summary of BMDS 3.1 Modeling Results for Female Mouse Liver (Hepatocellular Adenoma/Hepatocellular Carcinoma) vs Liver GST Dose (Aiso et al., 2014)

Standard Models	Restrict.***	10% Extra Risk		P Value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL				
Gamma	Restricted	1446.2	706.01	0.08571	183.39119	Questionable	Goodness of fit p-value < 0.1
Log-Logistic	Restricted	1598.8	778.77	0.06904	183.66883	Questionable	Goodness of fit p-value < 0.1
Multistage Degree 2*	**Restricted**	**1408.7**	**762.31**	**0.13986**	**182.61744**	**Selected, Multistage**	
Multistage Degree 1 (Quantal Linear)	Restricted	807.21	621.21	0.09583	183.43529	Questionable	Goodness of fit p-value < 0.1
Weibull	Restricted	1509.9	736.61	0.10410	183.03450	Viable - Alternate	
Dichotomous Hill	Unrestricted	1598.8	778.77	NA	185.66883	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Logistic	NA	1732.7	1440.0	0.37410	180.34516	Viable - Alternate	
Log-Probit	Unrestricted	1496.2	772.70	0.04600	184.41190	Questionable	Goodness of fit p-value < 0.1 Goodness of fit p-value < 0.05
Probit**	NA	**1595.1**	**1332.8**	**0.37801**	**180.32441**	**Selected, Full Model Suite**	**Lowest AIC**
Non-Standard Models							
Dichotomous Hill	Restricted	1598.8	778.77	0.06904	183.66883	Questionable	Goodness of fit p-value < 0.1
Log-Probit	Restricted	1495.6	1075.0	0.04600	184.41189	Questionable	Goodness of fit p-value < 0.1 Goodness of fit p-value < 0.05
Gamma	Unrestricted	1446.3	689.33	0.08571	183.39119	Questionable	Goodness of fit p-value < 0.1
Log-Logistic	Unrestricted	1599.2	778.77	0.06904	183.66883	Questionable	Goodness of fit p-value < 0.1
Multistage Degree 3	Unrestricted	673.69	248.13	NA	182.44800	Questionable	BMDL 3x lower than lowest non-zero dose d.f.=0 (Goodness of fit cannot be calculated)
Multistage Degree 2	Unrestricted	1408.4	762.31	0.13986	182.61744	Viable - Alternate	
Multistage Degree 1	Unrestricted	807.21	621.21	0.09583	183.43529	Questionable	Goodness of fit p-value < 0.1
Weibull	Unrestricted	1509.9	736.07	0.10411	183.03450	Viable - Alternate	

*Selected, Multistage (Yellow); residuals for doses 0, 1127, 2435, and 5203 were -0.255660408, 0.981438585, -1.050357536, and 0.324699593, respectively.
**Selected, Full Model Suite (Green); residuals for doses 0, 1127, 2435, and 5203 were -0.581452723, 1.103963499, -0.61310587, and 0.087362998, respectively.
***Restrictions defined in the BMDS 3.1 User Guide; NA = Not Applicable


BMDS 3.1 Standard Model Plots for Liver (Hepatocellular Adenoma/Hepatocellular Carcinoma) vs Liver GST (Aiso et al., 2014)
Response
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
1000
2000
3000
4000
5000
Dose
Frequentist Gamma Estimated Probability
Frequentist Log-Logistic Estimated Probability
Frequentist Multistage Degree 3 Estimated Probability
Frequentist Multistage Degree 2 Estimated Probability
Frequentist Multistage Degree 1 Estimated Probability
Frequentist Weibull Estimated Probability
Frequentist Dichotomous Hill Estimated Probability
Frequentist Logistic Estimated Probability
Frequentist Log-Probit Estimated Probability
Frequentist Probit Estimated Probability

Selected, Multistage - Multistage 2 Restricted; Extra Risk, BMR = 0.1

User Input

Info	
Model	Multistage degree 2 v1.0
Dataset Name	Aiso et al. (2014) Female Mouse Liver (Hepatocellular Adenoma/Hepatocellular Carcinoma)
Formula	P[dose] = g + (1-g)*[1-exp(-b1*dose^1-b2*dose^2)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Liver GST Dose
Independent Variable	[Tumor Incidence]
Total # of Observation	4

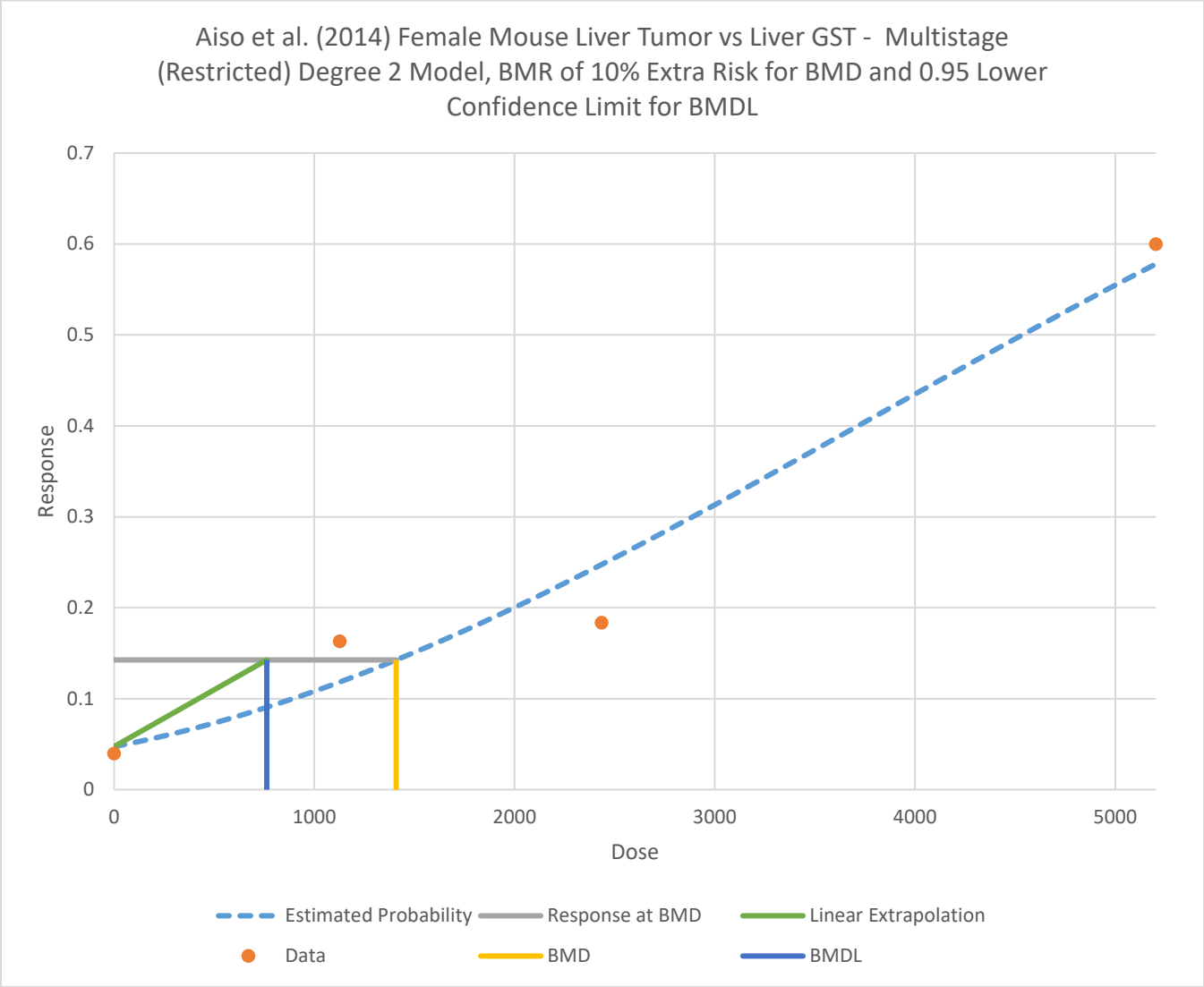
Model Results

Benchmark Dose	
BMD	1408.701273
BMDL	762.3062298
BMDU	2170.280873
AIC	182.6174393
P-value	0.13985562
D.O.F.	1
Chi^2	2.179547016
Slope Factor	0.000131181

Model Parameters	
# of Parameters	3
Variable	Estimate
Background (g)	0.047407152
Beta1	4.44581E-05
Beta2	2.15337E-08

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.047407152	2.370357576	2	50	-0.246468
1127	0.118405041	5.801846992	8	49	0.9719417
2435	0.247610695	12.13292403	9	49	-1.036921
5203	0.578032473	28.90162363	30	50	0.3145217

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-87.22399352	0	-	-	-
Fitted Model	-88.30871965	3	2.16945225	1	0.1407764
Reduced Model	-110.7896779	1	47.1313687	3	<0.0001


Aiso et al. (2014) Female Mouse Liver Tumor vs Liver GST - Multistage (Restricted) Degree 2 Model, BMR of 10% Extra Risk for BMD and 0.95 Lower Confidence Limit for BMDL
Response
Dose
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0
1000
2000
3000
4000
5000
Estimated Probability
Response at BMD
Linear Extrapolation
Data
BMD
BMDL

Selected, Full Model Suite - Probit - Extra Risk, BMR = 0.1

User Input

Info	
Model	Probit v1.0
Dataset Name	Aiso et al. (2014) Female Mouse Liver (Hepatocellular Adenoma/Hepatocellular Carcinoma)
Formula	P[dose] = CumNorm(a+b*Dose)

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Liver GST Dose
Independent Variable	[Tumor Incidence]
Total # of Observation	4

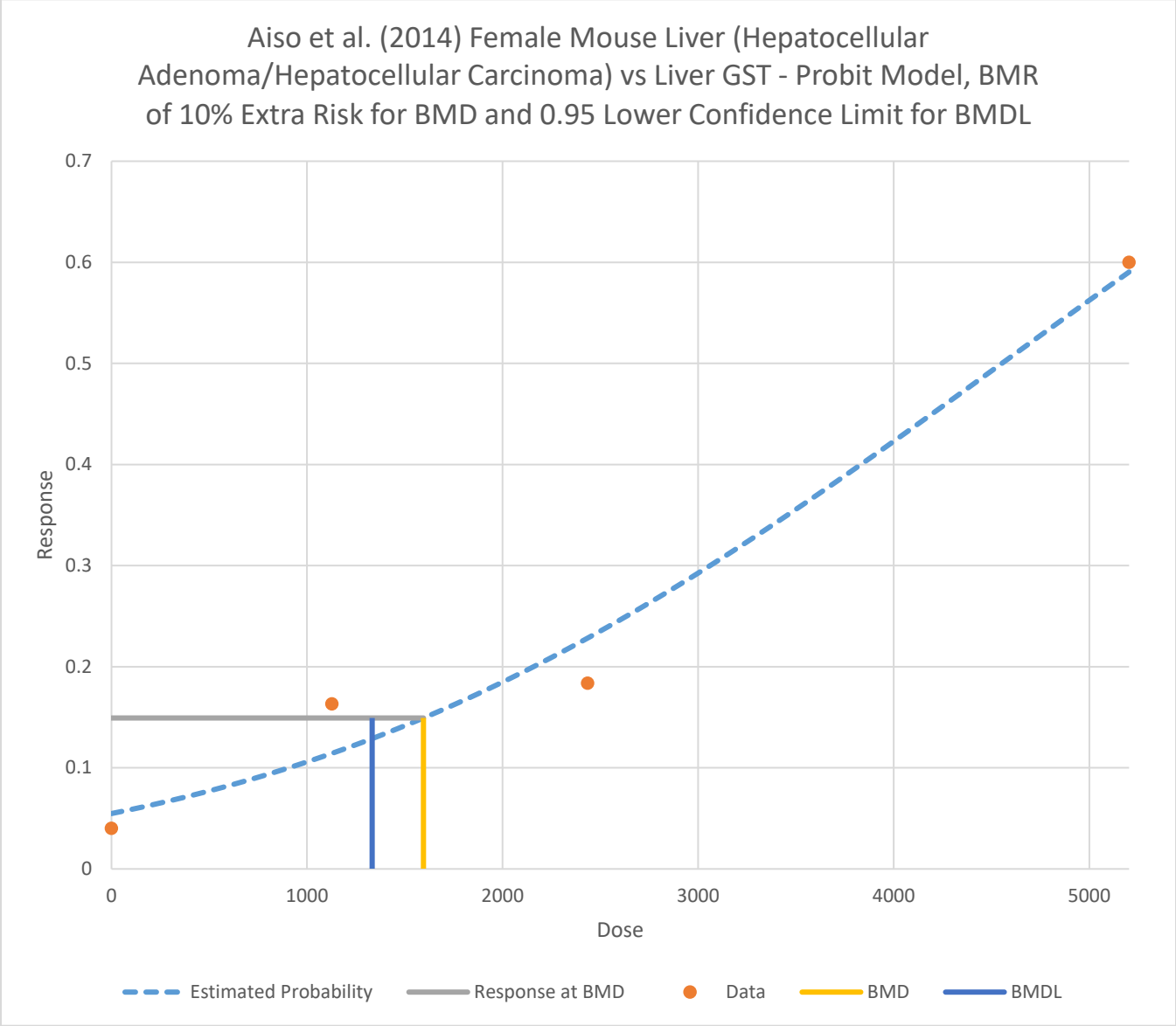
Model Results

Benchmark Dose	
BMD	1595.107529
BMDL	1332.777247
BMDU	1907.524552
AIC	180.3244078
P-value	0.37800892
D.O.F.	2
Chi^2	1.945674973

Model Parameters	
# of Parameters	2
Variable	Estimate
a	-1.599925117
b	0.00035145

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.054807598	2.740379913	2	50	-0.460033
1127	0.114325487	5.601948877	8	49	1.0765936
2435	0.228394439	11.19132752	9	49	-0.745708
5203	0.590436635	29.52183177	30	50	0.1375145

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-87.600959	-87.22399352	0	-	-
Fitted Model	-88.5357146	-88.1622039	2	1.87642075	2
Reduced Model	-111.355023	-110.7896779	1	47.1313687	3


Aiso et al. (2014) Female Mouse Liver (Hepatocellular Adenoma/Hepatocellular Carcinoma) vs Liver GST - Probit Model, BMR of 10% Extra Risk for BMD and 0.95 Lower Confidence Limit for BMDL
Response
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
1000
2000
3000
4000
5000
Dose
Estimated Probability
Response at BMD
Data
BMD
BMDL

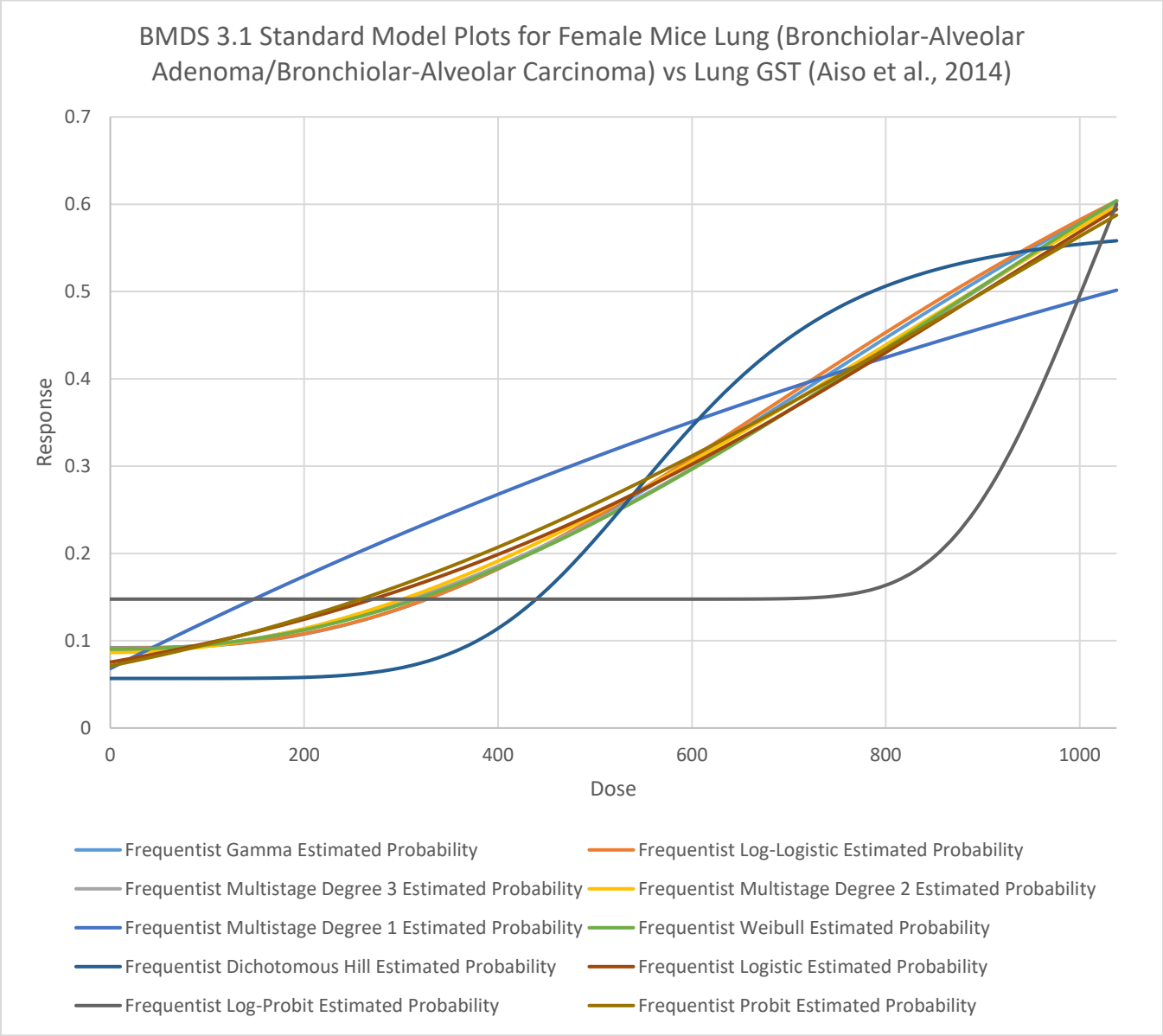
8.2. Lung (Bronchiolar-Alveolar Adenoma/Bronchiolar-Alveolar Carcinoma)

Lung GST dose	[N]	[Incidence]
0	50	5
229.8	50	5
489.3	49	12
1038	50	30

Summary of BMDS 3.1 Modeling Results for Female Mice Lung (Bronchiolar-Alveolar Adenoma/Bronchiolar-Alveolar Carcinoma) vs lung GST Dose (Aiso et al., 2014)

Standard Models	Restriction**	10% Extra Risk		P Value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL				
Gamma	Restricted	401.07	240.69	0.66795	193.05738	Viable - Alternate	
Log-Logistic	Restricted	399.76	247.30	0.66396	193.06230	Viable - Alternate	
Multistage Degree 2*	**Restricted**	**371.93**	**223.47**	**0.83445**	**191.24117**	**Selected, Multistage and Selected, Full Model Suite**	**Multistage-cancer guidance (EPA, 2014); Lowest AIC**
Multistage Degree 1 (Quantal Linear)	Restricted	174.79	131.52	0.04565	197.41738	Questionable	Goodness of fit p-value < 0.1 Goodness of fit p-value < 0.05
Weibull	Restricted	395.77	233.52	0.57702	193.18852	Viable - Alternate	
Dichotomous Hill	Unrestricted	438.65	252.35	NA	194.87252	Questionable	d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Logistic	NA	325.53	271.12	0.62543	191.81268	Viable - Alternate	
Log-Probit	Unrestricted	881.06	165.24	0.01917	198.04778	Questionable	Goodness of fit p-value < 0.1 Goodness of fit p-value < 0.05 BMD/BMDL ratio > 5
Probit	NA	300.72	251.83	0.53476	192.10948	Viable - Alternate	
Non-Standard Models							
Dichotomous Hill	Restricted	460.87	252.46	NA	194.87047	Questionable	d.f.=0 (Goodness of fit cannot be calculated)
Log-Probit	Restricted	404.99	256.99	0.79485	192.93864	Viable - Alternate	
Gamma	Unrestricted	401.10	240.69	0.66794	193.05738	Viable - Alternate	
Log-Logistic	Unrestricted	399.74	247.30	0.66396	193.06230	Viable - Alternate	
Multistage Degree 3	Unrestricted	408.34	198.94	NA	194.87051	Questionable	d.f.=0 (Goodness of fit cannot be calculated)
Multistage Degree 2	Unrestricted	415.78	227.89	0.64104	193.08908	Viable - Alternate	
Multistage Degree 1	Unrestricted	174.79	131.51	0.04565	197.41738	Questionable	Goodness of fit p-value < 0.1 Goodness of fit p-value < 0.05
Weibull	Unrestricted	395.70	233.52	0.57703	193.18852	Viable - Alternate	

*Selected, Multistage & Selected, Full Model Suite (Green); residuals for doses 0, 229.8, 489.3, and 1038 are 0.353291028, -0.472348654, 0.038830428, and 0.056725116, respectively.
**Restrictions defined in the BMDS 3.1 User Guide; NA = Not Applicable


BMDS 3.1 Standard Model Plots for Female Mice Lung (Bronchiolar-Alveolar Adenoma/Bronchiolar-Alveolar Carcinoma) vs Lung GST (Aiso et al., 2014)
Response
Dose
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0
200
400
600
800
1000
Frequentist Gamma Estimated Probability
Frequentist Log-Logistic Estimated Probability
Frequentist Multistage Degree 3 Estimated Probability
Frequentist Multistage Degree 2 Estimated Probability
Frequentist Multistage Degree 1 Estimated Probability
Frequentist Weibull Estimated Probability
Frequentist Dichotomous Hill Estimated Probability
Frequentist Logistic Estimated Probability
Frequentist Log-Probit Estimated Probability
Frequentist Probit Estimated Probability

Selected, Multistage & Selected, Full Model Suite - Multistage 2 Restricted; Extra Risk, BMR = 0.1

User Input

Info	
Model	Multistage degree 2 v1.0
Dataset Name	Female Mice Lung (Bronchiolar-Alveolar Adenoma/Bronchiolar-Alveolar Carc.) (Aiso et al., 2014)
Formula	P[dose] = g + (1-g)*[1-exp(-b1*dose^1-b2*dose^2)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Lung GST Dose
Independent Variable	[Tumor Incidence]
Total # of Observation	4

Model Results

Benchmark Dose	
BMD	371.9343533
BMDL	223.4690891
BMDU	447.743515
AIC	191.2411713
P-value	0.834454353
D.O.F.	2
Chi^2	0.361954474
Slope Factor	0.000447489

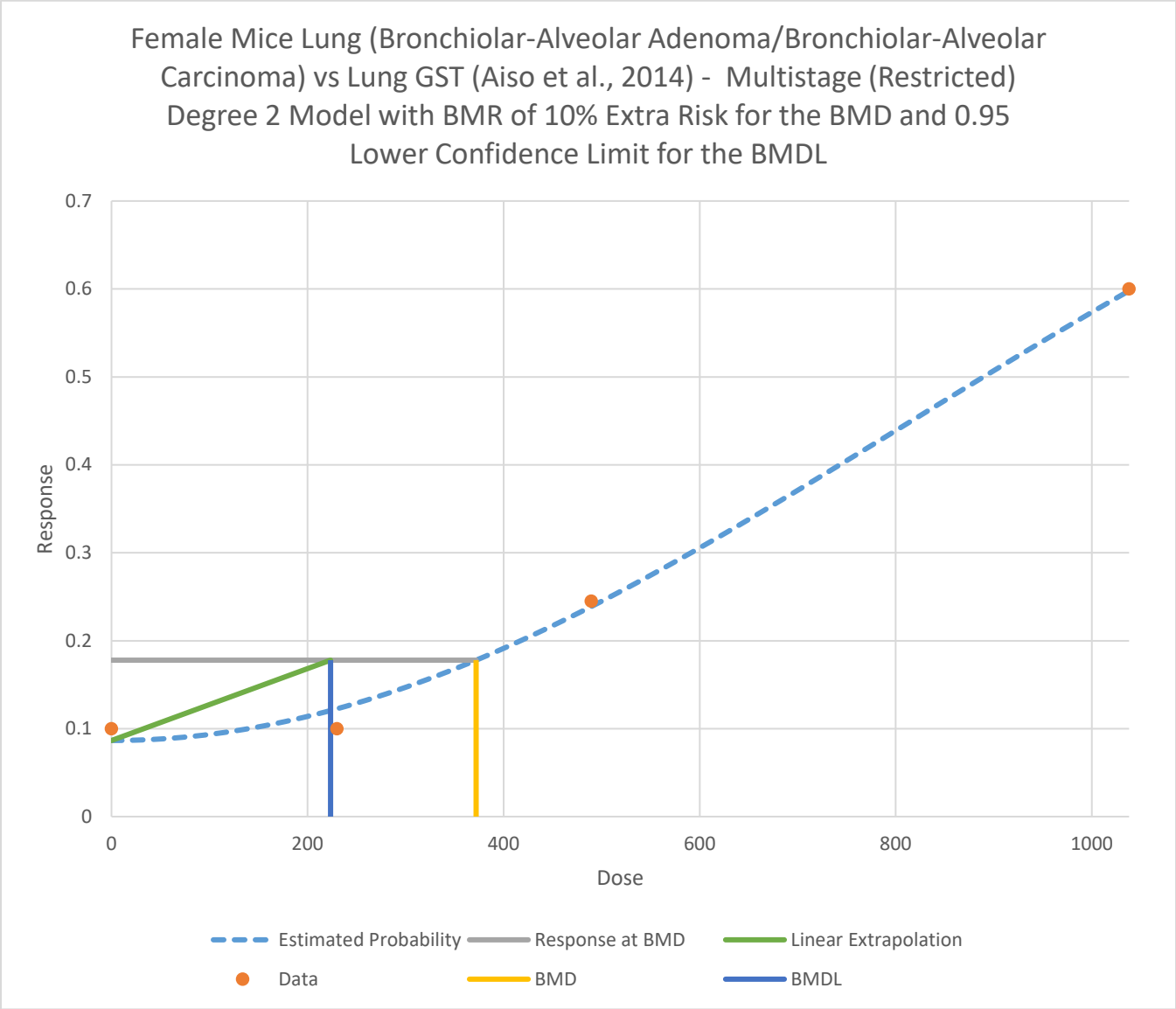
Model Parameters	
# of Parameters	3
Variable	Estimate
Background (g)	0.086540256
Beta1	0
Beta2	7.61632E-07

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.086540256	4.327012821	5	50	0.3385073
229.8	0.122550852	6.127542608	5	50	-0.486271
489.3	0.238801991	11.70129755	12	49	0.1000859
1038	0.597931185	29.89655926	30	50	0.0298353

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-93.43523273	0	-	-	-
Fitted Model	-93.62058567	2	0.37070588	2	0.830811
Reduced Model	-114.3093965	1	41.7483275	3	<0.0001


Female Mice Lung (Bronchiolar-Alveolar Adenoma/Bronchiolar-Alveolar Carcinoma) vs Lung GST (Aiso et al., 2014) - Multistage (Restricted) Degree 2 Model with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
200
400
600
800
1000
Dose
Estimated Probability
Response at BMD
Linear Extrapolation
Data
BMD
BMDL

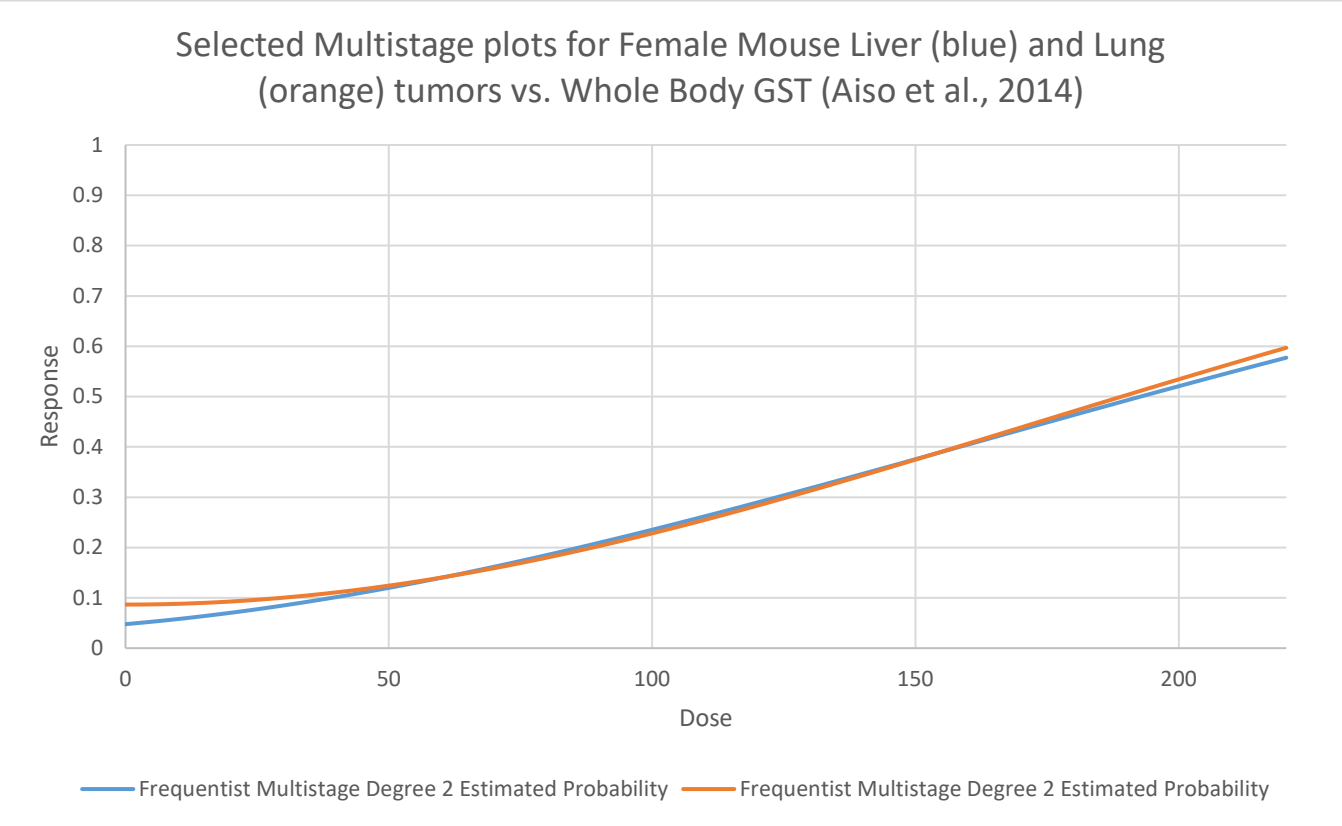
8.3. Liver or Lung Tumor

Female Mouse Liver (Hepatocellular Adenoma/Carcinoma) (Aiso et al., 2014)		
Whole body GST dose	[N]	[Incidence]
0	50	2
47.79	49	8
103.2	49	9
220.4	50	30
Female Mouse Lung (Bronchiolar-Alveolar Adenoma/Carcinoma) (Aiso et al., 2014)		
Whole body GST dose	[N]	[Incidence]
0	50	5
47.79	50	5
103.2	49	12
220.4	50	30

Summary of BMDS 3.1 Multi-tumor (MS_Combo) Modeling Results for Female Mouse Liver (Hepatocellular Adenoma/Carcinoma) and Lung (Bronchiolar-Alveolar Adenoma/Carcinoma) vs. Whole Body GST Dose (Aiso et al., 2014)

Models*	Dataset	10% Extra Risk		Slope Factor	P Value	AIC	BMDS Recommendation Notes
		BMD	BMDL				
Multi-tumor (MS_Combo)	Combined Risk	44.90091	25.30172	3.95e-3	NA	NA	-
Multistage Degree 2	Liver Tumors	59.71416	32.3186	3.09e-3	0.139811	182.6181	Multistage-cancer guidance (EPA, 2014)
Multistage Degree 2	Lung Tumors	78.8968	46.73242	2.14e-3	0.843905	191.2181	Multistage-cancer guidance (EPA, 2014)

*Multistage models used in the BMDS multi-tumor (MS_Combo) model are restricted as described in the BMDS 3.1 User Guide. The selected Multistage model was chosen from among all relevant model runs (see detailed results for all relevant Multistage degrees below) in accordance with EPA's technical guidance for choosing the appropriate stage of a multistage model for cancer modeling.



Multi-tumor (MS_Combo) Results for Female Mouse Liver (Hepatocellular Adenoma/Carcinoma) and Lung (Bronchiolar-Alveolar Adenoma/Carcinoma) vs. Whole Body GST Dose (Aiso et al., 2014)

User Input

Info	
Model	Multi-tumor v1.0

Model Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Results

Benchmark Dose	
BMD	44.90090916
BMDL	25.30171599
BMDU	62.0867887
Slope Factor	0.003952301
Combined Log-Likelihood	-181.918071
Combined Log-Likelihood Constant	165.8293306

Female Mouse Liver (Hepatocellular Adenoma/Carcinoma) (Aiso et al., 2014) - Multistage 1 Restricted; Extra Risk, BMR = 0.1

User Input

Info	
Model	Multistage degree 1 v1.0
Dataset Name	Female Mouse Liver (Hepatocellular Adenoma/Carc.) (Aiso et al., 2014)
Formula	P[dose] = g + (1-g)*[1-exp(-b1*dose^1)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Whole Body GST
Independent Variable	[Tumor Incidence]
Total # of Observation	4

Model Results

Benchmark Dose	
BMD	34.20378883
BMDL	26.32253773
BMDU	46.65003073
AIC	183.4415706
P-value	0.095541486
D.O.F.	2
Chi^2	4.696389425
Slope Factor	0.003799026

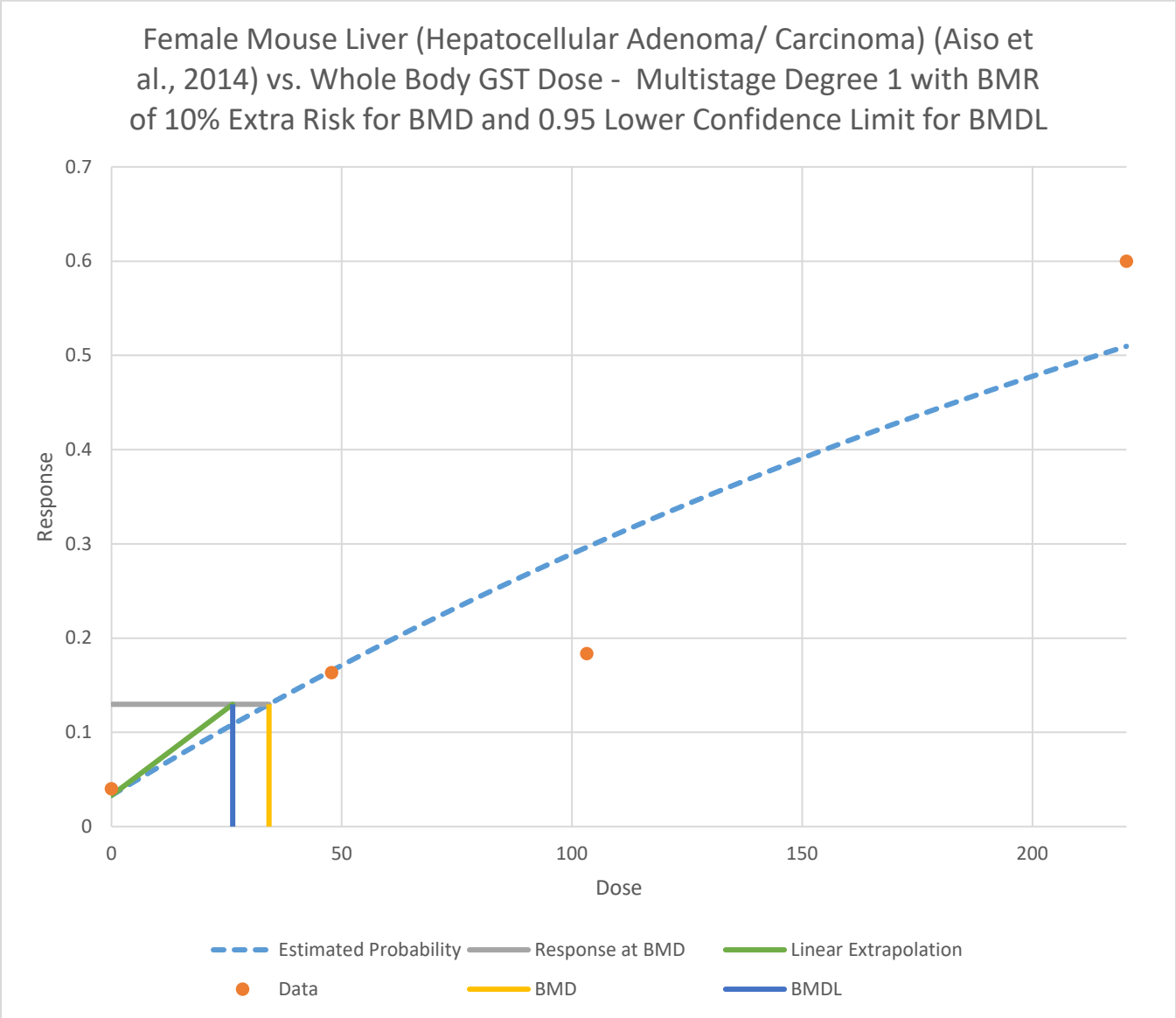
Model Parameters	
# of Parameters	2
Variable	Estimate
Background (g)	0.03310213
Beta1	0.003080376

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.03310213	1.655106503	2	50	0.2726351
47.79	0.165459123	8.107497027	8	49	-0.041327
103.2	0.296408371	14.52401019	9	49	-1.728028
220.4	0.509621228	25.48106138	30	50	1.2783856

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-87.22399352	0	-	-	-
Fitted Model	-89.72078532	2	4.99358359	2	0.0823488
Reduced Model	-110.7896779	1	47.1313687	3	<0.0001


Female Mouse Liver (Hepatocellular Adenoma/ Carcinoma) (Aiso et al., 2014) vs. Whole Body GST Dose - Multistage Degree 1 with BMR of 10% Extra Risk for BMD and 0.95 Lower Confidence Limit for BMDL
Response
Dose
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0
50
100
150
200
Estimated Probability
Response at BMD
Linear Extrapolation
Data
BMD
BMDL

Female Mouse Liver (Hepatocellular Adenoma/Carcinoma) (Aiso et al., 2014) - Multistage 2 Restricted (Selected Multistage Degree); Extra Risk, BMR = 0.1

User Input

Info	
Model	Multistage degree 2 v1.0
Dataset Name	Female Mouse Liver (Hepatocellular Adenoma/Carcinoma) (Aiso et al., 2014)
Formula	P[dose] = g + (1-g)*[1-exp(-b1*dose^1-b2*dose^2)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Whole Body GST
Independent Variable	[Tumor Incidence]
Total # of Observation	4

Model Results

Benchmark Dose	
BMD	59.71415711
BMDL	32.3186036
BMDU	91.9425009
AIC	182.6180846
P-value	0.139811174
D.O.F.	1
Chi^2	2.18003619
Slope Factor	0.003094193

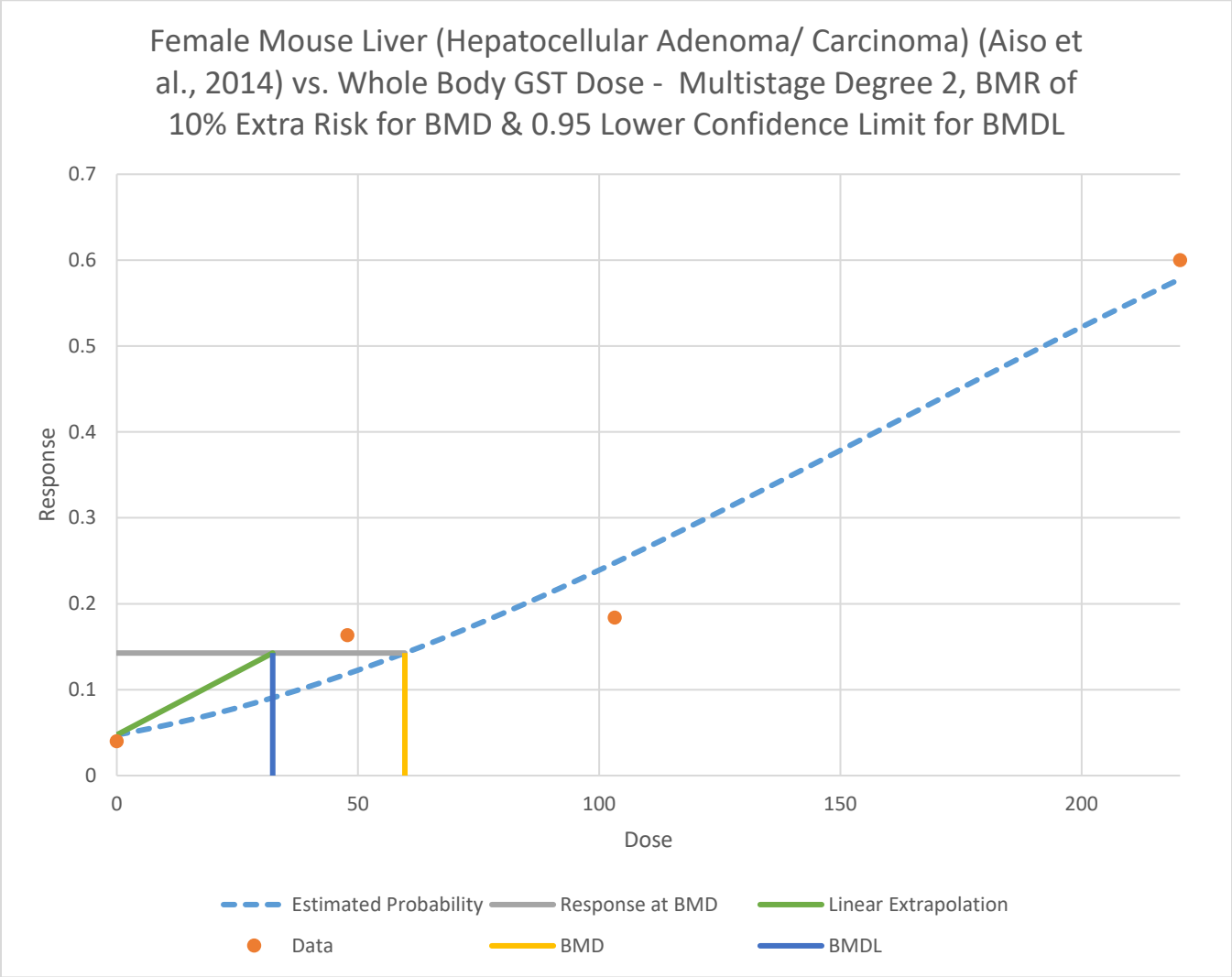
Model Parameters	
# of Parameters	3
Variable	Estimate
Background (g)	0.047397565
Beta1	0.001047255
Beta2	1.20099E-05

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.047397565	2.369878248	2	50	-0.246173
47.79	0.118416103	5.802389055	8	49	0.9716628
103.2	0.247641509	12.13443395	9	49	-1.037378
220.4	0.57800676	28.90033801	30	50	0.3148872

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-87.22399352	0	-	-	-
Fitted Model	-88.30904231	3	2.17009758	1	0.1407173
Reduced Model	-110.7896779	1	47.1313687	3	<0.0001


Female Mouse Liver (Hepatocellular Adenoma/ Carcinoma) (Aiso et al., 2014) vs. Whole Body GST Dose - Multistage Degree 2, BMR of 10% Extra Risk for BMD & 0.95 Lower Confidence Limit for BMDL
Response
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
50
100
150
200
Dose
Estimated Probability
Response at BMD
Linear Extrapolation
Data
BMD
BMDL

Female Mouse Lung (Bronchiolar-Alveolar Adenoma/Carcinoma) vs. Whole Body GST Dose (Aiso et al., 2014) - Multistage 1 Restricted; Extra Risk, BMR = 0.1

User Input

Info	
Model	Multistage degree 1 v1.0
Dataset Name	Female Lung (Bronchiolar-Alveolar Adenoma/ Carcinoma) (Aiso et al., 2014)
Formula	P[dose] = g + (1-g)*[1-exp(-b1*dose^1)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Whole Body GST
Independent Variable	[Tumor Incidence]
Total # of Observation	4

Model Results

Benchmark Dose	
BMD	36.91414083
BMDL	27.77338153
BMDU	52.26999119
AIC	197.2451823
P-value	0.04932767
D.O.F.	2
Chi^2	6.018540187
Slope Factor	0.00360057

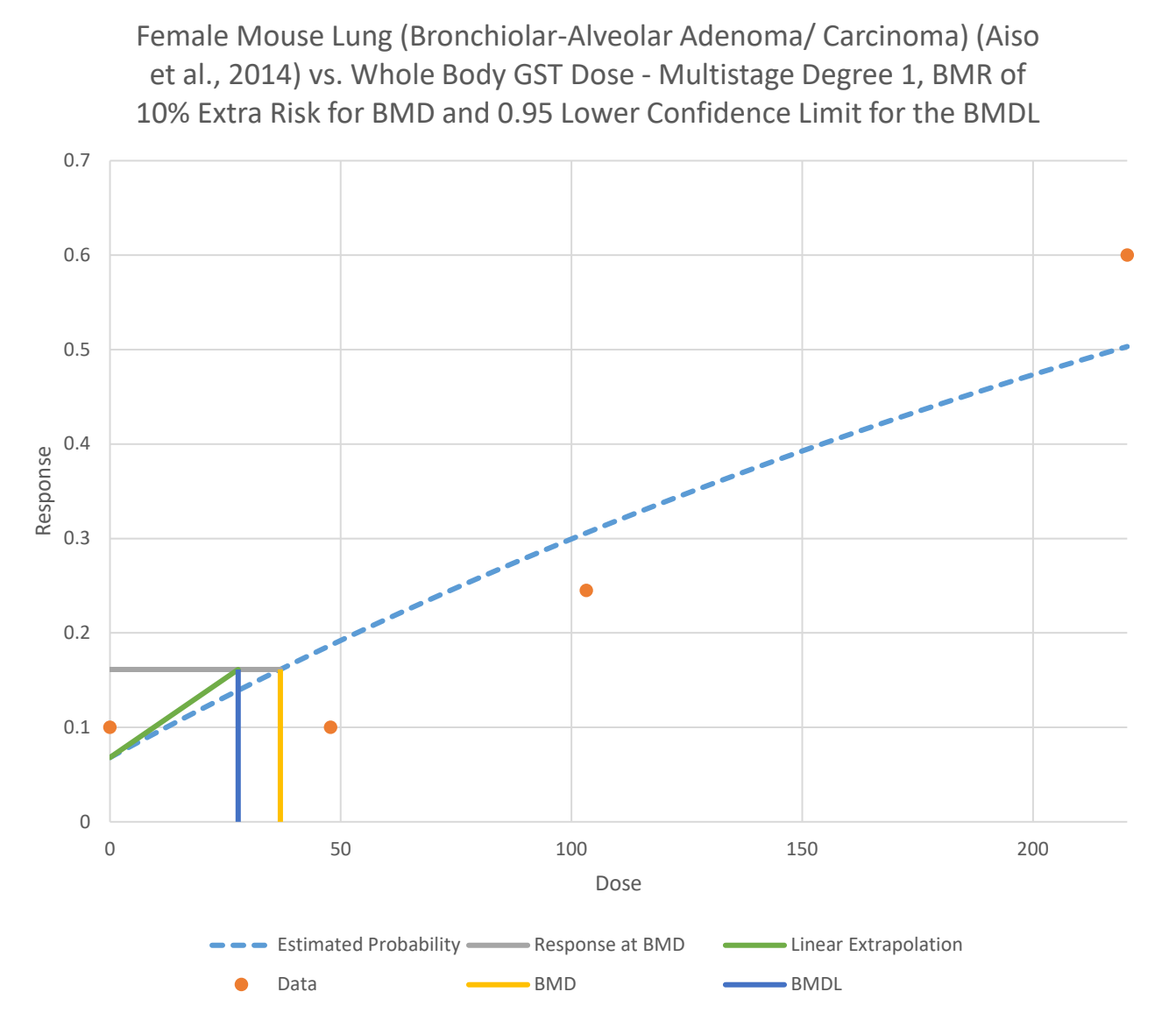
Model Parameters	
# of Parameters	2
Variable	Estimate
Background (g)	0.068115075
Beta1	0.002854205

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.068115075	3.405753745	5	50	0.8948858
47.79	0.186938387	9.34691934	5	50	-1.576833
103.2	0.305872676	14.98776114	12	49	-0.926313
220.4	0.503222315	25.16111576	30	50	1.3686716

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-93.43523273	0	-	-	-
Fitted Model	-96.62259117	2	6.37471688	2	0.0412808
Reduced Model	-114.3093965	1	41.7483275	3	<0.0001


Female Mouse Lung (Bronchiolar-Alveolar Adenoma/ Carcinoma) (Aiso et al., 2014) vs. Whole Body GST Dose - Multistage Degree 1, BMR of 10% Extra Risk for BMD and 0.95 Lower Confidence Limit for the BMDL
Response
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
50
100
150
200
Dose
Estimated Probability
Response at BMD
Linear Extrapolation
Data
BMD
BMDL

Female Mouse Lung (Bronchiolar-Alveolar Adenoma/Carcinoma) vs. Whole Body GST Dose (Aiso et al., 2014)- Multistage 2 Restricted (Selected Multistage Degree); Extra Risk, BMR = 0.1

User Input

Info	
Model	Multistage degree 2 v1.0
Dataset Name	Female Mouse Lung (Bronchiolar-Alveolar Adenoma/Carcinoma) (Aiso et al., 2014)
Formula	P[dose] = g + (1-g)*[1-exp(-b1*dose^1-b2*dose^2)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Whole Body GST
Independent Variable	[Tumor Incidence]
Total # of Observation	4

Model Results

Benchmark Dose	
BMD	78.89679983
BMDL	46.73241659
BMDU	95.00278902
AIC	191.2180574
P-value	0.843905042
D.O.F.	2
Chi^2	0.339430601
Slope Factor	0.002139842

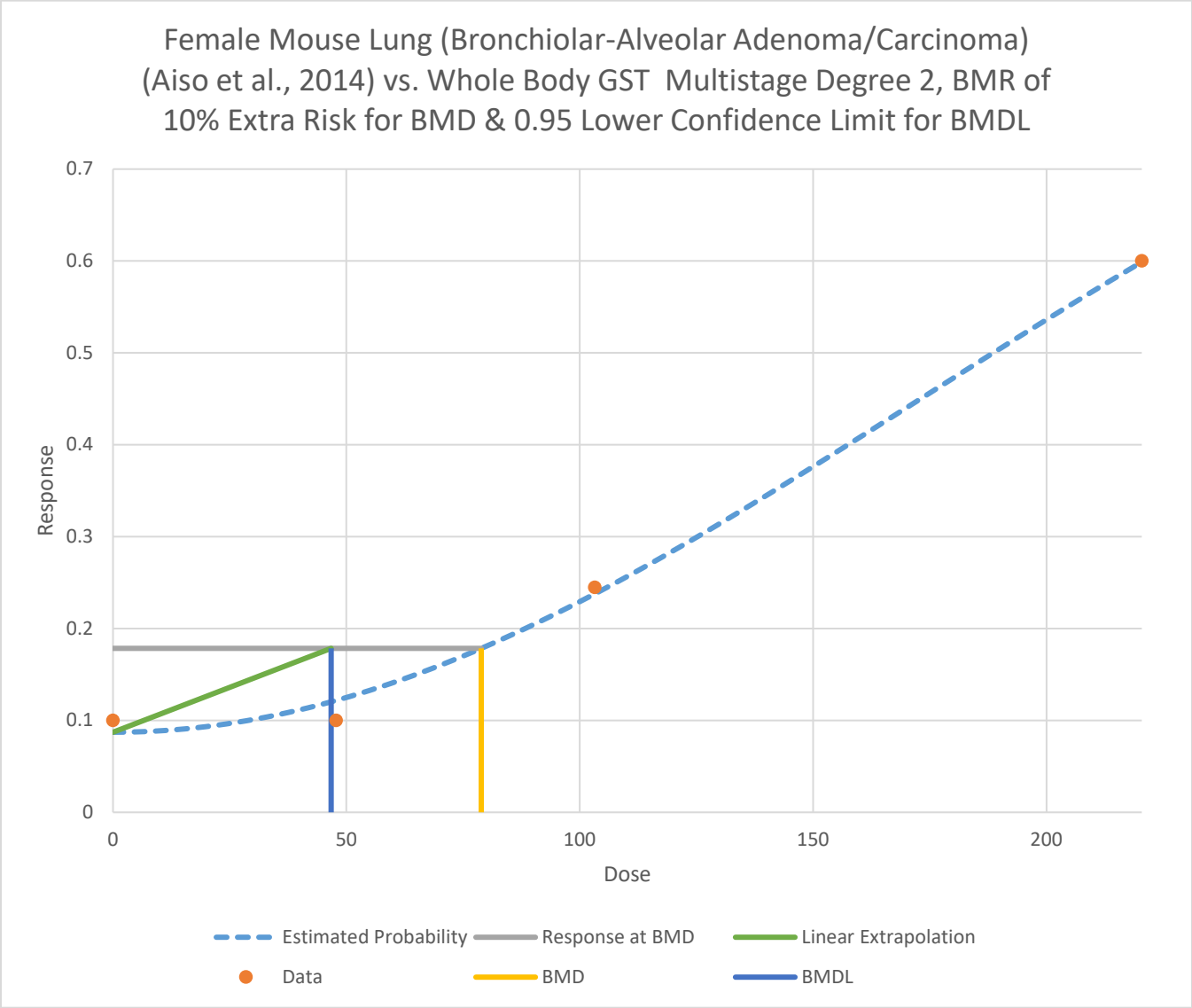
Model Parameters	
# of Parameters	3
Variable	Estimate
Background (g)	0.087158217
Beta1	0
Beta2	1.69262E-05

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.087158217	4.357910841	5	50	0.3219277
47.79	0.12177298	6.088649008	5	50	-0.470787
103.2	0.237734723	11.64900141	12	49	0.1177899
220.4	0.598842769	29.94213844	30	50	0.0166952

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-93.43523273	0	-	-	-
Fitted Model	-93.6090287	2	0.34759193	2	0.8404684
Reduced Model	-114.3093965	1	41.7483275	3	<0.0001


Female Mouse Lung (Bronchiolar-Alveolar Adenoma/Carcinoma) (Aiso et al., 2014) vs. Whole Body GST Multistage Degree 2, BMR of 10% Extra Risk for BMD & 0.95 Lower Confidence Limit for BMDL
Response
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
50
100
150
200
Dose
Estimated Probability
Response at BMD
Linear Extrapolation
Data
BMD
BMDL

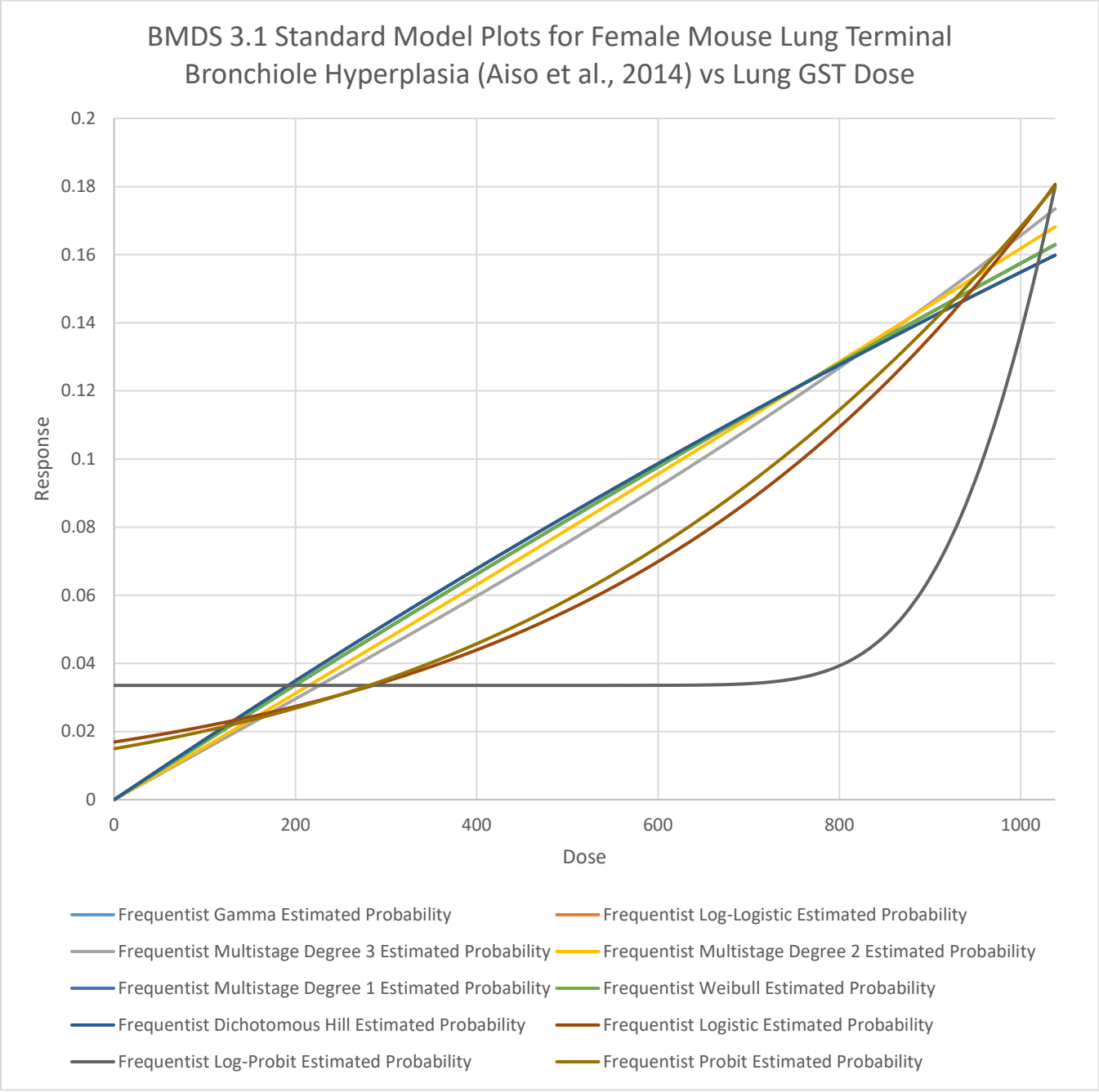
8.4. Lung Terminal Bronchiole Hyperplasia

Lung GST dose	[N]	[Incidence]
0	50	0
229.8	50	3
489.3	49	2
1038	50	9

Summary of BMDS 3.1 Modeling Results for Female Mouse Lung Terminal Bronchiole Hyperplasia (Aiso et al., 2014)

Standard Models	Restriction**	10% Extra Risk		P Value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL				
Gamma	Restricted	614.95	408.09	0.41428	92.432770	Viable - Alternate	
Log-Logistic	Restricted	608.82	390.73	0.41207	92.477298	Viable - Alternate	
Multistage Degree 3*	Restricted	648.42	411.28	0.40258	92.32310	Selected, Full Model Suite	Lowest AIC
Multistage Degree 2	Restricted	626.79	408.91	0.40391	92.402314	Viable - Alternate	
Multistage Degree 1 (Quantal Linear)	Restricted	614.95	408.07	0.41428	92.432770	Viable - Alternate	
Weibull	Restricted	614.95	408.09	0.41428	92.432770	Viable - Alternate	
Dichotomous Hill	Unrestricted	608.83	2.9245	0.18299	94.477298	Questionable	BMD/BMDL ratio > 20 BMD/BMDL ratio > 5 BMDL 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose
Logistic	NA	823.80	671.04	0.26255	93.711124	Viable - Alternate	
Log-Probit	Unrestricted	993.19	0	0.08892	96.914737	Unusable	BMD failed; lower limit includes zero BMDL not estimated Goodness of fit p-value < 0.1
Probit	NA	795.89	633.93	0.26182	93.617017	Viable - Alternate	
Non-Standard Models							
Dichotomous Hill	Restricted	608.82	311.91	NA	96.477319	Questionable	d.f.=0 (Goodness of fit cannot be calculated)
Log-Probit	Restricted	993.16	530.81	0.08892	96.914737	Questionable	Goodness of fit p-value < 0.1
Gamma	Unrestricted	612.83	299.97	0.18934	94.425923	Viable - Alternate	
Log-Logistic	Unrestricted	608.80	2.9409	0.41211	92.477298	Questionable	BMD/BMDL ratio > 20 BMD/BMDL ratio > 5 BMDL 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose
Multistage Degree 3	Unrestricted	924.27	127.43	NA	94.548029	Questionable	BMD/BMDL ratio > 5 d.f.=0 (Goodness of fit cannot be calculated)
Multistage Degree 2	Unrestricted	626.78	342.90	0.40393	92.402314	Viable - Alternate	
Multistage Degree 1	Unrestricted	614.95	408.07	0.41428	92.432770	Viable - Alternate	
Weibull	Unrestricted	613.13	300.46	0.18795	94.429084	Viable - Alternate	

*Selected, Full Model Suite (Green); residuals for doses 0, 229.8, 489.3, and 1038 were -0.000872639, 1.012433378, -0.883101828, and 0.121805828, respectively.
**Restrictions defined in the BMDS 3.1 User Guide; NA = Not Applicable


BMDS 3.1 Standard Model Plots for Female Mouse Lung Terminal Bronchiole Hyperplasia (Aiso et al., 2014) vs Lung GST Dose
Response
Dose
0
0.02
0.04
0.06
0.08
0.1
0.12
0.14
0.16
0.18
0.2
0
200
400
600
800
1000
Frequentist Gamma Estimated Probability
Frequentist Log-Logistic Estimated Probability
Frequentist Multistage Degree 3 Estimated Probability
Frequentist Multistage Degree 2 Estimated Probability
Frequentist Multistage Degree 1 Estimated Probability
Frequentist Weibull Estimated Probability
Frequentist Dichotomous Hill Estimated Probability
Frequentist Logistic Estimated Probability
Frequentist Log-Probit Estimated Probability
Frequentist Probit Estimated Probability

Selected, Full Model Suite - Multistage 3 Restricted; Extra Risk, BMR = 0.1

User Input

Info	
Model	Multistage degree 3 v1.0
Dataset Name	Female Mouse Lung Terminal Bronchiole Hyperplasia (Aiso et al., 2014)
Formula	P[dose] = g + (1-g)*[1-exp(-b1*dose^1-b2*dose^2 - ...)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Lung GST Dose
Independent Variable	[Tumor Incidence]
Total # of Observation	4

Model Results

Benchmark Dose	
BMD	648.4247437
BMDL	411.2842164
BMDU	1045.455128
AIC	92.32309959
P-value	0.40257905
D.O.F.	2
Chi^2	1.819727605
Slope Factor	0.000243141

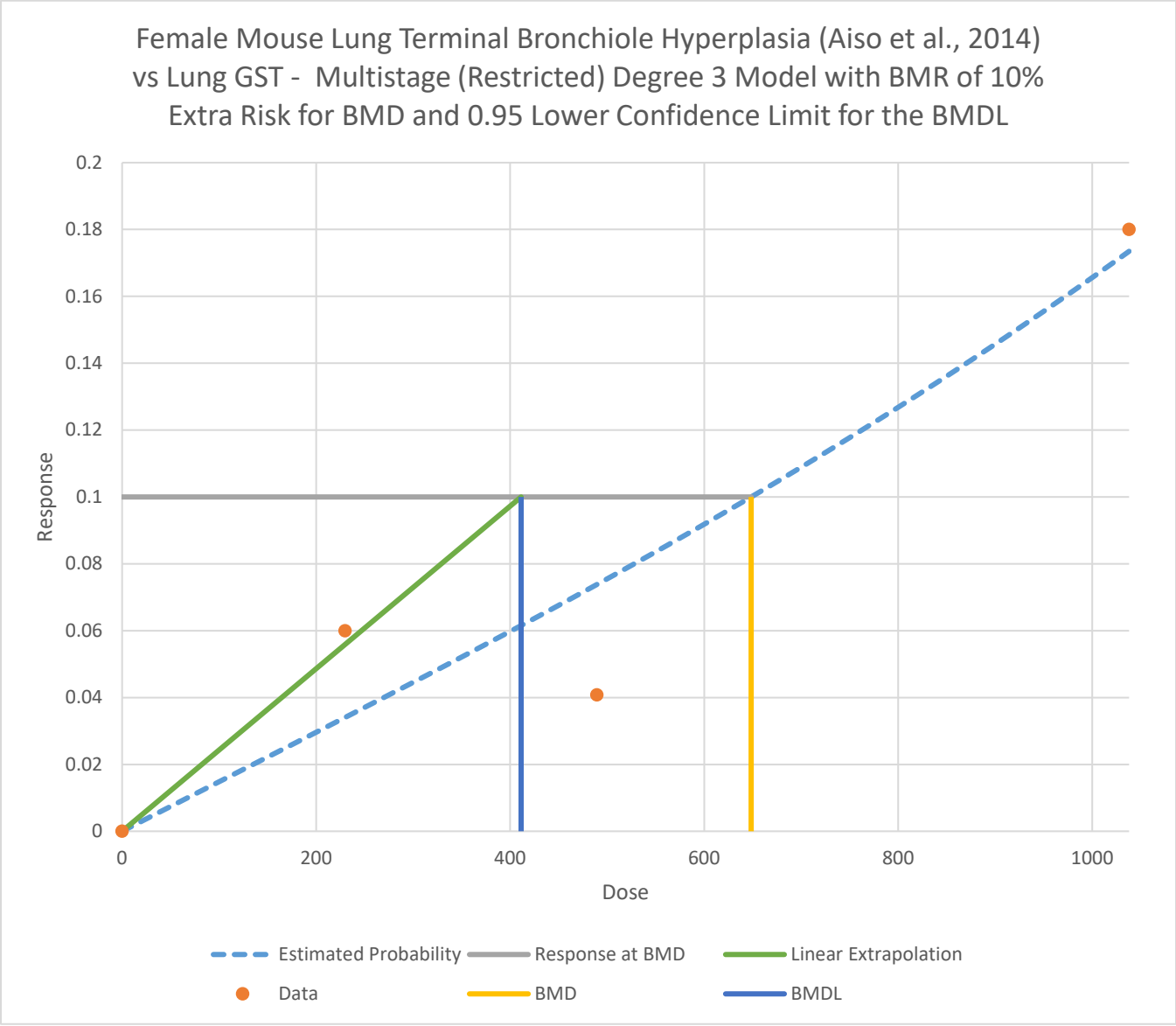
Model Parameters	
# of Parameters	3
Variable	Estimate
Background (g)	1.523E-08
Beta1	0.000149005
Beta2	0
Beta3	3.20643E-11

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	7.61499E-07	0	50	-0.000873
229.8	0.034037766	1.701888321	3	50	1.0124334
489.3	0.073799454	3.616173253	2	49	-0.883102
1038	0.173477235	8.673861756	9	50	0.1218058

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	Full Model	-43.27401353	0	-	-
Fitted Model	Fitted Model	-44.16154979	2	1.77507252	2
Reduced Model	Reduced Model	-50.65502987	1	14.7620327	3


Female Mouse Lung Terminal Bronchiole Hyperplasia (Aiso et al., 2014) vs Lung GST - Multistage (Restricted) Degree 3 Model with BMR of 10% Extra Risk for BMD and 0.95 Lower Confidence Limit for the BMDL
Response
0.2
0.18
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
0
200
400
600
800
1000
Dose
Estimated Probability
Response at BMD
Linear Extrapolation
Data
BMD
BMDL

9. BMD Modeling for NTP (1986) Male Mice

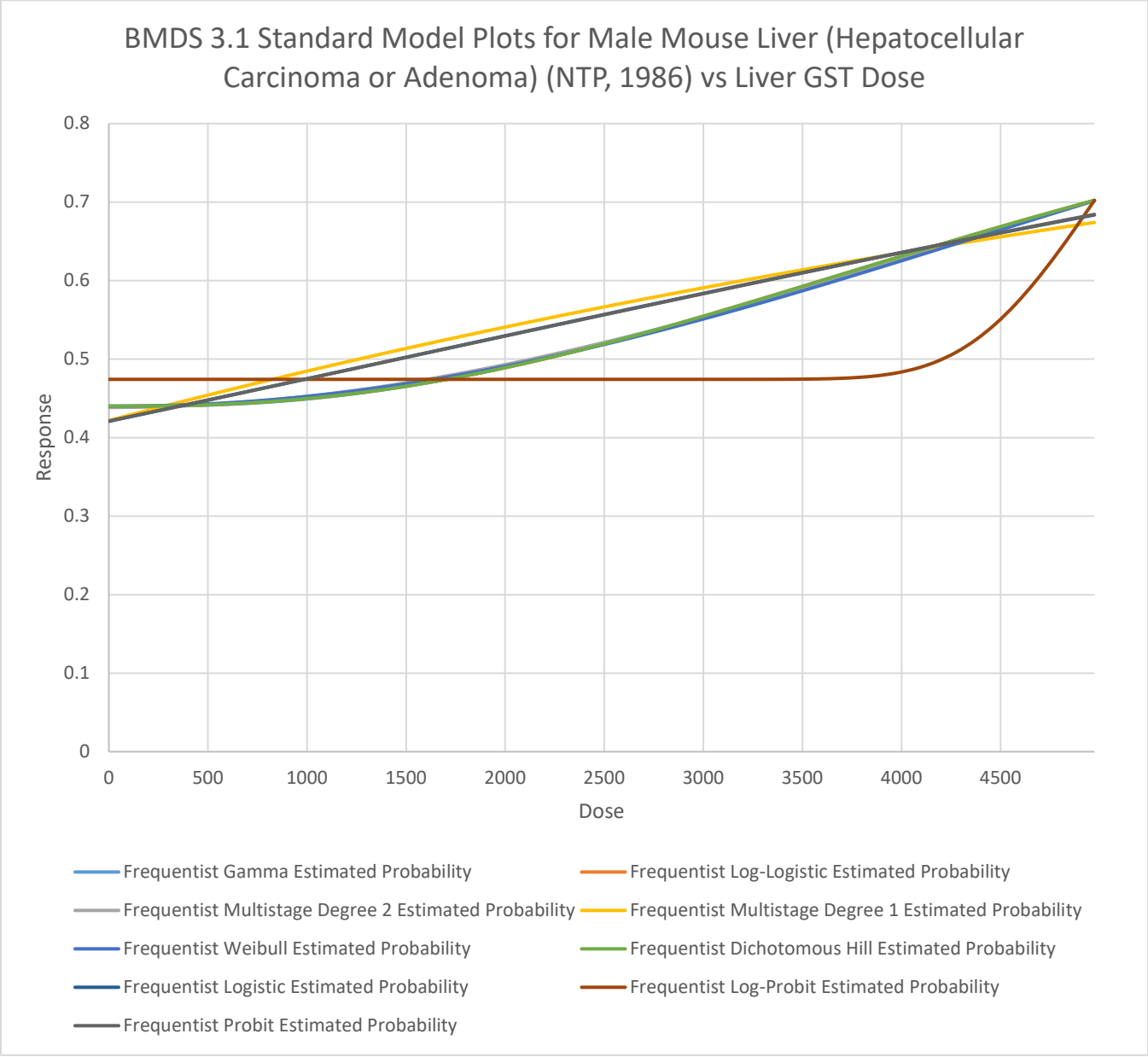
9.1. Liver (Hepatocellular Carcinoma or Adenoma)

Liver GST dose	[N]	[Incidence]
0	50	22
2364.7	47	24
4973.5	47	33

Summary of BMDS 3.1 Modeling Results for Male Mouse Liver (Hepatocellular Carcinoma or Adenoma) (NTP, 1986)

Standard Models	Restriction***	10% Extra Risk		P Value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL				
Gamma	Restricted	2119.2	577.84	NA	196.97831	Questionable	BMDL 3x lower than lowest non-zero dose d.f.=0 (Goodness of fit cannot be calculated)
Log-Logistic	Restricted	2123.4	448.45	NA	196.97831	Questionable	BMDL 3x lower than lowest non-zero dose d.f.=0 (Goodness of fit cannot be calculated)
Multistage Degree 1 (Quantal Linear)*	Restricted	914.22	544.51	0.40410	195.67397	Selected, Multistage	Multistage-cancer guidance (EPA, 2014) BMDL 3x lower than lowest non-zero dose
Weibull	Restricted	2099.0	577.83	NA	196.97831	Questionable	BMDL 3x lower than lowest non-zero dose d.f.=0 (Goodness of fit cannot be calculated)
Dichotomous Hill	Unrestricted	2123.4	25.248	65535	198.97831	Questionable	BMD/BMDL ratio > 20 BMD/BMDL ratio > 5 BMDL 10x lower than lowest non-zero dose
Logistic	NA	1069.2	733.73	0.50852	195.41475	Viable - Alternate	BMDL 3x lower than lowest non-zero dose
Log-Probit	Unrestricted	4386.7	0.2925	NA	197.46348	Questionable	BMD/BMDL ratio > 20 BMD/BMDL ratio > 5 BMDL 10x lower than lowest non-zero dose d.f.=0 (Goodness of fit cannot be calculated)
Probit**	NA	1072.4	740.82	0.51449	195.40253	Selected, Full Model Suite	Lowest AIC BMDL 3x lower than lowest non-zero dose
Non-Standard Models							
Dichotomous Hill	Restricted	2123.9	448.45	65535	198.97831	Viable - Alternate	BMDL 3x lower than lowest non-zero dose
Log-Probit	Restricted	4222.0	985.19	NA	197.46348	Questionable	d.f.=0 (Goodness of fit cannot be calculated)
Gamma	Unrestricted	2123.4	25.248	65535	198.97831	Questionable	BMD/BMDL ratio > 20 BMD/BMDL ratio > 5 BMDL 10x lower than lowest non-zero dose
Log-Logistic	Unrestricted	2121.9	9.4046	NA	196.97831	Questionable	BMD/BMDL ratio > 20 BMD/BMDL ratio > 5 BMDL 10x lower than lowest non-zero dose d.f.=0 (Goodness of fit cannot be calculated)
Multistage Degree 3	Unrestricted	2123.4	25.248	NA	196.97831	Questionable	BMD/BMDL ratio > 20 BMD/BMDL ratio > 5 BMDL 10x lower than lowest non-zero dose d.f=0 (Goodness of fit cannot be calculated)
Multistage Degree 2	Unrestricted	2105.0	436.56	NA	196.97831	Questionable	BMDL 3x lower than lowest non-zero dose d.f.=0 (Goodness of fit cannot be calculated)
Multistage Degree 1	Unrestricted	914.24	544.51	0.40410	195.67397	Viable - Recommended	BMDL 3x lower than lowest non-zero dose Lowest AIC
Weibull	Unrestricted	2099.8	16.210	NA	196.97831	Questionable	BMD/BMDL ratio > 20 BMD/BMDL ratio > 5 BMDL 10x lower than lowest non-zero dose d.f.=0 (Goodness of fit cannot be calculated)

*Selected, Multistage (Yellow); residuals for doses 0, 2364.7, and 4973.5 were 0.261074977, -0.677561922 and 0.410919726, respectively.
*Selected, Full Model Suite (Green); residuals for doses 0, 2364.7, and 4973.5 were 0.261074977, -0.677561922 and 0.410919726, respectively.
***Restrictions defined in the BMDS 3.1 User Guide; CF = Computation failed; NA = Not Applicable


BMDS 3.1 Standard Model Plots for Male Mouse Liver (Hepatocellular Carcinoma or Adenoma) (NTP, 1986) vs Liver GST Dose
Response
Dose
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0
500
1000
1500
2000
2500
3000
3500
4000
4500
Frequentist Gamma Estimated Probability
Frequentist Log-Logistic Estimated Probability
Frequentist Multistage Degree 2 Estimated Probability
Frequentist Multistage Degree 1 Estimated Probability
Frequentist Weibull Estimated Probability
Frequentist Dichotomous Hill Estimated Probability
Frequentist Logistic Estimated Probability
Frequentist Log-Probit Estimated Probability
Frequentist Probit Estimated Probability

Selected, Multistage - Multistage 1 Restricted; Extra Risk, BMR = 0.1

User Input

Info	
Model	Multistage degree 1 v1.0
Dataset Name	Male Mouse Liver (Hepatocellular Carcinoma or Adenoma) (NTP, 1986)
Formula	P[dose] = g + (1-g)*[1-exp(-b1*dose^1)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Liver GST Dose
Independent Variable	[Tumor Incidence]
Total # of Observation	4

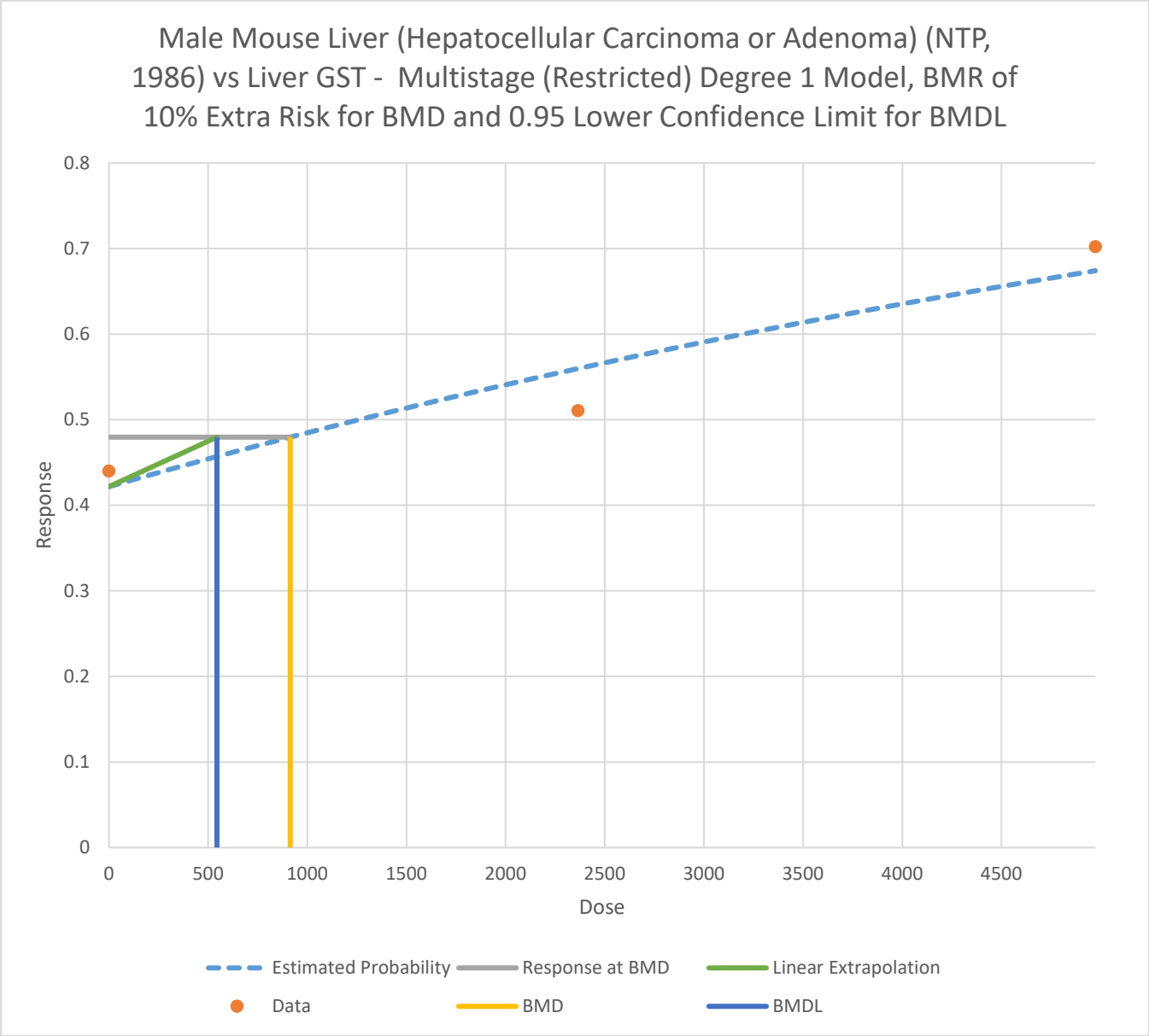
Model Results

Benchmark Dose	
BMD	914.2177942
BMDL	544.5121572
BMDU	2570.728336
AIC	195.673967
P-value	0.404095465
D.O.F.	1
Chi^2	0.696105323
Slope Factor	0.000183651

Model Parameters	
# of Parameters	2
Variable	Estimate
Background (g)	0.421766589
Beta1	0.000115247

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0.421766589	0.421766589	0.421766589	0.421766589	0.421766589	0.421766589
0.000115247	0.000115247	0.000115247	0.000115247	0.000115247	0.000115247
0.421766589	0.421766589	0.421766589	0.421766589	0.421766589	0.421766589

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-95.48915354	0	-	-	-
Fitted Model	-95.83698349	2	0.69565991	1	0.4042459
Reduced Model	-99.13156225	1	7.28481743	2	0.0261892


Male Mouse Liver (Hepatocellular Carcinoma or Adenoma) (NTP, 1986) vs Liver GST - Multistage (Restricted) Degree 1 Model, BMR of 10% Extra Risk for BMD and 0.95 Lower Confidence Limit for BMDL
Response
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
500
1000
1500
2000
2500
3000
3500
4000
4500
Dose
Estimated Probability
Response at BMD
Linear Extrapolation
Data
BMD
BMDL

Selected, Full Model Suite - Probit - Extra Risk, BMR = 0.1

User Input

Info	
Model	Log-Probit v1.0
Dataset Name	Male Mouse Liver (Hepatocellular Carcinoma or Adenoma) (NTP, 1986)
Formula	P[dose] = CumNorm(a+b*Dose)

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Liver GST Dose
Independent Variable	[Tumor Incidence]
Total # of Observation	4

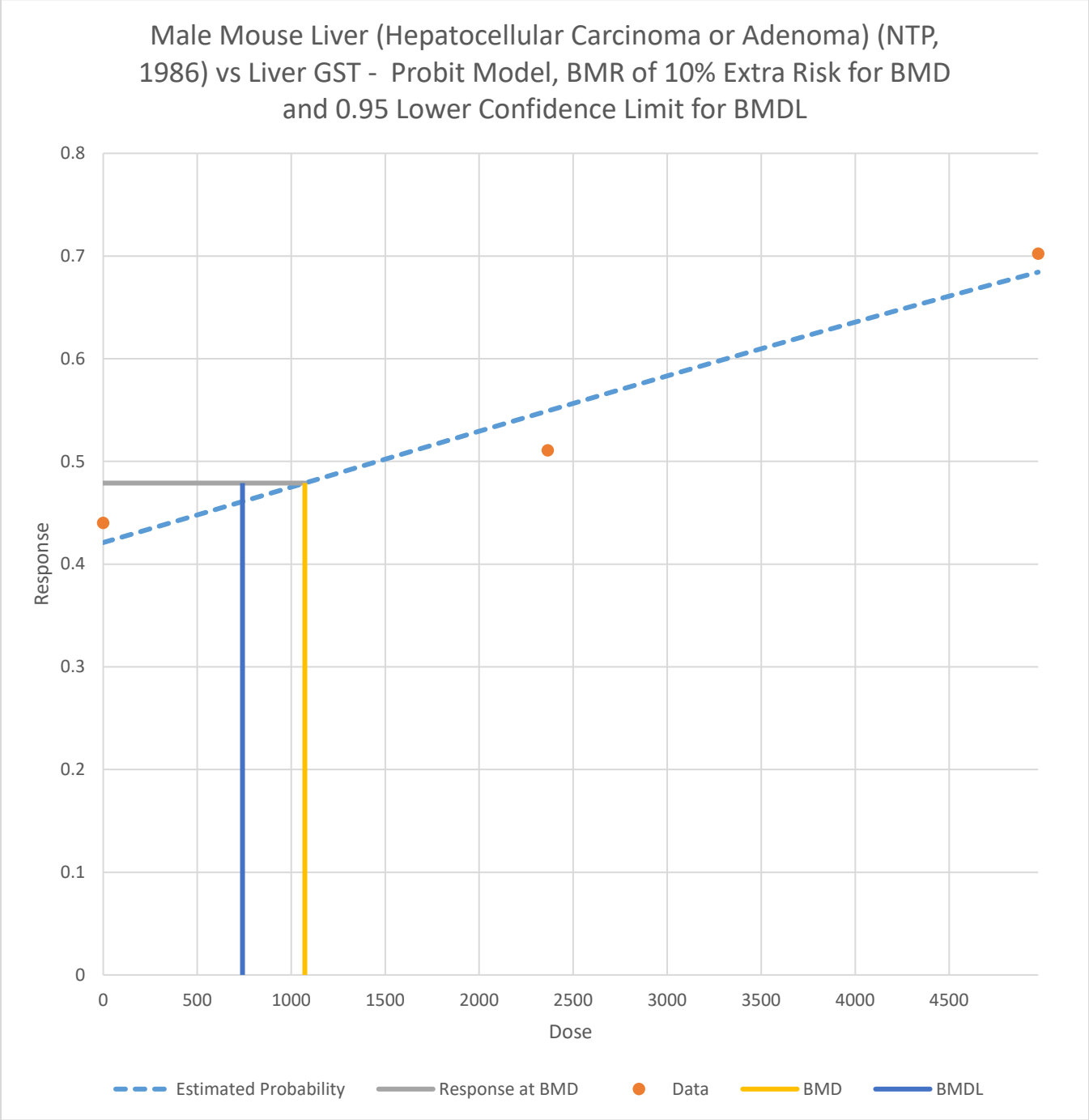
Model Results

Benchmark Dose	
BMD	1072.373626
BMDL	740.8220139
BMDU	2495.283352
AIC	195.4025344
P-value	0.514485175
D.O.F.	1
Chi^2	0.424934224

Model Parameters	
# of Parameters	2
Variable	Estimate
a	-0.199206894
b	0.000136525

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.421050453	21.05252267	22	50	0.2713916
2364.7	0.549197834	25.81229819	24	47	-0.53128
4973.5	0.684316129	32.16285808	33	47	0.2627215

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	Full Model	-95.48915354	0	-	-
Fitted Model	Fitted Model	-95.70126721	2	0.42422735	1
Reduced Model	Reduced Model	-99.13156225	1	7.28481743	2


Male Mouse Liver (Hepatocellular Carcinoma or Adenoma) (NTP, 1986) vs Liver GST - Probit Model, BMR of 10% Extra Risk for BMD and 0.95 Lower Confidence Limit for BMDL
Response
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
500
1000
1500
2000
2500
3000
3500
4000
4500
Dose
Estimated Probability
Response at BMD
Data
BMD
BMDL

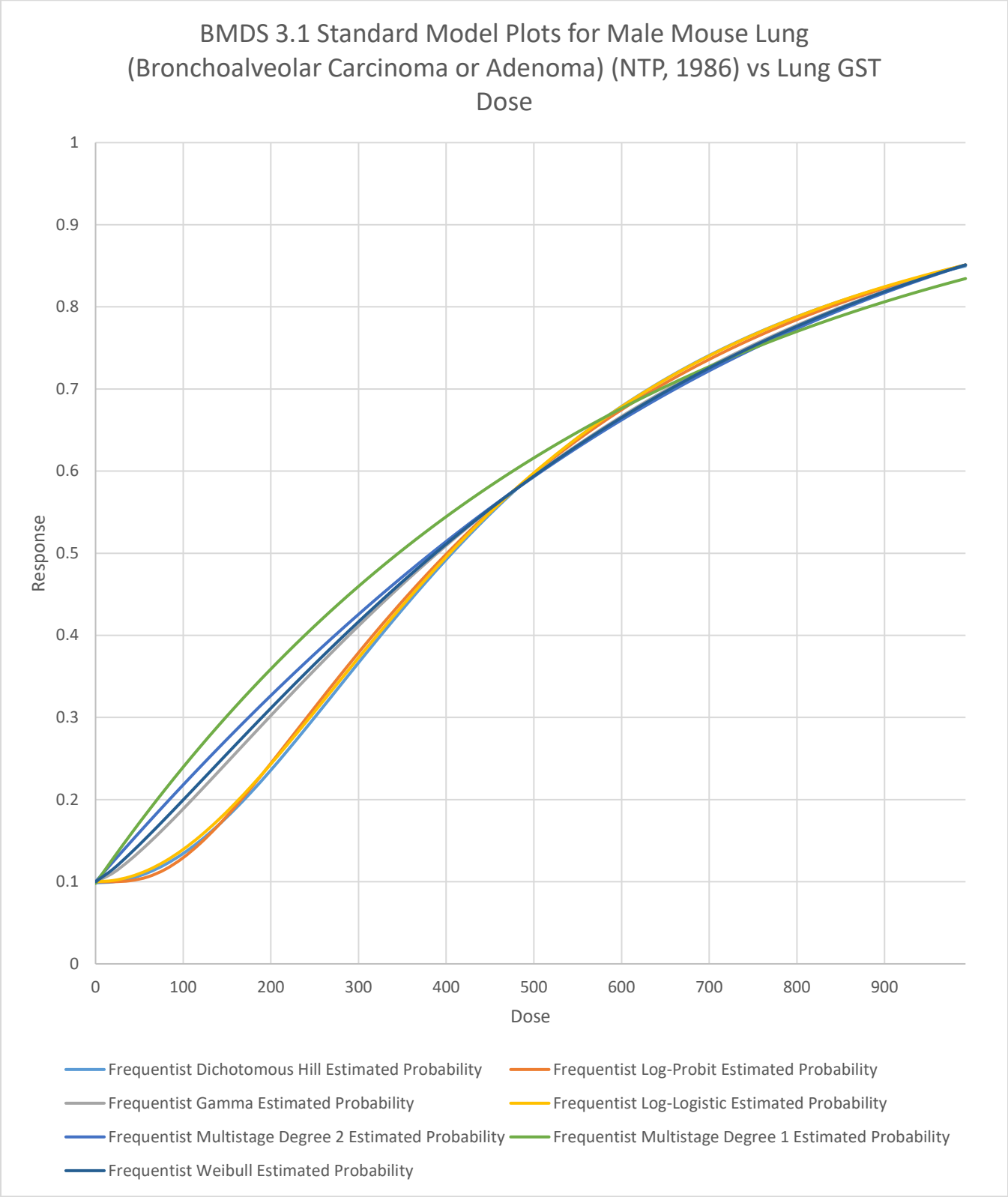
9.2. Lung (Bronchoalveolar Carcinoma or Adenoma)

Lung GST dose	[N]	[Incidence]
0	50	5
475.1	47	27
992.4	47	40

Summary of BMDS 3.1 Modeling Results for Male Mouse Lung (NTP, 1986)

Standard Models	Restriction**	10% Extra Risk		P Value	AIC	BMDS Recommends	BMDS Recommendation Notes
		BMD	BMDL				
Gamma	Restricted	101.13	49.110	NA	142.17847	Questionable	BMD 3x lower than lowest non-zero dose BMDL 3x lower than lowest non-zero dose d.f.=0 (Goodness of fit cannot be calculated)
Log-Logistic	Restricted	154.16	29.332	NA	142.17847	Questionable	BMD/BMDL ratio > 5 BMD 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose d.f.=0 (Goodness of fit cannot be calculated)
Multistage Degree 1 (Quantal Linear)*	Restricted	61.674	48.646	0.64077	140.39807	Selected, Multistage and Full Model Suite	Lowest AIC BMD 3x lower than lowest non-zero dose BMDL 3x lower than lowest non-zero dose Multistage-cancer guidance (EPA, 2014);
Weibull	Restricted	91.325	49.103	NA	142.17847	Questionable	BMD 3x lower than lowest non-zero dose BMDL 3x lower than lowest non-zero dose d.f.=0 (Goodness of fit cannot be calculated)
Dichotomous Hill	Unrestricted	154.15	25.047	65535	144.17847	Questionable	BMD/BMDL ratio > 5 BMD 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose
Logistic	NA	152.67	121.58	0.15323	142.22560	Viable - Alternate	BMD 3x lower than lowest non-zero dose BMDL 3x lower than lowest non-zero dose
Log-Probit**	Unrestricted	158.14	26.644	NA	142.17847	Questionable	BMD/BMDL ratio > 5 BMD 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose d.f.=0 (Goodness of fit cannot be calculated)
Probit	NA	146.25	119.58	0.14797	142.2822	Viable - Alternate	BMD 3x lower than lowest non-zero dose BMDL 3x lower than lowest non-zero dose
Non-Standard Models							
Dichotomous Hill	Restricted	159.31	29.331	65535	144.17847	Questionable	BMD/BMDL ratio > 5 BMDL 10x lower than lowest non-zero dose
Log-Probit	Restricted	158.17	90.029	NA	142.17847	Questionable	BMD 3x lower than lowest non-zero dose BMDL 3x lower than lowest non-zero dose d.f.=0 (Goodness of fit test cannot be calculated)
Gamma	Unrestricted	101.15	2.3408	NA	142.17847	Questionable	BMD/BMDL ratio > 20 BMD/BMDL ratio > 5 BMD 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose d.f.=0 (Goodness of fit test cannot be calculated)
Log-Logistic	Unrestricted	154.16	25.049	NA	142.17847	Questionable	BMD/BMDL ratio > 5 BMD 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose d.f.=0 (Goodness of fit test cannot be calculated)
Multistage Degree 2	Unrestricted	75.555	39.224	NA	142.17847	Questionable	BMD 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose d.f.=0 (Goodness of fit test cannot be calculated)
Multistage Degree 1	Unrestricted	61.674	48.647	0.64077	140.39807	Viable - Alternate	BMD 3x lower than lowest non-zero dose BMDL 3x lower than lowest non-zero dose Lowest AIC
Weibull	Unrestricted	91.325	7.3553	NA	142.17847	Questionable	BMD/BMDL ratio > 5 BMD 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose d.f.=0 (Goodness of fit test cannot be calculated)

*Selected, Multistage & Selected, Full Model Suite (Green); residuals for doses 0, 475.1 and 992.4 were 0.047491478, -0.348706833 and 0.306410218, respectively.
**Restrictions defined in the BMDS 3.1 User Guide; CF = Computation failed; NA = Not Applicable


BMDS 3.1 Standard Model Plots for Male Mouse Lung (Bronchoalveolar Carcinoma or Adenoma) (NTP, 1986) vs Lung GST Dose
Response
Dose
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
100
200
300
400
500
600
700
800
900
Frequentist Dichotomous Hill Estimated Probability
Frequentist Log-Probit Estimated Probability
Frequentist Gamma Estimated Probability
Frequentist Log-Logistic Estimated Probability
Frequentist Multistage Degree 2 Estimated Probability
Frequentist Multistage Degree 1 Estimated Probability
Frequentist Weibull Estimated Probability

Selected, Multistage and Selected, Full Model Suite - Multistage 1 Restricted; Extra Risk, BMR = 0.1

User Input

Info	
Model	Multistage degree 1 v1.0
Dataset Name	Male Mouse Lung (Bronchoalveolar Carcinoma or Adenoma) (NTP, 1986)
Formula	P[dose] = g + (1-g)*[1-exp(-b1*dose^1)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Lung GST Dose
Independent Variable	[Tumor Incidence]
Total # of Observation	4

Model Results

Benchmark Dose	
BMD	61.67444792
BMDL	48.64640298
BMDU	80.22384093
AIC	140.3980736
P-value	0.640768023
D.O.F.	1
Chi^2	0.217739118
Slope Factor	0.00205565

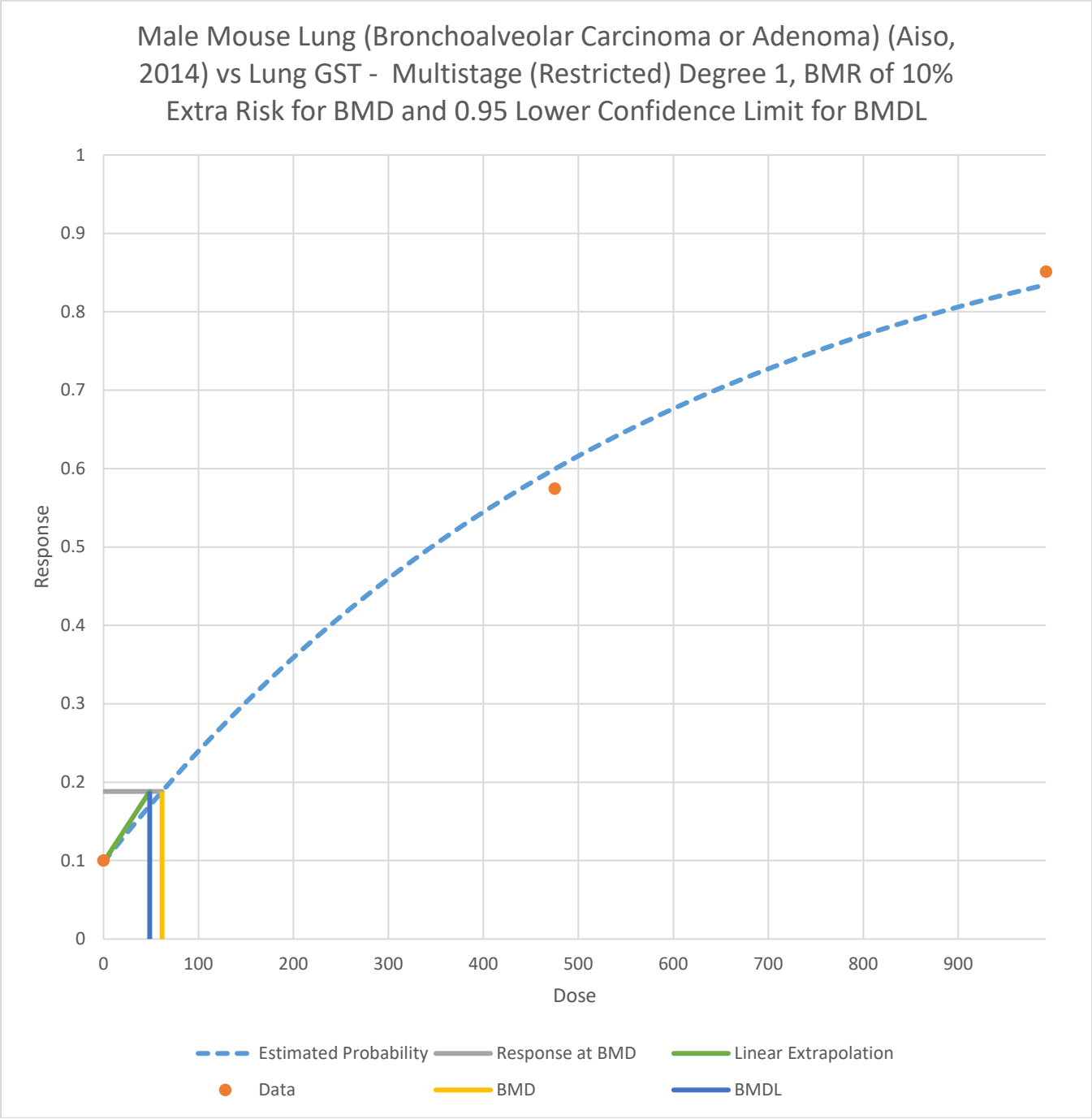
Model Parameters	
# of Parameters	2
Variable	Estimate
Background (g)	0.098003115
Beta1	0.001708333

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.098003115	4.90015573	5	50	0.0474915
475.1	0.599392599	28.17145216	27	47	-0.348707
992.4	0.83445202	39.21924495	40	47	0.3064102

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-68.08923317	0	-	-	-
Fitted Model	-68.19903682	2	0.21960731	1	0.6393393
Reduced Model	-99.813194	1	63.4479217	2	<0.0001


Male Mouse Lung (Bronchoalveolar Carcinoma or Adenoma) (Aiso, 2014) vs Lung GST - Multistage (Restricted) Degree 1, BMR of 10% Extra Risk for BMD and 0.95 Lower Confidence Limit for BMDL
Response
Dose
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
100
200
300
400
500
600
700
800
900
Estimated Probability
Response at BMD
Linear Extrapolation
Data
BMD
BMDL

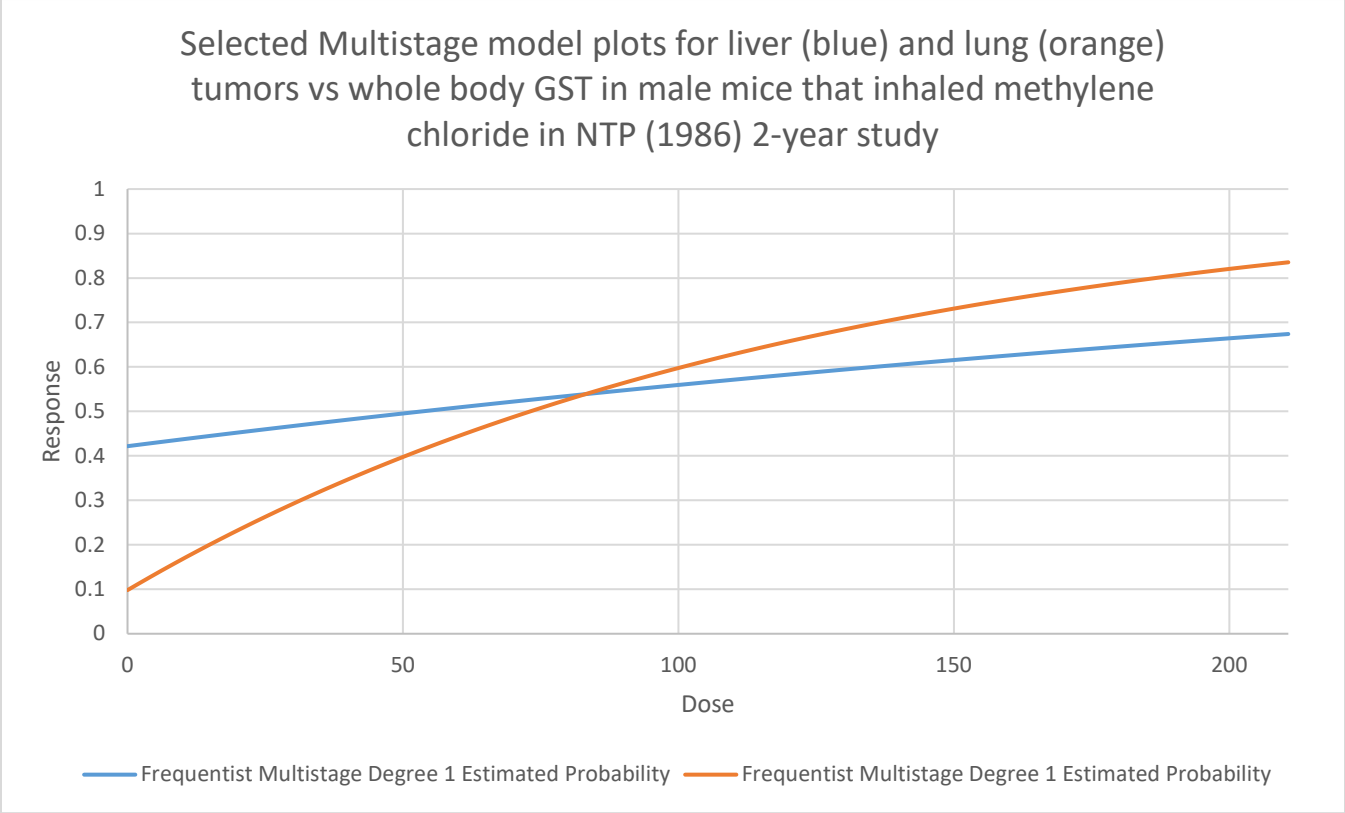
9.3. Liver or Lung Tumor

Male Mouse Liver (Hepatocellular Carcinoma or Adenoma) (NTP, 1986)		
Whole body GST dose	[N]	[Incidence]
0	50	22
100.2	47	24
210.7	47	33
Male Mouse Lung (Bronchoalveolar Carcinoma or Adenoma) (NTP, 1986)		
Whole body GST dose	[N]	[Incidence]
0	50	5
100.2	47	27
210.7	47	40

Summary of BMDS 3.1 Multi-tumor (MS_Combo) Modeling Results for Male Mouse Liver (Hepatocellular Carcinoma or Adenoma) and Male Mouse Lung (Bronchoalveolar Carcinoma or Adenoma) (NTP, 1986) vs Whole Body GST Dose

Models*	Dataset	10% Extra Risk		Slope Factor	P Value	AIC	BMDS Recommendation Notes
		BMD	BMDL				
Multi-tumor (MS_Combo)	Combined Risk	9.764454	7.752931	4.66e-2	NA	NA	NA
Multistage Degree 1	Liver Tumor	38.73476	23.06951	1.93e-3	0.403940	195.6744	Multistage-cancer guidance (EPA, 2014) BMDL 3x lower than lowest non-zero dose
Multistage Degree 1	Lung Tumor	13.05575	10.29661	9.71e-3	0.656862	140.3774	Multistage-cancer guidance (EPA, 2014) BMD 3x lower than lowest non-zero dose BMDL 3x lower than lowest non-zero dose

*Multistage models used in the BMDS multi-tumor (MS_Combo) model are restricted as described in the BMDS 3.1 User Guide. The selected Multistage model was chosen from among all relevant model runs (see detailed results for all relevant Multistage degrees below) in accordance with EPA's technical guidance for choosing the appropriate stage of a multistage model for cancer modeling.



Multi-tumor (MS_Combo) Results for Male Mouse Liver (Hepatocellular Carcinoma or Adenoma) and Male Mouse Lung (Bronchoalveolar Carcinoma or Adenoma) (NTP, 1986) vs Whole Body GST Dose

User Input

Info	
Model	Multi-tumor v1.0

Model Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Results

Benchmark Dose	
BMD	9.764453771
BMDL	7.752931464
BMDU	12.85165147
Slope Factor	0.012898347
Combined Log-Likelihood	-164.0259348
Combined Log-Likelihood Constant	151.5180253

Male Mouse Liver (Hepatocellular Carcinoma or Adenoma) - Multistage 1 Restricted (Selected Multistage Degree); Extra Risk, BMR = 0.1

User Input

Info	
Model	Multistage degree 1 v1.0
Dataset Name	Male Mouse Liver (Hepatocellular Carcinoma or Adenoma) (NTP, 1986)
Formula	P[dose] = g + (1-g)*[1-exp(-b1*dose^1)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Whole Body GST
Independent Variable	[Tumor Incidence]
Total # of Observation	4

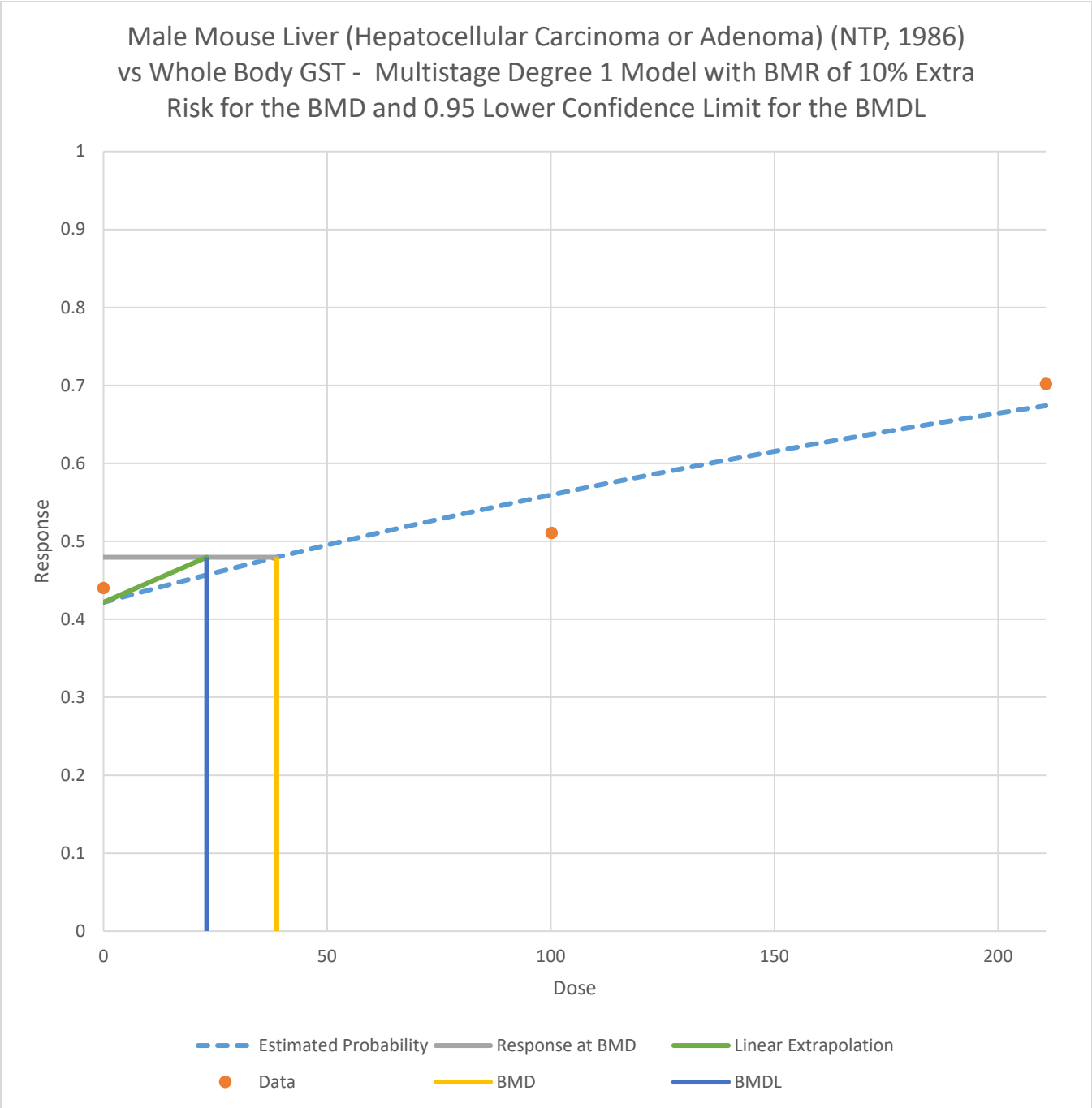
Model Results

Benchmark Dose	
BMD	38.7347609
BMDL	23.06950774
BMDU	108.9198654
AIC	195.6744286
P-value	0.403939629
D.O.F.	1
Chi^2	0.696567039
Slope Factor	0.004334726

Model Parameters	
# of Parameters	2
Variable	Estimate
Background (g)	0.421778128
Beta1	0.002720051

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.421778128	21.0889064	22	50	0.2609088
100.2	0.55972102	26.30688795	24	47	-0.677841
210.7	0.67401774	31.67883378	33	47	0.4111269

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-95.48915354	0	-	-	-
Fitted Model	-95.83721432	2	0.69612157	1	0.40409
Reduced Model	-99.13156225	1	7.28481743	2	0.0261892


Male Mouse Liver (Hepatocellular Carcinoma or Adenoma) (NTP, 1986) vs Whole Body GST - Multistage Degree 1 Model with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
Dose
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
50
100
150
200
Estimated Probability
Response at BMD
Linear Extrapolation
Data
BMD
BMDL

Male Mouse Lung (Bronchoalveolar Carcinoma or Adenoma) (NTP, 1986) - Multistage 1 Restricted (Selected Multistage Degree); Extra Risk, BMR = 0.1

User Input

Info	
Model	Multistage degree 1 v1.0
Dataset Name	Male Mouse Male Mouse Lung (Bronchoalveolar Carcinoma or Adenoma) (NTP, 1986)
Formula	P[dose] = g + (1-g)*[1-exp(-b1*dose^1)]

Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	Whole Body GST Dose
Independent Variable	[Tumor Incidence]
Total # of Observation	4

Model Results

Benchmark Dose	
BMD	13.05575031
BMDL	10.29661058
BMDU	16.98527498
AIC	140.377441
P-value	0.656861654
D.O.F.	1
Chi^2	0.197358299
Slope Factor	0.009711934

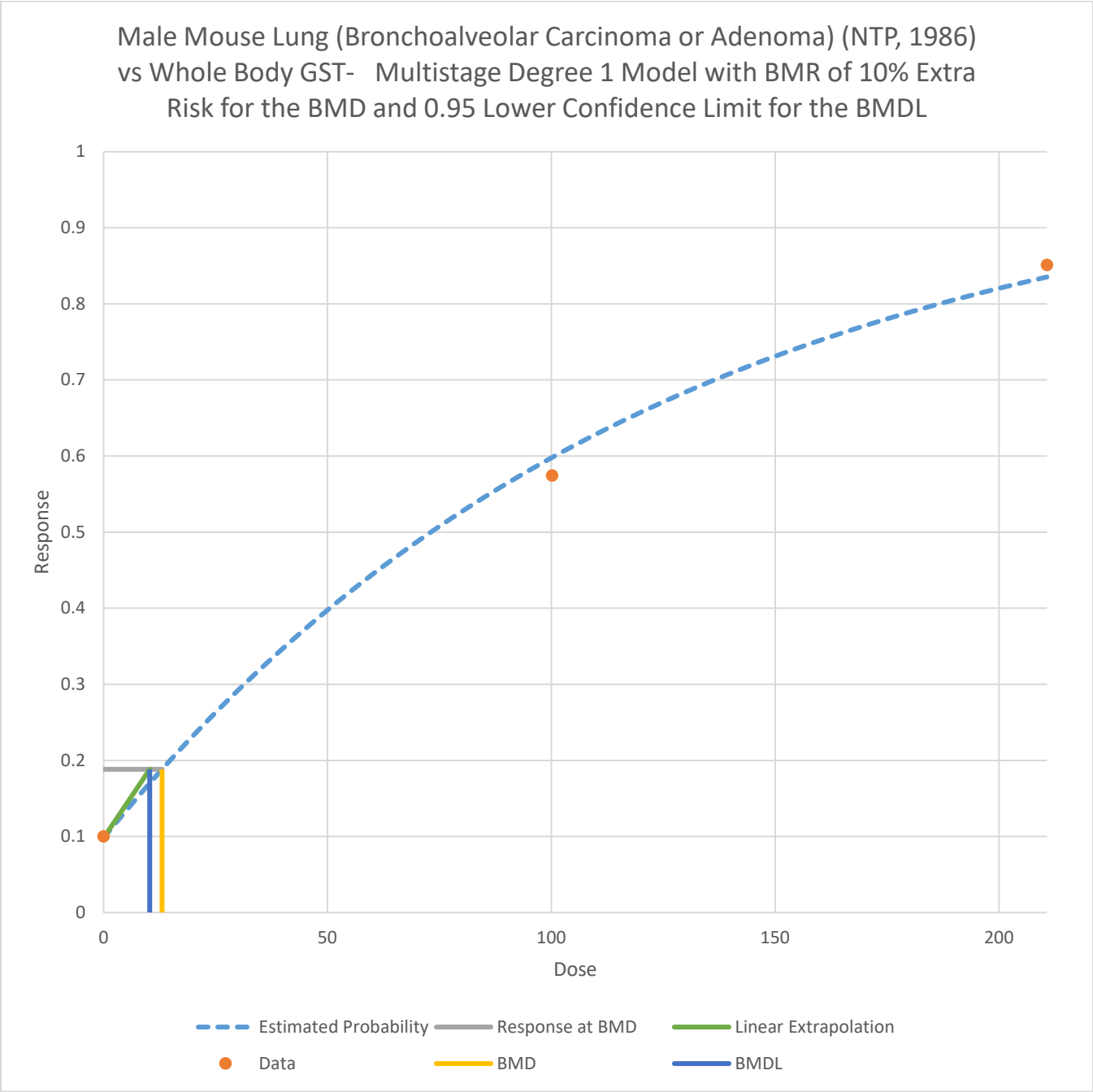
Model Parameters	
# of Parameters	2
Variable	Estimate
Background (g)	0.098079248
Beta1	0.008070047

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.098079248	4.90396242	5	50	0.045665
100.2	0.598218676	28.11627777	27	47	-0.332123
210.7	0.835293055	39.2587736	40	47	0.2914919

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-68.08923317	0	-	-	-
Fitted Model	-68.18872052	2	0.1989747	1	0.6555497
Reduced Model	-99.813194	1	63.4479217	2	<0.0001


Male Mouse Lung (Bronchoalveolar Carcinoma or Adenoma) (NTP, 1986) vs Whole Body GST- Multistage Degree 1 Model with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
Dose
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
50
100
150
200
Estimated Probability
Response at BMD
Linear Extrapolation
Data
BMD
BMDL

Appendix A: OCSPP Request to ORD NCEA

Request for ORD to

1) run PBPK and BMD models to estimate cancer risk for methylene chloride from Aiso et al (2014), and

2) run PBPK/dichotomous BMD models for the previous inhalation cancer study (NTP, 1986) with the endpoints from the IRIS assessment

- Use mouse, rat and human PBPK models described in the Toxicological Review of Methylene Chloride (EPA, 2011) to model dose-response (Andersen et al., 1991; Marino et al., 2006; David et al., 2006) with any additions of data/parameters used for the models as used in the IRIS Assessment.
- Use the same internal dose metrics as in the Toxicological Review of Methylene Chloride (EPA, 2011). NTP, 1986 and Aiso 2014 used the same exposure concentration groups (0, 1000, 2000, 4000 ppm in rats and mice) except NTP 1986 did not have a mice 1000 ppm group. The internal dose metrics were:
    - mammary gland tumors used AUC in slowly perfused tissue
    - liver tumors used mg DCM metabolized via GST pathway / L liver tissues / day
    - lung tumors used mg DCM metabolized vis GST pathway /L lung tissue /day and
    - lung and liver tissues used the sum of dichloromethane metabolized via the GST pathway in the lung plus the liver, normalized to total BW (i.e., [lung GST metabolism (mg/day) + liver GST metabolism (mg/d)]/kg BW). Units = mg dichloromethane metabolized via GST pathway in lung and liver/kg-day.
    - For non-cancer endpoints (foci), use the rat PBPK model that was used for the RfC in the 2011 IRIS assessment if that is relevant - this was the CYP only model (*or* if fits to the new non-cancer data from Aiso are warranted, please feel free to determine which model works best with the data).
- ***Aiso et al. (2014):*** See Table 1 for endpoints and incidence data and Appendix B for reasons certain endpoints were not chosen.
    - **CANCER**
      Endpoints chosen: Preference for positive trend test, significant pairwise differences from controls, clearest dose-response data of tumors evaluated
    - **NONCANCER** - Pre-Neoplastic Lesions – Foci and Hyperplasia
      Endpoints chosen: Preference for increasing d-r or d-r that may have plateaued and sig. pairwise comparisons. [no trend tests seem to be conducted for these lesions]
- ***NTP (1986):*** See Table 2 for endpoints and incidence data
    - **CANCER**
      Endpoints chosen: Same as IRIS Assessment
- Run all dichotomous models (including multistage) available with the BMDS (don't run Bayesian model averaging)
- Use 10% BMR – cancer and non-cancer
    - Justification: As stated in the 2011 IRIS assessment (and based on the 2012 BMD technical guidance) "A BMR of 10% was selected because, in the absence of information regarding the magnitude of change in a response that is thought to be minimally biologically significant, a BMR of 10% is generally recommended, as it provides a consistent basis of comparison across assessments."

- For both mice and rats for the cancer endpoints *and hyperplasia*, model cancer risk for the full population (including GST+/+, GST+/-, GST-/-). You can present the information also for GST +/+ only individuals.

Table 1: Tumor or Foci Incidence from Aiso et al., 2014

Concentration (ppm)		0	1000	2000	4000	0	1000	2000	4000	Ref.
Number of animals examined		50	50	50	50	50	50	50	50	
Rat[a]		**Males**				**Females**				
Tumors										
Subcutis	Combined: fibroma/fibrosarcoma	1	4	8	12	-	-	-	-	Table 2, p440
Mammary gland	Combined: Fibroadenoma/ adenoma [c]	2	2	3	8	-	-	-	-	
	Combined: fibroadenoma/ adenoma/ adenocarcinoma	3	2	3	8	7	9	10	14	
Non-Neoplastic Foci										
Acidophilic Cell Foci		-	-	-	-	3	8	14	23	Table 3, p442
Basophilic Cell Foci		-	-	-	-	18	37	40	36	
Mice[b]		**Males**				**Females**				
Tumors										
Lung	Combined: bronchiolar-alveolar adenoma/ bronchiolar-alveolar carcinoma	8	17	26	42	5	5	12	30	Table 5, p444
Liver	Combined: hepatocellular adenoma/hepatocellular carcinoma	15	20	25	29	2	8	9	30	
Hyperplasia										
Number of animals examined		50	50	50	50	50	50	49	50	Table 6, p445
Terminal bronchiole		0	1	5	13	0	3	2	9	

[a] For rats, the same concentrations are used in this study as the NTP study

[b] For mice, there is an extra concentration (1000 ppm) not used in the NTP study
[c] Males only were run because the dose-response fit might be better than the combined fibroadenoma/adenoma/adenocarcinoma even though preference was given to including adenocarcinomas, because all are considered adverse

Table 2: Male Mouse Tumor Incidence[a] from NTP, 1986 (Appendix G.2 in IRIS Assessment)

Concentration (ppm)		0	2000	4000
Number of Animals Examined		50	47	47
Lung	Bronchoalveolar carcinoma or adenoma	5	27	40
Liver	Hepatocellular carcinoma or adenoma	22	24	33

[a] Note that the 2011 IRIS assessment presented an IUR for combined lung and liver tumors

Appendix B: OCSPP Justification for Endpoints Not Chosen

The following are tumor types/endpoints for each species that showed positive trend tests but that were not chosen for modeling from Aiso et al., 2014 for various reasons (e.g., no clear dose-response when looking at incidences or no pairwise differences compared with controls for individual concentration levels). The species and tumors types or endpoints that were not modeled and associated reasons are as follows:
s

- **Rats**

  Liver (males)
  - Combined hepatocellular adenoma/carcinoma - Unclear dose-response relationship (incidences of 1, 0, 2 and 3 at 0, 1000, 2000 and 4000 ppm, respectively). These showed no statistically significant pairwise comparisons, and incidences were small.

  Uterus (females)
  - Endometrial stromal polyps - Unclear dose-response relationship (incidences of 8, 11, 6 and 9 at 0, 1000, 2000 and 4000 ppm, respectively) , no statistically significant pairwise comparisons
  - Combined: endometrial stromal sarcoma, leiomyosarcoma - no statistically significant pairwise comparisons, tumor incidence difficult to model (incidences of 0, 0, 0 and 3 at 0, 1000, 2000 and 4000 ppm, respectively)

  Spleen (females)
  - Mononuclear cell leukemia – no statistically significant pairwise comparison at the highest concentration and the dose-response relationship is not completely clear (incidences of 2, 4, 8 and 7 at 0, 1000, 2000 and 4000 ppm, respectively)
  - *However, given some association with leukemia in humans, future modeling efforts could include this tumor type.*

  Peritoneum (males)
  - Mesothelioma – no statistically significant pairwise comparisons, and the dose-response relationship is not completely clear (incidences of 3, 1, 0 and 7 at 0, 1000, 2000 and 4000 ppm, respectively)

  Subcutis (males)
  - Fibroma – not run because preference was given to modeling combined fibroma/fibrosarcoma, assuming benign tumors may lead to malignant tumors

  Mammary gland
  - Fibroadenoma (males/females) and combined fibroadenoma/adenoma (females) – not run because preference was given to modeling combined fibroadenoma/adenoma/adenocarcinoma because all were assumed to be relevant for cancer. Note; this was also run to compare the trend with the same combination of tumors from NTP (1986) as modeled in the IRIS assessment, which evaluated combined tumors; see also footnote to Table 1 of Appendix A in this document.

  Acidophilic and basophilic cell foci (males)

- Dose-response relationship not clear (22, 31, 33, 24 for acidophilic; 13, 36, 21, 18 for basophilic)

- **Mice**

Lung

- Bronchiolar-alveolar adenoma and bronchiolar-alveolar carcinoma (males/females) –dose response curves (separated by tumor type) not considered because it was assumed that benign tumors may lead to malignant tumors and therefore, combined tumors were considered more relevant; also didn't include adenosquamous carcinomas because incidence didn't differ when adding it to other tumor types for females and data were not available for males

Liver

- Hepatocellular adenoma and hepatocellular carcinoma (males/females) - dose response curves (separated by tumor type) not considered because it was assumed that benign tumors may lead to malignant tumors and the combined was therefore considered more relevant; also hepatoblastomas not added because incidence didn't differ when adding it to other tumor types for males and data were not available for females
- Hemangioma (males) – dose-response not clear and incidence smaller than other liver tumors
- Combined hemangioma/hemangiosarcoma (males/females) – no sig. pairwise comparisons, smaller incidence than other tumors in liver, females had less clear dose-response than for other tumors

Adrenal gland

- Pheochromocytoma (males) – no statistically significant pairwise comparisons and the dose-response relationship is not clear (incidences of 1, 0, 1 and 3 at 0, 1000, 2000 and 4000 ppm, respectively)

All site

- Hemangiomas (males) – The dose-response relationship is not as positive as other tumor types; *However, because there is a significant pairwise change at the highest dose, and the trend is significant at $p < 0.01$, EPA can consider running this later if needed.*

Hyperplasia

- Bronchiolar-alveolar, alveolar duct (males/females) – no statistical significant pairwise comparisons

Liver foci

- No statistically significant pairwise comparisons and generally no clear dose-response

Appendix C. Model Selection Considerations for POD Computation

The following approach is recommended for selecting the model(s) to use for computing the BMDL to serve as the POD for a specific dataset according to EPA Benchmark Dose Guidance (U.S. EPA, 2012a). Some of these decisions are best performed by or in collaboration with experts in the statistical procedures and potential pitfalls of this type of analysis.

1) Assess goodness-of-fit, using a value of $\alpha \geq 0.1$ to determine a critical value (or $\alpha = 0.05$ or $\alpha = 0.01$ if there is reason to use a specific model(s)) rather than fitting a suite of models.

2) Further reject models that apparently do not adequately describe the relevant low-dose portion of the dose-response relationship, which can be determined by examining residuals and graphs of the models and data.

3) Because the remaining models have met the recommended default statistical criteria for adequacy and visually fit the data, any of them theoretically could be used for determining the BMDL. Criteria 4-6 below, for selecting the BMDL from these remaining models, are necessarily somewhat arbitrary and are suggested as defaults.

4) If the BMDL estimates from the remaining models are sufficiently close (given the needs of the assessment) and reflect no particular influence of individual models, then the model with the lowest AIC may be used to calculate the BMDL for the POD. This criterion is intended to help arrive at a single BMDL value in an objective, reproducible manner. If two or more models share the lowest AIC, the simple average or geometric mean of the BMDLs with the lowest AIC may be used. Note that this is not the same as "model averaging," which involves weighing a fuller set of adequately fitting models. In addition, such an average has drawbacks, including the fact that it is not a 95% lower bound on the average BMD; it is just the average of the particular BMDLs under consideration (i.e., the average loses the statistical properties of the individual estimates).

5) If the BMDL estimates from the remaining models are not sufficiently close, some model dependence of the estimate can be assumed. Expert statistical judgment may help at this point to judge whether model uncertainty is too great to rely on some or all of the results. If the range of results is judged to be reasonable, there is no clear remaining biological or statistical basis on which to choose among them, and the lowest BMDL may be selected as a reasonable conservative estimate. Additional analysis and discussion might include consideration of additional models, the examination of the parameter values for the models used or an evaluation of the BMDs to determine if the same pattern exists as for the BMDLs. Discussion of the decision procedure should always be provided.

6) In some cases, modeling attempts may not yield useful results. When this occurs and the most biologically relevant effect is from a study considered adequate but not amenable to modeling, the NOAEL (or LOAEL) could be used as the POD. The modeling issues that arose should be discussed in the assessment, along with the impacts of any related data limitations on the results from the alternate NOAEL/LOAEL approach.

PART B:
Excerpt of BMD Modeling from 2011 IRIS Assessment (U.S. EPA, 2011)

F.2. INHALATION RfC: BMD MODELING OF LIVER LESION INCIDENCE DATA FOR RATS EXPOSED TO DICHLOROMETHANE VIA INHALATION FOR 2 YEARS (Nitschke et al., 1988a)

BMD and BMDL refer to the model-predicted dose (and its lower 95% confidence limit) associated with 10% extra risk for the incidence of hepatic vacuolation in female F344 rats exposed to dichloromethane via inhalation for 2 years (Nitschke et al., 1988a) (Table F-3).

Table F-3. Incidence data for liver lesions (hepatic vacuolation) and internal liver doses based on various metrics in female Sprague-Dawley rats exposed to dichloromethane via inhalation for 2 years (Nitschke et al., 1988a)

Sex	Exposure (ppm)	Liver lesion incidence[a]	Rat internal liver dose[b]			
			CYP	GST	GST and CYP	Parent AUC
Male	0	22/70 (31)	Not modeled because results from male rats were not provided for the 50 and 200 ppm groups			
	50	Not reported	Not modeled because results for middle two doses were not reported			
	200	Not reported				
	500	28/70 (40)				
Female (BW = 229 g)	0	41/70 (59%)	0	0	0	0
	50	42/70 (60%)	285.3	6.17	291.4	1.18
	200	41/70 (58%)	665.3	93.2	758.5	17.8
	500	53/70 (76%)[c]	782.1	360.0	1,142.1	68.6

[a]Number affected divided by total sample size.
[b]Internal doses were estimated using a rat PBPK model using exposures reported by study authors (50 ppm = 174 mg/m^3, 200 ppm = 695 mg/m^3, and 500 ppm = 1,737 mg/m^3) and are weighted-average daily values for 1 week of exposure at 6 hours/day, 5 days/week. CYP dose is in units of mg dichloromethane metabolized via CYP pathway/L tissue/day; GST dose is in units of mg dichloromethane metabolized via GST pathway/L tissue/day; GST and CYP dose is in units of mg dichloromethane metabolized via CYP and GST pathways/L tissue/day; and Parent AUC dose is in units of mg dichloromethane × hours)/L tissue.
[c]Significantly ($p < 0.05$) different from control with Fisher's exact test.

Source: Nitschke et al. (1988a).

All available dichotomous models in the BMDS (version 2.0) were fit to male and female rat internal tissue doses of dichloromethane metabolized by the CYP pathway and incidences for animals with these liver lesions observed at the time of death (Table F-4). The log-probit model was the best fitting model for the female incidence data based on lowest AIC value among models with adequate fit (U.S. EPA, 2000c). (If two or more models share the lowest AIC, $BMDL_{10}$ values from these models may be averaged to obtain a POD. However, this average is no longer a lower confidence bound that provides the stated coverage, and thus should be referred to only as an average of $BMDL_{10}$ values. U.S. EPA does not support averaging BMDLs in situations in which AIC values are similar, but not identical, because the level of stated

coverage is lost and no consensus exists regarding a specific cut-off between similar and dissimilar AIC values.)

Table F-4. BMD modeling results for incidence of liver lesions in female Sprague-Dawley rats exposed to dichloromethane by inhalation for 2 years, based on liver specific CYP metabolism metric (mg dichloromethane metabolized via CYP pathway/L liver tissue/day)

Model[a]	BMD_{10}	$BMDL_{10}$	χ^2 goodness of fit *p*-value	AIC
Gamma[a]	622.10	227.29	0.48	367.24
Logistic	278.31	152.41	0.14	369.77
Log-logistic[a]	706.50	506.84	0.94	365.90
Multistage (3)[a]	513.50	155.06	0.25	368.54
Probit	279.23	154.52	0.14	369.76
Log-probit[a,b]	**737.93**	**531.82**	**0.98**	**365.82**
Weibull[a]	715.15	494.87	0.95	365.88

[a]These models in U.S. EPA BMDS version 2.0 were fit to the rat dose-response data shown in Table 5-5 by using internal dose metrics calculated with the rat PBPK model. Gamma and Weibull models restrict power ≥1; log-logistic and log-probit models restrict to slope >1, multistage model restrict betas ≥0; lowest degree polynomial with an adequate fit reported (degree of polynomial in parentheses).
[b]Bolded model is the best-fitting model in the most sensitive sex (females), which is used in the RfC derivation.

Source: Nitschke et al. (1988a).

Log Probit Model, Female Rats (Nitschke et al., 1988a), CYP Metabolism (Rate of Production) Metric

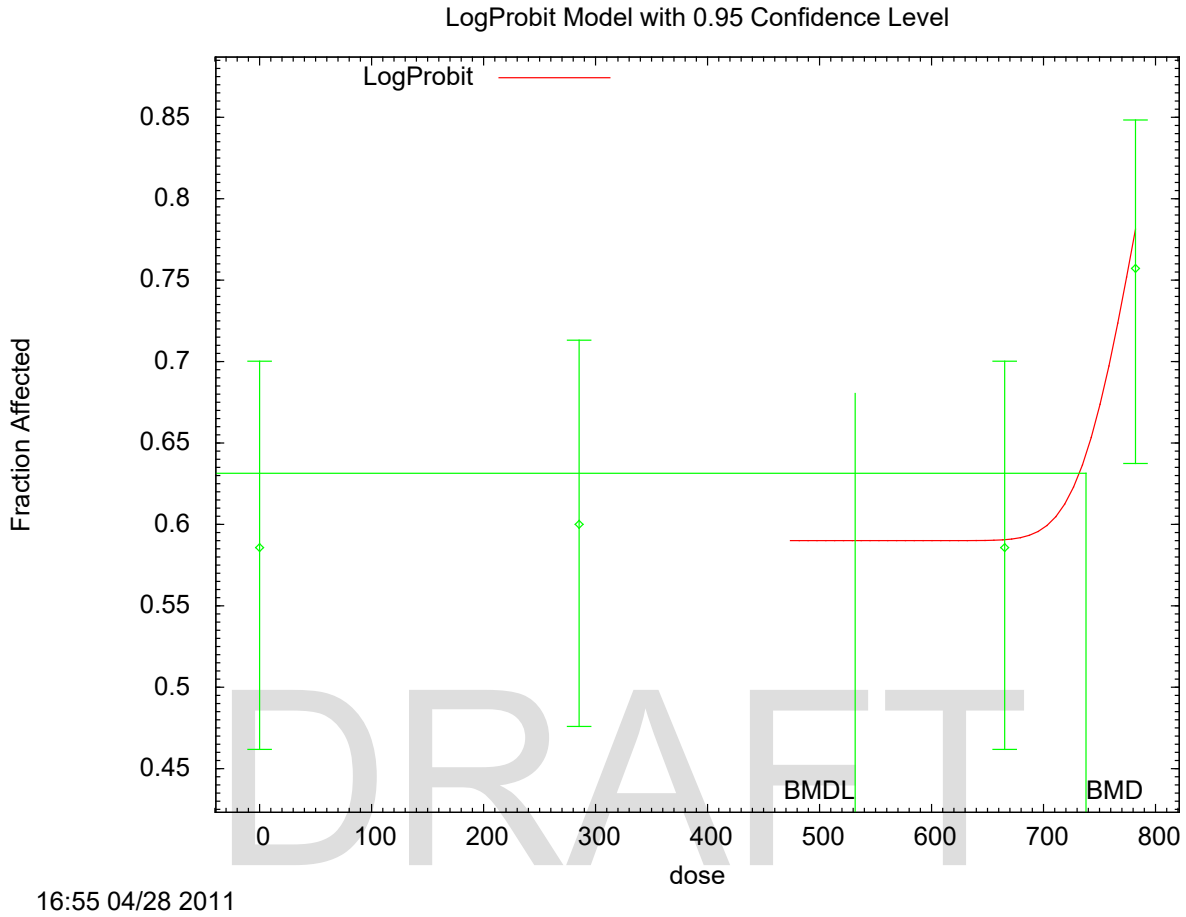


Figure F-2. Predicted (log-probit model) and observed incidence of noncancer liver lesions in female Sprague-Dawley rats inhaling dichloromethane for 2 years (Nitschke et al., 1988a).

```
=================================================================
        Probit Model. (Version: 3.1;  Date: 05/16/2008)
        Input Data File: C:\Usepa\BMDS21\Data\lnpNitschke_new_CYPSetting.(d)
        Gnuplot Plotting File:  C:\Usepa\BMDS21\Data\lnpNitschke_new_CYPSetting.plt
                                              Thu Apr 28 16:55:00 2011
 =================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

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

   where CumNorm(.) is the cumulative normal distribution function


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

Total number of observations = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
background = 0.585714
intercept = -7.71354
slope = 1

Asymptotic Correlation Matrix of Parameter Estimates

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

	background	intercept
background	1	-0.37
intercept	-0.37	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.590372	0.0339907	0.523751	0.656992
intercept	-120.151	0.346802	-120.831	-119.471
slope	18	NA		

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

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-180.889	4			
Fitted model	-180.909	2	0.0403892	2	0.98
Reduced model	-184.186	1	6.5937	3	0.08604

AIC: 365.818

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.5904	41.326	41.000	70	-0.079
285.3000	0.5904	41.326	42.000	70	0.164
665.3000	0.5907	41.350	41.000	70	-0.085
782.1000	0.7571	52.998	53.000	70	0.001

Chi^2 = 0.04 d.f. = 2 P-value = 0.9800

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 737.929

BMDL = 531.817