

User Manual for
“MSW” Multistage Weibull Time-to-Tumor Model

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Acknowledgements and Disclaimers

The “MSW” program described in this manual was developed by Battelle Memorial Institute¹ for the U.S. Environmental Protection Agency² (“EPA”) during 2006-2009 (under EPA contract EP-C-04-027). Minor changes may have been made by EPA subsequently (as noted in source code comments). The MSW program and associated documentation are available at EPA’s BMDS web site.³ MSW was compiled using the GNU GCC compiler provided with MinGW5.0.

The MSW program uses the C version (donlp2-intv) of the optimizer *donlp2*, copyrighted by Peter Spellucci.⁴ A condition of use specified by the author is: “The use of donlp2 must be acknowledged, in any publication which contains results obtained with it or parts of it. Citation of the authors name and netlib-source is suitable.”⁵

The MSW programs and related documentation were developed for use by EPA staff and contractors performing work for EPA, principally but not exclusively for conducting time-to-tumor analyses to support risk assessments under the IRIS program. These programs and related documentation are made available publicly to insure that the methods and calculations used for such analyses are transparent and reproducible.

The MSW program was developed using quality control and testing methods as described in the “Methodology” and “Testing” documents. This does not entirely preclude errors and “bugs.” Users are asked to report suspected problems using the BMDS web site.

This software was externally reviewed and approved for release in accordance with U.S. Environmental Protection Agency policy. Mention of trade names or commercial products does not constitute endorsement.

¹ The principal developer was Ken Shirakawa and the project leader was Bob Lordo; other Battelle staff made significant contributions.

² The Government has unlimited rights in the MSW software and this manual, *per* Federal Acquisition Regulation SubPart 27.4.

³ www.epa.gov/ncea/bmds

⁴ web page: http://www.mathematik.tu-darmstadt.de:8080/ags/ag8/Mitglieder/spellucci_de.html
email: spellucci@mathematik.tu-darmstadt.de

⁵ Another condition is that “The free use of donlp2 and parts of it is restricted for research purposes”; “commercial uses require permission and licensing from P. Spellucci.”

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User Manual for “MSW” Multistage Weibull Time-to-Tumor Model

Publications using solutions obtained with MSW should acknowledge both MSW and the optimizer donlp2.⁶

MSW Model

The multistage Weibull (MSW) time-to-tumor model describes the probability of a test subject exhibiting a specific carcinogenic response by observation time t , when the subject is exposed to a carcinogen at dosage rate d . As used here, "tumor" refers loosely to a cancer or a relevant precancerous lesion (e.g., an adenoma that can progress to a carcinoma). One specific cancer type (along with associated precancerous lesions) is modeled using the MSW model, specific to a particular tissue or organ in one sex and strain of animal (e.g., hepatocellular carcinomas and adenomas in female B6C3F1 mice). This model is usually applied to bioassay experiment data. Note that the model is usually called a “time-to-tumor” model but really models the time to an operationally defined event, herein a tumor-related response. Thus, users may find this program useful for modeling time to response with other toxicology data, if individual animal data are available and if the time to the censoring event (death or sacrifice) is not associated with the time to response (i.e., if censoring is uninformative).

Here we consider two forms of tumor-related response:

- Death of the subject, with death resulting from a cancer (“death from cancer”)
- Appearance of a carcinogenic lesion that is detectable by pathologic methods, generally upon examination following death. Time of appearance is primarily of interest when the tumor is considered non-fatal. “Appearance” is used as shorthand here for the time at which a carcinogenic lesion is first detectable by the methods used in the study providing the data, and should not be equated with onset of the carcinogenic process.

The MSW software module allows fitting two distinct multistage Weibull models corresponding to these two types of responses.

For some positive integer k , the k -stage Weibull model for fatal tumors characterizes the probability of death from the cancer in question. Under this model, the probability of death occurring prior to some specified observation time t upon exposure to a toxic agent at dose level d is given by the function

$$F(t, d | t_0, c, \beta_0, \beta_1, \dots, \beta_k) = 1 - \exp \left\{ - (t - t_0)^c \sum_{i=0}^k \beta_i d^i \right\} \quad (1)$$

⁶ An example acknowledgement: “These solutions were obtained with the use of donlp2-intv, copyright by P. Spellucci, and the MSW software distributed by the U.S. Environmental Protection Agency <here, cite the source you obtained it from>.”

where $c, t_0, \beta_0, \beta_1, \dots, \beta_k$ are model parameters.

The *k-stage Weibull model for non-fatal tumors* characterizes the probability of appearance of a detectable tumor. Under this model, the probability of observing the tumor prior to some specified observation time t upon exposure to a toxin at dose level d is given by the function

$$G(t, d | c, \beta_0, \beta_1, \dots, \beta_k) = 1 - \exp \left\{ -t^c \sum_{i=0}^k \beta_i d^i \right\} \quad (2)$$

Currently, the MSW model restricts the number of stages k to a maximum of 6. The model parameters satisfy the restrictions $c \geq 1$, $t > t_0 \geq 0$, and $\beta_i \geq 0$, $i = 0, 1, \dots, k$. The requirement for non-negative coefficients β_j follows the accepted practice of requiring a monotonically increasing dose-response function.

Modeling Non-Fatal vs. Fatal Tumors

The same executable module and data file structure serve for both models. The model that will be fitted by MSW depends on the type of data and whether user sets parameter t_0 equal to zero. The model for fatal tumors is fitted if there are any observations with context “F”⁷, otherwise the model for non-fatal tumors is fitted. However, certain options must be selected correctly by the user. Correct use and interpretation depends critically upon the user's knowledge of whether the cancer is fatal or non-fatal (see the section “Difficult Datasets”, below, for further discussion).

The MSW model for non-fatal tumors will be fitted when all observed tumors have been assigned the context “I”, provided that two other data file items are correctly set (see Appendix 1). (1) The user must set parameter t_0 equal to zero on data file line 9 (removing it from the model). (2) The data file code controlling BMD computation at line 13, item 3, must be set to zero. The model and BMD can be said to describe the event “appearance of a detectable carcinogenic lesion”, i.e. “tumor appearance.” With suitable caveats, this model might be used for tumors that only rarely cause death and do not alter the risk of death from another cause.

The MSW model for fatal tumors will be fitted when some data have the context “F”. Parameter t_0 should be estimated (except in special circumstances - see section below on estimating t_0). The model can estimate either the BMD for the event “death from the cancer,” or the BMD for “appearance of a detectable tumor”. The choice is made by setting line 13, item 3, in the data file to 1 or 0. If there were no “I” observations, only “F”, the model may be used to estimate the risk of death from cancer, but obviously not “tumor appearance”. (In a plot of cumulative probability of event versus time, the two distributions have the same shape and that for death from tumor is shifted t_0 units to the right of that for the tumor appearance.). For most risk

⁷ Each observation is assigned a context: “C” for right-censored (no tumor observed), “I” for “Incidental” (tumor observed on necropsy, incidental to another cause of death), “F” for “Fatal” (tumor observed on necropsy and identified as cause of death), or “U” (“Unknown”). See “Data and Tumor Context”, below.

assessments, the risk response “appearance of detectable tumors” will be chosen for computing the BMD (line 13, item 3 is zero) rather than “death from tumor”.

Parameters

The *shape parameter* c determines how rapidly the risk of a tumor response increases over time. For fatal tumors, the *location parameter* t_0 is interpreted as the time interval between appearance of a detectable tumor and death from the cancer, and its value is assumed to be the same for all subjects. The *polynomial coefficient scale parameters* $\beta_0, \beta_1, \dots, \beta_k$, determine the curvature of the dose-response curve.

The model parameters are constrained to satisfy the restrictions $c \geq 1$, $t > t_0 \geq 0$, and $\beta_i \geq 0$, $i = 0, 1, \dots, k$. There is no provision for allowing negative β_i . Parameter t_0 is also constrained by an upper limit t_m , i.e., the smallest observation time for tumor context F found in the data.

The user selects the maximum number of stages (the maximum power, up to 6, in the polynomial of dose, with terms $\beta_i d^i$) and the program estimates these. Some of these beta coefficients may be set to zero (because of the constraint $\beta_i \geq 0$) during maximum likelihood estimation.

Model Selection (number of stages)

The principal task is to evaluate goodness of fit for models differing in the maximum number of stages. This will involve model comparisons using the Akaike Information Criterion (AIC),⁸ the log-likelihood, and a graphical comparison of data to the fitted models.⁹ When models with increasing numbers of stages fit the data about equally well, users are advised to choose the simplest adequate model (i.e., least number of stages).

The model does not report a Chi-square goodness of fit table such as that reported by BMDS quantal models. Methods similar to the Chi-square goodness of fit testing applied to BMDS quantal model estimates do not apply to the MSW model with censored data, and development of a satisfactory hypothesis test, especially for heavily censored data, is difficult (Lawless, 2003).¹⁰

Data and Tumor Context

Time-to-tumor data consist of dose, tumor response category (tumor context), and time of the observation, for individual animals.

⁸ AIC differences smaller than 3 suggest that models fit equally well (Burnham and Anderson 2002, §2.6).

Differences between log-likelihoods for models of orders k and $k-1$ will be approximately distributed as $\frac{1}{2} \chi^2(1)$. Fit should also be compared graphically.

⁹ The graphical module “gofplot_msw” is available as an R program

¹⁰ In principle, it should be possible to implement a bootstrap goodness-of-fit test (Lawless 2003).

The test subject's response is classified within one of the following four outcome categories, or *tumor contexts* (Peto et al., 1980):

- Censored response (C). The subject is removed from the study at time t (because of sacrifice, or death from some cause other than the tumor being modeled) and no tumors are detected when the subject is examined. Represents a right-censored observation.
- Death from fatal tumor (F). The subject dies at time t , a cancer is detected when the subject is examined, and death is attributed to this cancer. An uncensored observation.
- Incidental tumor (I). The subject is removed from the study at time t (because of sacrifice, or death from a cause other than the tumor being modeled), and a carcinogenic lesion is detected when the subject is examined, but this lesion is judged not to be the cause of death. The MSW time to tumor model assumes that incidental tumors have no influence over probability or time of death. Represents a left-censored observation.
- Unknown response observed (U). The subject is removed from the study at time t ; however, the presence or absence of tumors cannot be determined when the subject is examined, e.g., due to decomposition or inconclusive necropsy. For modeling purposes, it is assumed that the subject did not die from a tumor at time t . When modeling non-fatal tumors, test subjects having data with context U are not considered, because they contribute no information about time of tumor appearance.

When modeling fatal tumors, data of all four types may be present, and some "F" observations must occur. Data used to model non-fatal tumors should contain only observations with contexts C and I (~~data with context U can be included, but will be ignored~~).¹¹

Comparison to Quantal Multistage Model

The quantal multistage model represents the cumulative incidence of a tumor at one time, usually at the end of a bioassay experiment. That model employs data consisting of a pair of numbers for each dose group: the number of animals at risk and the number of animals found, upon necropsy, to have the cancer at any time up to the end of the study (cumulative incidence). Thus, time of observing the tumor does not play a role in estimation.¹²

By applying a time-to-tumor model for the same time point (i.e., end of study), and with sufficient data, a more accurate BMD estimate should be produced for that time point.

Note that for the MSW time-to-tumor model, data may be 'grouped' when 2 or more animals have the same dose, observation time, and tumor context, but this is only a book keeping convention. The data consist of records for individual animals, and all observation times are

¹¹ If "U" observations are included, they will be treated like "C" observations by the non-fatal model. The program was intended to ignore them, and should be corrected in the near future. (Noted on 17 June 2010)

¹² Cumulative incidence can be 'adjusted', based on observation times, to better account for biasing effects of early mortality - essentially, an age-adjusted estimator of cumulative incidence. See Piegorsch and Bailer (1997).

utilized in estimation. Thus, one must have data for individual animals to apply the time-to-tumor model.

Special Options

User-selected settings include:¹³

Number of stages (maximum degree of polynomial)

Recommended default: number of dose groups minus two

Whether to assign t_0 a specified value or estimate it (only for modeling fatal tumors)

Recommended default: estimate t_0 when modeling fatal tumors, and always set $t_0 = 0$ when modeling non-fatal tumors.

Whether to specify that certain parameters take fixed values, e.g., $\beta_2 = 0$ in a 3-stage model, for the purpose of evaluating alternative models.

Recommended default: estimate all parameters

Difficult or Exceptional Datasets

If no tumors were observed (i.e., no F or I tumor contexts occur), then the data contain no useful information on time to tumor appearance or death from tumor, and MSW model fitting should not be attempted on these data. Similarly, if the data have no context “C” observations, only “F”, “I”, or a mixture of “F” and “I”, model fitting should not be attempted. (The software may appear to converge on a solution in such cases, but it is not an MLE).

If nearly all tumor observations are classified as fatal (F), and if it is plausible that the tumor is rapidly fatal after its appearance, then t_0 could be fixed at zero or at one time unit (e.g., 1 week, or another value deemed to be biologically appropriate). However, it is important to verify this from other studies and sources, rather than assuming it. Indeed, the data being analyzed might tend to refute this assumption, if a large number of deaths or sacrifices occurred before or concurrently with Fatal tumor contexts.

Some data sets may not provide cause of death. In that case, one must rely on expert sources and professional literature to decide whether the model for fatal or non-fatal tumors is appropriate. However, applying the model for fatal tumors is problematic when cause of death is not reported. Unless the tumor is rapidly fatal and there is little risk from other, competing causes of death which act as quickly, one cannot fairly assume that all observed tumors were fatal, and there is no way to distinguish fatal (F) and incidental (I) tumor observations. If the tumor is known to be late-appearing and if animals most likely succumbed to other causes of death in the bioassay, then it seems reasonable to treat all tumor observations as Incidental.

¹³ The user must assign these values in the data file.

Some types of data may lead to problems in obtaining reliable estimates. One or more very large standard error estimates among the model parameters is one indicator of such cases. If the occurrences of tumor contexts (I , F , and C) are highly confounded with dosage (d) or observation time (t), estimates may be suspect. Model diagnostic plots and the table of response categories by dose groups will help to identify such cases. Users should exercise caution when interpreting the results from such cases.

The MSW model software for fatal tumors has exhibited failures to converge on a BMDL solution when t_0 is being estimated or when it is specified at a non-zero value, for some data sets at some specified risks and times. This may be associated with an ill-conditioned problem, indicated by parameter correlations close to 1 and large or undefined¹⁴ standard errors. This reflects the difficulty of obtaining a solution owing to the shape of the likelihood function for the data in question. If convergence on a BMDL fails, the model will report no estimates, and should be run again without requesting a confidence limit for the BMD. Then, try setting t_0 equal to its estimated value and running the model again, this time requesting a confidence limit for BMD. Also be aware that the BMDL search number (on line 14 of the data input file), which controls the upper limit of the search for the BMD confidence interval, may need to be changed to obtain convergence.

Estimation and Interpretation of t_0 (MSW model for fatal tumors only)

The parameter t_0 represents the lag time between when a lesion is first observable in a necropsy and death from the cancer. By requiring the parameter t_0 to be constant across all test subjects, the multistage Weibull model makes some implicit assumptions:

- a. The time between “appearance” and death from cancer is the same across all subjects. As currently specified, the multistage Weibull model does not allow for subjects to die from the cancer at varying time intervals after “appearance” of tumors. This may be a reasonable approximation if the distribution of t_0 is narrow compared with the distribution of times of appearance or of death, but we are not aware of any studies examining this assumption.
- b. A tumor inevitably leads to death. The model implicitly assumes that the cancer is eventually fatal if the animal lives long enough.

Unless a sufficient number of both F and I responses are observed, the data may not contain enough information to obtain a reliable estimate of t_0 . Therefore, the user should always review the reported standard error and confidence interval for t_0 . If there are relatively few observations of Fatal or Incidental cancers, a user might have a concern about the reliability of estimated t_0 . In such a case, it may be helpful to evaluate the sensitivity of risk estimates to a series of selected values for t_0 (by specifying a series of fixed values for t_0 in the data input file). If one is mainly interested in the BMD for tumor appearance, and there are few “F” observations, it will also be

¹⁴ Thus, not reported by MSW in the Parameter Estimates table.

instructive to evaluate sensitivity by changing contexts “F” to “I” and fitting the model for non-fatal tumors (setting $t_0 = 0$, of course).

The foregoing issues do not arise when modeling non-fatal tumors using the MSW model, because then all tumor observations will be Incidental and t_0 is not part of the model.

Reviewing Model Output

Convergence

Convergence may not have been sufficient to give a good approximation to the MLEs if any of the following occur:

- any parameter estimate is identical to its initial value (in the table “Default Initial Parameter Values”)
- the likelihood for the fitted model is extraordinarily large or small
- predicted responses do not agree well with observed responses (in the Data Summary table)

If non-convergence is suspected, parameter estimates can be compared for different settings of initial values, including the reported estimates and a wider range based on the tabled initial values. Instructions are provided in the data file spreadsheet template and in Appendix I.

Parameter Standard Errors

Unusually large standard errors (e.g., an order of magnitude larger than the parameter estimate) should be a cause for concern, prompting closer review of model output and goodness of fit.

Weibull Shape Parameter c

Users should be skeptical about unusually large or small estimates of the shape parameter (c). Portier et al. (1986) reported estimates of the Weibull shape parameter for tumors occurring in control-group mice and rats for the National Toxicology Program's carcinogenicity studies. These estimates ranged from less than 1 to 15, but 85% fell between 1 and 8 and only 11% were less than 2.

Parameter Constraints and Inference

In some cases, the output will indicate that a parameter estimate has hit a boundary of the parameter space (for example, estimates $\beta_j = 0$, $c = 1$, $t_0 = 0$, or $t_0 = t_m$, the smallest observed time for Fatal context, reported beneath the data summary table). In this case, either no standard error will be reported for the parameter, or it should be ignored. In such cases, the Wald confidence intervals for the other parameters are not asymptotically correct.

While the 2-sided, profile-likelihood confidence interval for the BMD is asymptotically correct when model parameter(s) are on a boundary, the 1-sided interval corresponding to the BMDL is

not correct.¹⁵ If only one model parameter is on a boundary, the 1-sided, 95% confidence interval for BMD (corresponding to the BMDL) reported by MSW (based on χ^2_1) will have asymptotic coverage between 0.9355 and 0.8342 (op.cit.). If more than one model parameter is on a boundary, numerical computation is required to determine the potential range of coverage for the 1-sided confidence interval. To adjust approximately for the under-coverage of BMDL, a user could increase the confidence level when a parameter is on a boundary.

Graphical Evaluation of Goodness of Fit

EPA has provided programs in the R statistical programming language¹⁶ for making graphical evaluations of goodness of fit of the MSW model by comparison with nonparametric models.

BMD Computation

There is no general analytic form for the BMD in terms of the BMR and the estimated model parameters for the multistage Weibull time-to-tumor model. Instead, BMD is solved numerically by finding the root of a nonlinear equation.

BMDL Computation

The BMR-defining equation is used as a non-linear constraint, and the minimum value of BMD is determined such that the log-likelihood is equal to the log-likelihood at the maximum likelihood estimates less the quantity

$$\chi^2_{1, 1-2\alpha} / 2$$

¹⁵ Self, S.S. and K-Y. Liang (1987) J.Am. Stat. Assoc. 82: 605-610. Hirose, H. and T.L. Lai (1997) Technometrics 39:199-210. Molenberghs, G. and G. Verbeke (2007) American Statistician 61: 22-27. Sinha, B.K., et al. technical report at http://www.math.umbc.edu/~kogan/technical_papers/index2007.html. Kopylev, L, and B.K. Sinha (2009) manuscript "On the Asymptotic Distribution of Likelihood Ratio Test when Parameters Lie on the Boundary".

¹⁶ The graphical module "gofplot_msw" is available as an R program. For R, see <http://www.r-project.org> and <http://cran.r-project.org>

Maximum Likelihood Estimation

For each tumor context, the likelihood associated with that context is as follows:

C: For fatal tumors, the subject is alive up to time t , but the a tumor has been detected up to this time. Therefore, death from tumor could not occur before time $t + t_0$:

$$1 - F(t + t_0, d) = \exp\left\{-t^c \sum_{i=0}^k \beta_i d^i\right\}$$

For non-fatal tumors, the subject is alive up to time t , but a tumor has not been detected up to this time:

$$1 - G(t, d) = \exp\left\{-t^c \sum_{i=0}^k \beta_i d^i\right\}$$

F: For fatal tumors, death from tumor occurs at observation time t :

$$\frac{\partial F(t, d)}{\partial t} = c(t - t_0)^{c-1} \sum_{i=0}^k \beta_i d^i \exp\left\{-(t - t_0)^c \sum_{i=0}^k \beta_i d^i\right\}$$

Parameter t_0 is constrained $0 \leq t_0 \leq \{\text{minimum observed time with context F}\}$.

For non-fatal tumors, the likelihood is not defined because death from tumor cannot occur.

I: For fatal tumors, the subject is alive up to time t , but a tumor is detected at this time. Therefore, death from tumor is predicted to have occurred between time t and $t+t_0$:

$$F(t + t_0, d) - F(t, d) = \exp\left\{-(t - t_0)^c \sum_{i=0}^k \beta_i d^i\right\} - \exp\left\{-t^c \sum_{i=0}^k \beta_i d^i\right\}$$

This applies if $t > t_0$. The constraint for t_0 noted under context F is applied, so if $t \leq t_0$, the first term becomes 1.

For non-fatal tumors, the subject is alive up to time t , but a tumor is detected at this time (i.e., tumor is known to have appeared before time t):

$$G(t, d) = 1 - \exp\left\{-t^c \sum_{i=0}^k \beta_i d^i\right\}$$

U: For fatal tumors, even though it cannot be determined when or if the animal died due to tumor, it is assumed that any such death would not have occurred prior to time t :

$$1 - F(t, d) = \exp\left\{-(t - t_0)^c \sum_{i=0}^k \beta_i d^i\right\}$$

For non-fatal tumors, the likelihood is not defined because the time of tumor appearance cannot be determined. Thus, test subjects having data with context U are not considered when modeling time-to-tumor data associated with non-fatal tumors.

Assume that test subjects are placed within one of $D > k$ dosage groups, and let d_j denote the dosage rate assigned to the j^{th} dosage group ($j = 1, \dots, D$). Furthermore, within each dosage group, assume that the subjects are grouped further into 'subject groups' according to observation time and tumor context. For test subject group s within dosage group j , let t_{js} denote the observation time, r_{js} denote the tumor context, and n_{js} denote the number of subjects in the group. Then the log-likelihood for fatal tumors is written as follows:

$$l(t_0, c, \beta_0, \beta_1, \dots, \beta_k) = \ln \left[\prod_{j=1}^D \left(\prod_{r_{js}=C} [1 - F(t_{js} + t_0, d_j)]^{n_{js}} \times \prod_{r_{js}=F} \left[\frac{\partial F(t, d)}{\partial t} \right]^{n_{js}} \right. \right. \\ \left. \left. \times \prod_{r_{js}=I} [F(t_{js} + t_0, d_j) - F(t_{js}, d_j)]^{n_{js}} \times \prod_{r_{js}=U} [1 - F(t_{js}, d_j)]^{n_{js}} \right) \right]$$

Because C and I are the only tumor contexts associated with non-fatal tumors, the log-likelihood for non-fatal tumors corresponds to the following:

$$l(c, \beta_0, \beta_1, \dots, \beta_k) = \ln \left[\prod_{j=1}^D \left(\prod_{r_{js}=C} [1 - G(t_{js}, d_j)]^{n_{js}} \times \prod_{r_{js}=I} [G(t_{js}, d_j)]^{n_{js}} \right) \right]$$

Values of $t_0, c, \beta_0, \beta_1, \dots, \beta_k$ that maximize the log-likelihood function are the *maximum likelihood estimates (MLEs)* of the model parameters.

MSW uses the optimizer 'donlp2-intv', copyright by P. Spellucci, for maximum likelihood computations.

The maximum likelihood (ML) estimation algorithm used for the MSW model is a modification of a ML estimation algorithm for the 3-parameter Weibull distribution [Hirose, 1996; Hirose and Lai, 1997] based on the Generalized Extreme Value (GEV) family. Both algorithms use a reparameterization of the Weibull to improve computational stability.

Asymptotic Properties and Confidence Intervals

Hirose [1996] and Hirose and Lai [1997] considered the asymptotic properties of maximum likelihood estimates and the likelihood ratio for the 3-parameter Weibull model and the Generalized Extreme Value (GEV) reparameterization of that model (also used for MSW). The key conclusions are: (1) grouping of the time data by rounding or discretization (e.g., grouping into weeks) eliminates the problems of non-regular estimation attending continuous data; (2) the GEV reparameterization avoids problems of infinite maximum likelihood estimates occurring with the Weibull parameterization. As a result, "... we can still apply likelihood methods to construct confidence intervals by reparameterization so that the three-parameter Weibull model can be embedded in the larger GEV family, for which the maximum of the likelihood function (based on grouped data) always lies in the interior of the parameter space." [Hirose and Lai, 1997]. They also note that the data-based choice of an upper bound for t_0 (i.e., t_m , the smallest observed time for a Fatal context) has no effect on the asymptotic properties of the MLEs of the parameters. Finally, Hirose and Lai (1997) demonstrated application of the profile likelihood method to finding confidence intervals for model parameters and gave reasons why these are preferable to Wald-type intervals.

However, the user is cautioned that when parameters are estimated at the boundary (i.e., when estimates $\beta_j = 0$, $c = 1$, $t_0 = 0$, or $t_0 = t_m$ (the smallest observed time for Fatal context, reported beneath the data summary table), then Wald confidence intervals for parameters, as well as the profile-likelihood confidence interval for the BMD, may not provide the specified coverage.

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APPENDIX 1: DATA FILE ASSEMBLY & SETTINGS

A simple way to create a new data file is to modify an existing one (after renaming and saving it), using a text editor like Windows Notepad. Below, we summarize the items most often requiring attention for a new model run or new data, using Example 1 below. Separately, we provide a spreadsheet template for data file assembly that contains line-by-line reminders.

Example 1 Input File “EXAMPLE1.(d)”, for Multistage Weibull Module

Line	
1	Multistage Weibull
2	2
3	EXAMPLE 1, To estimated, BMD for Risk Type = Fatal Risk
4	EXAMPLE1.set
5	EXAMPLE1.out
6	1
7	0
8	144
9	-9999.0 -9999.0 -9999.0 -9999.0 -9999.0
10	0
11	8 32 32
12	36 1.0e-8 1.0e-8
13	1 0.10 1 0 104
14	1 8 0.95
15	1 10.000 79.0
16	1 4 0.95
17	DOSE CLASS TIME
18	0 C 105
	0 C 88
	0 I 105
	<i>etc.</i>
	<i>(144 data input lines)</i>

Lines 1-16: Program Information Settings

- Line 1 should read “Multistage Weibull”
- Line 2 specifies the maximum order k of the model to be fitted (2^{nd} order in the example)
- Line 3 is text that will be printed in the header of the output file
- Line 4 is not currently used but must be present, if only as a blank line.
- Line 5: output file name. Your output will appear in a file with this exact name (including file extension), in the subdirectory from which you run the model in the command window.
- Line 6: if 0, the output file is over-written; if 1, new results are appended
- Line 7: grouped or ungrouped data indicator: a 0 tells MSW the data are ungrouped, with one observation (corresponding to one animal) per line and with three data columns (dose, context, and time); a 1 indicates grouped data, which must have a fourth data column giving the number of animals for that line.

- Line 8 must agree exactly with the number of data lines (lines 18+).
- Line 9 is used to tell MSW whether to estimate a parameter (-9999) or whether the user is specifying a value for the parameter by providing a value on line 9. The fields (items), from left to right, represent parameters c , t_0 , β_0 , β_1, \dots, β_k . Thus, the second field should be 0 rather than -9999 when the data all have an Incidental context. There must be as many fields for β as the maximum model order requested on Line 2 plus one (for β_0). Thus, there are three instances of '-9999' in the example after the first two (which correspond to parameters c and t_0). Only the first $(k + 3)$ values on Line 9 are read; additional instances of '-9999' will be ignored.
- Line 10: the indicator value [0] in Line 10 tells MSW to compute the starting parameter values (default starting values option). This should suffice in almost all cases. Alternatively, a user could set the indicator in this line to [1] and would then have to provide starting values for each one of the $k+3$ parameters on the next line.
- Line 11: When Line 10 holds a 0, Line 11 provides codes to the automatic initialization routines in MSW. The first item gives the number of automatic initializations. The second number sets the grid count for a search that initializes the shape parameter c (i.e., if the second number is n , $2n+1$ grid points are used). The third number sets the grid count for initializing the location parameter, t_0 . If Line 10 holds a 1, Line 11 would provide a list of user-supplied initial values for each parameter (using -9999 for those that were specified as fixed values on Line 9).
- Line 12: Optimization parameters. The first number [36] is the factor which, when multiplied by the number of free parameters in the models, determines the maximum number of iterations in each call of the numerical optimization algorithm. The remaining two numbers are currently inactive but may be modified for future use.
- Line 13 provides MSW information about the BMD calculation. Set the first item to 1 to estimate a BMD (or 0 for no BMD calculation). The second item specifies the level of risk [e.g., 0.100]. The third item* specifies the risk response used for BMD computation (0 for tumor "appearance" [as defined on page 1], i.e., Incidental Risk, or 1 for death from tumor, or Fatal Risk). The fourth item specifies the risk type (0 for extra risk, 1 for added risk). The fifth item specifies the time (same units as the data) at which to calculate BMD.
- Line 14, set the first item to 1 to calculate the confidence interval for BMD. The second item sets the upper bound of the search for an upper confidence limit, as a multiple of this value times the BMD.. The third item is the confidence level (e.g., 0.95) for the interval (BMDL, BMDU). The 1-sided interval (BMDL, ∞) is expected to have half this nominal coverage if no parameters are at a boundary.

Lines 17 onward: Data

Data columns can be cut and pasted from Notepad or a spreadsheet. Data fields can be separated by tabs or spaces. Because 17 lines precede the first data line, you can 'count' the data lines by moving to the last data line (using Ctrl-End) (be sure the cursor is *within* the last line of data), reading the line number on the Notepad status line (bottom of the window), and subtracting 17. If the Notepad status line is not in view, activate it by selecting the View menu item and clicking on "Status Bar."

Example 1 applies to ungrouped data; ungrouped data represent one animal per line. For grouped data, each line may represent more than one observation; there will be one line for each unique combination of dose, context (class) and observation time. Grouped data have a fourth data column ("N"), and the indicator "1" on line 7 tells MSW that the data are grouped. If the indicator on line 7 is 0 (ungrouped data), there must not be a fourth data column, and a fourth symbol must not appear on line 17!

Warning: there must be nothing following the last text on line 17 (e.g., no blank or tab), and there must be no lines following the last data line!

Applying the MSW Model for Fatal Tumors

The model for Fatal tumors is estimated when at least one observation has context "F" (obviously, one wants many "F" and "I" observations to obtain reasonable estimates for time to death from tumor with estimation of parameter t_0). On line 9, the second field should be -9999, indicating that MSW should estimate t_0 . On Line 13, item 3 can be 0 (causing the model to estimate the BMD corresponding to the distribution for "appearance of a detectable tumor", i.e., Incidental Risk) or 1 (whence MSW will estimate the BMD corresponding to the distribution of time to death from the tumor, i.e., Fatal Risk).

Applying the MSW Model for Non-Fatal Tumors

The model for Non-Fatal tumors is estimated when no observations have context "F." On Line 13, item 3 should be 0. On line 9, the second item must be 0; t_0 will be fixed at zero, removing it from the model.

Incidental vs. Fatal Risk Response for BMD Computation

The Risk Response is selected using line 13, item 3 of the data file. This choice is meaningful only when the MSW Model for Fatal Tumors is applied, i.e. when both Incidental and Fatal tumor contexts are present in the data. For most risk assessments, the Incidental Risk response (for appearance of detectable tumors) will be chosen for computing the BMD (line 13, item 3 is zero) rather than the Fatal Risk response (death from tumor). If the data have some "F" but no "I" contexts, setting item 3 on line 13 to 0 (i.e., requesting an estimate of the BMD for the Incidental Risk Response when there are no "I" data to support it) can result in failure to complete estimation or nonsensical estimates.

When the MSW Model Does Not Solve the BMDL

In some unusual cases, MSW may fail to solve the BMDL. In such cases, we have found it helpful to try the following.

- (a) Review the parameter estimates, and the BMD. Are the values reasonable? Is the BMD between zero and the highest dose? Are there any warning signs, such as very large standard errors for parameters, or power parameter 'c' less than 2?

- (b) If some parameter MLEs are zero, try fixing them at zero on line 9. When modeling only incidental tumors, be sure to set the second number on line 9 to zero (fixing " t_0 " = 0).
- (c) In some cases when the higher-order coefficients (e.g., beta_2 and beta_3) have MLEs of zero, and subsequently the number of stages on line 2 is restricted to (e.g., 1) so as to omit the higher-order coefficients, there may be difficulty solving the BMDL. In such a case, setting number of stages on line 2 to a higher value will allow the BMD confidence interval search to cover a larger parameter space and may result in a solution for the BMDL.
- (d) If MSW still does not solve the BMDL, try changing the maximum number of iterations (first number on line 12) and the starting values on line 11.
- (e) When the data contain both Fatal and Incidental contexts, first run the model with parameter t_0 estimated. If parameter estimates are reported but convergence on a BMDL fails, then try setting t_0 equal to its estimated value and run the model again.
- (f) *Only as a last resort*, one could try fixing a parameter like 'c' to its MLE on line 9 (see also the preceding item 'e'). This will restrict the parameter space for the profile confidence interval search and will result in a shorter confidence interval having less than the specified coverage. Whether the confidence interval is shortened more on the left (BMDL) or right (BMDU) is not known. In all cases examined, the gradient of the profile is much steeper on the left, suggesting that the BMDL is less strongly affected than BMDU. In a case like this, one should examine the profile plots for the unrestricted and restricted runs (there may be useful data on 'gev_pl.txt' even if the BMDL search was not successful).

User-Selected Initial Parameter Values for Optimization

In some cases, a user may want to test convergence by choosing various starting values for the maximum likelihood optimization. Details on how to configure the data file to accept user-specified initial values are found in the dataset spreadsheet template and in notes to the data assembly example, just above.

APPENDIX 2: INSTALLING AND RUNNING MSW.EXE

Download MSW.EXE, preferably to a dedicated subdirectory like “C:\Program Files\MSW” or “C:\MSW.” If you are downloading a ZIP file, unzip it in that subdirectory.

For future compatibility with BMDS, the example data files are named using a file extension “.d”, and data files are referred to this way in the MSW documentation.¹⁷

Running MSW

Suppose you saved MSW under “C:\Program Files\MSW” and suppose your project directory containing data is “C:\Documents and Settings\jgraham\My Documents\projects\”.

Open a Command Prompt window.¹⁸ Type `>cd C:\Documents and Settings\jgraham\My Documents\projects` and hit “Enter”. The prompt will change to `C:\Documents and Settings\jgraham\My Documents\projects>`

MSW is run in the Windows Command Prompt, so you will want to familiarize yourself with cutting and pasting text in that window.¹⁹ You may also want to learn some commands.²⁰

Because MSW is in a different directory, you will need to tell Windows where to find MSW.

(1) You could permanently add the path to MSW to the Path Environment Variable, if you have Administrator privileges and know what you are doing. (2) You could temporarily add the path by typing this command: `> path C:\Program Files\MSW;%path%`

Assuming the data file ‘mydata.d’ is ready, run MSW by typing `> msw mydata.d`
Expect lots of text to scroll by in the command window – it is of no use to most users.
When MSW has run to completion, scrolling will stop and the command prompt will return.

Look for the output file in the same directory. It is convenient to open a Windows Explorer window for your project directory (in this example, “C:\Documents and Settings\jgraham\My Documents\projects\”). Remember that the output file name was given on line 5 of the data file.

¹⁷ MSW does not require this file extension, and you may, e.g., use the extension “.msw”, after checking that none of your other programs use files having that extension. If you don’t know how to check – DON’T do this. A safer way to distinguish MSW data from BMDS data is to add text to the file name, e.g. “mydata_msw.d”, “mswdata1.d”, etc., or to keep data in separate folders.

¹⁸ Look for the black “Command Prompt” icon on the Windows Start menu under Programs > Accessories. You can save a copy on your taskbar or on your desktop for faster access.

¹⁹ Click on the icon in the upper left of the title bar and move the mouse arrow to “Edit”. Experiment. Also try copying text from Notepad (copy the commands like those below, pointing to your own folders) and right clicking in the Command Prompt window to paste in the text.

²⁰ Available commands are listed by entering the command ‘help’ and details are listed by entering ‘help CD’ for example (CD is a command name).

APPENDIX 3: OUTPUT FILE FORMAT

The output ‘.out’ file format for the Multistage Weibull module is consistent with those for BMDS modules. The first (top) half of the output consists of model inputs into the modeling software, and the second (bottom) half consists of the model calculation results, including all user requested estimates. To illustrate, the output file “EXAMPLE1.out” generated by executing Example 1 above is examined in sequence, section-by-section.

First Half of ‘EXAMPLE1.out’ Example Output (Model Inputs)

The top section of the output file contains the standard output header:

```
=====
Multistage Weibull Model. (Version: 1.6.1; Date: 11/24/2009)
Solutions are obtained using donlp2-intv, (c) by P. Spellucci
Input Data File: example1.(d)
Tue Nov 24 15:34:36 2009
=====

EXAMPLE 1, To estimated, BMD for Risk Type = Fatal Risk

~~~~~
```

The header shows the model type [Multistage Weibull Model], version [1.6.1] and date [11/24/2009] of the software, the name of the input data file [EXAMPLE1.(D)], and the time and date when the module was run to produce the output [Tue Nov 24 15:34:36 2009]. Just below the main header are the user comments that were specified in the input file: [EXAMPLE 1, To estimated, BMD for Risk Type = Fatal Risk].

The specified Multistage Weibull model is shown in the next section:

```
The form of the probability function is:
P[response] = 1-EXP{-(t - t_0)^c *
               (beta_0+beta_1*dose^1+beta_2*dose^2)}

The parameter betas are restricted to be positive
```

The probability function indicates that a 2-stage Weibull model was specified. The β values are currently fixed to be non-negative.

The next section gives a basic description of the dataset and additional descriptions of the model:

```
Dependent variable = CLASS
Independent variables = DOSE, TIME

Total number of observations = 144
Total number of records with missing values = 0
Total number of parameters in model = 5
Total number of specified parameters = 0
Degree of polynomial = 2
```

Descriptions of the data include variable names [CLASS, DOSE, and TIME], number of observations [144], and the number of records (i.e., data lines) with missing values [0]. The additional model descriptions include the number of model parameters [6], the number of model parameters that are specified to a fixed value by the user [1], and the degree of the polynomial. If any parameters were specified by the user, these will be reported (not applicable in this case).

The following section provides information on the optimization, including the optimization parameter settings and starting values:

```
Maximum number of iterations = 36
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008
```

```
Default Initial Parameter Values
c      =      3
t_0    =    51.2121
beta_0 = 4.36846e-007
beta_1 = 2.99274e-009
beta_2 = 9.03452e-012
```

The first number [36] is the factor which, when multiplied by the number of free model parameters, specifies the maximum number of iterations in each call of the numerical optimization. The next two numbers for relative function and parameter convergence are currently inactive. The starting values for the numerical maximum likelihood estimation of the model parameters are shown next. If any of these were specified (fixed a priori) by the user, the title will read “User Inputs Initial Parameter Values”, and “Specified” will be printed to the right of the parameter.

Second Half of 'EXAMPLE1.out' Example Output (Results)

The estimated asymptotic correlation of the parameter estimates, and the parameter estimates with associated standard errors and confidence intervals are the first model results in the output:

Asymptotic Correlation Matrix of Parameter Estimates					
	c	t_0	beta_0	beta_1	beta_2
c	1	-0.64	-0.99	-0.85	-0.9
t_0	-0.64	1	0.64	0.5	0.66
beta_0	-0.99	0.64	1	0.84	0.9
beta_1	-0.85	0.5	0.84	1	0.55
beta_2	-0.9	0.66	0.9	0.55	1

Parameter Estimates				
Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval	
			Lower Conf. Limit	Upper Conf. Limit
c	3.11974	0.706582	1.73487	4.50461
t_0	53.6983	6.2269	41.4938	65.9028
beta_0	2.52452e-007	8.22822e-007	-1.36025e-006	1.86515e-006
beta_1	1.60446e-009	6.96173e-009	-1.20403e-008	1.52492e-008
beta_2	5.95162e-012	1.68082e-011	-2.69919e-011	3.88951e-011

Parameters that have either been estimated at their boundary (i.e., have no standard error) or are fixed by the user (i.e., have standard error 0) are excluded from the correlation matrix. This is consistent with the listing of the parameter estimates in BMDS modules, which exclude those parameters fixed by the user (i.e., t_0) and provide no standard error estimates for parameters at their boundary (i.e., β_0 and β_1). Parameters that have been estimated at their boundary will be marked by "NA" in the Std.Err. column and a footnote will be printed below the parameter table.

The loglikelihood and AIC are next in the output:

	Log(likelihood)	# Param	AIC
Fitted Model	-118.142	5	246.283

The “Data Summary” table displays the number of test subjects for each dose level categorized by tumor context. The minimum observation time for tumor context F is reported, because it is the upper limit for the t_0 parameter in the multistage Weibull model for fatal tumors. The Expected Response is calculated as the sum of expected probabilities for all subjects using the observed times for each subject with the maximum likelihood parameter estimates in the MSW model equation.

DOSE	Data Summary					
	CLASS				Total	Expected Response
	C	F	I	U		
0	33	0	15	0	48	1.65
3.5e+002	27	3	18	0	48	3.29
7e+002	16	8	24	0	48	6.40

Minimum observation time for F tumor context = 65

The final section documents the outcome of the benchmark dose (BMD) calculations:

```

Benchmark Dose Computation
Risk Response      =      Fatal
Risk Type          =      Extra
Specified effect   =      0.1
Confidence level   =      0.95

Time               =      104

      BMD =      189.514
     BMDL =      75.7263
     BMDU =      300.348

```

The BMD estimate [189.514] is for a Fatal Extra risk level of 0.1 at time $t = 104$. The BMDL [75.7263] and BMDU [300.348] represent lower and upper bounds, respectively, of the 95% [0.95] confidence interval for the estimated BMD for the fatal risk response.