**Technical Background for MS_Combo Program**

The purpose of the MS_Combo program in BMDS is to allow the user to calculate BMDs and BMDLs for a combination of tumors (corresponding to a defined risk of getting one or more of those tumors) when the individual tumor dose-responses have been modeled using a Multistage-Cancer model. Thus, the output of an MS_Combo run will present the results of fitting each individual tumor (including the BMD and BMDL for that tumor) plus the combined log-likelihood, BMD and BMDL for the combination of specified tumor responses.

In practice, the user should investigate each tumor individually and determine which degree of the Multistage-Cancer model is most appropriate for each individual tumor. That determination will involve all the usual considerations of fit, AIC, etc. Once a specific form of the Multistage-cancer model is chosen for each of the tumors of interest (they need not have the same degree across all of the tumors in question), the user should specify those choices in the MS_Combo run. It is important to note that the following descriptions are valid only when the tumors are assumed to be independent of one another (conditional on dose level).

Because of the form of the multistage model, the MLE estimates for the combined risk are a function of the parameter values obtained for the individual tumor multistage model fits. In fact, the combined probability function has a multistage model form:

$$P(d) = 1 - \exp\{-(\beta_0 + \beta_1 d + \beta_2 d^2 + \ldots)\}$$

and the terms of the combined probability function ($\beta_0$, $\beta_1$, …)are specified as follows

$$\beta_0 = \Sigma\beta_{0i}$$

$$\beta_1 = \Sigma\beta_{1i}$$

$$\beta_2 = \Sigma\beta_{2i}$$

etc.

where the sums are over i = 1, …, t, with t being the number of tumors under consideration, and $\beta_{xj}$ being the $x^{th}$ parameter (0, 1, …) for tumor j. The $\beta_{xj}$ values are available directly from the Multistage-Cancer runs performed on the individual tumors, but MS_Combo performs the calculations for the user, completing the summations of the individual terms and computing the BMD based on the combined parameter values and the user-specified BMR.

A profile likelihood approach is used to derive the BMDL. Given the BMD and the log-likelihood associated with the MLE solution, a target likelihood is defined based on the user-specified confidence level (e.g., 95%). That target likelihood is derived by computing the percentile of a chi-square (1 degree of freedom) corresponding to the confidence level specified by the user (actually, the alpha associated with the confidence level, times 2). That percentile is divided by 2 and subtracted from the maximum

log-likelihood. That derivation is based on a likelihood ratio test with one degree of freedom; it can be shown that estimating the BMDL corresponds to losing one degree of freedom, regardless of the number of tumors being combined.

The BMDL for the combined response (one or more of the tumors of interest) is defined as the smallest dose, D, for which the following two conditions are satisfied:

a. There is a set of parameters such that the combined log-likelihood using D and those parameters is greater than or equal to the target likelihood), and
b. For that set of parameters, the risk at D is equal to the user-specified BMR.

Note that the combined log-likelihood is a function of the fits of the individual tumors (the sum of the individual log-likelihoods), obtained using their tumor-specific β values. Thus, the search for the parameters of the combined Multistage-Cancer model varies the individual-tumor β values in such a way that the individual log-likelihoods add up to a combined likelihood within the range desired (greater than or equal to the target). However, in order to satisfy the second constraint, the sums of the individual-tumor parameters (shown above to be the parameters of the combined probability function) are used to evaluate the risk for any proposed BMDL, D.

Note that the individual tumors need not be modeled with the same degree of the Multistage-Cancer model. Any terms not included for an individual tumor are assumed to be zero (and will remain at zero during BMDL optimization) in the summations shown above. The optimizer DONLP2 is used for the combined BMDL estimation; further information about that optimizer may be found at the following site: http://www.mathematik.tu-darmstadt.de/fbereiche/numerik/staff/spellucci/DONLP2/.