APPENDIX F

Lay Description of the Linearized Multistage Model

Lay Description of the Linear Multistage Model

The assessment of human cancer risk associated with some specified chemical exposure is a complex process that requires careful review of all the pertinent information by appropriately trained individuals including statisticians, toxicologists, epidemiologists, and pathologists. In a small number of instances, epidemiological data are suitable for quantitative estimates of risk and permit a dose-response relationship to be developed directly from human data. Should epidemiological data be available from either occupational or case-control studies, these studies should be evaluated for their applicability in establishing causal relationships and their suitability for inclusion in quantitative risk assessment.

In the majority of cases, the available epidemiological studies are inadequate and assessment of human cancer risk is based on animal bioassays. Carcinogenicity bioassays are usually designed as screening procedures with the primary focus being hazard identification, rather than risk assessment. In such studies, a limited number of animals may be exposed to a maximum tolerated dose that is several orders of magnitude higher than that encountered by humans. That being the case, two extrapolations are necessary to convert the animal data to appropriate human risk estimates: the first extrapolation is from animals to humans and the second is from high experimental doses to the low doses encountered by humans.

In extrapolation from animal data to humans, the appropriate route, species, tumor type, and dose units (i.e., those which provide an adequate model of human carcinogenicity) are not always known with certainty. When several bioassays of a chemical exist, it is necessary to select for analysis those experiments that are most appropriate for making quantitative estimates. Toxicological and statistical considerations apply in that selection.

Ideally, the process of selecting a key study from among the various available bioassays, in which different species, strains, sexes, or routes of administration may have been tested, should maximize the biological correlations between animal species and humans. Available information on comparative metabolism, pharmacokinetics, and mechanisms of action should be considered when making a choice of data to use. Specific guidelines for evaluating studies for use in risk assessment have been proposed by the EPA (1989). Those studies with suitable dose-response data that meet statistical and toxicological criteria are then included in a quantitative risk assessment.

Once particular experiments have been selected for analysis, it is necessary to select the specific tumor responses that are used to estimate a dose-response relationship. Tumor

response that may be considered include: tumors located at sites related to the metabolism, storage, or elimination of the chemical; tumor types related to chemical exposure in epidemiological studies; or, tumors that show a statistically significant dose-related trend or significant increased incidence in treated animals when compared to control. In the absence of quantitative information describing differences in metabolism, pharmacokinetics, or pharmacodynamics between animals and humans, quantitative estimates of human cancer risk are usually based on those tumor responses that show a statistically significant increased incidence in specific organs or tissues.

There are a number of statistical issues in the analysis and interpretation of animal carcinogenicity studies that should be considered. For example, in the analysis of tumor incidence data, survival differences among groups should be taken into account. However, no rigid statistical "decision rule" should be employed in the interpretation of carcinogenicity data. Even if a study has been carefully designed and appropriate statistical methodology employed, interpretation of results is a complex process. Carcinogenic responses should be evaluated carefully as to their biological relevance with respect to human carcinogenic risks. Special consideration should be given to the evaluation of rare tumors or to tumors at sites with a high spontaneous background.

Extrapolation from high to low dose is based on a presumed dose-response relationship, with parameters estimated from the experimental data. The mathematical form of the dose-response model selected is an important consideration, as different models can provide very different estimates of risk outside of the experimental range of exposure levels. It has been argued that the dose-response function for carcinogenicity could be linear or that it is unlikely to exceed linearity in the low dose region. The dose-response model used most commonly is the multistage model for quantal data (i.e., data indicating only the number of animals with cancer) (Crump et al. 1977; Crump 1984). This model expresses upper confidence limits on cancer risk as a linear function of dose in the low dose range.

The multistage model is based on the Armitage and Doll (1961) model that assumes that a cell line goes through a number of distinct stages (k) in its progression to becoming cancerous. For a spontaneous tumor, the rate at which it progresses through a specific stage is assumed to be constant. Different cell lines are assumed to compete independently in producing tumors. The underlying basis for the multistage model is that cancer incidence will increase as a function of age ($[age]^{k-1}$), which agrees with the observation that the age-specific incidence rates of many human cancers, particularly carcinomas in organs other than sex organs, increase as $(age)^{x}$, where x ranges between 3 and 6 (Crump and Howe 1984). Crump and Howe (1984) have extended the

Armitage-Doll model to include the effect of exposure to a carcinogen by assuming that the transition rate at which a cell goes through each stage is linearly related to the dose rate (i.e., that

$$\gamma_i = \alpha_i + \beta_i d$$

where d is the dose rate of a continuously applied carcinogen). Here α_i is the background transition rate in the absence of an applied dose, and β_i represents the increase in the transition rate per unit dose. Through a series of complicated mathematical steps, this formula is transformed into the linearized multistage model. The mathematical form of the linearized multistage model is

$$P(d) = 1 - \exp(-q_0 - q_1 d - \ldots q_k d^k)$$

where q_1, which is called the linear term, is equal to or greater than zero, d is the average lifetime daily dose of the chemical in mg/kg/day, P(d) is the lifetime probability of cancer from the dose level d, and $q_0,\ldots,q_k$ are nonnegative parameters estimated by fitting the model to experimental animal carcinogenicity data. The input into this model is the experimental dose, the number of animals with the specific tumor, and the number of animals at risk or examined for that specific tumor. This is often referred to as quantal data.

The quantity of principal interest is not the absolute probability of a cancer P(d), but rather the extra lifetime risk of cancer resulting from exposure to dose d. This risk is defined as

$$[P(d)-P(0)]/[1-P(0)],$$

and can be interpreted as the probability of the occurrence of a tumor at a dose of d, given that no tumor would have occurred in the absence of the dose.

Parameters (q values) are estimated by fitting the model to experimental animal carcinogenicity data using the maximum likelihood method. In addition to maximum likelihood estimates of model parameters, an upper bound or upper confidence limit[1] on

[1] Since, there is an inherent, mathematical uncertainty in an extrapolation from high doses to low doses using a small number of data points, confidence limits are estimated. A confidence limit is a statistical term that describes the degree of confidence that the estimated risk is not likely to differ by more than a specified amount from the risk that would be predicted by the model if more data were available. The EPA generally uses the 95% upper confidence limit as an upper bound on low-dose cancer risks. By using the 95% upper confidence limit, there is only a 5% chance that the risk predicted by the model would be higher than the risk value that is used. The confidence limit gives an indication of how well the data fit the model at high-dose levels but cannot

the dose-response curve is calculated, reflecting the uncertainty of extrapolating the curve to low doses at which human exposures are anticipated to occur. This upper bound or confidence limit can be considered to represent the largest reasonable linear extrapolation to low doses consistent with the data. The method for determining the upper confidence limits for extra risk and the lower confidence limits for risk-related doses is based on the largest value for the linear term q_1 that is consistent with the data. This new term is the q_1^*, also referred to as the unit potency estimate or unit cancer estimate. The estimated dose-response curve will be linear at low doses whenever the estimate of the linear coefficient, q_1, is greater than zero. The upper bound, specifically the q_1^*, is always linear, since there is always some model with a positive coefficient that is consistent with the data.

The output value from the multistage model, q_1^*, is the 95% upper confidence limit on the linear term q_1, and represents the unit risk expressed in units of $(mg/kg/day)^{-1}$ that is directly applicable to humans, when appropriate "scaling up" dose conversions are applied to the experimental data prior to application of the dose-response models. Similarly, the output Maximum Likelihood Estimate (MLE) and statistical lower bounds on risk related doses are directly applicable to humans. At low doses, estimates of the upper bound on extra cancer risk can be obtained using the equation

$$\text{Risk} = q_1^* \ (mg/kg/day)^{-1} * \text{exposure dose } (mg/kg/day).$$

In addition, animal-to-human extrapolation is accomplished by assuming that animals and humans are equally susceptible (in terms of extra risk) when the dose is measured in the same units for both species. EPA methodology assumes that doses measured in units of mg/m^2 surface area/day ("surface area" equivalency) give equal risks in animals and humans.

Some of the difficulties in risk assessment, whether bioassay or epidemiologically-based, arise when exposures are intermittent. In this case, it is problematical whether or not an average dose adequately reflects the exposure history or if less than lifetime human exposures can be estimated from experiments dosing animals for their entire lifespan.

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indicate how well the model reflects the true low-dose risks.