Appendix C
Benchmark Dose Calculations

I. Methods for Modeling

The quantal endpoints were modeled using the Weibull and polynomial models:

Weibull model: $P(d) = 1 - \exp\{-\alpha - \beta*(d-d_0)^{\gamma}\}$, Eq. 1

where P(d) is the probability of response at dose d and the four unknown parameters, α, β, d_0, and γ are estimated by maximum likelihood methods. The parameter γ is not constrained to be an integer, but it is constrained to be greater than or equal to 1. The "threshold" parameter, d_0, was included in the modeling only when a sufficient number of dose groups were available (at least 4) and when the model without a threshold provided a relatively poor fit to the data.

The polynomial model can be described as:

$P(d) = 1- \exp\{-q_0 - q_1*(d-d_0) - q_2*(d-d_0)^2 - ... - q_k*(d-d_0)^k\}$, Eq. 2

where the parameters, the q_i's and d_0, are estimated by maximum likelihood methods. The degree of the polynomial was restricted to be no greater than the number of dose groups minus one. The same restrictions on estimation of the threshold parameter, d_0, were applied here as with the Weibull model. In the case of the polynomial model, the total number of parameters estimated was constrained to be no greater than the number of dose groups.

For the continuous endpoints, the modeling approach described by Gaylor and Slikker (1990) and elaborated by Crump (1995) was used. This approach uses all of the information contained in the original observations, but defines BMDs/BMCs in terms of probability of response.

Use of these models requires definition of a background incidence of abnormality, p_0, or the specification of a level of response that can be considered the cut-point between normal and abnormal responses, x_0. Specification of p_0 (and of the type of distribution -- assumed here to be normal for all endpoints) implicitly defines a cut-point, x_0, when the parameters for the background mean and variability are estimated as part of the modeling. Similarly, specification of a cut-point determines the background incidence once the background mean and variability are estimated. The BMD is then defined as the lower bound on dose at which the increased probability of an abnormal response is equal to 5% or 10% (see below). In the absence of endpoint-specific toxicology data to support a choice of a p_0 or an x_0 value, a range of p_0 values that bracketed reasonable choices was used. Specific values of p_0 were emphasized when toxicological data supporting a choice were available.

Two models are available to describe how the probability of response is assumed to vary with dose. The first is an adaptation of the Weibull model:

$$P(d) = p_0 + (1-p_0)\,[1 - \exp\{-(\beta*d)^{\gamma}\}, \quad \text{Eq. 3}$$

where P(d) is the probability of response at dose d and the unknown parameters, β and γ, as well as a background mean response level and a fixed standard deviation estimate for all dose groups, are estimated by maximum likelihood methods. The parameter γ is not constrained to be an integer, but it is constrained to be greater than or equal to 1. If a normal distribution is assumed, the Weibull model can be expressed as the change in mean as a function of dose:

$m(d) = m(0) + \sigma[N^{-1}(1-p_0) - N^{-1}((1-p_0)\exp\{-(\beta*d)^{\gamma}\})]$, Eq. 4

where N^{-1} is the inverse normal function, σ is the standard deviation (assumed constant for all doses), β and γ are as shown in Equation 1, and m(0) is the mean response level at zero dose. Note that the operand of the second inverse

normal function in Equation 3 is equivalent to 1-P(d). Thus, Equation 3 shows how changes in the mean values for continuous data can be expressed in terms of probability of response.

The power model was also used to model continuous endpoints:

$$m(d) = \alpha + (\beta * d)^k, \qquad \text{Eq. 5}$$

where m(d) is the mean response at dose d and the three unknown parameters, α, β, and k, as well as the dose group standard deviations, are estimated by maximum likelihood methods. The dose group standard deviations estimated by the model account for both the variation in the data and for the difference between the observed mean and the mean estimated by the model. The parameter k is not constrained to be an integer, but it is constrained to be greater than or equal to 1.

Just as there was an equation specifying m(d) when P(d) was given by the Weibull model, so too are there equations giving the probabilities of response that correspond to changes in the means as given by the power model, i.e.,

$$P(d) = 1 - N[N^{-1}(1-p_0) - (\beta * d)^k/\sigma], \qquad \text{Eq. 6}$$

where N is the cumulative normal function, N^{-1} is its inverse, and σ is the standard deviation assumed to hold for the normal variation at all doses. This form is for those cases in which increased values of the endpoint are adverse. When decreased values are considered adverse, the corresponding equation for probability of response is

$$P(d) = N[N^{-1}(p_0) + (\beta * d)^k/\sigma]. \qquad \text{Eq. 7}$$

While the continuous form of the Weibull model assumes that the standard deviation is constant for all dose groups, the power model can be run either using the same or different standard deviations for each group. In Equations 6 and 7, a standard deviation common to all groups has been assumed; these equations will be used in the assessment of slopes (see below). However, in addition to the fixed standard deviation case, each endpoint was modeled using the power model with group-specific (different) standard deviations. Although the standard deviations do not appear explicitly in the power model (Equation 5), they are also estimated in the modeling and affect estimates of the probability of response (see Equations 6 and 7). Because the standard deviations define the spread of the data around the means predicted by Equation 5, constraining the standard deviations may affect the model fit to the extent that the predictions of the means must be altered in order to accommodate the single fixed standard deviation for all groups. When, as in the case of many of the epidemiological data sets considered here, no dose groups are defined, all models consider only a single standard deviation, assumed to be appropriate at all dose levels.

The benchmark response (BMR) levels can be defined in terms of either additional or extra risk, for all the endpoints. Additional risk is defined as

$$P(d) - P(0),$$

and extra risk is defined as

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

Because the p_0 values considered here correspond to a relatively small percentage of the unexposed population having abnormal values (i.e., $P(0) = p_0$ was relatively small), the difference between additional risk and extra risk would be minimal. We used additional risk as the basis for BMR definition in this analysis. This option is recommended for two reasons. First, the comparisons of BMDs and NOAELs done by Allen et al. (1994a, 1994b) and Kavlock et al. (1995) were done using additional risk; changing to extra risk might alter the relationships that were uncovered there and which, at this time, drive a number of decisions regarding the response levels to use for BMD

definition. Second, the software that is currently in use for applying the Weibull or power models for probability of response for continuous endpoints will only calculate additional risk.

The appropriate definition of the benchmark response is less understood for continuous endpoints than it is for quantal endpoints. For the modeling of continuous data based on probability of response, the most commonly used value of p_0 is 0.05 (5% of controls deficient); p_0 values of 0.05, 0.025, 0.01, and 0.001 were used to evaluate the sensitivity of the predicted NOAEL to the selection of p_0. Using the power model, a p_0 of 0.05 and a BMR of 0.1 is equivalent to defining the BMD as the dose that results in change in the mean response equal to 0.6 times the standard deviation (Crump, 1995). Kavlock et al. (1995) found that, for a fetal weight endpoint, a BMR defined as $sd_0/2$ yielded BMDs that were on average similar to the corresponding NOAELs for a set of developmental endpoints. Thus, in the absence of additional information, the combination of $p_0 = 0.05$ and BMR = 0.1 appears to be an appropriate choice for the BMD using the continuous models that predict results in terms of the probability of response. However, sufficient toxicological information was available for several endpoints to allow us to determine a best choice of p_0 in those cases, as discussed in the Results section. Because several authors (e.g., Jarup et al., 1988; Elinder et al., 1985) defined an adverse effect in their occupational studies as above the 97.5th percentile for the amount of β2-microglobulin in urine, we also included a p_0 value of 0.025. The use of an additional p_0 value at the upper end of the range may appear contradictory to a growing tendency toward considering lower background levels of response realistic. Low background levels of response are appropriate for many endpoints in laboratory animal studies conducted with homogeneous strains, but there is likely to be much wider variability in the human population.

It should be noted that none of the treatments of the continuous endpoints considered in Allen et al. (1994a) or Kavlock et al. (1995) corresponds to the proposed approach for the continuous endpoints in this analysis. Because of that uncertainty, many combinations of BMR (5% and 10%), p_0 (0.05, 0.01, 0.001), and models (Weibull and power, the latter with and without a single standard deviation) have been explored.

Determining Goodness of Fit

For the continuous models, goodness of fit was determined on a "global" basis by comparing the model predicted mean responses for each dose group to the corresponding observed means, and summing the squared differences. That sum of squares can be "normalized" and evaluated for significant differences by considering the variability of the observations within each dose group. More formally, an F-test was performed. This test automatically normalizes the differences between the observed and predicted means and accounts for the degrees of freedom associated with the predictions and those associated with the within-group variability.

The definition of degrees of freedom depends somewhat on the context. In cases where the experimental mean values for each dose group are compared with values predicted by the model (as is the case for the models considered here), the number of degrees of freedom is the difference between the number of dose groups and the number of parameters estimated in the model. In general, degrees of freedom specify how many residuals (differences between the model predictions and observations) are unconstrained by the model. When no dose groups are defined, this test can not be performed. No alternatives were considered in this analysis.

For some of the runs, the degrees of freedom was zero, so the p values could not be calculated; all statistical evaluations of fit require at least one degree of freedom. These cases are listed as "n/a" in the tables presenting the results. When degrees of freedom did exist, p-values for the F-test of 0.01 or less were considered indicative of potentially problematic fits; these cases were examined to determine the cause of the poor fits. Graphical examination was included in order to visualize the shape of the dose-response relationships to see where the model predictions were high or low relative to the observations. Similar, qualitative evaluations of the fit were conducted when no degrees of freedom were available.

To assess the model-dependence of the fit of the models to the data sets, the best-fitting Weibull model and power model with a single standard deviation were compared to one another. When the two models have the same number of parameters, the one with the greater log-likelihood can be considered the better fitting model. No test of

statistical significance is associated with this comparison. The power model that allowed for different standard deviations could not be compared to the other two continuous models in this manner. The additional parameters representing the separate standard deviations provide additional fit flexibility, so that allowing separate standard deviations for each experimental group will always result in fit at least as good (i.e., likelihoods at least as large) as using a single standard deviation for a given choice of model. However, this generalization does not hold when comparing across different models.

II. Data for Modeling

For all of the studies of kidney function measurements, two different definitions of the BMR were considered. First, modeling was considered based on defining an adverse level of urinary β2-microglobulin, and defining the BMR based on that adverse level, using a consistent urinary β2-microglobulin level as a cutpoint in all of the studies. This approach could not be used for modeling of the quantal data, because the data were reported in terms of the cutpoints used by the study authors. It was also unclear whether methodological differences among the studies would mean that the studies *should* have different cutpoints. These differences include variation in the method of urine sampling (spot versus 24-hour) and in whether pH was controlled to avoid degradation of the β2-microglobulin. In addition, comparison with age-matched controls is important, because kidney function deteriorates with age. Therefore, it was decided to define the BMR for each study relative to the control distribution for each level. Several of the study authors (e.g., Mason et al., 1988) defined proteinuria as values above the 95th percentile (although others, such as Jarup et al., 1988, used the 97.5 percentile) for the control population. Consistent with the former practice, a p_0 of 0.05 (i.e., a background response of 0.05) was used in the modeling of continuous endpoints, although BMCs based on p_0 of 0.025 were also calculated.

Modeling based on liver or kidney cadmium levels, as an internal dose measure of exposure, was considered, but excluded in favor of modeling cumulative exposure. This was because the numerous uncertainties in both the calculation of the critical kidney concentration and in converting that level into an exposure concentration outweigh the uncertainty in exposure determination. Much of the basis for the "threshold of 200 ppm" discussed by Kjellstrom et al. (1984), Roels et al. (1981), and others, and used as the basis for the current cadmium RfD (IRIS, 1996) comes from liver cadmium data. However considerable uncertainties are involved in the conversion from liver to kidney concentrations. Additional large uncertainties are associated with all of the parameters used in estimating cumulative exposure from the kidney level. In particular, it is difficult to account for the increase in cadmium excretion (and decrease in kidney cadmium) once kidney function is impaired. To some degree this is accounted for by using liver cadmium, and then converting to kidney cadmium, but liver cadmium will also not accurately reflect exposure if excretion is increased. By contrast, extensive cumulative occupational exposure data are available. Urinary cadmium levels were not modeled for studies of kidney function, because insufficient data were provided.

Inhalation

The kidney function data of Mason et al. (1988) were modeled. Only grouped data were reported for most endpoints, while individual data were reported for urinary RBP (expressed per millimole creatinine) versus cumulative exposure. These data were reported in two ways. First, data were reported as the difference in RBP from the matched control, versus individual exposure level. Second, tubular proteinuria was defined as urinary RBP >95th percentile for the referent population, and the incidence of proteinuria was reported for grouped exposure levels. Any differences between the BMC calculated using the two data sets can be attributed to two factors: (1) The second method uses grouped data rather than individual data, and is inherently less precise; and (2) Because kidney function deteriorates with age, the data based on differences from age-matched controls better reflects kidney dysfunction that can be attributed to cadmium. Both of these endpoints were modeled, the first based on individual data obtained from the study authors, and the second based on the grouped data (using the individual data to calculate the appropriate exposure levels for the groupings shown in Figure 4 of Mason et al., 1988).

Davison et al. (1988) evaluated lung function and chest radiographs in the same cohort as that studied by Mason et al. (1988). A significant trend with cumulative exposure index or liver cadmium levels was observed for

TLCO and KCO, but not for FEV_1 or FEV_1/FVC%. However, these data could not be modeled, because no information on variability was provided. Individual data were provided for the observed minus expected (O-E) KCO versus cumulative exposure, and the O-E values for KCO were modeled as a continuous endpoint.

Thun et al. (1989) evaluated kidney function in 45 male workers at a cadmium recovery plant and 32 age-matched male controls. Individual data were presented for several endpoints versus cumulative exposure. The individual data were modeled for β2-microglobulin and RBP, since these are the endpoints for which other studies provide data and for which there is information on what levels are adverse.

Elinder et al. (1985) evaluated β2-microglobulin levels in 58 males and 2 females exposed to cadmium in cadmium-containing solders for 4-24 years. Cumulative exposure was calculated on an individual basis by classifying each person's activities as high, medium, low, or no exposure, and estimating exposure levels for each category based on 1976 measurements. The grouped data were modeled, estimating the exposure levels as the midpoint of the reported ranges for each group. However, this study is limited by the estimate of cumulative exposure based only on measurements during one year, and by the uncertainty in the average exposure in the lowest cumulative exposure group (reported only as <1000 $\mu g/m^3$ year).

Jarup et al. (1988) evaluated cumulative cadmium exposure, cadmium blood levels, and urinary β2-microglobulin levels in 326 men and 114 women exposed to cadmium oxide dust for at least 3 months in a battery factory. β2-microglobulin exceeding 35 μg/mmol creatinine (310 μg/g creatinine) was defined as tubular proteinuria. This value was chosen based on the upper 2.5 percentile in populations without tubular dysfunction reported by other authors. Only the grouped data were reported. This study is limited because the only available definition of renal dysfunction is external to this study, and there is no method for controlling for variability in sampling methodology or subject age. However, the authors noted that similar dose-response functions were observed for the exposed subjects >60 years old and <60 years old. The incidence of tubular dysfunction was modeled, based on the grouped data with the reported cumulative exposure means.

Ellis et al. (1985) evaluated the effect of cadmium exposure on kidney function in 82 male workers, including 40 active and 21 retired cadmium production workers, 8 active and 4 retired office workers (unexposed), and 3 active and 6 retired nonproduction workers, many of whom had earlier prior exposure to cadmium. Abnormal kidney function was defined as β2-microglobulin levels >200 μg/g creatinine or total protein >250 μg/g creatinine, to be consistent with the definitions used by Roels et al. (1981). Kidney function data were reported on an individual cumulative exposure basis, but only as abnormal or normal, with no continuous data reported for urinary protein levels. The quantalized kidney function data were modeled, using individual exposure levels.

Oral

Nogawa et al. (1989) evaluated kidney function and cadmium exposure in a group of 1850 subjects exposed to cadmium in contaminated water and rice (878 males and 972 females), and 294 controls in Japan. β2-microglobulinuria was defined as >1000 μg/L, or as >1000 μg/g creatinine, and the incidence of microglobulinurea was presented as a function of grouped total cadmium intake. The incidence of β2-microglobulinurea was modeled based on the definition of 1000 μg/g creatinine; cumulative doses in mg/kg were estimated from the reported doses in mg using a default body weight of 70 kg. In light of the short stature of Japanese people, this is probably an overestimate of the actual body weight, and hence an underestimate of the actual dose. This study is limited because only the percent with kidney dysfunction were reported, and the definition of kidney dysfunction is much less conservative than that used by investigators of effects of cadmium following inhalation exposure to cadmium (typically 200-600 μg/g creatinine).

In an investigation of a population living in a cadmium-polluted area, Buchet et al. (1990) evaluated renal function and urinary cadmium in 1699 subjects. Cadmium intake by this population occurred via direct inhalation of cadmium, ingestion of contaminated water, and ingestion of contaminated food. Urinary excretion of RBP, N-acetyl-β-glucosaminidase, β2-microglobulin, amino acids, and calcium were associated with urinary cadmium excretion. The

study authors used a logistic regression model to estimated urinary cadmium levels at which >10% of the population would have abnormally high excretion of these markers (i.e., abnormal kidney function), but did not report confidence limits. This study could not be modeled for this analysis, because no information on the variability of the continuous response measure was reported.

III. Results

Quantal human data are presented in Tables C-1 and C-2 for inhalation and oral studies, respectively. Table C-3 presents the results from modeling of the continuous, individual human occupational epidemiology studies. Tables C-4 (inhalation) and C-5 (oral) summarize all studies considered for modeling, and present the BMD/BMC values of greatest relevance.

Grouped/Quantal Occupational Epidemiology Data

Modeling of the grouped data from the occupational inhalation studies provided generally quite good fits (Table C-1). Relatively poorer fits were due to nonmonotonicity of the data. For example, in Mason et al. (1988), the response at the second dose is lower than that at the lowest dose, and response at the third dose is higher than that at the fourth dose. Although an acceptable fit was obtained when all of the Jarup et al. (1988) data were modeled ($p = 0.07$), the fit was consistently biased in the low-dose region (predictions < observed) when all groups were included, even though the data in the low-dose region exhibited a smooth increase. The data were modeled, without the two highest doses and the overall fit improved somewhat ($p = 0.24$), and the BMC decreased to 1030 $\mu g/m^3$ x years, from 1530 $\mu g/m^3$ x years.

Three studies quantalized the response data into those with and without proteinuria, at least in part based on levels of urinary β-2microglobulin, although the cutpoint for an adverse response differed somewhat among the studies. Ellis et al. (1985) defined abnormal kidney function as β2-microglobulin levels >200 µg/g, or total protein >250 mg/g creatinine. The cutpoint for β2-microglobulin was lower than that used in other studies, and was defined to be consistent with the value used by Roels et al. (1981), which was derived in an unreported manner from the data of Buchet et al. (1980) on β2-microglobulin levels in unexposed workers. Unlike the other two studies, Ellis et al. also defined kidney dysfunction based on total protein. The number of people who did not meet the β2-microglobulin criterion but did meet the criterion based on total protein was not reported. Elinder et al. (1985) defined tubular dysfunction as >300 µg/g creatinine, based on "the upper 95 or 97.5 percentile for urinary excretion of β2-microglobulin among persons without tubular dysfunction...(Kjellstrom et al., 1977; Buchet et al., 1980; Kowal and Zirkes, 1983)." Similarly, Jarup et al. (1988) defined tubular proteinuria as >310 µg/g creatinine, based on the upper 2.5 percentile among "persons without tubular dysfunction" in the same studies. Although both of these studies report the cutpoint as being defined based on subjects without tubular dysfunction, it appears that the cutpoints were actually defined based on unexposed subjects, since no prior screening for kidney function was conducted (e.g., Kjellstrom et al., 1977). If this is the case, the cutpoints define a background level of response (p_0) (~2.5%) in the unexposed population, and the corresponding response levels define a cutpoint in the same sense as the cutpoint (x_0) used for BMC modeling. It is possible to fix either of these parameters (but not both) for the benchmark modeling. Kjellstrom et al. (1977) noted, however, that the definition of proteinuria used in the epidemiology studies may not be the same as the clinical definition of proteinuria.

The BMCs (in units of $\mu g/m^3$ x years) for the Ellis, Elinder, and Jarup studies correlated with the authors' cutpoints, with cutpoints of >200, >300, and >310 µg/g creatinine resulting in BMCs of 116, ~300, and 1030 $\mu g/m^3$ x years, respectively. Although the cutpoints used by Elinder et al. (1985) and Jarup et al. (1988) are quite similar, a much lower BMC was calculated using the Elinder data, due to the higher response at the lowest cumulative dose and the overall steeper dose-response in the Elinder study. Differences in sampling methodologies may also account for part of variation in BMCs relative to the cutpoints. Ellis et al. (1985) used 24-hour urine samples and adjusted the pH to improve protein stability, Elinder et al. (1985) used spot urine samples and also adjusted pH, and Jarup et al. (1988) did not report the type of urine sampling or whether urinary pH was adjusted. Thus, although the size of the cutpoint appears to be a major determinant of the BMC, other factors also play a role.

In light of an expected background incidence of kidney tubular dysfunction in the subject population, the modeling was conducted by allowing the computer to compute the background term. For most of the studies, a nonzero background of reasonable size (0.01-0.03) was calculated. A considerably larger background (0.15 using the polynomial model and 0.22 using the Weibull model) was calculated for the Elinder data, and a considerably smaller background (0.004) was calculated for the Jarup data with the two high doses dropped. With the exception of the Elinder data, these values are generally consistent with the background incidences used in the corresponding studies. The high background in the Elinder study is related to the overall trend of the data, and, for the Weibull model, the flattening of the dose-response curve at the lower doses which is characteristic of these models. This high background also contributes to the lower BMC for this study compared to Jarup, since a BMR defined based on extra risk includes [1-P(0)] in the denominator. One would expect greater similarities between the BMCs calculated for the Jarup and Elinder studies using additional risk.

Mason et al. (1988) quantalized their data by defining tubular proteinuria as a urinary retinol binding protein (RBP) level greater than the 95th percentile in the control population (i.e., a background response of 5%). For this analysis, the exposure levels were calculated for the grouped data based on the individual exposure levels separately provided by the authors; a BMC of about 180 was estimated, based on the grouped data. Unlike for the continuous data in this study, no comparison to the matched referent or adjustment for age-related changes in RBP excretion were made for the quantalized data. Because the study authors did not report the RBP level at the 95th percentile, and did not state the corresponding level of β2-microglobulin, a direct comparison with the other quantalized studies is not easy. However, based on the individual data, OSHA (1992) estimated the 95th percentile as corresponding to 338 µg RBP/g creatinine. OSHA (1992) also conducted a log-log regression comparing the RBP and β2-microglobulin levels for samples in this study for which both values were available. It was estimated that a β2-microglobulin level of 300 µg/g creatinine, the cutpoint used in other studies, corresponds to an RBP level of 156 µg/g creatinine. Thus, the cutpoint used by Mason et al. appears to be markedly higher than that used by other studies, even though the BMC is lower. The lower BMC can be attributed to the steep dose-response curve for this study for the direct determination based on RBP levels.

Continuous Data

Modeling of the continuous data based on individual responses might be considered to be less successful than modeling of the quantalized data. There was a high degree of scatter in the individual data, and this scatter was reflected in generally poor model fits and, to some degree, greater model dependence. It should be emphasized, however, that these fitting problems were a direct result of the incomplete correlation between dose and response, reflecting the inherent variability of the data, rather than being related to difficulty in fitting mathematical models to the data. The scatter may be due to miscalculation of cumulative exposures, the uncontrolled nature of these studies, and inherent human variability. As described in the Methods section, goodness-of-fit p values were not calculated for the continuous data. The data variability was smoothed out when the subjects were grouped by cumulative exposure level and the study authors quantalized the response, as for the studies discussed above. An additional source of uncertainty for most of the continuous data is related to the fact that the exposure and response levels were estimated by digitizing data points on graphs in published papers. Since several of the graphs were rather small, especially in the Thun et al. (1989) study, the resolution of this technique is limited. This concern does not apply to the Mason et al. (1988) data, which were modeled based on the individual data provided by the study authors.

In light of the discussion above on the background level of response, p_0 values of 0.025-0.05 were emphasized in the data analysis. P_0 values of 0.05 were chosen as most relevant, because they lead to model estimates of the cutpoint (x_0) more consistent with values used by other authors (Elinder et al., 1985; Jarup et al., 1988). BMRs of 10% were chosen for all studies, consistent with the emphasis on 10% risk.

Continuous data on kidney function was available both for β2-microglobulin levels, and using RBP as a marker protein. Most of the dose-response curve for the β2-microglobulin levels in Thun et al. (1989) can be attributed to five individuals (one data point, at 62756 µg/g creatinine, appeared to be an outlayer). Aside from these five points, the dose-response curve is essentially flat, with a slight positive slope. BMCs of 1838-1964 $\mu g/m^3$ x years were

estimated for a p_0 of 0.05, and BMCs of 2444-2616 μg/m^3 x years for a p_0 of 0.025. A better dose-response curve was observed for RBP levels in this study, although there was still considerable data scatter. Because the Weibull model curves downward in the low-dose region, while the predicted power model was straight, considerable model dependency was observed, with a lower BMC predicted by the Weibull model (646 μg/m^3 x years) than by the power model (1975 μg/m^3 x years).

As mentioned in the Methods section, modeling of continuous data can be conducted either using a defined background response level (p_0), or using a defined cutpoint (x_0). Since we chose to use a defined p_0, it is informative to compare the x_0 value calculated by the model with the cutpoints used by other authors. This comparison could only be done for β2-microglobulin, since that was the only endpoint for which authors defined a numerical cutpoint. As shown in Table C-2, the x_0 values calculated for the Thun study (12,700-12,800 for p_0 of 0.05, 15,100-15,200 for p_0 of 0.025) are much higher than the values of 200-300 used by Ellis et al., Elinder et al., and Jarup et al. The large values estimated for x_0 can be attributed to the relatively high estimate of the background mean (~240 μg/g creatinine based on the Weibull model and ~135 μg/g creatinine based on the power model) and the large degree of scatter in the data. The hybrid model approach estimates both the background mean and standard deviation. The high variability (scatter) around the model-predicted means entails a high x_0 corresponding to p_0 values of 0.05 and 0.025.

As mentioned above, Mason et al. (1988) presented their results not only as grouped data, but also as individual comparisons with the matched controls. The latter method has the advantage of taking age-related changes in kidney function into account. The BMCs calculated based on the individual data showed model dependence, with a BMC of 251 μg/m^3 x years calculated by the Weibull model and a BMC of 1340 μg/m^3 x years calculated by the power model, although the MLE estimates differed by less than a factor of 2. Because response was measured as difference from the matched control, the modeled curve should go through 0 response at 0 dose. As shown in Figure 11, both the power and Weibull models approach this response pretty well. The Weibull model predicts a BMC closer to the BMC calculated using the same data, as quantalized by the study authors (~1801 μg/m^3 x years; see discussion above and Table C-1). The development of models for which the background mean response can be fixed at a particular value would allow the model to be forced through the origin for data sets such as this.

Davison et al. (1988) studied lung function in the same cohort as studied by Mason et al. (1988). Although numerous endpoints were assessed, data appropriate for modeling on the basis of exposure were provided only for carbon monoxide transfer (KCO). As for the other individual data sets, there was considerable scatter, but the data exhibited a clear dose-related trend. Considerable model dependence was observed. A BMC of 262 μg/m^3 x years was calculated by the Weibull model, compared with a BMC of 2090 μg/m^3 x years using the power model (Table C-3). Because KCO was reported as the difference from the expected value, the response should go through 0 at zero dose. The power model should accomplish this much better than the Weibull model, due to the upward curvature of the Weibull model in the low-dose range.

Comparison of Modeled Values with NOAELs and LOAELs

Throughout this discussion, no mention has been made of the NOAELs and LOAELs identified in the epidemiology studies. The primary reason for this is that most of the studies did not identify NOAELs, and most of the LOAELs can be directly related to arbitrary grouping of exposure levels. No threshold was evident in modeling of any of the continuous data for individuals (Mason et al., 1988; Davison et al., 1988; Thun et al., 1989). Limited data from studies with quantalized data provide information on a NOAEL. Ellis et al. (1985) observed no effect (0/9) in the group with a cumulative exposure of ≤20 μg/m^3 x years (mean, 7.5 μg/m^3 x years), and a response of 1/10 in the group with an average exposure of 54 μg/m^3 x years. However, this study is limited by the small sample sizes. Jarup et al. (1988) found 3/264 cases (1.1% response, a NOAEL) in the group with cumulative exposure <359 μg/m^3 x years (mean 131 μg/m^3 x years). The LOAEL was the group with 359-<1710 μg/m^3 x years (mean 691 μg/m^3 x years), with a response of 7/76, or 9.2%.

Oral Epidemiology Data

Only one oral study was available for modeling. Nogawa et al. (1989) assessed the prevalence of β2-microglobulinuria in an area of Japan with high cadmium levels in the water, and estimated dose for each individual based on years of residence in the region and the concentration of cadmium in the rice. The study authors defined β2-microglobulinuria as levels ≥1000 µg/g creatinine, a much higher cutpoint than that used in the occupational studies. Poor fits ($p<10^{-6}$) were obtained for both the male and female data, although visually the models appear to fit the female data reasonably well, especially in the low-dose region. It would be of interest to determine if dropping the one outlier in the female data at about 45 mg/kg would lead to an acceptable fit. As for the occupational data, the poor fit results from the scatter of the data, rather than from a general inability of the models to represent the dose-response trends apparent in the data. For the males, groups of the data points appear fall on separate dose-response curves apearing to begin at a dose of about 34 mg/kg and a response of 0). It is unclear if these data suggest an error in the study author's calculation of doses. The age categories for females (Table 4 in Nogawa et al., 1989) show an orderly upward progression from 57 to 77 years, while the age categories for males in the same table repeat ages near 59 years multiple times. However, if the reported doses were underestimates, the correct data would have an even greater data scatter. Use of an incorrect age in the calculation of cumulative dose may have led to the apparent wide scatter of the data. A BMD of 28.2-33.4 mg/kg was calculated for males, and a BMD of 19.2-23.1 mg/kg/was calculated for females. The data scatter in the Nogawa et al. (1989) study makes it difficult to identify a NOAEL and LOAEL. However, the NOAEL for males appears to be 21 mg/kg (response of 1/32 [3%]) and the LOAEL is about 28 mg/kg (response of 3/45 [7%] at 27.7 mg/kg and 2/10 at 28.3 mg/kg). For females, the NOAEL is 21 mg/kg (response of 2/51, or 4%), and the LOAEL is 27 mg/kg (response of 11/116, or 9.5%). The NOAELs and BMDs for this study are generally in good agreement, and the values for males and females are fairly close to each other. The slightly lower BMDs calculated for females is related to at least some degree to the fact that a default of 70 kg body weight was used for both males and females. The BMDs for males and females would have been more similar if doses were calcualted using sex-specific body weights.

Several factors would tend to bias the calculated BMD both above and below the "correct" BMD. Because the cutpoint used by the authors to define kidney dysfunction (1000 µg β2-microglobulin/g creatinine) was higher than those used in the occupational studies, the response may have been underestimated, leading to an *over*estimate of the BMD. However, cadmium intake in water was not included in the estimated dose. The study authors stated that more than 70% of the total cadmium intake in that region is derived from rice. Thus, dose may have been underestimated by as much as 42% (30/70), or ~80%. Body weights of the subjects were also probably lower than the default of 70 kg used to calculate dose in mg/kg from the dose in mg, leading to further underestimation of the dose. These underestimates of the dose would lead to an *under*estimate of the BMD. In light of these considerations, and the dosage uncertainty inherent in epidemiological studies, it is encouraging that the NOAEL calculated based on pharmacokinetic considerations is within an order of magnitude of BMDs calculated based on intake, and either set of values would be appropriate as the basis for an RfD.

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Table C-1. Quantal Endpoints for Inhalation Epidemiological Studies of Cadmium

Model	BMR	MLE	BMD	Log-likelihood	G-O-F P-value	Chi-square
Ellis et al. 1988, Kidney Dysfunction, Human						
Polynomial Quantal	1.00e-01	1.64e+02	1.16e+02	-3.41e+01	9.03e-01	1.05e+00
Polynomial Quantal	5.00e-02	7.99e+01	5.63e+01	-3.41e+01	9.03e-01	1.05e+00
Weibull Quantal	1.00e-01	1.64e+02	1.16e+02	-3.41e+01	9.59e-01	1.05e+00
Weibull Quantal	5.00e-02	7.98e+01	5.63e+01	-3.41e+01	9.59e-01	1.05e+00
Elinder el al. 1985, Kidney Tubular Dysfunction, Human						
Polynomial Quantal	1.00e-01	8.32e+02	3.04e+02	-3.32e+01	8.23e-01	3.89e-01
Polynomial Quantal	5.00e-02	4.09e+02	1.48e+02	-3.32e+01	8.23e-01	3.89e-01
Weibull Quantal	1.00e-01	1.66e+03	2.93e+02	-3.35e+01	6.55e-01	8.47e-01
Weibull Quantal	5.00e-02	1.25e+03	1.43e+02	-3.35e+01	6.55e-01	8.47e-01
Jarup et al. 1988, Kidney Tubular Dysfunction, Human						
Polynomial Quantal	1.00e-01	2.07e+03	1.53e+03	-1.03e+02	7.18e-02	8.60e+00
Polynomial Quantal	5.00e-02	1.01e+03	7.47e+02	-1.03e+02	7.18e-02	8.60e+00
Weibull Quantal	1.00e-01	2.07e+03	1.53e+03	-1.03e+02	7.18e-02	8.60e+00
Weibull Quantal	5.00e-02	1.01e+03	7.47e+02	-1.03e+02	7.18e-02	8.60e+00
Jarup et al. 1988, Kidney Tubular Dysfunction, Human (2 high dropped)						
Polynomial Quantal	1.00e-01	1.43e+03	1.03e+03	-8.38e+01	2.39e-01	2.86e+00
Polynomial Quantal	5.00e-02	6.97e+02	5.00e+02	-8.38e+01	2.39e-01	2.86e+00
Weibull Quantal	1.00e-01	1.43e+03	1.03e+03	-8.38e+01	2.39e-01	2.86e+00
Weibull Quantal	5.00e-02	6.97e+02	5.00e+02	-8.38e+01	2.39e-01	2.86e+00

Table C-1. Quantal Endpoints for Inhalation Epidemiological Studies of Cadmium (continued)

Model	BMR	MLE	BMD	Log-likelihood	G-O-F P-value	Chi-square
Mason et al. 1988, Kidney effects-Incidence of proteinurea, Human						
Polynomial Quantal	1.00e-01	3.70e+02	1.81e+02	-2.97e+01	1.33e-01	5.60e+00
Polynomial Quantal	5.00e-02	1.89e+02	8.80e+01	-2.97e+01	1.33e-01	5.60e+00
Weibull Quantal	1.00e-01	4.98e+02	1.85e+02	-2.96e+01	1.42e-01	5.44e+00
Weibull Quantal	5.00e-02	3.04e+02	8.99e+01	-2.96e+01	1.42e-01	5.44e+00

Table C-2. Quantal Endpoints for Epidemiological Studies of Oral Exposure to Cadmium

Model	BMR	MLE	BMD	Log-likelihood	G-O-F P-value	Chi-square
Nogawa et al 89 % ß2-Microglobulinuria in Human Males (Wt=70kg)						
Polynomial Quantal	1.00e-01	3.89e+01	2.82e+01	-3.72e+02	1.21e-06	4.44e+01
Polynomial Quantal	5.00e-02	1.99e+01	1.38e+01	-3.72e+02	1.21e-06	4.44e+01
Weibull Quantal	1.00e-01	6.00e+01	3.34e+01	-3.73e+02	3.01e-07	4.76e+01
Weibull Quantal	5.00e-02	5.01e+01	2.07e+01	-3.73e+02	3.01e-07	4.76e+01
Nogawa et al 89 % ß2-Microglobulinuria in Human Females (Wt=70kg)						
Polynomial Quantal	1.00e-01	2.25e+01	1.92e+01	-4.85e+02	0.00	8.16e+01
Polynomial Quantal	5.00e-02	1.10e+01	9.36e+00	-4.85e+02	0.00	8.16e+01
Weibull Quantal	1.00e-01	2.71e+01	2.31e+01	-4.86e+02	1.05e-14	8.20e+01
Weibull Quantal	5.00e-02	1.76e+01	1.37e+01	-4.86e+02	1.05e-14	8.20e+01

Table C-3. Continuous Endpoints for Inhalation Epidemiological Studies of Cadmium

Model	Standard Deviation	P0	X0	BMR	MLE	BMD	Upper Bound	Log-likelihood	G-O-F P-value
Thun et al. 1989, human occupational inhalation, ß2 microglobulin									
Weibull, P0 fixed	One	5.00e-02	1.28e+04	1.00e-01	3.48e+03	1.84e+03	5.53e+03	-6.51e+02	n/a
Weibull, P0 fixed	One	5.00e-02	1.28e+04	5.00e-02	2.62e+03	1.15e+03	4.60e+03	-6.51e+02	n/a
Weibull, P0 fixed	One	2.50e-02	1.52e+04	1.00e-01	4.14e+03	2.44e+03	6.19e+03	-6.51e+02	n/a
Weibull, P0 fixed	One	2.50e-02	1.52e+04	5.00e-02	3.18e+03	n/a	n/a	-6.51e+02	n/a
Weibull, P0 fixed	One	1.00e-02	1.80e+04	1.00e-01	5.04e+03	3.34e+03	7.10e+03	-6.51e+02	n/a
Weibull, P0 fixed	One	1.00e-02	1.80e+04	5.00e-02	4.00e+03	2.34e+03	6.00e+03	-6.51e+02	n/a
K Power, P0 fixed	One	5.00e-02	1.27e+04	1.00e-01	3.45e+03	1.96e+03	5.86e+03	-6.51e+02	n/a
K Power, P0 fixed	One	5.00e-02	1.27e+04	5.00e-02	2.36e+03	1.17e+03	4.63e+03	-6.51e+02	n/a
K Power, P0 fixed	One	2.50e-02	1.51e+04	1.00e-01	4.30e+03	2.62e+03	6.71e+03	-6.51e+02	n/a
K Power, P0 fixed	One	2.50e-02	1.51e+04	5.00e-02	3.10e+03	1.68e+03	5.45e+03	-6.51e+02	n/a
K Power, P0 fixed	One	1.00e-02	1.79e+04	1.00e-01	5.40e+03	3.56e+03	7.81e+03	-6.51e+02	n/a
K Power, P0 fixed	One	1.00e-02	1.79e+04	5.00e-02	4.14e+03	2.49e+03	6.58e+03	-6.51e+02	n/a

Table C-3. Continuous Endpoints for Inhalation Epidemiological Studies of Cadmium (continued)

Model	Standard Deviation	P0	X0	BMR	MLE	BMD	Upper Bound	Log-likelihood	G-O-F P-value
Thun et al. 1989, human occupational inhalation, RBP Level									
Weibull, P0 fixed	One	5.00e-02	3.66e+02	1.00e-01	1.55e+03	6.46e+02	3.81e+03	-3.77e+02	n/a
Weibull, P0 fixed	One	5.00e-02	3.66e+02	5.00e-02	8.63e+02	3.15e+02	2.74e+03	-3.77e+02	n/a
Weibull, P0 fixed	One	2.50e-02	4.14e+02	1.00e-01	2.20e+03	9.21e+02	4.68e+03	-3.77e+02	n/a
Weibull, P0 fixed	One	2.50e-02	4.14e+02	5.00e-02	1.27e+03	4.46e+02	3.40e+03	-3.77e+02	n/a
Weibull, P0 fixed	One	1.00e-02	4.71e+02	1.00e-01	3.34e+03	1.58e+03	6.68e+03	-3.77e+02	n/a
Weibull, P0 fixed	One	1.00e-02	4.71e+02	5.00e-02	2.02e+03	7.67e+02	4.44e+03	-3.77e+02	n/a
K Power, P0 fixed	One	5.00e-02	3.81e+02	1.00e-01	2.69e+03	1.98e+03	4.58e+03	-3.77e+02	n/a
K Power, P0 fixed	One	5.00e-02	3.81e+02	5.00e-02	1.59e+03	1.18e+03	3.18e+03	-3.77e+02	n/a
K Power, P0 fixed	One	2.50e-02	4.30e+02	1.00e-01	3.56e+03	2.63e+03	5.64e+03	-3.77e+02	n/a
K Power, P0 fixed	One	2.50e-02	4.30e+02	5.00e-02	2.28e+03	1.69e+03	4.08e+03	-3.77e+02	n/a
K Power, P0 fixed	One	1.00e-02	4.87e+02	1.00e-01	4.82e+03	3.56e+03	7.42e+03	-3.77e+02	n/a
K Power, P0 fixed	One	1.00e-02	4.87e+02	5.00e-02	3.40e+03	2.50e+03	5.45e+03	-3.77e+02	n/a

Table C-3. Continuous Endpoints for Inhalation Epidemiological Studies of Cadmium (continued)

Model	Standard Deviation	P0	X0	BMR	MLE	BMD	Upper Bound	Log-likelihood	G-O-F P-value
Mason et al. 1988, human occupational inhalation, difference in RBP									
Weibull, P0 fixed	One	5.00e-02	9.24e+00	1.00e-01	8.90e+02	2.51e+02	1.73e+03	-7.47e+01	n/a
Weibull, P0 fixed	One	5.00e-02	9.24e+00	5.00e-02	5.50e+02	1.25e+02	1.19e+03	-7.47e+01	n/a
Weibull, P0 fixed	One	2.50e-02	9.83e+00	1.00e-01	1.24e+03	4.19e+02	2.21e+03	-7.47e+01	n/a
Weibull, P0 fixed	One	2.50e-02	9.83e+00	5.00e-02	8.01e+02	2.24e+02	1.56e+03	-7.47e+01	n/a
Weibull, P0 fixed	One	1.00e-02	1.05e+01	1.00e-01	1.81e+03	7.51e+02	2.95e+03	-7.47e+01	n/a
Weibull, P0 fixed	One	1.00e-02	1.05e+01	5.00e-02	1.23e+03	4.36e+02	2.15e+03	-7.47e+01	n/a
K Power, P0 fixed	One	5.00e-02	9.72e+00	1.00e-01	1.65e+03	1.34e+03	2.24e+03	-7.79e+01	n/a
K Power, P0 fixed	One	5.00e-02	9.72e+00	5.00e-02	9.87e+02	7.98e+02	1.39e+03	-7.79e+01	n/a
K Power, P0 fixed	One	2.50e-02	1.03e+01	1.00e-01	2.20e+03	1.78e+03	2.92e+03	-7.79e+01	n/a
K Power, P0 fixed	One	2.50e-02	1.03e+01	5.00e-02	1.41e+03	1.14e+03	1.94e+03	-7.79e+01	n/a
K Power, P0 fixed	One	1.00e-02	1.09e+01	1.00e-01	2.99e+03	2.42e+03	3.91e+03	-7.79e+01	n/a
K Power, P0 fixed	One	1.00e-02	1.09e+01	5.00e-02	2.10e+03	1.69e+03	2.79e+03	-7.79e+01	n/a

Table C-3. Continuous Endpoints for Inhalation Epidemiological Studies of Cadmium (continued)

Model	Standard Deviation	P0	X0	BMR	MLE	BMD	Upper Bound	Log-likelihood	G-O-F P-value
Davison et al. 1988, human occupational inhalation, Carbon monoxide diffusion									
Weibull, P0 fixed	One	5.00e-02	2.83e+00	1.00e-01	6.86e-01	2.62e-01	5.14e+00	1.96e+01	n/a
Weibull, P0 fixed	One	5.00e-02	2.83e+00	5.00e-02	3.33e-01	1.27e-01	3.76e+00	1.96e+01	n/a
Weibull, P0 fixed	One	2.50e-02	2.78e+00	1.00e-01	7.75e-01	2.70e-01	6.32e+00	1.96e+01	n/a
Weibull, P0 fixed	One	2.50e-02	2.78e+00	5.00e-02	3.77e-01	1.31e-01	4.64e+00	1.96e+01	n/a
Weibull, P0 fixed	One	1.00e-02	2.73e+00	1.00e-01	8.70e-01	2.76e-01	8.58e+00	1.96e+01	n/a
Weibull, P0 fixed	One	1.00e-02	2.73e+00	5.00e-02	4.23e-01	1.34e-01	6.06e+00	1.96e+01	n/a
K Power, P0 fixed	One	5.00e-02	2.61e+00	1.00e-01	3.06e+00	2.09e+00	6.32e+00	1.89e+01	n/a
K Power, P0 fixed	One	5.00e-02	2.61e+00	5.00e-02	1.83e+00	1.25e+00	4.52e+00	1.89e+01	n/a
K Power, P0 fixed	One	2.50e-02	2.50e+00	1.00e-01	4.08e+00	2.78e+00	7.78e+00	1.89e+01	n/a
K Power, P0 fixed	One	2.50e-02	2.50e+00	5.00e-02	2.62e+00	1.79e+00	5.69e+00	1.89e+01	n/a
K Power, P0 fixed	One	1.00e-02	2.37e+00	1.00e-01	5.54e+00	3.78e+00	1.03e+01	1.89e+01	n/a
K Power, P0 fixed	One	1.00e-02	2.37e+00	5.00e-02	3.88e+00	2.65e+00	7.49e+00	1.89e+01	n/a

Table C-4. Summary of Inhalation Epidemiology Studies of Cadmium

Study	Endpoint/BMR definition	NOAEL ($\mu g/m^3$ x years)	LOAEL ($\mu g/m^3$ x years)	NOAEL(HEC) ($\mu g/m^3$)	BMC ($\mu g/m^3$ x years)	BMC(HEC) ($\mu g/m^3$)
Ellis et al. 1985	Incidence of kidney dysfunction, based on β2-microglobulin >200 µg/g creatinine or total protein >250 mg/g creatinine	7.5	54	0.036	116	0.57
Jarup et al. 1988	Incidence of kidney dysfunction, based on β2-microglobulin >310 µg/g creatinine, derived from upper 2.5 percentile among unexposed populace	131	691	0.69	1030	5.2
Elinder et al. 1985	Incidence of kidney dysfunction, based on β2-microglobulin >300 µg/g creatinine, derived from upper 2.5-5 percentile among unexposed populace	N/A	N/A	N/A	293-304	1.5
Mason et al. 1988	Incidence of tubular proteinuria, defined as urinary RBP >95th percentile of referent population. Estimated by OSHA (1992) as corresponding to ~650 µg β2-microglobulin/g creatinine	N/A	N/A	N/A	181	0.93
	Difference from matched referent for urinary RBP, $p_0 = 0.05$	N/A	N/A	N/A	251 (Weibull) 1340 (Power)	1.3 (Weibull) 6.8 (Power)
Davison et al. 1988	Observed - expected for carbon monoxide transfer coefficient, $p_0 = 0.05$	N/A	N/A	N/A	2090	11
Thun et al. 1989	β2-microglobulin, $p_0 = 0.05$	N/A	N/A	N/A	1838-1964	9.3-10
	RBP, $p_0 = 0.05$	N/A	N/A	N/A	646 (Weibull) 1975 (Power)	3.3 (Weibull) 10 (Power)

Table C-5. Summary of Oral Epidemiology Studies of Cadmium

Study	Endpoint/BMR definition	NOAEL (total mg/kg)	LOAEL (total mg/kg)	NOAEL mg/kg/day	BMD (total mg/kg)	BMD mg/kg/day
Nogawa et al. (1989) Males	Incidence of kidney dysfunction, based on β2-microglobulin >1000 µg/g creatinine	21	28	0.0008	28.2-33.4	0.001-0.0013
Nogawa et al. (1989) Females	Incidence of kidney dysfunction, based on β2-microglobulin >1000 µg/g creatinine	21	27	0.0008	19.2-23.1	0.00075-0.0009