mesothelioma risk from exposures in early life" [Ex. 312a, p. 8].

In addition, Crump performed a statistical analysis which demonstrated that the use of a delay model (such as the one proposed by OSHA) will always result in higher estimates of mortality rates at older ages than use of a model which does not incorporate a delay. He concluded that "Thus, rather than compensating for the reduction in risk, OSHA's use of a model with a delay exacerbates the tendency to overestimate risk at older ages" [Ex. 312a, p. 9].

As pointed out by Drs. Crump and Schneiderman, most studies of mesothelioma risk demonstrate that mortality risks are a power of elapsed time since first exposure, and this formulation has received widespread support. In general, the selection of a power of 3 is a reasonable choice and has been used by other reputable bodies (e.g. CHAP, Ex. 84-256). As noted by Dr. Schneiderman, the choice of a power of 3 will tend to give lower estimates of risk other choices of exponents which are also consistent with the available data. In addition, while Crump raised some doubts about the use of a "delay" model, the model also has widespread support in the scientific community (e.g. NAS/NRC, Ex. 321, CHAP. Ex. 84-256). Moreover, Dr. Crump's multistage model also contains a form of delay.

While there is some indication that these risks are, by no means overestimates, the benzene decision gave OSHA leeway to make assumptions which err on the side of overprotection of workers. Thus, OSHA believes the model it has used in the proposal to predict mesothelioma to be a reasonable consideration of the available data and has not changed it for the final rule.

In addition to the selection of the time factor, Dr. Crump also expressed concern over OSHA's assumption that the dose-response relationship was linear. He noted that:

> The second assumption, namely a linear dose response, is particularly subject to doubt for mesothelioma because there is virtually no dose response data for this cancer. Finkelstein (1983) [Ex. 84-240] contains a table showing dose-response data for mesothelioma derived from a total of only nine mesotheliomas. The Simpson Report (Health and Safety Executive, 1979 [Ex. 84-216]) contained a table (Table 31X) showing a dose response for mesothelioma derived from a case control analysis of data of McDonald *et al.*; however, the table did not appear in the published paper (McDonald *et al.*, 1980) [Ex. 237A, p. 35].

Crump plotted the Finkelstein mesothelioma data with linear, quadratic and cubic dose-response curves and observed that "The linear model appears to fit only slightly better than the quadratic, and even the cubic model falls well within the crude 90% confidence bounds" [Ex. 237A, p. 36]. *Crump concluded that:*

> Consequently, a linear dose response for mesothelioma is an assumption which has not been verified observationally. Since it seems biologically implausible that a dose response for cancer would ever be supralinear (Crump 1984) the linear assumption appears very unlikely to lead to an underestimate of risk from exposure to low concentrations. However, it could possibly provide an overestimate. There have been two general arguments which suggest that a linear dose response is plausible for many carcinogens. One such argument applies for carcinogens that "act by directly causing a mutation in DNA" (NRC, 1977). However, this argument may not be applicable to the carcinogenic mechanism of asbestos in producing mesotheliomas because asbestos has not been shown to be particularly mutagenic. The other general argument holds for carcinogens that produce cancers by the same mechanism by which background tumors are produced (Peto, 1978). However, since the background rate of mesotheliomas is either zero or—at most—very small, this argument is not applicable either [Ex. 237A, p. 36].

In an effort to investigate the effects of the choice of the model for mesothelioma, Crump fit a multistage model to the mesothelioma data used by OSHA. He described the model thus:

> The multistage model, in its most detailed and complete form (Day and Brown, 1980 and Crump and Howe, 1984), is derived from the assumptions that cancer is initiated in a single cell only after the cell passes through several stages. Cells compete independently to be the first to produce a tumor. The rate at which a cell passes through a dose-related stage is assumed to be proportional to the instantaneous dose.
>
> The model predicts a linear response at low dose whenever either 1) cancers occur "spontaneously" without a carcinogenic insult, or 2) there is only one dose-related stage; otherwise the model predicts a nonlinear response (Crump *et al.*, 1976). The evidence for spontaneous occurrence of mesotheliomas is lacking; consequently, the only way the multistage model can predict a linear response at low dose is for there to be only one dose-related stage. Since there is essentially no dose-response data for mesothelioma, the number of dose-related stages for mesothelioma is open to question [Ex. 237A, p. 44].

At the hearing, Dr. Nicholson defended the use of the linear dose-response assumption to predict mortality from mesothelioma, stating that:

> There's no indication that mesothelioma develops as a result of asbestos fibers acting separately at different stages in the cancer process, which would be required in the multi-stage model to elicit a nonlinear response.
>
> I know of no mechanistic basis that . . . or no experimental data that indicate that that is the case at all.
>
> The limited data what we have, and it is less than that for lung cancer, suggests that linearity is compatible with the data that exists. The data are sufficiently uncertain that one can't say that absolutely linearity is the case. The fact that it's applicable in the case of lung cancer, [a]nd has plausibility of an asbestos fiber doing something, [a]nd the probability of that something being done would be proportional to the number of fibers available to do it exists, and, thus linearity is a most reasonable choice. . . .
>
> One could envision, for example, that mesothelioma comes from those fibers that manage to penetrate the lung wall and get to the pleura. And that in heavy exposure circumstances, the fibrosis that would be present would limit the number that would cross the wall. Thus, you would have in the heavy exposed circumstances fewer mesotheliomas because fewer fibers can penetrate to the pleura than in lower exposure circumstances, giving you a concave downward dose response relationship.

That's just a speculation, as is the speculation of a multi-fiber action at one site. And I don't think either have sufficiently substantive backing to deviate from the use of the linear dose response relationship, which has stood us in good stead in most other circumstances [Tr. 6/19, p. I-140-142]

TABLE 3.— ESTIMATES OF K_M and Goodness of Fit From Six Studies of Occupational Exposure to Asbestos[a]

		Selikoff (180)[b]	Seidman (14)	Finkelstein (11)	Peto (7)	Dement (1)	Weill (2)
OSHA[c]	K_M[d]	1.0	5.7	12	0.7	0.22	0.07
	P[e]	0.07	0.74	0.39	.99	0.67	0.001
MS1[f]	K_M	110	300	7,600	40	12	3.6
	P	0.76	0.12	0.97	0.99	0.32	0.037
MS2[g]	K_M	12	100	270	1.9	4.4	0.76
	P	0.62	0.39	0.99	0.69	0.39	0.39
MS3[h]	K_M	0.59	2.4	15	0.061	3.1	0.016
	P	0.62	0.73	0.83	0.99	0.39	0.90

[a] Crump (Ex. 237A).
[b] Number of Mesothelioma Deaths.
[c] Estimates derived from OSHA model (Ex. 84-392). P values and K_M for Dement et al. and Weill et al. from Crump (Ex. 237A).
[d] $K_M \times 10^8$
[e] P Value associated with Chi-squared goodness-of-fit test.
[f] Estimates derived from multistage model with one dose-related stage.
[g] Estimates derived from Multistage model with two dose-related stages.
[h] Estimates derived from multistage model with three dose-related stages.