

**Integrating Animal and Human Data: A Health Based Risk Assessment
for Acrylonitrile**

By

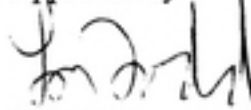
Mark Schulz

A technical report submitted to the Faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Master of Science in Public Health in the Department of Environmental Sciences and Engineering.

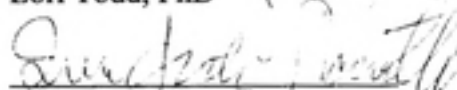
Chapel Hill

1998

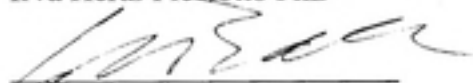
Approved by:



Lori Todd, PhD



Irva Hertz-Picciotto PhD



Louise M. Ball PhD

Abstract

Epidemiologic studies of workers exposed to acrylonitrile (ACN) have not found a significant increase in central nervous system (CNS) cancer mortality. In contrast, bioassays have consistently found elevated incidence of CNS cancer.

A linearized multistage model for estimating excess lifetime risk from bioassay data was used to examine whether the CNS cancers predicted from a rat bioassay and the CNS cancers observed in epidemiologic studies were consistent. Several steps were performed to complete the calculation of the CNS cancers predicted from the rat bioassay in human cohorts- (1) the excess lifetime risk was adjusted for less than complete lifetime follow-up in the epidemiologic study, and applied to all cohort members and, (2) the predicted excess deaths were added to the expected background deaths for the cohort and compared to the observed.

The model predicted 1.88 and 1.83 CNS cancer deaths for two large epidemiologic studies- (Collins *et al.*, 1989, *J. Occup. Med.* 31, 368-371) and (Swaen *et al.*, 1992, *J. Occup. Med.* 34, 801-809)- similar to the observed CNS cancer deaths, and well within the 95% CI of the observed, (0.03-5.6) and (0.6-8.8), respectively.

Small numbers of excess CNS cancer deaths were predicted because of low exposure levels and large adjustments for less than complete lifetime follow-up in the epidemiologic studies.

Integrating Animal and Human Data: A Health Based Risk Assessment for Acrylonitrile

Introduction

Acrylonitrile is an important chemical because it is widely used in industry. In 1978 the National Institute for Occupational Safety and Health (NIOSH, 1978) estimated that approximately 125,000 workers were potentially exposed to acrylonitrile during its production and use. Worldwide consumption of acrylonitrile increased 52% between 1976 and 1988 (EPA, 1983). Acrylic fibers are the largest use of acrylonitrile; other significant uses are in resins and nitrile elastomers and as an intermediate in the production of adiponitrile and acrylamide (Brazdil, 1993). Production of acrylonitrile and especially acrylic fibers is moving away from the United States, Western Europe, and Japan to newly industrialized nations where the regulation and monitoring of exposure levels may not be as stringent (Knorr, 1993).

The first carcinogenicity bioassay of acrylonitrile (Maltoni, *et al.*, 1977) and first epidemiologic study (O'Berg, 1980) were published over 15 years ago. Results of the occupational epidemiology studies of workers exposed to acrylonitrile and the bioassays of animals exposed to acrylonitrile are contradictory. The many epidemiology studies have been inconsistent in their findings, and none have found a significant increase in central nervous system (CNS) cancer incidence or mortality. In contrast, bioassays have consistently found elevated incidence of cancer, particularly CNS cancer.

The U.S. Environmental Protection Agency (EPA, 1983) conducted a risk assessment of acrylonitrile for cancer at all sites combined and compared the cancer risk from acrylonitrile to that from other chemical carcinogens. The only published acrylonitrile risk assessment for CNS cancer is based on a bioassay using the oral route of exposure (Ward and Starr, 1993).

However, the U.S. Occupational Safety and Health Administration (OSHA) (Federal Register, 1978) and the American Conference of Government Industrial Hygienists (ACGIH, 1991) have not based their occupational exposure limits for acrylonitrile on quantitative risk assessments. Rather, the ACGIH occupational exposure limits (OELs) are developed in a qualitative manner based on a review of the literature.

Some have argued that occupational exposure limits need to be based on a more solid scientific footing and especially that the data used for setting occupational exposure limits be peer reviewed (Rappaport, 1993). Even though risk assessment is not an exact science, we believe it can be used to improve the process of setting occupational exposure limits. A quantitative risk assessment makes explicit the assumptions that are made in going from the published toxicology and epidemiology studies to setting an occupational exposure limit. In addition, a risk assessment quantifies the level of protection that the occupational exposure limit purports to provide.

In this paper, we conduct a quantitative assessment of the risk of CNS cancer associated with acrylonitrile exposure based on a bioassay which used the inhalation route of exposure, and we fit the bioassay dose-response results to the epidemiologic data. The purpose of this paper is to explore the role of dose in explaining the contradictory results regarding CNS cancer and exposure to acrylonitrile. Hertz-Picciotto and Neutra (1994) highlighted the important role that dose may play in explaining contradictory results between nonexperimental studies.

Background

Bioassays

Inhalation is the most relevant route of exposure when bioassays are used for risk assessment of acrylonitrile workers because the workers are primarily exposed to acrylonitrile by inhalation and only secondarily by skin absorption. There have been three bioassays for acrylonitrile using inhalation as the route of exposure; all three used rats as the test species.

The risk assessment conducted in this paper is based on the inhalation bioassay of Quast *et al.*(1980), which was used by the U.S. EPA to develop their animal based inhalation unit risk factor for all cancers. This bioassay found a statistically significant increased incidence of brain and/or spinal cord tumors (benign and malignant) in male and female

rats. The rats in the experimental group were exposed to either 20 ppm or 80 ppm of acrylonitrile, six hours per day, five days per week for two years. The Zymbal gland was the only other target organ to show a significant increase in tumors in both genders. However, the Zymbal gland does not have a human equivalent so it is not used in this risk assessment.

The other two inhalation bioassays were published by the Maltoni group (Maltoni *et al.*, 1977) and (Maltoni *et al.*, 1988). The 1977 bioassay exposed the rats for only 12 months out of an average rat lifespan of two years and the highest concentration of acrylonitrile used was only 40 ppm. Consequently, the power of this assay to detect an effect was low. Three and two encephalic gliomas were observed in the rats exposed to the two highest acrylonitrile concentrations. Although not statistically significant, this finding is noteworthy in light of the results of other bioassays at higher doses of greater duration. The 1988 Maltoni bioassay exposed the rats to 60 ppm of acrylonitrile for a total 104 weeks, but the exposures started while the rats were still in utero (i.e., the mothers inhaled acrylonitrile while pregnant and then the offspring continued to be exposed throughout their life). This bioassay found a statistically significant increase in brain tumors, however, this exposure scenario is likely to be the exception rather than the rule among workers; therefore it was not chosen as the basis for this risk assessment. A statistically significant increase in brain and/or spinal cord tumors has been shown in both male and female rats in most oral and gavage bioassays as well (EPA, 1983).

Epidemiological Studies

The published and unpublished epidemiology studies of workers exposed to acrylonitrile are not as consistent in their findings as the animal bioassays. Therefore it is difficult to justify using any of them as the basis for a risk assessment of acrylonitrile. There have been at least 14 studies of which Ward and Starr (1993) reviewed 13 in their paper. Rothman (1994) reviewed 12 published papers, but only found eight that were appropriate for inclusion in his meta-analysis. Rothman focused on all cancers combined and respiratory cancer in his meta-analysis. Respiratory cancer is the cancer site that showed a statistically significant excess in four of the epidemiologic studies. He calculated combined standardized mortality ratios (SMRs) and 90% confidence intervals of 1.03(0.92-1.15) for all cancers combined and 1.07(0.89-1.28) for respiratory cancer. These results are not consistent with a large excess either of all cancers or of respiratory cancer associated with exposure to acrylonitrile.

A second limitation of the epidemiology studies is that different studies combine cancer types together differently and some include nonspecific categories such as "all other cancers". More importantly, only four studies report on brain cancer mortality (Swaen *et al.*, 1992), (Collins *et al.*, 1989), (Mastrangelo *et al.*, 1993), and (Werner and Carter, 1981). Three of these studies report an excess of observed as compared with expected brain cancer deaths. However, all of the numbers are small and in each case the 95%

confidence interval for the SMRs are very wide and include the null value of one (Table 1). It would be interesting to know the number of observed brain cancer deaths in the four studies that did not report on brain cancer mortality separately but that might have included them with for example "all other cancers". For instance, (O'Berg *et al.*, 1985) reports two incident cases of brain cancer, but reports no information on brain cancer mortality. (Chen *et al.*, 1987) reports one incident case of brain/central nervous system cancer and one death in an unspecified category of mortality. It has been noted (Rothman, 1994) that the data on cancer outcomes besides respiratory cancer are sparse even when aggregated over all eight studies; and it may well be that acrylonitrile is carcinogenic at some site, but there is insufficient power to see a statistically significant elevated relative risk.

A third limitation of the epidemiology studies is that only two (Swaen *et al.*, 1992), (Collins *et al.*, 1989) provide quantitative exposure assessments. Without a quantitative exposure assessment, an epidemiology study cannot be used for a risk assessment because one cannot estimate a dose-response relationship. To quantify the qualitative exposure assessments made in the other seven studies, arbitrary assumptions based on little information would need to be made about the exposures associated with individuals. No investigator had access to significant exposure measurements before 1977 even though exposure time for the cohorts in the nine studies began between 1940 and 1959. Employers apparently began measuring and recording worker exposures to acrylonitrile

only after the association between cancer and acrylonitrile exposure in animals was first published in 1977 (Stewart *et al.*, 1995).

Even in the Swaen *et al.* (1992) and Collins *et al.* (1989) studies, in which quantitative exposure estimates were made with the assistance of industrial hygienists, the quantitative exposure groups were used in the analysis of lung cancer only. Swaen *et al.* (1992) and Collins *et al.* (1989) assembled two of the largest cohorts of workers exposed to acrylonitrile. Even so, the follow-up time was limited in each study. Fewer than 9% (237 of 2671) of the Collins *et al.* (1989) cohort and fewer than 5% (134 of 2842) of the Swaen *et al.* (1992) cohort had died by the end of the respective follow-up periods. There was only one CNS cancer death in the Collins *et al.* (1989) cohort and three CNS cancer deaths in the Swaen *et al.* (1992) cohort (Table 1). Thus even using only a few exposure groups there were more exposure groups than CNS cancer deaths, and a dose-response analysis was impractical.

In their analysis of CNS cancer, all the epidemiologic studies classified their cohorts into two exposure groups-- exposed and unexposed-- or they only compared the exposed group to an external comparison population. Because all the exposed workers are grouped together, these sorts of analyses would have difficulty detecting an increased risk of CNS cancer that was only associated with the higher levels of acrylonitrile exposure to which some workers have been exposed. Any increased risk associated with a small

number of highly exposed workers would tend to be swamped by the absence of any increased risk among the majority of workers exposed to lower levels.

In summary, the qualitative exposure assessments used in these studies (1) limit the use of the studies in a risk assessment unless arbitrary assumptions about past exposure levels are made and (2) increase the possibility the studies may miss an increased risk of brain cancer associated with higher levels of acrylonitrile exposure because all workers exposed to various levels of acrylonitrile are grouped together in the analysis of brain cancer.

Methodology

Estimation of the Potency from the Bioassay Dose-Response Results

A linearized multistage model for estimating excess lifetime risk from bioassay data was used to estimate the brain cancer specific inhalation potency of acrylonitrile. Global 86, a risk assessment software package, was used to calculate the excess lifetime risks (Howe *et al.*, 1986). Global 86 uses a linearized multistage model to estimate the hypothesized linear non-threshold dose-response relationship.

In the Quast *et al.* (1980) inhalation bioassay, the rat exposure groups used were 0 ppm, 20 ppm, and 80 ppm. The rats were exposed to acrylonitrile six hours a day five days a week for two years. Following the methods of the EPA (1983), the ppm concentration in

the rats is assumed to be equivalent to the same ppm concentration in humans. This assumption is made because exposure of the rats was by inhalation and because acrylonitrile is partially soluble in water. The assumption is supported by the observation that the minimum alveolar concentration of anesthetic gases necessary to produce a given stage of anesthesia is similar in man and animals (Brunner, 1977).

The dose-response curves for CNS cancer estimated using Global 86 from the CNS cancer data in the Quast *et al.* (1980) inhalation bioassay are presented in Figure 1 (males) and Figure 2 (females). Global 86 calculates both a maximum likelihood and a 95 % upper confidence limit estimate of the low-dose slope (potency). These potencies are presented in Table II. We use the 95% upper confidence limit potency estimates in our risk estimates of continuous lifetime exposure to the OEL. This follows the example of the EPA (1983) which uses the 95% upper confidence potency to ensure that their risk estimates are protective of health. However, the maximum likelihood potency estimates are used when fitting the bioassay dose-response results to the epidemiologic data.

Fitting the Bioassay Dose-Response Results to the Epidemiologic Data

Following the example of Hertz-Picciotto *et al.* (1987) two approaches are used to examine whether the CNS cancers predicted from the animal bioassay and the CNS cancers observed in the epidemiologic studies are consistent: direct proportionality and modeling of the animal data.

Direct Proportionality: In the direct proportionality method Eq. (1), the predicted excess lifetime risk of CNS cancer is calculated by multiplying the percent difference in CNS tumors between the low-dose animals and the unexposed animals $(t_L/n_L - t_0/n_0)$ by the ratio of the continuous lifetime exposure in the human epidemiology study to the continuous lifetime exposure in the animal study (d_H/d_A) .

$$\text{Eq. (1)} \quad P(d) = (t_L/n_L - t_0/n_0) (d_H/d_A)$$

Multistage model: In the animal modeling method the animal dose-response data is fit using the multistage model. The predicted excess lifetime risk of CNS cancer is calculated from the following equation:

$$\text{Eq.(2)} \quad P(d) = 1 - \exp(-q_1 d_H)$$

Where q_1 is the maximum likelihood estimate (MLE) of the low dose potency and d_H is the continuous lifetime exposure in the human epidemiology study.

After either method of obtaining an estimate of excess lifetime risk of CNS cancer, three additional steps are performed to complete the calculation of the CNS cancers predicted from the animal bioassay in the particular human cohort. First, the predicted excess lifetime risk is adjusted for the less than complete lifetime follow-up in the epidemiology study (See below). Second the adjusted excess lifetime risk is applied to the human cohort to estimate the predicted excess CNS cancer deaths for the cohort. Finally, the

predicted excess CNS cancer deaths are added to the expected CNS cancer deaths for the cohort and compared with the observed CNS cancer deaths.

Adjustment for less than complete lifetime follow-up: Adjustment for less than complete lifetime follow-up in the epidemiology studies is the same for both methods. First, the expected number of CNS cancer deaths in the cohort is divided by the number of workers in the cohort to get an estimate of the cumulative lifetime risk of CNS cancer in the cohort. Next, the cumulative probability of CNS cancer death by age 74 is calculated by applying a lifetable to the male 1990-1994 United States age specific all-cause and brain-cancer death rates (SEER, 1997) and (Vital Statistics, 1992). Finally, the ratio of the cohort's cumulative lifetime risk of CNS cancer death to the US male population's cumulative probability of CNS cancer death by age 74 is used to adjust the predicted excess lifetime risk of CNS cancer.

Power Analysis

Power analysis was used to interpret the results of the fitting process. Epidemiological studies were considered to be consistent or not inconsistent with the animal bioassay if they either detected a statistically significant ($p=0.05$) excess of CNS cancer or had less than 80% power to detect the excess CNS cancer deaths projected from the animal bioassay. Power $p(R)$ to detect a given relative risk is calculated using the formula given by Beaumont and Breslow (1981) and a one sided significance level of $\alpha = 0.05$,

$$\text{Eq.(3)} \quad p(R) = 1 - F[1.645 - 2(R^{1/2} - 1)E^{1/2}]$$

where R, the relative risk in this formula, is the ratio of deaths expected with an acrylonitrile effect to deaths expected with no acrylonitrile effect (E). The numerator of R is the sum of E and the appropriate excess cancers projected from the rat studies. F[x] is the standard cumulative normal distribution function.

Risk Assessment for Continuous Working Lifetime Exposure to Acrylonitrile)

For the risk assessment of CNS cancer and a working lifetime exposure to acrylonitrile at the current OEL of the ACGIH (1997), equation (2) is used to calculate the predicted excess lifetime risk. The continuous lifetime dose used in the risk assessment was calculated from the following equation.

$$\text{Eq.(4)} \quad D = C \times ED / AT$$

where D equals lifetime dose, C is the concentration of acrylonitrile in the air, ED is the exposure duration (8 hours per day, 240 days per year for 45 years) and AT is the average lifetime (a lifetime of 70 years for males and 78 years for females).

Results

Direct Proportionality Analysis

As is typically the case with bioassays, the lowest dose rats in the Quast *et al.* (1980) study were exposed to a substantially greater continuous lifetime exposure than the most highly exposed workers observed in epidemiology studies. The rats were exposed to 20

ppm of acrylonitrile for 6 hours/day for 5 days/week over their lifetime. Their continuous lifetime exposure was thus 3.57 ppm. In the positive Swaen *et al.* (1992) study, 59 percent of the individuals in the cohort had cumulative exposures between 1.0 and 10.0 ppm-years; and the remainder of the individuals in the cohort were almost evenly divided between those with greater and lesser cumulative exposures. Taking 5 ppm-years as an estimate of cumulative exposure of all the individuals in the cohort, the continuous lifetime exposure was estimated as 0.0157 ppm. The 1,774 exposed workers in the negative study by Collins *et al.* (1989) accumulated 35,310 person years of exposure. The person years were divided into three groups. The intermediate group (0.7-7.0 ppm x years) had over 43 percent of the person years, and the remainder of the person years were split with 33 percent in the low exposure group and 24 percent in the high exposure group. On the basis of this data, 3.8 ppm-years was taken as an estimate of cumulative exposure of the each individual in the cohort and the estimated continuous lifetime exposure was 0.012 ppm. The conversion of each time weighted average daily exposure to a continuous lifetime exposure is shown in Table III.

The CNS cancer rate of the low-dose rats was 4 percent higher than that of the unexposed rats. The ratio of the continuous lifetime exposure in Swaen *et al.* (1992) cohort to the continuous lifetime exposure of the Quast *et al.* (1980) low dose rats is 0.0044. Thus the predicted excess lifetime risk of CNS cancer mortality is 0.018 percent for the Swaen *et al.* (1992) cohort. When applied to the 2,842 workers in the cohort and adjusted for less

than complete lifetime follow-up, 0.075 excess CNS cancer deaths are predicted which is consistent with three observed (1.71 expected). Table IV shows the adjustment factors for less than complete lifetime follow-up developed for each cohort.

The continuous lifetime exposure of the 1,774 exposed workers in the negative study by Collins *et al.* (1989) is only 0.0033 of the continuous lifetime exposure of the Quast *et al.* (1980) low dose rats. Direct proportionality with adjustment for less than complete lifetime follow-up predicts 0.063 excess CNS cancer deaths while one was observed (1.79 expected). Table V compares the observed CNS cancer deaths with the predictions from the animal data using the direct proportionality method.

Multistage Model

The potency is estimated from the rat CNS cancer data of Quast *et al.* (1980) as 0.0163 deaths/ppm. When this potency is applied to predict the excess deaths in the positive Swaen *et al.* (1992) study and the negative study of Collins *et al.* (1989), the excess deaths are 0.73 and 0.34 respectively. However, when the excess deaths are adjusted for less than complete lifetime follow-up in each cohort, the excess deaths become very small. As shown in Table VI, the excess deaths in the Swaen *et al.* (1992) study are reduced to 0.117, while in the negative Collins *et al.* (1989) study the excess deaths are reduced to 0.093.

Table VI also shows the predicted deaths which are equal to the sum of the expected deaths for the cohort plus the excess deaths in the cohort due to the acrylonitrile exposure. The predicted deaths--1.88 in the Collins *et al.* (1989) study and 1.83 in the Swaen *et al.* (1992) study-- are well within the range of observed CNS cancer deaths for both the studies.

Power Analysis of Epidemiology Studies

The *post hoc* power analysis provides an additional way to interpret the results of the multistage model analysis. Table VII shows projected SMRs for both the Collins *et al.* (1989) and Swaen *et al.* (1992) cohorts. The predicted deaths are the numerator and the expected deaths are the denominator of the projected SMR. The Swaen *et al.* (1992) and Collins *et al.* (1989) cohorts both have projected SMRs only slightly greater than one, and each cohort has very limited power (approximately 6 percent) to detect projected SMRs so similar to one.

Risk Assessment (Continuous Working Lifetime Exposure to OEL)

Table VIII shows the calculation of the lifetime dose corresponding to the current Occupational Exposure Limit (OEL) of both OSHA and the ACGIH (2 ppm) as well as the lifetime dose corresponding to concentrations of 1 ppm and 0.2 ppm. The latter two concentrations were considered by OSHA as possible Permissible Exposure Limits (PELs) when they revised the acrylonitrile standard in 1978 (Federal Register, 1978).

The excess risk of brain cancer from exposure for a working lifetime to acrylonitrile at the existing and proposed OELs is displayed in Table IX. At the current OEL of 2 ppm, the excess risk of brain cancer above the background rate of brain cancer is 0.6 percent. In contrast, if OSHA had adopted a PEL of 0.2 ppm (the lowest PEL they considered during the standard setting process for acrylonitrile in 1977-1978) the predicted extra risk for workers exposed to this concentration for their working lifetime would be 0.06 percent.

Applying these excess risk estimates to the NCI brain cancer mortality rates (SEER, 1997) gives one a fuller perspective of what these excess risks mean in human terms. For white males age 60-64 in 1990-94 the annual brain cancer mortality rate was 16.7 per 100,000. Taking this as the background rate for this group, the annual rate for white males workers exposed for a working lifetime to 2 ppm would be $0.000167 \times 1.006 = 0.000168 = 16.8$ per 100,000.

Discussion and Conclusions

Comparing Bioassays and Epidemiologic Studies

This study explored the role of dose in explaining the contradictory results between the toxicologic and the epidemiologic literature regarding CNS cancer and exposure to acrylonitrile. The rodent bioassays have found elevated incidence of CNS cancer. In contrast, none of the epidemiologic studies have observed a significant increase in CNS

cancer incidence or mortality. In order to investigate these contradictory results we used two methods-- direct proportionality and the multistage model-- to fit the bioassay dose-response data to the epidemiologic data.

The two methods produced similar results. Each method predicted very small numbers of excess CNS cancer deaths in the two large epidemiologic cohorts studied. For the Swaen *et al.* (1992) cohort 0.075 excess deaths were predicted by direct proportionality while 0.117 were predicted by the multistage model. Similarly, for the Collins *et al.* (1989) cohort, 0.063 excess deaths were predicted by direct proportionality and 0.093 excess deaths by the multistage model (Tables V & VI).

An important element of our analysis is the adjustment for less than complete lifetime follow-up in epidemiologic cohorts. This adjustment reduces the excess CNS cancers predicted when the animal bioassay dose-response data is fit to the epidemiologic data. The reductions are substantial: 73% for the Swaen *et al.* (1992) cohort and 84% for the Collins *et al.* (1989) cohort (Table IV). The reductions are large because the cumulative probability of CNS cancer death increases at a greater than linear rate with age (Fig. 3) as do most other cancers. This is particularly important because both cohorts were relatively young at the time they were studied.

In addition, two other elements of our analysis are worthy of note. First, we estimated the cumulative exposure of each cohort based on the cohort-specific exposure assessments. Second, we selected an animal bioassay based on its route of exposure (inhalation) being the primary route of exposure for workers to which we extrapolated the dose-response relationship.

We found that both the studies conducted by Swaen *et al.* (1992) and by Collins *et al.* (1989) had negligible power to detect excess CNS cancers (Table VII). In contrast, Ward and Starr (1993) concluded in their post-hoc power analysis of the epidemiologic studies of acrylonitrile and cancer that the Collins *et al.* (1989) cohort had enough power to detect excess CNS cancers. However, their analysis used a less accurate adjustment for less-than-complete lifetime follow-up in the epidemiologic studies. Their adjustment factor was simply an estimate of average years of follow-up for the cohort divided by 50 years. This adjustment factor fails to account for the fact that CNS cancer death rates increase at a greater than linear rate with age. In addition, ingestion rather than inhalation was the route of exposure in the Quast bioassay which they chose to fit to the epidemiologic data. Finally, they did not use the cohort-specific exposure-assessment information to estimate average daily exposure. Instead, they used the general industry estimate of average daily exposure for the historical time period of interest offered by Sandonato (1983).

Whether or not the epidemiology studies should have been able to detect excess CNS cancer deaths is an important question. If the epidemiology studies had sufficient power to detect the excess of CNS cancer deaths predicted by the rat bioassays, under reasonable assumptions about past worker exposure levels, then the lack of an observed excess would cast doubt on whether acrylonitrile contributes to CNS cancer in humans.

This study suggests that workers should not be particularly reassured by the fact that the epidemiology studies published to date have not found an excess of CNS cancers among workers exposed to acrylonitrile that is statistically significant at a 95% confidence level. It is clear from this examination of the currently available epidemiology data that the CNS cancer potency for acrylonitrile derived from the Quast *et al.* (1980) inhalation bioassay with rats is statistically consistent with human experience. At estimates of the level and duration of past worker exposures developed by the investigators themselves, neither the Swaen *et al.* (1992) cohort nor the Collins *et al.* (1989) cohort yielded predicted CNS cancer deaths that were significantly different from the observed totals. Predicting excess risk of CNS cancer based on extrapolation from the Quast *et al.* (1980) rat inhalation bioassay seems appropriate or at least has not been shown to be inappropriate.

Excess Risk and the Current OELs

This study also is the first attempt at quantifying the excess risk to workers of exposure to acrylonitrile at the current OEL. Neither the documentation of the ACGIH Threshold Limit Value (TLV) (ACGIH, 1991) nor the rationale for the PEL published by OSHA (Federal Register, 1978) attempt to quantify the CNS cancer risk or any other risk associated with their OELs.

Our risk assessment suggests that there is a slight (0.6%) excess risk of CNS cancer over and above the population background rate of CNS cancer mortality associated with exposure for a working lifetime to 2 ppm of acrylonitrile, the current OEL. However, if the working lifetime average exposure were only 0.2 ppm the excess risk above the background rate would become very small (0.06%).

Limitations

A limitation of this risk assessment is that it is based on an animal bioassay at high doses relative to the low doses to which workers are exposed. The continuous lifetime exposures in the Quast *et al.* (1980) inhalation study are 200 to 300 times the continuous lifetime exposure concentrations of acrylonitrile workers in the United States and Western Europe studied by Collins *et al.* (1989) and Swaen *et al.* (1992) (Table V). However, animal experiments at the doses that workers are exposed to would be costly and difficult if not impossible to perform well (Schneiderman *et al.*, 1975).

Of course, the linear non-threshold dose-response relationship that was hypothesized for the low doses to the rat may be incorrect. However, it is the most health protective of the models that have been hypothesized for dose-response relationships at low doses. As such, it has been the choice of the EPA (1983). Other models of the dose-response relationship at low doses would result in smaller unit risk factors. Likewise, using Global 86's maximum likelihood estimate of the slope of the dose response function at low doses instead of the 95% upper confidence limit of the estimate results in fewer projected excess cancer deaths. A smaller excess in cancer deaths requires more powerful epidemiological studies to detect.

Recommendations

Based on this study a few recommendations seem justified. They can be divided into three categories, risk assessment methodology, future research needs, and public health recommendations.

Regarding risk assessment methodology there are two recommendations. First, when comparing animal bioassays and epidemiologic studies that appear to be contradictory it is a good idea to fit the animal dose-response results to the epidemiologic data. This enables an investigator to examine whether the apparently contradictory results are due to differences in dose which are typically large between the bioassays and the epidemiologic studies.

Second, when comparing animal bioassays and epidemiologic studies it is important to remember that bioassays are experiments, and the usual design is to follow the animals for a period equal to their average lifetime before killing them for necropsy. In contrast, the epidemiological studies are observational studies. Follow-up time will vary among the cohort members, the average follow-up time of the cohort will generally be less than their average lifetime, often much less, and cancer mortality increases more than linearly with age. Therefore, it is important to adjust for less-than-complete follow-up in the epidemiologic studies.

Regarding future research, epidemiological studies of workers exposed to acrylonitrile should examine CNS cancer mortality and possibly incidence as outcomes because the current epidemiologic studies cannot be considered to be inconsistent with the animal bioassays. Future epidemiological studies should be designed to have enough power to detect the excess CNS cancers predicted by the Quast *et al.* (1980) inhalation bioassay since the epidemiological studies completed to date do not appear to have had enough power. Finally they should include a detailed exposure assessment so that a dose-response relationship for CNS cancer can be evaluated.

Three public health recommendations conclude the recommendations. First, the ACGIH and OSHA should consider reducing their OEL's for acrylonitrile to 0.2 ppm as a time

weighted average for an eight-hour day, and industries manufacturing or using acrylonitrile should continue to improve control methods for acrylonitrile. The lifetime excess risk of brain cancer mortality is estimated by the risk assessment in this study to be 0.6% for workers exposed for a working lifetime to an average acrylonitrile concentration of 2 ppm (the current OEL). This results in one excess brain cancer death per year per million exposed workers since the annual brain cancer mortality rate was 16.7 per 100,000 for white males age 60-64 in 1990-94 (most acrylonitrile workers in the United States have been white males). Lowering the OEL from 2 ppm to 0.2 ppm would reduce the estimated excess lifetime risk by an order of magnitude to 0.06%.

As is evident from Zaebst *et al.* (1994), significant progress has been made in controlling workplace exposures to acrylonitrile. The geometric mean of all exposure measurements of all job titles at the eight U.S. plants studied was below 0.13 ppm for each year for the period 1980-87. From these numbers it appears as though an OEL of 0.2 ppm is very realistic for the industry in the 1990s even though it may have been difficult to attain in 1978 when OSHA's acrylonitrile standard was promulgated .

Second, risk assessments should be integrated into the occupational standard-setting process for occupational carcinogens and suspected occupational carcinogens. Risk assessments have the advantage of requiring that the assumptions underlying the OEL be made explicit. Explicitly stated assumptions could facilitate more informed debate about

the level of health risk that workers and society are willing to accept. Just as importantly, highlighting the assumptions and data limitations which are responsible for the uncertainty in a risk assessment should encourage and focus research by the scientific community aimed at closing the knowledge gaps and thereby increasing the confidence in the risk assessment and the related OEL.

Finally, given the continuing movement of acrylonitrile operations to the rapidly industrializing countries, chemical firms and regulatory agencies should be careful that acrylonitrile exposure is well monitored and controlled at these new production sites so that the relatively high exposure levels prevalent before 1978 are not exported to the rapidly industrializing countries.

TABLE 1
Summary of Observed and Expected CNS Cancers in Published Epidemiologic
Studies on Acrylonitrile

Study	Observed deaths	Expected deaths	Standardized mortality ratio	95% confidence interval
Werner & Carter, 1981	2	0.7	290	(35-1031)
Collins <i>et al</i> , 1989	1	1.79	56	(2-311)
Swaen <i>et al</i> , 1992	3	1.71	175	(35-513)
Mastrangelo <i>et al</i> , 1993	1	0.38	263	(7-1465)

TABLE 2
CNS Cancer Potencies Calculated by Global 86 from the Quast *et al.* Inhalation Bioassay Data

	95% Upper Confidence Limit of Max. Likelihood Estimate
male	2.21E-02 per ppm
female	2.40E-02 per ppm
	Maximum Likelihood Estimate
male	1.63E-02 per ppm
female	1.80E-02 per ppm

TABLE 3
Conversion of TWA Daily Exposure to Continuous Lifetime Exposure

Study Cohort	Estimated Daily TWA Exposure (ppm)	Exposure Time (yrs)	Cumulative Exposure (ppm* yrs)	Proportion of days exposed	Proportion of hours Exposed	Average Lifetime (yrs)	Continuous Lifetime Exposure (ppm)
Quast <i>et al.</i> , 1980	20	2	40	5/7	6/24	2	3.57
Collins <i>et al.</i> , 1989	NA	NA	3.8*	240/365	8/24	70	0.0119
Swaen <i>et al.</i> , 1992	NA	NA	5*	240/365	8/24	70	0.0157

*Estimated from study-specific exposure information presented in the article

TABLE 4
Adjustment for Less Than Complete Lifetime Follow-up in the Epidemiology Studies

Study Cohort	Number in Cohort	Expected # of CNS Deaths in Cohort	Estimate of Cumulative Lifetime Risk of CNS Death in the Cohort	Cumulative Probability of CNS Death by Age 74 in US Males	Adjustment Factor
Collins <i>et al.</i> , 1989	1774	1.79	0.0010090	0.0037661	0.27
Swaen <i>et al.</i> , 1992	2852	1.71	0.0006017	0.0037661	0.16

TABLE 5
Comparison of Observed CNS Cancer Deaths with Predictions from Quast *et al.*
Inhalation Bioassay Using the Direct Proportionality Method

Study Cohort	Ratio of Continuous Lifetime Exposures (human/rat)	Difference in CNS Cancer Rate between Low Dose and Unexposed Rats	# in Cohort	Adjustment Factor for less than Complete Lifetime Follow-up	Excess CNS Deaths	Expected Deaths	Predicted Deaths	Observed Deaths
Collins <i>et al.</i> , 1989	0.0033	0.04	1774	0.27	0.063	1.79	1.85	1
Swaen <i>et al.</i> , 1992	0.0044	0.04	2852	0.16	0.075	1.71	1.79	3

TABLE 6
Comparison of Observed CNS Cancer Deaths with Predictions Extrapolated from
Quast *et al.* Inhalation Bioassay Using the Multistage Model

Study Cohort	Equivalent Continuous Lifetime Exposure (ppm)	MLE Potency (deaths/ppm)	Excess Lifetime Risk	Adjustment Factor if less than Complete Lifetime Follow-up	# in Cohort	Excess Deaths	Expected Deaths	Predicted Deaths	Observed Deaths	95% CI
Collins <i>et al.</i> , 1989	0.0119	0.0163	0.0002	0.27	1774	0.093	1.79	1.88	1	0.03-5.6
Swaen <i>et al.</i> , 1992	0.0157	0.0163	0.0003	0.16	2852	0.117	1.71	1.83	3	0.6-8.8

TABLE 7
Post hoc Power Analysis for CNS Cancer

Study cohort	Excess lifetime risk*	Less than complete lifetime follow-up adjustment factor	N	Excess deaths	Expected (background) deaths	Projected SMR	Power to detect excess (%)
Collins <i>et al.</i> , 1989	0.00019	0.27	1774	0.0929	1.79	1.05	5.75
Swaen <i>et al.</i> , 1992	0.00026	0.16	2852	0.1168	1.71	1.07	5.97

*Excess lifetime risk is calculated from $P(d) = 1 - \exp(-qd)$; where q is the potency from the Quast bioassay and d is the continuous lifetime exposure for the cohort.

TABLE 8
Calculation of Continuous Lifetime Dose Corresponding to the Current OEL and Proposed OELs*

Sex	OEL (ppm)	Working Years / Average Lifespan	Continuous Lifetime Exposure (ppm)
Male	2	45/70	0.2818
Male	1	45/70	0.1409
Male	0.2	45/70	0.02818
Female	2	45/78	0.25290
Female	1	45/78	0.12645
Female	0.2	45/78	0.02529

*Assuming eight hours per day and 240 days per year as the standard work regimen

TABLE 9
Extra Risk from Exposure for a Working Lifetime to Acrylonitrile at Existing and Proposed OELs

Sex	OEL (ppm)	Continuous Lifetime Exposure (ppm)	$[Q_1]$ 95% Upper Confidence Limit of Potency (tumors/ppm)	$[P_1(d) = 1 - \exp -(Q_1 \cdot d)]$ Extra Risk above Background Rate
male	2	0.2818	2.21E-02	6.208E-03
male	1	0.1409	2.21E-02	3.109E-03
male	0.2	0.02818	2.21E-02	6.226E-04
female	2	0.2529	2.40E-02	6.051E-03
female	1	0.12645	2.40E-02	3.030E-03
female	0.2	0.02529	2.40E-02	6.068E-04

REFERENCES

- ACGIH (American Conference of Governmental Industrial Hygienists). (1997). *1997 TLVs and BEIs*, Cincinnati, Ohio.
- ACGIH (American Conference of Governmental Industrial Hygienists). (1991). *Documentation of Threshold Limit Values and Biological Exposure Indices Sixth Edition*, Cincinnati, Ohio.
- Beaumont J., Breslow N. (1981). Power considerations in epidemiologic studies of vinyl chloride workers. *Am. J. Epidemiol.* **5**, 725-734.
- Brazdil, J. F. (1993). Acrylonitrile. In *Kirk-Othmer Encyclopedia of Chemical Technology Fourth Edition Volume 1* (J. I. Kroshwitz, and M. Howe-Grant, Eds.), pp. 352-369, John Wiley & Sons, New York, NY.
- Brunner E. A. (1977). Fundamentals of inhalation anesthesia. In *Introduction to Anesthesia The Principles of Safe Practice 5th Edition* (R. D. Dripps, J. E. Eckenhoff, and L. D. Vandam, Eds.), pp.115-132. W.B. Sanders Company, Philadelphia, PA, USA.
- Chen, J. L., Walrath, J., O'Berg, M. T., Burke, C. A., and Pell, S. (1987). Cancer incidence and mortality among workers exposed to acrylonitrile. *Am. J. Ind. Med.* **11**, 157-163.
- Collins, J. J., Page, L. C., Caporossi, J. C., Utidjian, H. M., and Saipher, J. (1989). Mortality patterns among employees exposed to acrylonitrile. *J. Occup. Med.* **31**, 368-71.
- EPA (U.S. Environmental Protection Agency). (1983). *Health Assessment Document for Acrylonitrile: Final Report*. USEPA-600/8-82-007F U.S. EPA, Washington, DC.
- Federal Register* (1978). Vol. 43 No. 192 pp. 45762-45819.
- Hertz-Picciotto I., Neutra R. R., Collins J. F. (1987). Ethylene oxide and leukemia (letter). *JAMA* **257**, 2290.
- Hertz-Picciotto I., and Neutra R. R. (1994) Resolving discrepancies among studies: The influence of dose on effect size. *Epidemiol.* **5**, 156-163.
- Howe, R., Crump, K., and Van Landingham, C. (1986). Global 86: A computer program to extrapolate quantal animal toxicity data to low doses. Prepared for Environmental Protection Agency under Subcontract 2-251U-2745 to Research Triangle Institute.
- Knorr, R.S. (1993). Fibers (Acrylic). In *Kirk-Othmer Encyclopedia of Chemical Technology Fourth Edition Volume 10* (J. I. Kroshwitz, and M. Howe-Grant, Eds.) pp. 559-598, , John Wiley & Sons, New York, NY.
- Maltoni, C., Ciliberti, A., and Di Malo, E. (1977). Carcinogenicity bioassays on rats of acrylonitrile administered by inhalation and by ingestion. *Med. Lav.* **68**, 401-411.
- Maltoni, C., Ciliberti, A., Cotti, G., and Perino, G. (1988). Long-term carcinogenicity bioassays on acrylonitrile administered by inhalation and by ingestion to Sprague-Dawley rats. *Ann. NY Acad. Sci.* **534**, 179-202.

Mastrangelo, G., Serena, R., and Marzia, V. (1993). Mortality from tumours in workers in an acrylic fibre factory. *Occup. Med.* **43**, 155-58.

NIOSH (National Institute for Occupational Safety and Health). (1978) *Criteria for a Recommended Standard- Occupational Exposure to Acrylonitrile*. DHEW (NIOSH) Pub. No. 78-116 NTIS No. PB-81-225-617/A02. National Technical Information Service, Springfield, VA.

O'Berg, M. T., Chen, J. L., Burke, C. A., Walrath, J., and Pell, S. (1985). Epidemiologic study of workers exposed to acrylonitrile: An update. *J. Occup. Med.* **27**, 835-840.

O'Berg, M. T. (1980). Epidemiological study of workers exposed to acrylonitrile. *J. of Occup. Med.* **22**, 245-252.

Quast, J. F., Schuetz, D. J., Balmer, M. F., Gushow, T. S., Park, C. N., and McKenna, M. J. (1980). *A Two-Year Toxicity and Oncogenicity Study with Acrylonitrile Following Inhalation Exposure in Rats*. Prepared by the Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical, USA, Midland, MI, for the Chemical Manufacturing Association, Washington, DC.

Rappaport, S. M. (1993). Threshold limit values, permissible exposure limits, and feasibility: The bases for exposure limits in the United States. *Am. J. Ind. Med.* **23**, 683-694.

Rothman, K. J. (1994). Cancer occurrence among workers exposed to acrylonitrile. *Scand. J. Work Environ. Health* **20**, 313-321.

Santodonato, J. (1985). *Monograph on Human Exposure to Chemicals in the Workplace: Acrylonitrile*. Center for Chemical Hazard Assessment, Syracuse Research Corporation, Syracuse, NY. Available from NTIS as PB861459191AS.

Schneiderman, M. A., Mantel, N., and Brown, C. C. (1975). From mouse to man- or how to get from the laboratory to Park Avenue and 59th Street. *Ann. NY Acad. Sci.* **246**, 237-48.

NCI (National Cancer Institute). (1997). *SEER Cancer Statistics Review, 1973-1994* (L. A. G. Ries, C. L. Kosary, B. F. Miller, A. Harras, B. K. Edwards, Eds.), p.108., NIH Pub. No. 97-2789, Bethesda, MD.

Stewart, P. A., Triolo, H., Zey, J., White, D., Herrick, R. F., Hornung, R., Dosemeci, M., and Pottern, L. M. (1995). Exposure assessment for a study of workers exposed to acrylonitrile. II. A computerized exposure assessment program. *Appl. Occup. Environ. Hyg.* **10**, 698-706.

Swaen, G. M. H., Bloemen, L. J. N., Twisk, J., Scheffers, T., Slangen, J. J. M., and Sturmans, F. (1992). Mortality of workers exposed to acrylonitrile. *J. Occup. Med.* **34**, 801-9.

NCHS (National Center for Health Statistics). (1996). *Vital Statistics of the United States, 1992, vol II, mortality, part A*. pp.14-15. DHHS Pub. No. (PHS) 96-1101, Washington DC.

Ward, C. E., and Starr, T. B. (1993) Comparison of cancer risks projected from animal bioassays to epidemiologic studies of acrylonitrile-exposed workers. *Regul. Toxicol. Pharmacol.* **18**, 214-232.

Werner, J. B. and Carter, J. T. (1981). Mortality of United Kingdom acrylonitrile polymerisation workers. *Br J Ind Med.* **38**, 247-253.

Zaebst, D. D., Bloom, T. F., Zey, J. N., and . An Overview of Acrylonitrile Historical Exposure Monitoring Data from Eight U.S. Plants. Presented at American Industrial Hygiene Conference, May 24, 1994, Anaheim, CA, in poster session 2- Industrial Hygiene General Practice.

Fig. 1

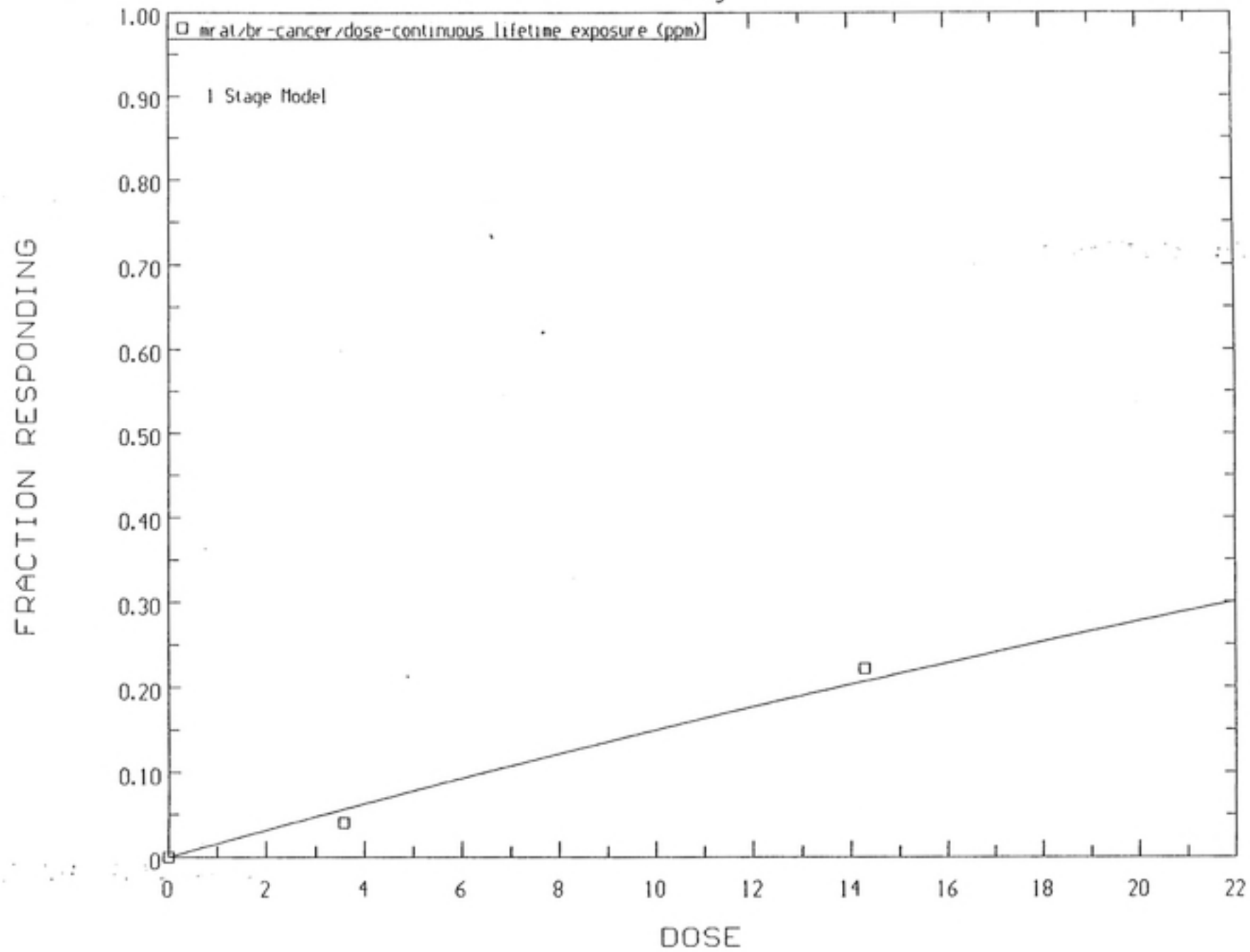


FIGURE 3
Cumulative probability of death due to CNS cancer for U.S. White males

