CNS tumors and exposure to acrylonitrile: Inconsistency between experimental and epidemiology studies

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Acrylonitrile is a potent CNS tumorigen in rats leading to concern that it may be a tumorigen in humans. There have been 12 epidemiology studies of 37,352 workers exposed to acrylonitrile which evaluate CNS cancers. We summarize and evaluate these epidemiology studies for CNS cancers using the methods of meta-analysis. Our analyses indicate that workers with acrylonitrile exposure have null findings for CNS cancer (relative risk = 1.1, 95% confidence interval 0.8–1.5), which are in stark contrast to the projected risk to humans using the rat findings (relative risk = 3.5, 95% confidence interval 3.0–4.0). We discuss several explanations for the inconsistency between animal and human findings, including the possibility that the acrylonitrile-induced rat CNS tumors may not be relevant to humans. Given the rarity of CNS tumors in humans and a lack of understanding of the causal mechanisms of these tumors in rats, however, a more definitive conclusion will have to await additional experimental and observational data. Nevertheless, the epidemiology evidence indicates that acrylonitrile is not a potent CNS tumorigen. *Neuro-Oncology* 1, 221–230, 1999 (Posted to *Neuro-Oncology [serial online]*, Doc. 99-10, June 9, 1999. URL <neuro-oncology.mc.duke.edu>)

Acrylonitrile (CAS No. 107-13-11) is an intermediary chemical used in the manufacture of acrylic fibers, resins, plastics, rubbers, and other chemi-

cals such as acrylamide. Acrylonitrile has been in commercial production since 1940. Currently, 125,000 workers are potentially exposed to acrylonitrile in the United States (OSHA, 1978). In the late 1970s, chronic bioassays of rats exposed to acrylonitrile through drinking water or inhalation produced cancers at several sites including the CNS (Strother et al., 1988). These findings in experimental animals and some small epidemiology studies (Keisselbach et al., 1980; O'Berg et al., 1980a; Thiess et al., 1980) led to speculation that acrylonitrile exposure by humans may increase their risk of CNS cancers (Thomas, 1994; Thomas and Waxweiler, 1986). Reviews of the epidemiology studies have focused on increased risks of lung and prostate cancer among acrylonitrile workers, but cancers of CNS have not been examined in detail (ATSDR, 1990; Blair and Kazerouni, 1997; Collins and Acquavella, 1998; Doll, 1991; EPA, 1990; Guirguis et al., 1984; IARC, 1987; Koerselman and van der Graaf, 1984; Rothman, 1994; Strother et al., 1988). Recently, three large epidemiology studies have examined cancer levels, including CNS cancers among workers exposed to acrylonitrile (Blair et al., 1998; Swaen et al., 1998; Wood et al., 1998). We will determine if the CNS cancer rates among acrylonitrile workers are consistent with the increased risk of CNS cancer observed in test animals.

Toxicity Studies

Acrylonitrile is a potent CNS tumorigen in rats. At least seven long-term studies have been conducted by various routes of exposure, and CNS tumors have been observed consistently in rats exposed for one year or longer (Strother et al., 1988). CNS tumor excesses have occurred at exposure to 20 ppm² in an inhalation study. Chronic bioassays on acrylonitrile have not been reported in other experimental species.

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²Abbreviations used are as follows: CI, confidence interval; mRR, meta-relative risk; ppm, parts per million; RR, relative risk.

³Quast, J.F., Schuetz, D.J., Balmer, M.F., Goshaw, T.S., Park, C.N., McKenna, M.J. (1983) Unpublished data.

Table 1. Estimated excess worker brain cancer deaths predicted from rat data for various exposure scenarios

Average daily exposure (ppm)	Exposure standard	Excess brain cancers predicted (per 1,000 workers) by years of exposure ^{a,b}		
		10 years	20 years	30 years
20	Pre-1978 exposure standard	19	38	57
2	Present OSHA standard	2	4	6
0.5	Current average exposure ^c	0.5	1	1

ppm, parts per million; OSHA, Occupational Safety and Health Administration.

^aMaximum likelihood estimate from multistage linear modeling of rat inhalation results using Tox Risk Version 4.0, which is a product of K.S. Crump Group (Rushton, LA).

^bData used is an unpublished report entitled “A two-year toxicity and oncogenicity study with acrylonitrile following inhalation exposure of rats” (1983) by Quast, J.F., Schuetz, D.J., Balmer, M.F., Goshaw, T.S., Park, C.N., and McKenna, M.J.

^cBased on Stewart et al. (1998).

The rat chronic bioassay findings have led to concern about increased cancer risk of workers exposed to acrylonitrile. This concern is amplified by the fact that exposure to acrylonitrile has been shown to produce CNS tumors in rats at concentrations in the upper range of past workplace exposures, or 20 ppm (Stewart et al., 1998). Rat tumor response at lower concentrations below 20 ppm has not been adequately evaluated. However, based on analogy to more robust dose-response data from drinking water studies, it can be reasonably expected that airborne concentrations below 20 ppm would produce observable tumor response in rats.

The rat data predict significant CNS cancer risk to humans when current and historical workplace exposure levels are used, as shown in Table 1. For example, at a 20-ppm exposure for 10 years, 19 excess CNS cancer deaths per 1,000 workers would be predicted. At 2 ppm, the current Occupational Safety and Health Administration standard in the U.S., the model predicts six excess brain cancer deaths after 30 years of exposure. These predictions are even more sobering because of recent comparative dosimetry work predicting that humans may experience higher brain concentrations of acrylonitrile’s epoxide metabolite than do rats at the current occupational exposure standard of 2 ppm (Kedderis and Held, 1998).

Epidemiology Studies

The epidemiology studies examine workers exposed to significant levels of acrylonitrile. Most workplace exposure to acrylonitrile results from inhalation, but exposure can also occur through the skin. Average inhalation exposure is generally highest in acrylic fibers production, especially in the polymerization and spinning processes (IARC, 1979; Stewart et al., 1998). Other significant exposures occur in the production of acrylonitrile, acrylonitrile-based resins, and nitrile rubber. Workers’ exposures above 20 ppm time-weighted average for 8 h (TWA8) have occurred in the past, although current operations have exposures at or below 1 ppm TWA8 (Stewart et al., 1998). Generally, exposure levels were higher in earlier years of operation (Stewart et al., 1998). Only four of the studies provide exposure level estimates for acrylonitrile workers (Blair et al., 1998; Collins et al., 1989; Swaen et al., 1998; Wood et al., 1998). From these four studies, the average exposure

level and duration appear consistent with 2 ppm for a 4-year duration as estimated by Ward and Starr (1993). The exposure levels in these studies are probably characteristic of the other epidemiology studies because of the similarity of the operations across studies.

The epidemiology studies of acrylonitrile workers have examined incidence and death from cancers of the CNS. The classification of the CNS cancers in these studies presents several methodological problems. First, CNS cancers include all cancers of the brain, spinal cord, cranial nerves, and the meninges (International Classification of Disease, 1988). Most of the CNS cancers (82%) are of the brain (Young et al., 1981). Second, most of the epidemiology studies on acrylonitrile are mortality studies that use the underlying cause of death from a death certificate to verify tumor diagnosis. Mortality studies often lack information on histology. We can assume most of the CNS cancers reported in these studies are glial neoplasms of the brain; 88% of adult brain primaries are astrocytomas (ICDO 940–944) (Velema and Percy, 1987). Third, CNS tumors on death certificates are classified as malignant (ICD9 code 191–192), benign (ICD9 code 225), or unspecified as to malignancy (ICD9 code 237.5–237.9). If the attending physician records “brain tumor” on the certificate, the death will be coded as unspecified as to malignancy. Pathologic review of unspecified brain tumors indicated that most are primary malignant tumors (Thomas, 1994). Deaths from benign and unspecified categories have not been reported in any of the studies of acrylonitrile workers. Fourth, not all brain tumors listed on the death certificates are pathologically confirmed. Metastatic brain tumors are thus sometimes classified as primary brain tumors on the death certificate. Between 1970 and 1971, 11% of the brain tumors identified on death certificates were not primary brain tumors, according to hospital records (Percy et al., 1981). Between 1985 and 1986, this percentage was reduced to 3% (Percy et al., 1990). Finally, pathologic confirmation also may be more common among workers in industry, making it difficult to choose an appropriate comparison group (Greenwald et al., 1981). This finding has led to speculation that high brain cancer in some industrial cohorts could be attributed to a diagnostic bias from using the general population as a comparison group. With all these limitations, however, we conclude that most of the brain cancers that occur as an underlying

cause of death on the death certificate are gliomas, and most of these gliomas are astrocytomas.

Methods

The epidemiology studies in this review were identified through a search of MEDLINE® retrieval service for the period of 1970 to 1995. We searched for carcinogenicity and acrylonitrile and synonyms (cyanoethylene, 2-propenenitrile, vinyl cyanide, and acrylic fiber). We also used reviews of acrylonitrile carcinogenicity (ATSDR, 1990; Doll, 1991; EPA, 1990; Guirguis et al., 1984; IARC, 1987; Koerselman and van der Graaf, 1984; Rothman 1994; Strother et al., 1988) to identify articles. We contacted companies making or using acrylonitrile and asked them for any unpublished studies on acrylonitrile. We also wrote to each author of the cohort studies for observed and expected deaths for brain cancer since they are not reported. Much of the data in this review have been presented previously (Collins and Acquavella, 1998).

We identified 29 studies. Twenty-four were published, (Benn and Osborne, 1998; Blair et al., 1998; Chen et al., 1987, 1988a, 1988b; Collins et al., 1989; Delzell and Monson, 1982; Keisselbach et al., 1980; Marsh, 1983; Mastrangelo et al., 1993; O'Berg, 1980a, 1980b; O'Berg et al., 1985; Ott et al., 1980, 1989; Siemiatycki et al., 1994; Swaen et al., 1992, 1998; Thiess et al., 1980; Thomas et al., 1987; Waxweiler et al., 1981; Werner and Carter, 1981; Wood et al., 1998; Zhou and Wang, 1991), and five were unpublished ("The Mortality Experience of Monsanto Workers Exposed to Acrylonitrile" by Zack, "Cohort Mortality Study of Scotts Bluff/Baton Rouge Uniroyal Plant" by Herman, "A Mortality Study of Workers Potentially Exposed to Acrylonitrile During Start-up: Monsanto Decatur Plant" by Gaffey and Strauss, "Mortality and Cancer Incidence among Workers Exposed to Acrylonitrile at the Memphis Plant" by Burke, and "Mortality and Cancer Incidence among Workers Exposed to Acrylonitrile at the Beaumont Works" by Burke). We omitted two studies because they studied workers exposed to both dimethylformamide and acrylonitrile (Chen et al., 1988a, 1988b), while a slightly earlier study on the same workforce provided data on only acrylonitrile workers (Chen et al., 1987). We also omitted studies where the RR of CNS cancers was not reported or where we could not obtain this information from the authors. We included only the most recent study unless CNS cancers were not reported in the latest update (Benn and Osborne, 1998; Werner and Carter, 1981). Twelve studies are included in the analysis to follow (Blair et al., 1998; Chen et al., 1987; Delzell and Monson, 1982; Keisselbach et al., 1980; Mastrangelo et al., 1993; Swaen et al., 1998; Thiess et al., 1980; Thomas et al., 1987; Werner and Carter, 1981; Wood et al., 1998), including unpublished studies of Herman and Burke (Memphis plant and Beaumont works).

To summarize the results of epidemiology studies, we used the methods of meta-analysis. Our analysis strategy focused on the evaluation of heterogeneity across studies as an indicator of factors that need to be considered in making a proper causal inference about acrylonitrile and

CNS cancers. Precision issues were a subordinate concern. We evaluated heterogeneity via graphical and statistical methods as described by Greenland (1987) and Dickersin and Berlin (1992). We used a fixed effects model to calculate the mRR, a measure of the average ratio of disease rates for those with and without acrylonitrile exposure, as an inverse variance weighted average of RRs from the individual studies (Greenland, 1987). We validated our calculations using Greenland's (1987) data for coffee and coronary heart disease and SAS software (SAS, 1993). When significant heterogeneity occurred, we calculated mRRs and related CIs using a random effects model that includes an additional component to the variance of each study's RR to reflect greater than expected differences among studies. This additional variance component was computed from the heterogeneity chi-square statistic as described by Shadish and Haddock (1994). The random effects model tends to equalize the contribution of individual studies to the mRR and increases the width of the CI.

The mRR calculations typically utilize a logarithmic transformation of CIs to derive standard errors and inverse variance weights. This transformation could not be utilized in studies where there were no exposed cases or where the lower confidence limit was 0. In these instances, we set the RR and lower confidence limit to 0.1, which will slightly increase the true mRR and slightly decrease the true heterogeneity estimates. We also evaluated these data excluding studies with a zero RR or lower confidence limit, and the results were similar.

We considered the impact on the mRR of a number of study characteristics including study design (cohort versus case-control), country (U.S. versus non-U.S.), and type of industry (acrylic fiber versus other). We also examined the impact of publication status and indicators of study quality. Personal or occupational confounding factors were not studied explicitly by any authors and, therefore, could not be considered in our analysis.

Publication bias is an important validity concern in meta-analysis; the publication process is selective. A related problem is that authors are selective in the reporting of findings, especially for rare diseases such as CNS cancers. In situations where reporting was selective, we contacted authors to obtain missing data on CNS cancers and incorporated these data into our analyses. In some instances when expected CNS cancer deaths were not reported for a specific cancer, we estimated expected number of deaths or cases based on the ratio of expected numbers of CNS cancers to total cancer. We obtained the ratios of CNS cancers to total cancers from the largest studies (the Wood et al., 1998, study for cancer incidence and the Blair et al., 1998, study for cancer mortality).

The predominant focus in the available studies was on worker mortality rates. However, one employer's studies also evaluated cancer incidence data as determined from the company's insurance system. We consider the incidence data separately.

There is disagreement in the literature about whether study quality should be used to weigh results of meta-analyses. Arguments against this proposition are that there is no objective measure of study quality and that aspects of study quality may impart conflicting effects on study results. Accordingly, Greenland proposed an analytic focus

Table 2. Description of 12 studies used in the analysis

Author	Company location	Use	Study design	Definition of brain cancer	Number of workers	Mean length of follow-up (years)	% Vital status follow-up complete	RR for brain and CNS cancers (95% CI) [obs/exp]
Keisselbach et al., 1977	Bayer, Leverkusen plant, Germany	Monomer and resins	Cohort mortality	ICD8 191–192	884	15	93	4.4 (0.9–13) [3/0.7] ^a
Theiss et al., 1980	BASF, 12 plants, Germany	Resins	Cohort mortality	NR	1,469	10	88	0.0 (0.0–5.7) [0/0.6] ^a
Werner & Carter, 1981	6 plants in the United Kingdom	Fibers and resins ^d	Cohort mortality	ICD8 191	1,111	12	98	2.9 (0.3–10.3) [2/0.7]
Herman (unpublished)	Uniroyal, Scotts Bluff & Baton Rouge plants, U.S.	Nitrile rubbers and resins	Cohort mortality	ICD8 191–192	1,077	12	97	3.0 (0.4–10) [2/0.7] ^a
Delzell & Monson, 1982	Goodrich, Akron plant, U.S.	Nitrile rubbers	Cohort mortality	NR	327	28 ^b	NR	0.0 (0.0–6.1) [0/0.6] ^a
Burke (unpublished)	DuPont, Memphis plant U.S.	Monomer	Cohort mortality and incidence	NR	700	16	90	3.0 (0.1–17) [1/0.3] ^{a,c}
Burke (unpublished)	DuPont, Beaumont plant, U.S.	Monomer	Cohort mortality and incidence	NR	472	15	95	0.0 (0.0–23) [0/0.2] ^{a,c}
Thomas et al., 1987	Populations of northern N.J., Philadelphia, and Gulf Coast of Louisiana	Farmers and workers in production of plastics and rubber	Case-control	ICD 191–192, 225,239.7 and only astrocytomas from medical record	27 exposed cases and 43 exposed controls	NA	NA	0.9 (0.5–1.6) 27 observed
Mastrangelo et al., 1993	Enichem-fibre, Porto Marghara, Italy	Fibers ^d	Cohort mortality	NR	671	19	100	2.6 (0.1–15) [1/0.4]
Swaen et al., 1998	8 plants, The Netherlands	Fibers and others	Cohort mortality	NR but 1 of 6 exposed deaths was an astrocytoma	2,842	23	100	1.7 (0.6–3.8) [6/3.4]
Wood et al., 1998	DuPont, Camden, and Waynesboro plants, U.S.	Fibers ^d	Cohort mortality and incidence	ICD9 191–192	2,559	28	99	1.1 (0.4–2.5) [6/5.3] ^c
Blair et al., 1998	8 plants, U.S.	Fibers and other	Cohort mortality	ICD8 191–192	25,460	21	96	0.7 (0.4–1.3) [12/17.1]

RR, relative risk; NR, not reported; NA, not applicable; obs/exp, observed deaths/expected deaths.

^aExpected deaths were not reported and were estimated (see text).

^bDuration of follow-up was estimated from an earlier report (Delzell and Monson, 1981).

^cIncidence data were available but are not shown.

^dMore than half of the workers in the study were exposed in fiber operations.

on individual aspects of study quality (Greenland, 1987). We chose this approach as preferable to one that uses an overall quality score-weighting procedure. We used the percentage of vital status follow-up in the cohort studies as an indicator of study quality where studies of 95% or more were higher quality. We also used average duration of follow-up as another indicator of quality. Twenty or more years of average duration of follow-up was considered high quality. Finally, we considered studies with an exposure assessment to be of higher quality than studies which provided no exposure assessment.

We used an approach proposed by Ward and Starr (1993) to compare experimental animal findings with epidemiology studies. We assumed that the average exposure in the epidemiology studies was 2 ppm, the average duration of exposure was 4 years, and the average length of follow-up was 20 years. Given the information from the three recent studies, these estimates are conservative (Blair et al., 1998; Swaen et al., 1998; Wood et al., 1998). The lifetime risk of developing CNS cancer from inhalation of acrylonitrile using the rat data is estimated to be 8.3×10^{-5} per $\mu\text{g}/\text{m}^3$ by Ward and Starr (1993). We detailed the

P-value function for the RR estimates to depict precision of the estimates unencumbered by specification of a confidence level (Poole, 1987). We used methods described by Breslow and Day (1987) to examine mortality trends for individual studies by exposure levels.

Results

Table 2 provides details of the studies that were used in the analysis. There is one case-control study and 11 cohort studies. This case-control study used ICD9 codes of 191, 192, 225, and 239.7 for possible cases, and then matched these possible cases with hospital records. Only astrocytoma, glioblastoma multiforme, and mixed glioma with astrocytic cells were included as cases. The 11 cohort studies only examined malignant CNS cancers, although six of these studies did not report how they defined CNS cancers (unpublished Burke Memphis plant and Beaumont works; Delzell and Monson, 1982; Mastrangelo et al., 1993; Swaen et al., 1998; Thiess et al., 1980), and one study only reports on malignant brain cancer (Werner and Carter, 1981). The predominant industries in the cohort studies were monomer production and fiber and resin manufacture. Overall, there were 60 deaths from cancers of the CNS, 27 in the case-control study and 33 in the cohort studies. There were also five incident cases from the studies of Burke (unpublished Beaumont works and unpublished Memphis plant) and Wood et al. (1998) not shown in the table. The average length of follow-up in the cohort studies ranged from 10 to 28 years, and the percentage of vital status follow-up ranged from 88 to 100%.

Fig. 1 presents the RRs and CIs for the 12 studies included in the analysis. The studies of Keisselbach et al. (1980), Werner and Carter (1981), Herman (unpublished), Burke (unpublished, Memphis plant), Mastrangelo et al. (1993), and Swaen et al. (1998) report RRs for brain or CNS cancers in excess of 1.0. The studies of Delzell and Monson (1982) and Burke (unpublished, Beaumont plant) report no CNS cancer deaths. The three recent cohort studies of Swaen et al. (1998), Wood et al. (1998), and Blair et al. (1998) are very large, as indicated by their narrow confidence limits, and have RR very close to 1.0.

Only three studies reported rates of CNS cancers by level or duration of exposure. These studies are shown in Table 3 with the rat findings of Quast et al.³ The rates of CNS cancers in the rat study show increasing risk of astrocytoma with increasing exposure level. The RR is 6.0 (95% CI 3.1–10.5) at 20 ppm lifetime exposure and 21.6 (95% CI 15.6–29.1) at 80 ppm lifetime exposure. The three epidemiology studies of Thomas et al. (1987), Swaen et al. (1998), and Blair et al. (1998) show no increasing risk with increasing exposure.

The mRRs and CIs for several groupings of data are presented in Table 4. The three studies that examined CNS cancer incidence had a mRR of 1.1 (95% CI 0.4–3.6), and the findings were consistent across studies as indicated by the *P* value for heterogeneity (0.61). This mRR was based on just five cases. The data from the 12 mortality studies included in the analysis produce a mRR of 1.1 (95% CI 0.8–1.5), and the findings were consistent

Fig. 1. Relative risk of brain cancer death from 12 studies.

(*P* value = 0.20). Since the mRRs for incidence and mortality are similar, we focused the remainder of the analysis and discussion on the mortality data.

The studies done on U.S. workers (mRR = 0.9, 95% CI 0.6–1.3) have a lower mRR than studies done on non-U.S. workers (mRR = 2.2, 95% CI 1.2–4.3). There was no difference in the mRR for acrylic fiber operations (mRR = 1.1, 95% CI 0.6–1.8) versus nonfiber operations (mRR = 1.1, 95% CI 0.8–1.7). Although the estimates were imprecise, the RRs were higher in the unpublished studies (mRR = 2.3, 95% CI 0.6–9.3) than in the published studies (mRR = 1.1, 95% CI 0.7–1.2). There also was a tendency not to report RRs >1.0. Studies reporting expected deaths had a mRR of 1.0 (95% CI 0.7–1.4) compared with a mRR of 2.2 (95% CI 0.3–2.2) for studies not reporting expected deaths. The studies with vital status follow-up completion of 95% or greater had lower mRR (1.1, 95% CI 0.7–1.6) than studies with follow-up completion <95% (mRR = 2.5, 95% CI 0.8–7.6). The studies with average duration of follow-up >20 years had a mRR of 0.9 (95% CI 0.6–1.5) compared with a mRR of 2.8 among studies with <20 years average duration of follow-up. Studies with an exposure assessment had a mRR of 1.0 (95% CI

Table 3. Relative risk of CNS tumors by exposure level for animal and human studies

Study	Description of exposure	Increasing exposure category						<i>P</i> value for linear trend
		None	1	2	3	4	5	
		RR (95% CI) [obs]	RR (95% CI) [obs]	RR (95% CI) [obs]	RR (95% CI) [obs]	RR (95% CI) [obs]	RR (95% CI) [obs]	
A. Rats								
Quast et al. (unpublished) ^a	Lifetime exposures for rats of both sexes in ppm (0, 20, 80)	0.0 (0.0–1.8) [0]	6.0 (3.1–10.5) [12]	21.6 (15.6–29.1) [43]				0.00000
B. Humans								
Thomas et al., 1987	Duration of exposed jobs in years (<5, 5–19, 20+)	1.0 (NR) [273]	1.5 (NR) [9]	1.2 (NR) [9]	1.3 (NR) [8]			NA
Swaen et al., 1998	CNS cancer mortality for humans at cumulative exposure in ppm-years (0.0, <10, 10–20, >20)	1.0 (0.0–5.8) [1]	3.1 (0.8–7.8) [4]	1.1 (0.0–5.9) [1]	0.0 (0.0–15.3) [0]			0.48
Blair et al., 1998	CNS cancer mortality for cumulative exposure in ppm-years (<0.13, 0.13–0.57, 0.57–1.5, 1.5–8.0, >8.0)	1.0	0.5 (0.1–1.8) [3]	0.2 (0.1–1.7) [1]	0.5 (0.1–2.3) [2]	0.8 (0.1–2.4) [4]	0.5 (0.1–2.5) [2]	0.74

RR, relative risk; obs, observed deaths; ppm, parts per million; NR, not reported; NA, could not be calculated, so confidence intervals not reported.

^aData used is an unpublished report entitled “A two-year toxicity and oncogenicity study with acrylonitrile following inhalation exposure of rats” (1983) by Quast, J.F., Schuetz, D.J., Balmer, M.F., Goshaw, T.S., Park, C.N., and McKenna, M.J.

0.6–1.5) compared with studies with no exposure assessment that had a mRR of 2.5 (95% CI 1.2–5.4).

Fig. 2 presents the projected deaths from CNS cancers using the animal data and human data modeled according to Ward and Starr (1993) assuming an average exposure of 2 ppm for 4 years with 20 years of follow-up. The model predicts a RR of 2.4 (95% CI 2.0–2.8) from the animal data compared with a RR of 1.0 (95% CI 0.7–1.3) in the epidemiology data. The *P*-value functions in Fig. 2 indicate that the CIs for the animal and human data do not overlap. We also used the other exposure assumption of Ward and Starr (1993). At an average exposure of 5 ppm for 4 years of exposure with 20 years of follow-up, the RR was 4.5 (95% CI 3.9–5.0). If we want to make the human and the animal findings consistent, we could assume an average exposure in the epidemiology studies of 0.005 ppm for 4 years after 20 years of follow-up.

Discussion

Most of the epidemiology studies that examine CNS cancer rates among acrylonitrile workers are cohort mortality investigations. The cohort studies in this review range in size from 327 to 25,460. These studies include 37,352 workers and 33 CNS cancer deaths. The single case-control study reported 27 astrocytoma deaths among workers with potential acrylonitrile exposure.

The general diagnosis of CNS cancers in the cohort studies precluded our examining CNS cancers by cell type or location in the CNS. However, because most CNS cancer deaths in humans are in the brain and most brain

cancers are astrocytomas, the cohort studies would be able to detect a moderate increase of astrocytomas deaths among acrylonitrile workers.

The levels of acrylonitrile exposure in all the studies are uncertain. Personal monitoring for acrylonitrile was not available before the mid-1970s, making exposure estimation before this time difficult. This lack of information made it impossible for us to examine exposure response for all studies or focus analysis on the highest exposed workers who would be most appropriate for an evaluation of acrylonitrile carcinogenicity. Some of the large recent cohort studies did estimate exposures in the past, and thus were more useful for causal inference. These large studies did not find an exposure response.

Evaluation of exposure to acrylonitrile in the case study of Thomas et al., however, was based on job history by next of kin. Jobs considered to have potential exposure to acrylonitrile in this study were primarily farmers. Acrylonitrile is a registered pesticide in the U.S. Acrylonitrile rarely has been used as a pesticide in the U.S., however, and its use is restricted to certified applicators (IARC, 1979). Therefore, it is unlikely that any farmers included in the Thomas et al. study had significant exposures to acrylonitrile.

Given the limitations just mentioned, the mRRs for CNS cancers are near null and consistent with no effect from acrylonitrile exposure. There was a tendency not to report positive findings for CNS cancers. For example, the three unpublished studies had a mRR of 2.3 (95% CI 0.6–9.3) compared with a mRR of 1.1 (95% CI 0.8–1.5) for nine published studies. This is directly opposite of what we expected if publication bias were present. Studies

Table 4. Meta-relative risk and 95% confidence intervals for selected mortality studies

Grouping	Number of studies	Number of CNS cases	Meta-relative risk	95% CI	P value heterogeneity
Incidence studies	3	5	1.1	0.4–3.1	0.61
Mortality studies	12	60	1.1	0.8–1.5	0.20
Region of study ^a					
U.S.	7	48	0.9	0.6–1.3	0.50
Non-U.S.	5	12	2.2	1.2–4.3	0.50
Type of study ^a					
Cohort	11	33	1.2	0.8–1.8	0.18
Case-control	1	27	0.9	0.5–1.6	NA
Type of operation ^a					
Fibers	3	9	1.1	0.6–1.8	0.36
Nonfibers	9	51	1.1	0.8–1.7	0.13
Publication status ^a					
Published	9	57	1.1	0.8–1.5	0.16
Not published	3	3	2.3	0.6–9.3	0.44
Reporting of relative risk ^b					
RR reported	6	27	1.0	0.8–1.5	0.36
RR not reported	5	6	2.2	0.7–6.4	0.17
Vital status follow-up completion ^b					
95% or better	7	29	1.1	0.7–1.6	0.31
<95%	4	4	2.5	0.8–7.6	0.18
Average duration of follow-up ^b					
20+ years	4	26	0.9	0.6–1.5	0.26
<20 years	7	7	2.8	1.3–6.0	0.62
Exposure assessment ^b					
Exposure assessment	3	24	1.0	0.6–1.5	0.23
No exposure assessment	8	9	2.5	1.2–5.4	0.48

CI, confidence interval.

^a Mortality studies only.^b Cohort mortality studies only.

with increased RRs tend to be more often reported than studies with null findings (Dickerson et al., 1992). Because CNS cancers were not the major focus of any of the cohort studies, the high rates of CNS cancers in the unpublished studies could result from chance. The CNS findings in the unpublished studies are based on only six CNS cases.

The higher quality cohort studies had a lower risk of CNS cancers than did the lower quality studies. Studies with average duration of follow-up of >20 years had a mRR of 0.9 (95% CI 0.6–1.5) compared with a mRR of 2.8 (95% CI 1.3–6.0) for the studies with <20 years of follow-up. The same pattern is observed when we examine the quality measure of vital status follow-up completion. The non-U.S. studies also had a higher mRR than the U.S. studies. This most likely reflects the fact that some of the non-U.S. studies had shorter follow-up periods and had lower percentages of vital status follow-up. We also observed that studies with an exposure assessment had a mRR of 1.0 (95% CI 0.6–1.5), while studies with no exposure assessment had a mRR of 2.5 (95% CI 1.2–5.4). The higher quality studies indicate no increased CNS cancer risk. However, while publication and study quality biases may be pres-

ent in these studies, they do not have significant impact on the overall size of mRR since the largest studies are both published and of high quality.

The experimental studies on rats show an association between acrylonitrile exposure and brain tumors. However, there was no indication in the epidemiology data of increased cancer risk among acrylonitrile workers. The animal and the human findings are inconsistent. There are several explanations that could explain the discrepancy.

The relevance of the acrylonitrile-induced rat CNS tumors to humans is not well understood. The histogenesis of the rat tumors, for example, has not been definitively established (Bigner et al., 1986). They are clearly primary brain tumors and have similarities to the spontaneous tumors that arise in rats, but they differ from the nitrosourea-induced tumors and virus-induced tumors that have the hallmarks of astrocytic lineage in rats. Also, the mechanism(s) that give rise to acrylonitrile-induced rat brain tumors are not well understood. Acrylonitrile-induced CNS tumors have not been linked to DNA adducts (Whysner et al., 1998a). Research investigating alternative mechanisms to direct genotoxicity has recently been reported (Jiang and Klaunig, 1998; Whysner et al., 1998b). This work shows elevated levels of

Fig. 2. P-value function of the projected relative risk for brain cancers from animal data and the actual relative risk from human studies.

oxidative DNA damage in the brains of rats exposed to tumorigenic doses of acrylonitrile, as indicated by the presence of 8-oxodeoxyguanosine, and considers the possibility that acrylonitrile may selectively induce oxidative stress in rat brain. Existing evidence suggests a need to better understand the rat as a CNS tumor model for predicting human response to acrylonitrile. Acrylonitrile, while causing CNS tumors in rats, may not cause CNS tumors in humans.

Because rats have been generally exposed to higher levels of acrylonitrile than have humans, the dose-response curve may be nonlinear at low doses. However, given the relatively narrow margin between past and current workplace standards and airborne concentrations that are tumorigenic in the rat, it seems unlikely that the striking differences between rat and human response to acrylonitrile exposure can be explained solely on the basis of faulty dose extrapolation. This is further reinforced if one considers the results of dosimetry modeling suggesting that humans may experience equivalent or higher tissue concentrations of acrylonitrile and its epoxide metabolite than do rats at current workplace exposure standards of 2 ppm (Kedderis and Held, 1998).

Only 33 CNS cancers have been reported among the acrylonitrile workers in the 11 cohort studies that have been done. These cancers are rare in humans, and the heterogeneity of CNS cancers will make the identification of causes difficult when they are grouped together as in the present case (Davis et al., 1996). While we can be somewhat certain that acrylonitrile exposure does not cause a large increase in risk in brain tumors, especially in astrocytomas as a group, we cannot be certain that a small increased risk is not present, especially among the rarer histologic types.

To compare the rat findings with the human findings, we had to translate the animal exposure to an exposure observed in the workplace. Increased risk of CNS cancer in rats is observed after a lifetime exposure to 20 ppm. A small percentage of workers in the epidemiology studies

have been exposed to 20 ppm TWA8 or more but these workers would only be exposed to these levels for a few years. So the animals received a higher cumulative exposure to acrylonitrile than humans. It could be that humans are exposed to less acrylonitrile than we have estimated, thus explaining the differences in risk by adjusting for dose.

Limitations in the design and execution of the epidemiology studies may have obscured a CNS cancer excess among exposed workers. We have already discussed the inability of the case-control study design to identify workers with significant exposure to acrylonitrile. Another potential limitation of the epidemiology studies is the short duration of follow-up of workers after exposure. Several epidemiology studies have only examined mortality rates of workers for <20 years after first exposure. If acrylonitrile exposure only leads to cancer deaths >20 years after exposure, these studies could not assess acrylonitrile carcinogenicity. Fortunately, the three recent large studies of acrylonitrile workers overcome these two limitations and can thus validly assess acrylonitrile carcinogenicity.

Conclusion

High exposure to acrylonitrile in rats increases their cancer risk. However, there is no indication of increased risk in humans exposed to lower levels of acrylonitrile. It is apparent that the animal risk from acrylonitrile exposure is not consistent with the extensive epidemiology data on acrylonitrile workers. While there are several possible explanations for this inconsistency, it may be that the findings in animals are not relevant to humans. Because of the rarity of CNS cancer in humans, however, and the lack of causal mechanisms of these tumors in rats, a more definitive conclusion will have to await additional experimental and observational data. Nevertheless, the epidemiology data indicate that acrylonitrile is not a potent CNS tumorigen in humans.

References

- ATSDR (Agency for Toxic Substances and Disease Registry) (1990) *Toxicological Profile for Acrylonitrile TP-90-02*. Atlanta: ATSDR.
- Benn, T., and Osborne, K. (1998) Mortality of United Kingdom acrylonitrile workers: An extended and updated study. *Scand. J. Work Environ. Health* **24** (Suppl. 2), 71–80.
- Bigner, D.D., Bigner, S.H., Burger, P.C., Shelburne, J.D., and Friedman, H.S. (1986) Primary brain tumours in Fischer 344 rats chronically exposed to acrylonitrile in their drinking-water. *Food Chem. Toxicol.* **24**, 129–137.
- Blair, A., and Kazerouni, N. (1997) Reactive chemicals and cancer. *Cancer Causes Control* **8**, 473–490.
- Blair, A., Stewart, P.A., Zaubst, D.D., Pottern, L., Zey, J.N., Bloom, T.F., Miller, B., Ward, E., and Lubin, J. (1998) Mortality study of industrial workers exposed to acrylonitrile. *Scand. J. Work Environ. Health* **24** (Suppl. 2), 25–41.
- Breslow, N.E., and Day, N.E. (1987) *Statistical Methods in Cancer Research: Volume II. The Design and Analysis of Cohort Studies*. Lyon: International Agency for Research on Cancer.
- 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.
- Chen, J.L., Fayerweather, W.E., and Pell, S. (1988a) Cancer incidence of workers exposed to dimethylformamide and/or acrylonitrile. *J. Occup. Med.* **30**, 813–818.
- Chen, J.L., Fayerweather, W.E., and Pell, S. (1988b) Mortality study of workers exposed to dimethylformamide and/or acrylonitrile. *J. Occup. Med.* **30**, 819–822.
- Collins, J.J., and Acquavella, J.F. (1998) Review and meta-analysis of studies of acrylonitrile workers. *Scand. J. Work Environ. Health* **24**, 71–80.
- Collins, J.J., Page, L.C., Caporossi, J.C., Utidjian, H.M.D., and Lucas, L.J. (1989) Mortality patterns among employees exposed to acrylonitrile. *J. Occup. Med.* **31**, 368–371.
- Davis, F.G., Malinski, N., Haenszel, W., Chang, J., Flannery, J., Gershman, S., Dibble, R., and Bigner, D.D. (1996) Primary brain tumor incidence rates in four United States regions, 1985–1989: A pilot study. *Neuroepidemiology* **15**, 103–112.
- Delzell, E., and Monson, R.R. (1981) Mortality among rubber workers: III. Cause specific mortality, 1940–1978. *J. Occup. Med.* **23**, 677–684.
- Delzell, E., and Monson, R.R. (1982) Mortality among rubber workers: VI. Men with potential exposure to acrylonitrile. *J. Occup. Med.* **24**, 767–769.
- Dickersin, K., and Berlin, J.A. (1992) Meta-analysis: State of the science. *Epidemiol. Rev.* **14**, 154–176.
- Dickersin, K., Min, Y.I., and Meinert, C.L. (1992) Factors influencing publication of research results: Follow-up of applications submitted to two institutional review boards. *JAMA* **267**, 374–378.
- Doll, R. (1991) Hazards of cancer in the chemical industry. *Br. Ind. Biol. Res. Assoc. Bull.* **30**, 183–188.
- EPA (Environmental Protection Agency) (1990) Health assessment document for acrylonitrile: General review and summary. *Sci Total Environ.* **90**, 337–352.
- Greenland, S. (1987) Quantitative methods in the review of epidemiologic literature. *Epidemiol. Rev.* **9**, 1–30.
- Greenwald, P., Friedlander, B.R., Lawrence, C.E., Hearne, T., and Earle, K. (1981) Diagnostic sensitivity bias—an epidemiologic explanation for an apparent brain tumor excess. *J. Occup. Med.* **23**, 690–694.
- Guirguis, S.S., Cohen, M.B., and Rajhans, G.S. (1984) A review of health risks in acrylonitrile industry. *G. Ital. Med. Lav.* **6**, 87–93.
- International Agency for Research on Cancer (1979) Evaluation of the carcinogenic risk of chemical to humans: Some monomers, plastics, synthetic elastomers, and acrolein. Vol. 19, IARC, Lyon, France. February.
- International Agency for Research on Cancer (1987) Evaluation of the carcinogenic risk of chemical to humans: Overall evaluations of carcinogenicity: An updating of IARC monographs. Vol. 1–42, Supplement 7, IARC, Lyon, France.
- International Classification of Disease Ninth Revision, Clinical Modification (1988). DHHS Publication no. 80-1260. Washington, D.C.: U.S. Government Printing Office.
- Jiang, J., Xu, Y., and Klaunig, J.E. (1998) Induction of oxidative stress in rat brain by acrylonitrile. *Tox. Sciences* **46**, 333–341.
- Kedderis, G.L., and Held, S.D. (1998) Refinement of the human dosimetry description for acrylonitrile. *Tox. Sciences* **42**, 1–S, 142 (Abstract No. 700).
- Kiesselbach, N., Korallus, U., Lange, H.J., Neiss, A., and Zwingers, T. (1980) Bayer acrylonitrile study 1977. (1980) Bayer acrylonitrile study 1977. *Central J. Indust. Med. Protection Labor, Indust. Hyg. Ergonomics* **7**, 1–46.
- Koerselman, W., and van der Graaf, M. (1984) Acrylonitrile: A suspected human carcinogen. *Int. Arch. Occup. Environ. Health* **54**, 317–324.
- Marsh, G.M. (1983) Mortality among workers from a plastics producing plant: A matched case-control study nested in a retrospective cohort study. *J. Occ. Med.* **25**, 219–230.
- Mastrangelo, G., Serena, R., and Maszia, V. (1993) Mortality from tumours in workers in an acrylic fibre factory. *Occup. Med. (Lond.)* **43**, 155–158.
- O'Berg, M.T. (1980a) Epidemiologic study of workers exposed to acrylonitrile. *J. Occup. Med.* **22**, 245–252.
- O'Berg, M.T. (1980b) Epidemiologic study of cancer incidence and mortality among workers exposed to acrylonitrile at a chemical plant which produces textile fibers. University Microfilms International, Ann Arbor, Michigan.
- 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.
- OSHA (Occupational Safety and Health Administration) (1978) Notice issuing final standard for acrylonitrile. *Federal Register* **43** 45762, Oct. 3.
- Ott, M.G., Kolesar R.C., Scharnweber, H.C., Schneider, E.J., and Venable, J.R. (1980) A mortality survey of employees engaged in the development or manufacture of styrene-based products. *J. Occup. Med.* **22**, 445–460.
- Ott, M.G., Teta, M.J., and Greenberg, H.L. (1989) Lymphatic and hematopoietic tissue cancer in a chemical manufacturing environment. *Am. J. Ind. Med.* **16**, 631–643.
- Percy, C., Stanek, E., III, and Gloeckler, L. (1981) Accuracy of cancer death certificates and its effect on cancer mortality statistics. *Am. J. Pub. Health* **71**, 242–250.
- Percy, C.L., Miller, B.A., and Gloeckler, L.A. (1990) Effect of changes in cancer classification and the accuracy of cancer death certificates on trends in cancer mortality. *Ann. N.Y. Acad. Sci.* **609**, 87–99.
- Poole, C. (1987) Beyond the confidence interval. *Am. J. Pub. Health* **77**, 195–199.
- Rothman, K.J. (1994) Cancer occurrence among workers exposed to acrylonitrile. *Scand. J. Work Environ. Health* **20**, 313–321.
- SAS (1993) *SAS User's Guide: Basics*. Version 5. Cary, N.C.: SAS Institute, Inc.
- Shadish, W.R., and Haddock, C.K. (1994) Combining estimates of effect size. In: Cooper, H., and Hedges G. (Eds.), *The Handbook of Research Synthesis*. New York: Russell Sage Foundation. pp. 261–281.
- Siemietycki, J., Dewar, R., Nadon, L., and Gerin, M. (1994) Occupational risk factors for bladder cancer: Results from a case-control study in Montreal, Quebec, Canada. *Am. J. Epid.* **140**, 1061–1080.
- Stewart, P.A., Zaubst, D., Zey, J.N., Herrick, R., Dosemeci, M., Hornung, R., Bloom, T., Pottern, L., Miller, B.A., and Blair, A. (1998) Exposure assessment for a study of workers exposed to acrylonitrile. *Scand. J. Work Environ. Health* **24** (Suppl. 2), 42–53.
- Strother, D.E., Mast, R.W., Kraska, R.C., and Frankos, V. (1988) Acrylonitrile as a carcinogen: Research needs for better risk assessment. *Ann. N.Y. Acad. Sciences* **534**, 169–178.

- Swaen, G.M.H., Bloemen, L.J.N., Slangen, J.J.M., Twisk, J., Scheffers, T., and Sturmans, F. (1992) Mortality update of workers exposed to acrylonitrile. *J. Occup. Med.* **34**, 801–809.
- Swaen, G.M.H., Bloemen, L.J.N., Twisk, J., Scheffers, T., Slangen, J.J.M., Collins, J.J., Berge, W.J., and Sturmans, F. (1998) Mortality of workers exposed to acrylonitrile in the Netherlands. *Scand. J. Work Environ. Health* **24** (Suppl. 2), 10–16.
- Thiess, A.M., Frentzel-Beyme, R., Link, R., and Wild, H. (1980) Mortalitätsstudie bei chemiefacharbeitern verschiedener produktionsbetriebe mit exposition auch gegenüber acrylnitril. *Zentralbl. Arbeitsmed. Arbeitsschutz. Propyl Ergonomie* **30**, 259–267.
- Thomas, T.L. (1994) Primary brain tumors associated with chemical exposure. In: Bleeker, M.L., and Hansen, J.A. (Eds.), *Occupational neurology and clinical neurotoxicology*. New York: Williams and Wilkins. pp. 187–206.
- Thomas, T.L., and Waxweiler, R.J. (1986) Brain tumors and occupational risk factors: A review. *Scand. J. Work Environ. Health* **12**, 1–15.
- Thomas, T.L., Stewart, P.A., Stermhagen, A., Correa, P., Norman, S.A., Bleeker, M.L., and Hoover, R.N. (1987) Risk of astrocytic brain tumors associated with occupational chemical exposures. *Scand. J. Work Environ. Health* **13**, 417–423.
- Velema, J.P., and Percy, C.L. (1987) Age curves of central nervous system tumor incidence in adults: Variation of shape by histologic type. *J. Nat. Cancer Inst.* **79**, 623–629.
- 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.
- Waxweiler, R.J., Smith, A.H., Falk, H., and Tyroler, H.A. (1981) Excess lung cancer risk in a synthetic chemicals plant. *Environ. Health Perspect.* **41**, 159–165.
- Werner, J.B., and Carter, J.T. (1981) Mortality of United Kingdom acrylonitrile polymerization workers. *Br. J. Ind. Med.* **38**, 247–253.
- Whysner, J., Ross, P.M., Conaway, C.C., Verna, L.K., and Williams, G.M. (1998a) Evaluation of possible genotoxic mechanisms for acrylonitrile tumorigenicity. *Regul. Toxicol. Pharmacol.* **27**, 217–239.
- Whysner, J., Steward, R.E., Chen, D., Conaway, C.C., Verna, L.K., Richie, J.P., Ali, N., and Williams, G.M. (1998b) Formation of 8-oxodeoxyguanosine in brain DNA of rats exposed to acrylonitrile. *Arch. Toxicol.* **72**, 429–438.
- Wood, S.M., Buffler, P.A., Burau, K., and Krivanek, N. (1998) Cohort study of DuPont employees exposed to acrylonitrile. *Scand. J. Work Environ. Health* **24** (Suppl. 2), 54–62.
- Young, J.L., Percy, C.L., and Asire, A.D. (1981) Surveillance, epidemiology, and end results: Incidence and mortality data, 1973–77. NCI monograph 57, NIH publication no. 812330. Washington, D.C.: U.S. Government Printing Office.
- Zhou, B., and Wang, T. (1991) Historical cohort study of causes of death in a chemical fiber factory. *J. Chinese Med. Univ.* **20**, 35–37.