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Review and meta-analysis of studies of acrylonitrile workers

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Twenty-five epidemiologic studies of acrylonitrile workers were reviewed and subjected to meta-analytic techniques in this study to assess the findings for 10 cancer sites. The analyses indicate that workers with acrylonitrile exposure have essentially null findings for most cancers, including lung [meta-relative risk (mRR) 0.9, 95% confidence interval (95% CI) 0.9—1.1], brain (mRR 1.2, 95% CI 0.8—1.7), and prostate (mRR 1.0, 95% CI 0.7—1.4) cancers. Bladder cancer rates were elevated (mRR 1.8, 95% CI 1.0—3.4), but the excess was not dose-related and was limited to plants with aromatic amines. Therefore, the bladder cancer excess is unlikely to be related to acrylonitrile exposure. Some evidence of publication bias was found in the examined literature, but the bias did not have a significant impact on risk estimates for individual cancers. It was concluded that the available studies do not support a causal relation between acrylonitrile exposure and cancer.

Key terms aromatic amines, bladder cancer, brain cancer, lung cancer, prostate cancer, publication bias.

Acrylonitrile (CAS number 107-13-11) is a high-volume industrial chemical used in the manufacture of acrylic fibers, resins, plastics, rubbers, and other chemicals such as acrylamide. Commercial production and use began in the 1940s. Worldwide over 3 billion pounds (1 360 791 metric tons) of acrylonitrile were produced in 1994, and demand continues to increase (1).

Published studies on the cancer rates of acrylonitrile workers were reviewed by Rothman in 1994 (2), but substantially more evidence has now been provided by 4 cohort studies reported in this issue (3—6). The purpose of this article was to review the totality of the evidence now available, including that provided by these 4 new studies and also unpublished studies we have been able to identify.

Workplace exposure

Inhalation is the primary route of acrylonitrile exposure, although exposure can also occur through dermal contact. Average inhalation exposure appears to have been highest in acrylic fiber production, especially in polymerization and spinning processes (3, 4). Exposure opportunity is also significant in the production of acrylonitrile, acrylonitrile-based resins, and nitrile rubber. Current operations have exposures at or below 0.5 ppm for an 8-hour time-weighted average (TWA_{8h}), but exposure levels measured by area air monitoring were much higher in the past, exceeding a TWA_{8h} of 20 ppm (P Stewart, National Cancer Institute, personal communication, 1996). Workers have frequently noted acrylonitrile odors in the workplace, and the odor threshold for acrylonitrile is known to vary between 1.6 and 22 ppm (5, 6). Excess cancers were found in chronic exposures of rats at 20 ppm (7 & one unpublished report "A Two-year Toxicity and Oncogenicity Study with Acrylonitrile Following Inhalation Exposure of Rats" by Quast et al).

Methods

We identified studies for this review primarily through a MEDLINE search using the key words cancer and acrylonitrile. We also searched MEDLINE using several synonyms for acrylonitrile (ie, cyanoethylene, 2-propenenitrile, vinyl cyanide, and acrylic fiber). Additional studies were identified through bibliographies (2 ,3 , 4, 6, 8—14), contacts with authors, and contacts with companies in acrylonitrile-related businesses.

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We identified 29 studies. Twenty were published (15—38), 4 were presented at this conference (35—38), and 5 were unpublished ("The Mortality Experience of Monsanto Workers Exposed to Acrylonitrile" by Zack, "Cohort Mortality Study of the 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 & 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 1 study because the authors did not present results in terms of relative risk (RR) estimates (21) and 2 studies because they concerned only workers exposed to both dimethylformamide and acrylonitrile (27, 28), while a slightly earlier study on the same work force provided data on all acrylonitrile workers (26).

Our analysis strategy focused on the evaluation of heterogeneity as an indicator of factors that need to be considered in making a proper causal inference about acrylonitrile and cancer. Precision issues were a subordinate concern. We evaluated heterogeneity via graphic and statistical methods as described by Greenland (39) and Dickinson & Berlin (40). We used a fixed-effects model to calculate the meta-relative risk (mRR), a measure of the average ratio of disease rates for those with and without acrylonitrile exposure, as an inverse variance-weighted average of relative risks from the individual studies (39). We used SAS (statistical analysis system) software to do the calculations and validated our program using Greenland's data for coffee and coronary heart disease (39, 41). When significant heterogeneity occurred, we calculated mRR values and related confidence intervals using a random effects model which included an additional component in the variance of the relative risk of each study to reflect greater-than-expected differences among studies. This additional variance component was computed from the heterogeneity chi-square statistic, as described by Shadish & Haddock (42). Greater heterogeneity tends to equalize the contribution of individual studies to the meta-RR and increases the width of the confidence interval.

Calculations of mRR typically utilize a logarithmic transformation of confidence intervals to derive standard errors and inverse variance weights. This transformation could not be utilized in studies for which there were no exposed cases or in which the lower confidence limit was 0. In these instances, we set the relative risk and lower confidence limit at 0.1, which slightly increased the mRR and slightly decreased the heterogeneity estimates. We also evaluated these data excluding studies with a zero relative risk 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-referent), country [United States (US) versus non-United States (non-US)], 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. We noted the potential for confounding by occupational exposures when specific cancers were found to be elevated only in a plant or plants where a known causal factor was also present. We used methods described by Breslow & Day (43) to examine mortality trends for individual studies by exposure levels.

Publication bias

Publication bias is an important validity concern in meta-analysis, the specific concern being that the publication process is selective. A related problem is the fact that authors are selective in their reporting of findings, especially for rare diseases. In situations in which reporting was selective, we contacted authors to get missing data and incorporated these data into our analyses. In some instances when expected deaths were not reported for a specific cancer, we estimated the expected number of deaths or cases on the basis of the ratio of expected numbers of cancers to total cancer from the largest studies [ie, the Wood et al study (36) for cancer incidence and the Blair et al study (35) for cancer mortality].

Outcome data

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.

Study quality

There is disagreement in the literature about whether study quality should be used to weight results of meta-analyses. Arguments against this proposition are the lack of an objective measure of study quality and the possibility of aspects of study quality imparting conflicting effects on study results. Accordingly, Greenland (39) proposed an analytic focus on individual aspects of study quality (eg, percentage lost to follow-up, percentage of death certificates obtained, type of comparison population, etc). We chose this approach as preferable to one which utilizes an overall quality-score-weighting procedure.

Results

Table 1 provides selected details of the studies found in the search. All but 4 studies were cohort investigations, the others being 2 nested case-referent studies and 2 general population-based case-referent studies (23, 25, 29,

34). The 2 population case-referent studies were restricted to bladder cancer (34) and astrocytic brain cancer (25) and were not specific for acrylonitrile exposure. The nested case-referent studies were restricted to prostate and lymphatic and hematopoietic cancers and acrylonitrile exposure (23).

The predominant industries represented in the cohort studies were monomer production and fiber and resin manufacture. Eight studies were subsequently updated [17, 20, 24, 26, 30, 32, & 2 unpublished reports ("The Mortality Experience of Monsanto Workers Exposed to Acrylonitrile" by Zack and "A Mortality Study of

Table 1. Description of studies found in the literature search.

Author	Company-location	Acrylonitrile use	Study design	Study period	Number of workers	Included in other study
Keisselbach et al, 1980 (15)	Bayer, Leverkusen plant, Germany	Monomer & resins	Cohort mortality	1950—1977	884	No
O'Berg, 1980 (16)	DuPont, Camden plant, United States	Fibers	Cohort mortality & incidence	1950—1976 mortality, 1950—1976 incidence	1345	Included in the O'Berg et al (24) study & the Wood et al study (36)
Theiss et al, 1980 (18)	BASF, 12 plants, Germany	Resins	Cohort mortality	1955—1978	1469	No
Ott et al, 1980 (19)	Dow, 4 plants, United States	Styrene	Cohort mortality copolymerization	1950—1975	100	No
Zack, 1980 (unpublished report)	Monsanto, Texas City & Decatur, United States	Monomer & fibers	Cohort mortality	1952—1977	352	Included in the Blair et al study (35)
Werner & Carter, 1981 (20)	6 plants, United Kingdom	Fibers & resins	Cohort mortality	1950—1978	1111	Included in the Benn & Osborne study (38)
Herman, 1981 (unpublished report)	Uniroyal, Scotts Bluff & Baton Rouge plants, United States	Nitrile rubbers & resins	Cohort mortality	1951—1977	1077	No
Gaffey & Strauss, 1981 (unpublished report)	Monsanto, Decatur plant, United States	Fibers	Cohort mortality	1952—1977	326	Included in the Blair et al study (35)
Delzell & Monson, 1982 (22)	Goodrich, Akron plant, United States	Nitrile rubbers	Cohort mortality	1940—1978	327	No
Marsh, 1983 (23)	Monsanto, Springfield plant, United States	Styrene polymerization	Nested case-referent	1949—1976	13 cases, 52 referents	No
O'Berg et al, 1985 (24)	DuPont, Camden plant, United States	Fibers	Cohort mortality & incidence	1950—1981 mortality, 1950—1980 incidence	1345	Included in the Wood et al study (36)
Burke, 1985 (unpublished report)	Dupont, Memphis plant, United States	Monomer	Cohort mortality & incidence	1957—1980 mortality, 1956—1983 incidence	700	No
Burke, 1985 (unpublished report)	Dupont, Beaumont plant, United States	Monomer	Cohort mortality & incidence	1962—1982 mortality, 1962—1983 incidence	472	No
Thomas et al, 1987 (25)	Populations of northern New Jersey, Philadelphia and Gulf coast of Louisiana	Farmers & workers in production of plastics & rubber	Case-referent	1978—1981	27 cases and 43 referents	No
Chen et al, 1987 (26)	Dupont, Waynesboro plant, United States	Fibers	Cohort mortality & incidence	1957—1981 mortality, 1956—1983 incidence	1083	Included in the Wood et al study (36)
Ott et al, 1989 (29)	3 Union Carbide facilities	Resins	Nested case-referent	1940—1978	6 cases of non-Hodgkin's lymphoma and 2 cases of leukemia	No
Collins et al, 1989 (30)	American Cyanamid, Santa Rosa & Fortier plant, United States	Fibers, monomer, & other	Cohort mortality	1950—1981	1774	Included in the Blair et al study (35)
Zhou & Wang, 1991 (31)	Fushun Chemical, Fushun plant, China	Fibers	Cohort mortality	1971—1988	1811	No
Swaen et al, 1992 (32)	8 plants, The Netherlands	Fibers & others	Cohort mortality	1956—1988	2842	Included in Swaen et al update (37)
Mastrangelo et al, 1993 (33)	Enichem-fiber, Porto Marghara, Italy	Fibers	Cohort mortality	1959—1990	671	No
Siemiatycki et al, 1994 (34)	Population of Montreal, Canada	Tailors using acrylic fiber	Case-referent	1979—1986	484 cases and 1879 referents	No
Blair et al, 1998 (35)	8 plants, United States	Fibers & other	Cohort mortality with case-referent	1950—1989	25 460	No
Wood et al, 1998 (36)	Dupont, Camden & Waynesboro plants, UnitedStates	Fibers	Cohort mortality & incidence	1947—1991 mortality, 1956—1991 incidence	2559	No
Swaen et al, 1998 (37)	8 plants, The Netherlands	Fibers & others	Cohort mortality	1956—1996	2842	No
Benn & Osborne 1998 (38)	6 plants, United Kingdom	Fibers & resins	Cohort mortality	1950—1991	2763	No

Workers Potentially Exposed to Acrylonitrile during Start-up: Monsanto, Decatur Plant" by Gaffey & Strause)]. Of the 14 unique study cohorts, 8 were done in the United States [19, 22, 29, 35, 36, & 3 unpublished reports ("Cohort Mortality Study of the Scotts Bluff/Baton Rouge Uniroyal Plant" by Herman, "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)], 2 in Germany (15, 18), and 1 each in the United Kingdom (38), The Netherlands (37), Italy (33), and China (31). The average duration of follow-up was 30.2 years for the cohort mortality studies and 28.6 years for the cohort incidence studies. The percentage lost in follow-up ranged from 0% to 12% in the cohort mortality studies with a mean of 4%. Loss to follow-up was not reported in the incidence studies. The percentage of death certificates not obtained in these studies ranged from 0% to 6% with a mean of 3%. The remaining analyses of these data has been limited to the 14 unique study cohorts and the 4 case-referent studies.

Table 2 summarizes the results for the unique study populations. All-cause mortality was about 20% less than the general population rates, and the results were heterogeneous (P<0.00001). Mortality from ischemic heart disease and accidents was also less than the population rates. All specific causes of cancer examined were near or below the expected levels with the single exception of bladder cancer [mRR 1.4, 95% confidence interval (95% CI) 0.9—2.0]. The results for all specific causes of death were homogeneous across studies with the single exception of those for colon cancer (heterogeneity P-value = 0.0062). The heterogeneity was due to the Mastrangelo et al study (33) with a standardized mortality ratio (SMR) of 10.5 (4 deaths, 95% CI 2.9—26.9) for colon cancer. The heterogeneity P-value was 0.33 for the remaining studies, and the mRR was 0.8 (95% CI 0.6—1.0).

Results for the cancer incidence studies were similar to the results of the mortality studies. The summary cancer incidence results were near the expected levels. The prostate cancer rates (mRR 1.4, 95% CI 0.8—2.6) were slightly elevated. The incidence rates from the 3 studies for all cancers were homogeneous. Since the mortality and incidence mRR values were similar for most of the cancers and there was substantially more mortality data, we limited further analyses to the mortality data, with the exception of prostate cancer.

In the analyses of study characteristics, only publication bias, country of study, and the potential for nonacrylonitrile plant exposures were predictive of study results. In this report we focus on total mortality, lung cancer, prostate cancer, brain cancer, and bladder cancer. These

Table 2. Meta-relative risks and 95% confidence intervals (95% CI) for the mortality studies and incidence studies by the 9th revision of the International Classification of Causes of Death.

Disease[a]	Number of studies	Observed	Expected	Meta-relative risk	95%CI	P value heterogeneity
Mortality studies						
All causes	13	2769	3739.3	0.8	0.7—0.9[b]	<0.00001
All cancer(140—209)	12	783	920.8	0.9	0.8—0.9	0.16
Stomach (151)	9	37	48.1	0.9	0.6—1.2	0.48
Colon (153)	9	55	65.4	1.1	0.6—2.1[b]	0.00062
Liver (155—156)	8	9	13.7	0.7	0.3—1.5	0.58
Lung (162)	12	315	339.4	0.9	0.8—1.1	0.33
Prostate (185)	10	35	33.7	1.0	0.7—1.5	0.47
Bladder (188)	10	30	23.1	1.4	0.9—2.0	0.18
Brain (191—192)	11	58	59.4	1.1	0.8—1.5	0.20
Hodgkin's Disease (201)	8	7	9.7	0.9	0.4—2.2	0.23
Leukemia (204—208)	10	23	32.5	0.7	0.5—1.1	0.53
Non-Hodgkin's lymphoma (202—203)	9	22	26.3	1.0	0.6—1.6	0.12
Ischemic heart disease (410—414)	6	579	707.5	0.8	0.8—0.9	0.11
Accidents (800—949)	6	200	243.2	0.9	0.7—1.0	0.21
Incidence studies						
All cancer (140—209)	3	118	121.5	1.0	0.8—1.2	0.97
Stomach (151)	3	1	2.7	0.3	0.0—2.1	0.81
Colon (153)	3	15	13.2	1.2	0.7—2.0	0.61
Liver (155—156)	2	1	0.3	1.8	0.2—20.8	0.26
Lung (162)	3	23	32.3	0.8	0.5—1.2	0.28
Prostate (185)	3	12	8.5	1.4	0.8—2.6	0.26
Bladder (188)	3	5	6.2	0.8	0.3—2.2	0.49
Brain (191—192)	3	5	4.2	1.1	0.4—3.1	0.62
Hodgkin's Disease (201)	2	4	2.1	2.4	0.7—8.0	0.11
Leukemia (204—208)	3	3	4.2	1.4	0.4—5.7	0.17

[a] Codes of the International Classification of Causes of Death (9th revision) in parentheses.
[b] Random effects estimate; otherwise fixed effects estimates.

cancer sites are of special interest because of the results of previous human or animal studies or, for bladder cancer, because of our overall meta-analysis findings.

Total mortality

Figure 1 presents the SMR values for total mortality for each study with their confidence intervals. The studies are arranged by the year of publication or, if unpublished, by the year of completion. With the exception of the study of Zhou & Wang (31), all the studies had SMR values equal to or less than 1.0. Zhou & Wang (31) did not describe the methods of follow-up used in their study and stated that the death information may not be comparable to the national population. However, the remaining studies, though somewhat similar in results on an absolute basis, still showed considerable heterogeneity (P=0.00004). The US studies were similar (P=0.43) with an mRR of 0.7 (95% CI 0.7—0.7). The non-US studies, however, still exhibited some variability (P=0.02), with an mRR of 0.8 (95% CI 0.8—0.9).

Lung cancer

The SMR values for lung cancer by study are shown in figure 2. The early studies were smaller than the 4 recent studies, as evidenced by the wide confidence intervals in the early studies. The recent studies of Blair et al (35), Wood et al (36), Swaen et al (37), and Benn & Osborne (38) all had narrow confidence intervals and the SMR values were close to 1.0. The mRR for all the studies was 0.9 (95% CI 0.9—1.1).

We examined the cumulative relative risk by the date of the study, as shown in figure 3. Before 1992, the cumulative relative risk for lung cancer mortality among acrylonitrile workers was slightly greater than 1.0. With the completion of the 4 large studies in 1997, the confidence interval was narrow, and the cumulative SMR was below 1.0.

Latency is the term often applied to the period between initial exposure and death from a disease. Most occupational carcinogens do not show increased risk for 15 or 20 years after first exposure (44). Eight studies considered latency periods of 15 years or longer. The studies which considered latency had an mRR of 1.0 (95% CI 0.9—1.1) compared with an mRR of 0.9 (95% CI 0.7—1.1) for the studies which did not. Only the studies of Blair et al (35) (RR 1.3, 95% CI 1.0—1.63) and Delzell & Monson (22) (SMR 1.7, 95% CI 0.7—3.5) had elevated rates in the longest latency category. The 6 other studies

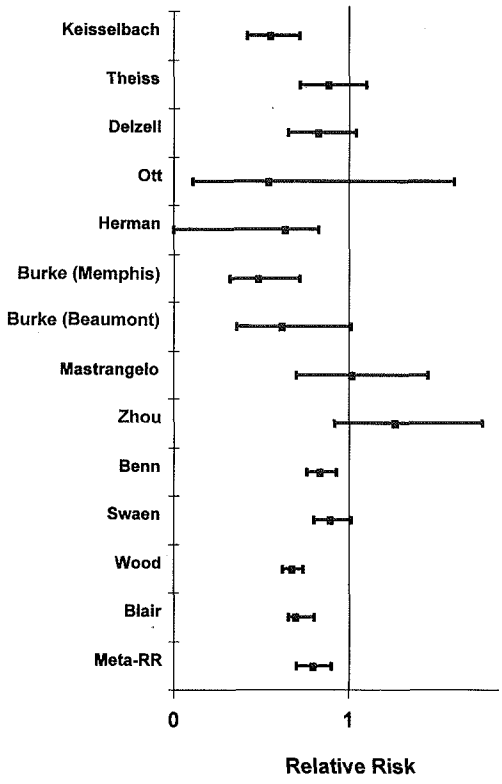

Figure 1. Relative risk for all causes of death (studies listed by first author).

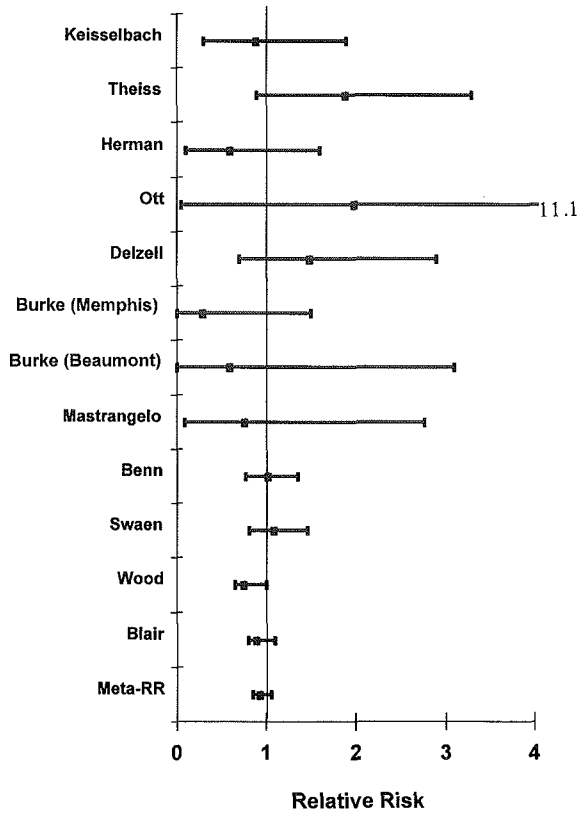

Figure 2. Relative risk for lung cancer death (studies listed by first author).

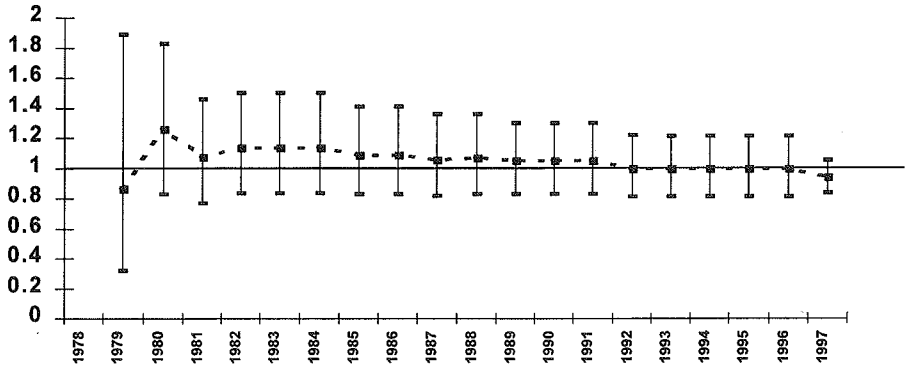

Figure 3. Cumulative relative risk and 95% confidence intervals for lung cancer by year of study.

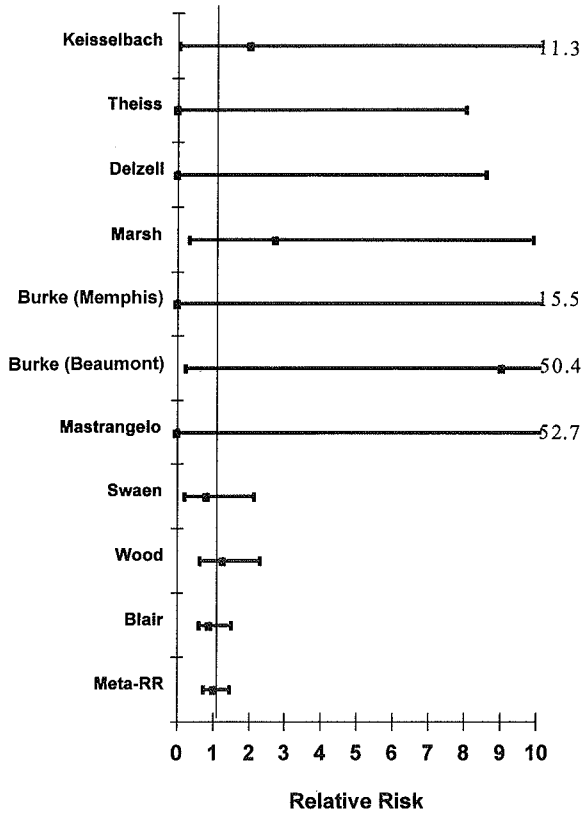

Figure 4. Relative risk for prostate cancer death (studies listed by first author).

reported SMR values ≤1.0 for this category. The mRR for this category was near null (mRR 1.2, 95% CI 1.0—1.4, heterogeneity P-value=0.52).

Several of the acrylonitrile studies examined worker mortality rates by level of exposure. These analyses are important to separate workers with low or brief exposures from more highly exposed workers who are obviously more relevant for causal inference. Unfortunately, only 7 studies examined cancer risk by level of exposure, and most of these evaluations were for lung cancer. These 7 studies (18, 22, 33, 35—38), which present data for highly exposed workers, had null rates for lung cancer (mRR 1.0, 95% CI 0.9—1.1), in comparison with a deficit for lung cancer (mRR 0.7, 95% CI 0.4—1.4) in the studies that did not examine workers with higher exposure. The highest-exposed workers in the 7 studies produced an mRR of 1.2 (95% CI 1.0—1.5, heterogeneity P-value=0.06). None of the studies found a trend with exposure level.

The aggregation of the results of the highest-ranked exposure group in studies should be viewed as a crude overview, since the respective categories in various studies may represent different exposure levels and the pooled results could potentially be confounded. Three studies (35—38) estimated exposure levels in parts per million (ppm), which allowed us to examine workers with comparable high exposures. The 3 studies which estimated the parts-per-million levels of exposure had an mRR of 0.9 (95% CI 0.8—1.0) for lung cancer in comparison with an mRR of 1.1 (95% CI 0.9—1.4) for the studies which did not estimate parts-per-million levels of exposure. We combined the 8 ppm-years category in the Blair et al study (35), the 10—50, 50—100, and 100 ppm-year category in the Wood et al study (36), and the 10 ppm-year category in the Swaen et al study (37). The mRR for these studies was 1.1 (95% CI 0.9—1.4, heterogeneity P-value=0.12).

Prostate cancer

The relative risks for prostate cancer mortality for individual studies is shown in figure 4. The studies of Theiss et al (18), Delzell & Monson (22), and Burke (Memphis plant) reported no prostate cancers, but they had wide confidence intervals. The studies of Keisselbach et al (15) and Wood et al (36) reported small excesses, and Burke (Beaumont works) reported an excess based on a single case. The large studies of Blair et al (35) and Swaen et al (37) reported slight deficits of prostate cancer. The mRR for the prostate cancer mortality was 1.0 (95% CI 0.7—1.5).

Only the Blair et al (35), Swaen et al (37), and Wood et al (36) studies reported exposure level analyses for prostate cancer risks, perhaps because most other studies had no more than 2 prostate cancer deaths. The mRR was 1.0 (95% CI 0.5—1.8, heterogeneity P-value=0.60) for the cumulative exposure level of 8 ppm in the Blair et al study (35) and 10 ppm in the Swaen et al (37) and Wood et al (36) studies. None of these studies showed an increasing risk with increasing exposure. The single nested case-referent study by Marsh (23) reported duration of exposure for prostate cancer cases and referents. There were no cases or referents in the highest exposure category of 10 years of exposure.

The 2 unpublished studies by Burke (Memphis plant and Beaumont works), which reported prostate cancer mortality, reported 1 death from prostate cancer (mRR 3.9) in comparison with an mRR of 1.0 for the published studies (data not shown). However, we also found some evidence of failing to report relative risks of less than 1.0 in the published studies. Two authors shared with us the prostate cancer results that were omitted from their original reports (18, 33). Taken together, there were 2 observed deaths and 2.1 expected.

The Wood et al study (36) found 12 prostate cancer cases versus 7.6 observed. The other 2 studies which examined incidence found no cancer cases, with 0.8 and 0.1 expected cases, respectively. The Wood et al (36) update of the earlier DuPont studies (24, 26) found only 1 new incident case versus 3.9 expected [standardized incidence ratio (SIR) 0.3, 95% CI 0.0—1.4] in the update period. The Chen et al (26) and O'Berg et al (24) studies reported that most cases of prostate cancer occurred in 1975 to 1983. Therefore, the cases of prostate cancer were limited in time. In addition, no trend with exposure level was observed in these studies.

Brain cancer

The studies of Keisselbach et al (15), Herman (unpublished), Burke (unpublished, Memphis plant), Mastrangelo (33), Swaen et al (37), and Wood et al (36) reported relative risks for brain and central nervous system cancers in excess of 1.0. (See figure 5.) Theiss et al (18), Delzell & Monson (22), Burke (unpublished, Beaumont works), Thomas et al (25), and Blair et al (35) reported relative risks of 1.0. The mRR for brain cancer was 1.2 (95% CI 0.8—1.7). Only 3 studies reported brain cancer rates by exposure level (25, 35, 37). There was no increase in risk with level of exposure in any of these studies.

Although the estimates were imprecise, the relative risks were higher in the unpublished investigations (mRR 2.3, 95% CI 0.6—9.3) than in the published studies (mRR 1.1, 95% CI 0.7—1.5). However, as with prostate cancer, there was also a tendency to not report SMR values of <1.0. Studies reporting expected deaths had an mRR of 2.2 (95% CI 0.7—6.4) in comparison with an mRR of 1.0 (95% CI 0.7—1.4) for studies not reporting expected deaths.

Bladder cancer

There were 10 studies which evaluated bladder cancer (figure 6). The early studies of Kiesselbach et al (15), Theiss et al (18), and Delzell & Monson (22) all reported SMR values of >1.0. The 2 studies by Burke (unpublished, Memphis plant and Beaumont works) and the study by Mastrangelo (33) found no cases although few were expected. The case-referent study of Siemiatycki et al (34) reported a small excess, and the 3 largest studies of Swaen et al (37), Blair et al (35), and Wood et al (36) reported SMR values close to 1.0. Blair et al (35), the only authors to report exposure levels for this cancer, found no increased risk with increasing exposure level. As with brain cancer, the studies reporting expected deaths had a larger mRR (2.9, 95% CI 0.9—9.7) than those which failed to report expected values (mRR 1.3, 95% CI 0.8—1.9).

Some of the most potent occupational causes of bladder cancer are aromatic amines (44). Three studies reported the presence of aromatic amines in the plant environment (15, 18, 22). The mRR for bladder cancer for studies reporting potential exposure to aromatic amines was

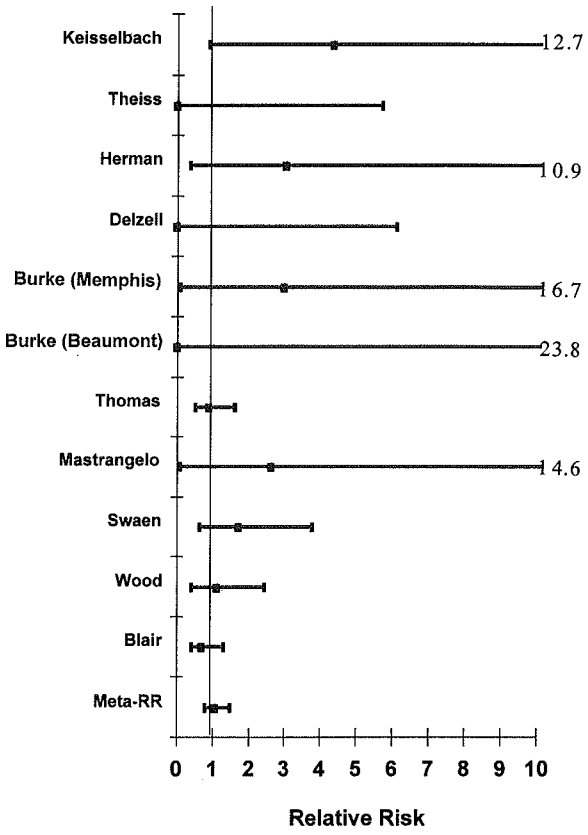

Figure 5. Relative risk for brain cancer death (studies listed by first author).

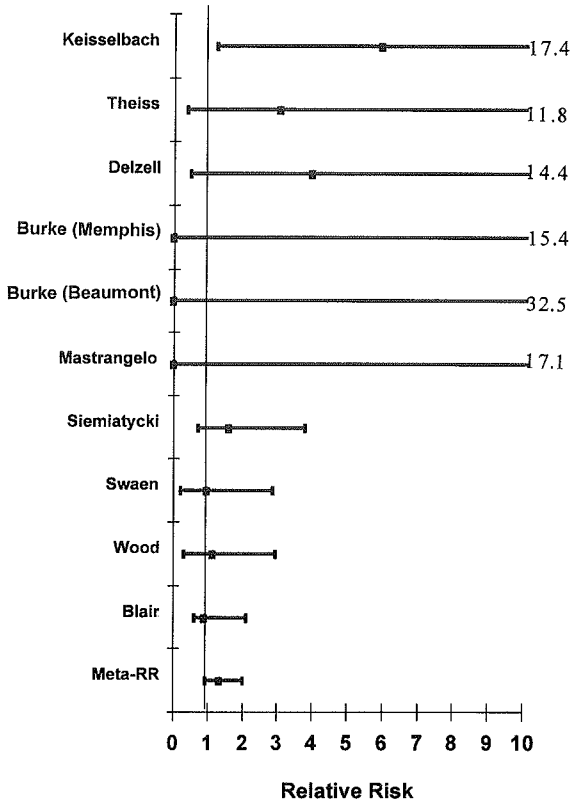

Figure 6. Relative risk for bladder cancer death (studies listed by first author).

4.5 (95% CI 1.8—10.9) based on 7 deaths. The mRR for studies with no aromatic amines reported was 0.9 (95% CI 0.5—1.5). These data are consistent with the possibility of confounding, but only 1 of the 3 studies indicated that the bladder cancer decedents (3 deaths) had exposure to aromatic amines (15).

Other potential confounding exposures

Since butadiene exposure occurred in some of the plants in various studies, we stratified for this potential exposure. We found no difference in the cancer rates from plants which had potential butadiene exposure from the plants which did not.

Discussion

Most of the available epidemiologic studies of acrylonitrile workers are cohort mortality investigations. The cohort studies in this review range in size from 100 to 25 460 workers. Taken together, the studies include 41 135 exposed workers and 2769 decedents.

The levels of exposure in many of the studies are uncertain since monitoring for acrylonitrile was not available before the mid-1970s. This lack of information made it difficult to focus our analysis on the highest-exposed workers, who would be the most relevant for an evaluation of acrylonitrile carcinogenicity.

We examined the impact of publication bias on the results. The published studies were, on the average, 4 times larger and followed workers for 7 years longer. However, there was little difference between the published and unpublished studies in completeness of vital status follow-up (97% versus 96%), completeness of death ascertainment (98% versus 96%), or mean duration of exposure (6.9 years to 7.5 years). The published studies had lower total mortality than the unpublished studies. The mRR for all causes was 0.6 (95% CI 0.5—0.7) for the unpublished studies and 0.8 (95% CI 0.7—0.9) for the published studies. The total cancer rates were slightly higher for the published studies (mRR 0.9, 95% CI 0.8—0.9) than for the unpublished studies (mRR 0.8, 95% CI 0.4—1.2). While we found some evidence of publication bias in the literature, it did not greatly affect the risk estimates for individual cancers. There was also an apparent tendency not to report null findings for certain cancer sites. For instance, while 10 of the cohort mortality studies reported lung cancer rates, only 4 of these studies reported prostate cancer rates. This finding lends some credence to the view that null findings may be omitted from papers, especially when there is no reason to believe that an exposure disease relationship is plausible, and that this omission exerts a positive bias in quantitative reviews of the literature. However, the omission of these null findings did not have a great impact on the risk estimates. We also found that the early studies tended to find relative risks of >1.0 for lung cancer. This could be a chance finding or it could reflect an early preference for the publication of positive findings. Taken together, these factors indicate that there was a slight positive bias in the published studies, but this bias did not have a great impact on the risk estimates for individual cancers.

As in a previous review of acrylonitrile studies, we found no excess of all cancer or lung cancer among the acrylonitrile workers (2). In addition, our results are similar to those reported by Rothman (2), even when recently available studies are considered and analyses are conducted with respect to exposure level and latency periods.

We were unable in our analyses to take the smoking habits of workers into account, which is important for evaluating lung cancer. Blair et al (35) systematically evaluated the smoking levels of workers. Their study of 25 460 workers found that the proportion of cigarette smokers was larger among workers exposed to acrylonitrile and that the proportion of smokers increased with increasing cumulative exposure category. If the findings of this large study can be generalized to the other studies, smoking may be an important confounder to be considered.

There was some indication of excess bladder cancer in 3 studies, a finding not reported previously. However, the excess seems to be restricted to plants with potential exposure to aromatic amines, and, therefore, it is unlikely to be related to acrylonitrile exposure. No trend with exposure level was observed (35).

The slight excess of prostate cancer incidence reported for 1 population by O'Berg et al (24), Chen et al (26), and Wood et al (36) has raised concern that exposure to acrylonitrile may increase prostate cancer incidence (6). However, there is no increase in cancer rates with increasing exposure, and this finding has not been seen in mortality studies (15, 18, 22, 33, 35—37) or in the incidence studies (both unpublished studies by Burke, Memphis plant and Beaumont works). The excess of prostate cancer in this 1 study was limited to a narrow reporting period (ie, 1978—1983). A deficit was observed (SIR 0.3, 95% CI 0.0—1.4) for 1984—1991. Taken together, these findings do not seem indicative of a causal association. Bias or chance are a more likely explanation.

Acrylonitrile is a multisite carcinogen in rats chronically exposed to 20 ppm. However, findings from humans show null or near null findings when studies are considered together. There were no patterns of risk indicative of a causal association in our study. Such results suggest, at most, a small increase in risk among workers for the length of follow-up included in the available studies.

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