

Review Article

Carcinogenicity and Other Health Effects of Acrylonitrile with Reference to Occupational Exposure Limit

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Abstract: The occupational exposure limit for acrylonitrile (AN) has been set by many organizations on the basis of its carcinogenicity. However, recent epidemiological studies do not afford evidence supporting the hypothesis that AN is carcinogenic to humans. Review of the 18 published cohort studies revealed that, although there is not adequate evidence in humans for carcinogenicity of AN, the possibility of a causal association between high exposure to AN and lung cancer in humans cannot be excluded. It was pointed out that carcinogenic potential of AN may be weak, if any, to humans, and the current occupational exposure limit (OEL) for AN of 2 ppm was evaluated as appropriate in view of AN exposure levels reported by epidemiological studies. Based also on review of the literature on health effects other than carcinogenicity, it was concluded that the current OEL for AN is a reasonable value and there is no need for a revision at present.

Key words: Acrylonitrile, Carcinogenicity, Acute health effects, Chronic health effects, Occupational exposure limit

Introduction

Acrylonitrile (AN) is a colorless and volatile liquid with the boiling point of 77.3°C. It is a reactive monomer used extensively for the manufacture of acrylic and modacrylic fibers, resins, plastics, elastomers and synthetic rubbers. Prompted by the results of long-term animal exposure studies showing carcinogenicity of AN¹⁾, considerable number of epidemiological studies have been published since 1980. In view of animal experiments and earlier unpublished epidemiological studies which suggested the carcinogenicity of AN on humans, US Occupational Safety and Health Administration set an occupational exposure standard for AN as 2 ppm for 8-hour time-weighted average in 1978. Threshold Limit Value (TLV) for AN recommended by American Conference of Governmental Industrial Hygienist (ACGIH) was lowered from 20 ppm to 2 ppm (time-weighted average) in 1980. Japan Society for Occupational Health also revised the Occupational Exposure Limit-Mean (OEL-

M) of AN from 20 to 2 ppm in 1988 considering the risk of carcinogenicity²⁾.

AN was evaluated by International Agency for Research on Cancer (IARC) in 1987 as *probably carcinogenic to humans (Group 2A)* based on epidemiological data available at that time (IARC, 1987)³⁾. In 1999, however, the evaluation of AN by IARC was revised on the basis of more recent epidemiological studies which had come to give less evidence for carcinogenicity (IARC, 1999)⁴⁾. Namely, the evidence for the carcinogenicity of AN to humans was judged as inadequate, and AN was classified as *possibly carcinogenic to humans (Group 2B)*.

The purpose of this paper is to review the literature concerning the carcinogenicity and other health effects of AN available at present and to evaluate the adequacy of current occupational exposure limits.

Epidemiological Data on Carcinogenicity

Eighteen cohort mortality studies on workers occupationally exposed to AN have been published and are available for the evaluation of its carcinogenicity [Kiesselbach *et al.* (1979)⁵, O'Berg (1980)⁶, Thiess *et al.* (1980)⁷, Ott *et al.* (1980)⁸, Werner and Carter (1981)⁹, Delzell and Monson (1982)¹⁰, O'Berg *et al.* (1985)¹¹, Chen *et al.* (1987)¹², Chen *et al.* (1988a)¹³, Chen *et al.* (1988b)¹⁴, Collins *et al.* (1989)¹⁵, Swaen *et al.* (1992)¹⁶, Mastrangelo (1993)¹⁷, Swaen *et al.* (1998)¹⁸, Benn and Osborne (1998)¹⁹, Blair *et al.* (1998)²⁰, Wood *et al.* (1998)²¹ and Marsh *et al.* (1999)²²].

In addition, five unpublished cohort studies [Monson (1978)²³, Zack (1980)²⁴, Gaffey and Strauss (1981)²⁵, Herman (1981)²⁶, Stallard (1982)²⁷] and four case-control studies partly referring to AN [Marsh (1983)²⁸, Thomas *et al.* (1987)²⁹, Ott *et al.* (1989)³⁰, Siemiatycki *et al.* (1994)³¹] are available, but these reports are of limited value for the evaluation of AN carcinogenicity.

Kiesselbach *et al.* (1979)⁵ studied cancer mortality of 884 male workers who had been exposed to AN. The workers had been engaged in AN production and other operations at 16 plants of Bayer Ltd. in West Germany for at least one year during the period from 1950 to the end of July 1977. Twenty deaths from cancer were observed while the expected number of cancer deaths calculated using the residents of Nordrhein-Westfalen State, West Germany, as a standard population was 20.4. Observed number of deaths from cancer of the respiratory system was 6 while the expected number was 6.9. The results showed no excess mortality from cancer in AN-exposed workers.

O'Berg (1980)⁶ reported morbidity and mortality data of 1345 male workers (mostly Caucasians) who had been engaged in operations potentially exposed to AN at an acrylic fiber plant of US DuPont during the period from 1950 (the opening of plant) to the end of 1966. The follow-up was done until the end of 1976. All DuPont employees were used as the standard population for the calculation of the expected number of deaths. In the whole cohort, the observed incidence of cancer was 25 while the expected incidence was 20.5. When the analysis was restricted to wage roll workers (1172 of the 1345 workers) who had been first employed between 1950 and 1952 and exposed to AN for at least six months, the ratio of observed to expected incidences of all cancers was 20/11.2 ($p < 0.05$). The O/E ratio of lung cancer incidence in the wage roll workers was 8/3.4 ($p < 0.05$). Thus, an excess incidence of lung cancer was noted in wage roll workers, particularly in those who

had been first employed during the period from 1950 to 1952 (O/E ratio was 8/2.6 [$p < 0.01$]). It was also seen that the cancer morbidity was higher in workers with longer duration and higher levels of AN-exposure although the trend was not statistically significant. Significant excess mortality from cancer was not demonstrated. It must be noted that most of these workers had also been exposed to dimethylformamide, a solvent used in the manufacturing process of acrylic fiber.

Thiess *et al.* (1980)⁷ reported mortality data of 1469 male workers who had been engaged in production of AN-containing polymers for at least six months at 12 plants of BASF Ltd. in West Germany during the period from 1956 (the use of AN started) to May 15, 1978. The 1469 workers consisted of 1081 Germans and 388 others, 98 and 56 percent of whom could be followed up, respectively. Residents in three regions (Ludwigshafen City, Rheinland-Pfalz State, and whole area of West Germany) served as standard populations. The observed number of deaths from all causes was 89 as compared with the expected deaths based on these regions being 92.3, 96.4, and 99.0, respectively. The ratio of observed to expected deaths from all cancers based on the whole area population of West Germany was 27/20.5. The observed number of deaths from lung cancer was 11 as compared with the expected deaths of 5.65 and 5.92 based on the whole area of West Germany and Rheinland-Pfalz State. This excess death from lung cancer in AN-exposed workers was statistically significant ($p < 0.05$). However, these workers had also been exposed to carcinogenic or suspected chemicals such as vinyl chloride, distillation residues containing polycyclic hydrocarbons, β -naphthylamine, dimethyl sulfate, epichlorohydrin, and cadmium. The authors excluded 78 workers exposed to known carcinogens at one of these plants from the study population and found that the excess deaths from lung cancer (9/4.37, $p < 0.05$) and from lymphatic malignancies (4/1.38, $p < 0.05$) still remained significant. It is doubtful, however, that the authors could have excluded all effects of mixed exposure to the above-mentioned chemicals. Moreover, smoking status of these workers was not fully described and AN-exposure levels were not mentioned.

Ott *et al.* (1980)⁸ studied 2904 workers involved in development or production of styrene-based products at four plants of the Dow company. Among 100 AN-exposed workers, there were one observed death from lung cancer versus 0.5 expected and three cases of leukemia versus 1.25 expected. Small size of exposed population, mixed exposure to other chemicals including styrene and the lack of AN-exposure information should be noted.

Werner and Carter (1981)⁹ studied a cohort of 934 workers

who had been engaged in polymerization of AN or spinning of acrylic fiber at six plants in UK for at least one year during the period from 1950 to the end of 1968. The authors followed up the workers until the end of 1978. Expected mortality was calculated from the mortality statistics in England and Wales. The ratio of observed to expected number of deaths from all causes was 68/72.4 and that for all cancers was 21/18.6. A significant excess mortality was noted for stomach cancer (5/1.9, $p < 0.05$). Deaths from cancers of the lungs, trachea, and bronchi were significantly higher (3/0.7, $p < 0.05$) in a sub-cohort at the age of 15–44 years whose duration of exposure had been short. The authors considered that the increased mortality from stomach cancer might be related to endemic rather than occupational factors and suggested the need of continued follow-up to clarify the causal relationship to lung cancer.

Delzell and Monson (1982)¹⁰ followed up 327 white male AN-exposed workers at a rubber plant in US for at least two years during the period from January 1, 1940 to July 7, 1971. The follow-up was continued until July 1, 1978. Expected deaths were calculated from the mortality statistics of male white Americans. The ratio of observed to expected deaths from all causes was 74/89.5. The O/E ratios for all cancers and for lung cancer were 22/17.9 and 9/5.9, respectively. A significantly higher mortality from lung cancer (4/0.8, $p < 0.01$) was noted only in a sub-cohort with its working duration of 5–14 years who could be followed up for more than 15 years. Because the rubber workers had been at risk of exposure to many carcinogens other than AN and no description of AN-exposure levels is given in the report, it is difficult to evaluate how much the AN-exposure might have contributed to the excess death.

O'Berg (1980)⁶ documented a significantly higher incidence of lung cancer in a cohort of 1345 workers (followed up until the end of 1976) in their previous report. O'Berg *et al.* (1985)¹¹ reported an updated study in which cancer incidences were followed to the end of 1983 and cancer deaths to the end of 1981. Expected morbidity and mortality were calculated from the DuPont's statistics as was in the previous study. The ratio of observed to expected incidence of all cancers was 43/37.1. For lung cancer, for which the morbidity was significantly higher than the expected value in the previous study, the observed incidence in the present study was 10, still slightly higher than but not significantly different from the expected value of 7.2. In this study, prostate cancer was significantly more frequent ($p < 0.05$, two-tailed) with the O/E ratio being 6/1.8. For mortality, the O/E ratios were 36/31.6 for all cancers, 14/11.6 for lung cancer and 1/1.0 for prostate cancer,

respectively. Thus, the updated results denied the significantly increased incidence of lung cancer described in the previous report (O'Berg *et al.*, 1980)⁶, but demonstrated a significantly higher morbidity from prostate cancer.

Chen *et al.* (1987)¹² reported cancer mortality and morbidity of 1083 male workers who had been at risk of exposure to AN at an acrylic fiber plant of DuPont in Virginia, US, during the period from 1944 to 1970. The authors followed up these workers until 1981 for cancer mortality and until 1983 for cancer morbidity. The number of total cancer deaths observed was 21, fewer than the expected values of 36.3 based on the US population and 30.0 based on DuPont employees. Site-specific deaths from cancer were also lower than the expected values. The ratio of observed to expected incidences were 37/36.5 for all cancers, 5/6.9 for lung cancer and 5/1.9 for prostate cancer, respectively. Of the five cases of prostate cancer, four had onset between 1975 and 1983, the incidence being significantly higher than the expected value of 0.9. The incidences of cancer at other sites were not higher than the expected values. The authors considered that the significantly higher incidence of prostate cancer might have occurred by chance due to multiple comparison. They pointed out the need of continued observation by reference to the study of O'Berg *et al.* (1985)¹¹ that had also reported the excess incidence of prostate cancer. The plant used in the Chen *et al.* study (1987)¹² was different from those in the O'Berg (1980)⁶ and O'Berg *et al.* (1985)¹¹ studies. There was no mention on AN-exposure levels, mixed exposure to other chemicals and smoking status.

Chen *et al.* (1988a)¹³ pointed out a problem inherent in the previous epidemiologic study designs, i.e. most of AN workers might have also been exposed to other chemicals, particularly dimethylformamide, a solvent used in the manufacturing process of acrylic fiber. To evaluate the effect of mixed exposure to dimethylformamide, the authors analyzed cancer morbidity of 2530 workers who had been exposed to dimethylformamide alone at the same DuPont plant, in addition to the cohort of 1345 workers used in the studies by O'Berg (1980)⁶ and O'Berg *et al.* (1985)¹¹. The follow-up was performed from 1950 to 1984. The DuPont employees and the whole US population served as standard populations. Because of no marked difference in the results between the two populations, the expected incidences calculated on the basis of the DuPont population are cited here. Among the cohort of 1345 AN workers, 1329 had also been exposed to dimethylformamide. Thus, workers exposed to AN alone were only 16. In the workers exposed to both AN and dimethylformamide, the ratios of observed to expected incidences were 41/39.8 for all cancers, 10/9.4

for lung cancer and 6/2.7 for prostate cancer, not achieving statistically significant differences between the observed and expected values. When the analysis was restricted to wage roll workers, a barely significant difference was seen in the incidence of prostate cancer (6/2.3, $p < 0.10$, two-tailed). However, the authors found no trend in the incidences of prostate cancer in association with exposure levels. In a sub-cohort of workers exposed to dimethylformamide alone, oral/pharyngeal cancer incidence was significantly more frequent (9/1.6, $p < 0.01$, two-tailed), but it was not associated with exposure levels and duration.

Chen *et al.* (1988b)¹⁴ reported mortality of the same cohort (Chen *et al.*, 1988a)¹³ as above during the period from 1950 to 1982. There was no significantly higher mortality in either the workers exposed to both AN and dimethylformamide or those exposed to dimethylformamide alone.

Collins *et al.* (1989)¹⁵ studied mortality of 2671 male workers who had been engaged in AN and acrylic fiber production at two plants of American Cyanamid Company from the opening of plants (the AN production was started in 1951 and the acrylic fiber manufacture in 1957) to the end of 1973. The authors analyzed the association of mortality (data collected until the end of 1983) with exposure levels to AN and smoking status. The results showed that neither the total nor site-specific cancer deaths were higher than the corresponding expected values. And no association of cancer mortality could be found with the AN-exposure levels.

Swaen *et al.* (1992)¹⁶ reported mortality of 2842 workers who had been at risk of exposure to AN at eight chemical plants (manufacturing of AN, acrylic fiber, latex rubber, acrylamide, various polymers, various synthetic resins, etc.) in the Netherlands for at least six months during the period from 1956 to June 1979. The authors collected mortality data until the end of 1987 and analyzed association with AN exposure using information on the past history of exposure. The results showed that neither the total nor site-specific cancer deaths were higher than the corresponding expected values. There was no association between cancer mortality and the AN-exposure levels.

Mastrangelo *et al.* (1993)¹⁷ reported mortality of 671 workers who had been at risk of exposure to AN at an acrylic fiber plant in Italy for at least 12 months since 1959 (the opening of plant). The authors followed up these workers during the period from 1959 to the end of 1990. Of these workers 571 had been exposed not only to AN but also to dimethylacetamide. General population at the location of plant served as a standard population. The mortality from intestinal/colon cancer was significantly higher than the

expected value (4/0.38) only in a sub-cohort of workers with exposure duration of 1–4 years who could be followed up for 1–9 years. Based on the results, the authors concluded that the mortality from cancer was not associated with the mixed exposure to AN and dimethylacetamide.

Swaen *et al.* (1998)¹⁸ updated the cohort mortality study (Swaen *et al.*, 1992)¹⁶ conducted on 2842 workers with past exposure to AN and 3961 unexposed reference workers. All 6803 workers were followed for mortality until 1 January 1996. Time-weighted average exposures (8-hours) were estimated and classified into 4 categories: 0–0.5, 0.5–1, 1–2, 2–5 ppm. Excess mortality from cancer was not found for any organ and no association was found between cancer mortality and exposure levels.

Benn and Osborne (1998)¹⁹ reported mortality of 2763 workers employed between 1950 and 1978 for at least one year at six factories in UK involved in the polymerization of AN and the spinning of acrylic fiber. This was an extended and updated study of the cohort reported by Werner and Carter (1981)⁹. The authors followed up the workers until the end of 1991. Expected deaths were calculated using national death rate for England and Wales for five factories and Scottish rate for one factory. Overall, cancer deaths did not exceed the expected numbers. There were, however, five deaths (vs. 0.8 expected) from lung cancer (SMR, 6.1 [95% CI, 2.0–14.6]) among workers holding high-exposure jobs and under 45 years of age. There were also seven deaths (vs. 2.6 expected) from lung cancer (SMR, 2.7 [95% CI, 1.1–5.5]) among those first employed after 1969 who held high-exposure jobs. The earliest measured exposures referred to the late 1970s gave mean values ranging from 0.4 to 2.7 ppm (8-hour TWA) with minimums ranging from nil to 0.2 ppm and maximums from 2 to 20 ppm (8-hour TWA).

Blair *et al.* (1998)²⁰ studied a cohort of 25 460 workers (18 079 white men, 4293 white women, 2191 nonwhite men, and 897 nonwhite women) employed in AN production or use in the 1950s through 1983 by following for vital status and cause of death through 1989. A large proportion of the workers in the study by Collins *et al.* (1989)¹⁵ were also included in this investigation. Exposure-response relationships were evaluated from quantitative estimates of historical exposures. Cumulative exposure categories were 0 (unexposed), 0.01–0.13 ppm-years, 0.14–0.57 ppm-years, 0.58–1.50 ppm-years, 1.51–8.00 ppm-years, and >8.00 ppm-years. Tobacco use was determined for a sample of workers to assess potential confounding. Mortality rates for exposed (348 642 person-years) and unexposed (196 727 person-years) workers were compared using Poisson regression analysis to minimize the healthy worker effect. Analyses

by cumulative, average, peak, intensity, duration, and lagged exposure revealed no elevated risk of cancers of the stomach, brain, breast, prostate or lymphatic and hematopoietic systems. Mortality from lung cancer was elevated for the highest quintile of cumulative exposure. Workers in the sub-cohort with the highest cumulative exposure (>8.00 ppm-years) and 20 years or more since first exposure had a relative risk of 2.1 (95%CI, 1.2–3.8), a significant increase over the referents. The conclusion by the authors is that the excess of lung cancer in the highest quintile of cumulative exposure may indicate carcinogenic activity at the highest levels of exposure, but analyses of exposure-response do not provide strong or consistent evidence for a causal association.

Wood *et al.* (1998)²¹ studied 2559 male workers exposed to AN during acrylic fiber manufacture at DuPont plants in South Carolina and Virginia, United States. Cohorts observed by O’Berg (1980)⁶, O’Berg *et al.* (1985)¹¹, Chen *et al.* (1987)¹², Chen *et al.* (1988a)¹³, Chen *et al.* (1988b)¹⁴ and newer employees who worked in exposed areas until the plants were closed in 1990 and 1991 were included in this study. Overall cancer mortality was lower than expected in comparison with the US population and all DuPont employees. The standardized mortality ratios for specific sites did not differ significantly from the expected values. Analyses of dose-response relationship did not reveal any significant trend between AN-exposure and mortality. Analyses of morbidity outcomes also showed no significant results.

Marsh *et al.* (1999)²² studied a cohort of 992 males who were employed for three or more months between 1960 and 1996 in a chemical plant in Lima, Ohio, USA. The follow-up was done until the end of 1996. Among 518 AN-exposed workers, the standardized mortality ratio for lung cancer was 1.32 (95%CI, 0.60–2.51) by external comparison using local county death rate and the risk ratio was 1.98 (95%CI, 0.60–6.90) by internal comparison. For lung cancer, exposure-response analyses of internal cohort rates showed monotonically increasing risk ratios with increasing AN exposure, with the risk ratio exceeding 2.0 in the highest exposure category although the trend was not statistically significant.

Five unpublished cohort studies are cited here briefly. Monson (1978)²³ reported cancer morbidity in Goodrich Company’s workers and members of the United Rubber, Cork, Linoleum, and Plastic Workers of America. The results showed a slightly higher incidence of lung cancer, genitourinary cancer, and Hodgkin’s disease, but the cohort size was not mentioned. Moreover, the subjects included in the study had been frequently exposed to other carcinogens.

Zack (1980)²⁴ followed up 352 white male workers who had been exposed to AN at Monsanto Ltd. in Texas for at least six months before the end of 1968. The follow-up until the end of 1977 showed no increase in cancer mortality. Gaffey and Strauss (1981)²⁵ followed up 326 white male workers who had been at risk of exposure to AN at a chemical plant in Alabama during the period from 1952 to 1953. The follow-up until the end of 1977 showed no increase in cancer mortality. Herman (1981)²⁶ followed up 989 male workers in two rubber plants in Louisiana for at least one year during the period from 1951 to 1977. The follow-up until the end of 1977 showed no increase in cancer mortality. The cohort was of relatively large size but the length of follow-up was rather short. Stallard (1982)²⁷ followed up 419 white male workers who had possibly been exposed to AN at an AN production plant in Ohio during the period from April 1960 to March 1980. The follow-up until March 1980 showed no increase in cancer morbidity. The shortness of the length of follow-up is also noted for this study.

Interpretation of Epidemiological Data

Epidemiological data suitable for the evaluation of carcinogenicity of AN are those from the eighteen published cohort studies described above. Significantly higher cancer morbidity in persons exposed to AN was noted in four reports by O’Berg (1980) (lung cancer)⁶, O’Berg *et al.* (1985) (prostate cancer)¹¹, Chen *et al.* (1987) (prostate cancer)¹², and Chen *et al.* (1988a) (prostate cancer)¹³. Significantly higher cancer mortality was noted in five reports by Thiess *et al.* (1980) (lung cancer)⁷, Werner and Carter (1981) (stomach cancer, lung cancer)⁹, and Delzell and Monson (1982) (lung cancer)¹⁰, Benn and Osborne (1998) (lung cancer)¹⁹ and Blair *et al.* (1998) (lung cancer)²⁰.

Significant increase in cancer mortality was not observed in eight reports by Kiesselbach *et al.* (1979)⁵, Chen *et al.* (1988b)¹⁴, Collins *et al.* (1989)¹⁵, Swaen *et al.* (1992)¹⁶, Mastrangelo (1993)¹⁷, Swaen *et al.* (1998)¹⁸, Wood *et al.* (1998)²¹ and Marsh *et al.* (1999)²². However, the most recent report by Marsh *et al.* (1999)²² showed monotonically increasing risk ratios for lung cancer with increasing AN exposure, with the risk ratio exceeding 2.0 in the highest exposure category although the trend was not statistically significant.

It must be noted that the cohorts of the above mentioned studies were not mutually independent. Some studies were updated and/or extended versions of the preceding reports. Among the studies which revealed significant cancer excess in AN-exposed workers, O’Berg *et al.* (1985)¹¹ is an updated

study of O'Berg (1980)⁶ and Chen *et al.* (1988a)¹³ is an updated/extended study of O'Berg (1980)⁶ and O'Berg *et al.* (1985)¹¹. Benn and Osborne (1998)¹⁹ is an updated/extended study of Werner and Carter (1981)⁹. Among the studies with negative results, Swaen *et al.* (1998)¹⁸ is an updated/extended study of Swaen *et al.* (1992)¹⁶. Moreover, Wood *et al.* (1998)²¹ is an updated/extended study of O'Berg (1980)⁶, O'Berg *et al.* (1985)¹¹, Chen *et al.* (1987)¹², Chen *et al.* (1988a)¹³, and Chen *et al.* (1988b)¹⁴. The cohort reported by Blair *et al.* (1998)²⁰ consists of AN-exposed workers at eight plants in US, including cohorts observed by Collins *et al.* (1989)¹⁵ and Marsh *et al.* (1999)²².

The advantages of more recent studies are larger cohort sizes, longer duration of follow-up, more adequate exposure assessment and more detailed analyses of exposure-response relationships. IARC (1999)⁴ relied mainly on four newest studies at that time [Swaen *et al.* (1998)¹⁸, Benn and Osborne (1998)¹⁹, Blair *et al.* (1998)²⁰, Wood *et al.* (1998)²¹] to evaluate the carcinogenicity of AN to humans.

IARC (1999)⁴ summarized and evaluated the findings in these reports as follows. There was no significant excess risk for any type of cancer when all exposed workers were compared with unexposed, or with external comparison population. Further, when the study subjects were subdivided by levels of exposure (cumulative exposure when feasible), for no site but lung was there any hint that risk increased with exposure. For lung cancer, there was an indication that workers with the highest exposures had relative risk estimates greater than 1.0. This finding was strongest in the largest of the studies, which had one of the most intensive exposure assessment protocols, but the other gave either negative or only weakly positive results. On balance and given the largely unresponsive findings from the other studies, the evidence from this one study was not considered to be sufficiently strong to conclude that there was a credible association between AN and lung cancer. Thus, the earlier indications of an increased risk among workers exposed to AN were not confirmed by the recent, more informative studies.

Based on the above mentioned interpretation of the available epidemiological data, IARC (1999)⁴ evaluated that there is inadequate evidence in humans for the carcinogenicity of AN and classified it as *possibly carcinogenic to humans (Group 2B)*.

However, in view of significant excess morbidity and/or mortality of lung cancer repeatedly found by studies on different AN-exposed cohorts, the possibility of a causal association between AN exposure and lung cancer in humans may not to be denied. Although recent epidemiological

studies have definite advantages over earlier reports as discussed above, they may still have several weak points such as dilution effect by including lower exposed population and noise effect by increased background deaths by longer follow-up. Detailed analyses of exposure-response relationship by subdividing a cohort may not be completely reliable since very high exposure to AN probably encountered at the beginning of its use could have been overlooked or could not have been adequately quantified. The size of such highly exposed population might have been very small. Lung cancer cases could have been induced by AN after rather short latent periods of 10–15 years or so, for example, subsequent to very high and not necessarily long AN-exposure.

Concerning possible oversight of very high exposure population, the series of reports on DuPont cohorts seems worthy of note. O'Berg (1980)⁶ reported an increased incidence of lung cancer (expected incidence of lung cancer was 1.6 after adjustment for smoking status as compared with observed value of 5) in workers with higher AN-exposure and follow-up of 15 years or longer. In two subsequent studies, however, O'Berg *et al.* (1985)¹¹ and Chen *et al.* (1988a)¹³ followed up the same cohort and found that the initial increase in lung cancer incidence was not remarkable and statistically not significant. This was because the relative risk of lung cancer decreased due to the increase in expected morbidity while observed value little changed. There seems to be a possibility that several lung cancer cases were induced earlier during lifetime of highly exposed workers while such small excess could have been masked by the increase of lung cancer incidence among control workers by aging.

Similarly in two studies using the same cohort (O'Berg *et al.*, 1985¹¹; Chen *et al.*, 1988a¹³), the latter study showed a decrease in the odds ratio for prostate cancer from 6/1.8 ($p < 0.05$, two-tailed) to 6/2.3 ($p < 0.10$, two-tailed). However, since the excess morbidity of prostate cancer was found only in limited cohorts and was not found by recent larger studies, the possibility of causal association with AN-exposure seems weak.

In summary, there is not adequate evidence in humans for the carcinogenicity of AN as IARC(1999)⁴ stated. However, there are epidemiological findings that still suggests the possibility of causal association between very high exposure to AN and lung cancer in humans. It may also be concluded that degree of carcinogenic potential of AN is rather weak, if any, to humans because no clear evidence of cancer excess could be found by recent cohort studies with longer follow-up and larger observed population.

Carcinogenicity Data in Experimental Animals

There are eight reports suitable for the evaluation of carcinogenicity of AN to experimental animals. Five studies are by oral administration in drinking water [Quast *et al.* (1980a)³², Beliles *et al.* (1980)³³, Bio/Dynamics Inc. (1980a)³⁴, Bio/Dynamics Inc. (1980b)³⁵, and Gallagher *et al.* (1988)³⁶], one study is by oral gavage [Bio/Dynamics Inc. (1980c)³⁷] and two are by inhalation exposure [Maltoni *et al.* (1977)¹ and Quast *et al.* (1980b)³⁸]. All these studies were performed in rats. Quast *et al.* (1980a)³² treated Sprague-Dawley rats with drinking water containing 0, 35, 100, or 300 ppm AN for 24 months, and found an increased incidence of malignant tumors in the central nervous system, Zymbal gland, stomach, mammary gland, and tongue. In the first study by Bio/Dynamics Inc. (1980a)³⁴, Sprague-Dawley rats were treated with drinking water containing 0, 1, or 100 ppm AN for 22 months (males) or 19 months (females), and an increased incidences of malignant tumors were noted in the central nervous system, Zymbal gland, and stomach. In the second study by Bio/Dynamics Inc. (1980b)³⁵, Fischer 344 rats were treated with drinking water containing 0, 1, 3, 10, 30, or 100 ppm AN for 26 months (males) or 23 months (females), and increased incidences of malignant tumors were noted in the central nervous system, Zymbal gland, stomach, and mammary gland. In the third study by Bio/Dynamics Inc. (1980c)³⁷, Sprague-Dawley rats were treated by oral gavage of AN at dose levels of 0, 0.1, or 10 mg/kg/day, five days per week, for 20 months, and increased incidences of malignant tumors were noted in the central nervous system, Zymbal gland, stomach, and mammary gland. Maltoni *et al.* (1977)¹ treated rats by inhalation of air containing 0, 5, 10, 20, or 40 ppm AN for four hours daily, five days per week, during the 52-week treatment period, and found increased incidences of malignant tumors in the stomach and mammary gland. Quast *et al.* (1980b)³⁸ treated male and female Sprague-Dawley rats (100 at each exposure level) by inhalation of air containing 0, 20, or 80 ppm AN for six hours daily, five days per week, during the 24-month treatment period, and found increased incidences of malignant tumors in the Zymbal gland, small intestine, brain, spinal cord, mammary gland, and tongue.

It is worth noting that all these studies showed increased incidences of cancer in many different organs such as the brain, pituitary gland, Zymbal gland, tongue, mammary gland, stomach, pancreas, uterus, and skin. Furthermore, the incidences in the brain and Zymbal gland were consistently high in all the studies. It should also be noted that AN induced cancer at relatively low concentration in

inhalation experiments. The above results demonstrate that AN is carcinogenic to experimental animals. The carcinogenicity of this compound to other animal species is unknown because of no available data.

Mutagenicity

In Ames tests using *Salmonella typhimurium*, the mutagenic potential of AN has been reported to be negative (Litton Bionetics, 1975³⁹; Stanford Research Institute, 1976⁴⁰; Venitt *et al.*, 1977⁴¹; Florin *et al.*, 1980⁴²) or positive (Haskell Laboratory, 1975⁴³; Milvy and Wolff, 1977⁴⁴; de Meester *et al.*, 1978⁴⁵, 1979⁴⁶; Lijinsky and Andrews 1980⁴⁷; Duverger-van Bogaert *et al.*, 1981⁴⁸; Ivanov, 1981⁴⁹; Zhurkov *et al.*, 1983⁵⁰). In several experiments, mutagenic potential may have been false negative because of inappropriate experimental conditions, particularly neglect of volatile nature of AN. Milvy and Wolff (1977)⁴⁴, de Meester *et al.* (1978, 1979)^{45, 46}, Duverger-van Bogaert *et al.* (1981)⁴⁸, and Ivanov (1981)⁴⁹ found positive response of *Salmonella typhimurium* to vapor of AN. Zhurkov *et al.* (1983)⁵⁰ reported concentration-dependent mutagenic response to AN. In many of these experiments, metabolic activation with liver microsome fraction was required for induction of mutagenic response, but not essential. Urine from rats and mice receiving intraperitoneal injection of AN was positive to Ames test in the absence of S-9 mix (Lambotte-Vandepaer *et al.*, 1980, 1981)^{51, 52}. The same was true on rats orally treated with AN (Lambotte-Vandepaer *et al.*, 1985)⁵³. Fennell *et al.* (1990)⁵⁴ analyzed metabolites of AN in urine from rats and mice and found that epoxide metabolites of 2-cyanoethylene oxide, a known carcinogen, accounted for approximately 60 and 80 percent of the urinary metabolites in rats and mice, respectively.

Induction of mutation was also reported in *Escherichia coli* by Venitt *et al.* (1977)⁴¹, and in yeast by Rizzi *et al.* (1983)⁵⁵ and Carls and Schiestl (1994)⁵⁶.

In experiments using cultured mammalian cells, the following positive responses were observed: transformation of Syrian golden hamster embryo cells (Parent and Casto, 1979)⁵⁷; induction of repairing synthesis in HeLa cells (Rizzi *et al.*, 1983)⁵⁵; sister-chromatid exchange in Chinese hamster ovary cells (CHO) (Ved-Brad and Williams, 1982)⁵⁸; and *in vitro* transformation of C3H/10T1/2 cells (embryo cells from C3H mice) and fibroblasts from NIH/3T3 mice (Banerjee and Segal, 1986)⁵⁹.

It is supposed that AN is metabolized to 2-cyanoethylene oxide, an epoxide, which is directly involved in carcinogenic effects (Guengerich *et al.*, 1981)⁶⁰. Solomon and Segal

(1989)⁶¹) demonstrated that 2-cyanoethylene oxide, when reacted with calf thymus DNA, produced several types of DNA adducts. Yates *et al.* (1993)⁶²) identified a single reaction product produced by the reaction of 2-cyanoethylene oxide with deoxythymidine, and also detected the same reaction product produced by the reaction of 2-cyanoethylene oxide with calf thymus DNA *in vitro*. Robbiano *et al.* (1994)⁶³) treated primary culture of human and rat hepatocytes with AN (1.0–5.6 mM), and found a dose-dependent break of DNA single-strand. Ahmed *et al.* (1992)⁶⁴) demonstrated that, in rats orally treated with [¹⁴C]-labeled AN, DNA from pulmonary tissues was covalently bound to radioactive substance originated from AN. The same authors also found that DNA repair in the lungs was increased by approximately twice after treatment with AN. Recio *et al.* (1990)⁶⁵) treated human lymphoblasts with 2-cyanoethylene oxide, and identified the location of point mutation, at molecular level, through analysis of DNA from the resulting hprt mutants.

As described above, *in vitro* mutagenicity experiments using bacteria and cultured mammalian cells revealed definite positive results. Binding to DNA was also demonstrated. However, there are no reliable *in vivo* data supporting positive mutagenicity of AN to humans and mammals. Thiess and Fleig (1978)⁶⁶) studied whether or not chromosomal aberrations of peripheral lymphocytes would increase in workers exposed to 1.5–5 ppm (estimated levels) of AN for an average of 10–15 years, and found no changes in the incidence of chromosomal aberrations. Rabello-Gay and Ahmed (1980)⁶⁷) showed that treatment of mice orally with 7–21 mg/kg/day of AN for 4–30 days did not result in increased chromosomal aberrations of bone marrow cells. Leonard *et al.* (1981)⁶⁸) reported that AN had negative results in both micronucleus test using murine erythrocytes and dominant lethal test using germs cells from male mice. Working *et al.* (1987)⁶⁹) also showed in dominant lethal test that oral administration to rats at dose levels up to 60 mg/kg/day resulted in negative results.

All these data suggest that AN is mutagenic *in vitro*, but *in vivo* results are equivocal. Reviews by IARC (1999)⁴) and by Leonard *et al.* (1999)⁷⁰) reached the same conclusion.

Other Health Effects of Acrylonitrile

Acute toxicity

Main acute toxic effects of AN are irritation to the skin and mucosa and depression of respiratory function similar to cyanide poisoning. The severity of acute toxic effects considerably differs among animal species. Acute oral LD50s have been reported to be 25–48 mg/kg in mice (Benes and

Cerna, 1959⁷¹); American Cyanamid Company, 1951⁷²); Tullar, 1947⁷³), 50–85 mg/kg in guinea pigs (Carpenter *et al.*, 1949⁷⁴); Tullar, 1947⁷³), 72–186 mg/kg in rats (Tullar, 1947⁷³); Benes and Cerna, 1959⁷¹); Borchardt *et al.*, 1970⁷⁵); Smyth and Carpenter, 1948⁷⁶); Paulet and Vidal, 1975⁷⁷); Zeller *et al.*, 1969⁷⁸); Monsanto, 1975⁷⁹) and 93 mg/kg in rabbits (Lefaux, 1966)⁸⁰). Acute inhalation LC50s have been reported to be 300 mg/m³ (138 ppm) (4 hours) in mice, 470 mg/m³ (217 ppm) (4 hours) in rats, and 990 mg/m³ (456 ppm) (4 hours) in guinea pigs (Knobloch *et al.*, 1971)⁸¹). Dudley and Neal (1942)⁸²) reported that minimum lethal concentrations after 4-hour inhalation exposure were 65, 260, 315, 575 and 600 ppm in dog, rabbit, rat, guinea pig and cat, respectively. Thus, species differences were 10 folds.

In most animal species, acute signs of intoxication after inhalation exposure to high levels of AN begin with respiratory stimulation indicated by shallow and rapid breathing. The animals then exhibit slow gasping, respiratory arrest, vomiting, convulsion and coma before death. Although slightly different among animal species, other signs such as redness of the ears, nose, and limbs and increased lacrimation, nasal discharge, and salivation are also observed. In guinea pigs relatively resistant to AN respiratory arrest during inhalation exposure is not observed. But guinea pigs show irritation to the airway and lungs as predominant symptoms and die of pulmonary edema after the termination of inhalation exposure.

Symptoms of acute inhalation exposure in humans are described below. In one case accidentally exposed to a high level of AN vapor during a chemical experiment, headache, dizziness, vomiting, tremor, involuntary movement, and convulsion were observed. The nausea and vomiting persisted for the subsequent 24 hours, together with slight hepatic enlargement. These symptoms disappeared in a few days with no sequela in any organs (Sartorelli, 1966)⁸³). For factory workers who had been exposed to moderate levels of AN, major symptoms were headache, dizziness, nausea, vomiting, wasting, irritations to the eyes, nose, and throat, pressure sensation of the chest, anxiety and irritated feeling (Wilson, 1944⁸⁴); Zeller *et al.*, 1969⁷⁸). For workers who had been exposed to relatively high levels of AN at an acrylic fiber plant shortly after the opening of the plant, irritations to the eyes and upper airways were often encountered and one of the characteristic symptoms was nasal discharge (Sakurai *et al.*, 1978)⁸⁵).

The liquid of AN or its vapor in high concentration is also irritating to the skin. Shortly after contact with AN liquid, the skin becomes red with heat sensation, and may form blisters and scabs (Dudley and Neal, 1942⁸²); Wilson

et al., 1948⁸⁶); Babanov, 1957⁸⁷); Zeller *et al.*, 1969⁷⁸). It is also reported that contact with the solution may cause allergic dermatitis (Hashimoto and Kobayashi, 1961⁸⁸); Balda, 1975⁸⁹). Contact with AN vapor in high concentration during operations in a tank etc. may cause irritation to the scrotum. This is probably because AN vapor is highly water-soluble. Some workers complain of itching in the skin exposed to AN (Zeller *et al.*, 1969)⁷⁸).

Acute toxic effects to organs such as the liver, kidneys, and stomach have also been reported.

Shortly after the start of the industrial use of AN, workers exposed to high levels of this chemical exhibited mild jaundice (Wilson, 1944⁸⁴); Wilson *et al.*, 1948⁸⁶). Liver function of AN-exposed workers was found to be slightly abnormal (Suzuki, 1961⁹⁰); Sakurai and Kusumoto, 1972⁹¹). Abdominal palpation showed that the liver was more frequently palpable in AN workers than in non-exposed workers (Sakurai *et al.*, 1978)⁸⁵). Acute poisoning during a chemical experiment resulted in slight hepatic enlargement (Sartorelli, 1966)⁸³). These findings suggest that acute exposure to AN may cause hepatic damages in humans. However, the hepatotoxic effects of acute AN-exposure have not been demonstrated in animal experiments.

Effects of AN on the kidneys were examined by intraperitoneal administration of 0, 10, 20, 40, 60, or 80 mg/kg to rats. Increased urine volume and glucose excretion in animals treated with 20 mg/kg or above and increased urinary N-acetyl-beta-glucosaminidase activity in those treated with 60 mg/kg were observed. Light microscopy showed morphologic changes such as increased lysosome in the epithelium of renal tubules in animals receiving 60 mg/kg or above. High-density particles, intracellular vacuolation and other changes were observed with electron microscopy. Four-hour inhalation exposure to 200 ppm AN was associated with the increases in urine volume, urinary protein, glucose, and urinary N-acetyl-beta-glucosaminidase activity 24 hours after the inhalation. The results suggest that AN may cause damage to the renal tubules (Rouisse *et al.*, 1986)⁹²). However, there have been no reports indicating nephrotoxic effects of AN to humans.

Three hours after subcutaneous injection of AN at a dose level of 30 or 50 mg/kg to rats, mucosal erosion was frequently observed in the stomach. The severity of damage was negatively associated with glutathione levels. These lesions could be prevented by premedication of glutathione, cysteine or other chemicals containing sulfhydryl group (Ghanayem *et al.*, 1985)⁹³). This is an interesting finding in view of a study reporting that AN workers complained of gastrointestinal symptoms such as anorexia, nausea,

vomiting, and heartburn more often than non-exposed workers (Kaneko and Omae, 1992)⁹⁶).

Chronic effects

Hepatic effects and various subjective symptoms have been reported in workers with repeated AN-exposure.

Cases of jaundice (Wilson, 1994⁸⁴); Wilson *et al.*, 1948⁸⁶) and increased number of cases of abnormal liver function (Suzuki, 1961⁹⁰); Sakurai and Kusumoto, 1972⁹¹) were reported at plants using AN shortly after the opening of plants. However, causal relationship between AN-exposure and these hepatic signs was not definite.

Sakurai *et al.* (1978)⁸⁵) performed a cross-sectional epidemiological study on health effects of AN at six plants owned by all seven companies manufacturing acrylic fibers in Japan (excluding the smallest two plants). A total number of AN workers was 1124 while the number of non-exposed workers whose working conditions (muscular work, type of shifts, etc.) had been the same as in the AN workers was 571. Out of 1124 workers, 453 workers exposed to AN for less than five years, 333 workers exposed to noxious substances other than AN, 384 workers not in shifts and four workers in managerial post were excluded. Of the remaining 296 workers, 20 workers randomly sampled from each plant for a total of 120 workers were used as the exposed group and subjected to medical examination including multiple clinical laboratory tests. Out of the 571 workers not exposed to AN, 10 workers age-matched to the exposed group were randomly sampled from each plant and 60 workers in total were used as the control group. The medical examinations could be performed on 119 workers from the exposed group and 58 workers from the control group. It was found, however, that the exposed group had included 13 workers with exposure duration of less than five years and four workers not exposed to AN. Thus, the number of subjects in each group was 102 in the exposed and 62 in the control group. The six plants were categorized according to AN levels in the working environment. Average exposure levels were 0.1 ppm in three plants (best category), 0.5 ppm in two plants (intermediate category), and 4.2 ppm in one plant (worst category). Examined items were routine hematology and clinical chemistry tests, indocyanine green exclusion test and urinary protein measurement. In any of these parameters, no significant difference was noted between the exposed and control group. By physical examination, redness of the eyes and throat and palpable liver were found at slightly higher incidences in the exposure group than in the control group, but the differences were not statistically significant. These results suggest that exposure to AN in

concentration around 4 ppm or less does not cause abnormal results in liver function and routine clinical laboratory tests, although early studies of AN-exposed workers indicated possible occurrence of liver damages after high level exposure to AN.

In addition to the above-mentioned irritations to the eyes and upper airway, subjective symptoms reported by AN workers were headache, dull headache, generalized malaise, fatigability, irritated feeling, anorexia, nausea, vomiting, heartburn, gastrointestinal discomfort, shortness of breath, nasal bleeding, sleep disturbance, heavy feeling in the arms, excessive perspiration, choking sensation and chest pain. Thus, AN workers complained of various symptoms, all of which were not serious (Babanov *et al.*, 1959⁹⁴); Sakurai and Kusumoto, 1972⁹¹); Zotova, 1975⁹⁵); Kaneko and Omae, 1992⁹⁶). These symptoms except for some acute symptoms were mostly chronic ones. In a study by Kaneko and Omae (1992)⁹⁶, almost all the AN workers in the same plants as in the Sakurai *et al.* study (1978)⁸⁵) were examined for subjective symptoms. The authors found a significantly increased incidence of subjective symptoms with no changes in objective parameters. In contrast, Muto *et al.* (1992)⁹⁷) examined hepatic function and subjective symptoms in 157 AN workers and 537 non-exposed workers in 1988 at seven AN fiber plants in Japan, and found no evidence of AN-related effects on liver function and subjective symptoms. In these plants, the workers had been exposed to 0.53 ppm AN (N=113, standard deviation, 0.52 ppm). The results suggest that AN levels of 0.5 ppm or less do not cause subjective symptoms and hepatic dysfunction.

Data on chronic effects other than cancer induction in experimental animals have been obtained from several lifetime exposure experiments in rats as described before. The inhalation exposure experiment reported by Quast *et al.* (1980b)³⁸) is particularly important and described below in detail.

Male and female Sprague-Dewley rats (100 at each exposure level) were forced to inhale air containing 0, 20, or 80 ppm AN for six hours daily, five days per week, during the 24-month treatment period. Cumulative mortality rates at exposure levels of 0, 20, and 80 ppm were 3, 6, and 18 percent on day 360, and 82, 86, and 96 percent on day 735 (study termination), respectively, being significantly higher in 80 ppm group. Mean body weight was also significantly decreased in 80 ppm group. Periodic tests on hematology, clinical chemistry, and urology during the exposure period revealed no abnormal findings in the liver, kidneys, and hematopoietic organ attributable to the AN-exposure. During the first six months, AN-treated rats showed higher water

consumption than the control. This finding may be related to the above-mentioned finding that AN workers had complained of excessive sweating (Kaneko and Omae, 1992)⁹⁶). More than 40 different organs and tissues were histopathologically examined. Except for neoplastic findings, pathologic lesions showing dose-response relation to the exposure to AN were observed only in the epithelium of nasal mucosa. In animals inhaling 20 or 80 ppm, degeneration and inflammatory changes attributable to irritating effects of AN were noted in the respiratory epithelium of nasal mucosa. In male rats inhaling 20 ppm, the incidence of hyperplasia in respiratory epithelium of the nasal cavity was slightly increased but not significant (0/11, 4/12, and 10/10 at dose levels of 0, 20, and 80 ppm, respectively). Incidence of hyperplasia of mucus secreting cells was significantly increased (0/11, 7/12, and 8/10, respectively). In female rats inhaling 20 ppm, inflammatory findings in the mucosa of nasal cavity were significantly increased (2/11, 6/10, 7/10, respectively), and squamous transformation in the respiratory epithelium of nasal cavity were significantly increased (1/11, 7/10, and 8/10, respectively). In 80 ppm group animals, these findings were more prominent and rhinitis with neutrophil infiltration was observed, accompanied by hyperplasia, focal erosion, and squamous transformation of the respiratory epithelium. There were no abnormal findings in the olfactory epithelium and airway below the bronchus.

This study demonstrated that repeated exposure to 20 ppm AN causes chronic inflammation of the nasal mucosa in rats. No-observed-effect level was not made clear by this experiment.

Teratogenicity and fetotoxicity

Murray *et al.* (1978)⁹⁸) treated pregnant rats with AN by oral or inhalation exposure and examined effects on fetuses. When rats were treated orally with 0, 10, 25, or 65 mg/kg/day from day 6 to day 15 of pregnancy, marked toxic effects were observed in both dams and fetuses with increased malformations at a dose level of 65 mg/kg/day. Similar findings of lower severity were observed in animals treated with 25 mg/kg/day, although there were no abnormal findings in animals receiving 10 mg/kg/day. Effects of inhalation exposure were also examined. Rats were treated by inhalation exposure to 0, 40, or 80 ppm (0, 87, or 174 mg/m³), six hours daily, from day 6 to day 15 of pregnancy. The results showed that similar toxic effects to those after oral administration occurred in animals inhaling 80 ppm, but not in those receiving 40 ppm.

Scheufler (1976, 1980)^{99, 100}) and Willhite (1981a, b)^{101, 102})

described fetotoxic effects of AN in mice and guinea pigs, respectively.

Reproductive toxicity

Tandon *et al.* (1988)¹⁰³ treated mice orally with 10 mg/kg for 60 consecutive days, and found that sorbitol dehydrogenase and acid phosphatase activities were decreased and lactic dehydrogenase and β -glucuronidase activities were increased in the testes. Histopathological examination showed that the seminiferous tubules were degenerated and sperms in the epididymis were decreased by 45 percent. The results suggest that AN may affect male fertility.

Wu *et al.* (1995)¹⁰⁴ performed an epidemiological study on 477 female AN-exposed workers and 5237 controls and reported that exposure to AN could result in an increased rate of preterm delivery and birth defects, but these workers were also exposed to other chemicals.

Exposure-Response Assessment for Carcinogenicity

Carcinogenicity to experimental animals

As described before, AN has been demonstrated to be carcinogenic to rats by several long-term exposure experiments. Based on these data, EPA (1983)¹⁰⁵ estimated the unit risk of AN-exposure to general population, using linearized multistage model and disregarding species difference between rat and humans. The upper limit of 95% confidence interval of unit risk for each $\mu\text{g/L}$ (drinking water), when calculated from the results of oral exposure experiments (Quast *et al.*, 1980a³²; Bio/Dynamics Inc., 1980a³⁴; Bio/Dynamics Inc., 1980b³⁵), was estimated to be in a range between 8.2×10^{-6} and 2.8×10^{-5} . The corresponding value for each $\mu\text{g/m}^3$ (air), calculated from the results of inhalation exposure experiment (Quast *et al.*, 1980b)³⁸, was 1.2×10^{-5} for males and 1.5×10^{-5} for females. The unit risk was calculated from incidences of rats suffering from tumors in at least one organ or tissue. The incidences at exposure levels of 0, 20, and 80 ppm were 5% (5/100), 9% (9/100), and 47% (47/100), respectively, in males, and 0% (0/100), 9% (9/100), and 31% (31/100), respectively, in females.

Carcinogenicity to humans

EPA (1983)¹⁰⁵ estimated the unit risk of cancer as 6.8×10^{-5} per 1 $\mu\text{g/m}^3$ (air) based only on data by O'Berg (1980)⁶ who reported the increased incidence of lung cancer. However, quantitative estimate of the cancer risk in humans cannot be justified by currently available epidemiological data.

Exposure-Response Assessment for Other Health Effects

Major acute toxic effects of AN are irritation to the skin and mucosa and respiratory depression similar to cyanide poisoning. Exposure-response relationships for these effects have not been established yet. Jakubowski *et al.* (1987)¹⁰⁶ treated six male volunteers with 2.3 or 4.6 ppm AN by inhalation exposure for eight hours, and examined urinary excretion of metabolites. None of the volunteers complained of subjective symptoms such as headache, vomiting, and weakness which had been known to occur after exposure to AN. The result suggests that acute effect may not be observed by inhalation exposure to AN of 4.6 ppm or less.

Muto *et al.* (1992)⁹⁷ examined 157 workers who had been exposed to 0.53 ppm AN on the average and 537 non-exposed workers. There were no difference between the two groups in the incidences of subjective symptoms and abnormal findings in multiple clinical laboratory test results including liver function parameters. The results suggest that chronic effects other than carcinogenicity may not be observed by occupational inhalation exposure to AN of 0.53 ppm (1.15 mg/m^3).

Quast *et al.* (1980b)³⁸ treated rats with 20 or 80 ppm AN by chronic inhalation exposure, and found that chronic inflammatory changes of the nasal mucosa occurred at both exposure levels. The results suggest that no-observed-effect level for toxicities other than carcinogenicity in experimental animals is lower than 20 ppm.

Murray *et al.* (1978)⁹⁸ treated pregnant rats with 40 or 80 ppm AN, six hours daily, from day 6 to day 15 of pregnancy, and found that fetal malformations were significantly increased in animals inhaling 80 ppm, but no abnormal findings were observed in those inhaling 40 ppm. The results suggest that no-observed-effect level for teratogenic effects of AN is 40 ppm.

Evaluation of Current Occupational Exposure Limits

The current Occupational Exposure Limit-Mean (OEL-M) for AN of 2 ppm was recommended by Japan Society for Occupational Health in 1988 under the consideration of the risk of carcinogenicity. Threshold Limit Value (TLV-TWA) by ACGIH is also 2 ppm. According to IARC, the evidence for the carcinogenicity of AN to humans was judged as inadequate on the bases of recent epidemiological studies which had given less support for its human carcinogenicity. Overall evaluation of AN by IARC was *possibly carcinogenic*

to humans (Group 2B), a lower category in the classification system by IARC. However, a review of available epidemiological findings still suggests the possibility of causal association between very high exposure to AN and lung cancer in humans as discussed in the foregoing section on the interpretation of epidemiological data in this article. It is considered that the OEL for AN should still be set with due regard to carcinogenicity, although OELs for many chemicals classified by IARC as *possibly carcinogenic (Group 2B)* have generally been recommended without consideration of their carcinogenicity. In the preceding section on the interpretation of epidemiological data, carcinogenic potential of AN was stated to be rather weak, if any, to humans because no clear evidence of cancer excess was found by recent cohort studies with longer follow-up and larger study population. Among the five most recent epidemiological studies, three included quantitative information on the exposure levels to AN. In the report by Swaen *et al.* (1998)¹⁸, exposure levels were categorized as <1 ppm-years, 1 to <10 ppm-years, and >10 ppm-years. In Blair *et al.* study (1998)²⁰, they were <0.13 ppm-years, 0.13 to <0.57 ppm-years, 0.57 to <1.5 ppm-years, 1.5 to <8.0 ppm-years, and >8.0 ppm-years, and in Wood *et al.* study (1998)²¹, they were <10 ppm-years, 10 to <50 ppm-years, 50 to <100 ppm-years, and >100 ppm-years. In all these studies, no clear exposure-response relationship was found between exposure levels and cancer mortality. If we assume that the AN-exposure to 50 ppm-years can be tolerated without excess cancer cases being detected in a cohort of several thousand workers, an exposure to the current OEL of 2 ppm (ca. 40-hours per week) for 25 years appears to be acceptable. In view of the lack of reliable evidence for the carcinogenicity of AN to humans, low dose extrapolation using no-threshold hypothesis for carcinogens cannot be regarded as appropriate and 2 ppm seems a reasonable value as far as carcinogenicity is concerned.

Exposure-response relationship for health effects other than carcinogenicity has not yet been sufficiently known. However, there are several data that should be referred to when adequacy of OEL is considered. Acute subjective symptoms including headache, vomiting, and weakness which had been known to occur after exposure to AN were not complained of by volunteers exposed to 4.6 ppm (Jakubowski *et al.*, 1987)¹⁰⁶. Chronic effects such as subjective symptoms and abnormal findings in multiple clinical laboratory test results could not be detected in workers regularly exposed to 0.53 ppm (Muto *et al.*, 1992)⁹⁷. Teratogenic effect was not found in rat exposed to 40 ppm (Murray *et al.*, 1978)⁹⁸. Slight inflammatory changes of

nasal mucosa were observed in rats chronically exposed to 20 ppm (Quast *et al.*, 1980b)³⁸. These data are not inconsistent with OEL of 2 ppm. Overall, it is concluded that the current OEL for AN of 2 ppm is a reasonable value and there is no need for its revision at present.

Summary

Occupational exposure limit for acrylonitrile (AN) has been set by many organizations on the basis of its carcinogenicity. However, recent epidemiological studies have not afforded evidence supporting the hypothesis that AN is carcinogenic to humans. Relevant data from the literature were reviewed and the adequacy of the current occupational exposure limit for AN was evaluated.

1. Review of the eighteen published cohort studies revealed that, although there is not adequate evidence in humans for carcinogenicity of AN, the possibility of a causal association between high exposure to AN and lung cancer in humans cannot be excluded. It was also pointed out that carcinogenic potential of AN may be weak, if any, to humans,
2. AN is carcinogenic to rat. The carcinogenicity of AN to other animal species is unknown because of no available data.
3. There are numerous findings indicative of genotoxic potential of AN but *in vivo* results are equivocal. Genotoxicity to humans remains to be elucidated.
4. Various subjective symptoms are reported to occur in workers after chronic exposure to relatively low concentration.
5. In experimental animals, inflammatory changes of nasal mucosa are a critical effect observed by inhalation exposure to low concentration.
6. Based on quantitative information available from epidemiological and experimental studies, it was concluded that the current occupational exposure limit for AN of 2 ppm is a reasonable value and there is no need for a revision at present.

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