North Carolina Department of Environment and Natural Resources
Division of Air Quality

Toxicity Assessment of Acrylonitrile:
A Report with Recommendations to revise the Acceptable Ambient Level
Secretary's Science Advisory Board on Toxic Air Pollutants

Executive Summary

The Secretary's Science Advisory Board for Toxic Air Pollutants (NCSAB) has re-assessed the Acceptable Ambient Level (AAL) for acrylonitrile (AN) in response to a request made by the North Carolina Division of Air Quality (DAQ). An AAL is an airborne concentration at or below which no appreciable risks of adverse health effects are expected in the general population. The current AAL for AN, established in 1989, is 1.5×10^{-4} mg/m^3, averaged annually. In 1989, AN was classified as an *experimental carcinogen* and the AAL was based on a lifetime cancer risk level of 10^{-5} (1 per 100,000).

In 1979, the International Agency for Research on Cancer (IARC) classified AN as a Group 2A ("probable human") carcinogen (IARC 1979). This classification was based on sufficient animal data and limited data in humans. EPA classified AN as a B1 ("probable human") carcinogen(U.S. Environmental Protection Agency 1983) based on a statistically significant increase in lung cancer in AN workers (see O'Berg 1980) as well as tumor incidence in two different rat strains via multiple routes of administration. O'Berg's 1980 study was updated in 1985 (O'Berg 1985), revealing that the excess lung cancer mortality noted in the 1980 study was no longer statistically significant. Another recent update of those studies by Symons et al. (Symons 2008) concludes that "…no mortality outcome of a priori interest, principally respiratory system cancer, is associated with increased AN exposure among fiber production workers *over five decades of follow-up*…" (emphasis added)

Reviews of epidemiologic evidence do not support a causal relationship between AN exposure and cancer incidence. IARC (IARC 1999) has since re-classified AN from "probably carcinogenic" to "possibly carcinogenic to humans" stating that "…the earlier indications of an increased risk among workers exposed to acrylonitrile were not confirmed by the recent, more informative studies…" (p. 91), and "…There is inadequate evidence in humans for the carcinogenicity of acrylonitrile…" (p. 91).

For these reasons, the NCSAB has decided to base its current AAL recommendation for AN on a non-cancer effect - irritancy.

Jakubowski et al. (Jakubowski 1987) reported no adverse acute effects among six healthy male volunteers exposed for 8 hours to 2.3 and 4.6 ppm (5 to 10 mg/m^3) of AN for two or three 8 hour periods (with 3 10-minutes breaks during each exposure period). Each volunteer was exposed to both concentrations, except for one who was exposed only at the higher concentration. Jakubowski et al. reported that the exposures produced no subjective acute symptoms (e.g., headache, nausea, general weakness) as have been described in other studies. The Jakubowski et al. data provide the basis for the acute exposure AAL recommendation.

Muto et al. (Muto 1992) conducted a cross-sectional study of 157 male workers and 537 non-exposed workers from 7 acrylic fiber factories. The average exposure duration was about 17 years; the average exposure concentration about 0.53 ppm (1.15 mg/m^3). These workers underwent a wide range of clinical tests including liver function studies, and there was no consistent evidence of adverse health effects. These data form the basis for the chronic exposure AAL recommendation.

Upon review of the updated toxicological and epidemiological literature, the NCSAB recommends revising the acrylonitrile AAL as follows:

AAL Type	Recommended AAL	DAQ Recommended Averaging Time
Acute Irritant	**1 mg/m^3**	**1 hour**
Chronic	**0.03 mg/m^3**	**24 hour**
Carcinogen	**None recommended**	**None recommended**

I. Background Information

Acrylonitrile (CAS 107-13-1) is a colorless, volatile, flammable, and explosive liquid with a pungent odor. AN has a molecular weight of 53.06 g/mole and the molecular structure shown in Figure 1.

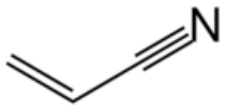

Figure 1- Molecular Structure of AN

AN has the following chemical and physical properties. AN is soluble in water, benzene, and acetone, and miscible with ethanol. The lower explosive limit (LEL) is 3.1% and upper explosive limit (UEL) is 17%. AN has a vapor density of 1.83 (air = 1) and vapor pressure of 100 mmHg @ 22.8ºC (13.3 kPa). 1 ppm AN = 2.2 mg/m^3 AN @ 25 ºC; 1 mg/m^3 AN = 0.46 ppm AN @ 25 ºC.

Acrylonitrile is a chemical intermediate used to make, for example, acrylic fibers for clothing, blankets and carpeting; durable plastics for computers, appliance and VCR housings, sports equipment and auto components; and nitrile rubber for automotive hoses and gasoline delivery. Exposure to AN can occur via inhalation, ingestion, and dermal absorption pathways. AN is classified by the US Environmental Protection Agency (USEPA 1983) as a B1 *probable human carcinogen*, and by the International Agency for Research on Cancer (IARC 1999) as Group 2B *possibly carcinogenic to humans*. Toxic effects in both humans and animals have been demonstrated in numerous studies via various routes of exposure. The Agency for Toxic Substances and Disease Registry (ATSDR) reports that short-term exposure to high concentrations of AN can result in nose and throat irritation, tightness in the chest, difficulty breathing, nausea, dizziness, weakness, headache, impaired judgment, and convulsions. Dermal exposure can produce burns on the skin, redness and blisters. ATSDR also reports that there is evidence that children are much more sensitive to AN exposure than adults.

Occupational Exposure Limits

Table 1 – Occupational Exposure Limits

Organization	Standard or Guideline	ppm	mg/m^3
ACGIH	TLV-TWA	2	4.3
	Ceiling	10	21.7
OSHA	PEL	2	4.3
	Ceiling	10	21.7
NIOSH	REL	1	2.2
	Ceiling	10	21.7
German TRK	TWA	3	6.6

ACGIH: American Conference of Governmental Industrial Hygienists

OSHA: Occupational Safety and Health Administration
NIOSH: National Institute for Occupational Safety and Health
TRK: German Technische Richtkonzentration

The basis for the ACGIH Threshold Limit Value (expressed as a time-weighted average) was two epidemiological studies (Ward 1993; Rothman 1994) and the Dudley et al. animal studies (Dudley 1942a, Dudley1942b).

Both NIOSH and OSHA recognize the potential for absorption of AN through the skin, and have given AN a “skin” notation.

As depicted in Figure 2, there are two primary pathways via which AN is initially metabolized:

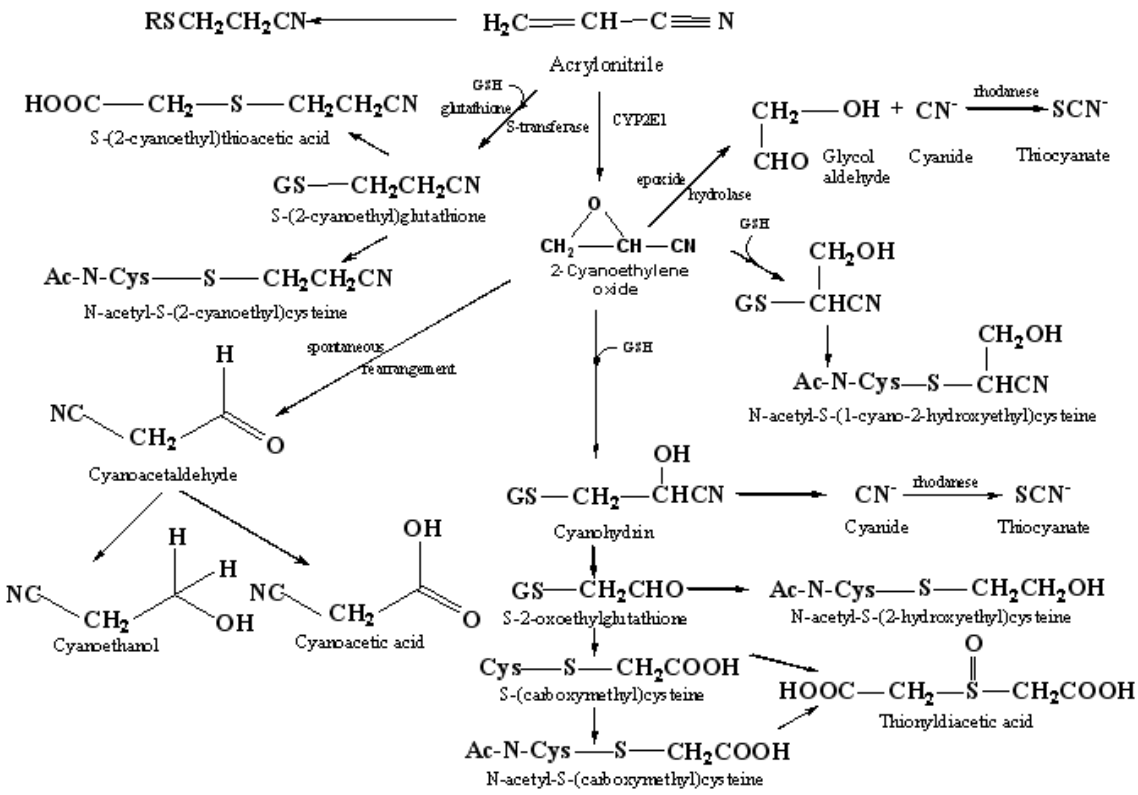

FIGURE 2 – Metabolic Pathways of AN

(1) 2-cyanoethylene oxide (CEO) production via epoxidation by cytochrome P4502E1, or (2) glutathione conjugation either non-enzymatically or by catalysis with glutathione-S-transferase (GST). The AN-glutathione conjugate can be further metabolized to mercapturic acid and excreted in urine. CEO can be metabolized by: (1) conjugation with glutathione, or (2) hydrolysis by epoxide hydrolase.

According to USEPA National-Scale Air Toxics Assessment (NATA) report (U.S. Environmental Protection Agency 1999), both the mean and the median ambient air concentrations of AN in North

Carolina are 4.2 x 10^{-7} mg/m^3 (1.9 x 10^{-7} ppm). The 95th percentile concentration is 2.6 x 10^{-6} mg/m^3 (1.2 x 10^{-6} ppm). Table 2 summarizes emissions by source type and percent contribution:

Table 2 – Contributions to Ambient Air from Source Types in North Carolina

Source Type	Approximate Contribution to Ambient Air Concentration, %
Point	18
Area and Other	82
Mobile	0

Acceptable Ambient Level (AAL) History

In 1987 the Air Toxics Panel of the North Carolina Academy of Sciences recommended adoption of an annual average AAL of 1.4 x 10^{-4} mg/m^3 for AN. The AAL was revised to 1.5 x 10^{-4} mg/m^3 in 1989. In 1991, the NCSAB recommended that the AAL be revised to 8.4 x 10^{-3} mg/m^3 based on an interim report (published 18 months into a 2-year study) (Bigner 1986) showing increased brain tumor incidence of Fischer 344 rats exposed to AN in drinking water. However, the current AAL for AN remains at 1.5 x 10^{-4} mg/m^3 as an annual average.

II. Animal Studies

Non-Cancer Endpoints

Quast et al. (Quast 1980a) exposed Sprague-Dawley rats (100 per sex per group) to AN vapor concentrations of 0, 20, and 80 ppm (0, 43, 176 mg/m^3) in a 2-year chronic inhalation study. Exposure duration was 6 hours/day, 5 days/week, for 2 years. Treatment-related effects were observed in the nasal turbinates (hyperplasia and metaplasia of the nasal turbinates, and hyperplasia of the mucus-secreting cells) in all rats exposed to 176 mg/m^3, and some rats exposed at 43 mg/m^3. It was concluded that these effects were due to the irritant nature of AN.

The United States Environmental Protection Agency (EPA) used the Quast et al. data (Quast 1980a) as the basis for the IRIS Reference Concentration (RfC) This RfC was established in 1991. It was determined that 43 mg/m^3 represented a Lowest Observable Adverse Effect Level (LOAEL) in rats. From the LOAEL, a Human Equivalent Concentration (HEC) was determined to be 1.9 mg/m^3. Using a total Uncertainty Factor (UF) of 1000 (3 for interspecies variability, 10 for intraspecies variability, 3 for LOAEL to NOAEL adjustment, 10 for incomplete database) yielded an RfC of 2 x 10^{-3} mg/m^3. The EPA considered the Quast et al. (1980a) study to be of medium confidence because (1) it was performed only on rats; (2) there was no NOAEL identified by the study; and (3) the target organ (nasal turbinates) was only examined at the end of the study in relatively few animals.

Dudley et al. (Dudley 1942a, Dudley 1942b) conducted studies in which several animal species were exposed to AN via inhalation. In the first of these, only qualitative results were published, animals were not identified by sex, and there were no control animals. Neurological effects (transitory limb weakness and paralysis in dogs and cats), renal effects (histopathological changes in rats and rabbits), upper respiratory tract irritation (nasal irritation in all species), and pulmonary effects (bronchopneumonia in all species except cats) were reported. Table 3 summarizes the results of these studies. “In these experiments, there was no evidence of cumulative action of AN.” (The Sapphire Group Inc. 2004).

Nemec et al. (Nemec 2008) conducted a two-generation reproductive toxicity in Sprague-Dawley rats (25/sex/group, exposed via whole body inhalation for 6 hr/day, 1 litter/generation, through F2 weanlings on postnatal day 28) to AN vapor at concentrations of 0, 5 (10.9 mg/m^3), 15 (32.6 mg/m^3), 45 (97.7 mg/m^3)(two offspring generations), and 90 ppm (195 mg/m^3)(one offspring generation). Exposure at 90 ppm was stopped after about three weeks due to excessive systemic toxicity in the male rats. There were no animal deaths attributed to exposure; neither functional effects on reproduction nor effects on reproductive organs were reported. Neither cumulative toxicity nor enhanced toxicity were observed in pregnant and/or lactating dams or in developing animals. Systemic toxicity in adults (both sexes and generations) was limited to body weight and food consumption deficits at exposure levels of both 45 ppm and 90 ppm, with greater effects in males than females. Increased liver weight was reported in F0 males and females exposed at 90 ppm and to F1 males exposed at 45 ppm. Neonatal toxicity (weight deficit) was observed in F1 offspring exposed at 90 ppm. Rats exposed at 90 ppm exhibited irritation both during and immediately following exposure. Microscopic examination of nasal tissues revealed lesions of the rostral nasal epithelium in some rats exposed at 5 ppm and 45 ppm. Nemec et al. reported the following NOAELs:

- 45 ppm: reproductive toxicity over two generations and neonatal toxicity;
- 90 ppm: reproduction in the F! generation;
- 15 ppm: systemic toxicity in the F0 generation.

Table 3 – Dudley et. al. (Dudley 1942a, Dudley 1942b) Summary

Species	No. Animals	Exposure Time	Avg. AN Exposure Conc., ppm (mg/m^3)	Results
Dogs	2	4 hr/day, 5 day/wk, 4 wks	56 (123)	1 died from convulsions following first exposure,1 exhibited transient paralysis of the hind legs after the 5th, 13th, and 14th exposures
Rhesus monkeys	4			Survived, no evidence of toxicity
Rats	16	4 hrs/day, 5 days/wk, 8 wks	100 (222)	Slight lethargy (3 of 7 females gave birth to and raised normal litters)
Guinea pigs	16			Gained weight moderately and exhibited slight lethargy during exposure
Rabbits	3			Survived, but drowsy and listless during exposure, showed no weight gain
Cats	4			Occasional vomiting, lethargy, lost weight. One developed transient paralysis of hind legs after 3rd exposure, and subsequently dies after 11th exposure. Other exhibited "few adverse effects."
Rats	16 (8 adult, 8 young)	4 hrs/day, 5 days/wk, 8 wks	153 (337)	Lost weight, coats became rough, general physical condition was poor. 50% died during 3rd-4th week of exposure. 8 young rats showed definite impairment of growth and marked eye and nose irritation. One died during 3rd week of exposure. All adult rats showed irritation of eyes and nose. 4 dies by end of 5th week of exposure.
Guinea Pigs	16			Irritation of eyes and nose and salivation during 1st week of exposure. 3 of 16 died during 5th week of exposure. Remainder showed slight increase in weight and were in fair condition at end of study.
Rabbits	4			Moderate irritation of eyes and nose. One died during 5th week of exposure.
Cats	4			All showed severe distress with each exposure, and frequently in collapse at end of exposure period. Marked nasal, conjunctival irritation, and all developed transitory weakness in hind legs. One died after 2nd exposure.
Rhesus monkeys	2			Sleepiness, weakness, loss of appetite, frequent salivation and vomiting. One died after 6 weeks of exposure and another in complete collapse after each exposure during last 2 weeks of study.

Exposures averaging 153 ppm (337 mg/m^3) were definitely toxic to guinea pigs, rats, and rabbits, and very toxic to monkeys and cats. "Even with exposure to such high concentrations, no definite evidence of cumulative action was observed" (The Sapphire Group Inc. 2004).

Cancer Endpoints

Kirman et al. (Kirman 2005) conducted a cancer dose-response assessment of AN using brain tumor incidence in rats as the endpoint. Twelve data sets were pooled for this analysis. Pharmacokinetic (PBPK) modeling was used to predict peak concentration of 2-cyanoethylene oxide in the brain. An ED_{05} for this internal dose metric was determined to be 0.017 mg/L and the corresponding LED_{05} was 0.014 mg/L; these were utilized as points of departure. Corresponding human equivalent airborne concentrations were determined to be 25.9 and 21.3 mg/m^3, respectively, by adjusting human inhalation exposure until the simulated internal dose matched the points of departure. Both a linear, non-threshold approach and a non-linear, threshold approach were used to derive: 1) a cancer potency factor (linear, non-threshold) and 2) a "cancer reference dose" (non-linear, threshold).

The National Toxicology Program (NTP) published a report on the toxicology and carcinogenesis of AN in 2001 (NTP 2001). Both a 14-week study and a 2-year gavage study of B6C3F1 mice were conducted. The 2-year study results were also reported by Ghanayem et al. (Ghanayem 2002). In the 14-week study, 10 male and 10 female mice per dose group were dosed by gavage at levels of 0, 5, 10, 20, 40, or 60 mg AN/kg, 5 days/week, for 14 weeks. All 10 males and 9 females in the 60 mg/kg dose group as well as 8 male and 3 female mice in the 40 mg/kg dose group died on the first day of exposure. Clinical findings were as follows:

- 10 mg/kg dose group:
  left cauda epididymis weight significantly greater than controls (males)

- 20 mg/kg dose group:
  mean body weight gain less than controls (males)
  leucocyte and lymphocyte counts decreased (males)
  heart weight significantly greater than controls (males)
  left cauda epididymis weight significantly greater than controls (males)

- 40 mg/kg dose group:
  lethargy, abnormal breathing
  leucocyte and lymphocyte counts decreased (females)
  minimal hemolytic anemia (females)
  incidence of forestomach chronic active inflammation and hyperplasia significantly greater than controls (females)

Ghanayem et al. (Ghanayem 2002) assessed the carcinogenicity of AN in B6C3F1 mice in a 2-year gavage study. AN (in deionized water) was administered by gavage in dosages of 0, 2.5, 10, or 20 mg/kg/day to 50 male and 50 female mice 5 days/week for 2 years. Urinary thiocyanate and N-acetyl-S-(2-cyanoethyl)-L-cysteine were used as exposure markers. Survival was markedly decreased in male and female mice exposed at the highest dose (20 mg/kg) relative to controls. Both neoplastic and non-neoplastic changes were observed in test animals. An increase in forestomach papillomas and carcinomas with increasing forestomach epithelial hyperplasia was observed in both male and female mice. The incidence of Harderian gland adenomas and carcinomas was also observed increasing with dose in both sexes. In female mice, the incidence of ovarian atrophy and cysts in the 10 mg/kg and 20 mg/kg dose groups was observed. Combined incidences of alveolar/bronchiolar adenoma or carcinoma were significantly increased in female mice in the 10 mg/kg/day dose group over the course of the two year study as was the incidence of benign or malignant granulosa cell tumors in the ovaries of the 10 mg/kg dose group. However, the lack of dose-response made these observations equivocal.

III. Human Studies

Acute and Chronic Non-Cancer Endpoints

Studies of occupational and non-occupational AN exposures (inhalation or dermal) indicate that neuropathological (acute and chronic) and respiratory effects are the primary non-cancer effects. Adverse effects are generally observed at exposure concentrations exceeding 5 ppm (10.9 mg/m^3) for occupational cohorts. Refer to Table 4 for neurological and respiratory effects in humans.

Numerous studies have reported acute neurological symptoms of nausea, vomiting, headache, vertigo, general weakness, and irritability with exposure concentrations ranging from 5 ppm to 100 ppm (10.9 to 217 mg/m^3) (Wilson 1944, Wilson 1948, Wilson 1949, Sartorelli 1966, Zeller 1969, Zotova 1975; World Health Organization 1983; Vogel 1984). Other acute neurological symptoms include fatigue, feelings of apprehension, tremors, uncoordinated movements, convulsions,

decreased work capacity, decreased appetite, insomnia, and hallucinations (Wilson 1944; Wilson 1948; Sartorelli 1966; Zotova 1975; Vogel 1984). Lorz (1950) reported the death of a 10 year old girl after a 4-hr dermal exposure to AN. Symptoms are typically observed after a 5-minute exposure. However, symptoms may not manifest for 45 minutes. Another study (Zotova 1975) indicated that workers complained of these symptoms within the first few months of employment.

Wilson et al. (Wilson 1948) reported that polymer workers exposed to airborne AN concentrations of 16-100 ppm (35-217 mg/m^3) for periods of 20-45 minutes complained of headaches, nasal and ocular irritation, chest discomfort, nervousness, and irritability. Nausea, vomiting, and general weakness were also reported. Some workers developed a mild jaundice, low-grade anemia, and leucocytosis. Exposure concentration data were not reported for these symptoms, and all workers recovered upon cessation of exposure.

Jakubowski et al. (Jakubowski 1987) reported no adverse acute effects to volunteers exposed for 8 hours to 2.3 and 4.6 ppm (5 to 10 mg/m^3) AN. Six male volunteers (all toxicologists), with no routine clinical abnormalities, were exposed to AN for periods of 8 hours (with 3 10-minutes breaks), using an 11.7 m^3 exposure chamber. Exposure concentrations were either 10 mg/m^3 or 5 mg/m^3. Each volunteer was exposed to both concentrations, except for one who was exposed only at the higher concentration. Jakubowski et al. reported that 8-hour exposures produced no subjective acute symptoms (e.g., headache, nausea, general weakness) as had been described in other studies.

Chronic AN exposures produced similar reactions, such as headache, nausea, general weakness, decreased work capacity, dizziness, fatigue, insomnia, and irritability (Babanov 1959; Sakurai 1972; Buchter 1984; Kaneko 1992). Other chronic neurological effects include depression, lability of autonomic functions, neurasthenic complaints, disturbance of memory, drowsiness, diminished vision and hearing, and “heavy arms” (Ageeva 1970; Stamova 1976; Buchter 1984; Bakker 1991; Kaneko 1992). Exposure concentrations reportedly ranged from 0.3 to 20 ppm (0.7 to 43.3 mg/m^3) and exposure time periods ranged from 3 to 14 years. Ginceva et al. (Ginceva 1977) observed no adverse chronic effects in 23 males exposed to 4.2 to 7.2 mg/m^3 AN for 3 - 5 years.

Several studies indicated that the most common respiratory effects observed were irritation to the nose, throat, upper respiratory tract, and eyes (Wilson 1944; Wilson 1948; Wilson 1949; Sakurai 1972; Sakurai 1978; World Health Organization 1983; Vogel 1984; Kaneko 1992; Sakurai 2000). Other reported respiratory effects include feelings of fullness in the chest, coughing, bronchitis, respiratory malfunction, lip cyanosis, nasal discharge, tongue trouble and choking lump in the throat (Wilson 1948; Ageeva 1970; Sakurai 1972; Sakurai 1978; Buchter 1984; Kaneko 1992). One study (Buchter 1984) reported respiratory arrest that led to death in one worker who had been exposed for a duration of 14 years. Ginceva et al. (Ginceva 1977) reported no adverse respiratory effects in 23 males.

Cardiovascular effects from exposures to AN include tachycardia followed by death (one case), lowered arterial pressure, labile pulse, changes in orthostatic reflex, cerebrovascular insufficiency due to disturbance of the circulatory function, arteriosclerosis, elevation of the erythrocyte sedimentation rate of unknown origin, and porphyrinuria (Grunske 1949; Babanov 1959; Ageeva 1970; Buchter 1984). Ginceva et al. (Ginceva 1977) observed no adverse cardiovascular effects in 23 males.

Reported hepatic effects include mild jaundice, tenderness, enlargement and low-grade anemia (Wilson 1948; Wilson 1949; Sartorelli 1966; World Health Organization 1983) . Other less common effects observed were pharyngeal congestion, changes in liver function tests, increase in palpable liver, and transient injury (Sartorelli 1966; Sakurai 1972; Sakurai 1978; Vogel 1984). Exposure concentrations ranged from 5 to 100 ppm (10.9 to 217 mg/m^3) and exposure times ranged from 20 minutes to 10 years.

Sakurai (Sakurai 1972) studied 576 acrylonitrile-exposed workers and found that for workers with exposures of <5 ppm, liver effects (positive urobilinogen test) increased in frequency with years of exposure. This was also seen in the higher exposure group (exposed to <20 ppm acrylonitrile) but at each exposure interval, the frequency of abnormalities was higher than in the lower exposed group. In the group with >10 years of exposure, 35% of those with <5 ppm acrylonitrile had liver abnormalities while in the higher exposure group 49% had liver abnormalities. Sakurai et al. (Sakurai 1978) looked at a randomly chosen sample of these same workers at a time when engineering controls had decreased exposures. No liver abnormalities were found in groups with an average of 0.5 ppm exposure or less but in the group with an average of 4.2 ppm exposure, 38.9% had a palpable liver vs. 10-18% in exposed and controls at factories with 1 ppm or less exposure. 30% of the "controls" at the plant with 4.2 ppm exposure also had palpable livers. Muto et al (Muto 1992) found no liver function abnormalities among workers at these same plants with an average acrylonitrile exposure of 0.53 ppm. The NOAEL for acrylonitrile effects on the liver appears to be 0.5 ppm.

Only slight irritation of the kidney has been reported. Exposure concentrations ranged from 16 to 100 ppm (34.7 to 217 mg/m^3) and time periods from 20 to 45 minutes (Wilson 1948). No adverse liver or kidney effects were observed in 23 males (Ginceva 1977).

Results from dermal AN exposures include erythema, blisters, and general irritation (e.g. itchy, painful, dry and scaly skin) (Dudley 1942a; Wilson 1948; Babanov 1959; Zeller 1969; Zotova 1975; Vogel 1984; Bakker 1991). Other less common effects were swelling, dermatitis, erythenatous patches, and a burning sensation on contact (Dudley 1942a; Zeller 1969; Davis 1973). These symptoms were observed within 5 minutes of contact and lasted up to 24 hours for exposure concentrations ranging from 0.3 to 100 pm. Babanov et al. (Babanov 1959) reported vocal chord inflammation, and nonspecific changes in the pale mucous membranes and skin of workers exposed to 0.3 to 3 ppm (0.65 to 6.5 mg/m^3) AN over a 3 year period. Ageeva (1970) reported diffuse dermographia and increased sweating in workers but did not specify the exposure concentration or time period. Irritation of the scrotal skin in workers exposed to 5 to 20 ppm (10.9 to 43.4 mg/m^3) AN over 10 years was reported by Ginceva et al. (Ginceva 1977). Stamova et al. (Stamova 1976) observed an increase in skin disease for workers exposed to 10 to 25 mg/m^3 AN over an unknown time period while Balda (Balda 1975) reported a skin rash in one worker and Bakker et al. (Bakker 1991) reported ten cases of contact dermatitis in occupational cohorts. No adverse skin or allergic effects to 23 males was reported by Ginceva et al. (Ginceva 1977).

Effects seen in the eye include general irritation, lacrimation, visual disturbances, blepharoconjunctivitis, irritation of the conjunctiva, and mild conjunctivitis with no corneal clouding (Wilson 1944; Wilson 1948; Grunske 1949; Davis 1973; Sakurai 1978; World Health Organization 1983; Vogel 1984). These effects were observed at exposure concentrations ranging from 5 to 100 ppm (10.9 to 217 mg/m^3) AN for exposure periods ranging from 20 minutes to 10 years. Ginceva et al. (Ginceva 1977) observed no adverse eye effects in 23 males. Sakurai et al. (Sakurai 1978) also found reddening of the conjunctiva and pharynx in 50% of workers (and 30% of "controls") at a plant with an average acrylonitrile exposure of 4.2 ppm. Incidences among exposed workers and controls at plants where exposures were 0.5 ppm or less ranged from 10-19.4% and did not differ between exposed and control groups. Muto et al. (Muto 1992) found no excessive respiratory symptoms among workers at these same plants with an average exposure of 0.53 ppm. The NOAEL for mucous membrane irritation with chronic acrylonitrile exposure appears to be 0.5 ppm.

AN has been observed to act like epinephrine, causing an increase in acetylcholine, serum creatinine phosphokinase, transamines, and myoglobinuria; reduction in acid phosphatase, myeloperoxidase, and succinate dehydrogenase activity in peripheral blood leucocytes; and is considered immunosuppressive (Babanov 1959; Ageeva 1970; Vogel 1984; Grigoreva 1990). Exposure concentrations were not reported in most studies examining these endpoints with the exception of

Babanov et al. (Babanov 1959), who reported concentrations ranging from 0.3 to 3 ppm (0.65 to 6.5 mg/m^3) and exposure duration ranging from 3 to 10 years. Most of the studies sited are older (circa 1985) and predate any control or exposure reduction techniques. Neither Ginceva et al. (Ginceva 1977) nor Sakurai et al. (Sakurai 1978) observed any adverse clinical chemistry effects from exposures to AN at similar concentrations and exposure periods.

Wilson et al. (Wilson 1944, Wilson 1948) reported low-grade anemia and leucocytosis to workers exposed to AN concentrations ranging from 16 to 100 ppm (34.7 to 217 mg/m^3) AN for 20 to 45 minutes. WHO (World Health Organization 1983) reported reduced hemoglobin levels, erythrocyte counts and leukocyte counts in workers exposed to AN concentrations greater than 5 ppm (10.9 mg/m^3) for an unspecified time period. Neither Ginceva et al. (Ginceva 1977) nor Sakurai et al. (Sakurai 1978) observed any adverse effects to the hematologic system from exposures to AN at similar concentrations and exposure periods.

Ivanescu et al. (Ivanescu 1990) reported a decrease in testosterone levels in workers exposed to AN, while Czeizel et al. (Czeizel 1999) observed *pectus excavatum* (sunken or funnel chest), undescended testes, and clubfeet in children of female non-workers living within 25 kilometers of an AN production facility between 1982 to 1992. One study (Dorodnova 1976) reported no reproductive effects of AN in 410 female workers.

Neither Ginceva et al. (Ginceva 1977) nor Kiesselbach et al. (Kiesselbach 1979) observed any adverse gastro-intestinal and endocrine system effects from exposures to AN.

Table 4 - A Summary of Neurological and Respiratory Effects in Humans

Reference	Number (Control)	Cohort	Exposure Time	Avg. AN Exposure Conc., ppm (mg/m^3)	Route of Exposure	Neurotoxicity		Respiratory
						Acute	Chronic	
Wilson, 1944	NS	O	NS	"mild"	NS	nausea, vomiting, weakness, headache, fatigue	--	Nasal irritation
Wilson *et.al.*, 1948	NS	O	20 to 45 mins	16-100 (35-219)	I / D	headache, nausea, feelings of apprehension, nervous irritability	--	Nasal and throat irritation, feeling of fullness in the chest
Wilson and McCormick, 1949	NS	O	NS	"mild"	NS	nausea, vomiting, headache, vertigo	--	Upper respiratory symptoms, nasal irritation
Lorz, 1950	1	NW	NS	NS	D	nausea, headache, dizziness followed by death	--	--
Babanov *et al.*, 1959 (reported in WHO, 1983)	NS	O	approx 3 years	0.3-3 (0.6-6.0)	NS	--	headache, insomnia, general weakness, decreased working capacity, and increased irritability	--
Sartorelli, 1966	1	O	NS	NS	I	headache, vertigo, vomiting tremors, uncoordinated movements, convulsions	--	--
Zeller, *et al.*, 1969	16, 50 (skin)	O	5 - 15 minutes	NS	I / D	nausea, vomiting, headache, vertigo	--	--
Ageeva, 1970 (reported in WHO 1983)	NS	O	NS	NS	NS	--	depression, lability of autonomic functions (*i.e.,* lowered arterial pressure, increased sweating, changes in orthostatic reflex, etc)	Dyspnea, coughing, irritation, bronchitis
Sakurai and Kusumoto, 1972	576	O	10 years	5-20 (11-45)	NS	--	headache, fatigue, nausea, insomnia	Irritancy (>5 ppm)

Zotova, 1975	NS	O	first few months of employment	NS	NS	headache, decreased work capacity, poor sleep, irritability, poor appetite	--	--
Stamova *et al.*, 1976	NS	O	NS	(10-25)	NS	--	neurasthenic complaints (undefined)	--
Ginceva *et al.*, 1977	23	M	3 to 5 years	(4.2-7.2)	NS	--	None	None

Table 4 – A Summary of Neurological and Respiratory Effects in Humans cont.

Sakurai *et al.*, 1978	102 (62)	O	>5 years	4.2 (9.1) avg. 8-hr exposure	NS	--	None	Upper respiratory tract irritation, nasal discharge
Kiesselbach *et al.*, 1979	884	O	NS	NS	NS	--	None	--
Vogel and Kirkendall, 1984	1	O	NS	NS	D	dizziness, nausea, vomiting, hallucinations, convulsions	--	Acute irritant
Buchter and Peter, 1984	1	O	14 years	NS	NS	--	disturbance of memory, weakness, headache, dizziness, drowsiness, diminished vision and hearing, and low blood pressure	respiratory malfunction, lip cyanosis, respiratory arrest leading to death
WHO, 1983; VROM, 1984	NS	O	NS	> 5 (11)	NS	headache, vertigo, limb weakness	--	irritation of the eyes, nose, throat and respiratory tract
Jakubowski *et al.*, 1987	NS	V	8 hours	2.3 and 4.6	NS	None	--	None
Bakker *et al.*, 1991	10	O	NS	not specified	NS	--	skin complaints, paresthesia	--
Kaneko and Omae, 1992 (dose-response relationship not observed)	NS	O	5.6 years 7 years 8.6 years	1.8 (4) 7.4 (16) 14.1(31)	NS	--	headache, fatigue, sweating, "heavy arms", general weakness	Irritation of the mucosa and upper respiratory tract (tongue trouble and choking lump in throat)

Muto *et al*., 1992	157 (537)	O	Average 17 years	1.13 (2.5) "most highly exposed group"	I	--	--	Nasal irritation
Sakurai, 2000	NS	NS	NS	>10	NS	--	--	Conjunctiva irritation, irritation of upper respiratory tract

NS - Not Stated
O – Occupational
NW – Nonworker
M- Male
V – Volunteer
I – Inhalation
D – Dermal

Cancer Endpoints

Five studies of workers exposed to high levels of acrylonitrile have shown significant increases in lung cancer rates. Thiess et al. (Theiss 1980) found elevated death rates among 1469 workers who were first exposed in 1956. O'Berg (O'Berg 1980) found elevated lung cancer death rates among DuPont workers first exposed in 1950. Delzell and Monson (Delzell 1982) found increased lung cancer death rates among workers exposed to acrylonitrile between 1940 and 1971. In a study of workers first exposed to acrylonitrile in 1950, Benn and Osborne (Benn 1998) found a significantly increased SMR for lung cancer in their highest exposed group. Blair et al. (Blair 1998) studied a cohort of workers who were first exposed to acrylonitrile in the 1950s and also found an increased risk of lung cancer in their highest cumulative exposure group (>8 ppm-years of exposure). These studies suggest that acrylonitrile may have carcinogenic activity at the highest levels of human exposure. However, in view of the lack of a dose-response relationship and the lack a carcinogenic effect in more recent studies of workers, there is no strong or consistent evidence for a causal association between acrylonitrile exposure and lung cancer risk in humans (Sakurai 2000).

The Sappire Group toxicological report on AN (The Sapphire Group Inc, 2004) has summarized the epidemiologic measures of cancer risk that have been developed for various cancer types. That summary is reproduced herein as Table 4-1 (in the appendix). Four specific risk analyses were selected for critical review and consideration for this risk assessment:

1. US Environmental Protection Agency (1983)

This study (US Environmental Protection Agency 1983) used (O'Berg 1980) as the basis of its risk assessment of acrylonitrile. O'Berg followed 1,345 workers who worked at the DuPont May plant in Camden, South Carolina from 1950-1966. Based on a determination of the SMR adjusted for smoking of 3.1 (5 obs/1.6 exp), a background lifetime probability of death from respiratory cancer derived from the 1976 US Vital Statistics via a lifetable calculation, and a NIOSH-estimated average (20 ppm = high, 10 ppm = low, negotiated by NIOSH with DuPont representatives) worker exposure of 15 ppm (33 mg/m^3) over an average 9-year duration (135 ppm-years), USEPA determined a lifetime (70-year) equivalent continuous exposure to be 0.5 ppm, and hence a unit exposure risk to be 1.5×10^{-4} per ppb (6.9×10^{-2} per mg/m^3).

2. World Health Organization (2000)

The WHO (World Health Organization 2000) used data from O'Berg et al.'s (O'Berg 1985) updated study to derive a lifetime unit risk value. O'Berg et al. updated the original study (O'Berg 1980) to the end of 1983 for cancer incidence and to the end of 1981 for overall mortality. Of 1,345 workers exposed to AN, 10 cases of lung cancer were observed with 7.2 expected. The SMR was reported to be 1.39 (0.75, 2.36) in the updated study.

3. Starr et al. (Starr 2004) re-analysis of Blair et al. (Blair 1998)

Starr et al. (Starr 2004) re-analyzed data from the Blair et al. (Blair 1998) epidemiologic study of 25,460 workers exposed to AN vapor in eight plants in the United States, focusing on lung cancer mortality within the largest race-sex subgroup of 18,079 white males. Blair et al. stratified cumulative exposure into five exposure quintiles and noted a slight, statistically insignificant, increase in lung cancer mortality in workers in the highest exposure quintile (> 8 ppm-years, rate ratio = 1.5 (0.9–2.4)). No significant exposure-response trends were observed.

Using a Cox proportional hazards model, Starr et al. determined that cumulative AN exposure unadjusted for other covariates was not a statistically significant predictor of lung cancer mortality. Furthermore, cumulative AN exposure remained insignificant when adjusted for plant (either 8 or 3 strata). However, plant of employment was a statistically significant predictor of lung cancer mortality in these plant-adjusted models. Three occupational exposure scenarios were nevertheless utilized to generate age-specific cumulative risk estimates for a high-end cumulative exposure of 50 ppm·working years attained by age 55. Assuming that ambient airborne AN concentration is negligible (in comparison to the assumed workplace concentrations), 50 ppm·working years would be equivalent to a continuous 78-year lifetime exposure of 0.14 ppm.

4. Symons et al. (Symons 2008)

Symons et al. (Symons 2008) updated the DuPont epidemiologic studies of worker exposure to AN in fiber production plants (O'Berg 1980; O'Berg 1985; Chen 1987; Wood 1998). Follow-up was extended by 11 years (through 2002). The cohort was comprised of 2548 male fiber production workers with a minimum of 6 months AN exposure at DuPont facilities, located in Waynesboro, VA and Camden, SC. Exposure concentration and cumulative exposure values were assigned following the standardized exposure classification procedure described by Wood et al. (Wood 1998). Estimated exposure categories ranged from less than 0.2 ppm (0.04 mg/m^3) to greater than 20 ppm (43 mg/m^3). Cumulative exposure was determined by summation of (mean exposure concentration for job assignment x time in job assignment). The authors reported that this updated follow-up of the DuPont cohort yielded no evidence for an association between AN exposure and cancer mortality (particularly respiratory and prostate cancer). While the total mortality rate at the South Carolina facility was slightly higher than that at the Virginia facility, this differential was attributed to the older age distribution at the South Carolina facility.

5. Collins April 2008 Presentation to the NCSAB

Dr. James J. Collins, Director of Epidemiology of the Dow Chemical Company also provided a comprehensive review of epidemiologic studies of AN for the NCSAB at its April, 2008 meeting. The intent of this review was to cover all the AN epidemiology studies since the last IARC review (IARC 1999). The 1999 IARC review resulted in a re-designation of AN as “possibly carcinogenic to humans based on no consistent increases in cancer risk related to AN exposure across multiple AN epidemiological studies. This presentation focused principally on four major epidemiological studies (the British Industry-wide study (Benn 1998), the Dutch industry-wide study (Swaen 2004), the National Cancer Institute U.S. industry-wide study) (Blair 1998), and the DuPont study (Symons 2008). Cancer sites in humans reported in the literature are lung cancer, prostate cancer, bladder cancer. Brain cancer was also included in this review because of the positive rat studies this site,. All of the studies reviewed by Dr. Collins have been published in the peer-reviewed scientific literature.

Dr. Collins concluded that there was no evidence for an association between AN exposure and human brain, bladder, or prostate cancer, but that an association with lung cancer at high exposure levels cannot be entirely ruled out.

IV. Genotoxicity

Animal Studies

Jiang et.al. (Jiang 1998) studied rats exposed to AN in drinking water. Concentrations were 0, 5, 10, 100, or 200 ppm. Animals were sampled after 14, 28, or 90 days of continuous treatment. It was found that increased levels of OH8dG (8-hydroxy-2'-deoxyguanosine), MDA (malondialdehyde), and

ROS (reactive oxygen species) were found in the brains of the AN-treated rats. Decreased levels of GSH and activities of catalase and SOD (superoxide dimutase) were also observed in the brains of AN-treated rats compared to the control group. Interestingly, there were no changes of these indicators of oxidative stress in the livers of AN-treated rats. Rat liver is not a target for AN-induced carcinogenesis. These data indicate that AN selectively induces oxidative stress in rat brain at doses that produced brain cancer in chronic exposure studies.

Rats chronically exposed to AN have shown a dose-related increase in incidence of astrocytomas in the brain. The mechanism(s) by which cancer is induced in rodents has not been established. AN does not appear to be directly genotoxic in the brain and a nongenotoxic mode of action has been proposed. Many nongenotoxic carcinogens inhibit gap junctional intercellular communication (GJIC). Kamendulis et al. (Kamendulis 1999) examined the effects of AN on GJIC in a rat astrocyte transformed cell line, DI TNC1 cells (a target cell for AN carcinogenicity) and primary cultured hepatocytes (a nontarget cell for AN carcinogenicity). It was found that AN inhibited GJIC in rat astrocytes in a dose-dependent manner. This was observed following 2 hours of treatment with 0.10 mmol/L and 1.00 mmol/L AN. GJIC inhibition plateaued after 4 hours of treatment and GJIC remained blocked throughout the entire experimental period examined. Inhibition was reversed by removal of AN from the culture medium after 4 or 24 hours of treatment. In primary cultured hepatocytes, exposure to AN did not result in inhibition of GJIC even after 48 hours of continued treatment. Cotreatment of astrocytes with vitamin E reduced the effect of AN-induced inhibition of GJIC. Similarly, inhibition of GJIC was prevented by treatment with 2-oxothiazolidine-4-carboxylic acid (OTC), a precursor of glutathione synthesis. Decreasing cellular glutathione by treatment with buthionine sulfoxamine alone (without AN) did not affect GJIC in astrocytes. Collectively, these results demonstrate that treatment with AN caused a selective inhibition of GJIC in rat DI TNC1 astrocytes (the target cell type), but not in rat hepatocytes (a nontarget tissue). Inhibition of GJIC in astrocytes was reversed by treatment with antioxidants and a potential role for oxidative stress in AN-induced carcinogenesis is suggested.

Kamendulis et al. (Kamendulis 1999) reported that rat glial cells and hepatocytes treated for 1, 4 and 24 hours with sublethal concentrations of AN induced an increase in oxidative DNA damage, as evidenced by increased production of 8-hydroxy-2'-deoxyguanosine (8-OH-dG) in glial cells but not in rat hepatocytes.

Zhang et al. (Zhang 2000) examined the ability of AN to induce morphological transformations and oxidative damage in SHE (Syrian Hamster Embryo) cells. Increases in morphological transformation were observed at doses of 50, 62.5 and 75 μg/ml (maximum sub-toxic dose tested) following 7 days of continuous treatment. No such increases were observed after 24 hours of exposure to AN. Morphological transformation was inhibited by co-treatment with the antioxidants alpha-tocopherol and (-)-epigallocathechin-3 gallate (EGCG) for 7 days. Treatment of SHE cells with 75 μg/ml AN produced a significant increase in 8-hydroxy-2'-deoxyguanosine that was also inhibited by co-treatment with alpha-tocopherol or EGCG. These results support the proposal that oxidative stress and the resulting oxidative damage is involved in AN-induced carcinogenicity.

Zhang et al. also examined the effects of AN on enzymatic and nonenzymatic antioxidants in SHE cells (Zhang 2002). SHE cells were treated with subcytolethal doses of AN (0, 25, 50, and 75 μg/ml) for 4, 24, and 48 hours. The 50 μg/ml and 75 μg/ml treatments increased the amount of ROS in SHE cells at all time points. The authors suggest that the induction of oxidative stress by AN involves a temporal decrease in antioxidants and increase in xanthine oxidase activity that is mediated by oxidative metabolism of AN.

Pu et al. (Pu 2006) examined the ability of AN to induce DNA damage in the DI TNC1 rat astrocyte

cell line using the alkaline Comet assay. Oxidized DNA damage also was evaluated using formamidopyrimidine DNA glycosylase treatment in the modified Comet assay. No increase in direct DNA damage was seen in astrocytes exposed to sublethal concentrations of AN (0-1.0 mM) for 24 hr. However, AN treatment resulted in a concentration-related increase in oxidative DNA damage after 24 hr. While AN does not directly damage astrocyte DNA, it does increase oxidative DNA damage. The oxidative DNA damage following AN exposure appears to arise mainly through the P450 metabolic pathway; moreover, glutathione depletion may contribute to the induction of oxidative DNA damage by AN.

However, Carrera et al. (Carrera 2007) reported on effects of AN on the viability of primary-cultured astrocytes as well as the oxidative damage generated by AN by measuring GSH levels in primary cultured astrocytes. Their study attempted to determine whether AN (2.5mM) toxicity could be avoided by using antioxidants such as taurine (5mM), N-acetylcysteine (20 mM), trolox (100 µM), estradiol (10 µM), and melatonin (100 nM-1mM). These antioxidants were not able to prevent AN-induced cell damage, with the exception of N-acetylcysteine, confirming that only GSH seems to play a key role in AN-derived toxicity. Additionally, different parameters of oxidative stress such as catalase activity, lipid peroxidation and GSH concentration, were determined as indicators of the potential oxidative stress mediated by the toxicity of AN, after exposure of Wistar rats to a concentration of 200 ppm AN for 14 days. At the concentration assayed, no evidence of oxidative damage was found in the brains of AN-treated rats.

El-Sayed et al. (El-Sayed 2008) examined the ability of hesperidin, an antioxidant flavonoid, to attenuate AN-induced alterations in lipid peroxidation in rat brains. The daily oral administration of AN to male albino rats in a dose of 50 mg/kg for a period of 28 days produced a significant elevation (107%) in brain lipid peroxides measured as malondialdehyde (MDA), accompanied by a marked decrease of 63% in brain-reduced glutathione (GSH) content. In addition, AN administration resulted in significant reductions in the enzymatic antioxidant parameters of brain; superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), and glutathione-S-transferase (GST) were reduced by 43%, 64%, 52%, and 43%, respectively. On the other hand, pre-treatment with hesperidin and its co-administration with AN once daily in a dose of 200 mg/kg for 28 days reduced AN-induced alterations in brain lipid peroxidation. These results suggest that hesperidin may have a protective role against AN-induced oxidative stress in the brain; an effect that is mainly attributed to the antioxidant property of hesperidin.

Human Studies

In Vitro Studies

Overall, studies using human-derived cells suggest that AN has much lower mutagenic potency compared to its putative toxic metabolite, 2-cyanoethylene oxide (CEO). In several *in vitro* studies it has been found that AN is slightly mutagenic at concentrations starting at about 400mM whereas CEO produces mutagenic effects at much lower concentrations (100 mM).

Exposure of human lymphocytes to 0.5 mM AN significantly increased sister chromatid exchange (SCE) with or without a rat liver metabolizing system (S-9 mix) (Perocco 1982). However Obe et al. (Obe 1985) were unable to reproduce this effect after exposures of 1.0 and 0.2 mM AN for 24 hours without S9 and for one hour with S9.

AN was shown to be both mutagenic and genotoxic at 0.18 and 0.036 mM in a DNA repair assay study using HeLa cells and [$_3$H]TdR in the presence and absence of hydroxyurea (Rizzi 1984). DNA repair in HeLa cells was not altered in a similar study by (Martin 1985).

Crespi et al. showed that mutagenicity increased when human lymphoblasts (TK6, *TK* locus) were exposed to AN both with and without metabolic activation (Crespi 1985). AN concentrations ranged from 0.1 – 1 mM for 3 hours (with S9) and for 20 hours (without S9). At AN concentrations 0.8 – 0.95 mM in the presence of S9, mutation frequency was observed to increase by a factor of 3.5. Mutation frequency was observed to increase 2-fold at 0.3 mM and 1.3-fold at 0.4 mM in the absence of S9.

Recio and Skopek (Recio 1988) exposed a TK human lymphoblast cell line to both AN and CEO. In the absence of S9, AN was not mutagenic, however in the presence of S9, there was a four-fold increase at concentrations of 1.4 mM. CEO on the other hand induced a 17-fold increase in mutation frequency at 0.1 mM. These results indicate the CEO may be the mutagenic metabolite of AN. Recio et al. (Recio 1990) conducted a follow up study using CEO to treat TK6 lymphoblasts at 0.15 mM. The results indicated that hprt mutations occurred in several coding regions.

Using human bronchial epithelial cells derived from autopsy samples, Chang et al. (Chang 1990) found that SCE increased at concentrations of 3 and 6 mM. Cytotoxicity occurred at 11mM.

In studies using F344 rat hepatocytes exposed to ≤10mM AN or <1mM CEO, no UDS (unscheduled DNA synthesis) was observed, but AN was observed to be cytotoxic (Butterworth 1992). In studies in which human epithelial cells were exposed to 0.1mM CEO, no UDS was observed; however at a concentration of 1 mM CEO, UDS and cytotoxicity were observed.

In Vivo Studies

Few *in vivo* studies have been reported in the peer-reviewed scientific literature. However, the results of the studies that have been reported indicate that AN may not be genotoxic at occupational exposure levels.

Chromosomal aberrations in peripheral lymphocytes were not observed to be increased over those in unexposed controls in 18 workers exposed over a 15.4 year period to an average reported level of 5 ppm (10.9 mg/m^3) AN (Thiess 1978). This average reported level was measured over a period of 10 years and was considered representative of normal operating conditions. Peak exposure levels were not measured and at the time of the study average exposure levels had been reduced to 1.5 ppm (3.26 mg/m^3).

One study (Borba 1996) reported chromosomal aberrations and SCEs in a study of 26 workers (14 in production and 12 in maintenance) exposed to AN in an acrylic fiber plant. Exposure levels, exposure duration, and exposures to other chemicals were not reported. Using 20 administrative workers as unexposed controls, no difference in SCEs was found between exposed and unexposed groups. Chromosomal aberrations were reported higher in maintenance workers than production workers and controls, but mixed exposures of the maintenance workers and the absence of increased aberrations in production workers confounds the attribution of such aberrations in the maintenance group to AN exposure.

Xu et al. reported on their study of AN-induced DNA strand breakage and sex chromosome aneuploidy in human spermatozoa (Xu 2003). The semen of 30 AN-exposed workers was examined. DNA strand breakage of was investigated using single cell gel electrophoresis (SCGE). The frequency of sex chromosome aneuploidy in sperm cells was analyzed in 9 exposed workers using fluorescence in situ hybridization (FISH). The geometric mean sperm density was 75 x 10^6 per mL in the exposure group, significantly lower than the control group value of 140 x 10^6 per mL. The

geometric mean sperm number per ejaculum was 205 x 10^6 in the exposure group, significantly lower than 280 x 10^6 in the control group. The rate of comet sperm nuclei were 28.7% in exposure group, significantly higher than the 15.0% observed in the control group. Mean tail length was 9.8 µm in exposure group, longer than 4.3 µm in the control. The frequency of sex chromosome disomy was 0.69% in exposure group, significantly higher than the 0.35% value observed in the control group. XY-bearing sperm was the most common sex chromosome disomy, with an average rate of 0.37% in exposure group, and 0.20% in the control. XX- and YY-bearing sperm accounted for an additional 0.09 and 0.23% in exposure group, and 0.05 and 0.10% in the control group. The results indicate that AN affects semen quality among exposed workers. The authors conclude that AN or its metabolites could induce reproductive defects as an in vivo multipotent genotoxic agent by inducing DNA strand breakage and sex chromosome non-disjunction in spermatogenesis.

Sram et al. (Sram 2004) reported on their use of a fluorescence in situ hybridization (FISH) technique with whole chromosome painting to detect chromosomal aberrations in 383 AN-exposed petrochemical workers and controls. No effect was observed with AN exposures less than 0.3 mg/m^3.

Beskid et al. (Beskid 2006) studied patterns of chromosomal aberrations using FISH painting (whole chromosomes #1 and #4) in workers occupationally exposed to any of the following acrylonitrile (AN), ethyl benzene (EB), carcinogenic polycyclic aromatic hydrocarbons (c-PAHs), and irradiation in nuclear power plants (NPP). An increase in reciprocal translocations was observed in the AN and NPP-exposed groups. An increase in the relative number of insertions was registered under all four conditions (significant in the AN, EB, c-PAH exposed groups, and marginally significant in the NPP-exposed group). Significant differences in the percentage of lymphocytes with aberrations on chromosome #1 (58.8+/-32.7%, versus 73.8+/-33.6% in the controls, $P < 0.05$), and chromosome #4 (47.0+/-34.1%, versus 29.4+/-32.2%, $P < 0.01$) were found in workers exposed to AN. Similarly, a decrease in the proportion of cells with aberrations on chromosome #1 (61.0+/-24.0%, versus 73.8+/-33.6%, $P < 0.05$) and an increase on chromosome #4 (45.6+/-24.6%, versus 29.4+/-32.2%, $P < 0.05$) were observed in workers exposed to EB. Frequency of aberrant cells as well as genomic frequency of translocations increased with age ($P < 0.001$). Aging also increased the percentage of translocations and reciprocal translocations ($P < 0.05$), but decreased the relative number of acentric fragments ($P < 0.01$). Smoking led to significantly increased genomic frequency of translocations ($P < 0.05$), but did not affect the pattern of chromosomal aberrations. Thus, different carcinogens may induce different patterns of chromosomal aberrations.

V. Quantitative Assessment

Acute Exposure

The NCSAB has selected the critical studies of acute human exposure summarized in TABLE 5:

TABLE 5 – Summary of Acute Exposure Studies in Humans

Study	Concentration (ppm)	Duration	Results
(Wilson 1948)	16 – 100 (35–217 mg/m^3)	20-45 minutes	Headache, nasal and ocular irritation, chest discomfort, nervousness, irritability
(Jakubowki 1987)	2.3, 4.6 (5-10 mg/m^3)	8 hrs.	No symptoms

The data from (Jakubowski 1987) indicate that a 4.6ppm (10 mg/m^3) exposure over an 8-hour period produced no acutely toxic effects. This exposure concentration is thus an appropriate candidate for an acute exposure AAL. Further, since this exposure took place over an 8-hour period, limiting the exposure time to a 1-hour period would provide and additional measure of protection.

Jakubowski et al. used "healthy workers", and since there is likely to be a range of sensitivities to AN exposure in the general population, an uncertainty factor of 10 is applied.

Table 6 – Point of Departure, and Candidate AAL for Acute Exposure

Study	Points of Departure (mg/m^3)	Candidate AALs (mg/m^3)
(Jakubowski 1987)	10	1.0

Chronic Exposure, Non-Cancer Endpoints

Animal Studies

Quast et al. (Quast 1980a) exposed Sprague-Dawley rats (100 per sex per group) to acrylonitrile vapor concentrations of 0, 20, and 80 ppm (0, 43, 176 mg/m^3) in a chronic inhalation study. Exposure to AN vapor was for 6 hours/day, 5 days/week, 2 years. It was found that there were treatment-related effects in the nasal turbinates (hyperplasia and metaplasia of the nasal turbinates, and hyperplasia of the mucus-secreting cells) in all rats exposed to 176 mg/m^3, and some of those exposed at 43 mg/m^3. It was concluded that the effects noted were due to the irritant nature of AN. Given that 43mg/m^3 is a LOAEL, adjusting this exposure concentration yields,

$$LOAEL_{adj} = 43\frac{mg}{m^3} \times \frac{6hrs}{24hrs} \times \frac{5days}{7days} = 7.7\frac{mg}{m^3}$$

Using the USEPA approach in The Integrated Risk Information System (IRIS), the adjusted LOAEL was converted to a human equivalent dose by multiplying the adjusted LOAEL by the Regional Gas Dose Ratio (RGDR). AN is a category 1 gas (gas that is highly water soluble and/or rapidly irreversibly reactive in the surface-liquid/tissue of the respiratory tract) and the effect is seen in the extrathoracic region (irritation to the nasal mucosa)

$$LOAEL_{HEC} = LOAEL_{adj} \times RGDR_{cat\ 1,ET}$$

The RGDR determined by USEPA for a category 1 gas and an extrathoracic effect is 0.252.

$$LOAEL_{HEC} = LOAEL_{adj} \times RGDR_{cat\ 1,ET} = 7.7\frac{mg}{m^3} \times 0.252 = 1.9\frac{mg}{m^3}$$

This is the point of departure.

The NCSAB then applied the following uncertainty factors to this point of departure:

Uncertainty Factor **Value** **Rationale**

LOAEL to NOAEL	3	Non-severe irritation endpoint
Interspecies Variability	3	Some of the variability is accounted for by means of dosimetric adjustments
Intraspecies Variability	10	Accounts for sensitive individuals in the general population
Study Duration	1	Chronic study
Database Completeness	1	The AN database is robust
TOTAL UNCERTAINTY	**100**	

$$candidate\ AAL = \frac{point\ of\ departure}{total\ uncertainty} = \frac{1.9\frac{mg}{m^3}}{100} = 0.02\frac{mg}{m^3}$$

Kirman et al. (Kirman 2008) used a modeling approach to derive chronic and subchronic inhalation reference values for AN. To derive a chronic inhalation reference value using nasal lesions as the endpoint, Kirman et al. also used (Quast 1980a) as the critical study; to derive a subchronic inhalation reference value, (Nemec 2008) was used. Based on Benchmark Dose modeling with a default response level of 10% for extra risk, a log-logistic model was reported to provide the best overall fit to these data. A $BMCL_{10}$ of 0.64 mg/m^3 was obtained with the chronic data; a $BMCL_{10}$ of 1.2 mg/m^3 was obtained with the subchronic data. Kirman et al. then applied the following uncertainty factors to these data:

Uncertainty Factor	**Value**	**Rationale**
LOAEL to NOAEL	1	BMD methods used, reliance on LOAEL not required
Interspecies Variability	3	Some of the variability is accounted for by means of dosimetric adjustments
Intraspecies Variability	3	Nasal lesions are "…not expected to depend on systemic factors that may vary from one individual to another…"
Study Duration	1	(Chronic study = 1), (subchronic study = 1)
Database Completeness	1	The AN database is robust
TOTAL UNCERTAINTY	**10**	

A chronic reference value of 0.06 mg/m^3 (0.64 mg/m^3/10) and a subchronic reference value of 0.12 mg/m^3 (1.2 mg/m^3/10) resulted from the Kirman et al. analyses (Kirman 2008).

Human Studies

The NCSAB selected Muto et. al. (Muto 1992) as the critical study to be used in developing a candidate AAL for chronic human exposure. Muto et al. conducted a cross-sectional study of 157 exposed and 537 unexposed workers in acrylic fiber factories. The average exposure for the exposed group was 0.53 ppm (1.15 mg/m^3) AN. These workers underwent a wide range of clinical tests including liver function studies, and there was no consistent evidence of adverse health effects arising from exposure. The findings in Muto et. al. were consistent with those of Sakurai et al. (Sakurai 1978) who found no liver effects in workers exposed to an average of 0.1 and 0.5 ppm (1 mg/m^3) acrylonitrile

If 1.15 mg/m^3 is taken to be a NOAEL, then

$$NOAEL_{adj} = 1.15\frac{mg}{m^3} \times \frac{8hrs}{24hrs} \times \frac{5days}{7days} = 0.27\frac{mg}{m^3}$$

$$candidate\ point\ of\ departure = 0.27\frac{mg}{m^3}$$

Sakurai et al. (Sakurai 1978), provided results from a cross-sectional epidemiological study of 102 workers randomly selected from 6 acrylic fiber production plants in Japan exposed to AN for at least 5 years age-matched with 62 non-exposed workers Average exposure was 0.1 ppm (0.2 mg/m^3) in the three plants with the lowest exposure; 0.5 ppm (1.1 mg/m^3) in two plants characterized as having "intermediate exposure;" and 4.2 ppm (9.1 mg/m^3) in one plant having the highest AN exposures. Medical examinations that included clinical chemistry tests did not detect any significant differences between exposed and control groups. Physical examination noted a "slightly higher" incidence of redness of the eyes and throat and a palpable liver in the highest exposed group (4.2 ppm) relative to that in the control group. No effects were seen in the groups exposed to 0.1 or 0.5 ppm.

If 0.5 ppm (1 mg/m^3) is taken to be a NOAEL, then

$$NOAEL_{adj} = 1\frac{mg}{m^3} \times \frac{8hrs}{24hrs} \times \frac{5days}{7days} = 0.24\frac{mg}{m^3}$$

$$candidate\ point\ of\ departure = 0.24\frac{mg}{m^3}$$

The NCSAB applied the following uncertainty factors to these candidate points of departure:

Uncertainty Factor	Value	Rationale
LOAEL to NOAEL	1	NOAEL used
Interspecies Variability	1	Human studies used
Intraspecies Variability	10	Accounts for sensitive individuals in the general population
Study Duration	1	Chronic study
Database Completeness	1	The AN database is robust
TOTAL UNCERTAINTY	**10**	

Applying the total uncertainty factor to the PODs yields candidate AALs listed in Table 7:

Table 7 – Points of Departure, Range of Risk, and Candidate AALs for Acute Exposure

Study	Candidate AAL (mg/m^3)
Muto (1992)	0.027
Sakurai (1978)	0.024

Cancer Endpoints

Animal Studies

The NCSAB selected (Quast 1980a) and (Kirman 2005) as the critical animal studies with which to evaluate cancer endpoints.

Quast et al. (Quast 1980a) exposed Sprague-Dawley rats (Spartan substrain) (100/sex/exposure level) via inhalation for two years at 6-hr/day, 5 days/week. The incidence of brain tumors was the primary endpoint of concern. Exposure-response data reported are:

Exposure Concentration (mg/m^3)	Brain Tumor Response		
	Males	Females	Total
0	0/100	0/100	0/200
44	4/99	8/100	12/199
176	22/99	21/100	43/199

Benchmark Dose (version 1.4.1c) modeling using a multi-stage cancer model on total (male + female) brain tumors (extra risk = 10%) yielded a benchmark concentration (BMC) = 75.8 mg/m^3 with a lower limit (BMCL) = 61.2 mg/m^3 (goodness of fit p = 0.998). A cancer potency factor was derived by dividing the extra risk by the BMCL = 1.6 x 10^{-3} per mg/m^3. The NCSAB used a risk level of 10^{-5} to generate a candidate AAL from these rodent data as follows:

$$candidate\ AAL = \frac{Risk\ Level}{Cancer\ Potency\ Factor} = \frac{10^{-5}}{\frac{1.6\times10^{-3}}{mg/m^3}} = 6.2\times10^{-3}\,\frac{mg}{m^3}$$

Kirman et al. also conducted a dose-response assessment (Kirman 2005) using brain tumors in rats as the critical endpoint. Twelve datasets were extracted from six studies (Maltoni 1978; Quast 1980a; Quast 1980b; Maltoni 1988; Johanssen 2002a; Johanssen 2002b), combining inhalation and ingestion exposure routes in this analysis. *NOTE: the Quast studies (Quast 1980a; Quast 1980b) were both used in the Kirman analysis.* PBPK modeling was used to predict internal peak CEO concentration resulting from the AN exposures. Benchmark Dose modeling yielded ED_{05}/LED_{05} values of 0.017mg/L / 0.014mg/L for these data. These were deemed to be appropriate points of departure. The human equivalent concentrations corresponding to the ED_{05} and the LED_{05} were determined by manual iteration of the PBPK model until the human equivalent internal dose agreed with the internal point of departure estimates. The resulting human equivalent airborne AN concentrations were reported to be 25.9 (ED_{05}) and 21.3 mg/m^3 (LED_{05}).

A cancer potency factor (linear, non-threshold approach) based on the LED_{05} and the response level was determined to be:

$$Cancer\ Potency\ Factor = \frac{Response\ Level}{LED_{05}} = \frac{0.05}{21.3\frac{mg}{m^3}} = 2.35\times10^{-3}\ per\ \frac{mg}{m^3}$$

A risk level of 1 in 100,000 (10^{-5}) yields a candidate AAL of:

$$candidate\ AAL = \frac{Risk\ Level}{Cancer\ Potency\ Factor} = \frac{10^{-5}}{\frac{2.35\times10^{-3}}{mg/m^3}} = 4.3\times10^{-3}\,\frac{mg}{m^3}$$

In addition to the linear, non-threshold approach, a non-linear, threshold approach was used by Kirman et al. to derive a "cancer reference dose." Kirman et al. used the same point of departure (discussed above) for this approach, and applied uncertainty factors to it to produce a cancer reference dose. For the exposure-response assessment, The NCSAB applied the following uncertainty factors:

Uncertainty Type	Uncertainty Value	Rationale
UF_a Interspecies Factor	3.2	Kinetic component = 1, dynamic component = 3.2
UF_h Intraspecies Factor	7.0	Kinetic component = 2.2, dynamic component = 3.2
UF_l LOAEL to NOAEL	1	Not used by the NCSAB
UF_s Chronic-Subchronic	1	Not used by the NCSAB
UF_d Database Factor	1	Not used by the NCSAB
TOTAL Uncertainty Factor	22	

A "cancer reference concentration" resulting from this non-linear, threshold approach would be:

$$Cancer\ Reference\ Concentration = \frac{LED_{05}}{Total\ Uncertainty\ Factor} = \frac{21.3\frac{mg}{m^3}}{22} = 1.0\,\frac{mg}{m^3}$$

In summary, the following are candidate AALs for a cancer endpoint based on animal studies include:

Table 9 – AAL Candidate Range of Risk for Cancer Endpoints based on Animal Studies

Study	Candidate AAL (mg/m^3)
Quast (1980b)	6.2×10^{-3}
Kirman (2005)	4.3×10^{-3}
Kirman (2005) (Non-linear, threshold)	1.0

Human Studies

In 1987 IARC classified AN as *probably carcinogenic to humans* based on information available at the time of the classification (IARC 1987). However, in 1999, IARC reclassified AN as *possibly carcinogenic to humans* based on additional, more recent, negative epidemiologic studies that showed at most a weak association between AN exposure and cancer in workers (IARC 1999). Since 1999, newly published epidemiologic studies and follow-ups to previously published studies have supported the conclusion that AN is at most a weak carcinogen in humans, possibly showing effects only at very high exposure levels. Symons et al. (Symons 2008) reported that there are no detectable effects in humans at much higher exposure levels than were reported in the NCI study (Blair 1998). Dr. Collins reinforced this conclusion in his presentation to the NCSAB on recent AN epidemiology.

The World Health Organization (IPCS 2002) has stated that "…Although the database is relatively extensive, there is no consistent, convincing evidence of an association between exposure to acrylonitrile and cancer of a particular site that fulfills traditional criteria for causality in epidemiological studies…"

In view of the lack of a consistent body of evidence for the carcinogenicity of acrylonitrile in man and the absence of a significant dose-response relationship between AN exposure and cancer outcomes, the NCSAB has concluded that neither a linear non-threshold approach nor a threshold approach for estimating potential human cancer risk from AN exposure is appropriate. The NCSAB therefore recommends that a non-cancer endpoint be utilized in determining a chronic AAL for acrylonitrile.

VI. Sources of Uncertainty

The NCSAB, by unanimous agreement of its members, has chosen not to propose a cancer-based AAL for AN. There are two main reasons for this:

- The evidence supporting the carcinogenicity of AN in humans is unconvincing, as demonstrated repeatedly in follow-up studies of the most highly exposed worker cohorts. While a statistically significant excess of lung cancer mortality was reported by Blair et al. (Blair 1998) for a cohort in excess of 25,000 workers, this excess was confined to the highest quintile of cumulative exposure, and a more refined analysis using cumulative exposure deciles revealed no further increase in relative risk at the highest levels of exposure. Blair et al. concluded that their analyses of exposure-response "do not provide strong or consistent evidence for a causal association."

- While there is little doubt that AN is a rodent carcinogen, there is a striking discordance between the findings in rats (brain cancer) and mice (forestomach and Harderian gland tumors) via the oral route that calls into question the utility of extrapolation of findings from rats to mice, and by extension, from either rodent to humans. Furthermore, the recent mechanistic work by Pu et al. (Pu 2006) suggests that reactive oxygen species related to toxicity induced by high AN doses appears to play a critical role in its carcinogenicity in the highly sensitive rat brain. Such a high-dose mode of carcinogenic action in a single species-specific target organ is not expected to be operative in humans at the far lower environmental exposure levels typified by a chronic AAL.

While uncertainty remains regarding the potential relevance of the animal findings to humans, the NCSAB prefers to rely on the human evidence in assessing the potential human carcinogenicity of AN, and as was noted previously, this evidence is unconvincing.

Available evidence provides little support for AN having a direct DNA-reactive MOA for the induction of genotoxic effects or cancer. Available in vitro studies provide more support for a non-DNA reactive or indirect MOA. All published studies of mutational effects in AN-treated animals are negative (see (Rabello-Gay 1980; Leonard 1981; Zhurkov 1983; Sharief 1986; Working 1987; Morita 1997; Nestorova 1999). A causal connection between genotoxicity and increased brain tumor incidence has not been demonstrated. However, there is relevant evidence that AN possesses genotoxic and carcinogenic activity by acting indirectly in the production of brain tumors in the rat, possibly via a high-dose mechanism involving oxidative stress and changes in gap junctional communication (see (Jiang 1998; Whysner 1998; Ghosh 1999; Kamendulis 1999; Zhang, Kamendulis 2000).

VII. Recommendations

The NCSAB recommends that based on the most sensitive endpoint, irritation, an acute exposure AAL for acrylonitrile be established at a concentration of 1 mg/m^3. The Division of Air Quality recommends an averaging time of 1 hour for this recommended AAL.

The NCSAB recommends that based on the most sensitive endpoint, irritation, a chronic exposure AAL for acrylonitrile be established at a concentration of 0.03 mg/m^3. The Division of Air Quality recommends an averaging time of 24 hours for this recommended AAL.

The NCSAB recommends that the existing AAL for acrylonitrile, 1.5×10^{-4} mg/m^3, based on carcinogenicity, be replaced with the aforementioned acute and chronic exposure AALs.

Table 4-1. Summary of Risk Measures for Selected Cancer Types from Epidemiological Studies

Cohort Description	Reference	Number	Study Period	Exposure Period	Quant. Exposure Estimates	Response Measure	Total Cancer	Lung	Brain/NS	Prostate	Other (Type)
Dupont Workers	O'Berg (1980)	1345	1956-1976	1950-1966	No	M[1] (O/E) I[2] (O/E)	20/17.4-24.5 (M) 25/20.5 (I)	8/6.1 (M) 8/4.4 (I) **8/3.4 (I-wage)**	NR NR	NR 3/0.9	NR 3/2.2 (colon)
	O'Berg *et al.* (1985)	1345	1957-1981 (M) 1957-1983 (I)	1950-1966	No	M (O/E) I (O/E)	36/31.6 (M) 43/36.7 (I)	14/11.6 (M) 10/7.2 (I)	NR	1/1.0 (M) **6/1.5-1.8 (I)**	4/3.7 (lymph M) 7/3.7 (lymph I) 3/0.6 (bladder M) 4/1.7 (bladder I) 8/8.2 (digestive M) 5/7.4 (digestive I)
	Burke (1985a, unpublished)	472	1962-1983	NR	No	M (O/E) I (O/E)	4/2.8 (M) 13/9.1 (I) 10/7.9 (I-wage)	1/NR (M) 2/1.3 (I)	NR	NR (M) 1/NR (I)	--
	Burke (1985b, unpublished)	700	1957-1983	NR	No	M (O/E) I (O/E)	5/4.7-6.2 (M) 11/10.1-12.0 (I)	1/NR (M) 0/NR (I)	NR	NR	--
	Chen *et al.* (1987)	1083	1956-1981 (M) 1956-1983 (I)	1944-1970	No	M (O/E) I (O/E)	21/30-36.4 (M) 37/36.5 (I)	7/7.9-8.8 (M) 5/6.9 (I)	NR (M) 1/1.2 (I)	1/0.9 (M) 5/1.9 (I) **4/0.9 (I-wage)**	4/2.2-2.7 (lymph M) 2/0.7 (lymph I) 5/3.4 (colon I)
	Chen *et al.* (1988a)	1335	1950-1984	1950-1970	No	I (O/E)	41/39.8	10/9.4	NR	6/2.7 **6/2.3 (wage)**	3/2.1 (bladder) 7/4.4 (lymph)
	Chen *et al.* (1988b)	1335	1950-1982	1950-1970	No	M (O/E)	37/36.3	14/13.2	2/1.6	NR	3/0.7 (bladder) 4/4.3 (lymph) 8/9.1 (digestive)
	Wood *et al.* (1998)	2559	1944-1991	1944-1991	Yes	M (SMR) I (SIR)	78 (64-93) (M) 97 (79-118) (I)	74 (55-99) (M) 86 (54-130) (I)	113 (41-247) (M) 111 (30-285) (I)	129 (64-230) (M) 158 (82-276) (I)	115 (31-295) (bladder M) 69 (19-177) (bladder I) 57 (26-109) (lymph M) 0 (--) (lymph I) 69 (45-100) (digestive M) 89 (56-134) (digestive I)
Dutch Workers	Swaen *et al.* (1992)	2842	1956-1988	1956-1979	Yes	M (O/E)	42/50.82	16/19.5	3/1.71	2/1.22	6/7.19 (digestive) 0/1.25 (bladder) 0/2.48 (lymph)
	Swaen *et al.* (1998)	2842	1956-1995	1956-1979	Yes	M (O/E)	97/110.78	47/42.82	6/3.45	4/4.8	3/3.07 (bladder) 11/15.1 (digestive)
	Swaen *et al.* (2004)	2842	1956-2001	1956-1979	Yes	M (O/E)	146/164.5	67/62.5	6/4.8	8/8.7	5/4.6 (bladder)
UK Workers	Werner & Carter (1981)	1111	1950-1978	1950-1968	No	M (O/E)	21/18.6	9/7.6 Total **3/0**	NR	NR	**5/1.9 (stomach)**
	Benn & Osbourne (1998)	2763	1950-1991	1950-1978	Yes	M (O/E)	121/137.12	53/51.54	NR	NR	11/11.44 (stomach) 5/10.02 (lymph) 11/8.75 (colon)
NCI/NIOSH	Zack (1980, unpublished)	352	1952-1977	1952-1968	No	M (O/E)	3/2.8	1/0.8	NR	1/0.03	--
	Gaffey & Strauss (1981, unpublished)	325	1952-1977	1952-1953	No	M (O/E)	4/11	2/3.7	NR	NR	2/0.3 (kidney)
	Collins *et al.* (1989)	1774	1951-1983	1951-1973	Yes	M (O/E)	43/42.6	15/15.8	1/1.8	2/1.34	5/4.8 (lymph) 8/10.25 (digestive)
	Blair *et al.* (1998)	15080 men 5190 women	1952-1989	1952-1983	Yes	M (SMR)	0.8 (0.7-0.9)	0.9 (0.8-1.1) **2.1**	0.7 (0.4-1.3)	0.9 (0.6-1.5)	0.8 (0.4-1.4) (stomach) 0.8 (0.4-1.8) (bladder)
	Marsh *et al.* (2001)	15080 men 5190 women	1952-1989	1952-1983	Yes	M (SMR)	NR	0.74-0.9 (0.6-1.1)	0.69-0.74 (0.4-1.3)	0.92-0.95 (0.5-1.5)	0.79-0.85 (0.4-1.5) (stomach)
Individual Cohorts	Monson (1978, unpublished)	NR	NR	NR	No	M (O/E)	NS increase	NR	NR	NR	--
	Kiesselbach *et al.* (1979)	881	1950-1977	1950-1965	No	M (O/E)	20/20.1	6/6.9	NR	NR	1/3 (stomach)
	Theiss *et al.* (1980)	1469	1956-1978	1956-1978	No	M (O/E)	27/20.5	11/5.6	NR	NR	4/1.7 (lymph)
	Ott *et al.* (1980)	100	1940-1975	1940-1975	Yes	M (O/E)	NR	1/0.5	NR	NR	3/1.25 (leukema)
	Herman (1981, unpublished)	1077	1951-1977	1951-1977	No	M (O/E)	11/16.1 (total) 4/11.2 (wage)	1/3.7 (wage)	NR	NR	--
	Delzell and Monson (1982)	327	1940-1978	1940-1971	No	M (O/E)	22/17.9	9/4.7-5.9	NR	NR	4/5.0 (digestive) 2/0.5 (bladder) 4/1.8 (lymph)
	Stallard (1982, unpublished)	419	1960-1980	1960-1980	No	M (O/E)	4/5.0	2/1.6	NR	NR	--
	Marsh (1983)	2490	1949-1976	1949-1966	No	M (SMR)	NR	NR	NR	**153.6 (cohort)**	101.8 (digestive-cohort)
	Zhou & Wang (1991)	1811	1971-1988	1971-1988	Yes	M (SMR)	1.25	NR	NR	NR	--
	Ives *et al.* (1993)	894	1960-1988	1960-1985	Yes	M (SMR)	0.91	1	NR	NR	1.15 (digestive)
	Mastrangelo *et al.* (1993)	671	1959-1990	1959-1988	No	M (SMR)	NR	0.8 (0.1-2.9)	2.6(9.1-14.7)	NR	3.4 (0.4-12.3) (stomach)
Support Cohort & Case Control	Waxweiler *et al.* (1981)	4806	1942-1973	1942-1973	No	M	NR	NR	NR	NR	--
	Siemiatycki *et al.* (1994)	484	1979-1986								
	Thomas *et al.* (1987)	300	1978-1981	NR	No	M (OR)	300	--	0.9 (0.5-1.6)	--	--
	Ott *et al.* (1989)	129	1940-1978		No	M (OR)	129	NR	NR	NR	**3.2 (non-Hodgkins OR)**
Meta-Analysis	Rothman (1994)	10835	1940-1988	1940-1979	No	M (O/E)	224/218.2	85/79.4	NR	NR	--
	Collins & Acquavella (1998)	51844	1940-1996	1940-1991	No	M (O/E) I (O/E)	0.9 (0.8-0.9) (M) 1.0 (0.8-1.2) (I)	0.9 (0.8-1.1) (M) 0.8 (0.5-1.2) (I)	1.1 (0.8-1.5) (M) 1.1 (0.4-3.1) (I)	1.0 (0.7-1.5) (M) 1.4 (0.8-2.6) (I)	0.9 (0.6-1.2) (stomach M) 0.3 (0.0-2.1) (stomach I) 1.4 (0.9-2.0) (bladder M) 0.8 (0.3-2.2) (bladder I)
	EU (2001)	50476	1940-1996	1940-1991	No	M (O/E) I (O/E)	0.9 (0.8-0.9) (M) 1.0 (0.8-1.2) (I)	0.9 (0.8-1.1) (M) 0.8 (0.5-1.2) (I)	1.1 (0.8-1.5) (M) 1.1 (0.4-3.1) (I)	1.0 (0.7-1.5) (M) 1.4 (0.8-2.6) (I)	0.9 (0.6-1.2) (stomach - M) 0.3 (0.0-2.1) (stomach - I) 1.1 (0.7-1.7) (bladder - M) 0.8 (0.3-2.2) (bladder - I)

Bolded red values indicate statistically significant results

[1] M = Mortality

[2] I = Incidence

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