ACRYLONITRILE

This substance was considered by previous Working Groups, in February 1978 (IARC, 1979) and March 1987 (IARC, 1987a). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Chemical and physical data

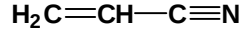
1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 107-13-1

Chem. Abstr. Name: 2-Propenenitrile

Synonyms: AN; cyanoethylene; propenenitrile; VCN; vinyl cyanide

1.1.2 *Structural and molecular formulae and relative molecular mass*



C_3H_3N Relative molecular mass: 53.06

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless liquid (Verschueren, 1996)

(*b*) *Boiling-point*: 77.3°C (Lide, 1995)

(*c*) *Melting-point*: –83.5°C (Lide, 1995)

(*d*) *Density*: d_4^{20} 0.8060 (Lide, 1995)

(*e*) *Spectroscopy data*: Infrared, nuclear magnetic resonance and mass spectral data have been reported (Sadtler Research Laboratories, 1980; Brazdil, 1991)

(*f*) *Solubility*: Soluble in water (7.35 mL/100 mL at 20°C); very soluble in acetone, benzene, diethyl ether and ethanol (Lide, 1995; Budavari, 1996)

(*g*) *Volatility*: Vapour pressure, 13.3 kPa at 23°C; relative vapour density (air = 1), 1.83 (Verschueren, 1996)

(*h*) *Stability*: Flash-point (open cup), 0°C; flammable; polymerizes spontaneously, particularly in the absence of oxygen, on exposure to visible light and in contact with concentrated alkali (Budavari, 1996)

(*i*) *Explosive limits*: Lower, 3.05%; upper, 17.0% (Budavari, 1996)

(*j*) *Octanol/water partition coefficient (P)*: log *P*, 0.25 (Hansch *et al*., 1995)

(*k*) *Conversion factor*: $mg/m^3 = 2.17 \times ppm$[1]

1.1.4 *Technical products and impurities*

Acrylonitrile of 99.5–99.7% purity is available commercially, with the following specifications (ppm by weight, maximum): acidity (as acetic acid), 10; acetone, 75; acetonitrile, 300; acrolein, 1; hydrogen cyanide, 5; total iron, 0.1; oxazole, 10; peroxides (as hydrogen peroxide), 0.2; water, 0.5%; and nonvolatile matter, 100. Hydroquinone monomethyl ether (MEHQ) is added as an inhibitor at concentrations of 35–45 mg/kg (ppm) (Cytec Industries, 1994, 1997). Trade names for acrylonitrile include Acritet, Acrylon, Carbacryl, Fumigrain and Ventox.

1.1.5 *Analysis*

Selected methods for the analysis of acrylonitrile in various matrices are presented in Table 1.

Table 1. Methods for the analysis of acrylonitrile[a]

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Air	Adsorb (charcoal); extract (acetone)	GC/NPD	26 μg/m^3	US Occupational Safety and Health Administration (1990) [Method 37]
	Adsorb (charcoal); extract (acetone in carbon disulfide)	GC/FID	1 μg/sample	Eller (1994) [Method 1604]
Water	Purge (inert gas); trap (Porapak-QS; Chromosorb 101); desorb as vapour (heat to 180°C, backflush with inert gas) onto GC column	GC/FID	0.5 μg/L	US Environmental Protection Agency (1996a) [Method 603] (1986) [Method 8030]
	Add internal standard (isotope-labelled dichloromethane); purge; trap and desorb as above	GC/MS	50 μg/L	US Environmental Protection Agency (1996b) [Method 1624]
Plastics, liquid foods	Dissolve in *ortho*-dichlorobenzene; inject headspace sample	GC/FID	2–20 μg/kg	US Food and Drug Administration (1987)
Solid foods	Cut or mash sample; inject headspace sample	GC/FID	2–20 μg/kg	US Food and Drug Administration (1987)

[a] Abbreviations: GC/FID, gas chromatography/flame ionization detection; GC/MS, gas chromatography/mass spectrometry; GC/NPD, gas chromatography/nitrogen-phosphorus detection

[1] Calculated from: mg/m^3 = (relative molecular mass/24.47) × ppm, assuming a temperature of 25°C and a pressure of 101 kPa

Exposure to acrylonitrile can be determined by measuring parent acrylonitrile, acrylonitrile metabolites, and adducts. Acrylonitrile metabolites have been measured in blood and urine, but, except for measurement of thiocyanate, these methods have not been developed for routine monitoring of exposed humans (Agency for Toxic Substances and Disease Registry, 1990).

1.2 Production and use

1.2.1 *Production*

Acrylonitrile was first prepared in 1893 by dehydration of either acrylamide or ethylene cyanohydrin with phosphorus pentoxide (Fugate, 1963).

Until 1960, acrylonitrile was produced commercially by processes based on hydrogen cyanide and ethylene oxide or acetylene. The growth in demand for acrylic fibres, starting with the introduction of Orlon by DuPont around 1950, spurred efforts to develop improved process technology for acrylonitrile manufacture. This resulted in the discovery in the late 1950s of a heterogeneous vapour-phase catalytic process for acrylonitrile by selective oxidation of propylene and ammonia, commonly referred to as the propylene ammoxidation process. Commercial introduction of this lower-cost process by Sohio in 1960 resulted in the eventual displacement of all other acrylonitrile manufacturing processes. Today, the ammoxidation process accounts for over 90% of the approximately 4000 thousand tonnes produced worldwide each year. In this process, propylene, ammonia and air react in the vapour phase in the presence of a catalyst (bismuth–iron; bismuth–phosphomolybdate; antimony–uranium; ferrobismuth–phosphomolybdate). Hydrogen cyanide and acetonitrile are the chief by-products formed. Sulfuric acid is used to remove excess ammonia from the reaction mixture, and the nitrile compounds are removed by absorption in water. High-purity acrylonitrile is obtained by a series of distillations (Langvardt, 1985; Brazdil, 1991).

Acrylonitrile was first produced in Germany and the United States on an industrial scale in the early 1940s. These processes were based on the catalytic dehydration of ethylene cyanohydrin. Ethylene cyanohydrin was produced from ethylene oxide and aqueous hydrocyanic acid at 60°C in the presence of a basic catalyst. The intermediate was then dehydrated in the liquid phase at 200°C in the presence of magnesium carbonate and alkaline or alkaline earth salts of formic acid. A second commercial route to acrylonitrile was the catalytic addition of hydrogen cyanide to acetylene. The last commercial plants using these process technologies were shut down in 1970 (Langvardt, 1985; Brazdil, 1991).

Worldwide production of acrylonitrile in 1988 was about 3200 thousand tonnes, with the following breakdown (thousand tonnes): western Europe, 1200; United States, 1170; Japan, 600; the Far East, 200; and Mexico, 60 (Brazdil, 1991). Production in the United States has been reported as (thousand tonnes): 1981, 906; 1984, 1006; 1987, 990; 1990, 1214; 1993, 1129; 1996, 1530. Production in Japan has been reported as (thousand tonnes): 1981, 477; 1984, 523; 1987, 573; 1990, 593; 1993, 594; 1996, 675 (Anon., 1985, 1988, 1991, 1994, 1997).

1.2.2 *Use*

Worldwide consumption of acrylonitrile increased 52% between 1976 and 1988, from 2500 to 3800 thousand tonnes per year. The trend in consumption over this time period is shown in Table 2 for the principal uses of acrylonitrile: acrylic fibre, acrylonitrile–butadiene–styrene (ABS) resins, adiponitrile, nitrile rubbers, elastomers and styrene–acrylonitrile (SAN) resins. Since the 1960s, acrylic fibres have remained the major outlet for acrylonitrile production in the United States and especially in Japan and the Far East. Acrylic fibres always contain a comonomer. Fibres containing 85 wt% or more acrylonitrile are usually referred to as 'acrylics' and fibres containing 35–85 wt% acrylonitrile are called 'modacrylics'. Acrylic fibres are used primarily for the manufacture of apparel, including sweaters, fleece wear and sportswear, and home furnishings, including carpets, upholstery and draperies (Langvardt, 1985; Brazdil, 1991).

The production of ABS and SAN resins consumes the second largest quantity of acrylonitrile. The ABS resins are produced by grafting acrylonitrile and styrene onto polybutadiene or a styrene–butadiene copolymer and contain about 25 wt% acrylonitrile. These products are used to make components for automotive and recreational vehicles, pipe fittings, and appliances. The SAN resins are styrene–acrylonitrile copolymers containing 25–30 wt% of acrylonitrile. The superior clarity of SAN resin allows it to be used in automobile instrument panels, for instrument lenses and for houseware items (Langvardt, 1985; Brazdil, 1991).

The chemical intermediates adiponitrile and acrylamide have surpassed nitrile rubbers as end-use products of acrylonitrile in the United States and Japan. Adiponitrile is further converted to hexamethylenediamine (HMDA), which is used to manufacture nylon 6/6. Acrylamide is used to produce water-soluble polymers or copolymers used for paper manufacturing, waste treatment, mining applications and enhanced oil recovery (Langvardt, 1985; Brazdil, 1991).

Nitrile rubbers, the original driving force behind acrylonitrile production, have taken a less significant place as end-use products. They are butadiene–acrylonitrile copolymers with an acrylonitrile content ranging from 15 to 45%, and find industrial applications in

Table 2. Worldwide acrylonitrile uses and consumption (thousand tonnes)[a]

Use	1976	1980	1985	1988
Acrylic fibres	1760	2040	2410	2520
Acrylonitrile–butadiene–styrene resins	270	300	435	550
Adiponitrile	90	160	235	310
Other (including nitrile rubber, styrene–acrylonitrile resin, acrylamide, and barrier resins)	420	240	390	460

[a] From Brazdil (1991)

areas where their oil resistance and low-temperature flexibility are important, such as in the fabrication of seals (O-rings), fuel hoses and oil-well equipment. New applications have emerged with the development of nitrile rubber blends with poly(vinyl chloride) (PVC). These blends combine the chemical resistance and low-temperature flexibility characteristics of nitrile rubber with the stability and ozone resistance of PVC. This has greatly expanded the use of nitrile rubber in outdoor applications for hoses, belts and cable jackets (Langvardt, 1985; Brazdil, 1991).

Other acrylonitrile copolymers have found specialty applications where good gas-barrier properties are required along with strength and high impact resistance. These barrier resins compete directly with traditional glass and metal containers as well as with poly(ethylene terephthalate) (PET) and PVC in the beverage bottle market. Other applications include packaging for food, agricultural chemicals and medicines (Brazdil, 1991).

A growing specialty application for acrylonitrile is in the manufacture of carbon fibres. These are produced by pyrolysis of oriented polyacrylonitrile fibres and are used to reinforce composites for high-performance applications in the aircraft, defence and aerospace industries. Other minor specialty applications of acrylonitrile are in the production of fatty amines, ion exchange resins and fatty amine amides used in cosmetics, adhesives, corrosion inhibitors and water-treatment resins (Brazdil, 1991).

In the past, acrylonitrile was used with carbon tetrachloride as a fumigant for tobacco and in flour milling and bakery food processing (Suta, 1979). Most pesticides containing acrylonitrile have now been withdrawn (Worthing & Hance, 1991).

1.3 Occurrence

1.3.1 *Natural occurrence*

Acrylonitrile is not known to occur as a natural product.

1.3.2 *Occupational exposure*

According to the 1990–93 CAREX database for 15 countries of the European Union (Kauppinen *et al.*, 1998) and the 1981–83 United States National Occupational Exposure Survey (NOES, 1997), approximately 35 000 workers in Europe and as many as 80 000 workers in the United States were potentially exposed to acrylonitrile (see General Remarks). Occupational exposures to acrylonitrile have been measured in monomer production and in the production of fibres, resins, polymers and other chemical intermediates from acrylonitrile.

(*a*) *Monomer production*

Surveys have reported full-shift personal exposures measured by the companies and the study investigators in four acrylonitrile production plants in the United States (Zey *et al.*, 1989; Zey & McCammon, 1990; Zey *et al*., 1990a,b). The monomer production operators had 8-h time-weighted average (TWA_8) personal exposures of about 1 ppm [2.2 mg/m^3] or less from about 1978 to 1986, with some TWA_8 levels greater than

10 ppm [22 mg/m^3] (Table 3). In three of these plants, maintenance employees averaged below 0.5 ppm [1.1 mg/m^3], but in one plant the TWA_8 for these workers was about 1.0 ppm [2.2 mg/m^3]. Typical exposures of loaders of acrylonitrile into tank trucks, rail cars or barges varied from about 0.4 to about 6 ppm [0.9–13 mg/m^3]. Respirator use was noted for some of the higher measurements for production and maintenance workers and loaders in these plants. Laboratory technicians in these plants averaged about 0.25 ppm [0.54 mg/m^3] (n = 176; 0.01–2.0 ppm [0.02–4.3 mg/m^3]), except for one plant where the average was 1.00 [2.2 mg/m^3] (n = 57; 0.1–9.4 ppm [0.2–20 mg/m^3]) (not shown in Table 3). Although measurement data were provided by year and several changes were made in these plants to reduce exposure levels, no trends over the years were observed.

Estimates of exposures in these same plants were developed for an epidemiological study (Blair *et al.*, 1998; Stewart *et al*., 1998). For years in which there were exposure measurements, means of the measurements were used (Zey *et al.*, 1989; Zey & McCammon, 1990; Zey *et al.*, 1990a,b). For years in which no measurement data were available, the measurements for each work site were adjusted based on specific conditions in that plant, including changes in the process, in operating and engineering controls, in tasks and other parameters. In the 1950s, two of these plants were in existence and the average estimate for the monomer operators' TWA_8 exposure was 1–2 ppm [2.2–4.4 mg/m^3]. In the 1960s, the average estimate for this job in three of the plants was between 1 and 4 ppm [2.2 and 8.8 mg/m^3] and in the fourth around 15 ppm [33 mg/m^3]. In the 1970s the range of the estimates for the four plants was 0.5–6 ppm [1.1–13 mg/m^3] for this job.

Other chemicals present in acrylonitrile production or in other non-acrylonitrile operations on sites of the companies in the epidemiological study by Blair *et al.* (1998) include acetylene, hydrogen cyanide, propylene, ammonia, acetic acid, phosphoric acid, lactonitrile, hydroquinone, sodium hydroxide, sulfuric acid, acrylamide, acetone cyanohydrin, melamine, methyl methacrylate, *meta*-methylstyrene, urea, methacrylonitrile, butadiene, ammonium hydroxide and ammonium sulfate (Zey *et al.*, 1989, 1990a,b; Zey & McCammon, 1990).

Loaders in a French plant had personal exposure levels of 2.8, 1.9 and 2.4 ppm [6.1, 4.1 and 5.2 mg/m^3] (the latter, a range of 0.1–27 ppm [0.2–59 mg/m^3]) for 30 min to 1.5 h (Cicolella *et al.*, 1981). Five-minute to one-hour samples taken near monomer equipment averaged about 20 ppm [44 mg/m^3], with levels up to 56 ppm [122 mg/m^3].

(*b*) *Fibre production*

Full-shift personal samples taken by the companies and the study investigators were reported across a number of jobs over the years 1977–86 in three fibre plants in the United States (Table 3) (Zey & McCammon, 1989; McCammon & Zey, 1990; Zey & Bloom, 1990). The average typical exposures for the operators at the polymerization reactor were 0.9–1.6 ppm [0.4–3.4 mg/m^3], based on more than 450 samples in each plant. Individual measurements were as high as 62 ppm [135 mg/m^3]. Respirators were

Table 3. Full-shift personal occupational exposures in the United States

Process	Job	No. of samples	Mean (mg/m^3)	Range (mg/m^3)	Time period	Reference
Monomer	Monomer production	638	1.1	NG–66	1977–86	Zey *et al.* (1990a)
		110	1.6	0.02–21	1978–86	Zey *et al.* (1990b)
		148	2.5	0.02–81	1977–86[a]	Zey *et al.* (1989)
		254	1.0	NG–25	1977–79, 1986	Zey & McCammon (1990)
	Maintenance	605	0.4	NG–18	1977–86	Zey *et al.* (1990a)
		23	0.6	0.2–1.7	1978–81, 1986	Zey *et al.* (1990b)
		928	2.2	0.04–64	1977–86[a]	Zey *et al.* (1989)
		357	0.7	NG–54	1977–79, 1986	Zey & McCammon (1990)
	Loader	114	5.6	NG–102	1977–86	Zey *et al.* (1990a)
		127	2.8	0.2–39	1978–86	Zey *et al.* (1990b)
		123	12.8	0.04–595	1977–86[a]	Zey *et al.* (1989)
		9	1.2	NG–3.5	1977–79	Zey & McCammon (1990)
Fibre	Polymer	488	3.4	0.4–35	1978–86	Zey & McCammon (1989)
	Dope	13	0.8	0.4–1.6	1978–88	Zey & McCammon (1989)
	Polymer	512	1.9	NG	1977–86	Zey & Bloom (1990)
	Dope, spinning	997	2.0	NG	1977–86	Zey & Bloom (1990)
	Cutting, baling	40	0.6	NG	1978–80, 1986	Zey & Bloom (1990)
	Polymer	645	3.0	NG–96	1979–86	McCammon & Zey (1990)
	Maintenance	7	0.5	0.2–0.8	1986	Zey & McCammon (1989)
		37	1.5	NG	1979–86	Zey & Bloom (1990)
		58	1.0	NG–46	1979–86	McCammon & Zey (1990)
	Tank-farm	93	1.2	0.4–24	1978–83, 86	Zey & McCammon (1989)
		23	1.3	NG	1980–86	Zey & Bloom (1990)

Table 3 (contd)

Process	Job	No. of samples	Mean (mg/m^3)	Range (mg/m^3)	Time period	Reference
Resin	Resin production	126	2.1	0.2–98	1978–86	Bloom & Zey (1990)
	Polymer production	645	0.6	0.2–30	1978–86	McCammon & Zey (1990)
	Compounding	196	0.2	0.2–1.5	1978–86	Bloom & Zey (1990)
	Maintenance	569	0.7	0.2–157	1978–86	Bloom & Zey (1990)
	Tank farm	30	0.5	0.2–11	1978–86	Bloom & Zey (1990)
Adiponitrile	Adiponitrile production	218	1.1	NG–13	1979–86	McCammon & Zey (1990)
Acrylamide	Acrylamide production	77	2.1	0.04–35	1977–86	Zey *et al.* (1989)

NG, not given

[a] For some workers who were wearing respirators, the actual exposure will have been lower than the measured value.

worn in some cases. The dope and spinning operators had exposures averaging below 1 ppm [2.2 mg/m^3]. Lower exposures for these workers occurred in the plants that dried the polymer before the spinning operation, resulting in a lower monomer content in the polymer. Higher exposures occurred in the other plant which had a continuous wet operation without the drying stage. Exposure of maintenance workers averaged 0.2–0.7 ppm [0.5–1.5 mg/m^3]. Tank-farm operators, who are likely also to unload acrylonitrile monomer from trucks, rail cars or barges, had homogeneous exposure levels (0.6–0.7 ppm [1.3–1.5 mg/m^3]) across these plants, as did the laboratory technicians (0.1–0.4 ppm [0.22–0.87 mg/m^3]) (not shown in Table 3).

Estimates of historical exposures were developed for these same plants (Blair *et al.*, 1998; Stewart *et al*., 1998). Using the measurements described above (Zey & McCammon, 1989; McCammon & Zey, 1990; Zey & Bloom, 1990), the average estimate for the polymer reactor operators' TWA_8 exposure in the 1950s and 1960s was about 7 ppm [15 mg/m^3] in one plant and around 15–20 ppm [33–44 mg/m^3] in the other two fibre plants. These levels fell to 3–9 ppm [6.5–19.5 mg/m^3] in the 1970s.

Other chemicals present in the fibres operation or in other operations on sites of the companies in the epidemiological study by Blair *et al.* (1998) include adiponitrile, hexamethylenediamine, polyester, polystyrene, vinyl acetate, *N*,*N*-dimethylacetamide, titanium dioxide, propionitrile, methyl methacrylate, zinc chloride, dyes and vinyl bromide (McCammon & Zey, 1990; Zey & McCammon, 1989; Zey & Bloom, 1990).

Other reports identifying measurement levels in Japan, Canada and Europe did not specify either the duration of the measurement or whether it was a personal or area evaluation. In Japan, Sakurai and Kusumoto (1972) reported that workers in five fibre plants could be divided into groups: one exposed to less than 5 ppm [11 mg/m^3] and the other to less than 20 ppm [44 mg/m^3]. In 1978, the same authors reported personal exposures for six fibre plants of 0.1 ppm [0.2 mg/m^3] (n = 11; 2 plants), 0.5 ppm [1.1 mg/m^3] (n = 37; geometric standard deviation (GSD) = 4.9; 3 plants) and 4.2 ppm [9.1 mg/m^3] (n = 14; GSD = 1.7, 1 plant) (Sakurai *et al*., 1978). Spot area samples gave average levels of 2.1 ppm [4.6 mg/m^3] (n = 116; 2 plants), 7.4 ppm [16 mg/m^3] (n = 394; 3 plants) and 14.1 ppm [31 mg/m^3] (n = 98; 1 plant). Some of the samples showed levels exceeding 100 ppm [220 mg/m^3]. The levels were believed to be representative of typical exposures; past exposures were thought to have been much higher. A third report by these authors indicated that the averages of area samples of two groups of fibre workers were 0.27 ppm (n = 62) and 0.87 ppm (n = 51) [0.59 and 1.9 mg/m^3] (Sakurai *et al*., 1990). These were considered by the authors to be comparable to personal exposures.

In Canadian fibre plants, personal TWA_8 levels were less than 1 ppm [2.2 mg/m^3] for unloading, reactors, wet spinning, maintenance and cleaning and processing in 1980 (Guirguis *et al*., 1984). [These measurements were identified as personal TWA_8 by the authors. It was not clear, however, how the measurements relate to workers' exposures, since they were identified by area descriptors].

In a French fibre plant, short-term measurements (< 2 h) were taken at the grinding (13.5 ppm; range, 2–28 ppm [29; 4.4–61 mg/m^3]), drying (3.4 ppm; 1–7 ppm [7.4;

2.2–15 mg/m^3]) and wringing stations (15.8 ppm; 3–46 ppm [34; 6.5–100 mg/m^3]) (Cicolella *et al*., 1981). These three stations each had local exhaust, but it was identified as being insufficient. An unspecified job had a mean exposure of 3 ppm [6.5 mg/m^3]. Cleaning reactors resulted in exposures of 19 ppm [41 mg/m^3]. A loader had a one-hour measurement of 33 ppm [72 mg/m^3] during loading and 19.8 (1–140 ppm) [43; 2.2–304 mg/m^3] during two disconnections. Sample collection from the reactor was found to result in an average exposure level of 1.7 ppm (0.6–3.4 ppm) [3.7; 13–7.4 mg/m^3] for 10 min.

An average of 3.5 ppm (range, 1.4–9.3 ppm) [7.6; 3–20 mg/m^3] in a Malon production unit was reported in 1973 in Yugoslavia (Orusev *et al*., 1973), and levels of 2.0–3.3 ppm [4.4–7.2 mg/m^3] in the summer and > 0.2 ppm [0.44 mg/m^3] in the winter in Bulgaria in 1976 were reported (Ginceva *et al*., 1977). Levels below 2 ppm [4.4 mg/m^3] were reported in a fibre plant in Portugal (Borba *et al*., 1996).

(*c*) *Resin production*

Personal, full-shift exposures, as measured by the companies and the study investigators, in two resin plants in the United States have been reported (Table 3). At a facility making Barex resin (an acrylonitrile–butadiene resin), the average exposure of the resin operators was about 1 ppm [2.1 mg/m^3], with individual measurements up to 45 ppm [98 mg/m^3] (Zey *et al*., 1990b). The other facility made acrylonitrile–butadiene–styrene (ABS) and styrene–acrylonitrile (SAN) resins and dispersions (Bloom & Zey, 1990). Exposure of resin operators averaged 0.26 ppm [0.6 mg/m^3], with levels up to 14 ppm [30 mg/m^3], while the compounders had lower levels (0.1 ppm [0.2 mg/m^3]). The average for maintenance workers in this plant was about 0.3 ppm [0.7 mg/m^3] and in the tank farm (unloading) about 0.2 ppm [0.5 mg/m^3]. Laboratory technicians had an average exposure of 2.2 ppm [4.8 mg/m^3] (not shown in Table 3). Estimates of exposures in the latter plant were developed as described above (Blair *et al*., 1998; Stewart *et al*., 1998). Based on these data, the TWA_8 exposure for a production labourer in the resin unit was about 7 ppm [15 mg/m^3] in the 1960s and fell to about 3 ppm [6.5 mg/m^3] in the 1970s.

Other chemicals present in the resins operation or in other operations on site in the resin company evaluated in the epidemiological study by Blair *et al.* (1998) include butadiene, styrene, formaldehyde, melamine, maleic anhydride, phosphoric acid and phenol (Zey *et al.*, 1990b).

In other reports, it was not clear whether the levels reported were full-shift evaluations or whether they represented personal or area exposures. In Canadian ABS plants, personal TWA_8 exposures were about 1.5 ppm [3.3 mg/m^3] at the reactors, about 1 ppm [2.2 mg/m^3] at the coagulation and drying, compounding and control room areas and about 0.5–0.7 ppm [1.1–1.5 mg/m^3] in the laboratory and during sample-taking and maintenance and cleaning in 1980 (Guirguis *et al*., 1984). [These measurements were identified as personal TWA_8 by the authors. It is not known how the measurements relate to workers' exposures, as they were identified by area descriptors].

In a plastics plant in the Netherlands, a reactor operator performing maintenance work had exposures of 0.3 and 1.8 ppm [0.65 and 3.9 mg/m^3] (Houthuijs *et al*., 1982). The panel operator had a weekly mean of 0.02 ppm [0.04 mg/m^3]. For five unspecified workers, average exposure was about 0.1 ppm [0.2 mg/m^3] (standard deviation (SD), 0.05; range, < 0.02–0.15 ppm) [SD, 0.11; range, 0.04–0.33 mg/m^3] on days when respirators were not in use, and 0.8 ppm [1.7 mg/m^3] (SD, 0.67; range, 0.03–1.8 ppm) [SD, 0.67; range, 0.07–3.9 mg/m^3] when respirators were being worn.

In another study, personal samples were taken of all workers in the polymerization and flocculation process areas of a plant in the United States, where the highest exposure was expected, and of some employees in other areas of the plant (Kutcher, 1978). The sampling duration was 4–6 h and conditions were considered representative of normal conditions. One outside reactor operator had a TWA of 2.9 ppm (n = 12; 0.6–4.3 ppm; total duration, 16.7 h) [6.3; 1.3–9.3 mg/m^3] and another had a TWA of 0.7 ppm [1.5 mg/m^3] (n = 12; total duration, 16.5 h). An inside reactor operator's measured exposure ranged from 0.1 to 0.4 ppm (n = 5). A latex handler had a TWA of 1.0 ppm (n = 12; 0.7–1.3 ppm; 14.7 h [2.2; 1.5–2.8 mg/m^3]). Three flocculation operators had a mean exposure of 3.1 ppm (n = 35; 0.7–9.3 ppm) [6.7; 1.5–20 mg/m^3] and a Banbury operator's measured exposures ranged from 0.1 to 1.2 ppm [0.2–2.6 mg/m^3] (n = 3). A mill operator's exposures ranged from 0.1 to 1.1 ppm [0.2–2.4 mg/m^3] (n = 8) and a packer's from 0.1 to 1.0 ppm [0.2–2.2 mg/m^3] (n = 5). A tank-farm operator had a single measurement of 0.1 ppm [0.2 mg/m^3]. Two laboratory technicians' measurements were 0.1 and 0.2 ppm [0.2 and 0.4 mg/m^3]. During reactor maintenance, acrylonitrile levels of 0.3–0.8 ppm [0.65–1.7 mg/m^3] (n = 6) were found.

In the manufacture of SAN and ABS and polymer dispersions (and also of chemical intermediates) under normal conditions, spot measurements of 5 ppm [11 mg/m^3] were found during 1963–74, and it was assumed that higher levels occurred under some conditions. In 1975–77, monthly readings averaged 1.5 ppm [3.3 mg/m^3] (Thiess & Fleig, 1978). In ABS factories in France, short-term (< 2 h) area measurements averaged 13.5 ppm (0–89 ppm) [29; 0–193 mg/m^3] at an open, unventilated polybutadiene loading operation (Cicolella *et al*., 1981). In the flocculation area, where local exhaust was insufficient, the average level was 2.3 ppm (0.6–4.4 ppm) [5.6; 1.3–9.5 mg/m^3]. Below the reactor during cleaning, the average level was 2.6 ppm (0.8–2.9 ppm) [5.6; 1.7–6.3 mg/m^3]. At an acrylic dispersion plant, loading of an acrylonitrile tank resulted in a mean level of 35.7 ppm (0.4–281 ppm) [77; 0.87–610 mg/m^3]. Workers at Canadian acrylic emulsion facilities in 1980 had personal TWA_8 values of less than 1 ppm [2.2 mg/m^3] at the unloading, reactor and packaging areas and where the product was being used (Guirguis *et al*., 1984). [These measurements were identified as personal TWA_8 by the authors. It is not known how they relate to workers' exposures, as the measurements were identified by area descriptors.]

(*d*) *Rubber and polymer production*

TWA_8 measurements in Canadian nitrile rubber plants averaged 2 ppm [4.4 mg/m^3] at the reactors and in maintenance and cleaning operations, 1.6 ppm [3.5 mg/m^3] at the

coagulation and drying area and 1 ppm [2.2 mg/m^3] during sample taking (Guirguis *et al*., 1984). [These measurements were identified as personal TWA_8 by the authors. It is not known how they relate to workers' exposures as they were identified by area descriptors.]

Short-term (< 6 h) measurements of nitrile rubber workers revealed average levels of 0.1–5.8 ppm [0.2–13 mg/m^3], ranging up to 12.1 ppm [26 mg/m^3] where equipment was hooded but insufficiently ventilated (Cicolella *et al*., 1981). Seven-hour samples at the flocculation area showed levels of 0.4 and 2.2 ppm [0.9 and 4.8 mg/m^3], and at the drying area 0.5 ppm [1.1 mg/m^3] was found. Cleaning the stripper for 3–6 h resulted in levels up to 30 ppm [65 mg/m^3]. The mean for two different individuals collecting samples for 15–20 min were 9.6 and 31.3 ppm [21 and 68 mg/m^3], with measurements up to 78 ppm [170 mg/m^3]. During two 30-min connections for loading or unloading in open air, levels of 1 and 14 ppm [2.2 and 30 mg/m^3] were measured.

Production of butadiene–styrene footwear was found to result in levels of 0.5–5.1 ppm [1.1–11 mg/m^3] acrylonitrile in Russia (Volkova & Bagdinov, 1969). In another rubber footwear plant in the Soviet Union, the mean ambient air concentration of 32 samples was 0.1 ppm (standard error, 0.03) [0.2; SE, 0.065 mg/m^3] over a range of < 0.002–1.0 ppm [0.004–2.2 mg/m^3] (Solionova *et al*., 1992). Seventeen of the samples were below the limit of detection of 0.002 ppm [0.004 mg/m^3]. In a company manufacturing rubber tyres and tubes, levels from two area samples under a Banbury mill were 0.15 ppm [0.33 mg/m^3] acrylonitrile and below the detectable level (Anon., 1976).

(*e*) *Organic chemical synthesis*

Full-shift personal samples on operators in an adiponitrile production unit gave an average of 0.5 ppm [1.1 mg/m^3] acrylonitrile (n = 218; up to 6.1 ppm [13.2 mg/m^3]) (Table 3) (McCammon & Zey, 1990). In an acrylamide operation, the average of the full-shift measurements on the production operators was 1.0 ppm (n = 77; 0.02–16.2 ppm) [2.2; 0.04–35 mg/m^3] (Zey *et al.*, 1989). Supporting operations for both the adiponitrile and acrylamide operations (i.e., maintenance, quality control and unloading) are included in the monitoring data reported for the fibre and monomer operations, respectively (Zey *et al.*, 1989; McCammon & Zey, 1990).

(*f*) *Miscellaneous*

In a thermosetting plastics plant, acrylonitrile levels at a moulding operation were found to be 0.6 ppm [1.3 mg/m^3] (Scupakas, 1968). No acrylonitrile was found at two injection moulding operations of ABS thermoplastics (n = 2) (Anon., 1978, 1980). In an aircraft manufacturer making moulded fibrous glass and plastic (ABS) components, two personal full-shift (6.5 h) samples gave levels of < 0.8 ppm [1.7 mg/m^3] for the oven operator. Two area samples of 3–4 h had levels of less than 1 and less than 1.4 ppm [2.2 and 3 mg/m^3] (Anon., 1979). It was reported that in Canada, minor uses of acrylonitrile, such as coating manufacture, typically resulted in acrylonitrile levels of less than 2 ppm [4.4 mg/m^3] and most were less than 1 ppm [2.2 mg/m^3] (Guirguis *et al*., 1984).

1.3.3 *Air*

Acrylonitrile has not been detected to occur at measurable concentrations in ambient air. Measurable levels of atmospheric acrylonitrile are associated with industrial sources. Mean 24-h acrylonitrile concentrations in atmospheric samples collected within 5 km of factories producing or using acrylonitrile ranged from less than 0.1 to 325 µg/m^3. The occurrence of acrylonitrile was correlated with wind patterns; the highest concentrations were downwind of and in close proximity to the plant. The median concentration of acrylonitrile for 43 measurements in 'source-dominated areas' (i.e., near chemical plants) was 2.1 µg/m^3 (Agency for Toxic Substances and Disease Registry, 1990).

In 1995, industrial releases of acrylonitrile to the environment, as reported to the Toxic Chemical Release Inventory of the United States Environmental Protection Agency, totalled about 2940 tonnes, including 2360 tonnes to underground injection sites and 576 tonnes to the atmosphere (United States National Library of Medicine, 1997a).

1.3.4 *Water*

Acrylonitrile is not a common contaminant of typical surface water or groundwater. In a state-wide survey of 1700 wells in Wisconsin, United States, acrylonitrile was not detected in any sample. Acrylonitrile was detected in 46 of 914 samples of surface water and groundwater taken across the United States, generally at levels less than 10 ppb (µg/L). Levels of acrylonitrile measured in the effluents from a variety of industrial sites (iron and steel factories, textile mills, chemical plants) have ranged from 20 to 4700 ppb (µg/L), resulting in concentrations in nearby rivers ranging from below detection limits to 4300 ppb (µg/L) (Agency for Toxic Substances and Disease Registry, 1990).

1.3.5 *Other*

Residual acrylonitrile has been detected in a limited number of samples of commercial polymeric materials derived from acrylonitrile (United States Consumer Product Safety Commission, 1978); however, current processes for fibre and polymer production are believed to have reduced residual levels significantly (Agency for Toxic Substances and Disease Registry, 1990).

Acrylonitrile has been detected in the smoke of cigarettes at levels of 3.2–15 mg per cigarette (IARC, 1986; Byrd *et al.*, 1990).

1.4 Regulations and guidelines

Occupational exposure limits and guidelines for acrylonitrile in several countries are given in Table 4.

Table 4. Occupational exposure limits and guidelines for acrylonitrile[a]

Country	Year	Concentration (mg/m^3)	Interpretation[b]
Australia	1991	4.3 (C2, sk)	TWA
Belgium	1991	4.3 (C2, sk)	TWA
Czechoslovakia	1991	0.5	TWA
		2.5	STEL
Denmark	1993	4 (C, sk)	TWA
Egypt	1993	4.3 (sk)	
Finland	1998	4.3 (sk)	TWA
		9	STEL (15 min)
France	1993	4.3 (C)	TWA
		32.5	STEL (15 min)
Germany	1998	7 (C2)	TRK
Hungary	1991	0.5 (C2, sk)	STEL
India	1993	4.3 (C, sk)	TWA
Japan	1991	4.3 (C2, sk)	TWA
The Netherlands	1993	9 (sk)	TWA
		22	STEL (10 min)
The Philippines	1993	43 (sk)	TWA
Poland	1993	10	TWA
Russia	1991	0.5 (sk)	STEL
Sweden	1991	4.3 (C3, sk)	TWA
		13	STEL
Switzerland	1991	4.3 (C, sk)	TWA
Turkey	1993	43 (sk)	TWA
United Kingdom	1991	4 (MEL, sk)	TWA
United States			
ACGIH (TLV)[c]	1997	4.3 (A2, sk)	TWA
NIOSH (REL)	1997	2.2 (Ca, sk)	TWA
		21.5	Ceiling
OSHA (PEL)	1996	4.3 (sk)	TWA
		43	Ceiling

[a] From International Labour Office (1991); US Occupational Safety and Health Administration (OSHA) (1996); American Conference of Governmental Industrial Hygienists (ACGIH) (1997a,b); US National Library of Medicine (1997b); Deutsche Forschungsgemeinschaft (1998); Ministry of Social Affairs and Health (1998)

[b] TWA, time-weighted average; STEL, short-term exposure limit; TRK, technical exposure limit; MEL, maximum exposure limit; REL, recommended exposure limit; PEL, permissible exposure limit; TLV, threshold limit value; min, minute; A2, suspected human carcinogen; C, suspected of being a carcinogen; C2, probable human carcinogen; C3, suspected of having a carcinogenic potential; Ca, potential occupational carcinogen; sk, skin notation

[c] Countries that follow the ACGIH recommendations for threshold limit values include Bulgaria, Colombia, Jordan, Korea (Republic of), New Zealand, Singapore and Viet Nam

2. Studies of Cancer in Humans

Epidemiological data on acrylonitrile have been reviewed by Koerselman and van der Graaf (1984), Rothman (1994) and Blair and Kazerouni (1997). These reviews were prepared before the publication of several recent reports.

Cohort studies (Table 5)

Kiesselbach *et al*. (1979) conducted a cohort mortality study of 884 male employees at a Bayer AG plant in North Rhine–Westphalia, Germany, who had handled acrylonitrile for at least one year between 1950 and 1 August 1977, in either production or processing. Mortality among these workers through 1 August 1977 was compared with rates for the male population of North Rhine–Westphalia for 1950–77. Sixty workers (6.8%) could not be traced to the closing date of the study. Duration of employment was used as a measure of exposure. The authors indicated that some of the workers also handled butadiene and styrene. Fifty-eight deaths occurred [overall standardized mortality ratio (SMR) 0.5; 95% confidence interval (CI), 0.4–0.7]. The SMR for total cancer was [1.0; n = 20; 95% CI, 0.6–1.5] and the proportionate mortality ratio (PMR) was [1.9]. The SMRs for specific cancers were [0.9] (6 observed, 6.7 expected) [95% CI, 0.3–2.0] for the respiratory tract and [1.3] (4 observed, 3 expected) [95% CI, 0.4–3.4] for stomach.

Thiess *et al*. (1980) evaluated the mortality experience of 1469 workers employed for at least six months at 12 acrylonitrile-using plants in Germany. The cohort was followed through 15 May 1978 for vital status. Tracing of German workers (n = 1081) was very successful (98%), but less so for foreign workers (n = 388) (56%). Mortality in the cohort was compared with local, regional and national mortality rates. SMRs presented here are based on national rates. The follow-up included 15 350 person–years and 89 deaths. Exposure levels were not estimated. The SMRs were [1.3] (27 observed, 20.5 expected) [95% CI, 0.9–1.9] for all cancers, [1.96] (11 observed, 5.9 expected) [95% CI, 0.9–3.3] for lung cancer and [2.3] (4 observed, 1.7 expected) [95% CI, 0.6–6.0] for lymphatic and haematopoietic cancers. SMRs for lung cancer by duration of employment were [2.2] for less than five years (2 observed, 0.9 expected), [3.9] for five to nine years (4 observed, 1.0 expected), and [2.2] for 10 or more years (3 observed, 1.3 expected).

Ott *et al.* (1980) performed a cohort mortality and incidence study of 2904 workers exposed to styrene-based products at four plants of the Dow company and included 100 workers exposed to acrylonitrile. The cohort was followed from 1 January 1940 to 31 December 1975. Mortality rates for the cohort were compared with those in the population of the United States. Vital status was determined for all but 88 (3%) of the workers. Among the acrylonitrile workers, there were one observed death from lung cancer versus 0.5 expected and three cases of leukaemia versus 1.25 expected.

Waxweiler *et al*. (1981) studied 4806 workers employed at a vinyl chloride monomer (IARC, 1987b) plant in the United States between 1942 and 31 December 1973. The

Table 5. Summary of non-overlapping epidemiological studies of workers exposed to acrylonitrile (SMR and 95% CI)

Reference, country	Standardized mortality ratio (observed/expected number)							
	Stomach	Lung	Breast	Brain	Prostate	Lymphatic/ haematopoietic	Liver	Bladder
Kiesselbach *et al*. (1979), Germany	[1.3] (4/3)	[0.9] (6/7) respiratory tract	NA	NA	NA	NA	NA	NA
Thiess *et al*. (1980), Germany	NA	[2.0] (11/5.5)	NA	NA	NA	[2.4] (4/1.6)	[0.8] (1/1.3)	[3.3] (2/0.6)
Delzell & Monson (1982), United States		1.5 (9/5.9)	NA	NA	NA	2.3 (4/1.8)	NA	NA
Mastrangelo *et al*. (1993), Italy	[3.4] (2/0.6)	[0.8] (2/2.6)	NA	[2.5] (1/0.4)	NA	NA	[10.5] (4/0.4)	NA
Swaen *et al*. (1998), Netherlands	0.3 (2/6.7)	1.1 (47/42.8)	NA	1.7 (6/3.4)	0.8 (4/4.8)	NA	1.3 (9/7.1)	1.0 (3/3.1)
Wood *et al*. (1998) (using Du Pont mortality rates), United States	0.5 (3/[6])	0.8 (46/[57.5])	NA	1.1 (6/[5.4])	1.3 (11/[8.5])	0.6 (9/[15])	0.6 (2/[3])	1.2 (4/[3.5])
Blair *et al*. (1998) (using unexposed workers as referents), United States	1.1 (12/10.9)	1.2 (134/111.7)	0.6 (5/8.3)	0.5 (12/24.0)	1.0 (16/16.0)	0.7 (27/38.6)	NA	NA
Benn & Osborne (1998), United Kingdom	1.0 (11/11.4)	1.0 (53/51.5)	NA	NA	NA	0.5 (5/10.0)	1.3 (11/8.8)	NA

NA, not available

cohort was followed for mortality through 1973 with only 73 (1.5%) lost to follow-up. Information on race was not available, but all were assumed to be white because the company indicated that less than 2% of the workforce was non-white. Mortality rates in the cohort were compared with those of the general population of the United States, adjusted for age and calendar time. Company personnel estimated exposures on an ordinal scale from one to five for some 20 chemicals including acrylonitrile. The serially additive expected dose (SAED) model was also used in the analyses (Smith *et al.*, 1980). Cumulative exposure among cases was compared with that of other employees who were under follow-up when the case occurred. Histological information from medical and pathology records was sought on the 45 deaths from lung cancer, obtained for 27 and reviewed by a panel of pathologists. The observed dose of acrylonitrile was lower among the lung cancer cases than among other employees. [Details on the work situation resulting in acrylonitrile exposure were not available and it was not possible to compare SAED results with those from other studies].

Mortality associated with acrylonitrile exposure was evaluated as part of a study of 15 643 male workers in a rubber plant in the United States (Akron, Ohio) (Delzell & Monson, 1982). Included in the analysis were 327 workers who were employed for at least two years in the plant between 1 January 1940 and 1 July 1971, and who had worked in two departments where acrylonitrile was used, i.e., 81 worked only in the nitrile rubber manufacturing operation where exposures to 1,3-butadiene (see this volume), styrene (IARC, 1994a) and vinylpyridine also occurred and 218 only in the department where the latex was coagulated and dried. [No information on levels of exposure to acrylonitrile was provided.] Mortality among these workers was assessed through 1 July 1978 and compared with age- and calendar-time-specific rates for white men in the United States. SMRs were 0.8 (n = 74; 95% CI, 0.7–1.0) for all causes of death, 1.2 (n = 22; 95% CI, 0.8–1.9) for all cancers combined, 1.5 (n = 9; 95% CI, 0.7–2.9) for lung cancer, 4.0 (n = 2; 95% CI, 0.5–14.5) for urinary bladder cancer and 2.3 (n = 4; 95% CI, 0.6–5.8) for cancers of the lymphatic and haematopoietic system. SMRs for lung cancer by duration of employment were [1.0] (4 observed, 3.8 expected) [95% CI, 0.3–2.7] for < 5 years, and [3.3] (5 observed, 1.5 expected) [95% CI, 1.1–7.8] for 5–14 years. No case was observed with duration ≥ 15 years.

Mastrangelo *et al*. (1993) studied a factory in Italy engaged in the manufacture of acrylic fibre for clothing and upholstery using acrylonitrile produced elsewhere. The cohort consisted of 671 workers employed for at least 12 months from the opening of the factory in 1959 through 1988. Follow-up for vital status was through 1990 (no individuals were lost to follow-up). Information on smoking was obtained from medical records. Exposure categories included polymerization (high exposure), fibre manufacture (low exposure) and maintenance (high but discontinuous exposure). [No information on exposure levels was provided.] SMRs were based on general population rates in the Veneto region, adjusted for age, sex and calendar time. SMRs were [1.0] (32 observed) [95% CI, 0.7–1.4] for all causes of death, [3.4] (2 observed) [95% CI, 0.4–12.3] for stomach cancer, [0.8] (2 observed) [95% CI, 0.1–2.9] for lung cancer and [2.6]

(1 observed) [95% CI, 0.1–14.7] for brain cancer. Both lung cancers were among maintenance workers exposed for less than 10 years.

Benn and Osborne (1998) enrolled 3013 male workers employed between 1950 and 1978 in any of six acrylonitrile polymerization and acrylic fibre plants in the United Kingdom. This was an expansion and extended follow-up of a cohort of 1111 workers reported by Werner and Carter (1981). The cohort was expanded by the inclusion of 2498 additional workers employed in polymerization or spinning between 1969 and 1978. Exclusion of 85 workers who could not be traced and 165 workers employed for less than one year left 2763 available for analysis. Exposures were estimated by job and categorized by acrylonitrile exposure and no acrylonitrile exposure. Following discussion with the company personnel, a number of workers from one plant (plant 5) who were classified as spinners in the original study and presumed to have relatively high exposures were reclassified as 'end of the line' workers with minimal or no exposure. [No explanation was provided for why this change was necessary.] The earliest exposure measurements (from the late 1970s) showed means of 0.4–2.7 ppm [0.9–5.9 mg/m^3] (8-h time-weighted average (TWA_8) for the highly exposed polymer workers and spinners. Expected numbers of deaths were derived from rates in the general population in England and Wales, except for a factory in Scotland, for which Scottish rates were used. The cohort contributed 63 058 person–years, of which 72% were from plant 5. SMRs for the cohort were 0.8 (n = 409) [95% CI, 0.76–0.9] for total mortality, 0.9 (n = 121) [95% CI, 0.7–1.1] for total cancer, 1.0 (n = 11) [95% CI, 0.5–1.7] for stomach cancer, 1.0 (n = 53) [95% CI, 0.8–1.3] for lung cancer and 0.5 (n = 5) [95% CI, 0.2–1.2] for lymphatic and haematopoietic cancer. Plant 5 showed deficits for various causes of death, while the other factories combined showed nonsignificant excesses. [This is of concern given the previous problems with assembling the cohort at plant 5.] Persons holding high-exposure jobs had SMRs of 1.7 (n = 7) [95% CI, 0.7–3.4] and 1.4 (n = 27) [95% CI, 0.9–2.1] for stomach and lung cancer, respectively. SMRs among the less exposed and little or not exposed groups were 1.0 (n = 3) [95% CI, 0.2–3.0] and 0.2 (n = 1) [95% CI, 0.0–1.3] for stomach cancer and 0.5 (n = 7) [95% CI, 0.2–1.1] and 1.0 (n = 19) [95% CI, 0.6–1.6] for lung cancer. No duration–response gradient was observed for any cancer. The authors reported that there were five deaths (versus 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 and an SMR of 2.7 (n = 7 [95% CI, 1.1–5.5]) among those first employed after 1969 who held high-exposure jobs.

Wood *et al*. (1998) studied 2559 male employees exposed to acrylonitrile during Orlon manufacture at Du Pont plants in South Carolina and Virginia, United States. This report subsumed workers previously included in cohorts reported by O'Berg (1980), O'Berg *et al.* (1985) and Chen *et al.* (1987, 1988a), plus new workers exposed to acrylonitrile at these plants since the earlier studies. Mortality was updated through 1991 using the National Death Index and Social Security Administration files. Cancer cases were identified among cohort members during employment using the Du Pont Cancer Registry which records diagnoses among active Du Pont employees. A

common exposure assessment procedure was applied to the work histories of individuals from the two plants. Exposure assessments by job title and work area were in ppm for a 40-h working week and were based on the monitoring data available, process descriptions, production records, work practices and information from employees. Estimates were placed in four exposure categories with arithmetic midpoint values of 0.11 ppm, 1.10 ppm, 11.0 ppm and 30.0 ppm [0.24, 2.4, 24 and 65 mg/m^3]. Cumulative exposures were derived as the summed products of these endpoint values and the time spent in each category and were classified as < 10 ppm–years (n = 879), 10–< 50 ppm–years (n = 746), 50–< 100 ppm–years (n = 391) and ≥ 100 ppm–years (n = 553). SMRs were calculated using mortality rates for the general United States population and deaths among active employees and retirees of the Du Pont company as the referent. Standardized incidence ratios (SIRs) were based on Du Pont cancer incidence rates. The cohort was composed of 2559 workers (1426 in the South Carolina plant and 1143 in the Virginia plant). Vital status as of 1991 was determined for all but 23 workers and death certificates were located for all but two of the 454 presumed decedents. SMRs (based on general population rates) for selected causes of death were 0.7 (n = 454; 95% CI, 0.6–0.8) for all causes, 0.8 (n = 126; 95% CI, 0.6–0.9) for all malignant neoplasms, 0.5 (n = 3; 95% CI, 0.1–1.5) for stomach cancer, 0.8 (n = 46; 95% CI, 0.5–1.0) for lung cancer, 1.1 (n = 6; 95% CI, 0.4–2.5) for brain cancer, 1.2 (n = 4; 95% CI, 0.3–3.0) for bladder cancer, 1.3 (n = 11; 95% CI, 0.6–2.3) for prostate cancer and 0.6 (n = 9; 95% CI, 0.3–1.1) for lymphatic and haematopoietic system cancer. SMRs were similar when mortality rates from Du Pont workers were used for comparison, with the all-cause mortality ratio still less than 1.0 (0.9; 95% CI, 0.8–1.0). Based on general population rates, the relative risk for death from prostate cancer showed an inverse association with latency, duration of exposure, highest ever exposure level and cumulative exposure. Mortality from respiratory cancer was typically less than expected by duration of exposure and across cumulative exposure categories; when analysed by highest ever exposure level, there were no deaths at the lowest level, SMR = 0.7 (n = 3) [95% CI, 0.1–2.0] for moderate level, SMR = 0.7 (n = 21) [95% CI, 0.4–1.1] for the high level and SMR = 1.2 (n = 23) [95% CI, 0.8–1.8] for the very high level. SIRs (based on Du Pont cancer rates) for selected cancers were 0.4 (n = 1; 95% CI, 0.0–2.4) for stomach cancer, 0.8 (n = 17; 95% CI, 0.5–1.3) for lung cancer, 1.6 (n = 12; 95% CI, 0.8–2.8) for prostate cancer, 1.1 (n = 4; 95% CI, 0.3–2.9) for brain cancer, 0.7 (n = 4; 95% CI, 0.2–1.8) for bladder cancer and [1.0] (n = 10; [95% CI, 0.5–1.8]) for lymphatic and haematopoietic cancers. For prostate cancer, the SIR was 0.8 (n = 4) [95% CI, 0.2–2.1] for < 20 years latency and 1.3 (n = 8; 95% CI, 0.6–2.4) for 20 or more years. SIRs for prostate cancer by cumulative exposure were 2.1 (n = 3; 95% CI, 0.4–6.2), 0.5 (n = 1; 95% CI, 0.0–2.8), 0.8 (n = 2; 95% CI, 0.0–2.9), and 2.3 (n = 4; 95% CI, 0.8–5.1) for low (< 10 ppm-years), moderate, high and very high categories of cumulative exposure, respectively. SIRs for respiratory cancer were generally less than 1.0 and showed no patterns by latency, duration, highest exposure level or cumulative exposure.

Swaen *et al*. (1998) studied eight companies in the Netherlands engaged in the production of acrylonitrile, latex rubber (IARC, 1987c), polymers, acrylic fibre, vinylidene/acrylonitrile polymers and acrylamide (IARC, 1994b) and a nitrogen-fixation plant where exposure did not occur. The vital status for this cohort has been recently extended through 1 January 1996 and only results from this recent follow-up are presented here. Criteria for inclusion of workers were exposure (or employment for the comparison plant) for six months before July 1979, male gender, Dutch nationality, residence in the Netherlands and no history of underground coal mining. Data for the study were abstracted by study investigators from the files of six companies, while two companies carried out the data abstraction themselves. The exposed cohort was composed of 2842 workers. Workers (n = 3961) from the nitrogen fixation plant were selected as an unexposed referent population. TWA_8 exposures by year were estimated for job groups with homogeneous exposures by the study industrial hygienist for seven plants. One company provided its own estimates because the study industrial hygienist was not allowed to visit the facility. Exposure estimates were placed in TWA_8 categories with ranges of 0–0.5 ppm, > 0.5–1 ppm, > 1–2 ppm and > 2–5 ppm [0–1.1, > 1.1–2.2, > 2.2–4.3 and > 4.3–10.9 mg/m^3]. No TWA_8 exposures were thought to be greater than 5 ppm. Peak exposures, use of respirators and potential exposure to other chemicals were also evaluated. Vital status was determined for all but 19 workers in the exposed cohort and all but 10 workers in the referent cohort. Cause of death could not be determined for nine decedents in the acrylonitrile cohort and 14 decedents in the referent cohort. SMRs for the exposed and unexposed cohorts were based on mortality rates of the Dutch male population, adjusted for age and calendar time. SMRs from the exposed and unexposed populations were 0.9 (n = 290; 95% CI, 0.8–1.0) and 0.8 (n = 983; 95% CI, 0.77–0.9) for total mortality, 0.9 (n = 97; 95% CI, 0.7–1.1) and 0.8 (n = 332; 95% CI, 0.7–0.9) for all cancers combined, 1.1 (n = 47; 95% CI, 0.8–1.5) and 0.8 (n = 124; 95% CI, 0.6–0.9) for lung cancer, 0.8 (n = 4; 95% CI, 0.2–2.1) and 0.5 (n = 13; 95% CI, 0.3–0.9) for prostate cancer, 1.7 (n = 6; 95% CI, 0.4–3.8) and 0.9 (n = 7; 95% CI, 0.3–1.8) for brain cancer, 1.00 (n = 3; 95% CI, 0.2–2.8) and 1.1 (n = 14; 95% CI, 0.6–1.8) for bladder cancer, and 1.7 (n = 5; 95% CI, 0.5–3.9) and 1.1 (n = 11; 95% CI, 0.6–2.0) for leukaemia. [The Working Group noted that direct comparisons between the exposed and unexposed cohorts were not performed, which might have yielded larger relative risks among the exposed.] SMRs for lung cancer by cumulative exposure were 1.0 (n = 5; 95% CI, 0.3–2.3) for < 1 ppm–year, 1.1 (n = 24; 95% CI, 0.7–1.6) for 1–10 ppm–years and 1.2 (n = 18; 95% CI, 0.7–1.9) for > 10 ppm–years (p for trend = 0.66). For leukaemia, there were no deaths in the lowest cumulative exposure category; SMRs were 0.6 (n = 1; 95% CI, 0.1–3.4) for 1–10 ppm-years and 4.4 (n = 4; 95% CI, 1.2–11.3) for > 10 ppm-years. SMRs for prostate and brain cancer showed no evidence of an exposure–response trend. No clear trend of SMRs with increasing latency was evident. SMRs for lung cancer by peak exposures were 1.2 (n = 15; 95% CI, 0.7–1.9) for no peak, 1.3 (n = 20; 95% CI, 0.8–2.0) for peaks < 10 ppm, 0.7 (n = 8; 95% CI, 0.3–1.2) for peaks 10–< 20 ppm and 1.6 (n = 4; 95% CI, 0.4–4.2) for peaks 20 ppm or greater. SMRs for lung cancer were 1.0

(*n* = 9; 95% CI, 0.5–1.9) among persons using respirators and 1.1 (*n* = 38; 95% CI, 0.8–1.5) among those not using respirators. The SMRs for lung cancer were 1.0 (*n* = 19; 95% CI, 0.6–1.5) among workers not exposed to other carcinogens and 1.2 (*n* = 28; 95% CI, 0.8–1.8) for those with potential exposure to other carcinogens.

Blair *et al*. (1998) conducted a cohort study of 25 460 workers from eight acrylonitrile-producing and -using plants in the United States to evaluate mortality by quantitative level of exposure. The study included 18 079 white men, 4293 white women, 2191 non-white men and 897 non-white women employed from the 1950s through 1983 and followed through 1989 to determine their vital status and cause of death. Vital status was determined for 96% of the cohort; 2038 were believed to be deceased, for which 1919 (94%) death certificates were found. Information on tobacco use was obtained for a sample of workers to assess the potential for confounding. Mortality rates for exposed workers (348 642 person–years) were compared with those for unexposed (196 727 person–years) workers in the cohort, using Poisson regression analysis to minimize the healthy worker effect. An external advisory committee reviewed and approved the protocol and provided guidance and advice to the investigators on all aspects of the study. Compared with rates in the general population of the United States, SMRs for unexposed and exposed were 0.7 (*n* = 702; 95% CI, 0.7–0.8) and 0.7 (*n* = 1217; 95% CI, 0.6–0.7) for total mortality and 0.9 (*n* = 216; 95% CI, 0.8–1.0) and 0.8 (*n* = 326; 95% CI, 0.7–0.9) for total cancer, respectively. Quantitative estimates of inhalation and dermal exposure to acrylonitrile were based on information from production procedures at the plants, interviews with management and labour, monitoring data from the companies, and monitoring conducted by the investigators specifically for the study (Stewart *et al*., 1998). Exposure to chemicals other than acrylonitrile occurred, but numbers of worker–years of exposure were small (≤ 55 000) compared with those for acrylonitrile (348 642). Relative risk (RR) analyses by various indicators of exposure including cumulative (ppm–years), average, peak, intensity, duration and lagged exposure revealed no elevated risk or trends for cancers of the stomach, brain, breast, prostate or lymphatic and haematopoietic system. Cumulative exposure categories were 0 (unexposed), 0.01–0.13 ppm-years, 0.14–0.57 ppm-years, 0.58–1.50 ppm-years, 1.5–8.0 ppm-years and > 8.00 ppm-years. Mortality from lung cancer was elevated among individuals in the highest quintile of cumulative exposure, compared with unexposed workers, and received special analytical attention. RRs and 95% CIs for lung cancer from the lowest to highest quintile of cumulative exposure were 1.1 (*n* = 27; 0.7–1.7), 1.3 (*n* = 26; 0.8–2.1), 1.2 (*n* = 28; 0.7–1.9), 1.0 (*n* = 27; 0.6–1.6) and 1.5 (*n* = 26; 0.9–2.4), respectively. Limiting analysis to 20 or more years since first exposure yielded RRs by quintile of 1.1 (*n* = 11; 0.6–2.2), 1.0 (*n* = 10; 0.5–2.1), 1.2 (*n* = 16; 0.6–2.2), 1.2 (*n* = 16; 0.6–2.1) and 2.1 (*n* = 21; 1.2–3.8). Analyses by duration, average, highest ever and lagged exposures yielded RRs for lung cancer similar to those seen for cumulative exposure, with the highest risks again occurring in the upper quintile. To evaluate RRs for lung cancer at a wider range of cumulative exposure, analyses were also conducted for decile categories. The RR did not continue to increase at higher levels and actually decreased

from the ninth (RR, 1.7) to the tenth (RR, 1.3) decile. There was concern about possible confounding from tobacco use. The RR for ever cigarette smokers compared to never smokers was 3.6 (95% CI, 1.6–8.2). Adjustment for 'ever cigarette use' in the case–cohort analysis changed the RR for lung cancer only slightly (RRs for lowest to highest quintile of cumulative exposure without lagging were 0.3 (n = 5; 95% CI, 0.1–1.0), 0.8 (n = 6; 95% CI, 0.3–1.8), 1.0 (n = 7; 95% CI, 0.4–2.4), 0.9 (n = 13; 95% CI, 0.4–1.9) and 1.6 (n = 9; 95% CI, 0.7–3.3)). Separate analyses for wage and salaried workers, long-term and short-term workers, fibre and non-fibre plants and by individual plants revealed no clear exposure–response pattern. Workers holding maintenance jobs were excluded in one analysis because of concern about exposure to asbestos. The RR in the upper quintile of cumulative exposure dropped from 1.5 (as in the total cohort) to 1.3 when these workers were excluded. There were no deaths from asbestosis or mesothelioma, however. A large proportion of the workers in the study by Collins *et al*. (1989) were also included in this investigation.

3. Studies of Cancer in Experimental Animals

In two unpublished studies described by Maltoni *et al*. (1987), inhalation exposure of male and female Sprague-Dawley rats to 80 ppm (174 mg/m^3) acrylonitrile for 6 h per day on five days per week for two years resulted in increased incidences of glial-cell tumours of the central nervous system (males and females), Zymbal gland tumours (males and females), mammary gland adenocarcinomas (females), small intestine tumours (males) and squamous-cell tumours of the tongue (males). Oral administration of up to 300 mg/L (ppm) acrylonitrile to Sprague-Dawley rats in the drinking-water for two years resulted in significant increased incidences of tumours of the forestomach, tongue, Zymbal gland and brain in males and of the mammary gland, Zymbal gland, tongue, forestomach and brain in females (see also Quast *et al.*, 1981). [The Working Group noted that full reports of these studies have not been published in the peer-reviewed scientific literature.]

3.1 Oral administration

Rat: Two groups of 50 male and 50 female Fischer 344 rats, six weeks of age, were administered acrylonitrile [purity unspecified] at concentrations of 100 or 500 mg/L (ppm) in the drinking-water for life; a group of 51 males and 49 females served as controls. An additional group of 147 males and 153 females was administered drinking-water containing 500 mg/L (ppm) acrylonitrile and selected animals were killed periodically during the study. Body weights and survival were not reported, but were described as lower than those of controls at both doses. At the time of reporting, 215 rats from the 500-ppm dose groups which either died or were killed between months 6 and 18 had been evaluated microscopically for brain lesions. Forty-nine animals [sex not specified] had primary brain tumours described as "similar to ... astrocytomas or anaplastic

astrocytomas". Zymbal gland tumours, stomach and skin papillomas and brain tumours were more frequently seen in acrylonitrile-treated groups than in controls [incidences not given] (Bigner *et al.*, 1986). [The Working Group noted the apparent marked brain tumour response in exposed rats, but also that the findings were preliminary; interpretation was hampered by incomplete reporting and a lack of information on control tumour rates.]

A group of 40 male and 40 female Sprague-Dawley rats, 10 weeks of age, was administered 5 mg/kg bw acrylonitrile (99.9% pure) by gavage in olive oil three times per week for 52 weeks. A similar group of 75 males and 75 females was administered olive oil alone and served as controls. Rats were allowed to live out their lifespan and received a complete gross necropsy and histological evaluation at death. Acrylonitrile exposure did not affect body weight gain or survival. No increase in the incidence of tumours at any site was observed (Maltoni *et al.*, 1977, 1987). [The Working Group noted the single dose level and the short duration of exposure.]

3.2 Inhalation exposure

Rat: Groups of 30 male and 30 female Sprague-Dawley rats, 12 weeks of age, were exposed to 0, 5, 10, 20 or 40 ppm [0, 11, 22, 43 or 86 mg/m^3] acrylonitrile (99.9% pure) by whole-body inhalation for 4 h per day on five days per week for 52 weeks. Rats were allowed to live out their lifespan and received a complete gross necropsy and histological evaluation at death. Exposure to acrylonitrile did not affect body weight gain or survival. No significant increase in the incidence of tumours at any specific site was observed, but incidence of total benign and malignant tumours, as well as that of total malignant tumours, were increased over those in controls. Glial cell tumours of the brain occurred in two males and one female given 40 ppm, and one male and one female given 20 ppm but not in controls (Maltoni *et al.*, 1977, 1987). [The Working Group noted the short duration of exposure and that rats may have tolerated exposure concentrations higher than 40 ppm.]

A group of 54 female Sprague-Dawley rats, 13 weeks of age, was exposed to 60 ppm [130 mg/m^3] acrylonitrile (99.9% pure) by whole-body inhalation for 4 h per day on five days per week for seven weeks. Twenty-two of these rats were pregnant at the start of the study and delivered litters. Male offspring were divided into groups of 67 (A) and 60 (B), and females into groups of 54 (A) and 60 (B). All groups were exposed for 4 h per day on five days per week during the first seven weeks after birth. Subsequently, the duration of exposure was increased to 7 h per day, and breeders and group A offspring were exposed on five days per week for 97 weeks. Group B offspring were similarly exposed for eight weeks. A group of 60 13-week-old female rats (24 pregnant) was exposed to air and served as controls. A total of 158 male and 149 female offspring also served as controls. Rats were allowed to live out their lifespan and received a complete gross necropsy and histological evaluation at death. Exposure to acrylonitrile did not affect body weight gain or survival. The number of rats bearing malignant tumours of any type was increased in all exposed groups. Incidence of malignant mammary tumours was

increased in female offspring exposed for 104 weeks (9/54 exposed versus 8/149 controls), as was that of extrahepatic angiosarcomas (3/54 exposed versus 0/149). The incidence of carcinomas of the Zymbal gland (10/67 exposed versus 2/158 controls) and of benign and malignant hepatocellular tumours (5/67 exposed versus 1/158 controls) was increased in male offspring exposed for 104 weeks. The incidence of glial cell tumours of the brain was increased in both male (11/67 versus 2/158) and female (10/54 versus 2/149) offspring exposed for 104 weeks (Maltoni *et al*., 1987).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

(*a*) *Inhalation exposure*

When volunteers were exposed to an atmosphere containing 20 mg/m^3 acrylonitrile for up to 4 h, retention in the respiratory tract was 46 ± 1.6%, which did not change significantly during the experimental period (Rogaczewska & Piotrowski, 1968).

Workers exposed to 0.13 ppm [0.3 mg/m^3] acrylonitrile vapour in a factory excreted unchanged acrylonitrile in their urine, the amounts being greatest at the end of the exposure period, declining rapidly thereafter until the beginning of the next workday. The amounts excreted in samples taken during the working week or on the following two days off ranged from 2 to 152 μg acrylonitrile/g creatinine (Houthuijs *et al.*, 1982).

(*b*) *Percutaneous absorption*

The percutaneous absorption rate of neat acrylonitrile applied to the forearm of four volunteers was 0.6 mg/cm^2/h (Rogaczewska & Piotrowski, 1968). Therefore, skin uptake of acrylonitrile can contribute to the body burden of this compound.

(*c*) *In-vitro reactions and metabolism in human tissue preparations*

Acrylonitrile is metabolized to the reactive cyanoethylene oxide (CEO) [also called glycidonitrile], mainly by CYP2E1, but also by other forms of human cytochrome P450. Incubation of CEO with human hepatic microsomes, but not cytosolic preparations, significantly increased its basal rate of hydration to the corresponding diol (0.69 nmol/min). This hydration activity was heat-sensitive and potently inhibited by 1,1,1-trichloropropene oxide (IC_{50}, 23 μM), indicating that epoxide hydrolase was the catalyst. The hydration of CEO catalysed by hepatic microsomes from six individuals showed normal saturation kinetics with K_m ranging from 0.6 to 3.2 mM and V_{max} from 8.3 to 18.8 nmol hydration products/min/mg protein. These data show that humans possess a detoxication pathway for CEO that is not active in rodents (see Section 4.1.2(*d*)) (Kedderis & Batra, 1993).

(*d*) *Biomonitoring of human exposure*

Although urinary assays afford a means of monitoring exposure to acrylonitrile, protein adducts are more toxicologically relevant biomarkers of exposure. Like many chemical carcinogens, acrylonitrile forms adducts with the N-terminal valine residues of haemoglobin, which can be cleaved by a modification of the Edman degradation and determined by mass spectrometric techniques, using stable labelled analogues as internal standards (Lawrence *et al*., 1996). This method has revealed far higher levels of the adduct (*N*-(2-cyanoethyl)valine; CEV) in factory workers exposed to acrylonitrile than in matched unexposed controls from the same factory. Exposed workers had CEV levels of 2.0–2.3 nmol/g globin, whereas in a group of control workers in the same factory, the values were 0.03 ± 0.09 nmol CEV/g globin. Levels of acrylonitrile exposure in the workplace were not reported. CEV levels in smoking mothers were about 0.2 nmol/g globin and 0.1 nmol CEV/g globin in their babies. Levels of CEV in nonsmokers were not detectable (Tavares *et al.*, 1996). Bergmark (1997) reported CEV levels of about 0.1 nmol CEV/g globin in smokers.

4.1.2 *Experimental systems*

(*a*) *Absorption and tissue distribution*

After oral administration to rats and mice, acrylonitrile is well absorbed from the gastrointestinal tract, giving rise to detectable amounts of unchanged compound and metabolites in the blood. The principal route of elimination is via the urine, between 77 and 104% of the dose being recovered, with less than 8% of the dose occurring in the faeces (Kedderis *et al*., 1993a). These data confirmed and extended those of Sapota (1982) in rats, which had similar excretion patterns when given 40 mg/kg doses of acrylonitrile labelled with ^{14}C in the cyanide moiety ([1-^{14}C]acrylonitrile) and in the vinyl group ([2,3-^{14}C]acrylonitrile). In both cases, oxidation to $^{14}CO_2$ was a minor pathway (less than 8% of the dose). The elimination pattern was the same after either intraperitoneal or oral dosing (Sapota, 1982) and was unaffected by dose over the range 0–28.8 mg/kg in rats and 0–10 mg/kg in mice (Kedderis *et al*., 1993a). Burka *et al*. (1994) showed that 11% of a 46 mg/kg dose of [2-^{14}C]acrylonitrile was excreted in the expired air of Fischer 344 rats as $^{14}CO_2$.

The tissue distributions of [1-^{14}C]- and [2,3-^{14}C]acrylonitrile (40 mg/kg) were compared in Wistar rats after intraperitoneal and oral administration (Sapota, 1982). The relative distributions of the two labelled forms were very similar and the principal locations of ^{14}C were erythrocytes, liver and kidney. After oral administration, the rate of elimination from tissues was slower for [*cyano*-^{14}C]- than for [1,2-*vinyl*-^{14}C]acrylonitrile. After gavage administration of 46 mg/kg bw [2-^{14}C]acrylonitrile to Fischer 344 rats, radioactivity was well absorbed from the gastrointestinal tract and distributed to all major tissues 24 h after dosing. The highest levels were found in the forestomach, blood and urinary bladder. Prior treatment of rats with phenobarbital had little effect on the pattern of distribution and excretion of ^{14}C, but the CYP inhibitor SKF-525A caused marked changes, with less excretion (less than 40% in urine in 24 h compared with over 60% in

untreated animals) and greater tissue retention, particularly in the blood, liver, kidney, lung, forestomach, glandular stomach, small intestine and urinary bladder (Burka *et al*., 1994).

Higher levels of radioactivity in Sprague-Dawley rats after intravenous administration of [1-^{14}C]acrylonitrile (100 mg/kg bw) were found in blood, liver, duodenum, kidney and adrenal gland than in other tissues (Silver *et al.*, 1987).

Sandberg and Slanina (1980) studied the tissue distribution of [1-^{14}C]acrylonitrile in Sprague-Dawley rats (26 mg/kg bw orally and after intravenous injection) and cynomolgus monkeys (4 and 6 mg/kg bw, orally only) by whole-body autoradiography. In all cases, radioactivity was detected in blood, liver, kidney, lung, adrenal cortex and stomach, the highest levels corresponding to the target organs of toxicity. The same technique was used in a later study of single doses of [2,3-^{14}C]acrylonitrile in rats (Sato *et al*., 1982). Higher concentrations of radioactivity were seen in blood, particularly erythrocytes, lung, liver and kidney, and longer retention was evident in brain and muscle than in other tissues. Most radioactivity was present in the cytosolic fractions prepared from brain, liver and kidney.

Ahmed *et al*. (1982) examined the distribution of [1-^{14}C]acrylonitrile (46.5 mg/kg bw orally) in rats. Some 55% of the dose was recovered in the excreta in 24 h (urine, 40%; faeces, 2%; exhaled as $^{14}CO_2$, 9%; as H^{14}CN, 0.5%; and acrylonitrile, 4.8%). In addition to appreciable retention in the erythrocytes (a feature of the behaviour of metabolically formed thiocyanate noted by Bollard *et al*., 1997), there occurred covalent binding to tissue macromolecules in liver, kidney, spleen, brain, lung and heart. Ahmed *et al.* (1983) also compared the tissue distribution of [1-^{14}C]- and [2,3-^{14}C]acrylonitrile in rats at the same dose level (46.5 mg/kg bw). There was much more covalent binding of radioactive species in all organs examined after administration of [2,3-^{14}C]acrylonitrile, suggesting that metabolites other than thiocyanate play a major role in its retention in the body.

In both rats and mice, the radioactivity derived from orally administered 2-cyano-[1,2-^{14}C]ethylene oxide, the epoxide metabolite of acrylonitrile, was widely distributed to the tissues with no particular accumulation in any organ and was rapidly depleted within 24 h after dosing (Kedderis *et al*., 1993b).

(*b*) *Toxicokinetics*

Gargas *et al*. (1995) have developed a physiological toxicokinetic model of acrylonitrile in rats which includes the behaviour of CEO. In-vitro kinetic studies of the metabolism of both acrylonitrile and CEO showed that epoxidation to CEO is saturable, while glutathione conjugation of acrylonitrile follows first-order kinetics. The model combines these kinetic parameters with tissue partition data to allow simulation of the urinary excretion of acrylonitrile metabolites and the formation of haemoglobin adducts (see below). The model has been further refined by Kedderis *et al*. (1996) to predict the behaviour of acrylonitrile and CEO after inhalation exposure to acrylonitrile.

(*c*) *Metabolic fate of acrylonitrile*

Urinary metabolites of acrylonitrile include *S*-(2-cyanoethyl)mercapturic acid, *N*-acetyl-3-carboxy-5-cyanotetrahydro-1,4-3*H*-thiazine and thiocyanate (Kopecký *et al*., 1979; Langvardt *et al*., 1980; Gut *et al*., 1981; Sapota, 1982). The proportion excreted as thiocyanate by rats is far higher (23% of dose) after oral dosing than after intraperitoneal, intravenous or subcutaneous administration (1–4% of dose; Gut *et al*., 1981). Other metabolites derived from the mercapturic acid pathway include *S*-carboxymethylcysteine, *S*-hydroxyethylmercapturic acid [*N*-acetyl-*S*-(2-hydroxyethyl)cysteine] and thiodiglycolic acid (Müller *et al*., 1987).

The formation of these various products can be rationalized by metabolism along two primary pathways, the products of which undergo extensive secondary and tertiary reactions, leading to a wide range of metabolites in the excreta (Figure 1). The carbon–carbon double bond undergoes epoxidation, mediated predominantly by CYP2E1 in rats and man (Guengerich *et al*., 1981; Kedderis *et al*., 1993c), to yield CEO, or addition of glutathione via a reverse Michael addition in which the sulfur atom is linked with the terminal carbon of acrylonitrile (Van Bladeren *et al*., 1981; Kedderis *et al*., 1995). The primary product of this latter pathway, *S*-(2-cyanoethyl)glutathione, is converted to *S*-(2-cyanoethyl)mercapturic acid and thence to *S*-(2-cyanoethyl)thioacetic acid (Kedderis *et al*., 1993a).

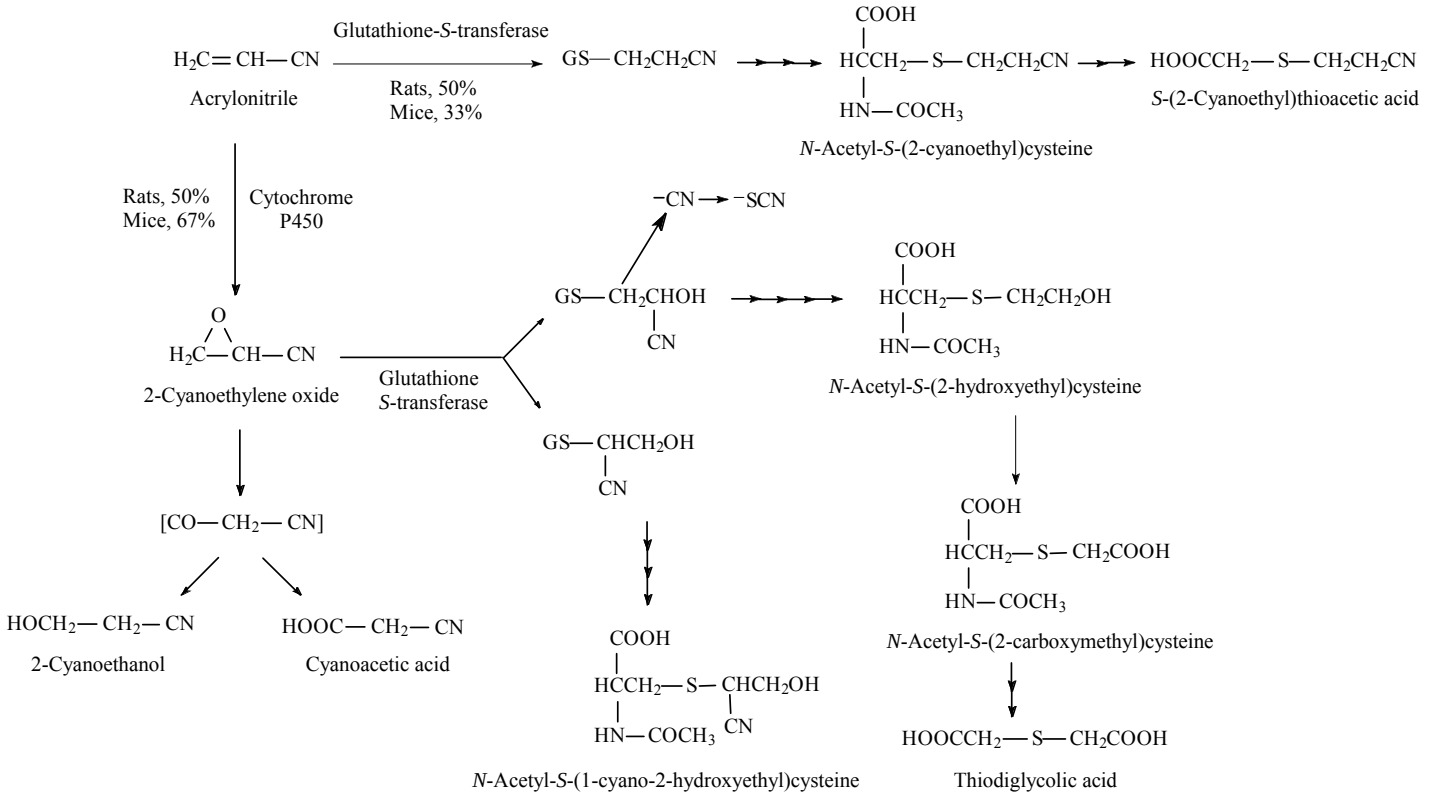
CEO is also a substrate for glutathione conjugation, giving the isomeric conjugates 1- and 2-*S*-glutathionyl-1-cyanoethanol (Van Bladeren *et al*., 1981; Kedderis *et al*., 1993a). The 1-*S*-glutathionyl conjugate is converted to the corresponding cysteinyl conjugate, which is then *N*-acetylated, giving *N*-acetyl-*S*-(1-cyano-2-hydroxyethyl)-cysteine in the urine. The 2-*S*-glutathionyl conjugate loses HCN, which is converted to thiocyanate, and gives rise to the mercapturic acid, *N*-acetyl-*S*-(2-hydroxyethyl)cysteine, which is excreted as such and also undergoes further metabolism to *N*-acetyl-*S*-(2-carboxymethyl)cysteine and thence to thiodiglycolic acid.

The metabolism of CEO gives rise to cyanoacetic acid, 2-cyanoethanol, cyanide, thiocyanate and $^{14}CO_2$ as in-vivo metabolites, which can be rationalized in terms of three distinct reactions: (i) enzymic hydration of the epoxide (Kedderis & Batra, 1993; Kedderis *et al*., 1995) giving a cyanohydrin, glycolaldehyde cyanohydrin, which has been shown *in vitro* to eliminate HCN, this then being converted by rhodanese to thiocyanate, (ii) rearrangement to the α-ketonitrile, pyruvonitrile, which would then be hydrolysed to acetate, the most likely precursor of $^{14}CO_2$, with elimination of cyanide, and (iii) rearrangement to cyanoacetaldehyde, which would then be oxidized to cyanoacetic acid or reduced to 2-cyanoethanol.

(*d*) *Metabolic studies in vitro*

Marked species differences have been reported for the metabolic activation of acrylonitrile to CEO *in vitro*. The V_{max} and V_{max}/K_m for microsomes from mouse liver and lung were approximately four and 13 times greater, respectively, than the kinetic parameters for rat liver and lung microsomes. The rate of CEO production in human liver

Figure 1. The metabolic disposition of acrylonitrile in rats and mice. The percentages given are the fluxes through each pathway after an oral bolus dose of 0.09 mg/kg bw. Modified from Kedderis et al. (1993a)



microsomes was similar to that with rat liver microsomes, but less than that with mouse liver microsomes (Roberts *et al*., 1991).

CEO is relatively stable in pH 7.3 buffer at 37°C ($t_{½}$ = 99 min) and undergoes hydration to the corresponding diol. Incubation of CEO with hepatic microsomes of cytosols from male Fischer 344 rats or B6C3F_1 mice did not enhance its basal rate of hydration, unlike human hepatic microsomes (see Section 4.1.1(*c*)). Prior treatment of rodents with either phenobarbital or acetone induced hepatic microsomal hydration activity towards CEO, whereas treatment with β-naphthoflavone, dexamethasone or acrylonitrile itself was without effect (Kedderis & Batra, 1993).

(*e*) *Influence of dose size and route of administration*

Rats were given acrylonitrile by three separate routes of administration: intravenous, intraperitoneal (both at doses of 0.6, 3 and 15 mg/kg bw) and inhalation (at 4, 20 and 100 ppm [9, 43 and 217 mg/m^3] for 6 h) and the main metabolites were determined in the 0–24-h urine (Tardif *et al*., 1987). The total recovery of metabolites was dose-related, but the pattern of metabolites was dependent upon the route of administration, with more of the mercapturic acids appearing in the urine after intravenous or intraperitoneal dosing, whereas the main metabolite was thiocyanate after inhalation exposure. The relative importance of the various metabolic pathways of acrylonitrile in rats and mice is dose-dependent (Kedderis *et al*., 1993a). The sulfur-containing metabolites derived from the glutathione conjugation of CEO increase in an approximately linear fashion with increasing dose of acrylonitrile in both rats (0–28.8 mg/kg bw) and mice (0–10 mg/kg bw). Differences occur in the patterns of the secondary and tertiary metabolites of the glutathione conjugates of CEO, but these are unlikely to have toxicological significance.

After inhalation exposure, the excretion of thiocyanate and acrylonitrile-derived mercapturic acids by Wistar rats was proportional to the dose over the range 57–271 mg/m^3 (Gut *et al*., 1985).

Burka *et al*. (1994) examined the effect of treatment of rats with phenobarbital and SKF-525A on the urinary metabolite profile of [2-^{14}C]acrylonitrile. Phenobarbital treatment increased the excretion of products attributed to the oxidation of acrylonitrile to CEO, while SKF-525A treatment enhanced the excretion of the mercapturic acid derived from the glutathione conjugation of acrylonitrile itself.

4.2 Toxic effects

4.2.1 *Humans*

Reported toxic effects of acrylonitrile in humans are summarized in Table 6.

(*a*) *Acute toxicity*

(i) *Inhalation exposure*

A 22-year-old chemist, who was exposed to acrylonitrile vapours, developed headache, vertigo, vomiting, tremors, uncoordinated movements and convulsions (Sartorelli, 1966). Vomiting and nausea persisted for 24 h. One day after exposure, slight liver

Table 6. Toxic effects of acrylonitrile in humans

Lesion/dysfunction	Exposure			Reference
	Type	Level	Duration	
Headache, tremor, convulsions	Inhalation	?	Acute	Sartorelli (1966)
Nausea, vomiting, headache, vertigo	Inhalation	35–220 mg/m^3	Acute	Zeller *et al.* (1969)
Dizziness, flushing, nausea, vomiting	Dermal, inhalation	NG	Acute	Vogel & Kirkendall (1984)
Erythema	Dermal	Conc. liquid	Acute	Wilson *et al*. (1948)
Skin burning, blisters	Dermal	Conc. liquid	Acute	Zeller *et al*. (1969)
Headache, poor sleep, chest pain	Inhalation	NG	Months	Zotova (1975)
Headache, weakness, fatigue, nausea, vomiting, nosebleeds, insomnia	Inhalation	NG	Years	Sakurai & Kusumoto (1972); Sakurai *et al*. (1978)
Headache, fatigue, tongue trouble, sweating	Inhalation	NG	Chronic	Kaneko & Omae (1992)
Reduced haemoglobin, other haematological disorders	Inhalation	2.5–5 mg/m^3	Chronic	Shustov (1968)
Blepharoconjunctivitis	Local (vapours?)	NG	Chronic	Delivanova *et al*. (1978)
Gastritis, colitis	Vapours?	5 mg/m^3	Chronic	Enikeeva *et al*. (1976)
Allergic dermatitis	Local	NG	Chronic	Spassovski (1976); Stamova *et al*. (1976)

NG, not given

enlargement and congestion of the oral pharynx, but no disorders of the central nervous system, were noted. After four days, no kidney, liver, cardiac or respiratory abnormalities were detected. Workers exposed to 'mild' concentrations of acrylonitrile in synthetic rubber manufacture developed nausea, vomiting, weakness, nasal irritation and an 'oppressive feeling' in the upper respiratory tract (Wilson, 1944). Headache, fatigue and diarrhoea were observed in some cases, and mild jaundice lasting for several days and accompanied by liver tenderness and low-grade anaemia in a few others. Jaundice lasted for four weeks in one case; this individual complained of lassitude and fatigue after one year. In 16 cases of acute inhalation of acrylonitrile fumes by workers, nausea, vomiting, headache and vertigo were experienced within 5–15 min; none of the workers needed hospitalization (Zeller *et al.*, 1969). Workmen exposed to concentrations varying from 35 to 220 mg/m^3 for 20–45 min during cleaning operations in polymerizers frequently complained of a dull headache, fullness in the chest, irritation of the eyes, nose and

throat, and feelings of apprehension and nervous irritability. Some workmen had 'intolerable itching' of the skin, but no accompanying dermatitis.

(ii) *Dermal exposure*

Zeller *et al*. (1969) reported 50 cases of skin damage resulting from occupational contact with acrylonitrile. A burning sensation developed within 5 min to 24 h followed by a reddening of the area, which often blistered after one day. A male laboratory worker who spilled 'small quantities' of liquid acrylonitrile on his hands developed diffuse erythema on both hands and wrists after 24 h, and blisters on the fingertips by the third day. The hands were slightly swollen, erythematous, itchy and painful. The fingers remained dry and scaly 10 days later (Dudley & Neal, 1942). Wilson *et al*. (1948) observed that direct skin contact led to irritation and erythema followed by scab formation; healing was slow.

In a 24-year-old man, dermal and inhalation exposure to acrylonitrile resulted in dizziness, flushing, nausea and vomiting. Furthermore, increases in serum creatinine phosphokinase, transaminases and myoglobinuria occurred, possibly as a consequence of tissue hypoxia (Vogel & Kirkendall, 1984).

Blisters developed at the sites of contact after 6–8 h in workers who had spilled liquid acrylonitrile on their legs. The skin of two workers who were cleaning apparatus (temperature 50°C) came into contact with 5% acrylonitrile solution; other possible substances in the mixture were not specified. Serious skin burns developed (Babanov, 1957).

Development of allergic dermatitis is possible; a 27-year-old individual developed a rash on his finger following the use for six weeks of a finger splint made from an acrylonitrile–methyl methacrylate copolymer. Patch testing gave positive reactions to the copolymer and 0.1% acrylonitrile (Balda, 1975). In another case report, skin lesions were first observed at the site of contact with liquid acrylonitrile, which then spread rapidly to other neighbouring regions. Several days after contact, the lesions spread rapidly to other parts of the body that had not been exposed, and these extensions were assumed to be an allergic reaction (Hashimoto & Kobayashi, 1961). The occurence of occupational contact dermatitis due to acrylonitrile among five employees in an acrylonitrile production factory was reported by Bakker *et al*. (1991).

(*b*) *Chronic toxicity—occupational exposure*

(i) *General toxicity*

Complaints of poor health, headache, decreased work capacity, poor sleep, irritability, chest pains, poor appetite and skin irritation (during the first months of employment only) came from workers employed in the manufacture of acrylonitrile (Zotova, 1975).

Sakurai and Kusumoto (1972) analysed records from health examinations of acrylonitrile workers at five acrylic fibre factories for a period of about 10 years up to 1970. The prevalence of subjective complaints and abnormal values for some of the liver function tests increased significantly with length of time spent in acrylonitrile-related jobs. It was later commented, however, that the study lacked adequate epidemiological

design, that the exposure levels were not reliably reported and that the findings were based upon routine health examinations (Sakurai *et al.*, 1978). In this latter publication, the results were described of a study of 102 workers whose exposure to acrylonitrile exceeded five years and in 62 matched controls, all of whom had been randomly sampled from six acrylic fibre factories in Japan. The six factories were classified into three groups on the basis of acrylonitrile concentrations in the workplaces. The most highly exposed group had an 8-hour average acrylonitrile concentration of 4.2 ppm [9.1 mg/m^3] by personal sampling, a mean urinary acrylonitrile concentration of 360 µg/L and a mean urinary thiocyanate concentration of 11.4 mg/L. Medical examination, including multiple clinical chemistry measurements and the indocyanine green excretion test, failed to detect any health effect attributable to acrylonitrile.

Babanov *et al*. (1959) reported that workers exposed to acrylonitrile concentrations of 0.6–6 mg/m^3 for approximately three years suffered from headache, insomnia, pains in the heart region, general weakness, decreased working capacity and increased irritability. The vocal cords were inflamed, and pale mucous membranes and skin were seen.

Changes in health status and laboratory tests were not observed in a group of 23 men who had been working for three to five years in an acrylonitrile plant, where exposure levels reached 4.2–7.2 mg/m^3 (Ginœva *et al*., 1977). Stamova *et al*. (1976) studied workers' health in the related polyacrylic fibre plant in which acrylonitrile exposure levels were around 10 mg/m^3, but could fluctuate upwards to 25 mg/m^3. Workers were also exposed to other chemical substances. An increased incidence was found for both skin diseases and various 'neurasthenic' complaints and diseases. Dorodnova (1976) did not find any differences in the gynaecological health status of 410 women working in a polyacrylic fibre plant compared with that of 436 unexposed women. Workers exposed to acrylonitrile were observed from 1950 to 1982 for mortality (Chen *et al*., 1988b). No dose–response relationship was observed between exposure and mortality. Subjective symptoms with significantly high prevalence in acrylonitrile-exposed workers in seven acrylic fibre-manufacturing factories were: headache, tongue trouble, choking lump in throat, fatigability, general malaise, heavy arms and heavy sweating (Kaneko & Omae, 1992). Neurotic status determinations did not reveal any differences between the group of workers investigated and a reference group.

(ii) *Other organs*

Liver

In a study of 102 workers from acrylic fibre factories in Japan, Sakurai *et al*. (1978) did not find any significant abnormality in liver function tests related to acrylonitrile exposure.

Nervous system

Nausea, vomiting, headache and vertigo (Wilson, 1944; Wilson *et al*., 1948; Zeller *et al*., 1969; Zotova, 1975; Sakurai *et al*., 1978) indicate a possible effect of acrylonitrile on the nervous system. Ageeva (1970) reported a significant decrease in an 'epinephrine-

like substance' and an increase in acetylcholine. Depression, lability of autonomic functions (lowered arterial pressure, labile pulse, diffuse dermographia, increased sweating, change in orthostatic reflex) were also observed in workers involved in acrylonitrile production.

4.2.2 *Experimental systems*

(*a*) *Acute toxicity*

In a variety of laboratory animals, acute LD_{50} values for acrylonitrile ranged from 25 to 186 mg/kg bw. For various routes of administration, mice were reported to be more sensitive towards acrylonitrile than rats, guinea-pigs and rabbits. For inhalation exposure, the LC_{50} was determined in most studies for a 4-h period of exposure to be between 140 and 1250 mg/m^3. In these studies, the dog was the most sensitive species, followed by the mouse, rabbit, cat, rat and guinea-pig (McOmie, 1949; Brieger *et al.*, 1952; Jedlicka *et al.*, 1958; Paulet & Desnos, 1961; Graham, 1965; Zeller *et al.*, 1969; Appel *et al.*, 1981).

A number of inhalation studies (Dudley & Neal, 1942; Brieger *et al*., 1952) and studies in which acrylonitrile was administered orally or parenterally (Paulet & Desnos, 1961; Graham, 1965; Paulet *et al*., 1966) have indicated that lethal concentrations or doses of acrylonitrile cause the following sequence of symptoms: excitability and increased breathing frequency, shallow rapid breathing, slow gasping breathing, apnoea and convulsions. Vomiting occurred in cats, dogs and monkeys after inhaling acrylonitrile, and in rats following parenteral administration. Reddening of the skin of the ears, nose and feet (also of the face and genital organs in rhesus monkeys) and mucosa was accompanied by lachrymation, nasal discharge and salivation, not only after inhalation exposure, but also following oral or subcutaneous administration, while hind-leg incoordination, paresis or paralysis were observed in rats after oral administration, and in rabbits after intravenous and intramuscular administration.

Buchter *et al*. (1984) exposed groups of male Wistar rats to acrylonitrile vapours of 4800 ppm [10 400 mg/m^3] for 30 min. Several compounds were given via different routes of administration 10 min after exposure ceased, in order to test their therapeutic efficiency against acute acrylamide poisoning. All untreated animals died. Observations of increased saliva, aqueous humour, spasms and diarrhoea suggested that inactivation of acetylcholinesterase by cyanethylation of serine was involved. In agreement with this hypothesis, atropine sulfate (50 mg/kg bw intravenously) turned out to be a potential antidote. However, *N*-acetylcysteine (300 mg/kg bw intravenously) was the most effective antidote, in line with earlier findings (Hashimoto & Kanai, 1965), demonstrating the excellent potency of thiols in the treatment of acute acrylonitrile toxicity.

Cote *et al*. (1984) and Vodicka *et al*. (1990) observed marked decreases in glutathione levels in a variety of organs such as brain, lung, liver and kidney of rats dosed with acrylonitrile either subcutaneously (75 mg/kg bw) or by inhalation (75–300 mg/m^3). These effects were less pronounced in mouse and hamster tissues. Covalent binding to tissue protein, a dose-dependent decrease in tissue glutathione, and an

increase in blood and brain cyanide levels were observed in acrylonitrile-treated Sprague-Dawley rats (Benz *et al*., 1997a). The authors concluded that depletion of hepatic glutathione is a critical event in acrylonitrile toxicity, exhausting the detoxifying capacity of the liver. The relative potency of various antidotes including L-cysteine, D-cysteine and *N*-acetyl-L-cysteine correlated with their capacity to suppress acrylonitrile metabolism, as monitored by increases in blood cyanide level (Benz *et al*., 1990). However, pretreatment of rats with acrylonitrile for 4 h per day over three consecutive days protected against acute acrylonitrile toxicity without protecting against poisoning by cyanide (Cote *et al*., 1983).

Target organs of acrylonitrile toxicity in experimental animals are listed in Table 7.

(i) *Blood parameters*

Intraperitoneal administration of acrylonitrile to male rats at a dose of 33 mg/kg bw per day for three days decreased serum levels of corticosterone to 30% and prolactin to 40%, but increased follicle-stimulating hormone (FSH) to 200% of control levels, and did not affect luteinizing hormone (LH) (Nilsen *et al*., 1980). In adult male Wistar rats, a single intraperitoneal administration of acrylonitrile of 10 mg/kg bw did not have any effect on serum glutamate-oxaloacetate transferase (SGOT) or serum glutamate-pyruvate transaminase (SGPT) activity, but increased activity of lactate dehydrogenase (LDH) to 200% and of sorbitol dehydrogenase (SDH) to 300% compared with the controls (Noel *et al*., 1978; Duverger-Van Bogaert *et al*., 1978). A 60% increase in serum SDH was found in rats given acrylonitrile at 500 mg/L in the drinking-water for 21 days (Silver *et al*., 1982).

Oral administration of acrylonitrile to male Sprague-Dawley rats at a dose of 80 mg/kg bw led to a significant reduction in packed blood cell volume, mean haemoglobin content per erythrocyte, and number of platelets per litre of blood, 1 h after treatment. Furthermore, significant perturbations of levels of red cell glutathione, 2,3-diphosphoglycerate, adenosine triphosphate, pyruvate and lactate were found (Farooqui & Ahmed, 1983). Gut *et al*. (1984) observed an elevation of blood glucose after a 12-h inhalation exposure of male Wistar rats to 57 mg/m^3 acrylonitrile and higher concentrations.

(ii) *Skin*

Direct application of liquid acrylonitrile to the shaved skin of rabbits immediately induced slight local vasodilatation, without any systemic effect (1–2 mL spread over 100–200 cm^2) or with an increased respiratory rate (3 mL spread over 300 cm^2) (McOmie, 1949). Zeller *et al*. (1969) found that an application of acrylonitrile on a cotton pad to shaved skin of rabbits for 15 min resulted in skin oedema, and for 20 h resulted in slight necrosis.

(iii) *Eye*

Oedema and slight necrosis of the conjunctiva after eight days were observed in rabbits treated with acrylonitrile (Zeller *et al*., 1969).

Table 7. Target organs of acrylonitrile toxicity in mammalian species

Target organ	Species	Type of dysfunction/lesion	Dosage	Duration of treatment	Reference
Skin	Rabbit	Vasodilatation	Dermal application	Acute	McOmie (1949)
		Oedema/necrosis	Dermal application	15 min/20 h	Zeller *et al.* (1969)
Eye	Rabbit	Conjunctivitis	Local application	1 h	McOmie (1949)
		Conjunctivitis/necrosis	Local application	Repeated (over 8 days)	Zeller *et al*. (1969)
Lung	Dog	Pulmonary oedema	100 mg/kg; intravenous	Single dose	Graham (1965)
	Guinea-pig	Pulmonary oedema	100 mg/kg; orally	Single dose	Jedlicka *et al*. (1958)
	Rat	Clara cell hyperplasia	46.5 mg/kg; orally	Single dose	Ahmed *et al*. (1992a)
Forestomach and stomach	Rat	Haemorrhagic gastritis	150 mg/kg; orally	Single dose (after 24 h)	Silver *et al.* (1982)
	Rat	Mucosal erosion and haemorrhage	30 mg/kg; subcutaneous	Single dose	Ghanayem *et al.* (1985)
Adrenals	Rat	Atrophic zona fasciculata	0.05% in drinking-water	21–60 days	Szabo *et al.* (1976)
		Necrosis	150 mg/kg; intravenous	Single dose	Szabo *et. al.* (1981)
Kidney	Rat	Increased urinary volume, glucose	20 mg/kg; orally	Single dose	Rouisse *et al.* (1986)
		Increased urinary *N*-acetyl-D-glucosaminidase	60 mg/kg; orally	Single dose	Rouisse *et al.* (1986)
Liver	Rat	Focal necrosis	150 mg/kg; orally	Single dose	Silver *et al.* (1982)

(iv) *Lung*

Respiratory disturbance and pulmonary oedema were observed in anaesthetized dogs given 100 mg/kg bw intravenously (Graham, 1965) and in guinea-pigs given 100 mg/kg bw orally (Jedlicka *et al*., 1958). After a single oral dose of 46.5 mg/kg bw acrylonitrile, moderate to marked hyperplasia of the Clara cells lining the bronchioles was observed in male Sprague-Dawley rats (Ahmed *et al*., 1992a).

(v) *Forestomach and stomach*

Haemorrhagic gastritis was found in rats necropsied 24 h after administration of acrylonitrile at 150 mg/kg bw in the drinking-water (Silver *et al*., 1982). Pretreatment of rats with cytochrome P450 inducers, such as Arochlor 1254 or phenobarbital, did not modify the extent of stomach/forestomach lesions but markedly increased the ulcerogenic action of acrylonitrile in the duodenum (Szabo *et al*., 1983). Subcutaneous administration of 30 or 50 mg/kg bw acrylonitrile to male Sprague-Dawley rats resulted in dose-dependent superficial mucosal erosion and haemorrhage of the glandular stomach (Ghanayem *et al*., 1985). The occurrence of these lesions was associated with a marked decrease of gastric intracellular reduced glutathione. Sulfhydryl-containing compounds and atropine protected against the acrylonitrile-induced gastric erosions (Ghanayem *et al*., 1985; Ghanayem & Ahmed, 1986).

(vi) *Adrenals*

The effect of lethal doses of acrylonitrile on the adrenals as a model for adrenal apoplexy or haemorrhagic adrenocorticol necrosis was described by Szabo and Selye (1971, 1972) and Szabo *et al*. (1980). After intravenous administration of high doses (150 or 200 mg/kg bw), haemorrhage was observed in both adrenals of most animals, and there was adrenal haemorrhage in some rats following oral administration of 10, 15 or 20 mg/kg bw. Various types of histological damage were observed, particularly in the inner layers of the adrenal cortex but not in the medulla, some of them within 30 min after acrylonitrile administration.

A possible mechanism involving lipid peroxidation in acrylonitrile-induced adrenal injury has been suggested by Silver and Szabo (1982). Szabo *et al*. (1980) investigated the pathogenesis of experimental adrenal haemorrhagic necrosis using various morphological, biochemical and pharmacological methods. Their results suggest that the presence of a functional adrenocortex is necessary for the development of cortical damage. Catecholamine release, endothelial injury in the cortical capillaries and retrograde medullary-cell embolism were suggested as critical events in acrylonitrile-induced adrenocortical necrosis (Szabo *et al*., 1981, 1984).

(vii) *Other organs*

In a human neuroblastoma cell line, Cova *et al*. (1992) found acrylonitrile to be highly toxic, showing an EC_{50} of 72.5 nM for cytotoxicity. The cytotoxic potency of potassium cyanide was 2.5 μM, thus acrylonitrile toxicity in these cells cannot be attributed to its metabolism to cyanide.

Acrylonitrile shows an inhibitory effect on potassium-stimulated respiration of guinea-pig brain cortex slices at 1 mM, but little effect on the liver at the same concentration. A stronger anaesthetic action of acrylonitrile was detected *in vitro* on the sciatic nerve of *Rana nigra maculata*, compared with some other anaesthetic agents (Hashimoto & Kanai, 1965).

In male Fischer 344 rats treated intraperitoneally with 0, 10, 20, 40, 60 or 80 mg/kg bw acrylonitrile, significant increases in urinary volume and glucose were observed 24 h after treatment with 20 mg/kg bw (Rouisse *et al*., 1986). Increased levels of urinary *N*-acetyl-β-D-glucosaminidase were detected after treatment with 60 mg/kg bw acrylonitrile. Symptoms of nephrotoxicity were also observed after a 4-h exposure to 200 ppm [434 mg/m^3] acrylonitrile. Histopathological examination revealed lesions in the proximal tubular region of the kidney.

In Sprague-Dawley rats treated orally with 50, 75, 100 or 150 mg/kg bw acrylonitrile, hepatic nonprotein sulfhydryl concentration was significantly decreased after 30 min (Silver *et al*., 1982). Twenty-four hours after administration of 150 mg/kg bw, focal liver necrosis was observed. In isolated rat hepatocytes, acrylonitrile (1 mM) treatment resulted in the formation of thiobarbituric acid-positive products (a test for malonaldehyde) and in depletion of non-protein sulfhydryl groups, but did not affect markedly the viability of the cells (Nerudová *et al*., 1988).

(*b*) *Chronic toxicity*

Observations have been made on animals treated with acrylonitrile in the drinking-water or food, through inhalation and by dermal application.

Taking into account a variety of toxic end-points of chronic acrylonitrile treatment in Fischer 344 rats, Salsburg (1990) calculated a lowest observable effect level of 3 ppm (mg/L) in drinking water, while 1 ppm acrylonitrile was estimated to be a ‘no mean effect level’.

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

The teratogenic potential of ingested or inhaled acrylonitrile was investigated by Murray *et al*. (1978). Groups of 29–39 pregnant Sprague-Dawley rats were given acrylonitrile in water at 10, 25 or 65 mg/kg bw per day by gavage from day 6 to day 15 of gestation. A control group of 43 rats was given water. Groups of 30 pregnant rats were exposed for 6 h per day to 0, 40 or 80 ppm [0, 87 or 174 mg/m^3] acrylonitrile by inhalation, during the same period of pregnancy. A dose of 65 mg/kg bw per day caused marked maternal toxicity, significant embryotoxicity and an increased incidence of fetal malformations. Findings of the two studies suggested a teratogenic effect at 25 mg/kg bw per day and at 40 ppm. At 10 mg/kg bw per day and 20 ppm, no embryotoxicity or terato-

genicity was found. There was no apparent correlation between the degree of toxicity seen in the individual dams and the occurrence of malformations in their offspring.

Single intraperitoneal injections of acrylonitrile of 32 mg/kg bw, given on the fifth and seventh days of pregnancy, induced an embryotoxic effect in mice from an inbred strain of AB Jena-Halle, but not in DBA and C57 C1 mice (Scheufler, 1980).

Kankaanpää *et al*. (1979) studied the embryotoxic effects of acrylonitrile using chick eggs, but did not find any clear evidence of teratogenicity.

Exposure of Sprague-Dawley rats to acrylonitrile in drinking-water at a concentration of 500 mg/L (ppm) led to decreased fertility and decreased viability of the young, and the females developed progressive muscular weakness in the hind legs about 16–19 weeks after the weaning of the second litter (Svirbely & Floyd, 1961).

Exposure of Sprague-Dawley rats to acrylonitrile by inhalation in the range of 12–100 ppm [26–220 mg/m^3] for six hours per day on days 6–20 of gestation resulted in fetotoxicity accompanied by overt signs of maternal toxicity at 25 ppm [54 mg/m^3] and higher concentrations. No significant teratogenicity was observed (Saillenfait *et al.*, 1993a).

Willhite (1981a,b) observed skeletal malformations in fetuses after administration of acrylonitrile at 80 mg/kg bw to pregnant hamsters. The histological study of both early embryos and term fetuses revealed mesodermal changes, including a reduction in the number of cells, shrinkage of the cell cytoplasm and enlarged extracellular spaces. In addition, a reduction in mitotic figures and focal necrosis were noted. The affected embryos were smaller and their development was delayed compared with untreated controls. Teratogenic effects were observed only when there was simultaneous maternal toxicity.

In a rat whole-embryo culture system, depletion of glutathione aggravated the embryotoxic and teratogenic effects of acrylonitrile (Saillenfait *et al.*, 1993b).

4.4 Genetic and related effects

4.4.1 *Humans*

There was no difference in the incidence of chromosomal aberrations in the peripheral lymphocytes between 18 workers who had been exposed to acrylonitrile (1.5 ppm [3.3 mg/m^3]) for an average of 15.3 years and 18 workers who had not been exposed to acrylonitrile (Thiess & Fleig, 1978). In another study, it was claimed that there was an excess of chromosomal aberrations (but not sister chromatid exchange) in 10 workers exposed to 2 ppm [4.3 mg/m^3] acrylonitrile, compared with five unexposed subjects. Urine from exposed workers was tested for gene mutagenic potential in *Salmonella typhimurium* TA98, following extraction, concentration and treatment with β-glucuronidase. No activity was found (Borba *et al.*, 1996). [The Working Group noted the inadequate reporting of exposure and cytogenetic data in this study.]

4.4.2 *Experimental systems* (see Table 8 for references)

Acrylonitrile was a subject of a large interlaboratory testing trial, results of which were published in 1985 and which contributed to the substantial quantity of available in-vitro test data.

Table 8. Genetic and related effects of acrylonitrile

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SAF, *Salmonella typhimurium* TM677, forward mutation	+	–	500	Liber (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	0.2% (vapour)	de Meester *et al.* (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500	Lijinsky & Andrews (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	(+)	19	Cerna *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	2500	Rexroat & Probst (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	2500	Matsushima *et al.* (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	500	Zeiger & Haworth (1985)
SA2, *Salmonella typhimurium* TA102, reverse mutation	–	–	1600	Baker & Bonin (1985)
SA2, *Salmonella typhimurium* TA102, reverse mutation	–	–	2500	Matsushima *et al.* (1985)
SA3, *Salmonella typhimurium* TA1530, reverse mutation	–	+	2.5	de Meester *et al.* (1978)
SA3, *Salmonella typhimurium* TA1530, reverse mutation	–	+	0.2% (vapour)	de Meester *et al.* (1979)
SA3, *Salmonella typhimurium* TA1530, reverse mutation	NT	+	372	Duverger-Van Bogaert *et al.* (1981)
SA3, *Salmonella typhimurium* TA1530, reverse mutation	NT	+	372	Duverger-Van Bogaert *et al.* (1982a)
SA3, *Salmonella typhimurium* TA1530, reverse mutation	NT	+	371	Duverger-Van Bogaert *et al.* (1982b)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	+	100	de Meester *et al.* (1978)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	+	50	Lijinsky & Andrews (1980)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	+	9.5	Cerna *et al.* (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	+	0.05	Zhurkov *et al.* (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	+	167	Zeiger & Haworth (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	2500	Rexroat & Probst (1985)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	100	de Meester *et al.* (1978)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	500	Lijinsky & Andrews (1980)

Table 8 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	2500	Rexroat & Probst (1985)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	100	de Meester *et al.* (1978)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	500	Lijinsky & Andrews (1980)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	5000	Zhurkov *et al.* (1983)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	2500	Rexroat & Probst (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	100	de Meester *et al.* (1978)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500	Lijinsky & Andrews (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	2500	Matsushima *et al.* (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	2500	Rexroat & Probst (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	3333	Zeiger & Haworth (1985)
SAS, *Salmonella typhimurium* TA1530, reverse mutation	–	+	100	de Meester *et al.* (1978)
SAS, *Salmonella typhimurium* TA102, reverse mutation	–	–	2500	Matsushima *et al.* (1985)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	2500	Matsushima *et al.* (1985)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	1667	Zeiger & Haworth (1985)
ECW, *Escherichia coli* WP2 *uvrA*, reverse mutation	+	+	53	Venitt *et al.* (1977)
EC2, *Escherichia coli* WP2, reverse mutation	+	+	53	Venitt *et al.* (1977)
ECR, *Escherichia coli* WP2 *uvrA polA*, reverse mutation	+	+	5.3	Venitt *et al.* (1977)
ECR, *Escherichia coli* WP2 *lexA*, reverse mutation	–	–	53	Venitt *et al.* (1977)
SCG, *Saccharomyces cerevisiae* D7, gene conversion	+	–	25	Arni (1985)
SCG, *Saccharomyces cerevisiae* JD1, gene conversion	–	+	250	Brooks *et al.* (1985)
SCG, *Saccharomyces cerevisiae* PV-2 and PV-3, gene conversion	–	–	800	Inge-Vechtomov *et al.* (1985)
SCG, *Saccharomyces cerevisiae* D7-144, gene conversion	+	+	0.8	Mehta & von Borstel (1985)
SCG, *Saccharomyces cerevisiae* D7, gene conversion	+	–	20	Parry & Eckardt (1985a)

Table 8 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SCH, *Saccharomyces cerevisiae* D7, homozygosis	–	–	50	Arni (1985)
SCH, *Saccharomyces cerevisiae* PV4a and PV4b, homozygosis	–	–	800	Inge-Vechtomov *et al.* (1985)
SCH, *Saccharomyces cerevisiae* D6 and D61-M, homozygosis	+	+	20	Parry & Eckardt (1985b)
SCH, *Saccharomyces cerevisiae* D61-M, homozygosis	+	NT	199	Zimmermann *et al.* (1985)
SCH, *Saccharomyces cerevisiae* RS112, homozygosis by mitotic recombination or gene conversion	+	+	645	Carls & Schiestl (1994)
ANG, *Aspergillus nidulans*, crossing-over	+	NT	806	Carere *et al.* (1985)
SCF, *Saccharomyces cerevisiae* D5, forward mutation	+	NT	30	Ferguson (1985)
SCF, *Saccharomyces cerevisiae* PV-1, forward mutation	–	–	800	Inge-Vechtomov *et al.* (1985)
SCR, *Saccharomyces cerevisiae* D7, reverse mutation	–	–	50	Arni (1985)
SCR, *Saccharomyces cerevisiae* PV-2 and PV-3, reverse mutation	–	–	800	Inge-Vechtomov *et al.* (1985)
SCR, *Saccharomyces cerevisiae* XV185-14C, reverse mutation	+	(+)	0.8	Mehta & von Borstel (1985)
SCR, *Saccharomyces cerevisiae* RM52, reverse mutation	–	–	800	Mehta & von Borstel (1985)
SCR, *Saccharomyces cerevisiae* D7, reverse mutation	–	–	200	Parry & Eckardt (1985a)
SCR, *Saccharomyces cerevisiae* D61-M, reverse mutation	+	+	20	Parry & Eckardt (1985b)
SZF, *Schizosaccharomyces pombe*, forward mutation	–	–	250	Loprieno *et al.* (1985)
SCN, *Saccharomyces cerevisiae* D6 and D61-M, aneuploidy	+	+	20	Parry & Eckardt (1985b)
SCN, *Saccharomyces cerevisiae* D61-M, aneuploidy	–	NT	792	Zimmermann *et al.* (1985)
SCN, *Saccharomyces cerevisiae* D61-M, aneuploidy	–	NT	2290	Whittaker *et al.* (1990)
TSM, *Tradescantia species*, mutation	(+)	NT	0.5	Schairer *et al.* (1982)

Table 8 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
DMG, *Drosophila melanogaster*, genetic crossing over or recombination	–		265 feed	Vogel (1985)
DMG, *Drosophila melanogaster*, genetic crossing over or recombination	–		805 inh	Wuergler *et al.* (1985)
DMM, *Drosophila melanogaster*, somatic mutation (and recombination)	+		424 feed	Fujikawa *et al.* (1985)
DMM, *Drosophila melanogaster*, somatic mutation (and recombination)	+		265 feed	Vogel (1985)
DMM, *Drosophila melanogaster*, somatic mutation (and recombination)	(+)		80 inh	Wuergler *et al.* (1985)
DMN, *Drosophila melanogaster*, aneuploidy	+		2.7 ppm inh	Osgood *et al.* (1991)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	–		3500 ppm inj	Foureman *et al.* (1994)
DIA, DNA strand breaks/alkali-labile sites, Syrian hamster embryo cells *in vitro*	+	NT	200	Parent & Casto (1979)
DIA, DNA strand breaks/alkali-labile sites, Fischer 344 rat primary hepatocytes *in vitro*	+	NT	66	Bradley (1985)
DIA, DNA strand breaks/alkali-labile sites, Chinese hamster ovary CHO cells *in vitro*	+	+	3710	Douglas *et al.* (1985)
URP, Unscheduled DNA synthesis, male Fischer 344 rat primary hepatocytes *in vitro*	–	NT	530	Probst & Hill (1985)
URP, Unscheduled DNA synthesis, male Fischer 344 rat primary hepatocytes *in vitro*	–	NT	100	Williams *et al.* (1985)
URP, Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	–	NT	53	Butterworth *et al.* (1992)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	(+)	(+)	200	Lee & Webber (1985)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	+	10	Rudd (1983)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	+	40	Amacher & Turner (1985)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	+	100	Lee & Webber (1985)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	NT	20	Myhr *et al.* (1985)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	(+)	+	30	Oberly *et al.* (1985)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	?	–	100	Styles *et al.* (1985)

Table 8 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
G51, Gene mutation, mouse lymphoma L5178Y cells, *hprt* locus *in vitro*	(+)	(+)	200	Garner & Campbell (1985)
G51, Gene mutation, mouse lymphoma L5178Y cells, Na^+/K^+ ATPase locus *in vitro*	–	–	200	Garner & Campbell (1985)
GML, Gene mutation, mouse lymphoma P388F cells, *tk* locus *in vitro*	–	+	161	Anderson & Cross (1985)
GIA, Gene mutation, mouse BALB/c 3T3 cells, Na^+/K^+ ATPase locus *in vitro*	NT	+	40	Matthews *et al.* (1985)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–	+	5.3	Ved Brat & Williams (1982)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	+	+	30	Gulati *et al.* (1985)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–	+	106	Natarajan *et al.* (1985)
SIR, Sister chromatid exchange, rat liver RL4 cells *in vitro*	–	NT	5.0	Priston & Dean (1985)
MIA, Micronucleus test, Chinese hamster ovary CHO cells *in vitro*	+	+	1600	Douglas *et al.* (1985)
CIC, Chromosomal aberrations, Chinese hamster Don-6 cells *in vitro*	(+)	NT	5.3	Sasaki *et al.* (1980)
CIC, Chromosomal aberrations, Chinese hamster lung CHL cells *in vitro*	+	NT	18	Ishidate *et al.* (1981)
CIC, Chromosomal aberrations, Chinese hamster liver CH1-L cells *in vitro*	+	NT	12.5	Danford (1985)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	–	(+)	100	Gulati *et al.* (1985)
CIC, Chromosomal aberrations, Chinese hamster lung CHL cells *in vitro*	+	NT	6.2	Ishidate & Sofuni (1985)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	+	+	53	Natarajan *et al.* (1985)
CIR, Chromosomal aberrations, rat liver RL4 cells *in vitro*	–	NT	10	Priston & Dean (1985)
AIA, Spindle damage, Chinese hamster liver CH1-L cells *in vitro*	–	NT	25	Parry (1985)
AIA, Aneuploidy, Chinese hamster liver CH1-L cells *in vitro*	–	NT	25	Danford (1985)
TBM, Cell transformation, BALB/c 3T3 mouse cells	(+)	+	7	Matthews *et al.* (1985)

Table 8 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
TCM, Cell transformation, C3H 10T1/2 mouse cells	–	(+)	16	Lawrence & McGregor (1985)
TCM, Cell transformation, C3H 10T1/2 mouse cells	+	NT	6.3	Banerjee & Segal (1986)
TCS, Cell transformation, Syrian hamster embryo cells, clonal assay	+	NT	0.01	Barrett & Lamb (1985)
TCS, Cell transformation, Syrian hamster embryo cells, clonal assay	+	NT	2	Sanner & Rivedal (1985)
TFS, Cell transformation, Syrian hamster embryo cells, focus assay	+	NT	50	Parent & Casto (1979)
TCL, Cell transformation, NIH/3T3 mouse cells	+	NT	12.5	Banerjee & Segal (1986)
T7S, Cell transformation, SA7/Syrian hamster embryo cells	+	NT	100	Parent & Casto (1979)
DIH, DNA strand breaks, alkali labile site, human bronchial epithelial cells *in vitro*	+	NT	200	Chang *et al.* (1990)
UIH, Unscheduled DNA synthesis, secondary cultures of human mammary epithelial cells *in vitro*	–	NT	53	Butterworth *et al.* (1992)
GIH, Gene mutation, human lymphoblastoid AHH-1 cells *hprt* locus *in vitro*	+	NT	25	Crespi *et al.* (1985)
GIH, Gene mutation, human lymphoblastoid TK6 cells *tk* locus *in vitro*	–	(+)	74	Recio & Skopek (1988)
GIH, Gene mutation, human lymphoblastoid TK6 cells *tk* locus *in vitro*	–	+	40	Crespi *et al.* (1985)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	–	+	26.5	Perocco *et al.* (1982)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	–	–	10	Obe *et al.* (1985)
SIH, Sister chromatid exchange, human bronchial epithelial cells *in vitro*	+	NT	150	Chang *et al.* (1990)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	–	NT	5.3	Cerna *et al.* (1981)
BFA, Bile from Sprague-Dawley rat, *Salmonella typhimurium* TA100, TA1535, TA1537, TA1538, TA98, reverse mutation	–		45 iv × 1	Connor *et al.* (1979)
BFA, Urine from NMRI mice or Wistar rats, *Salmonella typhimurium* TA1530, reverse mutation	(+)		30 ip × 1	Lambotte-Vandepaer *et al.* (1980)
UPR, Unscheduled DNA synthesis, Fischer 344 rat hepatocytes *in vivo*	–		75 po × 1	Butterworth *et al.* (1992)

Table 8 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
UVR, Unscheduled DNA synthesis, Fischer 344 rat spermatocytes *in vivo*	–		75 po × 1	Butterworth *et al.* (1992)
SVA, Sister chromatid exchange, C57BL/6 mouse bone-marrow cells *in vivo*	(+)		45 ip × 1	Sharief *et al.* (1986)
MVM, Micronucleus test, NMRI mouse bone-marrow cells *in vivo*	–		30 ip × 1	Leonard *et al.* (1981)
CBA, Chromosomal aberrations, Swiss albino mouse, Sprague-Dawley rat bone-marrow cells *in vivo*	–		40 po × 16	Rabello-Gay & Ahmed (1980)
CBA, Chromosomal aberrations, NMRI mouse bone-marrow cells *in vivo*	–		30 ip × 1	Leonard *et al.* (1981)
CBA, Chromosomal aberrations, mouse bone-marrow cells *in vivo*	–		140 inh	Zhurkov *et al.* (1983)
CBA, Chromosomal aberrations, C57BL/6 mouse bone-marrow cells *in vivo*	–		30 ip × 1	Sharief *et al.* (1986)
CGG, Chromosomal aberrations, mouse, spermatogonia treated *in vivo*, spermatogonia observed	–		140 inh	Zhurkov *et al.* (1983)
DLM, Dominant lethal test, male NMRI mice	–		30 ip × 1	Leonard *et al.* (1981)
DLM, Dominant lethal test, male mice	–		140 inh	Zhurkov *et al.* (1983)
DLR, Dominant lethal test, male Fischer 344 rats	–		60 po × 5	Working *et al.* (1987)
ICR, Inhibition of intercellular communication, Chinese hamster lung V79 cells *in vitro*	(+)	NT	50	Elmore *et al.* (1985)

[a] +, positive; (+), weak positive; –, negative; NT, not tested; ?, inconclusive

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day; inh, inhalation; inj, injection; iv, intravenous; ip, intraperitoneal; po, oral

Acrylonitrile was mutagenic to bacteria, usually but not exclusively in the presence of an exogenous metabolic system. Urine from acrylonitrile-treated rats and mice, but not the bile from rats, also was mutagenic to bacteria, an exogenous metabolic system not being required. In fungi, acrylonitrile produced variable results, positive and negative outcomes being obtained in tests for mutation, gene conversion, mitotic recombination and aneuploidy. It was weakly mutagenic in a single study with the plant, *Tradescantia spp.*, while, in the insect, *Drosophila melanogaster*, it did not induce sex-linked recessive lethal mutations, again in a single study, or genetic crossing over. Consistently positive results were obtained in *D. melanogaster*, however, for somatic cell mutation, and aneuploidy was induced in one study.

In cultured mammalian cells, acrylonitrile induced DNA strand breakage, gene mutation, sister chromatid exchanges and chromosomal aberrations, but not aneuploidy or unscheduled DNA synthesis in rat hepatocytes, at least if the silver grain counting method was used. [Studies using the less reliable scintillation counting method have not been summarized.] Cell transformation was induced in several test systems and gap-junctional intercellular communication was inhibited in one study with Chinese hamster V79 cells.

In studies with human cells *in vitro*, acrylonitrile induced DNA strand breakage in a single study, gene mutations in two studies and sister chromatid exchanges in two of three studies, but not unscheduled DNA synthesis or chromosomal aberrations in single studies.

In rodents treated *in vivo*, acrylonitrile did not induce unscheduled DNA synthesis in hepatocytes or spermatocytes of rats, chromosomal aberrations in the bone marrow of mice or rats, chromosomal aberrations in spermatogonia of mice, micronuclei in the bone marrow of mice, or dominant lethal effects in either rats or mice. Sister chromatid exchanges were, however, induced in mouse bone marrow.

Binding to macromolecules

Peter and Bolt (1981) showed that the time-dependent covalent binding of [2,3-^{14}C]acrylonitrile to rat liver microsomal protein does not necessarily require metabolic activation and noted, in particular, extensive binding to heat-inactivated liver microsomes. Binding was inhibited by a variety of soluble thiol compounds, such as cysteine, glutathione and diethyl dithiocarbamate. Guengerich *et al.* (1981) showed that a substantial level of binding to microsomal protein, but not to DNA, occurred in the absence of NADPH due to direct alkylation by both [1-^{14}C]- and [2,3-^{14}C]acrylonitrile. At least two-thirds of the protein binding was not the result of metabolism. These findings suggest that the protein binding of acrylonitrile may be mediated at least in part by direct alkylation of nucleophilic centres. In the presence of NADPH, irreversible binding to DNA did occur and protein binding was increased. Metabolic activation was also supported by a reconstituted cytochrome P450 system, whereas experiments with human liver microsomal preparations from six people provided no evidence of protein binding and only a very low level of DNA binding in incubations with one of the six preparations tested.

Later experiments showed that most of the label bound to DNA, RNA or polynucleotides after incubation with [2,3-^{14}C]acrylonitrile was removed by chromatography on hydroxyapatite. When [2,3-^{14}C]acrylonitrile was administered to rats, label was also incorporated in the natural bases of RNA. In addition, there was some evidence for modified DNA bases occurring at levels too low to permit identification (Peter *et al.*, 1983). Using a radiometric derivative assay, Hogy and Guengerich (1986) found that DNA alkylation occurred only at very low levels in liver (0.014–0.032 *N7*-(2-oxoethyl)guanine adducts per 10^6 DNA bases) of rats treated with acrylonitrile by intraperitoneal injection. If adducts occurred in the brain, they were at or below the detection level. Nuclear DNA 8-oxodeoxyguanosine levels were increased in the brain, but not in the liver of rats exposed to acrylonitrile, this result being consistent with oxidative damage rather than direct adduct formation (Whysner *et al.*, 1998). A single oral dose of [2,3-^{14}C]acrylonitrile to Sprague-Dawley rats has been reported to lead to association of radioactivity with DNA isolated from brain (Farooqui & Ahmed, 1983), gastric tissue (Abdel-Rahman *et al.*, 1994) and testis (Ahmed *et al.*, 1992b). Unfortunately, the DNA-processing conditions were not stringent enough to eliminate the possibility of covalent binding to contaminating protein. [The Working Group noted that hydrolysis of DNA and identification of any abnormal nucleotides is essential for the demonstration of covalent binding to DNA, particularly for a substance such as acrylonitrile that binds strongly to proteins.]

CEO binds irreversibly to calf thymus DNA and rat microsomal protein, the binding of radioactivity being greater when the ^{14}C label is in carbons 1 and 2, rather than in the nitrile group (Guengerich *et al.*, 1981). 2-Cyano[1,2-^{14}C]ethylene oxide also binds to protein in the liver and brain of rats injected intraperitoneally, but stable binding to DNA or RNA was at or below the limits of detection (Hogy & Guengerich, 1986).

4.4.3 *Mechanistic considerations*

Acrylonitrile is mutagenic, especially after bioactivation by a microsomal system. Since formation of DNA adducts with acrylonitrile *in vitro* is strongly increased by formation of its epoxide, it is very likely that the genotoxicity of acrylonitrile is mediated primarily by this metabolite. The epoxide, therefore, may be implicated in the carcinogenicity of acrylonitrile.

Acrylonitrile is toxic at high dose in several organs, which is possibly related to its glutathione-depleting activity. This toxicity might lead to tumour formation by an indirect mechanism, although no data to support this are evident from the available toxicity data, such as increased cell turnover or DNA labelling.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Acrylonitrile is a monomer used in high volume principally in the manufacture of acrylic fibres, resins (acrylonitrile–butadiene–styrene, styrene–acrylonitrile and others) and nitrile rubbers (butadiene–acrylonitrile). Other important uses are as an intermediate in the preparation of adiponitrile (for nylon 6/6) and acrylamide and, in the past, as a fumigant. Occupational exposures to acrylonitrile occur in its production and use in the preparation of fibres, resins and other products. It is present in cigarette smoke and has been detected rarely and at low levels in ambient air and water.

5.2 Human carcinogenicity data

The potential carcinogenicity of acrylonitrile in occupationally exposed populations has been investigated in several epidemiological studies. Studies carried out in the 1970s and 1980s suggested a possible increased risk of lung cancer among workers exposed to acrylonitrile. However, these were inconclusive because of one or more of the following actual or potential problems: small sample sizes, insufficient length of follow-up, incompleteness of follow-up, inadequate exposure assessment, potential confounding by other occupational carcinogens, and potential confounding by smoking. Consequently, larger and better studies were undertaken, in most cases building upon the same cohorts that had previously been assembled. Four such studies (two in the United States, one in the United Kingdom and one in the Netherlands) were carried out and these now provide the most relevant, informative data on which to base an evaluation. All of the studies made some attempt to establish exposure levels, although for the British study, this was rather cruder than for the others. The two studies from the United States were carried out in similar industries, but the range of cumulative exposure values was quite different between the two, raising questions about the inter-study comparability of methods of exposure assessment. The four studies employed different strategies for comparing exposed with unexposed. While the British study used a classic SMR comparison with national rates, the Dutch study did the same, but also compared the exposed with a different unexposed cohort. One of the studies from the United States compared the exposed with national rates and with rates of mortality and incidence in other plants of the same large company. The other compared the exposed with workers in the same plants who were unexposed to acrylonitrile. Typically, in each study, a number of analyses were carried out, varying comparison groups and other parameters.

There was no significant excess risk for any type of cancer when all exposed workers were compared with unexposed, or with an 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

studies gave either negative or only weakly supportive results. Even in the largest study (where the relative risk in the highest exposure quintile ranged from 1.2 to 1.7 depending on the parameters in the analysis), the finding was not consistently significant; there was no coherent dose–response pattern throughout the range of exposures and the risk in the highest decile of exposure was lower than that in the second highest decile. On balance and given the largely unsupportive 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 acrylonitrile and lung cancer. Thus, the earlier indications of an increased risk among workers exposed to acrylonitrile were not confirmed by the recent, more informative studies.

5.3 Animal carcinogenicity data

Acrylonitrile has been tested for carcinogenicity in one study in rats by inhalation with pre- and postnatal exposure. This study confirmed the findings of increased incidences of glial cell tumours of the central nervous system found in several previous studies that had not been fully reported and also found increases in malignant mammary tumours, Zymbal gland carcinomas, benign and malignant hepatocellular tumours and extrahepatic angiosarcomas.

5.4 Other relevant data

Acrylonitrile forms adducts with proteins and glutathione. It also forms DNA adducts *in vitro*, but only after cytochrome P450 bioactivation, most likely through its epoxide metabolite (cyanoethylene oxide), which is also formed *in vivo*. Acrylonitrile–haemoglobin adducts have been detected in exposed workers.

Both acrylonitrile and cyanoethylene oxide can conjugate with glutathione, leading to detoxification of these reactive compounds. At high doses of acrylonitrile, as used in animal studies, glutathione in certain tissues may be depleted. Such glutathione depletion will probably not occur at low-level human exposure.

Acrylonitrile is mutagenic *in vitro*; in *Salmonella* systems, bioactivation (to cyanoethylene oxide) is required, but in *Escherichia coli* and in rodent systems, bioactivation by an added microsomal system is not required. The results of genotoxicity experiments *in vivo* have in most cases been negative, although acrylonitrile is mutagenic in *Drosophila*.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of acrylonitrile.

There is *sufficient evidence* in experimental animals for the carcinogenicity of acrylonitrile.

Overall evaluation

Acrylonitrile is *possibly carcinogenic to humans (Group 2B)*.

6. References

Abdel-Rahman, S. Z., Nouraldeen, A. M. & Ahmed, A. E. (1994) Molecular interaction of [2,3-^{14}C]acrylonitrile with DNA in gastric tissue of rat. *J. Biochem. Toxicol.,* **9**, 191–198

Ageeva, T.S. (1970) The condition of the metabolism of mediating substances in workers producing acrylonitrile. *Tr. Sarat. med. Inst*., **78**, 10–13 (in Russian)

Agency for Toxic Substances and Disease Registry (1990) *Toxicological Profile for Acrylonitrile* (Report No. TP-90/02), Atlanta, GA

Ahmed, A.E., Farooqui, M.Y.H., Upreti, R.K. & El-Shabrawy, O. (1982) Distribution and covalent interactions of [1-^{14}C]acrylonitrile in the rat. *Toxicology*, **23**, 159–175

Ahmed, A.E., Farooqui, M.Y.H., Upreti, R.K. & El-Shabrawy, O. (1983) Comparative toxicokinetics of 2,3-^{14}C- and 1-^{14}C-acrylonitrile in the rat. *J. appl. Toxicol.*, **3**, 39–47

Ahmed, A.E., Abdel-Aziz, A.H., Abdel-Rahman, S.Z., Haque, A.K., Nour-Al Deen, A.M. & Shouman, S.A. (1992a) Pulmonary toxicity of acrylonitrile: covalent interaction and effect on replicative and unscheduled DNA synthesis in the lung. *Toxicology*, **76**, 1–14

Ahmed, A. E., Abdel-Rahman, S. Z. & Nour-Al Deen, A. M. (1992b) Acrylonitrile interaction with testicular DNA in rats. *J. Biochem. Toxicol.,* **7**, 5–11

Amacher, D. E. & Turner, G. N. (1985) Tests for gene mutational activity in the L5178Y/TK assay system. *Prog. Mutat. Res.,* **5**, 487–496

American Conference of Governmental Industrial Hygienists (1997a) *1997 TLVs® and BEIs®*, Cincinnati, OH, p. 15

American Conference of Governmental Industrial Hygienists (1997b*) Guide to Occupational Exposure Values—1997*, Cincinnati, OH, p. 3

Anderson, D. & Cross, M. F. (1985) Suitability of the P388F mouse lymphoma system for detecting potential carcinogens and mutagens. *Food chem. Toxicol.,* **23**, 115–118

Anon. (1976) *Goodyear Tire & Rubber Company, Gadsden, Alabama* (Health Hazard Evaluation Report No. 74-120-260), Cincinnati, OH, National Institute for Occupational Safety and Health

Anon. (1978) *Packard Electric, Division of General Motors Corporation* (Health Hazard Evaluation Report No. HHE-77-92-541), Cincinnati, OH, National Institute for Occupational Safety and Health

Anon. (1979) *Piper Aircraft Corporation, Vero Beach, Florida* (Health Hazard Evaluation Report No. 78-110-585), Cincinnati, OH, National Institute for Occupational Safety and Health

Anon. (1980) *Bell Helmets, Inc., Norwalk California* (Health Hazard Evaluation Report No. 79-36-656), Cincinnati, OH, National Institute for Occupational Safety and Health

Anon. (1985) Facts and figures for the chemical industry. *Chem. Eng. News*, **63**, 22–66

Anon. (1988) Facts and figures for the chemical industry. *Chem. Eng. News*, **66**, 34–82

Anon. (1991) Facts and figures for the chemical industry. *Chem. Eng. News*, **69**, 28–81

Anon. (1994) Facts and figures for the chemical industry. *Chem. Eng. News*, **72**, 28–74

Anon. (1997) Facts and figures for the chemical industry. *Chem. Eng. News*, **75**, 38–79

Antonev, A.A. & Rogailin, V.I. (1970) Professional dermatoses caused by acrylonitrile and their prophylaxis. *Tr. Perm. Gos. med. Inst*., **99**, 103–106 (in Russian)

Appel, K.E., Peter, H. & Bolt, H.M. (1981) Effect of potential antidotes on the acute toxicity of acrylonitrile. *Int. Arch. occup. environ. Health*, **49**, 157–163

Arni, P. (1985) Induction of various genetic effects in the yeast *Saccharomyces cerevisiae* strain D7. *Prog. Mutat. Res.,* **5**, 217–224

Babanov, G.P. (1957) Local manifestation of the action of acrylonitrile on the skin and mucosa. *Vrach. Delo*, **5**, 511–514 (in Russian)

Babanov, G.P., Kljuchikov, V.N., Karajeva, N.I. & Lileeva, Z.V. (1959) Clinical symptoms of chronic poisoning by acrylonitrile. *Vrach. Delo*, **8**, 833–836 (in Russian)

Baker, R. S. U. & Bonin, A. M. (1985) Tests with the *Salmonella* plate-incorporation assay. *Prog. Mutat. Res.,* **5**, 177–180

Bakker, J.G., Jongen, S.M.J., van Neer, F.C.J. & Neis, J.M. (1991) Occupational contact dermatitis due to acrylonitrile. *Contact Derm*., **24**, 50–53

Balda, B.R. (1975) Acrylonitrile as a contact allergen. *Hautarzt*, **26**, 599–601 (in German)

Banerjee, S. & Segal, A. (1986) In vitro transformation of C3H/10T1/2 and NIH/3T3 cells by acrylonitrile and acrylamide. *Cancer Lett.,* **32**, 293–304

Barnes, J.M. (1970) Effects on rats of compounds related to acrylamide. *Br. J. ind. Med*., **27**, 147–149

Barrett, J. C. & Lamb, P. W. (1985) Tests with the Syrian hamster embryo cell transformation assay. *Prog. Mutat. Res.,* **5**, 623–628

Benn, T. & Osborne, K. (1998) Mortality of United Kingdom acrylonitrile workers—an extended and updated study. *Scand. J. Work Environ. Health*, **24** (Suppl. 2), 17–24

Benz, F.W., Nerland, D.E., Pierce, W.M. & Babiuk, C. (1990) Acute acrylonitrile toxicity: studies on the mechanism of the antidotal effect of D- and L-cysteine and their *N*-acetyl derivatives in the rat. *Toxicol. appl. Pharmacol*., **102**, 142–150

Benz, F.W., Nerland, D.E., Corbett, D. & Li, J. (1997a) Biological markers of acute acrylonitrile intoxication in rats as a function of dose and time. *Fundam. appl. Toxixol*., **36**, 141–148

Benz, F.W., Nerland, D.E., Li, J. & Corbett, D. (1997b) Dose dependence of covalent binding of acrylonitrile to tissue protein and globin in rats. *Fundam. appl. Toxicol*., **36**, 149–156

Bergmark, E. (1997) Hemoglobin adducts of acrylamide and acrylonitrile in laboratory workers, smokers and nonsmokers. *Chem. Res. Toxicol.*, **10**, 78–84

Bigner, D.D., Bigner, S.H., Burger, P.C., Shelburne, J.D. & Friedman, H.S. (1986) Primary brain tumors in Fischer 344 rats chronically exposed to acrylonitrile in their drinking water. *Food chem. Toxicol*., **24**, 124–137

Blair, A. & Kazerouni, N. (1997) Reactive chemicals and cancer. *Cancer Causes Control*, **8**, 473–490

Blair, A., Stewart, P.A., Zaebst, D.D., Pottern, L., Zey, J.N., Bloom, T.F., Miller, B., Ward, E. & Lubin, J. (1998) Mortality study of industrial workers exposed to acrylonitrile. *Scand. J. Work Environ. Health*, **24** (Suppl. 2), 25–41

Bloom, T.F. & Zey, J.N. (1990) *Industrywide Studies Report of an Industrial Hygiene Survey at Monsanto Chemical Company, Addyston, Ohio* (Report No. 84.12) Cincinnati, OH, National Institute for Occupational Safety and Health

Bollard, M.E., Stribbling, S., Mitchell, S.C. & Caldwell, J. (1997) The disposition of allyl isothiocyanate in the rat and the mouse. *Food chem. Toxicol.*, **35**, 933–943

Borba, H., Monteiro, M., Proença, M.J., Chaveca, T., Pereira, V., Lynce, N. & Rueff, J. (1996) Evaluation of some biomonitoring markers in occupationally exposed populations to acrylonitrile. *Teratog. Carcinog. Mutag*., **16**, 205–218

Bradley, M. O. (1985) Measurement of DNA single-strand breaks by alkaline elution in rat hepatocytes. *Prog. Mutat. Res.,* **5**, 353–357

Brazdil, J.F. (1991) Acrylonitrile. In: Kroschwitz, J.I. & Howe-Grant, M., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th Ed., Vol. 1, New York, John Wiley, pp. 352–369

Brieger, H., Rieders, F. & Hodes, A.B. (1952) Acrylonitrile: spectrophotometric determination, acute toxicity, and mechanism of action. *Ind. Hyg. occup. Med*., **6**, 128–140

Brooks, T. M., Gonzalez, L. P., Clavert, R. & Parry, J. M. (1985) The induction of mitotic gene conversion in the yeast *Saccharomyces cerevisiae* strain JD1. *Prog. Mutat. Res.,* **5**, 225–228

Buchter, A., Peter, H. & Bolt, H.M. (1984) *N*-Acetylcysteine as an antidote in accidental acrylonitrile poisoning. *Int. Arch. occup. environ. Health*, **53**, 311–319 (in German)

Budavari, S., ed. (1996) *Merck Index*, 12th Ed., Whitehouse Station, NJ, Merck & Co., pp. 248–249

Burka, L.T., Sanchez, I.M., Ahmed, A.E. & Ghanayem, B.I. (1994) Comparative metabolism and disposition of acrylonitrile and methylacrylonitrile in rats. *Arch. Toxicol.*, **68**, 611–618

Butterworth, B. E., Eldridge, S. R., Sprankle, C. S., Working, P. K., Bentley, K. S. & Hurtt, M. E. (1992) Tissue-specific genotoxic effects of acrylamide and acrylonitrile. *Environ. mol. Mutag.,* **20**, 148–155

Byrd, G.D., Fowler, K.W., Hicks, R.D., Lovette, M.E. & Borgerding, M.F. (1990) Isotope dilution gas chromatography-mass spectrometry in the determination of benzene, toluene, styrene and acrylonitrile in mainstream cigarette smoke. *J. Chromatog.*, **503**, 359–368

Carere, A., Conti, G., Conti, L. & Crebelli, R. (1985) Assays in *Aspergillus nidulans* for the induction of forward-mutation in haploid strain 35 and for mitotic nondisjunction, haploidization and crossing-over in diploid strain P1. *Prog. Mutat. Res.,* **5**, 307–312

Carls, N. & Schiestl, R. H. (1994) Evaluation of the yeast DEL assay with 10 compounds selected by the International Program on Chemical Safety for the evaluation of short- term tests for carcinogens. *Mutat. Res.,* **320**, 293–303

Cerna, M., Kocisova, J., Kodytkova, I., Kopecky, J. & Šram, R. J. (1981) Mutagenic activity of oxiranecarbonitrile (glycidonitrile). In: Gut, I., Cikrt, M. & Plaa, G. L., eds, *Industrial and Environmental Xenobiotics, Metabolism and Pharmacokinetics of Organic Chemicals and Metals*, Berlin, Springer Verlag, pp. 251–254

Chang, C. M., Hsia, M. T., Stoner, G. D. & Hsu, I. C. (1990) Acrylonitrile-induced sister-chromatid exchanges and DNA single-strand breaks in adult human bronchial epithelial cells. *Mutat. Res.,* **241**, 355–360

Chen, J.L., Walrath, J., O'Berg, M.T., Burke, C.A. & Pell, S. (1987) Cancer incidence and mortality among workers exposed to acrylonitrile. *Am. J. ind. Med*., **11**, 157–163

Chen, J.L., Fayerweather, W.E. & Pell, S. (1988a) Cancer incidence of workers exposed to dimethylformamide and/or acrylonitrile. *J. occup. Med*., **30**, 813–818

Chen, J.L., Fayerweather, W.E. & Pell, S. (1988b) Mortality study of workers exposed to dimethylformamide and/or acrylonitrile. *J. occup. Med*., **30**, 819–821

Cicolella, A., Voirin, D., Hecht, G., Gerber, J.-M., Ducos, P. & Limasset, J.-C. (1981) Monitoring of atmospheric concentrations of acrylonitrile in eleven French factories. *Med. Lav*., **3**, 165–167

Collins, J.J., Page, L.C., Caporossi, J.C., Utidjian, H.M. & Lucas, L.J. (1989) Mortality patterns among employees exposed to acrylonitrile. *J. occup. Med*., **31**, 368–371

Connor, T. H., Forti, G. C., Sitra, P. & Legator, M. S. (1979) Bile as a source of mutagenic metabolites produced *in vivo* and detected by *Salmonella typhimurium*. *Environ. Mutag.,* **1**, 269–276

Cote, I.L., Bowers, A. & Jaeger, R.J. (1983) Induced tolerance to acrylonitrile toxicity by prior acrylonitrile exposure. *Res. Commun. chem. Pathol. Pharmacol*., **42**, 169–172

Cote, I.L., Bowers, A. & Jaeger, R.J. (1984) Effects of acrylonitrile on tissue glutathione concentrations in rat, mouse, and hamster. *Res. Commun. chem. Pathol. Pharmacol*., **43**, 507–510

Cova, D., Fumagalli, P. & Santagostino, A. (1992) Toxicity of acrylonitrile in a human neuroblastoma cell line and its effect on glutathione and glutathione-S-transferase. *Bull. environ. Contam. Toxicol*., **49**, 886–891

Crespi, C. L., Ryan, C. G., Seixas, G. M., Turner, T.R. & Penman, B.W. (1985) Tests for mutagenic activity using mutation assays at two loci in the human lymphoblast cell lines TK6 and AHH-1. *Prog. Mutat. Res.,* **5**, 497–516

Cytec Industries (1994) *Acrylonitrile: General Sales Specifications*, Charlotte, NC

Cytec Industries (1997) *Material Safety Data Sheet: Acrylonitrile*, Charlotte, NC

Danford, N. (1985) Tests for chromosome aberrations and aneuploidy in the Chinese hamster fibroblast cell line CH1-L. *Prog. Mutat. Res.,* **5,** 397–411

Delivanova, S., Popovski, P. & Orusev, T. (1978) Blepharoconjunctivitis in workers of the polyacrylonitrile synthetic fibre industry. *God. Zb. Med. Fak. Skoje*, **24**, 279–282 (in Macedonian)

Delzell, E. & Monson, R.R. (1982) Mortality among rubber workers: VI. Men with potential exposure to acrylonitrile. *J. occup. Med*., **24**, 767–769

Deutsche Forschungsgemeinschaft (1998) *List of MAK and BAT Values 1998* (Report No. 34), Weinheim, Wiley-VCH Publishers, pp. 111, 128, 167

Dorodnova, N.S. (1976) Gynaecological morbidity and specific functions of the female organism under the conditions of chemical production in 'Nitron'. *Gig. Zabol*., **8**, 45–46 (in Russian)

Døssing, M. & Ranek, L. (1984) Isolated liver damage in chemical workers. *Br. J. ind. Med*., **41**, 142–144

Douglas, G. R., Blakey, D. H., Liu-Lee, V. W., Bell, R. D. L. & Bayley, J. M. (1985) Alkaline sucrose sedimentation, sister-chromatid exchange and micronucleus assays in CHO cells. *Prog. Mutat. Res.,* **5**, 359–366

Dudley, H.C. & Neal, P.A. (1942) Toxicology of acrylonitrile (vinyl cyanide). I. Study of the acute toxicity. *J. ind. Hyg. Toxicol*., **24**, 27–36

Dudley, H.C., Sweeney, T.R. & Miller, J.W. (1942) Toxicology of acrylonitrile (vinyl cyanide). II. Studies of effects of daily inhalation. *J. ind. Hyg. Toxicol*., **24**, 255–258

Duverger-Van Bogaert, M., Lambotte-Vandepar, M., Noël, G., Roberfroid, M. & Mercier, M. (1978) Biochemical effects of acrylonitrile on the rat liver, as influenced by various pretreatments of the animals. *Biochem. biophys. Res. Commun*., **83**, 1117–1124

Duverger-Van Bogaert, M., Lambotte-Vandepaer, M., de Meester, C., Rollmann, B., Poncelet, F. & Mercier, M. (1981) Effect of several factors on the liver extract mediated mutagenicity of acrylonitrile and identification of four new in vitro metabolites. *Toxicol. Lett.,* **7**, 311–319

Duverger-Van Bogaert, M., Lambotte-Vandepaer, M., de Meester, C., Mercier, M. & Poncelet, F. (1982a) Role of glutathione in liver-mediated mutagenicity of acrylonitrile. *Toxicol. Lett.,* **11**, 305–311

Duverger-Van Bogaert, M., Lambotte-Vandepaer, M., de Meester, C., Mercier, M. & Poncelet, F. (1982b) Vinyl chloride and acrylonitrile: activation mechanism and mutagenicity. *Toxicol. Eur. Res.,* **4**, 35–37

Eller, P.M., ed. (1994) *NIOSH Manual of Analytical Methods* (DHHS (NIOSH) Publ. No. 94-113), 4th Ed., Cincinnati, OH, National Institute for Occupational Safety and Health [Method 1064]

Elmore, E., Korytynski, E. A. & Smith, M. P. (1985) Tests with the Chinese hamster V79 inhibition of metabolic cooperation assay. *Prog. Mutat. Res.,* **5**, 597–612

Enikeeva, N.A., Ostrovskaja, R.S., Syso, L.V., Podrez, Z.G., Braginskaja, L.L., Gvozdev, N.P., Nesterova, N.E., Musserskaja, A.N., Suzdaltreva, N.A. & Efremov, A.M. (1976) Industrial hygiene and health status of workers involved in the manufacture of the synthetic fibre Nitron. *Gig. Tr. Ohr. Zdor. Rab. Nef. Neftehim. Prom-sti*, **9**, 22–25 (in Russian)

Farooqui, M.Y.H. & Ahmed, A. E. (1983) In vivo interactions of acrylonitrile with macromolecules in rats. *Chem.-biol. Interact.,* **47**, 363–371

Farooqui, M.Y.H. & Ahmed, A.E. (1983) The effects of acrylonitrile on hemoglobin and red cell metabolism. *J. Toxicol. environ. Health*, **12**, 695–707

Ferguson, L. R. (1985) Petite mutagenesis in *Saccharomyces cerevisiae* strain D5. *Prog. Mutat. Res.,* **5**, 229–234

Foureman, P., Mason, J. M., Valencia, R. & Zimmering, S. (1994) Chemical mutagenesis testing in *Drosophila*. IX. Results of 50 coded compounds tested for the National Toxicology Program. *Environ. mol. Mutag.,* **23**, 51–63

Fugate, W.O. (1963) Acrylonitrile. In: Kirk, R.E. & Othmer, D.F., eds, *Encyclopedia of Chemical Technology*, 2nd Ed., Vol. 1, New York, John Wiley, pp. 338–339

Fujikawa, K., Ryo, H. & Kondo, S. (1985) The *Drosophila* reversion assay using the unstable zeste-white somatic eye color system. *Prog. Mutat. Res.,* **5**, 319–324

Gargas, M.L., Andersen, M.E., Teo, S.K.O., Batra, R., Fennell, T.R. & Kedderis, G.L. (1995) A physiologically based dosimetry description of acrylonitrile and cyanonitrile oxide in the rat. *Toxicol. appl. Pharmacol.*, **134**, 185–194

Garner, R. C. & Campbell, J. (1985) Tests for the induction of mutations to ouabain or 6-thioguanine resistance in mouse lymphoma L5178Y cells. *Prog. Mutat. Res.,* **5**, 525–529

Ghanayem. B.I. & Ahmed, A.E. (1986) Prevention of acrylonitrile-induced gastrointestinal bleeding by sulfhydryl compounds, atropine and cimetidine. *Res. Commun. chem. Pathol. Pharmacol*., **53**, 141–144

Ghanayem, B.I., Boor, P.J. & Ahmed, A.E. (1985) Acrylonitrile-induced gastric mucosal necrosis: role of gastric glutathione. *J. Pharmacol. exp. Ther*., **232**, 570–577

Ghanayem, B.I., Elwell, M.R. & Eldridge, S.R. (1997) Effects of the carcinogen, acrylonitrile, on forestomach cell proliferation and apoptosis in the rat: comparison with methacrylonitrile. *Carcinogenesis*, **18**, 675–680

Gineeva, N., Stamova, N., Hinkova, L., Spasovski, M., Hristeva, V. & Muhtarova, M. (1977) Study of the health status of workers from acrylonitrile department (Abstract). In: *Proceedings of the International Symposium on Occupational Health in the Production of Artificial Fibers, Finland, 6–10 June 1977*, p. 41

Graham, J.P.D. (1965) Hydroxycobalamin as an antidote to acrylonitrile. *Toxicol. appl. Pharmacol*., **7**, 367–372

Grunske, F. (1949) Ventox and ventox-poisoning. *Dtsch. med. Wochenschr*., **74**, 1081 (in German)

Guengerich, F.P., Geiger, L.E., Hogy, L.L. & Wright, P.L. (1981) In vitro metabolism of acrylonitrile to 2-cyanoethylene oxide, reaction with glutathione, and irreversible binding to proteins and nucleic acids. *Cancer Res.*, **41**, 4925–4933

Guengerich, F.P., Kim, D.-H. & Iwasaki, M. (1991) Role of human cytochrome P-450 IIE1 in the oxidation of many low molecular weight cancer suspects. *Chem. Res. Toxicol.*, **4**, 168–179

Guirguis, S.S., Cohen, M.B. & Rajhans, G.S. (1984) A review of health risks in acrylonitrile industry. *Med. Lav*., **6**, 87–93

Gulati, D.K., Sabharwal, P.S. & Shelby, M.D. (1985) Tests for the induction of chromosomal aberrations and sister chromatid exchanges in cultured Chinese hamster ovary (CHO) cells. *Prog. Mutat. Res.,* **5**, 413–426

Gut, I., Kopecký, J. & Filip, J. (1981) Acrylonitrile-^{14}C metabolism in rats: effect of the route of administration on the elimination of thiocyanate and other radioactive metabolites in urine and feces. *J. Hyg. Epidemiol. Microbiol. Immunol.*, **25**, 12–16

Gut, I., Nerudová, J., Frantík, E., Mirejovská, E. & Holuša, R. (1984) Acrylonitrile inhalation in rats: I. Effect on intermediary metabolism. *J. Hyg. Epidemiol. Microbiol. Immunol*., **28**, 369–376

Gut, I., Nerudová, J., Stiborová, A., Kopecký, J. & Frantik, E. (1985) Acrylonitrile inhalation in rats: II. Excretion of thioethers and thiocyanate in urine. *J. Hyg. Epidemiol. Microbiol. Immunol.*, **29**, 9–13

Hansch, C., Leo, A. & Hoekman, D. (1995) *Exploring QSAR*, Washington DC, American Chemical Society, p. 5

Hashimoto, K. & Kanai, R. (1965) Studies on the toxicology of acrylonitrile, metabolism, mode of action and therapy. *Ind. Health*, **3**, 30–45

Hashimoto, K. & Kobayashi, T. (1961) A case of acute dermatitis caused by contact with acrylonitrile. *Rodo Kagaku Kiho (Q. J. Lab. Res*.), **9**, 21–24 (in Japanese)

Hogy, L.L. & Guengerich, F.P. (1986) In vivo interaction of acrylonitrile and 2-cyanoethylene oxide with DNA in rats. *Cancer Res.,* **46,** 3932–3938

Houthuijs, D., Remijn, B., Willems, H., Boleij, J. & Biersteker, K. (1982) Biological monitoring of acrylonitrile exposure. *Am. J. ind. Med*., **3**, 313–320

IARC (1979) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 19, *Some Monomers, Plastics and Synthetic Elastomers, and Acrolein*, Lyon, pp. 73–113

IARC (1986) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 38, *Tobacco Smoking*, Lyon

IARC (1987a) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: an Updating of* IARC Monographs *Volumes 1 to 42*, Lyon, p. 79

IARC (1987b) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: an Updating of* IARC Monographs *Volumes 1 to 42*, Lyon, pp. 373–376

IARC (1987c) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: an Updating of* IARC Monographs *Volumes 1 to 42*, Lyon, pp. 332–334

IARC (1994a) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 60, *Some Industrial Chemicals*, Lyon, pp. 233–320

IARC (1994b) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 60, *Some Industrial Chemicals*, Lyon, pp. 389–433

Inge-Vechtomov, S.G., Pavlov, Y.I., Noskov, V.N., Repnevskaya, M.V., Aarpova, T.S., Khromov-Borisov, N.N., Chekuolene, J. & Chitavichus, D. (1985) Tests for genetic activity in the yeast *Saccharomyces cerevisiae*: study of forward and reverse mutation, mitotic recombination and illegitimate mating induction. *Prog. Mutat. Res.*, **5**, 243–255

International Labour Office (1991) *Occupational Exposure Limits for Airborne Toxic Substances*, 3rd Ed. (Occupational Safety and Health Series No. 37), Geneva, pp. 6–7

Ishidate, M.J. & Sofuni, T. (1985) The in vitro chromosomal aberration test using Chinese hamster lung (CHL) fibroblast cells in culture. *Prog. Mutat. Res.*, **5**, 427–432

Ishidate, M.J., Sofuni, T. & Yoshikawa, K. (1981) Chromosomal aberration tests *in vitro* as a primary screening tool for environmental mutagens and/or carcinogens. *Gann Monogr. Cancer Res.*, **27**, 95–108

Ivanov, V., Rahier, J. & Lauwerys, R. (1989) Lipid peroxidation in acrylonitrile-treated rats, evidenced by elevated ethane production. *J. appl. Toxicol.*, **9**, 353–358

Jedlicka, V., Pasek, A. & Gola, J. (1958) Pesticides in foods. III. Acrylonitrile as a food insecticide. *J. Hyg. Epidemiol. Microbiol. Immunol.*, **1**, 116–125

Kaneko, Y. & Omae, K. (1992) Effect of chronic exposure to acrylonitrile on subjective symptoms. *Keio J. Med.*, **41**, 25–32

Kankaanpää, E.E., Hemminki, K. & Vainio, H. (1979) Embryotoxicity of acrolein, acrylonitrile and acrylamide in developing chick embryos. *Toxicol. Lett.*, **4**, 93–96

Kauppinen, T., Toikkanen, J., Pedersen, D., Young, R., Kogevinas, M., Ahrens, W., Boffetta, P., Hansen, J., Kromhout, H., Blasco, J.M., Mirabelli, D., de la Orden-Rivera, V., Plato, N., Pannett, B., Savela, A., Veulemans, H. & Vincent, R. (1998) *Occupational Exposure to Carcinogens in the European Union in 1990–93*, Carex (International Information System on Occupational Exposure to Carcinogens), Helsinki, Finnish Institute of Occupational Health

Kedderis, G.L. & Batra, R. (1993) Species differences in the hydrolysis of 2-cyanoethylene oxide, the epoxide metabolite of acrylonitrile. *Carcinogenesis*, **14**, 685–689

Kedderis, G.L., Sumner, S.J.C., Held, S.D., Batra, R., Turner, M.J., Jr, Roberts, A.E. & Fennell, T.R. (1993a) Dose-dependent urinary excretion of acrylonitrile metabolites by rats and mice. *Toxicol. appl. Pharmacol.*, **120**, 288–297

Kedderis, G.L., Batra, R., Held, S., Loos, M.A. & Teo, S.K.O. (1993b) Rodent tissue distribution of 2-cyanoethylene oxide, the epoxide metabolite of acrylonitrile. *Toxicol. Lett.*, **69**, 25–30

Kedderis, G.L., Batra, R. & Koop, D.R. (1993c) Epoxidation of acrylonitrile by rat and human cytochromes P450. *Chem. Res. Toxicol.*, **6**, 866–871

Kedderis, G.L., Batra, R. & Turner, M.J. (1995) Conjugation of acrylonitrile and 2-cyanoethylene oxide with hepatic glutathione. *Toxicol. appl. Pharmacol.*, **135**, 9–17

Kedderis, G.L., Teo, S.K.O., Batra, R., Held, S.D. & Gargas, M.L. (1996) Refinement and verification of the physiologically based dosimetry description for acrylonitrile in rats. *Toxicol. appl. Pharmacol.*, **140**, 422–435

Kiesselbach, N., Korallus, U., Lange, H.-J., Neiss, A. & Zwingers, T. (1979)Acrylonitrile—epidemiological study—Bayer 1977. *Zentralbl. Arbeitsmed*., **10,** 257–259

Koerselman, W. & van der Graaf, M. (1984) Acrylonitrile: a suspected human carcinogen. *Int. Arch. occup. environ. Health*, **54**, 317–324

Kopecký, J., Zachardová, D., Gut, I. & Filip, J. (1979) Metabolism of acrylonitrile in rats *in vivo*. *Prac. Lek*, **31**, 203–207 (in Czech)

Kutcher, R.J. (1978) *Occupational Exposure to Acrylonitrile in the Manufacture of ABS Plastics*, Masters thesis, Chapel Hill, NC, University of North Carolina

Lambotte-Vandepaer, M., Duverger-Van Bogaert, M., de Meester, C., Poncelet, F. & Mercier, M. (1980) Mutagenicity of urine from rats and mice treated with acrylonitrile. *Toxicology,* **16**, 67–71

Langvardt, P.W. (1985) Acrylonitrile. In: Gerhartz, W. & Yamamoto, Y.S., eds, *Ullmann's Encyclopedia of Industrial Chemistry*, 5th rev. Ed., Vol. A1, Weinheim, VCH Publishers, pp. 177–184

Langvardt, P.W., Putzig, C.L., Braun, W.H. & Young, J.D. (1980) Identification of the major urinary metabolites of acrylonitrile in the rat. *J. Toxicol. environ. Health*, **6**, 273–282

Lawrence, N. & McGregor, D.B. (1985) Assays for the induction of morphological transformation in C3H/10T1/2 cells in culture with and without S9 mediated metabolic activation. *Prog. Mutat. Res.,* **5**, 651–658

Lawrence, R.M., Sweetman, G.M.A., Tavares, R. & Farmer, P.B. (1996) Synthesis and characterization of peptide adducts for use in monitoring human exposure to acrylonitrile and ethylene oxide. *Teratog. Carcinog. Mutag.*, **16**, 139–148

Lee, C.G. & Webber, T.D. (1985) The induction of gene mutations in the mouse lymphoma L5178Y/TK$^{+/-}$ assay and the Chinese hamster V79/HGPRT assay. *Prog. Mutat. Res.,* **5**, 547–554

Leonard, A., Garny, V., Poncelet, F. & Mercier, M. (1981) Mutagenicity of acrylonitrile in mouse. *Toxicol. Lett.,* **7**, 329–334

Liber, H.L. (1985) Mutation tests with *Salmonella* using 8-azaguanine resistance as the genetic marker. *Prog. Mutat. Res.,* **5**, 213–216

Lide, D.R., ed. (1995) *CRC Handbook of Chemistry and Physics*, 76th Ed., Boca Raton, FL, CRC Press, p. 3–88

Lijinsky, W. & Andrews, A.W. (1980) Mutagenicity of vinyl compounds in *Salmonella typhimurium*. *Teratog. Carcinog. Mutag.*, **1**, 259–267

Loprieno, N., Boncristiani, G., Forster, R. & Goldstein, B. (1985) Assays for forward mutation in *Schizosaccharomyces pombe* strain P1. *Prog. Mutat. Res.*, **5**, 297–306

Lorz, H. (1950) On the percutaneous poisoning by acrylonitrile (Ventox). *Dtsch. med. Wochenschr*., **75**, 1087–1088 (in German)

Maltoni, C., Ciliberti, A. & Di Maio, V. (1977) Carcinogenicity bioassays on rats of acrylonitrile administered by inhalation and by ingestion. *Med. Lav*., **68**, 401–411

Maltoni, C., Ciliberti, A., Cotti, G. & Perino, G. (1987) *Experimental Research on Acrylonitrile Carcinogenesis* (Maltoni, C. & Mehlman, M.A., eds, *Archives of Research on Industrial Carcinogenesis*, Vol. VI), Princeton, NJ, Princeton Scientific Publishing

Mastrangelo, G., Serena, R. & Marzia, V. (1993) Mortality from tumours in workers in an acrylic fibre factory. *Occup. Med*., **43**, 155–158

Matsushima, T., Muramatsu, M. & Haresaku, M. (1985) Mutation tests on *Salmonella typhimurium* by the pre-incubation method. *Prog. Mutat. Res.*, **5**, 181–186

Matthews, E. J., Delbalzo, T. & Rundell, J. O. (1985) Assays for morphological transformation and mutation to ouabain resistance of Balb/c-3T3 cells in culture. *Prog. Mutat. Res.*, **5**, 639–650

McCammon, C.S. & Zey, J.N. (1990) *Industrywide Studies Report of an Industrial Hygiene Survey at Monsanto Chemical Company, Decatur, Alabama* (Report No. 84.20.13), Cincinnati, OH, National Institute for Occupational Safety and Health

McOmie, W.A. (1949) Comparative toxicity of methacrylonitrile and acrylonitrile. *J. ind. Hyg. Toxicol*., **31**, 113–116

de Meester, C., Poncelet, F., Roberfroid, M. & Mercier, M. (1978) Mutagenicity of acrylonitrile. *Toxicology,* **11**, 19–27

de Meester, C., Duverger-Van Bogaert, M., Lambotte-Vandepaer, M., Roberfroid, M., Poncelet, F. & Mercier, M. (1979) Liver extract mediated mutagenicity of acrylonitrile. *Toxicology,* **13**, 7–15

Mehta, R.D. & von Borstel, R.C. (1985) Tests for genetic activity in the yeast *Saccharomyces cerevisiae* using strains D7-144, XV185-14C and RM52. *Prog. Mutat. Res.*, **5**, 271–284

Ministry of Social Affairs and Health (1998) *Finnish Occupational Exposure Limits 1998*, Helsinki

Montesano, R., Bartsch, H. & Tomatis, L., eds (1980) *Molecular and Cellular Aspects of Carcinogen Screening Tests* (IARC Scientific Publications No. 27), Lyon

Müller, G., Verkoyen, C., Soton, N. & Norpoth, K. (1987) Urinary excretion of acrylonitrile and its metabolites in rats. *Arch. Toxicol.*, **60**, 464–466

Murray, F.J., Schwetz, B.A., Nitschke, K.D., John, J.A., Norris, J.M. & Gehring, P.J. (1978) Teratogenicity of acrylonitrile given to rats by gavage or by inhalation. *Food Cosmet. Toxicol*., **16**, 547–551

Myhr, B., Bowers, L. & Caspary, W.J. (1985) Assays for the induction of gene mutations at the thymidine kinase locus in L5178Y mouse lymphoma cells in culture. *Prog. Mutat. Res.*, **5**, 555–568

Natarajan, A.T., Bussmann, C.J.M., Van Kesteren-Van Leeuwen, A.C.M., Meijers, M. & Van Rijn, J.L.S. (1985) Tests for chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary (CHO) cells in culture. *Prog. Mutat. Res.,* **5**, 433–437

Nerudová, J., Gut, I. & Savolainen, H. (1988) Consequences of acrylonitrile metabolism in rat hepatocytes: effects on lipid peroxidation and viability of the cells. *Environ. Res*., **6**, 133–141

Nilsen, O.G., Toftgard, R. & Eneroth, P. (1980) Effects of acrylonitrile on rat liver cytochrome P-450 benz(*a*)pyrene metabolism, and serum hormone levels. *Toxicol. Lett*., **6**, 399–404

Noel, G., Lambotte-Vandepaer, M., Duverger-van Bogaert, M., Roberfroid, M. & Mercier, M. (1978) Hepatoxic effects of acrylonitrile in rats. *Arch. Int. Physiol. Biochim.*, **86**, 951–952

NOES (1997) *National Occupational Exposure Survey 1981–83*, Unpublished data as of November 1997, Cincinnati, OH, US Department of Health and Human Services, Public Health Service, National Institute for Occupational Safety and Health

Normandeau, J., Chakrabarti, S. & Brodeur, J. (1984) Influence of simultaneous exposure to acrylonitrile and styrene on the toxicity and metabolism of styrene in rats. *Toxicol. appl. Pharmacol*., **75**, 346–349

O'Berg, M.T. (1980) Epidemiologic study of workers exposed to acrylonitrile. *J. occup. Med*., **22**, 245–252

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

Obe, G., Hille, A., Jonas, R., Schmidt, S. & Thenhaus, U. (1985) Tests for the induction of sister-chromatid exchanges in human peripheral lymphocytes in culture. *Prog. Mutat. Res.,* **5**, 439–442

Oberly, T. J., Bewsey, B. J. & Probst, G.S. (1985) Tests for the induction of forward mutation at the thymidine kinase locus of L5178Y mouse lymphoma cells in culture. *Prog. Mutat. Res.,* **5**, 569–582

Orusev, T., Bauer, S. & Popovski, P. (1973) Occupational exposure to acrylonitrile in a plant for production of acrylic synthetic fibers. *God. Zb. Med. Fak.* Skopje, **19**, 445–449 (in Macedonian) [*Chem. Abstr*., **81**, 29030t]

Osgood, C., Bloomfield, M. & Zimmering, S. (1991) Aneuploidy in *Drosophila*, IV. Inhalation studies on the induction of aneuploidy by nitriles. *Mutat. Res.,* **259**, 165–176

Ott, M.G., Kolesar, R.C., Scharnweber, H.C., Schneider, E.J. & Venable, I.R. (1980) A mortality survey of employees engaged in the development or manufacture of styrene-based products. *J. occup. Med.*, **22**, 445–460

Parent, R.A. & Casto, B.C. (1979) Effect of acrylonitrile on primary Syrian golden hamster embryo cells in culture: transformation and DNA fragmentation. *J. natl Cancer Inst.,* **62**, 1025–1029

Parry, E.M. (1985) Tests for effects on mitosis and the mitotic spindle in Chinese hamster primary liver cells (CH1-L) in culture. *Prog. Mutat. Res.,* **5**, 479–485

Parry, J.M. & Eckardt, F. (1985a) The detection of mitotic gene conversion, point mutation and mitotic segregation using the yeast *Saccharomyces cerevisiae* strain D7. *Prog. Mutat. Res.,* **5**, 261–269

Parry, J.M. & Eckardt, F. (1985b) The detection of mitotic aneuploidy, point mutation and mitotic crossing over in the yeast *Saccharomyces cerevisiae* strains D61-M and D6. *Prog. Mutat. Res.,* **5**, 285–295

Paulet, G. & Desnos, J. (1961) Acrylonitrile, toxicity-mechanism of therapeutic action. *Arch. int. Pharmacodyn*., **131**, 54–83 (in French)

Paulet, G., Desnos, J. & Battig, J. (1966) Toxicity of acrylonitrile. *Arch. Mal. prof*., **27**, 849–856 (in French)

Perocco, P., Pane, G., Bolognesi, S. & Zannotti, M. (1982) Increase of sister chromatid exchange and unscheduled synthesis of deoxyribonucleic acid by acrylonitrile in human lymphocytes *in vitro*. *Scand. J. Work Environ. Health*, **8**, 290–293

Peter, H. & Bolt, H.M. (1981) Irreversible protein binding of acrylonitrile. *Xenobiotica*, **11**, 51–56

Peter, H., Appel, K.E., Berg, R. & Bolt, H.M. (1983) Irreversible binding of acrylonitrile to nucleic acids. *Xenobiotica*, **13**, 19–25

Priston, R.A.J. & Dean, B.J. (1985) Tests for the induction of chromosome aberrations, polyploidy and sister-chromatid exchanges in rat liver (RL4) cells. *Prog. Mutat. Res.*, **5**, 387–395

Probst, G.S. & Hill, L.E. (1985) Tests for the induction of DNA-repair synthesis in primary cultures of adult rat hepatocytes. *Prog. Mutat. Res.*, **5**, 381–386

Quast, J.F., Humiston, C.G., Wade, C.E., Carreon, R.M., Hermann, E.A., Park, C.N. & Schwetz, B.A. (1981) Results of a chronic toxicity and oncogenicity study in rats maintained on water containing acrylonitrile for 24 months (Abstract No. 467). *Toxicologist*, **1**, 129

Rabello-Gay, M.N. & Ahmed, A.E. (1980) Acrylonitrile: in vivo cytogenetic studies in mice and rats. *Mutat. Res.*, **79**, 249–255

Recio, L. & Skopek, T.R. (1988) Mutagenicity of acrylonitrile and its metabolite 2-cyanoethylene oxide in human lymphoblasts *in vitro*. *Mutat. Res.*, **206**, 297–305

Rexroat, M.A. & Probst, G.S. (1985) Mutation tests with *Salmonella* using the plate-incorporation assay. *Prog. Mutat. Res.*, **5**, 201–212

Roberts, A.E., Kedderis, G.L., Turner, M.J., Rickert, D.E. & Swenberg, J.A. (1991) Species comparison of acrylonitrile epoxidation by microsomes from mice, rats and humans: relationship to epoxide concentrations in mouse and rat blood. *Carcinogenesis*, **12**, 401–404

Rogaczewska, T. & Piotrowski, J. (1968) Routes of acrylonitrile absorption in man. *Med. Pr.*, **19**, 349–353

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

Rouisse, L., Chakrabarti, S. & Tuchweber, B. (1986) Acute nephrotoxic potential of acrylonitrile in Fischer-344 rats. *Res. Commun. chem. Pathol. Pharmacol*., **53**, 347–360

Rudd, C. J. (1983) *L5178Y TK$^{+/-}$ Mouse Lymphoma Cell Forward Mutation Assay of Acrylonitrile* (Final Report Prepared for Environmental Protection Agency under Contract No. 68-02-3703; SRI Project LSU-3447), Washington DC, Government Printing Office

Ruhe, R.L. & Jannerfeldt, E.R. (1981) *Metamora Products Corporation, Elkland, Pennsylvania* (Health Hazard Evaluation Report No. 80-188-797), Cincinnati, OH, National Institute for Occupational Safety and Health

Sadtler Research Laboratories (1980) *The Sadtler Standard Spectra, Cumulative Index,* Philadelphia, PA

Saillenfait, A.-M., Bonnet, P., Guenier, J.P. & de Ceaurriz, J. (1993a) Relative developmental toxicities of inhaled aliphatic mononitriles in rats. *Fundam. appl. Toxicol*., **20**, 365–375

Saillenfait, A.-M., Payan, J.-P., Langonné, I., Beydon, D., Grandclaude, M.-C., Sabaté, J.-P. & de Ceaurriz, J. (1993b) Modulation of acrylonitrile-induced embryotoxicity *in vitro* by glutathione depletion. *Arch. Toxicol*., **67**, 164–172

Sakurai, H. & Kusumoto, M. (1972) Epidemiologic study of health impairment among acrylonitrile workers. *J. Sci. Labour (Tokyo)*, **48**, 273–282 (in Japanese)

Sakurai, H., Onodera, M., Utsunomiya, T., Minakuchi, H., Iwai, H. & Matsumura, H. (1978) Health effects of acrylonitrile in acrylic fibre factories. *Br. J. ind. Med*., **35**, 219–222

Sakurai, H., Omae, K. & Minaguchi, H. (1990) Health profiles of workers exposed to acrylonitrile (Abstract). In: *Proceedings of the 23rd International Congress on Occupational Health, Montreal, Canada, September 22–28, 1990*, p. 295

Salsburg, D. (1990) Estimating dose response in chronic toxicity studies: 24-month administration of acrylonitrile in drinking water of Fischer 344 rats. *Sci. total Environ*., **99**, 289–305

Sandberg, E.C. & Slanina, P. (1980) Distribution of [1-^{14}C]acrylonitrile in rat and monkey. *Toxicol. Lett.*, **6**, 489–494

Sanner, T. & Rivedal, E. (1985) Tests with the Syrian hamster embryo (SHE) cell transformation assay. *Prog. Mutat. Res.,* **5**, 665–671

Sapota, A. (1982) The disposition of [^{14}C]acrylonitrile in rats. *Xenobiotica*, **12**, 259–264

Sartorelli, E. (1966) Acute acrylonitrile intoxication. *Med. Lav*., **57**, 184-187 (in Italian)

Sasaki, M., Sugimura, K., Yoshida, M.A. & Abe, S. (1980) Cytogenetic effects of 60 chemicals on cultured human and Chinese hamster cells. *Kromosoma,* **20**, 574–584

Sato, M., Hirasawa, F., Ogata, M., Takizawa, Y., Kojima, H. & Yoshida, T. (1982) Distribution and accumulation of [2,3-^{14}C]acrylonitrile in rat after single injection. *Ecotoxicol. Environ. Saf.*, **6**, 187–191

Schairer, L.A., Sautkulis, R.C. & Tempel, N.R. (1982) Monitoring ambient air for mutagenicity using the higher plant *Tradescantia*. *Environ. Sci. Res.,* **25**, 123–140

Scheufler, H. (1980) On the embryotoxic effectiveness of acrylonitrile in the laboratory mouse. *Z. ges. Hyg.*, **26**, 564–565 (in German)

Scupakas, D. (1968) Industrial hygiene conditions during the reworking of plastics and problems of improving them. In: Yavnaist, E.Y., ed., *Proceedings of the First Conference on Actual Problems of Industrial Hygiene and Occupational Pathology, 1967*, Riga, Medical Institute, pp. 128–132 (in Russian) [*Chem. Abstr.*, **72**, 47094k]

Sharief, Y., Brown, A.M., Backer, L.C., Campbell, J.A., Westbrook-Collins, B., Stead, A.G. & Allen, J.W. (1986) Sister chromatid exchange and chromosome aberration analyses in mice after in vivo exposure to acrylonitrile, styrene, or butadiene monoxide. *Environ. Mutag.,* **8**, 439–448

Shustov, S.J. (1968) Clinical manifestation and haematological changes in workers employed in the production of acrylonitrile at the Saratov Chemical Combine. *Gig. Tr. prof. Zabol.*, **3**, 27–29 (in Russian)

Silver, E.H. & Szabo, S. (1982) Possible role of lipid peroxidation in the actions of acrylonitrile on the adrenals, liver and gastrointestinal tract. *Res. Commun. chem. Pathol. Pharmacol*., **36**, 33–43

Silver, E.H., McComb, D.J., Kovacs, K. & Szabo, S. (1982) Limited hepatotoxic potential of acrylonitrile in rats. *Toxicol. appl. Pharmacol*., **64**, 131–139

Silver, E.H., Szabo, S., Cahill, M. & Jaeger, R.J. (1987) Time-course studies of the distribution of [1-^{14}C]acrylonitrile in rats after intravenous administration. *J. appl. Toxicol.*, **7**, 303–306

Smith, A.H., Waxweiler, R.H. & Tyroler, H.A. (1980) Epidemiologic investigation of occupational carcinogenesis using a serially additive expected dose model. *Am. J. Epidemiol*., **112**, 787–797

Solionova, L.G., Smulevich, V.B., Turbin, E.V., Krivosheyeva, L.V. & Plotnikov, J.V. (1992) Carcinogens in rubber production in the Soviet Union. *Scand. J. Work Environ. Health*, **18**, 120–123

Spassovski, M. (1976) Health hazards in the production and processing of some fibres, resins, and plastics in Bulgaria. *Environ. Health Perspect.*, **17**, 199–202

Stamova, N., Gincheva, N., Spassovski, M., Bainova, A., Ivanova, S., Kurkchiev, S., Hinkova, L., Khristeva, V., Mukhtaraova, M., Karadzhova, N., Tsaneva, L. & Fikova, E. (1976) Labour hygiene during the production of synthetic fibres 'Bulana'. *Hyg. Zdrav*., **2**, 134–140 (in Russian) [*Chem. Abstr.*, **86**, 176464u]

Stewart, P.A., Zaebst, D., Zey, J.N., Herrick, R., Dosemeci, M., Hornung, R., Bloom, T., Pottern, L., Miller, B. & Blair, A. (1998) Exposure assessment for a study of workers exposed to acrylonitrile. Overall methods. *Scand. J. Work Environ. Health*, **24** (Suppl. 2), 42–53

Styles, J.A., Clay, P. & Cross, M.F. (1985) Assays for the induction of gene mutations at the thymidine kinase and the Na^+/K^+ ATPase loci in two different mouse lymphoma cell lines in culture. *Prog. Mutat. Res.*, **5**, 587–596

Suta, B.E. (1979) *Assessment of Human Exposures to Atmospheric Acrylonitrile*, Prepared for USEPA, Contract No 68-02-2835, Task 20, Research Triangle Park, NC, SRI International

Svirbely, J.L. & Floyd, E.P. (1961) *Toxicologic Studies of Acrylonitrile and Oxydipropionitrile. III. Chronic Studies* (Meeting paper) Detroit, MI, AINA-ACSIH

Swaen, G.M.H., Bloemen, L.J.N., Twisk, J., Scheffers, T., Slangen, J.J.M. & Sturmans, F. (1992) Mortality of workers exposed to acrylonitrile. *J. occup. Med*., **34**, 801–809

Swaen, G.M.H., Bloemen, L.J.N., Twisk, J., Scheffers, T., Slangen, J.J.M., Collins, J.J., ten Berge, W.F.J.P. & Sturmans, F. (1998) Mortality update of workers exposed to acrylonitrile in the Netherlands. *Scand. J. Work Environ. Health*, **24** (Suppl. 2), 10–16

Szabo, S. & Selye, H. (1971) Adrenal apoplexy and necrosis produced by acrylonitrile. *Endokrinologie*, **57**, 405–408

Szabo, S. & Selye, H. (1972) Effects of phenobarbital and steroids on the adrenal apoplexy produced by acrylonitrile in rats. *Endocrinol. Exp*., **6**, 141–146

Szabo, S., Reynolds, E.S., Komanicky, P., Moslen, M.T. & Melby, J.C. (1976) Effect of chronic acrylonitrile ingestion on rat adrenal (abstract). *Toxicol. appl. Pharmacol.*, **37**, 133

Szabo, S., Hüttner, I., Kovacs, K., Horvath, E., Szabo, D. & Horner, H.C. (1980) Pathogenesis of experimental adrenal hemorrhagic necrosis ('apoplexy'). Ultrastructural, biochemical, neuropharmacologic, and blood coagulation studies with acrylonitrile in the rat. *Lab. Invest.*, **42**, 533–546

Szabo, S., McComb, D.J., Kovacs, K. & Hüttner, I. (1981) Adrenocortical hemorrhagic necrosis. The role of catecholamines and retrograde medullary-cell necrosis. *Arch. Pathol. Lab. Med*., **105**, 536–539

Szabo, S., Silver, E.H., Gallagher, G.T. & Maull, E.A. (1983) Potentiation of duodenal ulcerogenic action of acrylonitrile by PCB or phenobarbital in the rat. *Toxicol. appl. Pharmacol*., **71**, 451–454

Szabo, S., Gallagher, G.T., Silver, E.H., Maull, E.A., Horner, H.C., Komanicky, P., Melby, J.C., McComb, D.J. & Kovacs, K. (1984) Subacute and chronic action of acrylonitrile on adrenals and gastrointestinal tract: biochemical, functional and ultrastructural studies in the rat. *J. appl. Toxicol*., **4**, 131–140

Tandon, R., Saxena, D.K., Chandra, S.V., Seth, P.K. & Srivastava, S.P. (1988) Testicular effects of acrylonitrile in mice. *Toxicol. Lett*., **42**, 55–63

Tardif, R., Talbot, D., Gérin, M. & Brodeur, J. (1987) Urinary excretion of mercapturic acids and thiocyanate in rats exposed to acrylonitrile: influence of dose and route of administration. *Toxicol. Lett.*, **39**, 255–261

Tavares, R., Borba, H., Monteiro, M., Proenca, M.J., Lynce, N., Rueff, J., Bailey, E., Sweetman, G.M.A., Lawrence, R.M. & Farmer, P.B. (1996) Monitoring of exposure to acrylonitrile by determination of *N*-(2-cyanoethyl)valine at the *N*-terminal position of haemoglobin. *Carcinogenesis*, **17**, 2655–2660

Thiess, A.M. & Fleig, I. (1978) Analysis of chromosomes of workers exposed to acrylonitrile. *Arch. Toxicol*., **41**, 149–152

Thiess, A.M., Frentzel-Beyme, R., Link, R. & Wild, H. (1980) Mortality study in chemical personnel of various industries exposed to acrylonitrile. *Z. Arbeitsmed. Arbeitsschutz*, **30**, 259–267 (in German)

Tullar, P.E. (1947) *Final Report on the Pharmacology and Toxicology of Acrylonitrile and Acrylon*, Washington DC, Palusowski Memorial Research Laboratory, George Washington University

United States Consumer Product Safety Commission (1978) *Assessment of Acrylonitrile Contained in Consumer Products*, Final Report, Contract No. CPSC-C-77-0009, Task No. 1014K, H.I.A./Economic Analysis, Washington DC

United States Department of Labor (1978) Occupational exposure to acrylonitrile (vinyl cyanide). Proposed standard and notice of hearing. *Fed. Regist.*, **43**, 2586–2621

United States Environmental Protection Agency (1986) *Method 8030—Acrolein, Acrylonitrile, Acetonitrile*, Washington DC

United States Environmental Protection Agency (1996a) Method 603—Acrolein and acrylonitrile. *US Code Fed. Regul.,* **Title 40**, Part 136, Appendix A, pp. 55–66

United States Environmental Protection Agency (1996b) Method 1624, Revision B - Volatile organic compounds by isotope dilution GC/MS. Methods for organic chemical analysis of municipal and industrial wastewater. *US Code Fed. Regul.,* **Title 40**, Part 136, Appendix A, pp. 231–243

United States Food and Drug Administration (1987) Acrylonitrile. In: Fazio, T. & Sherma, J., eds, *Food Additives Analytical Manual*, Vol. II, *A Collection of Analytical Methods for Selected Food Additives*, Arlington, VA, Association of Official Analytical Chemists, pp. 1–24

United States National Library of Medicine (1997a*) Toxic Chemical Release Inventory (TRI87, TRI90, TRI95) Databases*, Bethesda, MD

United States National Library of Medicine (1997b) *Registry of Toxic Effects of Chemical Substances (RTECS) Database*, Bethesda, MD [Record No. 4289]

United States Occupational Safety and Health Administration (1990) *OSHA Analytical Methods Manual*, Part 1: *Organic Substances*, Vol. 3, *Methods 55-80*, Salt Lake City, UT [Method 56]

United States Occupational Safety and Health Administration (1996) Labor. *US Code Fed. Regul.,* **Title 29**, Part 1910.1000

Van Bladeren, P.J., Delbressine, L.P.C., Hoogeterp, J.J., Beaumont, H.G.M., Breimer, D.D., Suetter-Berlage, F. & Van Der Gen, A. (1981) Formation of mercapturic acids from acrylonitrile, crotononitrile and cinnamonitrile by direct conjugation and via an intermediate oxidation process. *Drug Metab. Dispos.*, **9**, 246–249

Ved Brat, S.V. & Williams, G.M. (1982) Hepatocyte-mediated production of sister chromatid exchange in co-cultured cells by acrylonitrile: evidence for extracellular transport of a stable reactive intermediate. *Cancer Lett.,* **17**, 213–216

Venitt, S., Bushell, C.T. & Osborne, M. (1977) Mutagenicity of acrylonitrile (cyanoethylene) in *Escherichia coli*. *Mutat. Res.*, **45**, 283–288

Verschueren, K. (1996) *Handbook of Environmental Data on Organic Chemicals*, 3rd Ed., New York, Van Nostrand Reinhold, pp. 347–348

Vodicka, P., Gut, I. & Frantík, E. (1990) Effects of inhaled acrylic acid derivatives in rats. *Toxicology*, **65**, 209–221

Vogel, E. W. (1985) The *Drosophila* somatic recombination and mutation assay (SRM) using the white-coral somatic eye color system. *Prog. Mutat. Res.,* **5**, 313–317

Vogel, R.A. & Kirkendall, W.M. (1984) Acrylonitrile (vinyl cyanide) poisoning: a case report. *Texas Med.*, **80**, 48–51

Volkova, Z.A. & Bagdinov, Z.M. (1969) Problems of labour hygiene in rubber vulcanization. *Hyg. Sanit.*, **34**, 326–333 (in Russian)

Waxweiler, R.J., Smith, A.H., Falk, H. & Tyroler, H.A. (1981) Excess lung cancer risk in a synthetic chemicals plant. *Environ. Health Perspect.*, **41**, 159–165

Werner, J.B. & Carter, J.T. (1981) Mortality of United Kingdom acrylonitrile polymerization workers. *Br. J. ind. Med.*, **38**, 247–253

Whittaker, S.G., Zimmermann, F.K., Dicus, B., Piegorsch, W.W., Resnick, M.A. & Fogel, S. (1990) Detection of induced mitotic chromosome loss in *Saccharomyces cerevisiae*—an interlaboratory assessment of 12 chemicals. *Mutat. Res.,* **241**, 225–242

Whysner, J., Steward, R.E., 3rd, Chen, D., Conaway, C.C., Verna, L.K., Richi, J.P., Jr, Ali, N. & Williams, G.M. (1998) Formation of 8-oxodeoxyguanosine in brain DNA of rats exposed to acrylonitrile. *Arch Toxicol.*, **72**, 429–438

Willhite, C.C., Ferm, V.H. & Smith, R.P. (1981a) Teratogenic effect of aliphatic nitriles. *Teratology*, **23**, 317–323

Willhite, C.C., Marin-Padilla, M., Ferm, V.H. & Smith, R.P. (1981b) Morphogenesis of axial skeletal (dysraphic) disorders induced by aliphatic nitriles. *Teratology*, **23**, 325–333

Williams, G.M., Tong, C. & Ved Brat, S. (1985) Tests with the rat hepatocyte primary culture/DNA repair test. *Prog. Mutat. Res.,* **5**, 341–345

Wilson, R.H. (1944) Health hazards encountered in the manufacture of synthetic rubber. *J. Am. med. Assoc*., **124**, 701–703

Wilson, R.H., Hough, G.V. & McCormick, W.E. (1948) Medical problems encountered in the manufacture of American-made rubber. *Ind. Med*., **17**, 199–207

Wood, S.M., Buffler, P.A., Burau, K. & Krivanek, N. (1998) Mortality and morbidity experience of workers exposed to acrylonitrile in fiber production. *Scand. J. Work Environ. Health*, **24** (Suppl. 2), 54–62

Working, P.K., Bentley, K.S., Hurtt, M.E. & Mohr, K.L. (1987) Comparison of the dominant lethal effects of acrylonitrile and acrylamide in male Fischer 344 rats. *Mutagenesis,* **2**, 215–220

Worthing, C.R. & Hance, R.J., eds (1991) *The Pesticide Manual*, Farnham, Surrey, British Crop Protection Council, p. 871

Wuergler, F.E., Graf, U. & Frei, H. (1985) Somatic mutation and recombination test in wings of *Drosophila melanogaster*. *Prog. Mutat. Res.,* **5**, 325–340

Wynder, E.L. & Hoffmann, D. (1967) *Tobacco and Tobacco Smoke. Studies in Experimental Carcinogenesis*, New York, Academic Press, p. 450

Zeiger, E. & Haworth, S. (1985) Tests with a preincubation modification of the *Salmonella*/microsome assay. *Prog. Mutat. Res.,* **5**, 187–199

Zeller, H., Hofmann, H.T., Thiess, A.M. & Hey, W. (1969) Toxicity of nitrile. Results of animal experiments and industrial experiences during 15 years. *Z. Arbeitsmed. Arbeitsschutz*, **19**, 226–238 (in German)

Zey, J.N. & Bloom, T.F. (1990) *Industrywide Studies Report of an Industrial Hygiene Survey at BASF, Williamsburg, Virginia* (Report No. 84.20.13), Cincinnati, OH, National Institute for Occupational Safety and Health

Zey, J.N. & McCammon, C. (1989) *Industrywide Studies Report of an Industrial Hygiene Survey at American Cyanamid, Santa Rosa Plant, Milton, Florida* (Report No. 84.20.14), Cincinnati, OH, National Institute for Occupational Safety and Health

Zey, J.N. & McCammon, C. (1990) *Industrywide Studies Report of an Industrial Hygiene survey at Sterling Chemicals, Inc., Texas City Plant, Texas City, Texas* (Report No. 84.20.10), Cincinnati, OH, National Institute for Occupational Safety and Health

Zey, J.N., McCammon, C. & Stewart, P. (1989) *Industrial Hygiene Survey at American Cyanamid, Fortier, Louisiana* (Report No. 84.20.12), Cincinnati, OH, National Institute for Occupational Safety and Health

Zey, J.N., Bloom, T.F. & Pottern, L.M. (1990a) *Industrywide Studies Report of an Industrial Hygiene Survey at Monsanto Chemical Company, Chocolate Bayou Plant, Alvin, Texas* (Report No. 84.20.16), Cincinnati, OH, National Institute for Occupational Safety and Health

Zey, J.N., McCammon, C. & Pottern, L. (1990b) *Industrywide Studies Report of an Industrial Hygiene Survey at BP America, Lima, Ohio* (Report No. 84.20.11), Cincinnati, OH, National Institute for Occupational Safety and Health

Zhurkov, V.S., Shram, R. & Dugan, A.M. (1983) Analysis of the mutagenic activity of acrylonitrile. *Gig. Sanit.,* **1**, 71–72 (in Russian)

Zimmermann, F.K., Heinisch, J. & Scheel, I. (1985) Tests for the induction of mitotic aneuploidy in the yeast *Saccharomyces cerevisiae* strain D61.M. *Prog. Mutat. Res.,* **5**, 235–242

Zotova, L.V. (1975) Working conditions in the production of acrylonitrile and their effect on workers. *Gig. Tr. prof. Zabol.*, **8**, 8–11 (in Russian)