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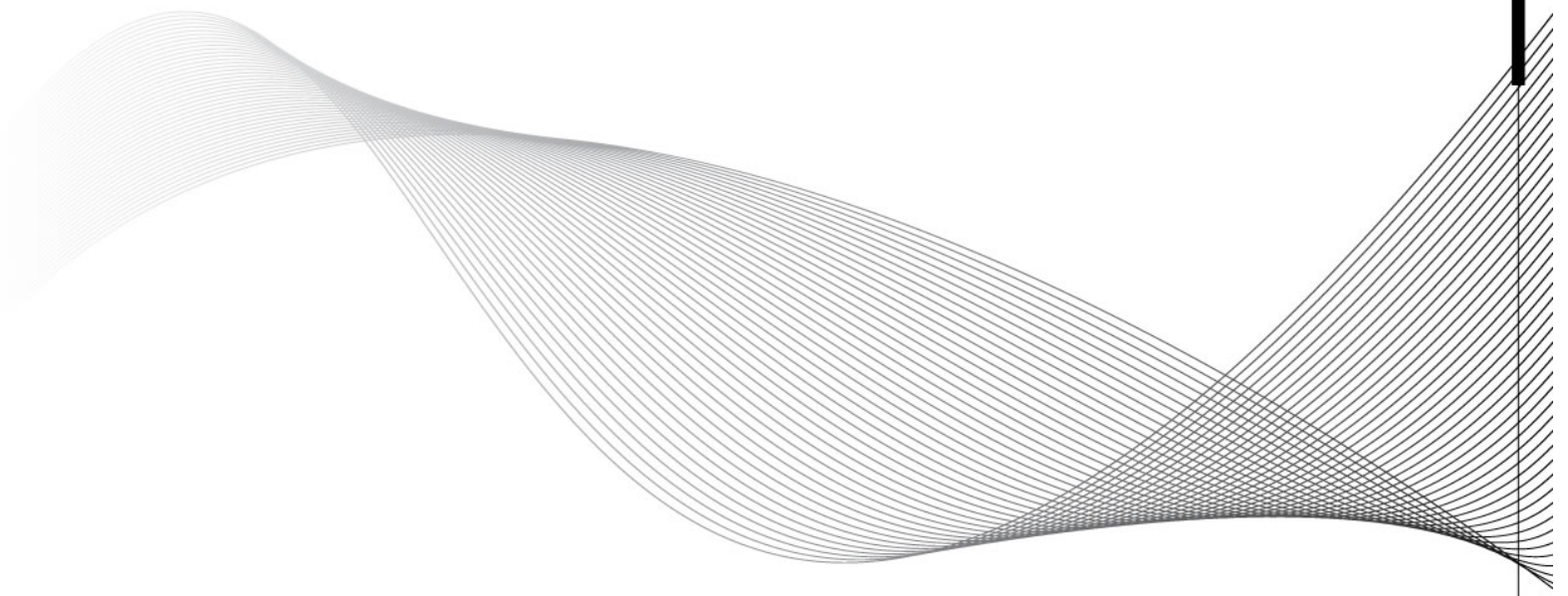

Recommendation from the Scientific Committee on Occupational Exposure Limits for acrylonitrile

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8-hour TWA	:	-
STEL (15 mins)	:	-
Additional classification	:	*Skin notation*

Substance Identity and Properties:

Acrylonitrile	C_3H_3N
Classification:	F; R11 Carc. Cat. 2; R45 T; R23/24/25 Xi; R38
Synonyms:	Vinyl cyanide, cyanoethylene
Chemical Name	2 - propenenitrile
Structural Formula:	CH_2 = CH - CN
CAS Number:	107 - 13 - 1
EINECS Number:	203 - 466 - 5
Molecular Weight:	53.06
Melting point:	-89.6^{O}C
Boiling point:	77.3^{O}C
Vapour pressure:	115 hPa at 20^{O}C
Conversion factors:	1 ppm = 2.20 mg/m^3
(20^{O}C, 101.3kPa)	1 mg/m^3 = 0.45 ppm

1. Occurrence and Use

Acrylonitrile is a clear colourless liquid with a characteristic, slightly pungent odour. A yellow coloration may develop in the presence of light. In the absence of stabilisers, spontaneous polymerisation may occur at increased temperatures, or in the presence of light, acid or alkalis. Acrylonitrile is produced in a closed system by catalytic "ammoxidation" of ammonia and propylene. Fractional distillation of the crude (85%) product, following scrubbing to remove ammonia, yields 99.9% pure acrylonitrile.

Current production volume in the EU is in excess of 1 250 000 tonnes per annum, US production is approximately 1 500 000 tonnes per annum, Japan produces approximately 600 000 tonnes per annum, and the rest of the world around 500 000 tonnes. There is a paucity of data for the former Soviet Union and Eastern European countries. In addition to a production volume of greater than 1 250 000 tonnes per year, it is estimated that the European Union imports a further 100 000 to 300 000 tonnes per annum from outside Europe. Approximately 52% of the total EU production of acrylonitrile is used in production of fibres, 15% in production of ABS and SAN resins, 15% in the production of acrylamide and adiponitrile and 18% for other uses (source: PCI World Acrylonitrile Report 1996).

2. Health Significance

Metabolism

Acrylonitrile is metabolized in humans and experimental animals via two pathways (Fennell *et al.* 1991, Kedderis *et al.* 1993b). A glutathione-dependent pathway (Michael addition of glutathione to acrylonitrile) leads via the primary metabolite S-cyanoethyl-glutathione to the mercapturic acid N-acetyl-S-cyanoethyl-cysteine, representing the final urinary excretion product. The glutathione-S-transferase (GST) isoenzyme(s) responsible for this pathway in humans is/are not known; the polymorphic GSTT1 and GSTM1 are not likely to be involved (Thier *et al.* 1999, Fennell *et al.* 2000). The alternative oxidative pathway is catalysed by the cytochrome P-450 isoenzyme CYP2E1 and leads to the epoxide cyanoethylene oxide (glycidonitrile, 2-cyano-oxirane) as primary metabolite (Kedderis *et al.* 1993a) which is genotoxic (Peter et al. 1983, Recio and Skopek 1988). There is extensive secondary metabolism of cyanoethylene oxide, one highly toxic metabolite arising from the oxidative pathway being cyanide. Observations in cases of acute acrylonitrile intoxication have led to the conclusion of a much higher impact of the oxidative metabolism of acrylonitrile in humans than in rodents (Thier *et al.* 2000). There is also a considerable degree of human interindividual variability in acrylonitrile metabolism and toxicity, probably based on a multiplicity of relevant gene-environment interactions (Thier *et al.* 2002).

2.1. Acute Toxicity

With respect to the acute effects of acrylonitrile in humans, there are mainly reports of specific incidents or accidents (Davis *et al.*, 1973). The findings and approximate dose levels thought to be involved in these human experiences are consistent with the information obtained from animal studies. These indicate that acrylonitrile is toxic by the oral and inhalation routes, and also via contact with skin, and causes neurotoxic effects which are related both to acrylonitrile itself, and to the metabolic release of cyanide (Thier *et al.* 2000).

With regard to the acute lethality of acrylonitrile in animals, dogs appeared to be the most sensitive species following exposure via inhalation. However the acute toxicity of acrylonitrile is for the greater part caused by the release of cyanide, to which dogs are much more sensitive because they have lower levels of the detoxifying enzyme rhodanase in the liver than other mammals. Inhalation studies provided an approximate LC_{50} of 200 mg/m^3/4 h in dogs, 300 mg/m^3/4 h in mice and 990 mg/m^3/4 h in guinea pigs. In rats. the data from Dudley *et al.* (1942) and Appel *et al.* (1981) provided a figure of between 1030 and 1210 mg/m^3/4 h, although a lower value of 470 mg/m^3/4 h was reported by Knobloch *et al.* (1971).

Following oral dosing, mice appeared to be the most sensitive species, with an oral LD_{50} ranging from 28 to 48 mg/kg body weight. The reported range in guinea pigs was 50-85 mg/kg, an oral LD_{50} of 93 mg/kg was reported in rabbits, while in rats the range was 72-186 mg/kg. No oral toxicity data exist for dogs.

The reported dermal LD_{50} for rats lay between 148 and 282 mg/kg bodyweight, the dermal LD_{50} in rabbits was 226 mg/kg and that in guinea pigs was between 260-690 mg/kg. The percutaneous LD_{50} in rabbits was only 3 times higher than the intravenous LD_{50}, and was approximately 3 to 10 times higher in guinea pigs, indicating that acrylonitrile can readily penetrate the skin. Acute administration of acrylonitrile produced pathological findings in the gastrointestinal tract, gastrointestinal bleeding apparently being independent of the route of administration since it was reported after oral or subcutaneous dosing, and changes have also been reported in the kidney, the liver and in haematological and clinical chemistry parameters. Acrylonitrile has been shown to induce dose- and time dependent cholinomimetic neurotoxicity in rats, regardless of the route of administration. This coincides with similar observations in exposed workers (Wei, 2000; Bolt *et al.*, 2003).

Inhalation

WHO (1983) and VROM (1984) summarised several cases of acrylonitrile poisoning whereby workers exposed to low acrylonitrile concentrations suffered from local effects such as irritation of the eyes, nose, throat and respiratory tract, headaches, vertigo and limb weakness at > 5ppm (11mg/m^3). Slight liver enlargement and jaundice have also been reported. Workers in a synthetic rubber manufacturing plant exposed to acrylonitrile vapour at levels of between 16 (35 mg/m^3) and 100 ppm (219 mg/m^3) acrylonitrile for 20 to 45 minutes experienced mucous membrane irritation, headaches, nausea, feelings of apprehension and nervous irritability (Wilson *et al.*, 1948). Low-grade anaemia, leucocytosis, kidney irritation and mild jaundice were also apparent; these effects subsided with exposure cessation. Zeller *et al.* (1969) observed that in 16 cases of acute inhalation of acrylonitrile fumes by workers, nausea, vomiting, headache and vertigo appeared within 5–15 minutes; none of the workers required hospitalisation.

More serious exposures have resulted in tremors, convulsions, unconsciousness, respiratory and cardiac arrest and even death (Buchter *et al.*, 1984). One reported fatal case involved a 3-year-old girl who slept overnight in a room recently sprayed with an acrylonitrile-based fumigant. Respiratory malfunction, lip cyanosis, and tachycardia were among the symptoms described prior to death (WHO, 1983). However, five adults who spent the night and much of the day in a room fumigated with an acrylonitrile-based product complained only of eye irritation and in general showed no signs of acrylonitrile poisoning (Grunske, 1949). The concentration of acrylonitrile in the air was not given. Several other cases of death in children were reported, but not described in detail, while adults only suffered mild irritation (Grunske, 1949).

Human volunteers exposed acutely (8 hours) to acrylonitrile at concentrations of 2.4 - 5.0 ppm (5.4 - 10.9 mg/m^3) exhibited no deleterious effects, indicating that acrylonitrile is not very irritating to the respiratory tract at these concentration levels (Jakubowski *et al.*, 1987).

2.2. Irritation

Little information exists regarding specific human studies involving skin or eye contact. A male laboratory worker spilled 'small quantities' of liquid acrylonitrile on his hands, resulting in diffuse erythema on both hands and wrists after 24 hours, followed by blisters on the fingertips on the third day. His hands were slightly swollen, erythematous, itchy and painful and the finger remained dry and scaly on the 10th day (Dudley and Neal, 1942). Wilson *et al*. (1948) noted that direct skin contact resulted in irritation and erythema and scab formation, with slow healing.

Skin contact has resulted in local irritation, erythema, swelling, blistering and burns. In one case report (Hashimoto and Kobayashi, 1961), lesions spread rapidly to parts of the body which had not been exposed and this was considered to be an allergic reaction. A producer of acrylonitrile reported 10 cases of skin complaints in employees (Bakker *et al.*, 1991). Of these, 5 had irritant dermatitis while the other 5 proved to have an allergy to acrylonitrile on patch testing. Paresthesia was reported in one patient.

With regard to human experiences of acute exposure to acrylonitrile as a liquid or vapour, a wide range of effects have been observed, including irritation of the mucous membranes of the nose, eyes and upper respiratory tract. Lacrimation, burning in the throat, coughing, sneezing, nausea, vomiting dizziness, visual disturbance, headache, coma, seizures and dermatitis have been described in some of the non-fatal cases (Davis *et al.*, 1973). The seriousness of some of these effects, however, reflect very high exposure levels following, for example, accidental release of a large quantity of acrylonitrile.

Jakubowski *et al.* (1987), exposed human volunteers to acrylonitrile for 8 hours at concentrations of 2.4 -5.0 ppm (5.4 - 10.9 mg/m^3). Volunteers exhibited no deleterious effects and acrylonitrile did not appear to cause irritation in the respiratory tract at these exposure levels.

Vogel and Kirkendall (1984) reported a case of a 24-year-old man whose face, eyes and body were sprayed by acrylonitrile when a valve burst while he was unloading the chemical from a ship. Within 30 minutes, the subject developed dizziness, flushing, nausea and vomiting. He showed generalised, erythema, but no skin rash was observed. There was mild conjunctivitis but no corneal clouding; and funduscopic examination was normal.

Grahl (1970) refers to one volunteer who exposed himself to acrylonitrile for 70 seconds at levels of 370 - 460 ppm (800 - 1000 mg/m^3) without experiencing an intolerable reaction, possibly indicating that acrylonitrile has little warning action even for acute high levels.

2.3. Sensitisation

2.3.1. Animal Studies

Koopmans and Daamen (1989) carried out a Guinea Pig Maximisation in compliance with EC and OECD guidelines. Sensitisation was induced by an intradermal injection of 2.5% acrylonitrile and an epidermal application of 2% acrylonitrile 7 days later. Animals challenged with acrylonitrile concentrations of 0.5% and 1.0% acrylonitrile showed a 95%

positive sensitisation rate. Exposure to 0.2% on challenge caused an 80% sensitisation rate. It can be concluded that acrylonitrile has marked sensitising properties and should be classified as sensitising, using the EU criteria. A sensitising effect is compatible with the direct reactivity (Michael addition) of acrylonitrile towards functional groups of proteins (Peter and Bolt 1981).

2.3.2. Human Studies

In a case reported by Hashimoto and Kobayashi (1961) 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 to other parts of the body that had not been in contact with the liquid. It was concluded that these later skin lesions were indicative of an allergic-type response to the initial exposure to acrylonitrile liquid.

A positive patch test for acrylonitrile was ascertained in 5 employees of an acrylonitrile processing and production plant who had contact dermatitis. The 8 control individuals did not show any allergic reaction to acrylonitrile (Bakker *et al.*, 1991).

Respiratory Sensitisation

There are no data available.

2.4. Repeated-Dose Toxicity in Humans

Human evidence from case reports and workplace surveys are suggestive of neuropathological effects following exposure to acrylonitrile, the primary routes of exposure being inhalation and physical contact with the substance. It is evident that there is usually co-exposure with other chemicals, which makes it very difficult to interpret these epidemiological studies in production and processing plants.

WHO (1983) summarised workplace studies indicating that effects such as reduced haemoglobin levels, erythrocyte counts and leucocyte counts occurred at 5 ppm (11 mg/m^3). Furthermore, symptoms of gastritis and colitis, as well as blepharoconjunctivitis and an immunosuppressive effect were reported.

Sakurai and Kusumoto (1972) reported that at exposure levels as low as 5 ppm (11 mg/m^3) some subjective complaints such as headache, fatigue, nausea, nose-bleeds, insomnia and some changes in liver function tests. These effects were positively associated with the length of exposure, but not with the exposure level or the age of the workers. However, it should be noted that in a later report by Sakurai et al. (1978) it was stated that the 'exposure levels were not reliably reported' and reflected historical data where the actual exposure levels were greatly in excess of 5 ppm (11 mg/m^3). In fact the study of Sakurai et al. (1978) in acrylonitrile workers indicated levels in excess of 10 ppm did not cause notable irritancy. WHO (1983) cited the study of Babanov *et al.* (1959), in which similar subjective complaints, together with inflammation of the vocal cords, were reported by workers exposed for approximately 3 years to airborne acrylonitrile levels of 0.6-6.0 mg/m^3 (0.3 - 3 ppm).

Overall, the human data are difficult to assess in relation to establishment of a dose-response relationship. However, many of the findings in the animal repeat-dose exposure studies, especially the neurological and irritation effects, reflect the reported findings in workers. The respiratory tract appears to be a key target organ following inhalation of acrylonitrile, both in humans and experimental animals.

2.5. Mutagenicity

Acrylonitrile is weakly mutagenic in reverse mutation assays in Salmonella typhimurium and specific strains of Escherichia coli, the effect generally requiring the presence of metabolic activation, although a number of authors have reported negative results in the Salmonella assay. Positive results have also been obtained in mutagenicity assays using yeast and Aspergillus, and in mammalian cell lines including mouse lymphoma cells (TK+/- locus and oua locus) and the TK6 human lymphoblast cell line, again generally in the presence of metabolic activation only and frequently only at cytotoxic concentrations. Acrylonitrile induces sister chromatid exchanges and chromosomal aberrations in *in vitro* studies. However, negative responses have generally been obtained in DNA repair assays using rat hepatocytes and human mammary epithelial cells *in vitro*.

A number of *in vitro* assays have included the metabolite epoxide cyanoethylene oxide, CEO (Peter *et al.*, 1983). The responses of the metabolite in several of the test systems described above indicate that it is a direct acting mutagen. Coupled with the observation that acrylonitrile is mutagenic *in vitro* mainly in the presence of S9, indicating that metabolic activation is required to exert the mutagenic potential, it may be concluded that the DNA active compound is CEO and that acrylonitrile itself has relatively low DNA reactivity. The epoxide has been shown to bind to DNA with a much greater affinity than acrylonitrile.

In *in vivo* studies, acrylonitrile overall appeared to be negative in a dominant lethal assay in rats, and was also negative in two mouse micronucleus studies, although the lack of experimental detail available on these latter studies makes them of limited value for risk assessment purposes. Conflicting results have been obtained in studies of unscheduled DNA synthesis. Negative results have been obtained in studies using rat liver hepatocytes *ex vivo* and in rat spermatocytes using autoradiographical techniques, while UDS has been reported in rats' lungs and in the gastrointestinal tract *in vivo*, using the methodological approach of determination of radioactivity associated with the nucleic acid cell fraction by liquid scintillation counting, which is regarded as being less reliable than autoradiography. A number of studies in Drosophila, using a range of genetic markers, have given positive results.

In summary, acrylonitrile appears weakly mutagenic in *in vitro* systems, indicative of a genotoxic potential. However these findings are not reliably reflected in the *in vivo* studies, suggesting that acrylonitrile or its active metabolites do not reach target tissues *in vivo*, possibly due to the detoxification of the epoxide metabolite CEO via a glutathione conjugation pathway which may not exist in *in vitro* test systems. Nevertheless, the overall body of evidence presented above on the *in vitro* mutagenicity of acrylonitrile, together with the positive results in Drosophila, leads to the conclusion that for the purposes of this risk assessment, acrylonitrile should be regarded as genotoxic, although non-genotoxic mechanisms of tumour induction in experimental animals may also be involved (Whysner *et al.*, 1998). Recent research has suggested a role for secondary processes as a result of oxidative stress (Kamendoulis *et al.*, 1999).

Very little human information is available which could help in determining of possible genotoxicity in man from exposure to acrylonitrile. Thiess and Fleig (1978) analysed chromosomal damage in peripheral lymphocytes of 18 workers exposed to acrylonitrile for an average of 15.4 years. There was co-exposure to styrene, ethylbenzene, butadiene and butylacrylate. Under normal conditions, air concentrations of acrylonitrile of 5 ppm (11 mg/m^3) were measured, although higher peak exposures will have been present due to faults and manual operation. The frequency of chromosomal aberrations in peripheral lymphocytes was not enhanced in workers when compared with the unexposed controls.

2.6. Carcinogenicity

Acrylonitrile is carcinogenic in rats following either oral administration or inhalation. Common target organs identified were the central nervous system (brain and spinal cord), Zymbal gland, gastrointestinal tract (tongue, non-glandular stomach and small intestine) and mammary gland. Also, as a result of irritation due to inhalation of acrylonitrile, inflammatory and degenerative changes (hyperplasia and metaplasia of the respiratory epithelium) were present in the nasal turbinates and a significantly increased number of rats at 80 ppm exposure levels showed focal gliosis and perivascular cuffing in the brain.

The carcinogenicity bioassays have been compiled and evaluated by the IARC (1999). Acrylonitrile exposure was found to be associated with tumours in rats' brains (astrocytomas), Zymbal glands and mammary glands. The experimental carcinogenicity of acrylonitrile has subsequently been confirmed in oral studies in Sprague-Dawley rats (Johannsen and Levinskas, 2002a/b), in Fischer 344 rats (Johannsen and Levinskas, 2002b) and in B6C3F1 mice (NTP 2001). In addition, a three-generation reproduction study in rats receiving acrylonitrile in drinking water reported about an increase in astrocytomas and Zymbal gland tumours in the parental generation (Friedman and Beliles 2003).

However, while there is no doubt that acrylonitrile is an animal carcinogen, the mechanism of action with respect to inducing carcinogenicity is still relatively unclear. Based on current information on the genotoxicity of its metabolite chloroethylene oxide and with no definitive evidence to the contrary, acrylonitrile must be regarded as a carcinogen for which a threshold cannot be reliably identified. It is therefore not possible to establish a safe threshold regarding exposure to acrylonitrile and a NOEL cannot in practice be estimated or established for this particular endpoint (see *Recommendations*).

There was some indication of excess bladder cancer in three ('new') epidemiological studies, a finding not reported in the 'old studies'. However, the excess seemed to be associated with exposure to aromatic amines and is unlikely to be related to acrylonitrile exposure. Furthermore, a reanalysis (Collins and Acquavella, 1998) in which two outlier studies, Kiesselbach *et al.* (1979) and Siemiatycki *et al.* (1994) were excluded, resulted in the bladder cancer meta relative risk (mRR) being reduced overall from 1.4 (95% CI 0.9 - 2.0) to 1.1 (95% CI 0.7 - 1.7).

Regarding the human epidemiological evidence available both the meta-analysis by Rothman *et al.* (1994) ('old studies') and the meta-analysis performed by Collins and Acquavella (1998) which included 4 more recent studies, no excess of all cancer or lung cancer was found among acrylonitrile workers. One advantage of the 'old studies' is the much higher average levels of exposure experienced compared with current levels. Cancer excesses were not obtained even at these levels, which reinforces the view that the current levels reflect probable safe limits. The study by Blair *et al.* (1998) had almost 5 times as many person-years of exposure Wood *et al.* (1998), but the latter had considerably more expected deaths from lung cancer than Blair *et al.* in the highest exposure group. It is possible that this difference in the highest exposure group was caused by different methods of exposure assessment. However, the study by Wood *et al.* included older workers with longer durations of exposure than the study by Blair *et al.*

The larger number of expected deaths in the study by Wood *et al.* (1998) in the higher exposure categories relative to Blair *et al.* may have been due to the fact that the workers were older and had longer durations of exposure to higher levels of acrylonitrile. Therefore, the study by Wood *et al.* (1998) may currently provide more information about higher cumulative exposure to acrylonitrile than that of Blair *et al.* (1998). With regard to lung

cancer, it is still possible that there is an increased risk of lung cancer in workers exposed to acrylonitrile, but this is likely to apply only to high levels of exposure and requires a lengthy exposure period to manifest itself.

The excess prostate cancer incidence reported by O'Berg *et al.* (1985), Chen *et al.* (1987) and confirmed by Wood *et al.* (1998) has raised the concern that exposure to acrylonitrile may increase prostate cancer incidence risk. However, there is no increase in cancer rates with increasing exposure, and this finding has not been seen in the mortality studies. In addition, the excess of prostate cancer in the study by Wood *et al.* (1998) is limited owing to the restricted reporting period, i.e. 1978 –1983. When improved diagnostic procedures were later introduced, a deficit was observed (SIR = 0.3, 95% CI 0.0 - 1.4) from 1983 to 1991. This indicates the potential for diagnostic bias as cases may have been "harvested" early. Accordingly, the overall evidence does not support an association between prostate cancer and acrylonitrile exposure.

Excess cancer at multiple sites were observed in rats exposed to relatively low levels of acrylonitrile. However, there is little evidence that acrylonitrile workers have increased cancer rates even though exposures in some groups of workers were at levels which caused tumours in rats. By excluding two possible outliers (Kiesselbach *et al.* (1979) and Siemiatycki *et al.* (1994) from meta-analysis (Collins and Acquavella, 1998) heterogeneity was reduced, as evidenced by the change in p-values from 0.18 to 0.45.

In summary, the excess risk of lung cancer from acrylonitrile exposure, if any, seems to be small. For less common cancers, e.g. of the brain or prostate, it is only possible to evaluate consistency across the available studies. Relatively imprecise risk estimates contradicting each other have been published for brain cancers in acrylonitrile workers (Collins and Strother, 1999; Schulz *et al.*, 2001). It has also been stressed that predictions of cancer potencies for acrylonitrile based on differing assessments from animal studies vary considerably, and it was suggested that most current risk assessment practices overestimated the acrylonitrile cancer potency for humans (Kirman *et al.* 2000).

In this general situation, acrylonitrile cannot be ruled out as cause of human cancer.

2.7. Reproductive effects

The results of a three-generation reproduction study, which is considered to be valid for risk assessment purposes despite some methodological deficiencies, did not show any effects on fertility, although effects were seen on pup viability and the bodyweights of pups in all 3 generations at 21 days were also reduced. These effects could be attributed to maternal toxicity. A number of other studies have also indicated that acrylonitrile is foetotoxic, as evidenced by dose-dependent reductions in pup weight at exposure levels which are also maternally toxic. A No Effect Level of 12 ppm for the foetotoxic effect was established in the study by Saillenfait *et al.* (1993).

Other studies have reported that acrylonitrile causes testicular toxicity in rats (at doses approaching the LD50), although no such effect was seen in a recent 90-day study in mice or in other repeat-dose toxicity studies. There are no data on fertility in humans.

A gavage study in rats and a study in hamsters using intraperitoneal administration indicated some developmental toxicity potential for acrylonitrile, and this was supported by the findings of an *in vitro* study of 10-day rat embryos. However, developmental effects *in vivo* were only seen in the presence of significant maternal toxicity, and there was little evidence for a developmental effect following exposure of rats by inhalation. An absence

of developmental effects following inhalation exposure was confirmed by another group of researchers using comparable exposure levels.

Overall, it can be concluded that existing animal data do not show any clear indication of fertility, dominant lethal, reproductive or teratogenic effects of acrylonitrile at doses below those producing parental toxicity. Consideration as "toxic for reproduction" is not considered appropriate, given the maternal toxicity seen in the Murray *et al.* study and the confounding influence of disease, the route of administration used in the hamster study of Willwhite *et al.* (1981), and the negative outcome of the study of Saillenfait *et al.* (1993).

There are no reports of effects on fertility in acrylonitrile-exposed workers. However, no specific epidemiological studies have been carried out. A recent case control study of 475 female workers exposed to acrylonitrile compared with 527 controls (Weiai *et al.*, 1995) suggested a higher incidence of premature delivery (RR 1.55, logistic regression analysis), birth defects (RR 1.84), pernicious vomiting during pregnancy (RR 1.64) and anaemia (RR 2.79) in the acrylonitrile-exposed population. An increased incidence of miscarriage was also reported, although this was not statistically significant. The exposed population worked in a plant for the manufacture of acrylonitrile itself and also butadiene rubber, ABS plastic and polyacrylonitrile fibre. Monitoring in the plant during the period 1988–1990 indicated that exposure levels were in excess of the OEL of 2 mg/m^3 (0.87 ppm). Levels as high as 92 mg/m^3 (40 ppm) were reported. The authors indicate that confounding factors such as age of the parents at pregnancy, drinking, smoking, health history, medication and X-ray were taken into account in their analysis. There was, however, concomitant exposure to other chemicals in the workplace, while it appears that the controls were involved in fabric processing, e.g. tailoring, and had little or no chemical exposure. Little confidence can be placed in this poorly reported study, and no conclusions can be drawn regarding a possible effect of acrylonitrile on pregnancy outcome.

Recommendation

Acrylonitrile is acutely highly toxic, by inhalation and by skin contact. Part of this toxicity is attributed to metabolic formation of cyanide. A number of fatalities have been documented in the literature following accidental over-exposure.

Animal experiments clearly show that acrylonitrile is carcinogenic. A high incidence of astrocytomas in the brain and spinal cord was the most consistent finding. In a two-year inhalation study (6h/d, 5d/wk) in rats, the lowest exposure associated with an increased incidence of astrocytomas was 20 ppm (Quast *et al.* 1980). The mechanism of the experimental tumour formation following exposure to acrylonitrile is not fully understood. Although its primary oxidative metabolite, cyanoethylene oxide ("glycidonitrile"), appears clearly genotoxic, acrylonitrile may also act via non-genotoxic mechanisms of carcinogenicity. Such argumentations, mainly focused on the experimental brain tumours, were based on the following (Chapman *et al.* 2002): (1) absence of DNA adducts in brain tissue after acrylonitrile exposure and absence of DNA repair on the basis of slide autoradiography; (2) oxidative DNA damage in astrocytes exposed to acrylonitrile but not in primary hepatocytes, with an apparent threshold response; (3) reversible loss of gap-junction intercellular communication in astrocytes exposed to acrylonitrile, but not in primary hepatocytes. However, as acrylonitrile appears from the rodent bioassays as a pluripotent (multi-organ) carcinogen, and given that the impact of genotoxicity cannot be ruled out, it appears prudent to consider a non-threshold mechanism. The available long-term bioassays by inhalation and by the oral route (gavage and drinking water studies) have been analysed as to the dose-dependence of tumours at the main target sites, using the Kaplan-Meier probability model. It has been concluded that the shape of

the different dose-response curves was sublinear (Chapman *et al.* 2002). The genotoxicity *in vivo*, at low levels of exposure, is not straightforward. IARC (1999) has concluded that "there is inadequate evidence in humans for the carcinogenicity of acrylonitrile", and "sufficient evidence in experimental animals" and has classified the compound as "possibly carcinogenic to humans" (Group 2B).

In general, the health risks from industrial handling of acrylonitrile appear to largely derive from its very pronounced acute and chronic toxicity, in combination with its clear potential for skin penetration, which leads to a high risk of accidents, possibly even fatal. This means that strict controls for the handling the compound in the workplace are required. Based on a review of the literature on health effects other than carcinogenicity, it has been concluded that current OELs in Western countries (i.e., ~2 ppm) offer adequate protection against health effects other than carcinogenicity (Sakurai 2000).

Acrylonitrile has been the subject of a substantial number of epidemiologic studies in exposed workers. A meta-analysis of 25 studies of acrylonitrile workers has indicated no excess for lung, brain and prostate cancer (Collins and Strother 1999). In a cohort study by the U.S. NCI and NIOSH, however, some excess of lung cancer was noted in the highest quintile of cumulative exposure to acrylonitrile (Blair *et al.* 1998). This finding has been countered by the argument that 67% of workers in the highest quintile originated from one plant, and that a prior history of exposure to asbestos also played a role (Chapman *et al.* 2002). Having reviewed 18 published cohort studies, Sakurai (2000) arrived at the conclusion that, although there was no adequate evidence in humans for carcinogenicity of acrylonitrile, the possibility of a causal association between high exposure and lung cancer in humans could not be excluded. In general, the evidence of carcinogenicity to humans is considered weak.

In essence, acrylonitrile is an established carcinogen in experimental animals; a genotoxic mechanism cannot be ruled out and epidemiological evidence does not exclude the possibility of carcinogenicity in humans. *In consequence, a health-based Occupational Exposure Limit cannot be derived for acrylonitrile.* Non-tumorigenic effects of acrylonitrile are not to be expected at exposure levels up to 1-2 ppm.

A *skin notation* is supported by reports of severe industrial intoxications following skin contact (Thier *et al.* 2000). This calls for effective means of biological monitoring. Available methods have been evaluated (DFG 1994). In industrial practice, suitable strategies could reasonably be based on analysis of acrylonitrile adducts to blood proteins (haemoglobin and/or albumin; Thier *et al.* 1999, 2000, 2002).

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