# NIOH and NIOSH basis for an occupational health standard

# Acrylamide: a review of the literature

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

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# NIOH AND NIOSH BASIS FOR AN OCCUPATIONAL HEALTH STANDARD

## Acrylamide: A Review of the Literature

by

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# PREFACE

A memorandum of understanding has been signed by two government agencies in the United States and Sweden—the Division of Standards Development and Technology Transfer of the National Institute for Occupational Safety and Health, U.S. Department of Health and Human Services (DSDTT/NIOSH), and the Criteria Group of Occupational Standard Setting, Research Department, National Institute of Occupational Health (NIOH) (formerly National Board of Occupational Safety and Health). The purpose of the memorandum is to exchange information and expertise in the area of occupational safety and health. One product of this agreement is the development of documents to provide the scientific basis for establishing recommended occupational exposure limits. These limits will be developed separately by the two countries according to their different national policies.

This document on the health effects of occupational exposure to acrylamide is the fourth product of that agreement. The document was written by Vlasta Molak, Ph.D., D.A.B.T. (DSDTT/NIOSH), and was reviewed by the Criteria Group and by DSDTT/NIOSH.

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# CONTENTS

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# 1 BACKGROUND

## 1.1 CHEMICAL AND PHYSICAL PROPERTIES

Acrylamide is an odorless, white, crystalline solid used as a monomer or as a raw material in the production of polyacrylamides and other compounds. Chemical and physical properties of acrylamide are given in Table 1. Because most of the acrylamide monomer is produced and used as an aqueous solution, the physical properties of a 50% aqueous solution of acrylamide are also given (Table 2).

## 1.2 PRODUCTION AND USE OF ACRYLAMIDE

In 1985, 140 million lb (63,600 metric tons) of acrylamide were produced in the United States, and predictions in 1988 indicated that 164 million lb (74,500 metric tons) of this chemical would be produced in 1989 [EPA 1988a]. Total acrylamide production capacity in western Europe was 93.5 million lb (42,500 metric tons) in 1984, and the estimated production in Japan was 90 million lb (41,000 metric tons) in 1982 [WHO 1985]. Acrylamide is also used and produced in the Soviet Union and China, but production estimates have not been reported [He et al. 1989].

The reactive acrylamide monomer is used in the production of other compounds (mostly polymers of acrylamide) and as a grouting agent in the construction or rehabilitation of dams, buildings, sewers, tunnels, and other structures.

Acrylamide grouts are used predominantly as barriers against groundwater seepage into sewers. About 95% of the acrylamide produced in the United States is consumed in the production of other compounds and polyacrylamide products that are widely used as (1) flocculents in potable water and wastewater treatment, mineral ore processing, and sugar refining, (2) water flow control agents in oil well operations, and (3) adhesives in papermaking and construction [Davidson et al. 1980]. The remaining 5% is used as a monomer [CMR 1985].

## 1.3 POTENTIAL FOR OCCUPATIONAL EXPOSURE

Data on worldwide occupational exposures to acrylamide are unavailable. However, since exposure occurs during acrylamide production and use, the potential for occupational exposure exists in all countries that produce or import acrylamide. The National Institute for Occupational Safety and Health (NIOSH) estimates that more than 10,000 U.S. workers were potentially exposed to acrylamide monomer during the period 1981–83, either in acrylamide manufacturing and processing or in grouting operations (particularly in sewer grouting) [NIOSH 1983]. Other workers that are potentially exposed to variable and intermittent airborne concentrations and possible dermal contact with acrylamide are the researchers and technicians involved in the preparation of polyacrylamide

**Table 1. Identifying information and chemical and physical properties of acrylamide***

| Item | Description |
|---|---|
| CAS registry number | 79-06-1 |
| RTECS number | AS3325000 |
| Synonyms | Acrylamide monomer, acrylic amide, propenamide |
| Formula (structure) | $C_3H_5NO$ ($CH_2$=CHC(=O)$NH_2$) |
| Molecular weight | 71.08 |
| Physical form | White, crystalline solid |
| Melting point | 84.5 ± 0.3°C (184.1° ± 0.5°F) |
| Boiling point | 125°C at 25 mm Hg (decomposes on boiling) |
| Density | 1.122 g/$cm^3$ at 30°C (86°F) |
| Vapor pressure | 0.007 mm Hg at 25°C ( 77°F), 0.033 mm Hg at 40°C (104°F), 0.070 mm Hg at 50°C (122°F) |
| Conversion factors | 1 ppm ≈ 2.9 mg/$m^3$ at 25°C, 1 mg/$m^3$ ≈ 0.34 ppm at 25°C |
| Solubilities (in g/100 ml at 30°C): | |
| Acetone | 63.1 |
| Acetonitrile | 39.6 |
| Benzene | 0.346 |
| Carbon tetrachloride | 0.038 |
| Chloroform | 2.66 |
| 1,2-Dichloroethane | 1.50 |
| Dimethylformamide | 119 |
| Dimethylsulfoxide | 124 |
| Dioxane | 30 |
| Ethanol | 86.2 |
| Ethylacetate | 12.6 |
| n-Heptane | 0.007 |
| Methanol | 155 |
| Pyridine | 61.9 |
| Water | 215.5 |

*Adapted from American Cyanamid Company [1969] and NIOSH [1976].

**Table 2. Physical properties of a 50% aqueous solution of acrylamide***

| Property | Value |
|---|---|
| Assay (WT% acrylamide) | 48–62 |
| pH | 5.0–6.5 |
| Polymer, max % | 0.05 |
| Viscosity | 2.71 centipoise at 25°C (77°F) |
| Specific gravity | 1.0412 at 25°C (77°F) |
| Melting point | 8°–13°C (47°–54°F) |
| Boiling point | 99°–104°C (210°–220°F) |
| Vapor pressure | 18 mm Hg at 23°C (73.4°F), 29.8 mm Hg at 31.2°C (88.2°F), 43.4 mm Hg at 37.8°C (100°F), 92.7 mm Hg at 52.7°C (126.9°F), 209.5 mm Hg at 70.5°C (158.9°F) |
| Specific heat (20°–50°C, range) | 0.83 cal/(g-deg) |
| Heat of dilution to 20 WT% | 1.1 cal/g of solution (or 2.0 Btu/lb of solution) [exothermic] |
| Heat of polymerization | 20.4 kcal/g mole [exothermic] |
| Heat of melting (solution) | 59.2 cal/g (106.5 Btu/lb) |
| Flammability | Nonflammable |

* Adapted from GCA [1980].

gels. The U.S. Environmental Protection Agency (EPA) [EPA 1988a] estimates that 100,000 to 200,000 of these U.S. workers have the potential for exposure.

Because acrylamide is produced by catalytic or sulfuric acid hydration of acrylonitrile (identified by the International Agency for Research on Cancer [IARC] as a probable human carcinogen [IARC 1987]), acrylamide production workers may also be exposed to acrylonitrile.

Evaluation of exposure data from industrial settings [Hills and Greife 1986] indicates that in all four U.S. acrylamide production plants, airborne concentrations were generally below 0.3 mg/m$^3$—the occupational exposure limit set by many countries (see the Appendix).

Of the ninety 8-hr time-weighted average (TWA) personal samples collected in the four U.S. acrylamide production plants, only two samples from one of the plants were above 0.3 mg/m$^3$ (0.38 and 0.39 mg/m$^3$). However, many samples exceeded the current Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) of 0.03 mg/m$^3$ adopted in 1989 [54 Fed. Reg. 2332 (1989)].

Hills and Greife [1986] noted that of the cases they reviewed, most adverse health effects were caused by dermal or oral exposures to acrylamide. The major routes of occupational exposure appear to be dermal absorption of the acrylamide monomers from solution and inhalation of the dry monomer or aerosols of acrylamide solution [Hills and Greife 1986; EPA 1987; He et al. 1989]. An EPA study of sewer workers involved in grouting operations indicated high dermal exposure estimates ranging from 0.6 to 5.0 mg/hr [EPA 1987]. Studies evaluating occupational exposures to acrylamide monomer indicate that dermal exposures may be more important with regard to the total body intake than inhalation exposures [Hills and Greife 1986; EPA 1988a; He et al. 1989].

## 1.4 EXISTING STANDARDS AND RECOMMENDATIONS

Many international standards for workplace exposures to acrylamide are 0.3 mg/m$^3$ with a skin notation. The current American Conference of Governmental Hygienists (ACGIH) threshold limit value (TLV®) [ACGIH 1989] and the current OSHA PEL [29 CFR 1910.1000] are both 0.03 mg/m$^3$. The current Swedish occupational exposure limit is 0.3 mg/m$^3$ with a skin notation and a short-term exposure limit (STEL) of 0.9 mg/m$^3$. See the Appendix for a list of the occupational exposure limits for airborne acrylamide in various countries and a discussion of the bases for recommendations that depart from the frequently cited limit of 0.3 mg/m$^3$.

# 2 TOXICOLOGY

## 2.1 METABOLISM

Acrylamide [$CH_2=CHC(=O)NH_2$] is a small organic molecule that is very soluble in water and can react at both its amide group and its double-bond vinyl group. This reactivity and ease of transport may account for the toxic effects of acrylamide. Studies show that the toxicokinetics and tissue distribution of acrylamide are not significantly dependent on the dose and route of exposure. The parent compound is rapidly eliminated from the tissues. The uptake, distribution, biotransformation, and elimination, which are summarized below, have been discussed in detail by Dearfield et al. [1988].

### 2.1.1 Uptake

No studies were found on the absorption of acrylamide by inhalation. All animal studies involved either oral or dermal exposure, and intraperitoneal (i.p.) or intravenous (i.v.) dosing. The uptake of acrylamide through the gastrointestinal tract of rats was rapid and complete, as indicated by similar excretion profiles of the chemical whether it was administered by i.v. injection or by gavage [Miller et al. 1982]. Dermal absorption in the rat is less than complete. By comparing blood concentrations after i.v. or dermal administration of acrylamide, Ramsey et al. [1984] calculated that 25% of the applied doses (2 or 50 mg/kg) of acrylamide were absorbed through the skin of rats during the first 24 hr. Frantz et al. [1985] reported that 26% of a 0.5% aqueous solution of acrylamide was absorbed through the skin of rats in 24 hr and that, after the skin was washed, an additional 35% remained in the skin. The data from in vitro experiments were similar [Frantz et al. 1985]. These researchers used excised skin preparations to show that 67% of the applied acrylamide was either absorbed or available for absorption (that is, 54% was absorbed and 13% remained in the skin after washing).

### 2.1.2 Distribution and Toxicokinetics

After rats received various doses of acrylamide (0.5 to 100 mg/kg) by i.v. or oral administration, the $^{14}C$-labeled chemical quickly distributed throughout the body [Hashimoto and Aldridge 1970; Edwards 1975; Miller et al. 1982; Ramsey et al. 1984]. Approximately 12% of the $^{14}C$-labeled chemical rapidly accumulated in red blood cells [Hashimoto and Aldridge 1970; Miller et al. 1982], and high levels persisted for at least 10 days. This persistence has been postulated to result from the reaction of acrylamide with sulfhydryl moieties present in hemoglobin [Hashimoto and Aldridge 1970]. Miller et al. [1982] reported that high percentages of the $^{14}C$-labeled chemical were found in muscle (48%), skin (15%), blood (12%), and liver (7%), whereas the neural tissues (brain, spinal

cord, and sciatic nerve) contained less than 1%. However, when the data were expressed as micromoles (μmoles) of acrylamide/g of tissue, the concentrations of acrylamide in the tissues were similar. In the neural tissues of rats there appears to be no preferential bioconcentration of acrylamide and/or its metabolites that can account for its neurotoxic effects [Miller et al. 1982].

Acrylamide has also been reported to distribute readily in the tissues of other animal species. For example, acrylamide was found in the blood, brain, heart, liver, kidneys, and lungs of miniature swine and beagle dogs, with the highest concentrations found in the liver and kidneys [Ikeda et al. 1985]. Because the authors did not analyze skin, muscle, and other tissues, it is difficult to compare the results with those reported by Miller et al. [1982]. In addition, autoradiographic studies have demonstrated a similar distribution of acrylamide in male and pregnant female mice [Marlowe et al. 1986]. Acrylamide was found to cross the placentas of rats, rabbits, dogs, pigs, and mice and to be uniformly distributed in those fetuses [Ikeda et al. 1983, 1985; Marlowe et al. 1986].

Ramsey et al. [1984] have examined the effects of multiple oral doses on tissue distribution. When rats were given acrylamide at 0.05 or 30 mg/kg for 13 consecutive days, the ratio of the $^{14}C$-labeled chemical in the tissues at the two doses was proportional to the ratio of the doses administered (that is, 600) except in the red blood cells (304), blood plasma (1,089), and testes (934). These data demonstrate that multiple doses of acrylamide do not greatly alter its distribution except at those three sites.

### 2.1.3 Biotransformation and Elimination

Conjugation with glutathione (GSH) is the major route for the biotransformation of acrylamide. Several studies show that acrylamide depletes GSH [Hashimoto and Aldridge 1970; Edwards 1975; Srivastava et al. 1983] and that hepatic GSH-S-transferases catalyze the reaction of acrylamide with GSH [Dixit et al. 1981]. The major urinary metabolite of acrylamide is N-acetyl-S-(3-amino-3-oxypropyl) cysteine, and it accounts for approximately 50% of the applied dose in rats [Miller et al. 1982; Ramsey et al. 1984]. Three other unidentified, nonsulfhydryl urinary metabolites accounted for an additional 14% [Miller et al. 1982]. When acrylamide was labeled at the carbonyl carbon, it was found that 4% to 6% of the labeled chemical was eliminated as $CO_2$ [Hashimoto and Aldridge 1970; Ramsey et al. 1984]. Because 15% of the dose appeared in the bile within 6 hr but only 6% was excreted in the feces, it was concluded that acrylamide (or its metabolites) underwent enterohepatic circulation [Miller et al. 1982].

Miller et al. [1982] used rats in a detailed study of the pharmacokinetics and distribution of acrylamide, both as the parent compound and as the total $^{14}C$-labeled chemical after an i.v. dose of 10 mg/kg. The elimination of the parent acrylamide was represented by a single compartment model. In the blood, the parent compound had a half-life of 1.7 hr, and the clearance of the unmetabolized acrylamide from all other tissues but the testes was similar. The testes showed a delay in the time necessary to reach peak concentration—an event attributed to their fat content. After the peak was attained, the parent acrylamide was cleared from the testes in a manner similar to that for other tissues [Miller et al. 1982].

The distribution and the elimination of the total $^{14}C$-labeled chemical (representing acrylamide and its metabolites) was slower than that of the parent compound and was best represented by a biphasic curve [Miller et al. 1982]. In addition, four tissues (liver, kidney, fat, and testes)

demonstrated absorptive phases for the total $^{14}$C-labeled chemical. Since no absorption phases were noted for the parent acrylamide in the liver and kidney, the increases in the $^{14}$C-labeled chemical in these two tissues were attributed to metabolite accumulation. The higher lipid content of the fat and testes and the polar nature of acrylamide were reported by Miller et al. [1982] to have delayed the absorption in these two tissues. The initial portion (half-life of 5 hr) of the biphasic curve was attributed to the metabolism of acrylamide and the binding of its metabolites to biological macromolecules, since only 2% of the total dose of administered acrylamide was excreted as the parent compound. The terminal portion (half-life of 8 days) of the biphasic curve was thought to be the result of the release of acrylamide metabolites from tissue depots and the degradation of acrylamide-protein adducts [Miller et al. 1982]. Support for these suppositions was provided by Ramsey et al. [1984], who analyzed urine, plasma, and tissue samples in male Fisher 344 rats following either i.v., gavage, or dermal administration of $^{14}$C-labeled acrylamide. Their data indicated that the initial phase was due to the loss of the parent compound and that the latter phase resulted from the clearance of acrylamide metabolites.

Because acrylamide affects reproduction, the very slow release of acrylamide or its metabolites from the testes is of particular interest. Although the fat content of the testes may have decreased the uptake of the parent acrylamide, it would not appear to account for its slow excretion. It is possible that acrylamide is metabolized and binds to constituents of the testes. Marlowe et al. [1986] reported that radioactivity appeared in the testes 1 hr after administration and migrated to the seminiferous tubules and head of the epididymis after 9 hr. After 9 days, radioactivity remained only in the tail of the epididymis and in the epithelium of the penis. Marlow et al. [1986] correlated this movement with that of the spermatids.

### 2.1.4 Factors That Can Affect Metabolism

Studies of the effects of altering microsomal mixed-function oxidase activity on the expression of acrylamide-induced neuropathy have given disparate results.

Pretreatment of rats with phenobarbital (PB) or DDT [Kaplan et al. 1973] or mice with PB [Hashimoto et al. 1981] reduced or delayed the neurological dysfunction caused by acrylamide administered by i.p. injection. However, Srivastava et al. [1985] found that pretreatment of rats with PB or DDT decreased the time necessary for onset of acrylamide-induced hind-limb paralysis. This disparity does not appear to be due to variations in experimental protocol, but it may be explained by differences in the animal strains.

The results of using drug metabolism inhibitors are difficult to interpret. For example, SKF 525A (which inhibits microsomal oxidation) has been reported to prevent acrylamide-induced enhancement of striatal dopamine receptor activity [Agrawal et al. 1981] and to increase the acute toxicity of acrylamide in rats [Kaplan et al. 1973], whereas cobalt chloride has been shown to cause a significant delay in the development of hindlimb paralysis in rats [Srivastava et al. 1985]. Presently, no correlation exists between the effects of modifying microsomal metabolism of acrylamide and expression of its toxic effects. Accordingly, identification of metabolic factors important in the toxic manifestations of acrylamide is not possible. Khanna et al. [1988] studied the role of protein deficiency on the neurobehavioral effects of acrylamide in rat pups exposed during pregnancy and early infancy. They demonstrated that acrylamide was more toxic in protein-deficient animals because it decreased the dopamine and benzodiazepam receptor binding and delayed the development of reflexes and other physical milestones in pups.

## 2.2 TOXICOLOGIC MECHANISMS

Because the most noticeable and earliest detectable effects of acrylamide exposures are neurological effects, numerous studies have attempted to find the mechanism of its action in neural tissues. Several mechanisms may account for the effects of acrylamide on the peripheral and central nervous systems. Biochemical studies indicate that acrylamide affects the proteins responsible for normal functioning of neural tissues. Berti-Mattera et al. [1986] found that acrylamide alters axonal protein phosphorylation and polyphosphoinositide metabolism. Another study revealed that acrylamide treatment in vivo induces changes in the composition of fast-transported proteins that are similar to those seen after axonotomy [Bisby and Redshaw 1987]. In vitro treatment of PtK1 cells by acrylamide resulted in rapid dephosphorylation of keratins [Eckert and Yeagle 1988]. Many of these changes may be explained by altered phosphorylation of cytoskeletal proteins [Howland and Ali 1986]. This phosphorylation may result from the binding of acrylamide to proteins, which has been demonstrated in vitro with bovine serum albumin (BSA) [Dixit et al. 1986]. Husain et al. [1986, 1987] found that acrylamide inhibits succinic dehydrogenase (SDH) activity in mitochondrial preparations from rat brain and causes changes in levels of biogenic amines and activities of monoamine oxidase and acetylcholine esterase. Biochemical changes may be responsible for the functional changes observed in neural tissues—for example, changes in membrane capacitance and sodium permeability [Brismar et al. 1987], changes in primary afferent terminal function [De Rojas and Goldstein 1987], reduction of neurofilament transport in rat sciatic nerve [Gold 1987], and alterations in spinal cord reflexes [Goldstein and Fincher 1986].

In light of the reported genotoxicity and carcinogenicity of acrylamide (see Sections 4 and 5), information on the binding of this compound to DNA is of considerable interest. Binding of acrylamide to DNA has been demonstrated to occur in the lung, liver, testes, stomach, and skin of mice 6 hr after oral or dermal administration of acrylamide [Carlson and Weaver 1985]. Whether or not the parent acrylamide or a metabolite was responsible for the in vivo acrylamide-DNA adducts, it was demonstrated that acrylamide can alkylate DNA in an in vitro system [Solomon et al. 1985]. Because the yield of alkylated DNA after 40 days of incubation was low (approximately 10%), the relevance of these in vitro binding studies to the in vivo DNA-binding studies reported by Carlson and Weaver [1985] remains to be established. However, the fact that acrylamide has been shown to interact with genetic material may have implications for its genotoxic and carcinogenic effects.

## 2.3 TOXICITY IN HUMANS AND ANIMALS

Polyacrylamide products are generally considered nontoxic [McCollister et al. 1965]. Human health hazards related to acrylamide monomer exposures are neurotoxicity, developmental and reproductive effects, genotoxicity, and carcinogenicity.

### 2.3.1 Neurotoxic Effects

The neurologic effects of acrylamide exposures were extensively reviewed in the National Institute for Occupational Safety and Health (NIOSH) criteria document on acrylamide [NIOSH 1976].

Exposure to acrylamide can produce serious neurotoxic effects in humans and animals [Spencer and Schaumburg 1975; Tilson 1981; Miller and Spencer 1985; O'Donoughue 1985]. These include peripheral nerve damage (paresthesia of the hands and feet, muscle weakness, ataxia, and decreased tendon reflexes) and central nervous system (CNS) effects (drowsiness, tremors, slurred speech, and hallucinations). Although most of these effects ceased after the individual was removed from exposure, some severely affected persons did not recover completely, indicating irreversible effects [Miller and Spencer 1985].

Spencer and Schaumburg [1974] reviewed acrylamide neurotoxicity in humans. The earliest and most obvious signs of local acrylamide contact are erythema and peeling of the palms caused by contact with acrylamide solution. This contact dermatitis precedes neurological symptoms by several weeks. Shortly after the appearance of contact dermatitis, exposed individuals may notice excessive fatigue, weight loss, and somnolence [Garland and Patterson 1967]. The neurological symptoms occur after chronic exposures. Exposed individuals experience unsteadiness, muscle weakness, and paresthesia, with numbness in the hands and/or feet. Sensory symptoms frequently precede overt motor signs [Takahashi et al. 1971]. If individuals are removed from exposure sources, signs of peripheral neuropathy gradually disappear [He et al. 1989]. In less severely affected individuals, complete recovery may occur within 2 to 12 months [Garland and Patterson 1967].

A recent study described the neurological and electroneuromyographic assessment of the effects of acrylamide on occupationally exposed workers in China [He et al. 1989]. The authors reported that more than 90 cases of acrylamide intoxication have occurred in China in the past 5 years as a result of increased acrylamide exposures in a number of small township-run or village-owned industries. He et al. [1989] investigated occupational exposures and toxic effects of exposure to acrylamide in a factory that began acrylamide and polyacrylamide production in 1984. The initial air concentrations of acrylamide were measured at 5.6 to 9.0 mg/m$^3$ during an exceptional increase in production from March to June 1985. After renovation of the factory in July 1985, the air concentrations dropped to an average of 0.03 mg/m$^3$. Heavy skin contamination by aqueous acrylamide monomer was common among the exposed workers because of inadequate personal protection, lack of awareness of acrylamide toxicity, and unsatisfactory personal hygiene. Water in which three exposed workers washed their hands contained 410 mg acrylamide/liter.

Seventy-one exposed workers (45 men and 26 women) were studied in October 1985 [He et al. 1989]. They had been exposed to variable concentrations of acrylamide for 1 to 18 months. Fifty-one unexposed blue collar workers from the same town (33 men and 18 women) served as a reference group; nobody in this group suffered from measurable neurological disease. All subjects were interviewed with the aid of a structured questionnaire to obtain information on demographic factors, occupational history, symptoms, past illnesses, and family history. Physical and neurological examinations, visual acuity and visual field testing, skin temperature measurements, electrocardiography, and electroencephalography were performed. The laboratory studies included routine blood and urine tests, liver function, serum hepatitis B surface antigen, serum glucuronidase, and immunoglobulins. Electroneuromyographic examinations were performed in 63 exposed and 48 unexposed workers. The exposed workers reported numerous symptoms that were nonexistent or rarely reported in the unexposed group. These included skin peeling from the hands, numbness in the hands and feet, lassitude, sleepiness, muscle weakness, clumsiness of the hands, anorexia, unsteady gait, coldness of the hands and feet, stumbling, falling, and difficulty in grasping. The initial symptoms were peeling of the skin and excessive sweating of the hands, which were mainly due to topical contamination by aqueous acrylamide. Muscle weakness of the legs and numbness and tingling of the hands and feet (indicating an involvement of the peripheral nervous system)

appeared in one-fifth of the exposed workers after 3 to 10 months of exposure. Nine workers developed lassitude, sleepiness, anorexia, and loss of body weight 1 month after initial symptoms; the symptoms progressed to inability to hold things tightly, unsteadiness in walking, and difficulty in lifting legs when climbing stairs. Three of the nine were found to have horizontal nystagmus, truncal ataxia, and clumsiness of the hands when they were admitted to a hospital in May 1985. They showed improvement in cerebellar function a month later but began losing tendon reflexes and their sensation of vibration. When interviewed in October 1985, these individuals showed considerable recovery.

Electroneuromyographic studies of the 69 acrylamide workers showed a prolonged duration of motor unit potentials in 40 workers and an increase of polyphasic potentials in 29 workers. In 25 of these 40 workers, there were no signs of neuropathology, such as impairment of distal sensation or reflexes. This finding suggests that a partial denervation of the distal muscles caused by axonal degeneration of peripheral nerves could be a subclinical abnormality in workers exposed to acrylamide. He et al. [1989] suggested that electroneuromyographic changes could be used for early detection of acrylamide neurotoxicity. Most of the workers diagnosed as suffering from occupational acrylamide intoxication handled a 27% to 30% aqueous solution of acrylamide. Their exposure to aqueous solutions of acrylamide suggests that dermal contact may have been the main route of exposure.

Several subchronic and chronic animal studies have demonstrated that the neurotoxic effects of acrylamide exposures in animals are similar to the effects in humans [Schaumburg and Spencer 1979; Burek et al. 1980]. Hind-limb ataxia appears to be one of the first symptoms of neuropathy in dogs [Satchell and McLoad 1981; Hersch et al. 1989], cats [Spencer and Schaumburg 1977b], monkeys [Merigan et al. 1982], and rats [Spencer and Schaumburg 1976a, 1977b; Tilson et al. 1979].

### 2.3.2 Developmental and Reproductive Effects

Data on developmental and reproductive effects in animals are summarized in Tables 3 and 4. No such data are available for humans. Acrylamide exposure affected both fetal and postnatal development in mouse and rat offspring when dams were orally dosed during pregnancy [American Cyanamid Company 1980; Zenick et al. 1986]. Neurotoxic effects occurred in neonates when the dam drank water containing acrylamide concentrations that were not toxic to her [American Cyanamid Company 1980].

Reproduction is also affected by acrylamide exposure. Testosterone levels were depressed in rats [Ali et al. 1983], and fertility decreased in male mice after oral exposure to acrylamide in drinking water [Sakamoto and Hashimoto 1986]. Degeneration of testicular epithelial tissue in male mice dosed by gavage [Hashimoto et al. 1981] has been observed as well as dominant lethal effects in male rats exposed through drinking water [Smith et al. 1986] and mice treated i.p. [Shelby et al. 1986]. Oral exposure of male or female mice and rats to acrylamide in drinking water caused an increased resorption rate [Nalco Chemical Company 1987; Sakamoto and Hashimoto 1986].

**Table 3. Reproductive effects of acrylamide exposure in female rats and mice and developmental effects in their offspring***

| Type of study and reference | Species, route, and dosage | Maternal | | Developmental | | Observed effects | |
|---|---|---|---|---|---|---|---|
| | | LOEL+ | NOEL+ | LOEL | NOEL | Maternal | Developmental |
| Developmental toxicity [Edwards 1976] | Porton rat; oral—diet; 0 ppm, 200 ppm, or 20 mg/kg per day, gd+ 0–22; 400 ppm or 40 mg/kg per day, gd 0–20; 100 mg/kg (i.v.), gd 9 | 200 ppm+ [20 mg/kg per day]+ | — | — | 400 ppm [400 mg/kg per day] | Ataxia; abnormal gait | *None*; it was shown, however, that acrylamide readily crosses the placenta |
| Reproduction and fertility [Zenick et al. 1986] | Long Evans rat; oral—drinking water; 0, 25, 50, 100 ppm for 2 weeks before mating and throughout gestation and lactation | 50 ppm | 25 ppm | 50 ppm | 25 ppm | Decreased body weight (50 ppm)<br>Decreased fluid intake (50 ppm)<br>Increased hind-limb splaying (100 ppm) | Decreased birth weight<br>Decreased body weight gain in pups through day 42 |
| Developmental/ neonatal [Walden et al. 1981] | Fischer 344 rat; oral—gavage; 20 mg/kg per day, gd 7–16 | — | — | 20 mg/kg per day | — | None reported | Changes in various intestinal enzyme concentrations measured in the neonate |
| Developmental toxicity (1-generation reproductive) [American Cyanamid Company, 1980] | Sprague-Dawley rat; oral—diet; 0, 25, 50 ppm or 0, 2.5, 5.0 mg/kg per day 3 weeks before mating, gd 1–19 | 50 ppm | 25 ppm | Dose unspecified | Dose unspecified | Decreased body weight gain; slight alopecia<br>Nerve fiber degeneration in sciatic and optic nerves | Wallerian degeneration of tibial nerve, unilateral optic nerve degeneration (dose unspecified) |

(Continued)

See footnotes at end of table.

**Table 3 (Continued). Reproductive effects of acrylamide exposure in female rats and mice and developmental effects in their offspring***

| Type of study and reference | Species, route, and dosage | Maternal | | Developmental | | Observed effects | |
|---|---|---|---|---|---|---|---|
| | | LOEL+ | NOEL+ | LOEL | NOEL | Maternal | Developmental |
| 1-Generation reproductive [Nalco Chemical Co. 1987] | Fischer 344 rat; oral—drinking water; 0, 0.5, 2.0, 5.0 mg/kg per day for 10 weeks throughout gestation and lactation | 2.0 mg/kg per day | 0.5 mg/kg per day | 5.0 mg/kg per day | 2.0 mg/kg per day | Increased peripheral neuropathy<br>Decreased body weight<br>Decreased body weight gain<br>Decreased number of litters (fecundity index)<br>Increased pre-implantation loss (5.0 mg/kg per day) | Increased resorptions per litter<br>Decreased litter size |
| Reproductive toxicity assay [Sakamoto and Hashimoto 1986] | ddY mouse, oral—drinking water; 0–5 mM for 4–6 weeks | 1.2 mM+ or 18.6 mg/kg per day | | | 1.2 mM or 18.6 mg/kg per day | Increased number of resorptions per dam<br>Slight hind-limb weakness | None reported |

* Adapted from EPA [1987].

+Abbreviations: gd = gestation day; LOEL = lowest-observable-effect level; NOEL = no-observable-effect level; mg/kg per day = milligrams per kilogram of body weight per day; mM = millimolar (concentration of acrylamide in drinking water); ppm = parts per million.

**Table 4. Reproductive effects of acrylamide exposure in male rats and mice***

| Type of study and reference | Species, route, and dosage | LOEL+ | NOEL+ | Observed effects |
|---|---|---|---|---|
| Dominant lethal and 1-generation reproductive [Nalco Chemical Co. 1987] | Fisher 344 rat; oral—drinking water; 0, 0.5, 2.0, 5.0 mg/kg per day for 10 weeks | 2.0 mg/kg per day+ | 0.5 mg/kg per day | Increased peripheral neuropathy<br>Decreased body weight<br>Decreased body weight gain<br>Decreased number of litters (fecundity index)<br>Increased preimplantation loss (5.0 mg/kg per day) |
| Testicular effects [Hashimoto et al. 1981] | ddY mouse; oral—gavage; 0, 35.5 mg/kg 2×/wk for 8–10 weeks; avg. daily dose = 10.1 mg/kg | 35.5 mg/kg per day<br>10.1 mg/kg | —<br>— | Degeneration of testicular epithelia<br>Weakness and ataxia in hind limbs |
| Dominant lethal [Smith et al. 1986] | Long Evans rat; oral—drinking water; 0, 15, 30, 60 ppm+ or 0, 1.5, 2.8, 5.8 mg/kg per day for 80 days | 2.8 mg/kg per day | 1.5 mg/kg per day | Increased preimplantation loss (highest dose only)<br>Increased postimplantation loss |
| Reproductive toxicity assay [Sakamoto and Hashimoto 1986] | ddY mouse; oral—drinking water; 0.3, 0.6, 0.9, 1.2 mM for 4–6 weeks | 0.6 mM+ or 8.8 mg/kg per day | 0.3 mM or 4.2 mg/kg per day | Decreased fertility rate<br>Decreased number fetuses/dam<br>Increased number resorptions/dam |

(Continued)

See footnotes at end of table.

**Table 4 (Continued). Reproductive effects of acrylamide exposure in male rats and mice***

| Type of study and reference | Species, route, and dosage | LOEL+ | NOEL+ | Observed effects |
|---|---|---|---|---|
| Reproduction and fertility [Zenick et al. 1986] | Long Evans rat; oral—drinking water; male: 0, 50, 100, 200 ppm or 0, 4.2, 7.9, 11.6 mg/kg per day for 10 weeks | 100 ppm [7.9 mg/kg per day] | 50 ppm [4.2 mg/kg per day] | Decreased copulatory performance<br>Increased hind-limb splaying |
| Dominant lethal [Sublet et al. 1986] | Long Evans rat; oral—drinking water; 0, 5, 15, 30, 45, 60 mg/kg per day for 5 days | 30 mg/kg per day | 15 mg/kg per day | Increased preimplantation loss<br>Increased postimplantation loss<br>Effects seen primarily in weeks 1–3 post mating |
| Testosterone assay [Ali et al. 1983] | Fischer 344 rat; intraperitoneal; 0, 10, 20 mg/kg per day for 20 days | 20 mg/kg per day | 10 mg/kg per day | Dose-dependent decrease of testosterone and prolactin |
| Dominant lethal [Shelby et al. 1986] | C3H X101 hybrid mouse; i.p. 125 mg/kg or 5× 50 mg/kg per day | 50 mg/kg per day | --- | Increased postimplantation loss |

* Adapted from EPA [1987].

+Abbreviations: LOEL = lowest-observable-effect level; NOEL = no-observable-effect level; mg/kg per day = milligrams per kilogram of body weight per day; mM = millimolar (concentration of acrylamide in drinking water); ppm = parts per million.

## 2.4 GENOTOXIC EFFECTS

The major concern about the genotoxicity of acrylamide is its clastogenic activity (that is, chromosomal breakage and other chromosomal abnormalities). The clastogenic effect of acrylamide appears more pronounced in the germ cells compared with somatic cells. The interaction with germinal tissues suggests the possible heritability of acrylamide-induced DNA alterations. Acrylamide has been shown to be a clastogenic agent both in vivo and in vitro [Moore et al. 1987].

Reports suggest that acrylamide binds to DNA [Carlson and Weaver 1985], induces DNA damage and repair effects, and causes in vitro cell transformation [Banerjee and Segal 1986]. In a recent study by Backer et al. [1989], various cytogenetic endpoints in both somatic and germ cells from acrylamide-treated male C57BL/6J mice were evaluated. Sister chromatid exchanges and micronuclei (but not chromosomal aberrations) were induced in spleen cells; synaptonemal complex irregularities (asynopsis) (but not chromosomal aberrations) were induced in germ cells.

### 2.4.1 Gene Mutation Assays

Acrylamide does not appear to induce gene mutations in the three types of gene mutation assays examined: the *Salmonella*/mammalian activation assay [Bull et al. 1984a; Lijinsky and Andrews 1980; Hashimoto and Tanii 1985], the CHO/HPRT mutation assay [American Cyanamid 1985], and the *Drosophila* sex-linked recessive lethal assay [American Cyanamid 1985]. The mouse lymphoma mutation data suggest that acrylamide may induce mutations in an eukaryotic gene mutation assay [Moore et al. 1987], but these data may reflect a clastogenic event associated with the predominant formation of small colonies. It may be relevant that the CHO subclone generally used in the CHO/HPRT mutation assay does not appear to be sensitive to clastogens [Hsie et al. 1986].

### 2.4.2 Chromosomal Assays

Studies that have examined the chromosomal effects of acrylamide have confirmed its clastogenic potential. This effect appears to be more pronounced in the germ cells than in somatic cells. The suggestive reciprocal translocation results raise the possibility that acrylamide-induced alterations to DNA may be transmissible to future generations. A study of heritable translocation in mice [Shelby et al. 1987] demonstrated that acrylamide is an effective inducer of translocations in postmeiotic germ cells. This result demonstrates that acrylamide may be capable of affecting heritable germ cells in a mammalian system.

In vivo and in vitro results suggest that acrylamide may induce aneuploidy. It is uncertain whether metabolic activation is required for acrylamide to exert its genotoxic effects, because most of the clastogenic activity was noted in in vivo studies. In vitro studies with human lymphocytes in which clastogenicity was observed were performed without activation [IHE 1985]. However, the metabolic activating capability of lymphocytes has not been totally explored, and it is known that lymphocytes are capable of activating chemicals such as cyclophosphamide to genotoxic forms [Waalkens et al. 1981]. The mouse lymphoma results demonstrate that acrylamide induces aberrations without activation [Moore et al. 1987].

## 2.5 CARCINOGENIC EFFECTS

### 2.5.1 Epidemiologic Findings

Collins et al. [1989] studied the mortality of workers in acrylamide production plants. This study was performed by scientists at major production plants. Mortality was tracked for a cohort of 8,854 males from 1925 to 1983. This cohort (2,293 of whom were exposed to acrylamide) consisted of four plant populations in the United States and the Netherlands. Followup was completed for 95% of the cohort. At the end of the study 2,148 individuals were deceased, and death certificates were obtained for 95%. The underlying cause of death was coded by a nosologist. Exposure estimates were developed for all jobs at each of the four plants using exposure data collected at each plant and information obtained from plant personnel who had knowledge of past jobs and processes. Exposure to acrylamide was defined as a cumulative exposure greater than 0.001 mg/m$^3$-years, which is approximately equivalent to a 1-day exposure to an average concentration of 0.3 mg/m$^3$. Data on smoking history were available for only a third of the cohort. Standardized mortality ratios (SMRs) and internally standardized rate ratios were employed to estimate the risk.

According to the authors, a particular strength of their study was the ability to detect a 25% increase in total cancer, a 50% increase in respiratory cancer, and a threefold increase in brain and other central nervous system cancers based on a two-tailed, 5% significance level with a power of 80%.

The SMRs for all causes for both exposed and unexposed groups were significantly less than expected, which may be the result of both initial selection and the ongoing benefits of employment (i.e., the healthy worker effect). An excess of total cancer deaths was not observed among the exposed workers. A slight increase in cancer of the respiratory system (30 observed versus 26.3 expected) was not statistically significant. Analyses of trends by cumulative exposure showed no increased risk of mortality with increasing exposure. Because smoking history was obtained for only a third of the cohort, it was impossible to determine whether smoking habits had confounded the results.

Sobel et al. [1986] examined mortality in a group of 371 workers assigned to acrylamide monomer or polyacrylamide operations. Exposure to acrylamide was categorized on the basis of a review of job classifications. Before 1957, personal TWA exposures to acrylamide in the monomer production areas were 0.1 to 1.0 mg/m$^3$. The data from 1957 to 1970 indicated that exposures to acrylamide were 0.1 to 0.6 mg/m$^3$. After 1970, personal exposures to acrylamide were $<0.1$ mg/m$^3$ for all job classifications. Associated with the production of acrylamide monomer is the potential for exposure to acrylonitrile. The possible confounding effect of this exposure was not formally addressed in this study; but in a previous epidemiologic study [Ott et al. 1980], no effects could be directly related to acrylonitrile under the conditions of exposure. The total number of deaths from malignancies was slightly elevated (11 observed versus 7.9 expected [$p<0.05$]), but this result was apparently due to the excess in a subgroup that was also exposed to organic dyes [Sobel et al. 1986]. Overall, the results did not indicate an excess of cancers from exposures to acrylamide. However, these results may be due to the small cohort size, limited followup, and short duration of exposure (274 workers were exposed for less than 5 years). Given the size of the total cohort and the period of observation, the study had only an 80% likelihood (power) of detecting a twofold or greater increase in total cancer incidence.

### 2.5.2 Evidence of Carcinogenicity in Animals

Studies in rats and mice indicate that acrylamide is an animal carcinogen [Bull et al. 1984a, 1984b; Johnson et al. 1986]. Acrylamide was tested for skin-tumor-initiating activity in Sencar mice and for the ability to induce lung adenomas in A/J mice [Bull et al. 1984a]. In a mouse skin initiation-promotion assay, 6- to 8-week old female Sencar mice were divided into groups of 40 and treated topically, by gavage, or by i.p. injection with acrylamide dissolved in water. Acrylamide was tested at doses of 12.5, 25, and 50 mg/kg for six applications by the three routes over a 2-week period, resulting in total doses of 75, 150, and 300 mg/kg. Ethyl carbamate, a known initiator, was used for a comparison in doses of 30, 100, and 300 mg/kg in one application administered topically, by gavage, or i.p. A tumor promotion regimen was started 2 weeks after the last of the tumor-initiating doses of acrylamide. One microgram of 12-0-tetradecanoyl-phorbol-13-acetate (TPA), a known tumor promoter, was applied topically 3 times/week for 20 weeks. Tumor incidences were charted from weekly observation. Surviving animals were sacrificed at 52 weeks and histopathological evaluations were done on all gross lesions. A highly significant ($p<0.01$) dose-response relationship existed for time to first tumor and for the total number of tumors in treated animals. The effect was more pronounced with i.p. and gavage treatment than with topical application. However, without application of TPA promotion, no increase occurred in tumor yield, either with acrylamide or ethyl carbamate treatment. In this assay system, acrylamide was therefore confirmed as being a tumor initiator.

In a bioassay for lung adenoma in mice, groups of 40 male and 40 female, 8-week-old A/J mice received doses of 6.25, 12.5, or 25 mg/kg of acrylamide by gavage in an aqueous solution three times/week for 8 weeks [Bull et al. 1984a]. Animals were sacrificed at 7 months of age. Acrylamide increased the yield of lung adenomas in both sexes in a dose-related manner; the average number of tumors per animal increased from 0.2 to 1.4. The dose-response relationship was statistically significant ($p<0.01$) when both the number of animals with tumors and the multiplicity of tumors in each dose group were tested using logit regression model analysis. In the same investigation, groups of 16 male and 16 female, 8-week-old A/J mice received i.p. injections of 1, 3, 10, 30, or 60 mg/kg acrylamide three times/week for 8 weeks. The average number of tumors per animal increased from 0.4 to 2.2. The number of lung adenomas increased with the dose up to 30 mg/kg. The dose-response relationship was statistically significant ($p<0.01$) by the logit regression model. Because acrylamide increased the lung tumor yield by two routes of administration in the absence of a promoter, the authors concluded that acrylamide acted as a complete carcinogen in this test system.

In a subsequent study [Bull et al. 1984b], groups of 40 female Swiss-ICR mice were administered an oral dose of 0, 12.5, 25, or 50 mg/kg acrylamide six times in a 2-week period. Ethyl carbamate served as a positive control and was administered in the same way at concentrations of 50 mg/kg. Two weeks after the last dose, a tumor promotion regimen was started. The regimen consisted of 3 weekly applications of 2.5 $\mu$g TPA dissolved in acetone to the shaved back of each animal. Another group of mice treated with 50 mg/kg acrylamide did not receive promotion treatment. The appearance of skin tumors was observed weekly, and after 52 weeks of study, the surviving animals were sacrificed and evaluated histologically for skin and lung tumors. When TPA treatment followed, acrylamide produced a dose-related increase in the number of animals that bore skin tumors (33% in the high-dose group versus none in the control group). Without TPA treatment there was no significant increase. The number of lung tumors (adenoma and carcinoma) was increased by acrylamide treatment in a dose-related manner (4 tumors in the control group and 11 tumors in the 50-mg/kg group). This increase was also observed in the absence of TPA (14 tumors

in the 50 mg/kg group). This study confirms the initiating effects of acrylamide on the skin of Sencar mice and the carcinogenic effects of acrylamide on the lungs of A/J mice.

Acrylamide administered in drinking water to female and male F344 rats for 2 years caused a statistically significant increase in the incidence of benign and malignant tumors at several sites in both sexes [Johnson et al. 1986]. Groups of 90 male and 90 female rats were maintained on drinking water providing acrylamide intakes of 0, 0.01, 0.1, 0.5, or 2.0 mg/kg per day. Ten rats per sex per treatment group were randomly selected for examination after 6, 12, or 18 months of study. Cumulative mortality showed no apparent dose relationship until the 21st month of study. From that time to the conclusion of the study at 24 months, mortality increased in the group receiving 2.0 mg/kg per day. No overt signs of neurotoxicity or other effects were attributable to acrylamide treatment. Rats in the group receiving the highest dose had an increased number of palpable masses, subsequently identified as subcutaneous or skin tumors. The number of tumors by site is listed in Table 5. In females, tumor incidence increased in the mammary glands, CNS, thyroid gland follicular epithelium, oral tissues, uterus, and clitoral gland. In males, tumor incidence increased in the CNS, the thyroid gland follicular epithelium, and the scrotal mesothelium. These increases occurred in the group receiving the highest dose (2.0 mg/kg per day). The only statistically significant increases ($p<0.05$) at the 0.5-mg/kg per day dose were the incidence of scrotal mesotheliomas in male rats and the incidence of combined mammary and clitoral gland tumors in female rats [Johnson et al. 1986].

**Table 5. Pooled tumor incidence data in F344 rats***

| Rat | Dose of acrylamide (mg/kg per day) | | | | |
|---|---|---|---|---|---|
| | 0.0 | 0.01 | 0.1 | 0.5 | 2.0 |
| Males: | | | | | |
| Number of animals with tumors+ (testes, thyroid, adrenal§) | 7/57 | 8/53 | 13/57 | 14/53 | 22/54 |
| Number of animals with malignant tumors (testes) | 3/57 | 0/53 | 7/57 | 11/53 | 10/54 |
| Females: | | | | | |
| Number of animals with tumors+ (thyroid, mammary, CNS**, oral, uterus) | 13/60 | 18/60 | 14/60 | 21/60 | 46/60 |
| Number of animals with malignant tumors (thyroid, mammary, CNS, uterus) | 4/60 | 5/60 | 3/60 | 4/60 | 20/60 |

* Adapted from Johnson et al. [1986] study of rats exposed to acrylamide in drinking water for 24 months.

+ Benign or malignant. Site must be statistically significant at the high dose (treated versus control) for tumors to be considered.

§ Includes only adrenal benign tumors.

** Tumors only (no "proliferations").

# 3 METHODS FOR MONITORING EXPOSURES

## 3.1 EXPOSURE MONITORING

A worker's exposure to airborne acrylamide should be determined by using a personal sampling train consisting of a glass-fiber filter in a Swinnex cassette (13-mm) followed by a silica gel tube. Plastic cassettes (37-mm) yielded poor recoveries of acrylamide and are therefore unsuitable. Samples should be collected at a maximum flowrate of 1 liter/min for a minimum of 2 hr; the maximum air volume should be 120 liters. The silica gel tube should then be treated with methanol to extract the acrylamide. An important step in this method is the transfer of the glass-fiber filters to glass vials containing 1 ml of methanol immediately after sampling to avoid losses of acrylamide from the filter by evaporation. Analysis should be conducted by gas chromatography using a nitrogen/phosphorus detector. The limit of detection for this procedure is 1.3 parts per billion (ppb) (0.004 mg/m$^3$). This method is described in Method 21 of the *OSHA Analytical Methods Manual* [OSHA 1985].

## 3.2 BIOLOGICAL MONITORING

The International Programme on Chemical Safety (IPCS) has recommended that a biological monitoring method for acrylamide be developed based on the determination of the adduct formed with hemoglobin [WHO 1985]. However, no biological monitoring test acceptable for routine use has yet been developed for acrylamide.

# 4 RELATIONSHIP BETWEEN EXPOSURE AND ADVERSE HEALTH EFFECTS

No data are available from studies in humans to establish an occupational exposure limit for acrylamide on the basis of neurotoxic, developmental, reproductive, or carcinogenic effects. However, many studies demonstrate a relationship between exposure and adverse health effects in animals. These studies are the bases for occupational exposure limits recommended by many organizations and government agencies. A few of these studies are described here.

EPA has used results from studies in animals to determine no-observable-effect levels (NOELs) and lowest-observable-effect levels (LOELs). With the use of the appropriate uncertainty factors, EPA has also recommended a "safe" concentration for human exposure (i.e., a concentration that is not expected to produce adverse health effects in exposed individuals) [EPA 1988b].

In 1988, EPA performed a detailed risk assessment of acrylamide based on animal studies of neurotoxicity, carcinogenicity, and reproductive effects [EPA 1988a]. Studies of neurotoxic effects in animals are summarized in Table 6. The NOEL was 0.2 to 2.0 mg/kg per day and the LOEL was 1.0 to 3.0 mg/kg per day. The reference dose (RfD) for acrylamide exposure (formerly acceptable daily intake, ADI) was calculated as 0.0002 mg/kg per day [EPA 1988b]. This value is based on an NOEL for neurotoxicity in a subchronic rat study of 0.2 mg/kg per day [Burek et al. 1980]. The exposure to 0.0002 mg/kg per day corresponds with a TWA concentration of 0.0014 mg/m$^3$ (assuming an average 70-kg human breathing 10 m$^3$ of air in an average working day with 100% absorption), which is approximately 20-fold lower than the OSHA PEL of 0.03 mg/m$^3$. The RfD was obtained by dividing the NOEL by a factor of 1,000 to account for the use of animal data and subchronic exposure. This safety (uncertainty) factor was suggested by the National Academy of Science [NAS 1977].

A designation of B2 (probable human carcinogen) was proposed according to EPA cancer guidelines on the basis of data from studies of two different animal species [EPA 1988a]. Because risks at low exposures cannot be measured directly by experiments in animals or by epidemiologic studies, a number of mathematical models have been developed to extrapolate from high to low doses. To assess the cancer risk posed by acrylamide, EPA used a linear model (i.e., linearized multistage procedure) [EPA 1988a]. Data from the Johnson et al. [1986] study were used to estimate risk from acrylamide exposure. The EPA guidelines for cancer risk assessment recommend pooling tumor incidence data on the grounds that risk estimates derived from the incidence of site-specific tumors may not predict (and may in fact underestimate) whole-body risks that are determined with the pooled animal data. The dose-response curves for each sex are based on the pooled tumor incidence (benign and malignant) and comprise the data sets of choice for risk assessment. The most sensitive sex and species observed in this study (female rats) was chosen to represent possible human risk.

**Table 6. Key animal studies of the neurotoxic effects of subchronic and chronic exposure to acrylamide*,+**

| Reference | Species (route) | Exposure duration | NOEL§ (mg/kg) | LOEL§ (mg/kg) |
|---|---|---|---|---|
| Burek et al. 1980 | Rats | 90 days | 0.2 | 1.0 |
| Johnson et al. 1986 | Rats | 2 years | 0.5 | 2.0 |
| Hamblin 1956 | Cats (i.v.) | 180 days | | 1.0 |
| Kuperman 1958 | Cats (i.p.) | 125 days | | 1.0 |
| McCollister et al. 1964 | Cats | 1 year | 0.3 | 1.0 |
| McCollister et al. 1964 | Monkeys | 1 year | 1.0 | 3.0 |
| Spencer 1979 | Monkeys | 1 year | 2.0 | 3.0 |
| Schaumburg et al. 1982 | Monkeys | 1.5 years | | 1.0 |

* Adapted from EPA [1988a].
+ All studies here except the two noted used the oral route of administration.
§ NOEL = no-observable-effect level; LOEL = lowest-observable-effect level.

The linearized multistage procedure was followed by EPA [1988a], with GLOBAL 86 as the computer program. Among the models that showed adequate fit with one to six stages, the model that gave the least $q_1^*$ (slope factor) was selected as the model with which to calculate carcinogenic risks using the lifetime average daily exposures provided by the exposure assessment for acrylamide. For the female rats with tumors of the thyroid, oral cavity, uterus, CNS, or mammary glands, this model had two stages. The cancer potency factor obtained for acrylamide by the linearized multistage procedure was 4.5 $(mg/kg\ per\ day)^{-1}$. The cancer potency factor describes the increased risk of developing cancer over a 70-year lifetime per unit of exposure where the unit of exposure is expressed as mg chemical/kg body weight per day. When based on an experimental animal study, the cancer potency factor is the 95% upper confidence limit slope of the dose-response relationship for a carcinogen as the dose approaches zero. Calculated upper-bound excess risks for individuals exposed to acrylamide are presented in Table 7. The highest risks were estimated for sewer repair workers, whose excess risks ranged from $10^{-1}$ to $10^{-2}$. EPA calculated that exposure to airborne concentrations of 0.03 $mg/m^3$ for a working lifetime of 40 years would result in an excess cancer risk of $2\times10^{-3}$ [EPA 1988a].

The previous American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV®) of 0.3 $mg/m^3$ [ACGIH 1971] was derived from a study of a small number of cats orally dosed with acrylamide and observed for neurotoxic effects [McCollister et al. 1964]. No effects were observed after feeding the cats acrylamide at the rate of 0.3 and 1 mg/kg per day, 5 days/week for 1 year. On the basis of these data, ACGIH recommended that human exposures not exceed a total intake of 0.05 mg/kg per day. The average 70-kg human who breathes 10 $m^3$ of air in an average working day would not exceed this recommended exposure limit if he or she were exposed solely to airborne concentrations that did not exceed 0.3 $mg/m^3$—the TLV adopted by ACGIH.

In 1989, OSHA adopted a new PEL for acrylamide—0.03 $mg/m^3$ with a skin notation [29 CFR 1910.1000]. This new PEL was based on the increased incidence of cancer in laboratory animals and demonstrated dermal absorption of acrylamide [54 Fed. Reg. 2332]. NIOSH agreed with the proposed PEL of 0.03 $mg/m^3$ and the supporting evidence of carcinogenicity [NIOSH 1988].

The World Health Organization reviewed cases of acrylamide poisoning in humans [WHO 1985]. Acute exposure to high doses of acrylamide appeared to affect the CNS, and long-term cumulative exposure to smaller doses produced peripheral neuropathy. Signs of peripheral neuropathy appeared after a latent period, which was dose-dependent and decreased with increasing dose.

On the basis of these neurotoxicity data, the World Health Organization recommended that the exposure not exceed a daily intake of 0.012 mg/kg body weight [WHO 1985]. For the average 70-kg human who breathes 10 $m^3$ of air in an average working day, is occupationally exposed to airborne concentrations only, and has 100% absorption, this intake would result from breathing air with an acrylamide concentration of 0.094 $mg/m^3$. This recommendation did not consider the risk of cancer or interference with reproduction.

**Table 7. Estimates of excess cancer risk for individuals exposed to acrylamide over a lifetime***

| Exposure category | Upper-bound individual risk estimates |
|---|---|
| Manufacturing/processing | $10^{-3}$ – $10^{-2}$ |
| Soil grouting (sewer workers) | $10^{-2}$ – $10^{-1}$ |
| Drinking water | $10^{-6}$ – $10^{-5}$+ |

* Adapted from EPA [1988a].
+ Worst case to typical case, based on residual acrylamide allowed.

# 5 RESEARCH NEEDS

Very few studies address dermal absorption of acrylamide, although the dermal route may be the most significant one for acrylamide exposure in the workplace [He et al. 1989]. Therefore, quantitative studies should be performed to assess the absorption of acrylamide through the skin. Because dermal exposure appears to be a significant route of acrylamide uptake and it is difficult to monitor dermal exposures routinely, it is important to develop biomonitoring that can accurately reflect total exposure to acrylamide. A valid biomonitoring technique for acrylamide is presently unavailable. However, the literature on the toxicokinetics of acrylamide indicates that biomonitoring may be feasible either in urine or blood. More than 50% of the given dose is reported to be excreted in urine as the metabolite N-acetyl-S-(3-amino-3-oxy-propyl)cysteine [Miller et al. 1982]. By collecting the urine of workers whose exposure is monitored, it may be feasible to correlate the total exposure (that is, both inhalation and skin) to acrylamide with measured concentrations or total amounts of metabolites in 24-hr urine samples.

Another possibility for biomonitoring is measurement of acrylamide binding to red blood cells. Hashimoto and Aldridge [1970] observed that after rats received a single i.v. dose of $^{14}C$ acrylamide, the radioactivity in blood after 24 hr was entirely associated with red blood cells. Miller et al. [1982] found that the concentration of $^{14}C$ in whole blood reached a plateau at 12% of the total dose after 1 hr and remained constant throughout the time period examined (7 days). The binding to erythrocytes accounted for essentially all of the remaining radioactivity in the whole blood. In vitro studies showed that acrylamide was covalently bound to cysteine residues in protein and, on acidic hydrolysis, the adduct yielded a compound with chromatographic properties identified as S-(2-carboxyethyl)cysteine (CEC) [Hashimoto and Aldridge 1970; Bailey et al. 1986].

Bailey et al. [1986, 1987] used gas chromatography to measure the presence of CEC in red blood cells of rats dosed with less than 1 mg/kg. Research is needed to increase the sensitivity of the method (using high-performance liquid chromatography and ion chromotography) and to determine its applicability to human biomonitoring.

Another area that may require more research is elucidation of dose-response relationships for neurotoxic effects. The quantitative data on dose response were adequately addressed in only one species (rat) [Burek et al. 1980]. Better quantitative studies in other species (mice, cats, or rabbits) may be useful.

In light of the reported genotoxicity and carcinogenicity of acrylamide, information on the binding of this compound to DNA is of considerable interest [Moore et al. 1987, Bull et al. 1984a, 1984b; Johnson et al. 1986]. Studies addressing the mechanisms of genotoxicity (in vivo and in vitro DNA binding and effects) would be useful.

Acrylamide is widely used in research laboratories for making polyacrylamide gels. EPA estimated that 100,000 to 200,000 U.S. laboratory workers are potentially exposed [EPA 1988a]. Because exposure data are currently not available on this working population, a survey of potential exposure to acrylamide in research laboratories would be very useful.

# 6 DISCUSSION AND EVALUATION

Studies in rats and mice indicate an association between the induction of cancer and exposure to acrylamide. Four types of response have been generally accepted as evidence of induction of neoplasms (tumors) [Williams and Weisburger 1986]: (1) the presence of tumors not observed in controls, (2) an increase in the incidence of a specific tumor type observed in controls, (3) the development of tumors earlier than those observed in controls, and (4) an increased number of tumors per animal. Acrylamide satisfies all these criteria. An increased incidence of tumors was observed in one strain of rats (female and male F344) and three strains of mice (male and female A/J, and female Sencar and Swiss-ICR). Increased incidences of lung adenoma and carcinoma occurred in ICR-Swiss female mice dosed by gavage six times over a period of 2 weeks. Similar increases in lung tumor incidence were observed in A/J male and female mice. In female and male rats, the increases in tumor incidence occurred at multiple sites (testes, thyroid, and adrenal gland in males and mammary gland, CNS, oral tissues, uterus, and clitoral gland in females). The incidence of tumors was dose-related both in rats and mice. In A/J mice, acrylamide increased the yield of lung tumors in both sexes in a dose-related manner. In addition, a highly significant dose-response relationship existed for the time to occurrence of first tumors and for the number of tumors per animal in female Sencar mice.

Although carcinogenicity has not been demonstrated in workers occupationally exposed to acrylamide, the limitations of the epidemiologic studies preclude any conclusions regarding the association of exposure to acrylamide monomer and the risk of cancer. Prudent public health practice calls for regarding acrylamide as a potential occupational carcinogen.

On the basis of studies in animals, the International Agency for Research on Cancer (IARC) determined in 1986 that sufficient evidence existed to conclude that acrylamide was carcinogenic in animals and classified it as a 2B carcinogen (a possible human carcinogen) [IARC 1986]. Animal studies also indicate that reproduction is adversely affected by acrylamide exposure. Testosterone levels were depressed in rats [Ali et al. 1983], and decreased fertility was observed in male mice following oral exposure to acrylamide in drinking water [Sakamoto and Hashimoto 1986]. Degeneration of testicular epithelial tissue in male mice treated by gavage has been observed [Hashimoto 1981], as have dominant lethal effects in male rats exposed by drinking water [Smith et al. 1986] and mice exposed i.p. [Shelby et al. 1986]. Oral exposure of male or female mice and rats to acrylamide in drinking water has caused an increased resorption rate [Nalco Chemical Company 1987; Sakamoto and Hashimoto 1986].

# 7 SUMMARY

Acrylamide is an odorless, white, crystalline solid used as a monomer or as a raw material in the production of polyacrylamides. Workers potentially exposed to acrylamide monomer are employed in acrylamide manufacturing and processing, grouting operations, and research and analytical laboratories.

Only the acrylamide monomer is toxic; polyacrylamide products are generally nontoxic. Acrylamide monomer may be neurotoxic, carcinogenic, genotoxic, and hazardous to reproduction. Recent studies confirm that acrylamide exposures cause cancer and reproductive effects in animals, but epidemiologic studies have not demonstrated these effects in humans.

**Key Words**: Acrylamide, carcinogenicity, dermal exposures, grouting, neurotoxic effects, occupational exposure, polyacrylamide, reproductive effects.

# 8 REFERENCES


ACGIH [1971]. TLVs®: threshold limit values; documentation of the threshold limit values for substances in workroom air. 3rd ed. Cincinnati, OH: American Conference of Governmental Industrial Hygienists, pp. 5–6.

ACGIH [1986]. Documentation of the threshold limit values and biological exposure indices. 5th ed. Cincinnati, OH: American Conference of Governmental Industrial Hygienists, pp. 12–13.

ACGIH [1989]. TLVs®: threshold limit values and biological exposure indices for 1989–90. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

Agrawal AK, Squibb RE, Bondy SC [1981]. The effects of acrylamide treatment upon the dopamine receptor. Toxicol Appl Pharmacol *58*(1):89–99.

Ali SF, Hong JS, Wilson W, Uphouse L, Bondy S [1983]. Effect of acrylamide on neurotransmitter metabolism and neuropeptide levels in several brain regions and upon circulating hormones. Arch Toxicol *52*:35–43.

American Cyanamid Company [1969]. Chemistry of acrylamide. Wayne, NJ: American Cyanamid Company, Process Chemicals Department.

American Cyanamid Company [1980]. Toxic Substances Control Act (TSCA) FYI submission. A fetal toxicity study of acrylamide in rats. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances, EPA Document No. FYI–OTS–0680–0076. Unpublished report.

American Cyanamid Company [1983]. Toxic Substances Control Act (TSCA) 8(d) submission. CHO/HGPRT mammalian cell forward gene mutation assay. Acrylamide. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances, EPA Document No. 878211686.

American Cyanamid Company [1985]. Toxic Substances Control Act (TSCA) 8(d) submission. Drosophila sex-linked recessive assay of acrylamide. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances, EPA Document No. 878216232.

Backer LC, Dearfield KL, Erexson GL, Campbell JA, Westbrook-Collins B, Allen JW [1989]. The effect of acrylamide on mouse germ-line and somatic cell chromosomes. Environ Mol Mutagen *13*:218–226.

Bailey E, Farmer PB, Bird I, Lamb JH, Peal JA [1986]. Monitoring exposure to acrylamide by the determination of S-(2-carboxyethyl)cysteine in hydrolyzed hemoglobin by gas chromatography-mass spectrometry. Anal Biochem *157*:241–248.

Bailey E, Farmer PB, Shuker DEG [1987]. Estimation of exposure to alkylating carcinogens by the GC-MS determination of adducts to hemoglobins and nucleic acid bases in urine. Arch Toxicol *60*:187–191.

Banerjee S, Segal A [1986]. In vitro transformation of C3H/10T 1/2 and NIH/3T3 cells by acrylonitrile and acrylamide. Cancer Lett *32*:293–304.

Berti-Mattera LN, Lopachin RM, Schrama L, Lowery J, Eichberg J [1986]. Acrylamide alters axonal protein phosphorylation and polyphosphoinositide metabolism. 16th Annual Meeting of the Society for Neuroscience, Part 1, Washington, DC, Nov. 9–14, 1986. Soc Neurosci Abstr *12*:(1)94.

Bisby MA, Redshaw JD [1987]. Acrylamide neuropathy: changes in the composition of proteins of fast axonal transport resemble those observed in regenerating axons. J Neurochem *48*:924–928.

Brismar T, Hildebrand C, Tegner R [1987]. Nodes of ranvier in acrylamide neuropathy: voltage clamp and electron microscopic analysis of rat sciatic nerve fibres at proximal levels. Brain Res *423*:135–143.

Bull RJ, Robinson M, Laurie RD, Stoner GD, Greisiger E, Meir JR, Stober JA [1984a]. Carcinogenic effects of acrylamide in sencar and A/J mice. Cancer Res *44*:107–111.

Bull RJ, Robinson M, Stober JA [1984b]. Carcinogenic activity of acrylamide in the skin and lung of swiss-ICR mice. Cancer Lett *24*:209–212.

Burek J, Albee R, Beyer J, Bell T, Carreon R, Morden D, Wade C, Hermann E, Gorzinski S [1980]. Subchronic toxicity of acrylamide administered to rats in the drinking water followed by up to 144 days of recovery. J Environ Pathol Toxicol *4*:157–182.

Carlson GP, Weaver PM [1985]. Distribution and binding of [$^{14}$C] acrylamide to macromolecules in sencar and BALB/c mice following oral and topical administration. Toxicol Appl Pharmacol *79*:303–313.

29 CFR 1910.1000. Air contaminants. Occupational Safety and Health Administration. Washington, DC: U.S. Government Printing Office, Office of the Federal Register.

CMR [1985]. Chemical profile: acrylamide. Chemical Marketing Reporter, January 7, 1985.

Collins JJ, Swaen GMH, Marsch GM, Utidjian HMD, Caporossi JC, Lucas LJ [1989]. Mortality patterns among workers exposed to acrylamide. J Occup Med *31*:614–617.

Cook WA [1987]. Occupational exposure limits—worldwide. Akron, OH: American Industrial Hygiene Association.

Davidson R, Volk H, Friedrick R [1980]. Polyacrylamides. Chapter 16. In: Handbook of water-soluble gums and resins. New York, NY: McGraw–Hill, pp. 1–19.

Dearfield KL, Abernathy CO, Ottley MS, Brantner JH, Hayes PF [1988]. Acrylamide: its metabolism, developmental, and reproductive effects, genotoxicity, and carcinogenicity. Mutat Res *195*:45–77.

De Rojas TC, Goldstein BD [1987]. Primary afferent terminal function following acrylamide: alterations in the dorsal root potential and reflex. Toxicol Appl Pharmacol *88*:175–182.

Dixit R, Mukhtar H, Seth PK, Murti CRK [1981]. Conjugation of acrylamide with glutathione catalyzed by glutathione-S-transferases of rat liver and brain. Biochem Pharmacol *30*(13): 1739–1744.

Dixit R, Das M, Seth PK, Mukhtar H [1986]. Interaction of acrylamide with bovine serum albumin. Environ Res *40*:365–371.

Eckert BS, Yeagle PL [1988]. Acrylamide treatment of PtK1 cells causes dephosphorylation of keratin polypeptides. Cell Motil Cytoskeleton *11*:24–30.

Edwards PM [1975]. The distribution and metabolism of acrylamide and its neurotoxic analogues in rats. Biochem Pharmacol *24*:1277–1282.

Edwards PM [1976]. The insensitivity of the developing rat foetus to the toxic effects of acrylamide. Chem Biol Interact *12*:13–18.

EPA [1987]. Assessment of airborne exposure and dermal contact to acrylamide during chemical grouting operations. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. EPA 560/5–87–009.

EPA [1988a]. Preliminary assessment of health risks from exposure to acrylamide. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances.

EPA [1988b]. Integrated risk information system (IRIS): Reference dose (RfD) for chronic oral exposure. Acrylamide. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office.

37 Fed. Reg. 329 [1972]. Food and Drug Administration. Food additives: acrylate-acrylamide resins.

54 Fed. Reg. 2332 [1989]. Occupational Safety and Health Administration: air contaminants; final rule. (To be codified at 29 CFR 1910.)

Frantz SW, Dryzga MD, Freshour NL, Watanabe PG [1985]. In vivo/in vitro determination of cutaneous penetration of residual monomer from polyacrylamides [Abstract]. Toxicologist *5*:39.

Garland TO, Patterson MWH [1967]. Six cases of acrylamide poisoning. Br Med J *4*:134–138.

GCA [1980]. Acrylamide technical control options analysis. Washington, DC: GCA Corporation. Prepared for EPA, Contract No. 68–01–5960, Report No. GCA–TR–80–75–G.

Gold BG [1987]. The pathophysiology of proximal neurofilamentous giant axonal swellings: implications for the pathogenesis of amyotrophic lateral sclerosis. Toxicology *46*:125–39.

Goldstein BD, Fincher DR [1986]. Paradoxical changes in spinal cord reflexes following the acute administration of acrylamide. Toxicol Lett *31*:93–99.

Hamblin D [1956]. The toxicity of acrylamide—a preliminary report. Hommage au Doyen René Fabre (Paris) Sede *3*:195–199.

Hashimoto K, Aldridge WN [1970]. Biochemical studies on acrylamide, a neurotoxic agent. Biochem Pharmacol *19*:2591–2604.

Hashimoto K, Sakamoto J, Tanii H [1981]. Neurotoxicity of acrylamide and related compounds and their effects on male gonads in mice. Arch Toxicol *47*:179–189.

Hashimoto K, Tanii H [1985]. Mutagenicity of acrylamide and its analogues in *Salmonella typhimurium*. Mutat Res *158*:129–133.

He F, Zhang S, Wang H, Li G, Zhang Z, Li F, Dong X, Hu F [1989]. Neurological and electroneuromyographic assessment of the adverse effects of acrylamide on occupationally exposed workers. Scand J Work Environ Health *15*:125–129.

Hersch MI, McLeod JG, Satchell PM, Early RG, Sullivan CE [1989]. Breathing pattern, lung inflation reflex and airway tone in acrylamide neuropathy. Respir Physiol *76*:257–276.

Hills BW, Greife AL [1986]. Evaluation of occupational acrylamide exposures. Appl Ind Hyg *13*:148–152.

Howland RD, Ali P [1986]. Altered phosphorylation of rat neuronal cytoskeletal proteins in acrylamide induced neuropathy. Brain Res *363*:333–339.

Hsie A, Recio L, Katz D, Lee C, Wagner M, Schenley R [1986]. Evidence for reactive oxygen species inducing mutation in mammalian cells. Proc Natl Acad Sci, USA *83*:9616–9620.

Husain R, Srivastava S, Srivastava SP, Seth PK [1986]. Effect of acrylamide on energy-linked functions in rat brain. Bull Environ Contam Toxicol *37*:427–432.

Husain R, Dixit R, Das M, Seth PK [1987]. Neurotoxicity of acrylamide in developing rat brain: changes in the levels of brain biogenic amines and activities of monoamine oxidase and acetylcholine esterase. Ind Health *25*:19–28.

IARC [1986]. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans: acrylamide. Vol. 39. Lyon, France: World Health Organization, International Agency for Research on Cancer.

IARC [1987]. Overall evaluations of carcinogenicity: an updating of IARC monographs, Vols. 1 to 42. Supplement 7. Lyon, France: World Health Organization, International Agency for Research on Cancer, pp. 32 and 43.

IHE [1985]. Studies on the genetic toxicology of acrylamide monomer, 1985, FYI submission. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances; Brussels, Belgium: Institute of Hygiene and Epidemiology, EPA Doc. Control No. FYI–OTS–0885–044A.

Ikeda GJ, Miller E, Sapienza PP, Michel TC, King MT, Turner VA, Blumenthal H, Jackson WE, Levin S [1983]. Distribution of $^{14}$C-labelled acrylamide and betaine in foetuses of rats, rabbits, beagle dogs, and miniature pigs. Food Chem Toxicol *21*:49–58.

Ikeda GJ, Miller E, Sapienza PP, Michel TC, King MT, Sager AO [1985]. Maternal-foetal distribution studies in the late pregnancy. II. Distribution of [1-$^{14}$C] acrylamide in tissues of beagle dogs and miniature pigs. Food Chem Toxicol *23*:757–761.

Johnson KA, Gorzinski SJ, Bodner KM, Campbell RA, Wolf CH, Friedman MA, Mast RW [1986]. Chronic toxicity and oncogenicity study on acrylamide incorporated in the drinking water of Fischer 344 rats. Toxicol Appl Pharmacol *85*:154–168.

Kaplan ML, Murphy SD, Gilles FH [1973]. Modification of acrylamide neuropathy in rats by selected factors. Toxicol Appl Pharmacol *24*:564–579.

Khanna VK, Husain R, Seth PK [1988]. Low protein diet modifies acrylamide neurotoxicity. Toxicology *49*:395–401.

Kuperman A [1958]. Effects of acrylamide on the central nervous system of the cat. J Pharmacol Exp Ther *123*:180–192.

Lijinsky W, Andrews A [1980]. Mutagenicity of vinyl compounds in *Salmonella typhimurium*. Teratogenesis Carcinog Mutagen *1*:259–267.

Marlowe C, Clark MJ, Mast RW, Friedman MA, Waddell WJ [1986]. The distribution of [$^{14}$C] acrylamide in male and pregnant Swiss-Webster mice studied by whole-body autoradiography. Toxicol Appl Pharmacol *86*:457–465.

McCollister DD, Oyen F, Rowe VK [1964]. Toxicology of acrylamide. Toxicol Appl Pharmacol *6*(2):172–181.

McCollister DD, Hake CL, Sadek SE, Rowe VK [1965]. Toxicologic investigations of polyacrylamides. Toxicol Appl Pharmacol *7*:639–651.

Merigan WH, Barkdoll E, Maurissen JPJ [1982]. Acrylamide-induced visual impairment in primates. Toxicol Appl Pharmacol *62*:342–345.

Miller MJ, Carter D, Sipes I [1982]. Pharmacokinetics of acrylamide in Fischer 344 rats. Toxicol Appl Pharmacol *63*:36–44.

Miller MS, Spencer PS [1985]. The mechanisms of acrylamide axonopathy. Ann Rev Pharmacol Toxicol *25*:643–666.

Moore MM, Amtower A, Doerr C, Brock KH, Dearfield KL [1987]. Mutagenicity and clastogenicity of acrylamide in L5178Y mouse lymphoma cells. Environ Mutagen *9*:261–267.

Nalco Chemical Company [1987]. Section 3e [Toxic Substances Control Act] combined two generation reproduction study and dominant lethal assay in Fischer 344 rats administered acrylamide in the drinking water. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances.

NAS [1977]. Drinking Water and Health. Vol. 3. Washington, DC: National Academy of Sciences, National Academy Press.

NIOSH [1976]. Criteria for a recommended standard: occupational exposure to acrylamide. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, DHEW (NIOSH) Publication No. 77–112.

NIOSH [1983]. National occupational exposure survey (NOES), 1981–1983. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. Unpublished data base; provisional data as of 1/1/90.

NIOSH [1988]. Testimony of the National Institute for Occupational Safety and Health on the Occupational Safety and Health Administration's proposed rule on air contaminants. Presented August 1, 1988, Washington, D.C. NIOSH policy statements. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health.

O'Donoughue JL, ed. [1985]. Acrylamide and related substances. In: Neurotoxicity of industrial and commercial chemicals. Vol. II. Boca Raton, FL: CRC Press, pp. 170–177.

OSHA [1985]. Analytical methods manual. Method 21. Salt Lake City, UT: U.S. Department of Labor, Occupational Safety and Health Administration, Analytical Laboratory.

Ott MG, Kolesar RC, Scharnweber HC, Schneider EJ, Venable JR [1980]. A mortality study of employees engaged in development or manufacture of styrene-based products. J Occup Med *22*:444–460.

Ramsey JC, Young JD, Gorzinski SJ [1984]. Acrylamide: toxicodynamics in rats. Midland, MI: Dow Chemical Company. Unpublished report.

Sakamoto J, Hashimoto K [1986]. Reproductive toxicity of acrylamide and related compounds in mice—effects on fertility and sperm morphology. Arch Toxicol *59*:201–205.

Satchell PM, McLoad JG [1981]. Megaoesophagus due to acrylamide neuropathy. J Neurol Neurosurg Psychiatry *44*:906–913.

Schaumburg HH, Arezzo J, Spencer PS [1982]. Short-latency somatosensory evoked potentials in primates intoxicated with acrylamide: implications for toxic neuropathies in man. Presented at the 1982 meeting of the Society of Toxicology, Boston, MA. Toxicologist *2*:139. Abstract No. 490.

Schaumburg HH, Spencer PS [1979]. Clinical and experimental studies of distal neuropathy—a frequent form of brain and nerve damage produced by environmental chemical hazards. Bronx, NY: Departments of Neurology, Neuroscience and Pathology (Neuropathology), Albert Einstein College of Medicine. Grant No. R01–OH–00535, NIOSHTIC, RN 00091771.

Shelby MD, Cain TK, Hughes L, Braden P, Generoso WM [1986]. Dominant lethal effects of acrylamide in male mice. Mutat Res *173*:313–324.

Shelby MD, Cain TK, Cornett CV, Generoso WM [1987]. Acrylamide: induction of heritable translocations in male mice. Environ Mutagen *9*:363–368.

Smith MK, Zenick H, Preston RJ, George EL, Long RE [1986]. Dominant lethal effects of subchronic acrylamide administration in the male Long-Evans rat. Mutat Res *173*:273–277.

Sobel W, Bond GG, Parsons TW, Brenner FE [1986]. Acrylamide cohort mortality study. Br J Ind Med *43*:785–788.

Solomon JJ, Fedyk J, Mukai F, Segal A [1985]. Direct alkylation of 2'-deoxynucleosides and DNA following in vitro reaction with acrylamide. Cancer Res *45*:3465–3470.

Spencer PS [1979]. A neuropathologic study of acrylamide intoxication. Unpublished final report. Washington, DC: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health. Contract No. OH 00535.

Spencer PS, Schaumburg HH [1974]. A review of acrylamide neurotoxicity. Part I. Properties, uses and human exposure. Can J Neurol Sci *1*:143–150.

Spencer PS, Schaumburg HH [1975]. Nervous system degeneration produced by acrylamide monomer. Environ Health Perspect *11*:129–133.

Spencer PS, Schaumburg HH [1976]. Central-peripheral distal axonopathy—the pathology of dying-back polyneuropathies. Prog Neuropathol *3*:253–295.

Spencer PS, Schaumburg HH [1977]. Ultrastructural studies of the dying-back process. IV. Differential vulnerability of PNS and CNS fibers in experimental central-peripheral distal axonopathies. J Neuropathol Exp Neurol *36*(2):300–320.

Srivastava SP, Das M, Seth PK [1983]. Enhancement of lipid peroxidation in rat liver on acute exposure to styrene and acrylamide: a consequence of glutathion depletion. Chem Biol Interact *45*:373–380.

Srivastava SP, Seth PK, Das M, Mukhtar H [1985]. Effects of mixed-function oxidase modifiers on neurotoxicity of acrylamide in rats. Biochem Pharmacol *34*:1099–1102.

Sublet V, Smith MK, Randall J, Zenick H [1986]. Spermatogenic stages associated with acrylamide (ACR) induced dominant lethality [Abstract]. Toxicologist *6*:292.

Takahashi M, O'Hara T, Hashimoto K [1971]. Electrophysiological study of nerve injuries in workers handling acrylamide. Int Arch Arbeitsmed *28*:1–11.

Tilson HA, Spencer PA, Cabe PS [1979]. Acrylamide neurotoxicity in rats: a correlated neurobehavioral pathological study. Neurotoxicology *1*:89–104.

Tilson HA [1981]. The neurotoxicity of acrylamide: an overview. Neurobehav Toxicol Teratol *3*:445–461.

Waalkens D, Joosten H, Taalman R, Scheres J, Yih T, Hoekstra H [1981]. Sister-chromatid exchanges induced in vitro by cyclophosphamide without exogenous metabolic activation in lymphocytes from three mammalian species. Toxicol Lett *7*:229–232.

Walden R, Squibb R, Schiller S [1981]. Effects of prenatal and lactational exposure to acrylamide on the development of intestinal enzymes in the rat. Toxicol Appl Pharmacol *58*:363–369.

WHO [1985]. Environmental Health Criteria 49: acrylamide. Geneva, Switzerland: World Health Organization, International Programme on Chemical Safety.

Williams GM, Weisburger JH [1986]. Chemical Carcinogens. In: Klaasen CD, Andrew MO, Doull J, eds. Casarett and Doull's Toxicology. New York, NY: Macmillan Publishing Company, pp. 99–173.

Zenick H, Hope E, Smith M [1986]. Reproductive toxicity associated with acrylamide treatment in male and female rats. J Toxicol Environ Health *17*:457–472.

# 9 APPENDIX. INTERNATIONAL STANDARDS FOR WORKPLACE EXPOSURES TO ACRYLAMIDE

This appendix lists occupational exposure limits for airborne acrylamide in various countries (Table A–1), and it contains a discussion of the bases for other recommendations that depart from the frequently cited limit of 0.3 mg/m$^3$.

**Table A–1. Occupational exposure limits* for airborne acrylamide in various countries***
**(mg/m$^3$)**

| Country | Time-weighted average (TWA) | Short-term exposure limit (STEL) | Ceiling |
|---|---|---|---|
| Austria | 0.3 | --- | --- |
| Belgium | S+ 0.3 | --- | --- |
| Denmark | S 0.3 | --- | --- |
| Federal Republic of Germany | S 0.3 | --- | --- |
| Finland | 0.3 | 0.9 | --- |
| Hungary | S 0.3 | S 1.5 | --- |
| Indonesia | S 0.3 | --- | --- |
| Italy | S 0.3 | --- | --- |
| Japan | 0.3 | --- | --- |
| Korea | 0.3 | 0.6 | --- |
| Mexico | S 0.3 | --- | --- |
| Netherlands | S 0.3 | --- | --- |
| Sweden | S 0.3 | S 0.9 | --- |
| Switzerland | S 0.3 | --- | --- |
| Taiwan | 0.3 | --- | --- |
| United Kingdom | S 0.3 | S 0.6 | --- |
| United States (OSHA) | S 0.03§ | --- | --- |
| Venezuela | S 0.3 | --- | S 0.6 |
| Yugoslavia | S 0.3 | --- | --- |

* Adapted from Cook [1987].
\+ "S" denotes potential absorption into the body through the skin.
§ In 1989, the Occupational Safety and Health Administration (OSHA) changed its permissible exposure limit (PEL) from S 0.3 mg/m$^3$ to S 0.03 mg/m$^3$ (TWA) [29 CFR 1910.1000].

In 1976, the National Institute for Occupational Safety and Health (NIOSH) recommended an exposure limit (REL) for acrylamide of 0.3 mg/m$^3$ (0.1 ppm) as a time-weighted average (TWA) for up to a 10-hr workshift (40 hr per week) [NIOSH 1976]. At that time, the available human and animal studies did not provide enough information to alter the previously established OSHA permissible exposure limit (PEL) of 0.3 mg/m$^3$ as an 8-hr TWA. The original OSHA PEL was based on the 1968 American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV®) [ACGIH 1971], which was derived mainly from a study of a small number of cats orally dosed with acrylamide and observed for neurotoxic effects [McCollister et al. 1964]. No effects were observed after feeding the cats acrylamide at the rate of 0.3 and 1 mg/kg per day, 5 days/week for 1 year.

The current Swedish standard for acrylamide [TWA = 0.3 mg/m$^3$] is the same as the previous ACGIH recommendation, with an added short-term exposure limit (STEL) of 0.9 mg/m$^3$.

Since 1968, ACGIH has designated acrylamide as an A2 substance (suspected human carcinogen) and assigned it a TLV of 0.03 mg/m$^3$ (0.01 ppm) as an 8-hr TWA with a skin notation [ACGIH 1986]. The revised TLV was based on data indicating a carcinogenic response in rats exposed to acrylamide in drinking water [Johnson et al. 1986]. The skin notation was assigned because of the demonstrated dermal absorption of acrylamide.

On the basis of studies in animals, the International Agency for Research on Cancer (IARC) determined in 1986 that there was sufficient evidence to conclude that acrylamide was carcinogenic in animals [IARC 1986] and classified it as a 2B carcinogen (a possible human carcinogen) [IARC 1987].

The World Health Organization recommended that acrylamide exposure not exceed a daily intake of 0.012 mg/kg body weight [WHO 1985]. For the 70-kg human who breathes 10 m$^3$ of air in an average workday, is occupationally exposed to airborne concentrations only, and has 100% absorption, this intake would result from breathing air with an acrylamide concentration of 0.094 mg/m$^3$. It should be emphasized that this value is based solely on the neurotoxicity of acrylamide and does not take into account the risk of cancer or interference with reproduction.

In 1989, OSHA adopted a new PEL for acrylamide—0.03 mg/m$^3$ as an 8-hr TWA with a skin notation [29 CFR 1910.1000]. This new PEL was based on the increased incidence of cancer in laboratory animals and demonstrated dermal absorption of acrylamide [54 Fed. Reg. 2332 (1989)]. OSHA considered evidence of carcinogenicity derived from the studies by Johnson et al. [1986] and Bull et al. [1984a, 1984b] and stated that the evidence was sufficient to conclude that acrylamide is a carcinogen. In addition, OSHA cited the ACGIH and IARC evaluations of acrylamide as a carcinogen. NIOSH agreed with the proposed PEL of 0.03 mg/m$^3$ and the supporting evidence of carcinogenicity [NIOSH 1988].

In 1988, the U. S. Environmental Protection Agency (EPA) proposed a reference dose (RfD) for acrylamide exposure (formerly acceptable daily intake, ADI) of 0.0002 mg/kg per day [EPA 1988b]. The RfD is based on a no-observable-effect level (NOEL) in a subchronic rat study of 0.2 mg/kg per day [Burek et al. 1980]. The RfD was obtained by dividing the NOEL by a factor of 1,000 to account for the use of animal data and subchronic exposure. This safety (uncertainty) factor was suggested by the National Academy of Science [NAS 1977]. The designation of B2 (probable

human carcinogen) was proposed for acrylamide according to EPA cancer guidelines on the basis of data from studies of two different animal species [EPA 1988a].

The U.S. Food and Drug Administration has recommended that residual acrylamide monomer not exceed 0.05% in molasses and in beet and cane sugar [37 Fed. Reg. 329 (1972)].



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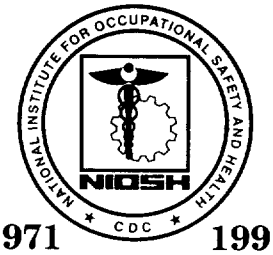


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