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SUPPORT DOCUMENT
DECISION NOT TO REQUIRE TESTING FOR HEALTH EFFECTS: ACRYLAMIDE

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I. INTRODUCTION

Section 4(e) of the Toxic Substances Control Act (TSCA: 90 Stat. 2003, 15 USC 2601 et seq.) established an Interagency Testing Committee (ITC) to recommend to the Administrator of the Environmental Protection Agency (EPA) a list of chemical substances and mixtures to be considered for the promulgation of testing rules under Section 4(a) of the Act. The ITC may have up to 50 of its recommendations designated at any one time for priority consideration by EPA. TSCA requires EPA to respond to such recommendations within 12 months of the date on which they are made either by initiating rulemaking proceedings under Section 4(a) or by publishing in the Federal Register reasons for not having taken such action.

The ITC recommended that acrylamide be tested for carcinogenic, mutagenic, teratogenic, and environmental effects and that an epidemiologic study be performed. The recommendations were based on (1) the possible entry of this highly water-soluble compound into surface water and groundwater as a result of its wide use as a chemical grout and that of its polymers in municipal and industrial wastewater treatment, paper strengthening and retention, and various other applications; (2) the severe neurotoxicity of acrylamide, which raises the possibility that other serious effects might result from long-term, low-level exposure; and (3) the potential exposure of about 20,000 workers to acrylamide during its manufacture, processing, use, and disposal and the potential widespread exposure of the general population via release of the compound to the environment.

EPA has completed its review of the health effects of acrylamide basing its evaluation on the following publicly available information: the ITC dossier (TSCA ITC 1978) and its references; studies and reports identified by an EPA supplementary literature search; public comments submitted in response to publication of the April 10, 1978, revision of ITC's original list which included the ITC's recommendations concerning

acrylamide; data supplied by acrylamide manufacturers; and a contract report prepared for the Agency by the Midwest Research Institute (Conway et al. 1979). The health effects of concern to the ITC plus the neurotoxicity of acrylamide were considered.

The contract report (Conway et al. 1979) evaluated studies related to mutagenicity, teratogenicity, carcinogenicity, as well as neurotoxicity and other health effects. EPA, having reviewed this work and a report by Shiraishi (1978) discussing chromosomal aberrations from acrylamide exposure, has focused its more detailed evaluation upon the very potent and relatively well-characterized neurotoxic properties of this compound to reach the tentative conclusions set forth in this Support Document and discussed in the notice in the FEDERAL REGISTER (FR) on

Two recent reviews (NIOSH 1976, US EPA 1976) and several primary sources formed the basis of the review by Conway et al. (1979), which is summarized here. EPA staff have consulted the primary sources to validate the secondary review findings.

II. PHYSICAL AND CHEMICAL PROPERTIES

Acrylamide (CH_2=CHCONH$_2$) occurs as white, odorless crystals that are stable at room temperature but polymerize on being heated to the melting point, resulting in a highly cross-linked, insoluble gel. It is also available as a 30-50 wt% aqueous solution. The important chemical and physical properties of the crystalline form of acrylamide are shown in Table 1. Synonyms for acrylamide include propenamide and propenoic acid amide.

Acrylamide reacts through its amide group or its conjugated ethylenic bond (Conway et al. 1979). Reactions of the amide group include hydrolysis, dehydration, and alcoholysis. Diels-Alder additions, polymerization, and the addition (with/without catalyst) of nucleophilic reactants across the double bond are characteristic reactions of the conjugated ethylenic group.

table 1. Chemical and Physical Properties of Acrylamide

CAS No.	79-06-1
NIOSH No.	A533250
Molecular formula	$CH_2=CHCONH_2$
Molecular weight	71.08
Melting point	84.5 ± 0.3° C
Vapor pressure	0.007 mmHg at 25° C 0.033 mmHg at 40° C 0.07 mmHg at 50° C
Appearance	White crystalline solid
Boiling point	87° C at 2 mmHg 103° C at 5 mmHg 125° C at 25 mmHg
Heat of polymerization	19.8 kcal/mole
Density	1.122 g/cm^3 at 30° C
Solubility in g/100 ml of solvent at 30° C	
acetone	63.1
benzene	0.346
chloroform	2.66
dimethyl sulfoxide	124
ethanol	86.2
ethyl acetate	12.6
n-heptane	0.0068
methanol	155
water	215.5

NIOSH (1976) and Conway et al (1979); portions were adapted from the Condensed Chemical Dictionary (1977) and the Handbook of Chemistry and Physics (1976).

Ammonia, aliphatic amines, bisulfite, chlorine, and dithiocarbamates represent some of the nucleophilic reactants that can be added across the double bond.

Acrylamide also combines with anions and undergoes homopolymerization or copolymerization. In most commercially useful methods for either reaction, free-radical initiators of redox catalytic systems are used.

III. EXPOSURE ASPECTS

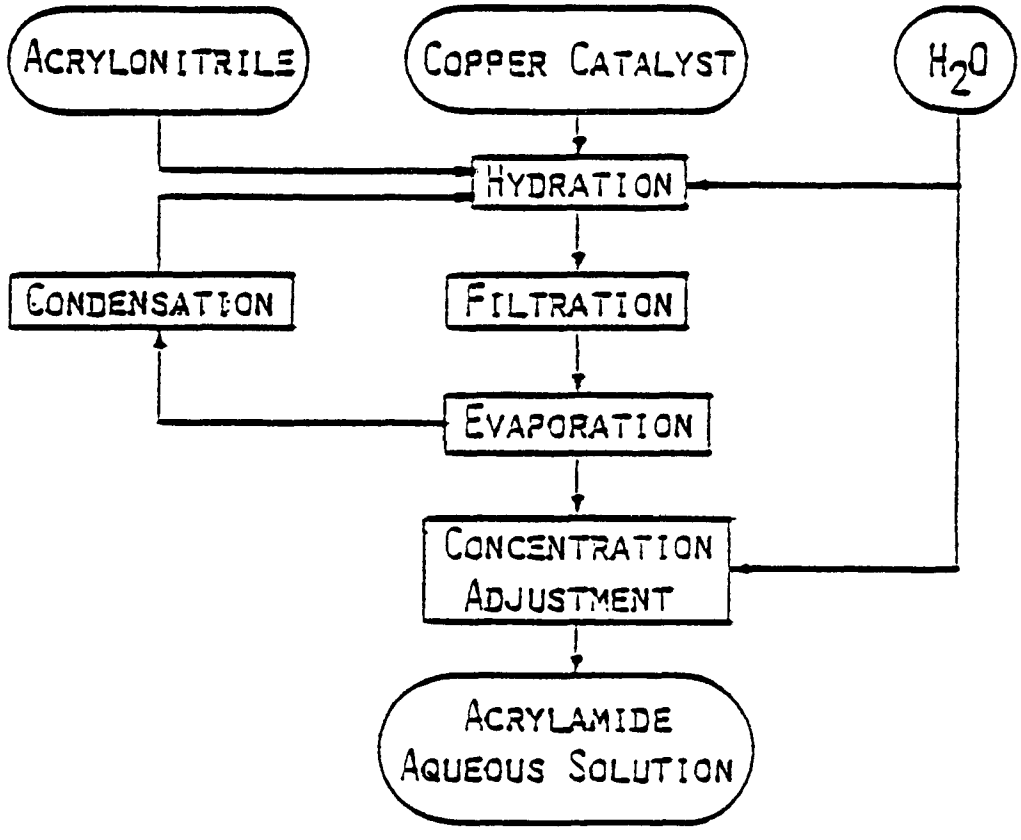
A. Manufacture

Acrylamide monomer has been manufactured by two processes: sulfuric acid hydration and catalytic hydration. Acrylonitrile is the starting material for both. Sulfuric acid hydration is no longer used and is only of historical interest. Since 1971, all domestically produced acrylamide has been made by the catalytic hydration of acrylonitrile (Figure 1). The conversion efficiency is high, and the resulting aqueous solution of acrylamide, after undergoing filtration and purging, has a purity of 99.5%-99.9% (Chem. Eng. 1973, Conway et al. 1979, Otsuka et al. 1975). Residual acrylonitrile, the primary contaminant, has been reported to be present at levels of about 50-100 ppm (American Cyanamid 1977) and 1-5 ppm (Dow Chemical 1980). Levels of contaminants in imported acrylamide are not known by EPA; however, the imported compound also is manufactured by catalytic hydration.

The manufacture of acrylamide essentially is a continuous process in which unreacted acrylonitrile is recycled into a reaction vessel, presumably in a closed system (US EPA 1976). Although monomer manufacture does not generate large volumes of by-products, acrylamide-containing waste streams are generated during polyacrylamide manufacture (Conway et al. 1979).

FIGURE 1

CATALYTIC HYDRATION METHOD



$$CH_2 = CHCN + H_2O \xrightarrow[\text{CATALYST}]{\text{COPPER}} CH_2 = CHCONH_2$$

Taken from Conway et al. 1979.

B. Production Volume and Trends

Currently acrylamide is produced in the U.S. by three manufacturers at four sites. A fourth manufacturer is scheduled to enter the market in 1980. At the beginning of 1978, Dow Chemical estimated that the domestic production of acrylamide was 40-50 million lb/yr (about 50% of capacity), with growth expected to continue at about 9%/yr, the historical growth rate (Conway et al. 1979). In the past, imports of acrylamide have been small, but this source may become more important as suppliers of acrylamide-based grout turn to foreign markets to replace material deleted from one domestic company's product line (Nitto Chemical 1979, Avanti International 1979).

A review of the production/import volume statistics for acrylamide shows that between 10 million and 51 million pounds of this chemical, which is listed in the initial TSCA Inventory (1977), were produced/imported in 1977. This production/import range information does not include any data claimed to be confidential by the person(s) reporting for the TSCA Inventory or any data that would compromise Confidential Business Information. The data submitted to the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

C. Use

Approximately 80%-85% of domestic acrylamide production is consumed in the manufacture of polyacrylamide polymers and copolymers (US EPA 1976). The level of residual acrylamide monomer in polyacrylamides ranges between 0.05% and 0.75%, depending on the intended use of the product (Conway et al. 1979). The level of residual acrylonitrile monomer in polyacrylamide products has been estimated to be about 1 ppm (AT Kearney, Inc. 1978).

Acrylamide is also used to manufacture a number of N-substituted acrylamide and methacrylamide derivatives; the production volume of the N-methylolacrylamide derivative is the

largest (US EPA 1976). These derivatives generally are used to produce polyacrylamides. Residual levels of acrylamide in these products are unknown.

The only example of a large-scale use of acrylamide monomer other than in the manufacture of polymers or monomeric derivatives is its use as a chemical grout, an application that will consume about 2.2 million lb of domestically produced monomer in 1980. Approximately another 2.2 million lb of acrylamide grout will be imported from Japan. The chemical grouts are used to repair sewer lines; waterproof mines, tunnels, and foundations; and consolidate soil around roadbeds and dams. In these specific applications, an aqueous solution of acrylamide monomer and suitable catalysts and initiators are injected into the site to be grouted, and polymerization is allowed to occur in situ. Although acrylamide grout represents only a small fraction of all the acrylamide used in the U.S., it also represents a situation in which toxic monomer is released directly to the environment. If the polymerization is incomplete, acrylamide grout can pose a potential environmental hazard (Conway et al. 1979).

In a recent communication, however, Dow Chemical (1980) informed EPA that there is technology for the in situ cross-linking of the polymer, rather than the monomer, in grouting operations. If adopted, this method would decrease the amount of acrylamide used for grouting purposes and, thus, the degree of exposure of grouting workers to this compound.

According to estimates, more than 43% of the acrylamide manufactured in 1973 was used to produce polyacrylamides for use in municipal and industrial wastewater treatment and municipal drinking water treatment (NIOSH 1976, Conway et al. 1979). These products included polyacrylamide flocculants and sewage dewatering aids. Approximately 20% was used to produce polyacrylamides for the pulp and paper industry, in which the polymers were used principally as dry strength agents and as retention and draining aids. In lesser quantities, acrylamide monomer was employed to produce polyacrylamides for use in

drilling muds; polyester-laminating resins; textile resins, flocculation of ores, mine tailings, and coal; friction reduction; thickening agents; soil stabilizers; oil-in-water de-emulsifiers; gel chromatography and electrophoresis; photography; dyeing; and ceramics (Bikales 1973, Flock and Rausch 1973, MacWilliams et al. 1973, NIOSH 1976, US EPA 1976, Conway et al. 1979. A more extensive list of uses can be found in these references).

D. Occupational Exposure

Although EPA does not have quantitative information on the extent of human exposure to acrylamide resulting from its manufacture, processing, distribution in commerce, use, or disposal, the principal opportunities for direct human exposure appear to be in occupational settings, including the use of acrylamide solutions for the in situ formation of polyacrylamide grouts. In 1976, NIOSH estimated that approximately 20,000 workers may be exposed to acrylamide in the U.S. (NIOSH 1976). There was no indication, however, that this estimate included grouting workers.

According to industry estimates, the acrylamide grout market could reach 4-5 million lb/yr by 1980. Based on this estimate and the number of existing grouting rigs, the number of grouting workers that could be exposed to acrylamide was conservatively estimated to be 2,000 (Conway et al. 1979). Although EPA is not aware of any monitoring data for grouting applications, there is reason to believe that grouting workers can be exposed to levels high enough to cause signs and symptoms of neurotoxicity. Of the 53 cases of acrylamide toxicity reported in the literature, 14 were associated with acrylamide grouts (see the Health Effects section).

The only monitoring study of an industrial environment was conducted in an acrylamide-manufacturing plant (NIOSH 1976). The compound was manufactured by sulfuric acid hydration, a process that was phased-out during the 1970's. Five months after the

plant began using this process in 1953, numbness and tingling of the hands together with general hand and leg weakness were noted in a small group (number undefined) of potentially exposed workers. Air sampling indicated only trace quantities of acrylamide. It was calculated that 1.8 mg/kg of acrylamide was the maximum amount that could have been inhaled over the 5-mo period. There are no monitoring data on worker exposures that may result during catalytic hydration.

Because of government activity in the areas of pollution and energy, the use of acrylamide in sewer repair and soil consolidation and polyacrylamides in wastewater treatment, mining, and drilling operations is likely to increase. This will increase the potential for the exposure of workers to acrylamide.

The American Conference of Governmental Industrial Hygienists has recommended that no more than 0.05 mg/kg/day of acrylamide be absorbed by workers. Assuming that the respiratory exchange is 10 m^3/day, an airborne limit of 0.3 mg/m^3 (0.1 ppm) may be calculated as a time-weighted average (TWA) concentration for a normal 8-hr workday or a 40-hr week (ACGIH 1971). This limit was based on the work of McCollister et al. (1964), which is discussed in the Health Effects section.

In 1976, after a critical evaluation of the data, NIOSH indicated that available animal and human studies did not provide an adequate basis for altering the existing Federal standard of 0.3 mg/m^3 of air as a TWA value.

E. General Population Exposure

Conway et al. (1979) estimated that 10%-12% of the U.S. population is exposed to acrylamide monomer in drinking water as a result of treatment with polyacrylamides. Most of the exposure was concentrated in Chicago, Kansas City, Las Vegas, Los Angeles, New Orleans, and St. Louis. These cities used 93% of the total amount of polyacrylamides designated for water clarification. City water supply officials who confirmed that they treat potable

water with polyacrylamides stated that they use them at a concentration of less than 1 mg/liter.

By obtaining data from municipal officials and extrapolating from the monomer concentration expected in the grade of polymer used to treat potable water, Conway et al. (1979) estimated the level of acrylamide monomer reaching the population via treated drinking water to be less than 0.5 ppb. Note, however, that this estimate does not take into account the presence of other residues of polyacrylamides in the finished drinking water that may also be soluble. The use of polyacrylamides for potable water treatment has been increasing at the rate of 2%/yr.* It is therefore possible that some drinking waters will contain increasing amounts of residual polyacrylamides or oligomeric or monomeric acrylamide.

Case reports of occupational and nonoccupational exposure are discussed in the Health Effects section.

F. Environmental Release

Acrylamide can enter the environment from a number of sources: from monomer- or polymer-manufacturing sites, from polymer-application sites as residual monomer, and from spills or leaks that may occur during transportation and handling (Conway et al. 1979, US EPA 1978). Few data are available on the release of acrylamide to the environment from these sources. The results of monitoring studies (US EPA 1978) performed near six plants that produce acrylamide and/or polyacrylamides showed, within analytical limits, no acrylamide monomer in air (i.e., less than 0.2 ug/m^3), in either the vapor or particulate form, or in soil or sediment samples (i.e., less than 0.02 ppm). Acrylamide, however, was detected at a level of 1,500 ppb in the discharge stream of one plant producing polyacrylamides (US EPA 1978). There is no information on the environmental

* EPA's office of Drinking Water is initiating assessments of direct and indirect additives in drinking water (including acrylamide monomer, polyacrylamides, and their by-products) to establish if there are human health risks associated with the presence of these substances.

release of acrylamide that may result from its transportation,* handling, and disposal.

Significant, localized, environmental concentrations of acrylamide may result from its use in soil grouting. In in situ soil grouting, unreacted acrylamide monomer may come into direct contact with surface water or groundwater and travel great distances in groundwater or deep rock aquifers, where biodegradation reportedly is absent (Conway et al. 1979). Other potential sources of environmental release are the monomer residues in polyacrylamide flocculants, products that are widely used to condition sludge and ore-tailing deposits and to clarify and purify municipal drinking water and industrial and municipal wastewaters (Conway et al. 1979, US EPA 1976).

No data or reliable estimates of acrylamide levels in wastewater treated with various types of polyacrylamide flocculants were found in the available literature. The release from this source is likely to increase as a result of the additional emphasis being placed on the cleanup of industrial and municipal wastewaters nationwide. The potential for acrylamide contamination of waters by treatment processes also is suggested by the results of one laboratory experiment. Croll et al. (1974) demonstrated that under conditions employed in many processes, such as chlorination at pH 8.5, acrylamide is not removed from the treated water.

G. Environmental Degradation

Studies of the biodegradation of acrylamide in river water and soils under various conditions suggest that acrylamide degrades to low to nondetectable levels over a period of 2-12 days (Conway et al. 1979). In most of these studies, however, acrylamide was measured indirectly and recoveries were low. In addition, factors such as the photopolymerization, chemical

* According to Conway et al. (1979), acrylamide manufacturers are not aware of any spills occurring during transportation; however, they practice and recommend special handling procedures.

degradation, or adsorption of acrylamide on container walls were not adequately characterized, precluding a quantitative interpretation of the results.

Lande et al. (1977) studied the leaching and mobility of acrylamide in topsoil according to procedures outlined in the Guidelines for Registering Pesticides in the United States (US EPA 1975). The results suggest that:

(1) The pathways of acrylamide degradation differ under aerobic and anaerobic conditions. Acrylamide may have a longer lifetime under anaerobic conditions.

(2) Acrylamide is degraded fairly rapidly by an apparent metabolic process in aerobic soils. The half-life is on the order of 20-45 hr for 25 ppm acrylamide at ambient temperature (22°C). Increasing the acrylamide concentration or decreasing the temperature increases the half-life.

(3) Acrylamide is mobile in various types of soil. When thin-layer chromatography was applied to Hilton loam (pH 4.8, organic matter 2.82%), Crogham loamy fine sand (pH 5.8, organic matter 3.85%), Williamston silt loam (pH 5.8, organic matter 8.25%), and silt clay (pH 6.7, organic matter 15.72%), the R_f values for acrylamide were 0.715, 0.805, 0.880, and 0.657, respectively. These experiments were run with lake water as a solvent; when seawater was used, the R_f values were slightly, but not significantly, lower.

Unfortunately, no studies have been made of the behavior of acrylamide in subsurface soil (the site of acrylamide polymerization in most grouting operations).

H. Biological Uptake

In a review document prepared for EPA (US EPA 1976), it was revealed that the available literature contains little or no data on the bioconcentration potential of acrylamide. However, calculation of log P (octanol/water partition coefficient) based on the methods of Hansch and Leo (1979) yields an approximate value of -1.65 (EPA estimate). The relationship of log P to bioconcentration potential, as calculated by Neely et al. (1974), indicates that only compounds with positive log P values near 3 or above are likely to be significantly concentrated in the fatty tissues of organisms. The negative log P value for acrylamide shows that the solubility of this compound in water is very high, compared with that in lipid, and it suggests that the bioconcentration of acrylamide would be minimal.

IV. HEALTH EFFECTS

The major effects of acrylamide toxicity are central-peripheral distal axonopathies and skin changes associated with the dermal route of exposure. With the exception of a few high-dose animal studies, there are no reports of adverse effects on other organ systems.

A. Case Reports

Acrylamide toxicity has been primarily an occupational problem. Of the 53 cases of acrylamide toxicity in the published literature (summarized in Tables 2 and 3), only 5 resulted from nonoccupational exposures (Igisu et al. 1975). The latter cases represent a Japanese family who ingested and briefly bathed in well water contaminated by acrylamide grout. Only one case of acrylamide poisoning has been reported in the U.S., although some authors allude to other probable cases (Kuperman 1958, NIOSH 1976, Spencer and Schaumburg 1974a).

Table 2. Case Reports of Human Acrylamide Toxicity

Number of cases	Source of exposure (location)	Reference
15	Polyacrylamide mfg. (Japan)	Takahashi et al. 1971
10	Monomer mfg. (Japan)	Fujita et al. 1960
6	Polyacrylamide mfg. (England)	Garland and Patterson 1967
6	Chemical grout (England)	Kesson et al. 1977
5	Contaminated well water (Japan)	Igisu et al. 1975
4	Monomer mfg. (France)	Morviller 1969
3	--- (Japan)	Satoyoshi et al. 1971
2	Chemical grout (France)	Graveleau et al. 1970 Cavigneaux and Cabasson 1972
1	Chemical grout (Canada)	Auld and Bedwell 1967
1	Polyacrylamide mfg. (U.S.)	Davenport et al. 1976

Based on a comparison of these case reports, a general pattern of acrylamide toxicity can be described, although each individual did not manifest all the signs and symptoms. The earliest sign of acrylamide toxicity appears to occur in the skin. Desquamation (skin peeling) of the hands and, less often, of the feet normally occurs within 2 weeks of the initial dermal contact with acrylamide. Erythema, dermatitis, and skin ulcerations often persist throughout the duration of exposure. Other early symptoms in the extremities include numbness and tingling, coldness of skin and tenderness to the touch, excessive sweating, bluish-red skin color, and muscle weakness, sometimes reflected as an inability to write or to climb stairs.

Concomitant with or shortly after the onset of these symptoms, fatigue and drowsiness may appear along with increasing muscle weakness. Other reported symptoms include mental confusion and other psychological changes, gastrointestinal problems, and weight loss. Weight loss appears to occur primarily in patients with longer term exposure to acrylamide.

Table 3: Signs and Symptoms from Human Case Reports.

	Takahashi et al. 1971	Fujita et al. 1960	Garland & Patterson 1967	Kesson et al. 1977	Igisu et al. 1975	Morviller 1969	Satoyoshi et al. 1971	Graveleau et al. 1970	Cavigneaux & Cabasson 1972	Auld & Bedwell 1967	Davenport et al. 1976
Changes in Extremities											
Desquamation of other skin changes	X		X	X		X		X	X	X	X
Numbness and tingling	X	X	X						X	X	
Coldness of Skin									X	X	
Tenderness to touch				X					X	X	X
Excessive sweating	X		X	X		X	X	X	X	X	X
Bluish-red skin color	X		X							X	
Muscle Weakness	X		X	X	X	X	X	X	X	X	X
Neurologic signs											
Ataxia	X	X	X		X					X	X
Weak or absent tendon reflexes	X	X	X			X		X			X
Inability to stand or collapse			X		X						
Slurred speech			X		X						X
Difficulty in Swallowing			X		X						X
Other signs and symptoms											
Fatigue, drowsiness	X		X	X	X				X	X	X
Mental confusion or other psychological complaints		X			X	X					
Gastrointestinal problems	X										
Weight loss		X	X			X		X	X		X

The above symptoms precede signs of overt peripheral neurological involvement. Neurological signs that may become evident in as little as 4 wk after the first exposure to acrylamide include ataxia and weak or absent tendon reflexes. As the axonopathy progresses, occasional inability to stand, body tremors, slurred speech, and mild difficulty in swallowing may occur. In some instances, these signs worsen progressively for up to 2 wk after the exposure period.

Peripheral and central nervous system involvement has been confirmed by clinical neurological examinations. Electrophysiologic examinations of the peripheral nervous system have revealed moderate disturbances of sensory nerve function, in terms of reduced action potential, and reduced sensory and, to a lesser extent, motor nerve conduction velocities (Davenport et al. 1976, Kesson et al. 1977, Takahashi et al. 1971). An examination of sural nerve biopsies suggested that simultaneous axonal degeneration and regeneration of nerve fibers had occurred (Davenport et al. 1976).

Although peripheral nerve damage appears to predominate in acrylamide toxicity, central nervous system involvement also has been found. Igisu et al. (1975), for example, have reported the occurrence of hallucinations and mental confusion in affected subjects. Many authors have reported instances of drowsiness that presumably are due to midbrain involvement (Garland and Patterson 1967). This presumption was confirmed by the EEG measurements of Takahashi et al. (1971). Other signs postulated to reflect central nervous system damage are slurred speech; coarse, generalized tremor; truncal ataxia; and ataxia disproportionate with the observed degree of muscle weakness and peripheral nerve deficiency (Garland and Patterson 1967). Fujita et al. (1960) further suggested the possibility of cerebellar involvement on the basis of the ataxia, positive Romberg sign, and positive finger-nose test (for coordinated movements of the extremities) observed in several patients.

No pertinent abnormalities were found in individuals in whom clinical tests of blood, urine, cerebrospinal fluid, and liver and kidney function were performed (Auld and Bedwell 1967, Davenport et al. 1976, Fujita et al. 1960, Garland and Patterson 1967, Takahashi et al. 1971). Tests usually were given on admission to the medical facility. Similarly, examination of the cardiovascular system, bones, and joints showed no pertinent deviations from normal (Auld and Bedwell 1967, Fujita et al. 1960, Garland and Patterson 1967), although marked wasting of the digital muscles of the hands, probably secondary to nerve loss, was noted in some cases (Davenport et al. 1976, Garland and Patterson 1967). Blood electrolyte levels were not explicitly reported in any of the cited studies.

A correlation between the level of acrylamide exposure and the neurotoxic effects manifested in humans is not possible because conditions surrounding the exposure incidents differed widely, and, in most cases, individuals were exposed to unknown concentrations of acrylamide that varied over time. The dermal route of exposure, with some respiratory exposure, predominated in all of the occupational incidents. It is possible that slight oral ingestion also occurred as a result of hand contamination. The exact time of the appearance of symptoms after dermal exposure was not reproducible. The onset times varied from 2 wk (Kesson et al. 1977) to 4 wk (Auld and Bedwell 1967, Garland and Patterson 1967, Igisu et al. 1975) to 8 yr (Takahashi et al. 1971). Time to recovery was related to the severity of the signs and symptoms rather than simply to length of occupational exposure. Although recovery generally occurred, two patients showed little sign of recovery 15 mo after diagnosis and cessation of exposure to acrylamide (Kesson et al. 1977). This finding plus central nervous system involvement, in which nerves do not regenerate but reserve capacity may allow functional recovery, indicate that permanent damage may occur.

B. Animal Studies

1. Acute and Short-Term Studies

Acrylamide toxicity has been studied in a variety of laboratory animals, including mice, rats, guinea pigs, rabbits, cats, dogs, and monkeys. LD_{50} values for rats range from 120 mg/kg via the intraperitoneal (ip) route (Druckery et al. 1953) to 203 mg/kg via oral administration (Fullerton and Barnes 1966). Keeler et al. (1975), however, reported single oral dose LD_{50} values of 240 mg/kg in female rats and 277 mg/kg in male rats of unspecified strain, age, and weight. McCollister et al. (1964) estimated the single oral dose LD_{50} for rats, guinea pigs, and rabbits to be in the range of 150-180 mg/kg. Although LD_{50} estimates are not available for cats or monkeys, deaths have been reported following two daily injections of 50 mg/kg ip in cats (Kuperman 1958) and two daily injections of 100 mg/kg ip in monkeys (McCollister et al. 1964). In most fatal exposures, death occurred 1-3 days after dosing.

Regardless of species, nearly all acute studies of acrylamide toxicity involve manifestations of various degrees of neurotoxicity (the major reported toxic effect in humans). Examples of these studies are presented here.

Hamblin (1956) reported that administration of 50 or 100 mg/kg/day to albino rats by oral intubation produced prostration and death after 15 and 3 days, respectively. Fullerton and Barnes (1966) observed that a single oral dose of 100 mg/kg produced only fine tremors in rats; when this dose was repeated 24 hr later, most of the animals died within 3 days. When rats were given 12 oral doses of 50 mg/kg over a 15-day period, they developed severe weakness and died within a few days after the final dose. Ataxia, labored respiration, convulsions, and behavioral changes resembling fright or excitement also have been noted in fatally exposed rats (Druckery et al. 1953). The direct cause of death in rats and cats has been attributed to respiratory failure associated with laryngeal spasm and pulmonary obstruction (Spencer and Schaumburg 1974b; Druckery et al. 1953).

Kuperman (1958) gave single intravenous (iv) or ip doses of 75-1,000 mg/kg to cats. The most consistent effects, in order of appearance, were ataxia, tremors, weakness, emesis, defecation, signs of mass sympathetic discharge, behavior suggestive of hallucinations, and periodic tonic-clonic convulsions prior to death.

In one monkey given an ip injection of 100 mg/kg acrylamide on 2 successive days, death occurred 1 day after the last injection (McCollister et al. 1964). Prior to death, the monkey had no sense of balance, but it was able to use its muscles for crawling. No convulsions were reported. The histopathological effects of acrylamide poisoning in this animal included congestion of the lungs, congestion of the kidneys with degeneration of the convoluted tubular epithelium and glomeruli, and necrosis and fatty degeneration of the liver. Rats that died after acute exposures showed only fine fatty infiltration of the liver.

2. Subacute, Subchronic, and Chronic Animal Studies

The studies described below provide information on the minimum levels of acrylamide monomer that cause signs of neurotoxicity, the effect of exposure route on the development of these signs, and pathologic alterations of the nervous system that occur after exposure.

a. Minimum Toxic Levels of Acrylamide

Table 4 (Conway et al. 1979) summarizes published data on acrylamide doses that produce observable signs of central-peripheral axonopathy in experimental animals. The table includes the route of administration, dosage schedule, time to onset of observable neurological signs, and total administered dose at the onset of these signs.

Cats developed neurological signs after exposure to as little as 1 mg/kg/day (ip or iv) five times per week over 125-180 days (Hamblin 1956, Kuperman 1958). Schaumburg et al. (1974) found that cats given single acrylamide doses as low as 3 mg/kg/day in drinking water exhibited neurological signs at 70

Table 4. Acrylamide Doses Producing Early Signs of Peripheral Neuropathy in Various Mammals

Organism	Route	Dose, schedule	Days to initial effect (No. of doses)	Total administered dose (mg/kg)	Reference
Rats (adult)	Oral	100 mg/kg, 2 doses/wk[c]	21(6)[a]	600	Fullerton and Barnes 1966
		100 mg/kg, 1 dose/wk	42(6)	600	
		100 mg/kg, 1 dose/2 wk	210(15)	1500	
	Ip	75 mg/kg, 1 dose/day	4.6[b]	345	Kaplan and Murphy 1972
	Ip	50 mg/kg, 3 doses/wk	18(7-8)	350-400	Suzuki and Pfaff 1973
	Ip	50 mg/kg, 1 dose/day	6.4[b]	320	Kaplan and Murphy 1972
	Oral	40 mg/kg/day[c]	14	560	McCollister et al. 1964
	Ip	40 mg/kg, 1 dose/day	6.7[b]	268	Kaplan et al. 1973
	Oral	30 mg/kg/day[c]	21	630	McCollister et al. 1964
	Ip	30 mg/kg, 1 dose/day	10.7[b]	321	Kaplan et al. 1973
	Oral	25 mg/kg, 5 doses/wk	28(20)	500	Fullerton and Barnes 1966
	Ip	25 mg/kg, 1 dose/day	16.8[b]	420	Kaplan and Murphy 1972
	Oral	9 mg/kg/day[c]	56[d]	504	McCollister et al. 1964
Cats	Ip	50 mg/kg, 1 dose/day	2(2)	100	Kuperman 1958
	Oral	20 mg/kg, 1 dose/day	14-21	280-420	Leswing and Ribelin 1969
	Ip	20 mg/kg, 1 dose/day	5	100	Schaumburg et al. 1974
	Ip	10 mg/kg, 1 dose/day	13-16	130-160	Schaumburg et al. 1974
	Sc	10 mg/kg, 1 dose/day	17-22	170-220	Prineas 1969
	Oral in chow	3 mg/kg, 5 doses/wk	68	144	McCollister et al. 1964
	Oral in water	3 mg/kg, 1 dose/day	70,163	210,489	Schaumburg et al. 1974
	Ip	1 mg/kg, 5-6 doses/wk	125	100	Kuperman 1958
	Iv	1 mg/kg, 5 doses/wk	180	130	Hamblin 1956
Dogs	Oral	15 mg/kg, 1 dose/day	21[a]	315	Thomann et al. 1974
	Oral	10 mg/kg, 1 dose/day	28-35[a]	280-350	Hamblin 1956
	Oral	5 mg/kg, 1 dose/day	21[a]	105	Thomann et al. 1974
Primates	Oral in fruit	20 mg/kg, 1 dose/day	16	320	Hopkins 1970
	Oral in fruit	25 mg/kg, 1 dose/day	42	630	Hopkins 1970
	Oral in fruit	10 mg/kg, 1 dose/day	42-97	420-970	Hopkins 1970
	Oral in water	10 mg/kg, 49 doses/69 days	48	340	McCollister et al. 1964

Source: Conway et al. (1979)
[a]Signs of intoxication probably appeared earlier than noted.
[b]Signs of intoxication based on electrorod measurements.
[c]Acrylamide mixed with food. Dose estimated by McCollister and coworkers, 1964.
[d]Effect noted in only 1/20 exposed animals.

and 163 days. In all three studies, the total administered doses were 100-489 mg/kg at the time of onset of signs.

Dogs* and primates appear to be somewhat less sensitive to acrylamide than cats, requiring daily doses of 5-25 mg/kg to develop early signs of central-peripheral axonopathy in the same time frame (Hamblin 1956, Hopkins 1970, McCollister et al. 1964, Thomann et al. 1974). Calculated total administered doses at the onset of signs varied from 105 to 970 mg/kg**, but they were generally around 325 mg/kg. Rats appeared to be relatively more resistant to acrylamide than dogs and primates. Total doses producing early neurological signs in rats typically fell in the range of 300-600 mg/kg (Kaplan and Murphy 1972, Kaplan et al. 1973, McCollister et al. 1964).

It should be noted that species may differ in the ease with which early signs can be identified by observers and in the complexity of their gaits.

b. No-Effect Levels

Table 5 (Conway et al. 1979) lists acrylamide doses found to have no apparent neurological effects on animals. The animals reportedly tolerated much higher total doses of acrylamide when the compound was given in low daily doses over prolonged periods of time. For example, total doses of 1,323-2,079 mg/kg given orally to rats over a 6 mo period caused no signs of limb impairment. In contrast, 560-630 mg/kg given over 2-3 wk resulted in obvious signs of hind limb weakness (McCollister et al. 1964). A similar, although less marked, comparison was made in the rat study of Fullerton and Barnes (1966). Relationships between duration of exposure and the effects of comparable total daily doses also are apparent with cats, primates, and dogs (McCollister et al. 1964, Hamblin 1956).

* Data of Thomann et al. (1974), and Hamblin (1956), are conflicting; dogs may not be less sensitive than cats based on a consideration of total administered dose.

** The monkey given this total dose was reportedly reluctant to consume all of its contaminated fruit; the next highest total dose administered was 820 mg/kg (Hopkins).

Table 5. Acrylamide Doses Reported To Produce No Observable Signs of Adverse Effects (All doses given orally)

Organism	Dose schedule	Days of Exposure (No. of doses)	Total administered dose (mg/kg)	Reference
Rats	3 mg/kg/day	90	270	McCollister et al. 1964
	10 mg/kg/day	70(55)	550	Fullerton and Barnes 196(
	10 mg/kg/day	116[a](116)	1,160	Fullerton and Barnes 196(
	7 mg/kg/day[b]	189	1,323	McCollister et al. 1964
	11 mg/kg/day[b]	189	2,079	McCollister et al. 1964
Cats	0.3 mg/kg/day	365(260)	78	McCollister et al. 1964
	1.0 mg/kg/day	367(257)	257	McCollister et al. 1964
Dogs	1 mg/kg/day	133	133	Hamblin 1956
	5 mg/kg/day	35	175	Hamblin 1956
	8 mg/kg/day	28	224	Hamblin 1965
Primates	1 mg/kg/day	363(255)	255	McCollister et al. 1964
	3 mg/kg/day	363(255)	765	McCollister et al. 1964.

Source: Conway et al. (1979).

[a]Duration not specified; estimate of minimum duration based on 1 dose/day.

[b]Acrylamide mixed with food; dose estimated by McCollister et al. (1964).

McCollister et al. (1964) concluded that a safe, no-effect acrylamide level for cats on long-term oral administration is probably 1.0 mg/kg/day and certainly at or above 0.3 mg/kg/day. They also concluded, from studies of monkeys given repeated oral doses of acrylamide over a 1-yr period, that no-effect levels for monkeys were between 1.0 and 3.0 mg/kg/day.

Spencer (1979) reported minor pathological central nervous system effects that consisted of scattered axonal swellings in the medulla oblongata (gracile tract) and lumbar spinal cord (ventromedial quadrant of gray matter) in one Rhesus monkey exposed to 3 mg/kg/day for 49 wk. No peripheral nerve effects were noted. Monkeys exposed to 1, 2, or 0.5 mg/kg/day for 338, 325, and 546 days, respectively, showed no effects upon being examined by modern histopathological or electron microscopic techniques. He concluded that 3 mg/kg/day, the dose reported by McCollister et al. (1964) as a no-effect level in primates, represents a level for nervous system damage and that 0.5 mg/kg/day is the lowest dose at which no effects were observed in monkeys.

Burek et al. (1979) conducted a 90-day study of rats given 0.05-20 mg/kg/day of acrylamide in drinking water. In three rats exposed to 1 mg/kg/day for 90 days, 25% of the fields examined by electron microscopy showed axolemma invaginations, with cell organelles and/or dense bodies being found in sciatic nerves. These changes were not apparent roughly 1 mo after exposure. Rats exposed to 0.05 or 0.2 mg/kg/day showed no effects. The author concluded that 1 mg/kg/day for 90 days is a minimal effect level in the rat.

3. Tissue Distribution

Edwards (1975) examined the distribution and metabolism of acrylamide in rats given a single dose of 100 mg/kg iv. When unbound acrylamide in the blood was analyzed as a function of time and the data were extrapolated back to zero time, concentrations very close to the theoretical value for dilution in

total body water (assumed to be 70% of total body weight) were obtained. This corresponded to a $\log_{10}$ concentration in blood of 3.22 nmol/ml. There were no indications or reports of the osmolality of urine or the osmoregulation of extracellular fluid. The results of this experiment indicate that acrylamide is completely distributed in the fluid compartments of the body within less than 30 min. Edwards gave the half-life of acrylamide in blood as 1.9 hr. However, this value may represent only the alpha phase, as the study ended after 4 hr.

In a similar study, Hashimoto and Aldridge (1970) found that although some acrylamide was freely distributed in vivo, the majority was bound to tissue and circulating protein, especially hemoglobin. Twenty-four hours after a single iv injection of [1-^{14}C]-acrylamide into rats, the highest levels of free/soluble and protein-bound label were recorded in whole blood, with decreasing levels being found in kidney, liver, brain, spinal cord, and sciatic nerve. By 14 days, the majority of free/soluble label had disappeared. Protein-bound label, however, remained at about 25% of the 24-hr level in all samples except for whole blood, which remained at 100% of the 24-hr level over the full 14-day period. The data of Hashimoto and Aldridge also suggest that the half-life of acrylamide in blood is 13 days; this value may represent the half-life of the beta phase.

Hashimoto and Ando (1975) studied the distribution and fate of ^{14}C-labeled acrylamide in rabbits. Single topical applications of 10%-30% aqueous acrylamide solutions rapidly penetrated intact skin and appeared in the blood as free monomer and as monomer bound to proteins, particularly hemoglobin. By 24 hr, acrylamide concentrations were higher in tissues than in the blood. These data suggest that acrylamide is distributed rapidly within the body.

C. Effect of Acrylamide on Nerve Tissue.

Acrylamide is readily absorbed through intact skin and rapidly distributed throughout the body. Although a large

percentage of the absorbed acrylamide may be eliminated from the body by metabolism and excretion (Hashimoto and Aldridge 1970, Spencer and Schaumburg 1974a), a small amount becomes bound to nervous system tissues, resulting in various morphologic signs of nerve tissue deterioration. Studies have demonstrated axonal degeneration with demyelination in mice (Bradley and Asbury 1970), rats (Fullerton and Barnes 1966, Suzuki and Pfaff 1973), cats (Leswing and Ribelin 1969, Prineas 1969, Schaumburg et al. 1974), dogs (Thomann et al. 1974), monkeys (Leswing and Ribelin 1969), baboons (Hopkins 1970), and humans (Davenport et al. 1976, Fullerton 1969).

Under the light microscope, the first sign of morphological deterioration appeared to be nodal or paranodal (nodes of Ranvier) axonal swelling (Hopkins 1970, Prineas 1969, Schaumburg et al. 1974, Spencer and Schaumburg 1974b). Examination by electron microscopy characterized these swellings as masses of neurofilaments, various dense bodies, and either enlarged or degenerating mitochondria (Suzuki and Pfaff 1973, Schaumburg et al. 1974, Prineas 1969). Subsequently, the myelin sheath retracted paranodally along the axon. This was followed by axonal degeneration and, frequently, myelin fragmentation (Hopkins 1970, Prineas 1969, Schaumburg et al. 1974). Extensive myelin breakdown, as opposed to retraction, occurred only after axonal degeneration (Fullerton and Barnes 1966). In these studies, the longer nerves were more affected than the shorter nerves, the distal parts of the nerves were more susceptible to damage than the proximal parts, and large-diameter axons appeared to be more susceptible than small-diameter axons.

Prineas (1969) and Spencer and Schaumburg (1974b, 1975, 1976) also have demonstrated that distal axonal degeneration and secondary demyelination occur in long ascending and descending spinal cord tracts, including the dorsal and lateral columns and the spinocerebellar tract. In more recent studies with acrylamide-intoxicated rats, Schaumburg and Spencer (1978) found axonal

degeneration in the hypothalamus, optic tract, and anterior cerebellum.

The distal axonal degeneration in vulnerable long tracts of the spinal cord, brain, and peripheral nervous system (central-peripheral distal axonopathy) seen in acrylamide toxicity represents a common reaction of the nervous system to chronic exposure to a variety of neurotoxic agents (Spencer and Schaumburg 1976). Three theories have been proposed to account for the action of acrylamide on nerve tissue (Cavanagh 1973, Pleasure et al. 1969, Spencer and Schaumburg 1974b), but the biochemical mechanism involved has not been demonstrated.

V. SUMMARY AND FINDINGS

EPA has reviewed the available information on the major health effects recommended for testing by the ITC. Except for neurotoxicity, an extensive evaluation of other health effects has not been performed since it has been consistently demonstrated that acrylamide produces central-peripheral axonopathies (Spencer and Schaumberg 1976). The animal species in which this effect was demonstrated include rats (Edwards 1975, Fullerton and Barnes 1966, Hashimoto and Aldridge 1970, Suzuki and Pfaff 1973), mice (Bradley and Asbury 1970), cats (McCollister et al. 1964, Kuperman 1958, Leswing and Ribelin 1969, Schaumburg et al. 1974), dogs (Hamblin 1956, Thomann et al. 1974), baboons (Hopkins 1970), and monkeys (McCollister et al. 1964). In addition, there are at least 48 published cases of the occupational toxicity and 5 cases of the nonoccupational toxicity of acrylamide to humans (NIOSH 1976, US EPA 1976, Conway et al. 1979), many of whom manifested a measurable degree of central-peripheral axonopathy.

In humans, the predominant signs of neurotoxicity are related to peripheral nerve involvement and, to a lesser extent, central nervous system involvement. A variety of other signs and symptoms also are generally reported, the most common ones occurring in the skin, hands, and feet. The onset of effects is

delayed following initial exposure, and the effects may be reversible, although this is not always the case.

Based on laboratory data, EPA has concluded that acrylamide is neurotoxic at very low levels, a conclusion that is substantiated by a 1 yr study in cats indicating a no-effect level of 0.3-1.0 mg/kg/day, given orally.

Thus, EPA does not plan to require the health effects testing recommended by the ITC. Instead, EPA plans to evaluate acrylamide for possible regulatory controls.

As previously stated, acrylamide causes significant neurological effects at very low levels. Thus, it is likely that any control adopted on the basis of acrylamide's neurotoxicity will provide a considerable degree of protection from other potential health hazards. Under such circumstances, the Agency does not believe it is in the public interest to perform a complete assessment of nonneurological effects. Rather, EPA believes that its rulemaking activities should be devoted to more pressing testing needs concerning chemicals about which much less is known. Thus, EPA has not conducted an in-depth evaluation of other health effects and does not plan to require testing for them.

EPA recognizes that in rejecting the alternative to require testing for effects which are not fully characterized, it is leaving gaps in the toxicity data base the Agency is trying to create. As a result, EPA may in some cases fail to reduce the risk of a health hazard to the extent it could if the effect were fully characterized. This is particularly true where the oncogenicity risk has not been evaluated. However, as discussed below, Dow Chemical Company plans to conduct oncogenicity testing. Thus, EPA believes that, as a matter of priorities and resource allocations, the Agency should not develop a test rule for the health effects of acrylamide to resolve remaining issues about its toxicity but instead should seek data on chemicals for which the need is greater.

EPA will reevaluate this decision if Dow fails to recommence the anticipated testing. Dow had started a 2 yr chronic toxicity oncogenicity study using CDF Fischer 344 rats in June 1979. Doses of 0.01-1 mg/kg/day were administered orally. Because of unexpected difficulties in maintaining the proper dose levels, however, Dow terminated the study as of February 1980 (Rosenstein 1980). EPA understands that Dow will resume the testing shortly. Although the proposed Dow study does not fully satisfy EPA's test standards for these studies, i.e., only one rodent species will be used, EPA anticipates that it will provide useful information concerning toxic effects other than neurotoxicity.

The Agency also is aware that a functional neurologic study in primates is under way at the University of Rochester (Maurissen 1979) sponsored by Dow Chemical Company and other chemical manufacturers. This study may provide information that will allow the "no-effect level" for the general population to be determined more precisely.

For these various reasons, EPA believes that additional testing resources should not be expended at this time to further characterize the health effects of acrylamide. EPA will initiate a preregulatory assessment of acrylamide based upon existing toxicity data.

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16. ABSTRACT

It has been found that acrylamide is neurotoxic, producing central-peripheral axonopathies. The animal species in which this effect was demonstrated include rats, mice, cats, dogs, baboons, and monkeys. In addition, there are at least 48 published cases of the occupational toxicity and 5 cases of the nonoccupational toxicity of acrylamide to humans, many of whom manifested a measurable degree of neurotoxicity (central-peripheral axonopathy).

In humans, the predominant signs of neurotoxicity are ralated to peripheral nerve involvement and, to a lesser extent, central nervous system involvement. A variety of other signs and symptoms also are generally reported, the most common ones occurring in the skin, hands, and feet. The onset of effects may be reversible, although this is not always the case.

Based on laboratory data, EPA has concluded that acrylamide is a potent neurotoxicant at very low levels. This conclusion has been substantiated by a 1-year (oral administration) study in cats indicating a no-effect level of 0.3-1.0 mg/kg/day.

EPA does not plan to require the health effects testing recommended by the Interagency Testing Committee. Instead, EPA plans to evaluate acrylamide for possible regulatory controls.

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