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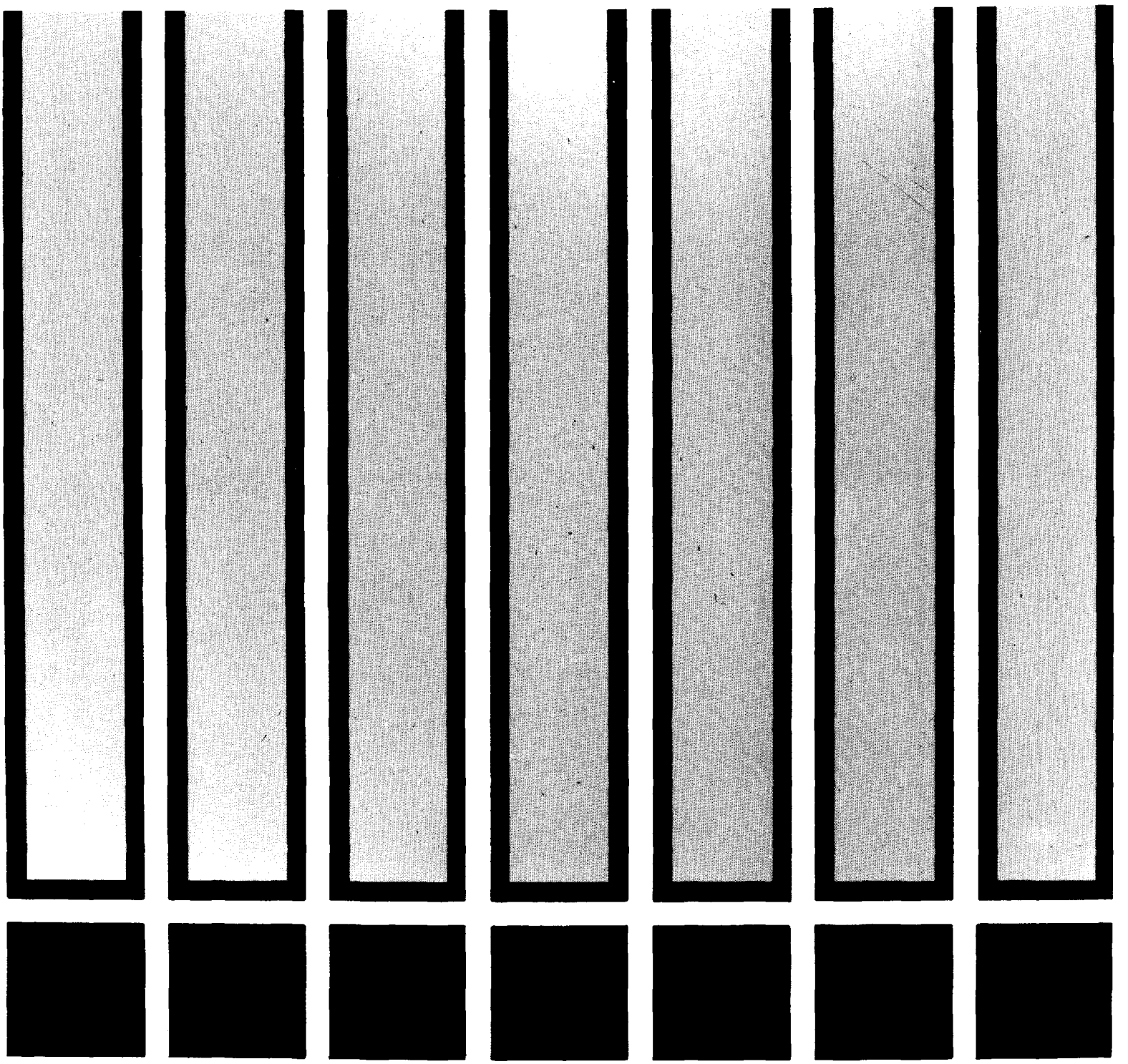

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Public Health Service / Center for Disease Control

National Institute for Occupational Safety and Health

criteria for a recommended standard....

OCCUPATIONAL EXPOSURE TO ACRYLAMIDE

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
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National Institute for Occupational Safety and Health
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CRITERIA DOCUMENT:
RECOMMENDATIONS FOR AN OCCUPATIONAL
EXPOSURE STANDARD FOR ACRYLAMIDE

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PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and safety of workers exposed to an ever-increasing number of potential hazards at their workplace. The National Institute for Occupational Safety and Health has projected a formal system of research, with priorities determined on the basis of specified indices, to provide relevant data from which valid criteria for effective standards can be derived. Recommended standards for occupational exposure, which are the result of this work, are based on the health effects of exposure. The Secretary of Labor will weigh these recommendations along with other considerations such as feasibility and means of implementation in developing regulatory standards.

It is intended to present successive reports as research and epidemiologic studies are completed and as sampling and analytical methods are developed. Criteria and standards will be reviewed periodically to ensure continuing protection of the worker.

I am pleased to acknowledge the contributions to this report on acrylamide by members of the NIOSH staff and the valuable constructive comments by the Review Consultants on acrylamide, by the ad hoc committees of the American Conference of Governmental Industrial Hygienists, American Academy of Occupational Medicine, American Academy of Industrial Hygiene, and American Occupational Medical Association, and by Robert B. O'Connor, M.D., NIOSH consultant in occupational medicine. The NIOSH recommendations for standards are not necessarily a consensus of all the consultants and

professional societies that reviewed this criteria document on acrylamide. The use of trademarks in this criteria document does not imply endorsement by the Health, Education, and Welfare Department. A list of Review Consultants appears on page vi.

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The Division of Criteria Documentation and Standards Development, National Institute for Occupational Safety and Health, had primary responsibility for development of the criteria and the recommended standard for acrylamide. The Division review staff for this document consisted of Keith H. Jacobson, Ph.D. (Chairman), Howard L. McMartin, M.D., Richard A. Rhoden, Ph.D., with Seymour D. Silver, Ph.D., Charles S. McCammon, Jr. (Division of Physical Sciences and Engineering) and Jack O. Geissert (Division of Surveillance, Hazard Evaluations, and Field Studies).

Stanford Research Institute (SRI) developed the basic information for consideration by NIOSH staff and consultants under contract CDC-99-74-31. Craig R. McCormack had NIOSH program responsibility and served as criteria manager.

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I. RECOMMENDATIONS FOR AN ACRYLAMIDE STANDARD

The National Institute for Occupational Safety and Health (NIOSH) recommends that employee exposure to acrylamide in the workplace be controlled by adherence to the following sections. The standard is designed to protect the health and safety of employees for up to a 10-hour work shift, 40-hour workweek, over a working lifetime. Compliance with all sections of the standard should prevent adverse effects of acrylamide on the health and safety of employees. Sufficient technology exists to permit compliance with the recommended standard. Although the workplace environmental limit is considered to be a safe level based on current information, it should be regarded as the upper boundary of exposure and every effort should be made to maintain the exposure at levels as low as is technically feasible. The criteria and standard will be subject to review and revision as necessary.

Synonyms for acrylamide include propenamide, acrylic amide, and akrylamid. The terms "acrylamide" or "acrylamide monomer" are used in this document interchangeably. "Action level" is defined as a time-weighted average (TWA) concentration of one-half the environmental limit. "Occupational exposure to acrylamide," because of systemic effects and dermal irritation produced by contact of acrylamide with the skin, is defined as work in an area where acrylamide is stored, produced, processed, or otherwise used, except as an unintentional contaminant in other materials at a concentration of less than 1% by weight. If an employee is occupationally exposed to airborne concentrations of acrylamide in excess of the action level, then all sections of the recommended standard shall be

complied with; if the employee is occupationally exposed at or below the action level, then all sections of the recommended standard shall be complied with except Section 8.

Section 1 - Environmental (Workplace Air)

(a) Concentration

The employer shall control workplace concentrations of acrylamide so that no employee is exposed at a concentration greater than 0.3 milligram per cubic meter of air determined as a TWA concentration for up to a 10-hour work shift, 40-hour workweek.

(b) Sampling and Analysis

Procedures for the collection and analysis of environmental samples shall be as provided in Appendices I and II, or by any method shown to be at least equivalent in accuracy, precision, and sensitivity to the methods specified.

Section 2 - Medical

Medical surveillance shall be made available to all persons subject to occupational exposure to acrylamide as described below.

(a) Preplacement medical examinations shall include:

(1) Comprehensive medical and work histories with special emphasis to such areas as weight loss and neurologic disturbances.

(2) Complete physical examination giving particular attention to the skin, eyes, and nervous system.

(3) Judgment of the worker's ability to use positive- or negative-pressure respirators.

(b) Periodic examinations shall be made available on an annual basis, or as otherwise determined by the responsible physician. These examinations shall include at least:

(1) Interim medical and work histories.

(2) Weekly examination by trained personnel of the fingertips of hands and other portions of the body exposed to acrylamide for evidence of skin peeling.

(3) Physical examination as outlined in paragraph (a)(2) of this section.

(c) In an emergency involving exposure to acrylamide, all affected personnel shall be provided immediate first-aid assistance and prompt medical attention, especially with respect to the skin and eyes. Medical attendants shall be informed of the need of observation and followup for any delayed neurologic effects.

(d) In the event of skin contact with acrylamide, grossly contaminated clothing and shoes shall be removed. Any exposed body area shall be immediately and thoroughly washed with soap and water. In the case of eye contact with acrylamide, eyes shall be flushed with copious amounts of water and a physician shall be consulted promptly.

(e) Pertinent medical records shall be maintained by the employer for all employees occupationally exposed to acrylamide. Such records shall be retained for 20 years after termination of employment. These records shall be made available to the designated medical representatives of the

Secretary of Labor, of the Secretary of Health, Education, and Welfare, of the employer, and of the employee or former employee.

Section 3 - Labeling and Posting

All labels and warning signs shall be printed both in English and in the predominant language of non-English-reading employees. All employees shall be trained orally and informed of the hazardous areas, with specific instructions given to illiterate employees and employees reading only languages other than that used on labels and posted signs.

(a) Labeling

Containers of acrylamide shall carry in a readily visible location a label stating:

ACRYLAMIDE

(PROPENAMIDE)

IRRITATING TO SKIN AND EYES

REPEATED SKIN CONTACT, INHALATION, OR SWALLOWING

MAY CAUSE NERVE DAMAGE

Avoid contact with skin, eyes, and clothing.
Avoid prolonged or repeated breathing of dust, mist, or vapor.
Wash thoroughly after handling.
Use with adequate ventilation.
Keep away from heat.

First Aid: In case of skin or eye contact, flush with plenty of water; call a physician.

(b) Posting

Areas where acrylamide is present shall be posted with a sign reading:

ACRYLAMIDE

(PROPENAMIDE)

IRRITATING TO SKIN AND EYES

REPEATED SKIN CONTACT, INHALATION, OR SWALLOWING

MAY CAUSE NERVE DAMAGE

Avoid contact with skin, eyes, and clothing.
Avoid prolonged or repeated breathing of dust, mist, or vapor.
Do not enter areas where used, unless adequately ventilated.

Section 4 - Personal Protective Equipment

(a) Protective Clothing

(1) Appropriate protective clothing, including gloves, aprons, long-sleeved overalls, footwear, and face shields (8-inch minimum), shall be worn where needed to limit skin contact with acrylamide. Impervious clothing may be needed in specialized operations. Appropriate eye protection (chemical safety goggles or face shields and safety glasses with side shields) shall be worn in any operation in which acrylamide (solid, liquid, or spray) may come in contact with eyes.

(2) The employer shall provide the employee with the appropriate equipment specified in paragraph (a)(1) of this section.

(b) Respiratory Protection

(1) Engineering controls shall be used if needed to keep acrylamide concentrations at or below the TWA environmental limit.

Respiratory protective equipment may be used:

(A) During the time necessary to install or test the required engineering controls.

(B) During emergencies or during the performance of nonroutine maintenance or repair activities which may cause exposures at concentrations in excess of the TWA environmental limit.

(2) When a respirator is permitted by paragraph (b)(1) of this section, it shall be selected and used pursuant to the following requirements:

(A) The employer shall establish and enforce a respiratory protective program meeting the requirements of 29 CFR 1910.134.

(B) The employer shall provide respirators in accordance with Table I-1 and shall ensure that the employee uses the respirator provided when necessary. The respiratory protective devices provided in conformance with Table I-1 shall comply with the standards jointly approved by NIOSH and the Mining Enforcement and Safety Administration (formerly Bureau of Mines) as specified under the provisions of 30 CFR 11.

(C) Respirators specified for use in higher concentrations of acrylamide may be used in atmospheres of lower concentrations.

(D) The employer shall ensure that respirators are adequately cleaned and maintained, and that employees are instructed in the proper use and testing for leakage of respirators assigned to them.

(E) Respirators shall be easily accessible, and employees shall be informed of their location.

TABLE I-1

RESPIRATOR SELECTION GUIDE

Concentration	Respirator Type
Less than or equal to 1 ppm (3 mg/cu m)	Supplied-air respirator, demand (negative pressure) mode, with half-mask facepiece
Less than or equal to 5 ppm (15 mg/cu m)	(1) Supplied-air respirator, demand mode, with full facepiece (2) Self-contained breathing apparatus, demand mode, with full facepiece
Less than or equal to 100 ppm (300 mg/cu m)	(1) Supplied-air respirator, continuous-flow type or pressure-demand (positive pressure) mode, with half-mask or full facepiece (2) Supplied-air respirator, continuous-flow type, with hood, helmet, or suit
Greater than 100 ppm (300 mg/cu m)	(1) Self-contained breathing apparatus with full facepiece operated in pressure-demand or other positive-pressure mode (2) Combination Type C supplied-air respirator with full facepiece operated in pressure-demand mode, with an auxiliary self-contained air supply
Emergency entry (into an area of unknown concentration)	(1) Self-contained breathing apparatus with full facepiece operated in pressure-demand or other positive-pressure mode (2) Combination Type C supplied-air respirator with full facepiece operated in pressure-demand mode, with an auxiliary self-contained air supply
Escape (from an area of unknown concentration)	(1) Gas mask, full facepiece, equipped with a combination organic vapor canister and a high-efficiency filter (2) Self-contained breathing apparatus operated in either demand or pressure-demand mode

(F) In case of an accident which could result in employee exposure to acrylamide in excess of the environmental limit, the employer shall provide respiratory protection as listed in Table I-1.

Section 5 - Informing Employees of Hazards from Acrylamide

(a) The employer shall ensure that each employee occupationally exposed to acrylamide is informed at the beginning of employment or on assignment to an acrylamide area of the hazards, relevant symptoms such as skin peeling, numbness ("pins and needles" in fingers), sleepiness, loss of weight, and weakness, appropriate emergency procedures, and proper conditions and precautions for the safe use of acrylamide. People engaged in maintenance and repair shall be included in these training programs. The employee shall be reinformed at least once a year. Each employee shall be advised of the availability of such relevant information kept on file, including the material safety data sheet.

(b) Required information shall be recorded on the "Material Safety Data Sheet" shown in Appendix III, or on a similar form approved by the Occupational Safety and Health Administration, US Department of Labor.

Section 6 - Work Practices

(a) Engineering Controls

(1) Ventilation systems if used shall be designed to prevent the accumulation or recirculation of acrylamide in the workplace, to maintain acrylamide concentrations at or below the recommended environmental limit, and to effectively remove acrylamide from the

breathing zones of employees. Ventilation systems shall be subject to regular preventive maintenance and cleaning to ensure effectiveness, which shall be verified by periodic performance measurements.

(2) A partially enclosed, ventilated, and automated system should be used to empty and transfer bags of solid acrylamide into a bin, so that dust are effectively removed. The bag should be cut open automatically and any dust should be removed by local exhaust ventilation.

(3) Concrete floors in operations areas shall be sealed in a manner that minimizes permeation of acrylamide into the concrete.

(b) Storage, Handling, and General Work Practices

(1) Containers of acrylamide shall be kept tightly closed when not in use. Only properly informed, trained, and equipped personnel shall be involved in storing, loading and unloading, or processing acrylamide.

(2) Acrylamide contact with skin and eyes of workers shall be prevented. Equipment, walls, and floors should be kept clean to limit worker exposure.

(3) Prior to maintenance work, sources of acrylamide and its vapor shall be eliminated to the extent feasible. If concentrations at or below the recommended workplace environmental limit cannot be ensured, respiratory protective equipment as specified in Table I-1 shall be used during such maintenance work.

(4) Employees whose skin becomes contaminated with acrylamide shall immediately wash or shower to remove all traces of acrylamide from the skin. Clothing contaminated with acrylamide shall be disposed of or cleaned before reuse.

(5) Any spills shall be either wet vacuumed or mopped up immediately and either decontaminated or disposed of appropriately in covered drums as contaminated waste; the spill area shall be decontaminated by washing.

(c) Waste Disposal

Solid acrylamide waste shall be disposed of either by burial in an environmentally acceptable manner or by burning in an approved manner. Liquid acrylamide waste shall be drained to a sump for subsequent treatment.

(d) Confined Spaces

(1) Confined spaces which previously contained acrylamide shall be thoroughly aerated, as well as inspected and tested for oxygen deficiency, acrylamide, and other known contaminant exposure concentrations prior to entry.

(2) Individuals entering confined spaces where they may be exposed to acrylamide shall wear respirators as outlined in Section 4.

(3) Confined spaces shall be ventilated while work is in progress to keep the concentration of acrylamide at or below the workplace environmental limit.

(4) When a person enters a confined space, another properly protected worker shall be on standby outside.

(e) Emergency Procedures

For all work areas where there is a reasonable potential for accidents involving acrylamide, the employer shall take all necessary steps to ensure that employees are instructed in and follow the procedures

specified below and any others appropriate for a specific operation or process.

(1) Procedures shall include prearranged plans for obtaining emergency medical care and for the necessary transportation of injured workers. Employees shall also be trained in administering immediate first aid and shall be prepared to render such assistance when necessary.

(2) Approved eye, skin, and respiratory protection as specified in Section 4 shall be used by persons involved in the cleaning procedure of the accident site.

(3) All persons who may be required to shut off sources of acrylamide, clean up spills, and repair leaks shall be properly trained in emergency procedures and shall be adequately protected against attendant hazards from exposure to acrylamide.

(4) Employees not essential to clean-up operations shall be evacuated from exposure areas during emergencies. Perimeters of hazardous exposure areas shall be delineated, posted, and secured.

(5) Eyewash fountains and showers shall be provided in accordance with 29 CFR 1910.151.

Section 7 - Sanitation

(a) Food preparation, dispensing (including vending machines), and eating shall be prohibited in work areas where acrylamide is present.

(b) Employees who handle any form of acrylamide shall be instructed to wash their hands thoroughly with soap or mild detergent and water before eating, smoking, or using toilet facilities.

(c) All contaminated gloves shall be washed before removal.

Section 8 - Monitoring and Recordkeeping Requirements

Within 6 months of the promulgation of a standard based on these recommendations, each employer who has a place of employment in which acrylamide is present shall determine by an industrial hygiene survey if exposures to airborne acrylamide at concentrations above the action level occur. Records of these surveys, including the basis for concluding that air levels are at or below the action level, shall be maintained. Surveys shall be repeated annually and within 30 days of any process change likely to result in an increase of airborne acrylamide concentrations. If it has been decided that the acrylamide environmental concentrations may exceed the action level, then the following requirements apply:

(a) Personal Monitoring

(1) A program of personal monitoring shall be instituted to identify and measure, or permit calculation of, the exposure of all employees occupationally exposed to airborne acrylamide.

(2) In all personal monitoring, samples representative of the exposure to airborne acrylamide in the breathing zone of the employee shall be collected.

(3) For each TWA determination, a sufficient number of samples shall be taken to characterize the employee exposures during each work shift. Variations in work and production schedules as well as employee locations and job functions shall be considered in deciding sampling times, locations, and frequencies.

(4) Each operation in each work area shall be sampled at least once every 3 months or as otherwise indicated by a professional industrial hygienist.

(5) If an employee is found to be exposed to acrylamide in excess of the recommended TWA environmental limit, the exposure of that employee shall be measured at least once a week, control measures shall be initiated, and the employee shall be notified of the exposure and of the control measures being implemented. Such monitoring shall continue until two consecutive determinations, at least 1 week apart, indicate that the employee's exposure no longer exceeds the recommended environmental limit; routine monitoring may then be resumed.

(b) Recordkeeping

Records of environmental monitoring shall be kept by the employer for at least 20 years. These records shall include the dates of measurements, job function and location of the employees at the worksite, sampling and analytical methods used, number, duration, and results of the samples taken, TWA concentrations estimated from these samples, type of personal protective equipment used, and exposed employees' names. All employees shall have access to information on their own environmental exposures. Environmental records shall be made available to designated representatives of the Secretary of Labor, and of the Secretary of Health, Education, and Welfare. Pertinent medical records shall be retained by the employer for 20 years after termination of employment. Records of environmental exposures applicable to an employee should be included in that employee's medical records. These medical records shall be made available to the designated medical representatives of the Secretary of Labor, of the Secretary of Health, Education, and Welfare, of the employer, and of the employee or former employee.

II. INTRODUCTION

This report presents the criteria and the recommended standard that were prepared to meet the need for preventing occupational disease or injury arising from exposure to acrylamide. The criteria document fulfills the responsibility of the Secretary of Health, Education, and Welfare under Section 20(a)(3) of the Occupational Safety and Health Act of 1970 to "...develop criteria dealing with toxic materials and harmful physical agents and substances which will describe...exposure levels at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience."

The National Institute for Occupational Safety and Health (NIOSH), after a review of data and consultation with others, formalized a system for the development of criteria from which standards can be established to protect the health and to provide for the safety of employees from exposure to hazardous chemical and physical agents. Criteria for any recommended standard should enable management and labor to develop better engineering controls resulting in more healthful work practices and should not be used as a final goal.

Development of these criteria for a recommended standard for acrylamide is part of a continuing series of documents published by NIOSH. The proposed standard applies only to workplace exposure to acrylamide arising from the processing, manufacture, or use of the substance as applicable under the Occupational Safety and Health Act of 1970. The standard was not designed for the population-at-large, and any extrapolation beyond occupational environments is not warranted. It is

intended to (1) protect against development of systemic toxic effects and local effects on the skin and eyes and (2) be attainable with existing technology.

The major concern in occupational exposure to acrylamide is its potential for causing neurologic disorders. In addition, acrylamide can cause eye irritation and dermatitis in humans.

There are a number of areas that need further research with respect to acrylamide. Epidemiologic studies, carcinogenic, mutagenic, teratogenic, or other reproductive effects of acrylamide have not been found in the literature. Further, present toxicologic information on acrylamide is deficient in all physiologic systems other than the nervous system. Animal toxicity experiments of acrylamide on other organ systems such as the cardiovascular, pulmonary, hepatic, and renal systems have not been investigated. Pharmacokinetic (absorption, distribution, metabolism, and excretion) studies are also needed to understand the mechanism of action of acrylamide. Research in all these areas should be initiated. Improved sampling and analytical methods should also be developed.

Adherence to all provisions of the recommended standard is required in work areas in which acrylamide is used, regardless of the airborne acrylamide concentration, because the available evidence indicates that the greatest danger to employees exposed to acrylamide is from skin contact; however, inhalation hazards cannot be neglected.

III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Acrylamide ($CH_2=CHCONH_2$), formula weight 71.08, is a white, crystalline solid which is assuming increasing industrial importance as a chemical intermediate and as a vinyl monomer that readily undergoes polymerization and copolymerization [1]. Acrylamide is highly soluble in water and is also moderately soluble in several other common solvents such as methanol, ethanol, and acetone. It is thermally stable, has a vapor pressure of 0.007 mmHg at 25 C, and sublimes at room temperature [1]. Some of the more important physical and chemical properties of acrylamide are shown in Table XII-1 [1]. Synonyms for acrylamide include propenamide, acrylic amide, and akrylamid [2]. Mixtures of acrylamide with small proportions of N,N'-methylenebisacrylamide have been marketed by American Cyanamid Company under the trademark AM-9 [3].

The acrylamide molecule consists of an amide and a vinyl group. It can undergo reactions both at the amide group and at the double bond (vinyl group) [1]. The double bond of the vinyl group can add halogens. The addition of bromine was the basis of a popular method of acrylamide analysis before gas-chromatographic and polarographic methods were used. Hydrolysis at the amide group with either acids or bases converts acrylamide to acrylic acid. Acrylamide molecules undergo homopolymerization and copolymerization by combining with anions in photochemical reactions; by exposure to ionizing radiation; and, lastly, in the most popular and commercially useful method, by the use of free radical

initiators of redox catalytic systems [1,4]. Molten acrylamide polymerizes vigorously with the evolution of heat [5].

Acrylonitrile is the major starting material used in all industrial methods for the manufacture of acrylamide [1]. The starting material is mixed with sulfuric acid, an exothermic reaction, and then diluted with water. Acrylamide is then prepared from acrylamide sulfate either by the lime process, ammonia process, carbonate process, or ion-exchange process. Acrylamide is difficult to recover at the aqueous stage since it may polymerize or undergo hydrolysis. Various processes have been devised by manufacturers to facilitate the recovery and to control the amount of heat generated in the procedure. Recently, a few manufacturers have developed pollution- and byproduct-free processes for direct production of acrylamide monomer via hydration of acrylonitrile over a catalyst [6].

Acrylamide monomer production has been estimated to have amounted to about 15-20 million pounds in 1966, 30 million in 1969, 32 million in 1972, 40 million in 1973, and approximately 70 million in 1974 [6]. During the past 20 years, the use of acrylamide polymers has also increased very rapidly with the increased production of acrylamide monomer [4]. In 1972, about 35 million pounds of acrylamide polymers were used in the United States alone. These are the latest years for which data are available.

The major use of acrylamide monomer is in the production of polymers [1]. Aqueous solutions of the monomers and a redox catalyst are used for soil stabilization. Polyacrylamides are very effective flocculants for finely divided solids in aqueous suspensions. AM-9 has found increasing application as a chemical grout. The largest market for acrylamide now is in the manufacture of polyacrylamides for waste and water treatment

flocculants, in products for aiding sewage dewatering, and in a variety of products for the water treatment industry. These uses consumed more than 40% of the acrylamide used in 1973 [6]. Acrylamide is also used to prepare polyacrylamides, which are used as strengtheners in papermaking and retention aids (to keep the fibers from being washed away). The pulp and paper industry accounted for about 20% of the acrylamide consumption in 1973. Some other uses of polyacrylamides are drilling-mud additives, textile treatment, and surface coatings. In very small quantities, acrylamide polymers are also used for flocculation of ores [4,7,8], mine tailings and coal, friction reduction [4], thickening [4,9], soil stabilization, gel chromatography and electrophoresis, photography, fog dissipation, breaking of oil-in-water emulsions, dyeing, ceramics, and clarification and treatment of potable water and foods [4].

Several other uses for monomeric acrylamide have been proposed by various investigators. Compounds such as N,N'-ethylene-bis-acrylamide and some bromo combinations have shown promise as antitumor agents in mice [10], in tomato plant tumors [11], and in plant tissue cultures [12].

NIOSH estimates that approximately 20,000 workers are potentially exposed to acrylamide in the United States. Table XII-2 [3] is a list of occupations with potential exposure to acrylamide monomer.

Historical Reports

Monomeric acrylamide was first made in Germany in 1893 and patented in the United States (Patent No. 2,021,763) by the Rohm and Haas Company in 1935. Interest was not shown in its preparation and properties until acrylonitrile became commercially available in 1940 [1]. It was first

offered by American Cyanamid Company for developmental consideration in 1952, and they began manufacture for the commercial market in 1954.

It was not until the advent of large-scale commercial production that some pharmacologic and toxicologic experiments were initiated by American Cyanamid Company at Hazleton Laboratories. After single large oral doses, death occurred as a consequence of convulsions and asphyxia in mice, rats, rabbits, and dogs. However, after repeated administration of acrylamide, a neurologic syndrome was characterized by postural and motor incoordination in these animals. The single-dose toxicity of monomeric acrylamide in animals was also reported by Druckrey et al [13] in 1953. The so-called average lethal dose by intraperitoneal (ip) injection was reported to be 120 mg/kg in rats which died within 1 or 2 days with severe pulmonary obstruction. A toxicologic study reported by Hamblin [14] in 1956 showed that the oral administration of acrylamide monomer produced neuropathy in mice, rats, and dogs.

Effects on Humans

In 1953, a new method of acrylamide production was undertaken at an American Cyanamid Company manufacturing plant [15] where acrylonitrile was hydrated by sulfuric acid to form acrylamide sulfate after which it was neutralized by ammonia, yielding free acrylamide. About 5 months after the new process was begun, a "handful" of the hundreds of potentially exposed plant workers noticed numbness and tingling of their hands and weakness of their hands and legs. Dermal contact of the workers was thought to have been limited because they wore protective clothing and gloves. The air in the plant was sampled and only traces of acrylamide were found. However,

by the use of methods (not described) of detection then in use, it was calculated that the maximum amount of acrylamide which could have been inhaled by one worker in a 5-month period was approximately 1.8 mg/kg. The whole manufacturing process was altered and the exposure of the workers to acrylamide was reduced or eliminated. Further details were not presented.

A total of 45 cases of intoxication from acrylamide have been reported in humans [16-22, DR Brinkley, written communication, June 1976] and up to 10 more have been suggested [15,16,19,20,23]. Of the 45, 3 were women (ages 17, 40, and 65), 2 children (a boy of 10 and a girl of 13), and 40 men (18-59 years old). All of the exposures were occupationally related, excepting a Japanese family of five who ingested and briefly used contaminated well water for bathing [22]. Monomeric acrylamide is a neurotoxin with an affinity for the peripheral ends of the spinal nerves in the extremities. Both motor and sensory nerves are affected but the sensory component usually more than the motor component. In some instances there was evidence of CNS involvement [20-22].

A pattern of reactions emerged when signs, symptoms, and results of neurologic examinations of the workers were compiled and compared (see Table III-1). Early reported symptoms typical of acrylamide intoxication in humans include, numbness of lower limbs [16,18,20-23], tingling of the fingers [18-22], tenderness to the touch [16,18], coldness [16,18], excessive sweating of feet and hands [16-21], bluish-red skin [16,20,21], peeling of the skin of the hands and less often of the feet [16-21], followed shortly by muscle weakness of the hands and feet (occasionally progressing to the inability to write or lift the feet when walking or climbing stairs) [16-23]. Later symptoms were loss of weight [17-20,23],

lassitude [16,18,21], sleepiness [20,22], and complete collapse (which occurred in two people after drinking alcoholic beverages) [20]. Still later, emotional changes [19,21-23] and finally, reactions typical of overt peripheral neuropathy, positive Romberg's sign [17,19-21,23,24], loss of vibration and position senses [17,19-21,23], weak or absent tendon reflexes such as the knee jerk [16-18,20-23], ataxic gait [16,20-23], foot drop [17,20,23], muscular atrophy (usually in the hand or thumb), and occasionally urinary and fecal retention [20,22] were observed. When patients were rested, it was found that conduction velocity was decreased in motor or sensory nerves or in both [21-23,25].

In hospitalized workers, clinical laboratory tests of blood, urine, cerebrospinal fluid (CSF), liver and kidney function, and electroencephalography were done [16,20,23]. Examination of the cardiovascular system, bones, and joints showed no pertinent deviations from normal [16,20,23]. These workers were only given symptomatic and supportive therapy. The length of time required for recovery, which was a few days to 2 years, was proportional to the severity of the reactions [16-21,23]. Only one affected worker [16] was reported to have returned to his occupation without further illness.

Some of the incidents of acrylamide intoxication which occurred in Japan were reported by Fujita et al [23]. They described in considerable detail the signs and symptoms which resulted from acrylamide exposure in 10 workers in one factory. Nine men and one woman ranging in age from 17 to 43 years were exposed at a pilot plant where manufacturing procedures were being developed. The length of employment in that plant varied from 3 to 12 months before signs and symptoms appeared. All of the workers had most

of the typical signs and symptoms of acrylamide intoxication relating more to the legs than to the arms. Of the three workers who were hospitalized because they were the most severly affected, one had been employed for 12 months and the other two for 3 months in their present jobs. Those three workers had, in addition to the typical reactions (tremor and numbness of the hands and feet, dizziness, loss of the knee jerk, heavy feeling of the legs, staggering, and positive Romberg's sign), emotional changes which were also somewhat similar to, but very much less severe than those of the family reported by Igisu et al [22], which is described in detail later. The symptoms were attributed to the presence of the peripheral neuropathy and the desquamation and sensitivity of the soles of the feet, which may also have been in contact with acrylamide. Fujita et al [23] also found sufficient signs and symptoms to postulate that the CNS and probably the cerebellum, in addition to peripheral nerves, were involved in acrylamide intoxication. All 10 workers improved during about 4 months of rest and supportive treatment.

Takahashi et al [21] described the reactions of 13 factory and 2 laboratory workers who were exposed to acrylamide from 2 months to 8 years. All of the workers were males aged 18-32 years. They were exposed during the polymerization of the monomer in the manufacture of papercoating materials. The described reactions conformed to the typical ones (numbness of lower limbs, ataxia, dizziness, gastrointestinal upset, and hand peeling). The authors [21] concluded that, although peripheral neuropathy was one of the most important effects in the patients, a few CNS effects also may have been present. When the work environment was changed to limit or prevent contact with acrylamide, the workers gradually recovered;

however, the authors [21] did not describe the controls used. Takahashi et al [21] also performed special studies in which motor and sensory nerve conduction velocities and action potentials were determined in some of the peripheral nerves in arms and legs of the affected workers. The motor nerves tested had essentially normal reactions, whereas the sensory nerves had decreased action potential amplitude. The authors [21] suggested that the defect in the action potential would precede decreases in conduction velocity and that this indicated sensory nerve injury.

Garland and Patterson [20] described six cases of acrylamide intoxication in workers in three factories in Great Britain where acrylamide flocculants were produced. The workers, all men and aged 19-59 years, had worked in the factories for periods varying from 1 to over 12 months. Although limited details of the medical histories and examinations were reported, the authors [20] suggested that what was recorded agreed with some of the signs and symptoms of the typical reactions (increased sweating of feet and hands, fatigue, muscle weakness and pain, hand peeling, sensory loss, and positive Romberg's sign). The authors stated that all of the men recovered after they were removed from exposure, although it took from 2 to 12 months. Garland and Patterson [20] interpreted that, because of the sleepiness of the men, the midbrain, as well as peripheral nerves, was involved. Fullerton [25] studied nerve conduction velocities in three of the patients reported by Garland and Patterson [20] while they were recovering from the ill effects of exposure. Maximal motor nerve conduction in the distal ends of median and ulnar nerves was found to be normal or slightly reduced and response to nerve stimulation in small muscles was dispersed irregularly. Fullerton

suggested that those changes were caused by degeneration and regeneration of the distal nerves (nerve endings near muscles). The action potentials of the sensory nerves were also decreased or absent; the author [25] indicated that the peripheral sensory nerves had been more severely damaged than their associated motor nerves. In addition to the determination of the neurophysiologic phenomena, Fullerton [25] microscopically examined biopsy specimens of nerves from the calf muscles from two of the three patients. The author [25] concluded that simultaneous nerve degeneration and regeneration occurred immediately after, and probably during acrylamide exposure, and that most probably nerve function was impaired before structural changes were evident.

Auld and Bedwell [16] in 1967 described in detail a mine worker's reaction to acrylamide exposure. The worker, a 21-year-old man, introduced a 10% aqueous solution of acrylamide monomer and the catalysts, 2-dimethylaminoproprionitrile (DMAPN) and ammonium persulfate, into holes previously drilled into the walls of a mine. He also loaded hoppers with the acrylamide solution. He did not avoid contact with the chemicals, which often splashed onto his hands and face. After about 2 weeks on the job, he noticed a red rash on his forearms. About 5 weeks after the rash began, he complained of leg weakness and soon after, of hand weakness. He also stumbled when walking and had difficulty climbing stairs, writing, and handling eating utensils. In about 2 more weeks, he noticed blueness and both a sensation of cold and profuse sweating of his arms, hands and fingers, as well as his lower legs, feet, and toes. He reported that his hands and feet felt "numb and tender when touched." With increasing weakness, stumbling gait, and excessive sweating, he was hospitalized 14

weeks after his first exposure to acrylamide. A general physical and neurologic examination corroborated his complaints, and the physician found, in addition, impairment of temperature, position and vibration senses, and absence of tendon reflexes (knee jerk, etc). His forearm and lower leg muscles were weak, and he was unsteady when standing or walking. Laboratory (clinical chemistry, hematology, urinalysis, and CSF) tests were performed, the results of which were within normal limits, except for elevated CSF protein which had decreased substantially at a second determination 2 weeks later. Therefore, the authors judged it was not significant. Removal from exposure, supportive therapy, and rest resulted in gradual and partial recovery in 6 weeks and in functionally complete recovery 14 weeks after hospitalization. The authors [16] stated that, because of a predisposition to the effects of acrylamide as described by Stokinger [26], the patient was strongly advised to avoid further contact with acrylamide. A coworker who had been simultaneously exposed to acrylamide had mild symptoms which disappeared spontaneously.

Two other incidents of acrylamide exposure similar to the case reported by Auld and Bedwell [16] occurred in France and were described by Graveleau et al [17] and Cavigneaux and Cabasson [18]. Exposure occurred while two workers were introducing monomeric acrylamide and catalyst into underground drilling operations. Signs and symptoms and results of neurologic examinations in both workers were typical of the described responses (numbness of the hands and feet, excessive sweating of the limbs, desquamation of the hands, and positive Romberg's sign). Morviller [19] described four cases of acrylamide exposure and implied that there were two more workers who were exposed to acrylamide and acrylonitrile during a

manufacturing project in a pilot plant. Adverse effects were similar to the typical effects (excessive sweating, desquamation of the hands, fatigue, weight loss, confusion, loss of reflexes, and positive Romberg's sign) of acrylamide intoxication. The author [19] also stated that the effects of acrylonitrile exposure were typical of those produced by acrylamide and that exposure for an undefined length of time to acrylonitrile had not resulted in similar adverse reactions in workers.

Igisu et al [22] reported five members of a Japanese family who were exposed to acrylamide through ingestion and external use of well water evidently contaminated by seepage from a waste system grouting operation. They began to show symptoms about 4 weeks after the grouting was done. Ten days after the onset of the symptoms, the well water was tested and found to contain 400 ppm of acrylamide and a trace of DMAPN. The mother, father, and grandmother were hospitalized, with strikingly similar symptoms 4-5 weeks after the well was grouted. They experienced marked rhinorrhea, coughing, dizziness, and irrational behavior. Mental changes consisting of poor orientation and memory, confusion, and severe hallucinations preceding unsteadiness in walking, sleepiness, and slurred speech occurred. General physical and neurologic examinations showed normal or hyperactive reflexes, normal cranial nerve reactions, ataxic gait (severe in both women), urinary and fecal retention (mother only), and ecchymoses of the extremities of both women. Electroencephalography showed excessive sleepiness patterns, but all other clinical laboratory tests performed were in the normal range. The only complaints referable to the skin, such as loss of touch, pain and sense of vibration, and a feeling of numbness in the extremities were made 2, 3, and 4 weeks after hospitalization by the mother, father, and

grandmother, respectively. They had mild dysesthesias of the fingers and feet. During the hospitalization period, the mother had no deep-tendon reflex response, and all three patients had slowed sensory but normal motor nerve conduction velocities. The two children of the family, who were away at school all day and presumably did not consume as much well water as the adults, had very mild sleep and gait disturbances (the boy) and mild personality changes (the girl). Both children recovered within 2 weeks. The father and grandmother recovered completely in 2 months and the mother in 4 months after hospitalization.

The Vistron Corporation (DR Brinkley, written communication, June 1976) supplied NIOSH with information concerning airborne acrylamide concentrations and occupational exposures. Eight-hour acrylamide samples were collected daily from stationary sites in the plant using an aqueous impinger technique and subsequently analyzed by a colorimetric procedure using a ferric chloride reagent. Limited personal monitoring was conducted. The stationary air monitoring site data were presented as weekly averages and ranged from 0.1 to 0.4 mg/cu m for the control room, 0.1 to 0.9 mg/cu m for the bagging room, and 0.1 to 0.4 mg/cu m for the second-floor processing area. Personal monitoring data showed that daily 8-hour average employee exposures ranged from a low of 0.1 to as high as 2.3 mg/cu m when stationary sites data taken on the same day showed concentrations ranging from 0.1 to only 0.3 mg/cu m.

Brinkley (written communication, June 1976) stated that attempts were made to maintain minimum employee contact with acrylamide by the installation of engineering controls and additional ventilation equipment with air-circulating fans. Emphasis was placed on personal hygiene as an

important factor in the prevention of acrylamide intoxication. Personal protective equipment, such as cartridge type respirators and dust masks and protective clothing, such as coveralls, safety glasses, caps, and gloves, were also provided. Despite these precautions, two employees experienced neurologic symptoms in May 1974. Prior to this date, no neurologic symptoms except finger tingling were noted in any employee. The initial symptoms of erythema and skin peeling were noted in almost every employee who was working in the acrylamide plant. If erythema or skin peeling or any of the following acrylamide-associated symptoms, such as increased sweating of feet and hands, muscular weakness or pain, abnormal skin sensations, sensory loss, absent reflexes, positive Romberg's sign, persisted after removal of the worker from the working environment, the employee would be transferred outside of the acrylamide unit. According to Brinkley, a statistical analysis of the stationary site data and the skin check records has suggested that the incidence of skin reactions could, at least to some degree, be explained by airborne concentrations of acrylamide. Because of the limited personal monitoring data, airborne acrylamide concentrations to which workers were actually exposed could not be correlated with skin reactions.

Epidemiologic Studies

No reports concerning epidemiologic studies of acrylamide monomer were found in the published literature.

Animal Toxicity

(a) Oral Studies

Hamblin [14] reported that the single-dose oral LD50 for male albino mice given acrylamide as a 2 or 5% aqueous solution was 170 (130-220, 95% confidence limits) mg/kg. Toxic signs consisted of slight tremors, convulsions, labored respiration, and ataxia. The single-dose oral LD50 determined by Fullerton and Barnes [27] in 8-week-old female albino rats was 203 (166-249) mg/kg. The duration of the observation period was not specified in either of these studies. In a study by Keeler et al [28], the single-dose oral LD50 for acrylamide was 240 (184-316) mg/kg in female rats and 277 mg/kg in male rats (95% confidence limits not calculable). No information on rat strain, age, weight, or observation period was provided.

In a 1956 study reported by Hamblin [14], repeated oral administration of acrylamide, 50 or 100 mg/kg/day, by stomach tube to albino rats produced prostration and death. The 100-mg/kg/day level killed all six animals after three daily doses. The 50-mg/kg/day dose caused loss of weight, depression, and marked weakness of the extremities; death occurred within 5 days after the last (15th) daily dose. Barnes [29] obtained qualitatively similar results in adult Porton-strain albino rats. Fullerton and Barnes [27] also observed that acrylamide administered to rats at a single dose of 100 mg/kg by stomach tube produced only fine tremors, but when repeated in 24 hours killed most of the animals within 3 days. General weakness was also observed in the dying rats. When intubated with 50-mg/kg doses, 12 times over a 15-day period, all rats (number not specified) developed severe weakness and died within a few days after the final dose. At necropsy, many rats (both males and females) had

gross distention of the bladder. Ten-week-old rats given acrylamide orally at a dose of 25 mg/kg/day, 5 days/week, developed the first signs of weakness after the fourth week. A dose of 10 mg/kg/day, 5 days/week, given for about 5 months, produced no signs of toxicity in six female rats.

Fullerton and Barnes [27] also measured motor nerve conduction velocity in the fibers supplying the small muscles on the plantar surface of the hind paws in Porton-strain albino rats. Nerve conduction velocity in control animals was 56 (SD 5.8) meters/second compared with 44 (SD 2.2) meters/second in the 11 of the 15 rats fed acrylamide in their diets (200 ppm for 6 months or 400 ppm for 2-3 months) and showed severe neurologic abnormalities of the hindlimbs. The conduction velocities were normal in the remaining four rats recovering from the severe leg weakness.

The influence of age on acrylamide-induced leg weakness was investigated by Fullerton and Barnes [27] in groups of six rats (sex not specified) aged 5, 8, 26, and 52 weeks and fed 100 mg/kg of acrylamide at weekly intervals. After four doses, the youngest animals were only mildly affected, whereas those aged 26 weeks at the start of study were severely affected. The 52-week-old rats were severely affected after only three doses. The authors stated that, when acrylamide feeding was discontinued, the recovery in young animals, which had shown weakness for only a few weeks, was rapid and complete. For the older rats, in which weakness had been present for months, recovery was slow, and mild ataxia continued for some months.

The effects of orally administered acrylamide on dogs were briefly reported by Hamblin [14] in 1956, but recently have been studied in more detail by Thomann et al [30]. In the earlier investigation [14], groups of

two dogs each were given acrylamide at doses of 1 mg/kg/day for 19 weeks, 5 mg/kg/day for 5 weeks, or 8 mg/kg/day for 4 weeks without overt signs of toxicity. However, a dose of 10 mg/kg/day for 4-5 weeks produced incoordination, weakness of the extremities, and impaired righting reflex. A single dose of 100 mg/kg produced these same effects in 24 hours. In the 1974 report by Thomann et al [30], experiments were performed on 6- to 12-month-old beagles. The dogs were given acrylamide orally in gelatin capsules in daily doses of 5 or 15 mg/kg. The first group (three males and three females) received 5 mg/kg/day for 60 days; the second group (five males and five females) received 15 mg/kg/day for 22 days. After the first 3 weeks of the experiment, the dogs in the 5-mg/kg/day group were inactive and had muscular weakness, which was particularly noticeable in the jaw muscles. In addition to muscular weakness, the animals in the 15-mg/kg/day group had dilated pupils, conjunctivitis, salivation, difficulty in breathing, muscular stiffness of the hindlegs, muscle twitching, head shaking, and convulsions. One female beagle in the latter group (15 mg/kg) died on day 24, 2 days after the end of treatment. Microscopic examination of peripheral nerves from one of the surviving dogs showed swelling of the myelin sheaths and fragmentation of the axons. In general, the distal branches of the sciatic nerve were more severely involved than were the proximal parts. Occasional swelling and fragmentation of nerve fibers of the distal branches were found in three of the six dogs in the 5-mg/kg group after 60 days of treatment. The authors [30] reported no structural alterations in the white or gray matter of the lumbar spinal cord on microscopic examination.

Hopkins [31] studied the effects of acrylamide administered to five female and two male baboons (Papio hamadryas). The female baboons weighed between 12.1 and 15.4 kg and the two males weighed 9.4 and 10.3 kg. Acrylamide was administered in oranges or bananas as a 10% aqueous solution. Because the dosage schedule for one of the seven baboons was questionable, the data for this animal are excluded from the discussion that follows. According to Hopkins [31], this particular baboon was reluctant to eat all of the fruit into which the acrylamide had been injected. Of the remaining six baboons, one was treated with 20 mg/kg/day for 29 days, another with 15 mg/kg/day for 94 days, and four with 10 mg/kg/day for an average of 110 (89-137) days. The cumulative doses received by the baboons were thus 580, 1,410, and about 1,100 mg/kg, respectively. Incoordination and weakness of the hindquarters were first noticed on the 16th day in the 20-mg/kg/day animal, on the 42d day in the 15-mg/kg/day animal, and on an average of the 62d (42-82) day in the 10-mg/kg/day animals. Forelimb weakness first occurred on the 28th, 73d, and 82d (61-96) days, respectively. Recovery began within 2-12 days after feeding was discontinued. The baboon which received a total of 580 mg/kg recovered completely in 62 days; those which received an average of 1,100 mg/kg recovered in 110 days, and the baboon which received a total of 1,410 mg/kg recovered in 270 days. The author [31] concluded that the onset of limbs weakness and the progression of recovery were dose dependent.

The peripheral nerves from a baboon given acrylamide at 10 mg/kg/day for 118 days and biopsied 19 days after the last treatment were examined by light microscopy [31]. The main pathologic changes were of the Wallerian degenerative type (degeneration of a nerve fiber which has been severed

from its nutritive centers). Microscopic examination of transverse sections of nerves indicated that both motor and sensory nerves were affected and that there was a marked reduction in the number of myelinated fibers in the nerves. The author [31] reported that inspection of moderately affected nerves suggested the involvement of large-diameter myelinated fibers. The proportion of such myelinated fibers decreased with an increase in the duration of exposure. At necropsy, it was observed that long nerves to muscles were more severely affected than short nerves. Nerve fibers to the extremities were affected only in their distal parts, the proximal sciatic nerve and spinal roots remaining normal in baboons which showed a severe loss of myelinated fibers in nerves to muscles of the feet.

Hopkins and Gilliatt [32] examined nerve conduction velocities and muscle action potentials of baboons treated with acrylamide. It appears that this study reports additional results from the experiment described above by Hopkins [31]. Conduction velocity and ascending nerve action potentials were measured in the median and anterior tibial nerves of the left limbs; all specimens for microscopic examination were taken from the right limbs. Muscle action potentials were recorded from the abductor pollicis brevis and extensor digitorum brevis. At acrylamide doses of 10 or 15 mg/kg/day, the gradual development of limb weakness in the baboons was accompanied by a progressive reduction in the amplitudes of muscle and nerve action potentials. In the baboon receiving acrylamide at 15 mg/kg/day, there was a progressive decline in amplitudes of muscle and nerve action potentials with an increase in latency period. Acrylamide administration was stopped on day 94; however, the amplitudes of action

potentials did not return to normal until 1 year later. The percentage reduction in the amplitude of the action potential was greater in the muscle of the foot than in that of the hand. These results supported the clinical observation that the disease was usually more severe in the lower than in the upper limbs. Reductions in nerve conduction velocities and nerve action potential amplitudes were also observed in baboons treated with acrylamide at 10 mg/kg/day for an average of 110 days and measured within 3 weeks after the end of treatment. The percentage decreases in both velocity and amplitude were greater for sensory than for motor conduction in the median nerve. This deterioration sometimes continued for several weeks after acrylamide was discontinued.

Hopkins and Gilliatt [32] also studied the return of conduction velocity and action potential amplitude values to normal in one baboon treated with acrylamide at a dose of 15 mg/kg/day for 94 days and in two baboons given 10 mg/kg/day for 89 and 115 days. The baboon receiving 15 mg/kg/day was severely affected and, while the amplitude of the nerve action potential was little changed until the end of the first year, it had returned to 80% normal by the end of the second year. Baboons receiving acrylamide at 10 mg/kg/day were less severely affected and the amplitude of the muscle action potential began to return to normal within 2-3 months. Hopkins and Gilliatt [32] also observed that a baboon treated with acrylamide at 20 mg/kg/day for 29 days remained severely paralyzed for 2 days after treatment was stopped. Yet, the maximal conduction velocity in all the nerves examined was within the normal range and the action potential amplitude was only slightly reduced. The motor nerve conduction was normal at the same time that the animal was severely paralyzed

suggested to these workers [32] that damage to the CNS also had occurred.

Bradley and Asbury [33] studied the effects of acrylamide added to the drinking water at a concentration of 250 ppm on 26 young adult female mice of BALB c Gn/J X SJL/J and SJL/J strains. Two mice from each strain were used as controls. Animals drank the treated water ad libitum for 45 days. Pairs of animals were selected at random and killed at 23, 30, 35, 40, 45, 50, 55, 60, 90, 120, or 165 days after the first exposure. The brain, spinal cord, sciatic nerve, and hamstring and gastrocnemius muscles of the mice were examined microscopically. No animals died during treatment with acrylamide at this dose. The first observed abnormality, difficulty in grasping and walking along the edge of the cage, appeared after 20 days of acrylamide administration, and by day 25, all animals either appeared unaware of the position of their hindlimbs or dragged their feet when walking. After 35 days, the mice had lost some weight and hair. Within 5 days of the withdrawal of acrylamide on day 45, the mice had gained some weight and their gait had improved. However, some signs of acrylamide poisoning persisted even 20 days after the withdrawal of acrylamide, as measured by the position of the lower limbs. Degenerating myelinated fibers were occasionally present in the sciatic nerve of mice killed 23 days after commencement of acrylamide and the proportion of such fibers increased with the duration of treatment. Multiple sections of the spinal cord showed no differences between acrylamide-treated and control mice. The results of microscopic studies of brain tissue were not mentioned. The hamstring and gastrocnemius muscles appeared wasted, although microscopic examination revealed only a slight increase in the number of areas of segmental necrosis and regeneration when compared with

control mice.

Hamblin [14] briefly described the effects on the growth of albino rats given acrylamide in the diet (10, 50, 100, or 300 ppm). No effects were reported at the 10- and 50-ppm levels. Diets containing 100 and 300 ppm of acrylamide produced growth retardation within 6 and 4 weeks, respectively.

Fullerton and Barnes [27] studied the effects of acrylamide on 6- to 8-week-old male albino rats. The animals were fed diets containing 100, 200, 300, or 400 ppm of acrylamide. According to the authors [27], these represented daily intakes of about 6-9, 10-14, 15-18, or 20-30 mg/kg, respectively. Control rats received a similar diet without acrylamide. Rats on the acrylamide diets developed slight leg weakness as follows: at 400 ppm after 3 weeks, at 300 ppm after 4 weeks, at 200 ppm after 12 weeks, and at 100 ppm after 40 weeks. Severe leg weakness developed in all except the 100-ppm rats on continuation of dietary treatment; the slight leg weakness observed at week 40 did not increase during the remaining 8 weeks of the experiment. The only macroscopic findings at necropsy were wasting of the hindlimb musculature and distended urinary bladders in all rats. Axons and myelin sheaths of the sciatic, tibial, median, and ulnar nerves examined microscopically at necropsy showed extensive degeneration in the peripheral nerves of all the clinically affected animals. Microscopic examination of kidney, spleen, pancreas, adrenal, lung, brain, and spinal cord tissues showed no abnormalities.

McCollister et al [34] studied the effects of acrylamide given at low concentrations in the diet. Groups of 10 male and 10 female 8-week-old rats of the Dow Wistar strain were maintained on diets containing 3, 9, or

30 ppm acrylamide for 90 days, and then killed and necropsied. As judged by their appearance, behavior, growth, mortality, organ weights, and microscopic examination of tissues, there was no evidence of adverse effects in either male or female rats. No signs of neurotoxicity were seen in two other groups of animals maintained on diets containing either 70 or 110 ppm of acrylamide for 189 days. In the same experiment, McCollister et al [34] also studied the effects on male and female rats of acrylamide given at high concentrations in the diet. At a 300-ppm acrylamide dietary level, the rats began to show loss of control of the hindquarters after 21 days. By day 42, all 10 males and 6 of 10 females were dead. Loss of hindquarter control was seen at 14 days in rats maintained at a diet containing 400 ppm of acrylamide. According to the authors [34], doses of 3, 9, 30, 70, 90, 110, 300, and 400 ppm of acrylamide in the diet were equivalent to 0.3, 0.9, 3, 7, 9, 11, 30, and 40 mg/kg/day, respectively.

In a 1-year feeding study on cats by McCollister et al [34], different concentrations of acrylamide were mixed with feed to deliver total calculated daily doses of 0.03, 0.1, 0.3, 1, 3, or 10 mg/kg. The acrylamide diets were fed to two cats for 5 days/week at each dose. Cats fed 10 mg/kg/day developed signs of neurotoxicity, definite weakness in the hindquarters by day 26, and were unable to stand by day 52. One of the two cats was then killed; the other, taken off the acrylamide diet, recovered completely 53 days later. The two cats receiving acrylamide at 3 mg/kg for 1 year survived to the end of treatment, but started showing twitching motions of the hindquarters by 26 days and signs of hindleg weakness by 68 days; the latter persisted for a further period of 299 days. One of two cats receiving the 1-mg/kg dose for 1 year showed some twitching in its

hindquarters by 26 days and signs of hindleg stretching when walking by 240 days. In the remaining three dosage groups (0.3, 0.1, and 0.03 mg/kg), five of the six cats died by day 106 from disease not attributable to acrylamide [34]. No toxic effects were seen in the only surviving cat (0.3 mg/kg) at the end of the study. Hematologic tests (not specified), blood clotting times, and blood cholinesterase activities in cats treated at 3, 1, or 0.3 mg/kg/day were not affected. Microscopic examination showed no evidence of adverse effects on central nervous tissues (brain and spinal cord) in any of the animals receiving acrylamide at any dose, including 10 mg/kg/day.

Leswing and Ribelin [35] studied physiologic and pathologic changes in 11 young adult cats administered acrylamide orally. Acrylamide was mixed in the diet to deliver a calculated dose of 20 mg/kg/day. Within 2-3 weeks, the cats showed slight weakness of the hindlimbs which progressed at variable rates to paralysis of the hindlimbs. Atrophy of the thigh and leg muscles was noticeable in severely paralyzed cats, and a few cats also had weakness of the forelimbs. The authors [35] reported that the cat cries became coarse, indicating possible involvement of the laryngeal nerves. Cats showed marked improvement when returned to their normal diet. Hindlimb strength was regained within 2-3 weeks, but complete recovery took several months and was directly related to the severity of the involvement. Microscopic examination of the nerves revealed degeneration of the myelin and axons of all four limbs. There was a suggestion of actual axon loss in the distal third or fourth portion of the tibial nerve fibers. Atrophy was evident grossly in nearly all muscles of the caudal limbs; however, microscopically, it was marked only in the digital muscles.

Leswing and Ribelin [35] also measured peripheral nerve conduction and nerve and muscle action potentials in cats and monkeys that had severe neurotoxic effects from acrylamide treatment. The cats were administered acrylamide at 20 mg/kg/day in their diet. Four monkeys were given acrylamide at 20 mg/kg/day, injected into bananas, for 8 weeks. The dose was then increased to 30 mg/kg/day. Acrylamide-treated animals required higher applied voltages to stimulate the nerve, and most had greatly reduced muscle and nerve spike amplitudes. Conduction velocity was reduced from preexposure levels in sciatic and tibial nerves by an average of about 29% in the cat and 24% in the monkey. "Substantial improvement" in conduction velocity was seen in both species on partial clinical recovery.

Schaumburg et al [36] studied ultrastructural changes in the nervous system of two cats given acrylamide at a dose of 3 mg/kg/day in drinking water. One cat received acrylamide for 252 days and the other for 294 days. Onset of gait disorder was noted after 70 days in one cat and after 163 days in the other cat. Hindfeet drop and distal muscle weakness were seen within 7 months. Tissues biopsied from the hindfeet after completion of the study showed a loss of all types of myelinated fibers in distal nerves. Only a few small and large myelinated nerve fibers were seen in plantar nerve twigs and most of the fibers were completely degenerated (bands of Bungner). Many unmyelinated nerve fibers were present. Most of the muscle fibers were vacuolated, shrunken, and had irregular borders--changes that the authors [36] considered secondary to denervation.

McCollister et al [34] also carried out a 1-year feeding study in female monkeys. One monkey was used at each dosage (0.03, 0.1, 1, 3, or 10 mg/kg/day, 5 days/week). Two monkeys received the 0.3-mg/kg dose and two

monkeys served as controls. The animals at the 10- and 3-mg/kg levels received their daily doses by intragastric administration of aqueous solutions of acrylamide. The other monkeys ate bananas injected with acrylamide given to them in the morning before any other food. The monkey on the 10-mg/kg dose showed some weakness of the hindquarters by day 48 and extreme weakness by day 69. The animal was transferred to a control diet on the 70th day and recovered completely 54 days after acrylamide was discontinued. The monkey fed 3 mg/kg of acrylamide did not show any loss in body weight. Neurologic examinations of this animal sometimes showed either knee jerk or pupillary reflexes that were somewhat sluggish when compared with the response of the controls. The authors [34] considered these responses as insignificant. "Terminal hematologic examinations" (unspecified) at 1 year showed no abnormalities. At autopsy, gross examination of the animal revealed no abnormalities. Liver and kidney weights were normal. Microscopic examination of the liver and kidney also showed no significant adverse effects on cells of these tissues. Microscopic examination of the brain and spinal cord showed no abnormalities attributable to acrylamide. The monkeys on other dose regimens showed no adverse effects as measured by growth, general appearance, behavior, periodic neurologic examinations, liver and kidney weights, gross necropsy, and microscopic examination of the tissues.

(b) Dermal and Eye Studies

Hashimoto and Ando [37] studied the dermal penetration of acrylamide in rabbits. A single application of acrylamide as a 10-30% aqueous solution penetrated the skin rapidly and appeared in the blood both as free compound and bound to proteins (mainly hemoglobin). Twenty-four hours

later, the concentrations of acrylamide in tissues (unspecified) were higher than in the blood. Seven successive applications of 30 minutes each day progressively increased the blood and tissue concentration of acrylamide. Autoradiographs showed that 14C-acrylamide concentrated around hair follicles. No quantitative data were given.

McCollister et al [34] investigated the possibility of skin irritation from acrylamide by applying an unspecified quantity of 10% aqueous solution to the ear and to the shaved intact abdominal skin of a rabbit. Applications to the ear and abdomen were repeated 10 times over a period of 2 weeks. In another experiment, an abraded area of the shaved belly was treated with a 10% aqueous solution of acrylamide for 3 consecutive days. No significant responses were observed except in the case of animals whose skins were abraded, which only showed a very slight reddening and slight edema that healed later. A 12.5% aqueous solution of acrylamide was applied to the skin of 12 rabbits and held in place with the aid of an impermeable sleeve for a 24-hour period. Two rabbits each received dermal applications of 0.063, 0.126, 0.5, and 1.0 g/kg of the acrylamide; four animals were treated with 0.252 g/kg. Only one rabbit that received the 1.0-g/kg application died within 2 days. Slight weight losses and reddening of the skin were noted in both rabbits treated with 0.5 g/kg of acrylamide. No other effects were observed in any of the other rabbits.

The effects of eye contact with 10 and 40% aqueous solutions of acrylamide were also studied by McCollister et al [34]. The solution was instilled into the right eye of a rabbit and washed within 30 seconds with a stream of water for 2 minutes. The left eye was treated with the same

amount of acrylamide solution but left unwashed. The eyes were examined with and without fluorescein staining, 2-3 minutes, 1 hour, and 24 hours later for conjunctival and corneal responses. The 10% aqueous solution caused signs of slight pain and slight conjunctival irritation immediately after contact, but the conjunctiva was completely normal within 24 hours. No injury to the cornea was reported. The application of the 40% aqueous solution of acrylamide to the unwashed eye caused signs of moderate pain, slight conjunctival irritation, and corneal injury. Although the conjunctival irritation was slow to heal, corneal healing was complete within 24 hours. Signs of moderate pain and slight conjunctival irritation were observed in the washed eye after administration of the 40% solution; however, there was no corneal injury, and the conjunctival irritation was nearly healed at 24 hours.

(c) Parenteral Studies

Hashimoto and Aldridge [38] studied the effects of acrylamide on body weights of male Porton-strain albino rats weighing about 200 g. Acrylamide was injected ip, twice a week, for 1 month. At 32 days after the first injection, there was a 28% reduction in body weight in rats injected with 50 mg/kg; those injected with 100 mg/kg showed a weight reduction of 63%. Rats in both groups were ataxic after 2 weeks.

Suzuki and Pfaff [39] studied the effects of acrylamide in white Osborne-Mendel strain suckling and adult rats. One group consisted of 30 suckling (1-day-old) rats weighing 5-8 g and the other of 28 adult rats weighing 150-300 g. The animals received ip injections of 50 mg/kg of acrylamide in saline, three times a week, for up to 18 injections; two additional adult rats each received a total of 26 injections. Controls

were injected with saline only. Suckling rats, both experimental and control, gained weight normally until their fifth or sixth injection, when weight gains of the acrylamide-injected animals slowed down. Slight weakness of the hindlimbs, noticeable in some of the young animals after five or six acrylamide injections, became more pronounced until the rats could no longer stand. In contrast to the results obtained in suckling rats, the body weights of the adults did not change. Weakness of the hindlimbs, noticeable after 7 or 8 injections, was followed by complete paralysis after 15-17 injections. At this time, wasting of the musculature of the hindlimbs was prominent. Weakness of the forelimbs was also noted in some rats. In the animals for which acrylamide treatment was terminated after the 16th injection, weakness of the extremities persisted for about 1 month but, in animals given 26 injections, it persisted for about 2 months. Animals with clinical signs of neuropathy showed prominent distention of the urinary bladder in pups and adults at autopsy. The other organs were congested, but otherwise normal.

Suzuki and Pfaff [39] observed on microscopic examination occasional myelin figures in Schwann cells and enlarged fibers within the sciatic nerve and their distal branches in acrylamide-treated suckling rats after the fourth injection. These changes became prominent after eight injections and myelin degeneration was observed after 12-14 injections. In adult rats, both myelin and axonal degeneration were prominent after 15 injections. According to the authors [39], rats which received 26 injections showed "severe axonal loss" in both the proximal and distal portions of the sciatic nerve, but this loss was more severe in the distal portions. In addition, the authors [39] reported an increased number of

Schwann cells, many of which had an abnormally high number of myelin figures in their cytoplasm. Light microscopic examination of sections of cerebrum, cerebellum, spinal cord, and brain stem showed degeneration of the spinal cord white matter and the presence of axonal spheroids in the cuneate nuclei of the medulla oblongata. No other CNS abnormalities were observed in adult rats. Hematoxylin and eosin-stained sections of lung, liver, spleen, pancreas, kidney, and adrenal showed no abnormalities.

With electron microscopy, the authors [39] found that the most common feature in suckling rats given nine injections of acrylamide was axons filled with fine filaments. Very few changes were noted in the adult rats killed after 10 or 12 injections. Many axons of the sciatic nerve were filled with neurofilaments; however, the myelin sheaths appeared normal. In addition to accumulations of neurofilaments, degeneration of axons and myelin sheaths was observed in adult rats receiving 15-18 injections. Sciatic nerves and their branches in adult rats which had received 26 injections had numerous Schwann cells and macrophages containing many myelin figures and fat droplets but very few myelinated fibers. There were many Schwann cells in the sections, but few of these sections contained axons. Microscopic examination of the nerves of adult rats killed 20 or 30 days after the last injection showed numerous axonal sprouts growing within the Schwann cells. Suzuki and Pfaff [39] concluded that, since degenerative changes of sciatic nerve axons seen only in adult rats in advanced stages of neuropathy were also frequently observed in suckling rats at the onset of paralysis, the peripheral nerves of suckling rats were more susceptible to acrylamide than were those of adults. The authors [39] suggested that the higher susceptibility of suckling rats could be a result

of the incomplete development of the barrier system of peripheral nerves.

Spencer and Schaumburg [40] examined the spatial-temporal distribution of hindlimb peripheral nerve degeneration in rats injected with acrylamide. Acrylamide, dissolved in saline, was administered daily by subcutaneous injection to 10 young-adult Spraque-Dawley rats in amounts of 10-60 mg/kg for 4-40 days. Sixteen age- and weight-matched rats were used as controls. The rats were killed before they developed signs of obvious hindlimb weakness. Nerve fibers separated from various sites in the sciatic, tibial, and plantar nerves were examined by light and electron microscopy. The large diameter fibers supplying the calf muscles and the long sensory fibers supplying the digits of the paws degenerated first. Degeneration of nerve fibers supplying the flexor digitorum brevis muscle occurred later. The findings from the electron microscopic examination showed accumulation of neurofilaments, abnormal mitochondria, and honeycombed, interdigitated Schwann cell-axon networks.

Kuperman [41] studied the neurotoxic effects of acrylamide on cats. Acrylamide was administered by various routes (iv, ip, im, oral, or subcutaneous) in daily doses of 1, 2, 5, 10, 15, 25, 40, or 50 mg/kg. Groups of 3-11 cats were used at each level. Effects of chronic poisoning from acrylamide, as measured by the development of ataxia, appeared at identical dose levels and after equivalent latent periods irrespective of the route of administration, whether iv, ip, im, subcutaneous, or oral. The length of the latent period from the start of the treatment was inversely related to the amount of the dose and varied between 125 days with 1 mg/kg and 2 days with 50 mg/kg. In this study [41], the average of the doses that killed eight cats was 320 mg/kg. Microscopic findings in

brain and spinal cord were normal.

McCollister et al [34] also studied the effects of acrylamide on one monkey given two ip injections 24 hours apart at doses of 100 mg/kg. Severe weakness was seen 24 hours after the second injection, and the monkey died on day 3. The findings from gross examination were congested lungs and kidneys and areas of necrosis in the liver. Microscopic examination of the kidneys showed degeneration of the convoluted tubular epithelium and of the glomeruli with albuminous material in the capsular space. Fatty degeneration of the liver was confirmed by the findings from the microscopic examinations.

Several investigators [36,40,42-46] have examined an acrylamide-induced degeneration of nerve fibers which begins in the distal portion of the fiber and proceeds slowly toward the cell body. This process, known as the "dying back" phenomenon, is a nonspecific type of nerve fiber degeneration that occurs simultaneously in the central and in the peripheral nervous systems. The nerves that are most commonly affected are those with the longest and largest axons. Sumner and Asbury [45] administered an acrylamide solution (100 mg/ml) by subcutaneous injection at a daily dose of 10 mg/kg to healthy adult cats of both sexes (number unspecified). Electrophysiologic measurements were carried out at various stages from 21 to 67 days after the start of the treatment. The first sign of neuropathy was slight hindleg ataxia, usually seen at about day 20 of treatment. The acrylamide-treated animals were divided into three groups, ie, A, B, and C. Group-A cats (21-34 days) had mild hindlimb ataxia. Group-B animals (38-44 days) had moderately severe hindlimb ataxia and depressed or absent Achilles tendon jerks. Group-C animals (47-67 days)

had extreme hindlimb ataxia that made walking very difficult. Achilles tendon jerks were absent in cats in this group. Conduction velocities were measured in a total of 1,001 afferent fibers isolated from animals in the three groups. All afferent fibers of the medial gastrocnemius nerve were conducted at 72-126 meters/second (Group-I velocity) or 24-72 meters/second (Group-II velocity). Maximal conduction velocities were similar in all three populations, but peak Group-I velocities were 108-114, 96-102, and 84-90 meters/second in groups A, B, and C, respectively. Many single fibers, when isolated, did not respond to electrophysiologic stimulation normally adequate for stretch receptors; these were termed nonresponsive units. In group-A animals, 10% of the fibers (38/366) were nonresponsive. In group B, the proportion of nonresponsive units increased to 68% (215/315). In group-C cats, 89% (285/320) of the fibers were nonresponsive. Sumner and Asbury [45] thus concluded that the number of nonresponsive single units isolated by systematic sampling of dorsal root filaments correlates well with the clinical severity of the neuropathy. They [45] also concluded from the similar maximal conduction velocities in all three groups that acrylamide produced no significant slowing of the conduction velocity in individual functioning fibers between the stimulating and recording electrodes.

At the end of each experiment and before the animal was killed, the medial gastrocnemius muscle and nerve were dissected free and fixed for microscopic examination. Microscopically, no nerve fibers were observed to have been lost or to have broken down in the medial gastrocnemius nerve before 55 days of acrylamide treatment; however, after 55 days, nerve breakdown ranged from 0 to 55% or more. The authors [45], in agreement

with Schaumberg et al [36], found that the muscle spindle nerve terminal was vulnerable to acrylamide. According to the authors [45], the results presented in this study indicated that interruption of nerve function may have been well advanced before any nerve fiber degeneration had occurred in nerve trunks. Hence, determination of conduction velocities would not have shown any abnormalities until nerve fiber degeneration had proceeded toward the cell body to the point at which the stimulating electrode had been placed.

Kaplan and Murphy [47] studied the influence of age on rotarod performance of male Holtzman rats treated with acrylamide. The rotarod test procedure involved the use of a partitioned enclosure containing a floor that could be electrified and a rod which turned at 8 rpm. Rats were trained to maintain their balance on the rod throughout three 2-minute trials. A rat that fell during any two of the three trials failed the test. Four groups of 12 rats each (5, 7, 11, and 14 weeks of age) were administered acrylamide ip at a dose of 50 mg/kg/day until all the rats in the respective age group failed the test. The onset of, duration of, and recovery from acrylamide poisoning were measured by rotarod performance; body weights were also recorded. Small reductions in body weights or slower-than-expected growth rates were observed during the administration of acrylamide for 18-22 days. The means for the onset to failure were 7.3, 6.4, 5.5, and 5.3 days, and the means recovery were 19.2, 15.6, 13.8, and 14.8 days for 5-, 7-, 11-, and 14-week-old rats, respectively. Thus, the delay in onset to failure was longer in younger animals; however, once impaired, they required a longer time to recover.

Prineas [42] employed light and electron microscopy in his observations on the tissues of cats treated with acrylamide. Acrylamide, 10 mg/kg, was administered daily by subcutaneous injection to five cats of both sexes weighing between 2.5 and 4 kg. One cat was killed 11 days after commencement of the injections but before the onset of neurologic signs. The animals developed neurologic signs between days 17 and 22 and were killed 22-49 days after injections were begun. The finding from light microscopic examination of nerves from the cat killed on day 22 were fragmented axons and myelin-ovoid formations in the intramuscular nerves and in the tibial nerve. Specially prepared sections of the upper cervical cord from cats examined at 32 or more days after commencing the injections showed degenerating myelin sheaths in the spinocerebellar tracts, in the gracile tracts, and in the white matter next to the anterior fissure; also, electron microscopy of occasional fibers in the tibial nerve showed increased numbers of neurofilaments. By day 22, however, a majority of the large-diameter fibers showed an increase in the number of neurofilaments. Myelin degeneration was usually evident by 49 days, first appearing at the nodes of Ranvier. In all animals treated with acrylamide for 32 days, the cell bodies in the dorsal root ganglia showed some loss of the normal parallel arrangement of granular endoplasmic reticulum, breakdown of polyribosomes with release of ribosomes into the cytoplasm, and an increase in the amount of electron-dense material in the cytoplasm. Similar changes were also found in the anterior horn cells. Other changes included striking changes in nerve fibers and terminal buttons in the anterior spinal gray matter at the S1 level. Small myelinated fibers frequently contained excessive numbers of neurofilaments which appeared to distend the

fiber in some instances. Between 5 and 15% of the terminal buttons were enlarged and contained excessive numbers of neurofilaments. Thus, this study [42] demonstrated structural damage in the distal CNS tracts of cats with signs of acrylamide poisoning.

Schaumburg et al [36], using techniques similar to those of Prineas [42], examined the early pathologic events in terminals of sensory and motor nerve fibers in the paws of cats treated ip with acrylamide. Two groups of animals were used for these parenteral studies. Five cats were injected with 10 mg/kg/day of acrylamide in an aqueous solution for 7-32 days; another five cats received 10 mg/kg/day, alternating with 20 or 40 mg/kg/day, either in interrupted or steady sequences. Six cats were used as controls. Tissues of acrylamide-intoxicated cats were obtained before and after total body perfusion with fixatives. With the cats under general anesthesia, biopsies of hindfeet toepad pacinian corpuscles, plantar lumbrical muscle, flexor digitorum brevis muscle, and twigs of the medial plantar nerve were performed and the tissues were examined under light and electron microscopy. The authors [36] observed that cats receiving 10 mg/kg/day developed a weaving gait, thought to be secondary to hindlimb unsteadiness, within 13 to 15 days. This evolved into a gross truncal ataxia. In the second group of animals, who received acrylamide at more than 10 mg/kg/day, a rapid and irregular head tremor was noted occasionally. After 28 days on the 10-mg/kg/day dose or 15 days on the higher doses, the cats were barely able to walk; however, foot drop and muscle wasting were not observed at this time. The authors [36] reported that the axons of pacinian corpuscles began to degenerate before sensory nerve terminals supplying muscle spindles. Pacinian corpuscles are

important to the animal's sense of position and they degenerated before the adjacent motor nerve terminals. These authors [36] concluded that sensory changes precede motor changes in the cat and that pathologic findings precede the occurence of clinical signs. They [36] also concluded that, in the dying-back phenomenon produced by acrylamide, changes occurred first in the distal parts of axons but not necessarily at the nerve terminal.

(d) Mechanism of Action

Various theories are provided in the literature explaining the pathogenesis of selective axonal lesions from acrylamide. One explanation is that acrylamide interferes with the metabolic pathways of the nerve cell body which gradually fail in their functions to provide nutrient material for the axon [48]. This leads to a depletion in the amount of material reaching the distal regions of axons where degeneration begins. Another hypothesis suggests that acrylamide interferes with the intracellular transport system by which substances, assembled in the neuron cell body, are transported along the axon [49]. A third theory [44,50] notes that acrylamide may have local toxic effects along the entire axon and that axons are more vulnerable than the cell bodies [42].

Interruption of transport of proteins along axons could result in the breakdown of the axons. To test this hypothesis, Pleasure et al [49] measured flowrates of newly synthesized proteins within sensory and motor axons of 12 healthy cats for comparison with those in 9 cats showing neuropathies induced by acrylamide at a dose of 20 mg/kg orally for 5 days/week. Axonal degeneration, predominantly distal, was found in hindlimb nerves after neurologic signs had appeared but no alterations in the cell bodies of motor or of sensory neurons were evident. The flowrates

of axonal proteins in motor and in sensory nerves were determined in nine cats, including two controls, at intervals from 4 hours to 2 weeks after an ip injection of 3H-L-leucine. One day after injection of tritiated leucine, the radioactivity in the ventral roots of cats in both the control and acrylamide-treated groups was maximal adjacent to the spinal cord, while maximal radioactivity in the dorsal root bordered the ganglion. In acrylamide-treated cats killed 2 or more days after receiving the isotope, maximal radioactivity in all seven cats remained at the border of the ganglion in the dorsal root and in five of the seven at the edge of the spinal cord in the ventral root. Pleasure et al [49] demonstrated the existence of a protein fraction moving along axons from motor and from sensory neurons at about 1.5 mm/day. Evidence of such transport was absent in most of the cats made neuropathic by acrylamide. The authors [49] indicated that the absence of a migrating protein peak in acrylamide-induced neuropathy may have been from inhibition of protein synthesis or a defect in the transport mechanism. The accumulation of radioactivity close to the cell bodies in cats treated with acrylamide suggested that protein synthesis had occurred and that the defect was in the transport process itself.

In a subsequent report, Bradley and Williams [51] studied both the fast and slow components of axonal transport from dorsal root ganglia along the proximal regions of the sciatic nerve of cats with mild-to-moderate degrees of acrylamide neuropathy. Young cats of mixed breed, 1.5-4.25 kg in weight, were given acrylamide orally at a dose of 20 mg/kg/day, 5 days/week. The dose of acrylamide was adjusted to induce mild-to-moderate incordination and weakness of the hindlimbs in 2-6 weeks. Cats were

injected with 3H-L-leucine in the seventh lumbar dorsal root ganglion only on one side. Control animals were injected with 3H-L-leucine only. Three control and three acrylamide-treated animals were killed 6 hours, 10 days, or 30 days after injection of the tritiated leucine. Contrary to the findings of Pleasure et al [49], the authors [51] found no difference in slow axonal transport between acrylamide-intoxicated and control cats. There was a decrease in the velocity of the crest of fast axon transport in the acrylamide-treated cats, but they [51] suggested that this reduction was unlikely to be responsible for the degeneration present in the distal portions of the axon.

Hashimoto and Ando [52] examined the effects of acrylamide on the in vitro incorporation of radioactive amino acids into the proteins of brain, spinal cord, sciatic nerve, and liver tissues. Eight-week-old male Sprague-Dawley rats were fed a diet containing 500 ppm of acrylamide for 4 weeks and no acrylamide for the next 4 weeks. The control group was fed the untreated diet only. The animals given acrylamide began to show weakness of the hindlimbs at 2 weeks, slight disturbances in walking at 3 weeks, and paralysis at 4 weeks. After removal of acrylamide from the diet, the paralyzed animals recovered in 5-6 weeks. The incorporation of 14C-lysine into tissue proteins was studied at 1, 2, 3, 4, 6, and 8 weeks after acrylamide feeding was begun. No differences in the incorporation in the brain and liver slices of the control and acrylamide-treated rats were seen at any of these intervals. However, more radioactivity from labeled lysine was counted in proteins of the spinal cords of treated than of control rats after 4 weeks of feeding and the difference continued to increase, particularly in the lower cord, until 6 or 8 weeks. In the

sciatic nerve, a slight decrease in radioactivity was noted after 2 or 3 weeks, but was followed by a larger increase beginning at 4 weeks.

The effects of acrylamide on the incorporation of 35S-methionine into proteins were studied at weekly intervals from weeks 2 to 6 of feeding [52]. The incorporation by the controls was highest at all times in the sciatic nerve followed by the liver, brain cortex, and spinal cord. A significant increase in incorporation was demonstrated at 6 weeks after start of the feeding in the spinal cord and sciatic nerve, but not in the brain or liver. In contrast to the results obtained with lysine, when methionine was used, no decrease in radioactivity was seen in the sciatic nerve protein at the early stages. The early decrease in 14C-lysine incorporation in the sciatic nerve may have been associated with the biochemical mechanism of neuropathy, such as interruption of the protein axoplasmic flow in nerve roots as postulated by Pleasure et al [49], and the decreased metabolism of proteins in the axons and Schwann cells. The increased incorporation of amino acids into the spinal cord during the recovery period may have been because of increased protein metabolism in the anterior horn cells, in which a large number of silver grains from 14C-lysine were visible in the autoradiograph. The increased incorporation of amino acids into the sciatic nerve during the later stages of neuropathy might have been related to the proliferation and increased metabolism of Schwann cells, in which many silver grains were demonstrated. Since amino acid incorporation in the brain and in the liver was not affected by acrylamide, these authors [52] suggested that the compound had a specific effect on the spinal cord and peripheral nerves.

Hollinger and Rossiter [53], in their study on Wallerian degeneration of peripheral nerves, found that beta-glucuronidase activity in the sciatic nerve of 56 cats markedly increased during the regenerative phase of the injury. Kaplan and Murphy [47] measured sciatic nerve beta-glucuronidase activity in 24 acrylamide-treated rats. Male Holtzman rats, weighing 200-300 g, were administered acrylamide ip at a dose of 50 mg/kg/day for 8 days. There was a slight but significant rise in beta-glucuronidase activity of sciatic nerves 1 week after the last dose of acrylamide; the enzyme activity continued to increase, reaching a peak of 340% of the control values 3 weeks after the last injection. The greatest increase in enzyme activity occurred after apparent recovery from the neuromuscular impairment produced by acrylamide. The investigators [47] suggested that, if the acrylamide-induced increase of beta-glucuronidase activity in the peripheral nerve reflected peripheral nerve regeneration and hence incomplete healing, an increased sensitivity to acrylamide might have been anticipated during this period. Indeed, at 30 days, when beta-glucuronidase activity in the sciatic nerve of cats was 320% of the control values, rats were significantly more susceptible to acrylamide. The mean days of failure, as measured by a rotarod performance test, for rats retreated with 50 mg/kg/day of acrylamide and their age-matched controls were 2.5 and 4 days, respectively. Conversely, at 90 days, when beta-glucuronidase activity of the sciatic nerve was 155% of control values, no differences in rotarod performance between retreated rats and their age-matched controls were evident. If the increased beta-glucuronidase activity in the sciatic nerve observed after acrylamide-induced neuropathy reflects peripheral nerve regeneration, then the

increased susceptibility of rats to retreatment with acrylamide suggests the addition of a new injury to a preexisting injury that is not functionally apparent.

Hashimoto and Aldridge [38] studied the distribution and excretion of acrylamide in rats. Six male Porton-strain albino rats weighing about 200 g were injected iv with radioactive acrylamide at a dose of 100 mg/kg. The 14C-radioactivity was measured in the expired air and in the urine. About 6% of the injected dose was exhaled as carbon dioxide in the first 8 hours; excretion was very low after that (reaching only slightly more than 6% in 24 hours). Urinary excretion of the 14C-radioactive material was very rapid, 40% of the injected dose excreted over the first day and a maximum of about 65% reached by day 4; the excreted metabolites were not identified. The distribution of 14C-radioactivity was studied in whole blood, plasma, brain, spinal cord, sciatic nerve, liver, and kidney at 1, 4, and 14 days after injection. At each of these intervals, the radioactive material was found in all tissues examined, with high counts in the blood. A considerable amount of radioactivity was present at 14 days; most of it was not extractable by 5% trichloroacetic acid and so was presumably protein-bound.

Edwards [54] recently reported on the half-life of acrylamide in the blood of male Porton-strain rats weighing 200 g. Acrylamide dissolved in 0.9% saline was injected iv at a dose of 100 mg/kg. The drop in the blood concentration of acrylamide was exponential and its half-life was 1.9 hours.

Kaplan et al [55] studied the effects of hepatic microsomal enzyme inducers on the functional neuronal deficit produced by acrylamide. The

authors observed that pretreatment with either DDT or phenobarbital noticeably delayed the onset of neurologic deficit. The total dose of acrylamide required for 100% failure of control rats in rotarod performance tests was 360 mg/kg; it was 520 and 600 mg/kg for the DDT- and phenobarbital-pretreated animals, respectively.

Edwards [56] also investigated the effects of DDT and phenobarbital on acrylamide-induced neurotoxicity; however, the results obtained in this study were different from those reported by Kaplan et al [55]. Animals were fed a diet containing 500 ppm of acrylamide. Slight ataxia developed in the controls (receiving acrylamide only) and in both experimental groups after 8-10 days on the acrylamide-treated diet. All rats recovered at the same time after treatment. There were two major differences in the experimental procedures used by Kaplan et al [55] and by Edwards [56]. In the former study, acrylamide was given daily by single ip dose; in the latter, it was given in the diet. However, the calculated daily dose of acrylamide in the study by Edwards [56] was similar to that given by Kaplan et al [55]. The second major difference in the two studies was the method of assessing neurotoxicity. In the study by Edwards [56], it was subjective and depended upon personal observations, whereas Kaplan et al [55] used the rotarod performance test which they claimed was more sensitive than subjective analysis.

Correlation of Exposure and Effect

Humans have been exposed to the monomeric form of acrylamide both in occupational [16-21,23] and nonoccupational [22] situations. Workers have been exposed in the manufacture of the acrylamide monomer from

acrylonitrile acid hydrolysis [23]; in the handling of a 10% aqueous solution in a mine [16]; in the production of flocculators from the monomer [20]; in the use of a resin mixture that apparently contained residual monomer in sealing processes [17,18]; and in the production of polymers while manufacturing papercoating materials [21]. The exposure of a Japanese family to acrylamide-contaminated well water, which they drank, cooked with, and bathed in (the latter for a few days only) was the single nonoccupational incident [22].

In all of the occupational incidents [16-21,23], the dermal route of exposure was predominant, with some respiratory exposure and with slight oral ingestion possible through hand contamination [16-21,23]. An example of dermal exposure was one worker who repeatedly splashed a 10% aqueous solution of acrylamide on his unprotected hands, forearms, and face [16]. Other workers who were filling pumps or working in areas where there were leaks in the pressurized delivery system were splashed with a resin containing an unknown amount of monomers. In contrast to those exposures, workers in a flocculator plant where all skin contact was avoided exhibited no signs of intoxication [20]. The authors [20] also stated that the crystalline monomer was heavy (large particle size) and did not form stable aerosols. The vapor pressure of solid monomeric acrylamide is 0.007 mmHg at 25 C [1], equivalent to a saturation concentration of 27 mg/cu m, so acrylamide vapor may pose a hazard in confined or poorly ventilated spaces. The more likely inhalation hazard from acrylamide solution is from aerosolization of the solution.

Although signs and symptoms that developed in some workers who were exposed dermally to monomeric acrylamide have been well documented [19-

21,23], the exact time of the appearance of symptoms after dermal exposure was not. The times of onset that were reported varied from 4 weeks [20] to about 24 months [21] except for one worker [21] who was employed for approximately 8 years before symptoms appeared. Not all of the exposed workers had recognized adverse effects [16,19-21,23]. Initial symptoms after skin exposure were numbness [16,18,20-22], tingling (paresthesia) [18-22], and "tenderness to the touch," followed in days (or 1-2 weeks) by coldness of the hands and fingers, and less often of the feet and toes [16,18]. Concurrently, or occasionally somewhat later, excessive sweating [16-21], bluish-red skin on the hands [18-21,23], and peeling of the skin of the hands and less often the feet [16-21] were followed by fatigue and marked weakness of the limb muscles [16,19,20].

Skin absorption in mammals has been confirmed by Hashimoto and Ando [37], who found that absorption of 14C-acrylamide in rabbits was rapid. The 14C-acrylamide was found free in the blood and bound to protein, mainly hemoglobin, within hours of skin application, and in unidentified tissues in 24 hours. Successive dermal applications increased the blood and tissue levels. McCollister et al [34] also found that the rabbit skin absorbed acrylamide. They made dermal applications of 1 g/kg which killed one of two rabbits.

Many of the effects reported in humans have been confirmed in animals. Muscular weakness also occurred in rats [14,27], dogs [14], cats [34], monkeys [34], and baboons [31]. Weight loss was noted in humans [16,18-20], especially those who handled 10% aqueous solutions of acrylamide [16], rats [14,38,39], monkeys [34], and mice [33]. Sleepiness and lassitude preceded death in rats [14]; however, these effects were more

evident in those humans who ingested acrylamide-contaminated water [22] than in those dermally exposed. Another manifestation, which occurred in adults who ingested acrylamide, was retention of feces and urine that resulted in constipation and overflow urinary incontinence [20,22]. Distended urinary bladders were also reported in animals [27,34]. Reddened skin from dermal contact with acrylamide has been reported in humans [17] and in rabbits [34].

It is notable and in marked contrast to the reactions of those people who were occupationally exposed (mainly dermally) to acrylamide [17-20,23] that the initial complaints of those exposed by ingestion [22] were not directed toward the extremities or the skin. When symptoms of mild dysesthesia did occur by oral ingestion and probably also by dermal absorption, the three adults [22] had been hospitalized for emotional problems for 2-4 weeks.

Electromyography and nerve conduction studies were performed on humans before [21,23] and during [25] recovery from acrylamide intoxication. Muscle response to nerve stimulation was abnormal, indicating damage of distal nerve terminals [21]. Conduction velocity was affected in only a few units of each motor nerve [21,25]. Structural abnormalities were also found in the distal portions of the long nerves [25]. Because both the action potentials and conduction times in the sensory nerves were more extensively affected than in the motor nerves, the author [25] concluded that the sensory fibers were damaged earlier and more severely than the motor fibers.

Microscopic examination by Fullerton [25] of biopsied sensory nerves from two patients in the Garland and Patterson [20] study showed the

presence of simultaneous degeneration and regeneration of the sensory nerves which seemed to have occurred before the onset of symptoms. Neuroanatomic and physiologic studies [39,41,42,47,49,52,53,55] on animals, performed on a much more extensive scale than in humans, confirmed these results. Excretion of 14C-acrylamide and the effects of hepatic microsomal enzyme inducers on the toxicity of acrylamide also have been studied. While these results have added to the information concerning the effects of acrylamide on various life processes, they do not describe the initial process whereby acrylamide produces peripheral neuropathy in humans and animals.

Other important and diagnostic manifestations of the acrylamide effect on humans are: dizziness [17,20,21,23]; vertigo [23]; positive Romberg's sign and inability to stand on one leg [17,19-23]; slurring of speech [20]; confusion, insecurity, and bizarre behavior [22]; poor memory and orientation [22]; writing inability or difficulty [19]; muscle pain [18,20,21]; adiadochokinesis [23,34]; gastrointestinal disturbance and dysphagia [18,23]; loss of temperature and touch and vibration senses [16,20-22]; dysarthria [20]; and paresthesia, dysesthesia, and hyperesthesia [21,22].

In summary, in the absence of pertinent exposure data, no useful correlation can be made between the type and extent of exposure and the degree of human intoxication produced by acrylamide in the industrial environment [16-21,23-25]. However, the signs and symptoms, results of general medical and neurologic examinations, and the treatment and cure or regression of reactions reported in humans [15-23], including the nerve conduction and microscopy studies [21,25], when compiled and summarized,

are very valuable for the recognition of the sequence and characterization of adverse effects produced on humans by exposure to monomeric acrylamide. The animal studies also are pertinent in understanding human effects since they are very similar. In the single report of a nonoccupational episode [22] found, three of five family members were hospitalized after ingesting well water containing an acrylamide concentration of 400 ppm. Just how much each ingested is unknown. It is evident that effects on the CNS, rhinorrhea, and coughing were the first symptoms which were noticed by the people who ingested acrylamide, while those dermally exposed first noticed paresthesias, skin changes, and muscle weakness of the extremities. In all known recorded human cases of and in all types of exposures to acrylamide, persons recovered in 2 weeks-2 years (latter associated with peripheral nerve defects); most persons recovered in 1-12 months after cessation of exposure to acrylamide.

Carcinogenicity, Mutagenicity, and Teratogenicity

No reports which address the subject of possible carcinogenic, mutagenic, or teratogenic properties of acrylamide monomer were found.

Summary Tables of Exposure and Effect

The effects of dermal and oral exposures on humans to acrylamide that were presented in Chapter III are summarized in Table III-1. The effects of short- and long-term exposures on animals to acrylamide are summarized in Table III-2.

TABLE III-1

SUMMARY OF EFFECTS OF ACRYLAMIDE EXPOSURE ON HUMANS

Number of Subjects	Duration and Route of Exposure	Observed Effects	References
6	3 - 24 mo dermal and possible inhalation	Erythema, excessive sweating, muscular weakness	16-18, Brinkley*
8	3 - 13 mo dermal and possible inhalation	Loss of weight, anorexia	17-20, 23
6	4 - 7 mo dermal and possible inhalation	Eye irritation, skin rash, fatigue, confusion	16,19
7	2 mo - 8 yr dermal and possible inhalation	Gastrointestinal upset	21
5	1 mo ingestion	Rhinorrhea, urinary and fecal retention, ecchymoses	22
9	7 - 12 mo dermal and possible inhalation	Vertigo, abnormal reflexes, emotional changes	16,17, 19,23
4	3 - 24 mo dermal and possible inhalation	Ataxia, hypoesthesia	16-18

TABLE III-1 (CONTINUED)

SUMMARY OF EFFECTS OF ACRYLAMIDE EXPOSURE ON HUMANS

Number of Subjects	Duration and Route of Exposure	Observed Effects	References
17	1 mo - 8 yr dermal and possible inhalation	Pain, tremor, desquamation, sensory loss	16,17, 20,21
10	1 - 15 mo dermal and possible inhalation	Positive Romberg's sign	17,19, 20,23

*From DR Brinkley (written communication, June 1976)

TABLE III-2

SUMMARY OF EFFECTS OF ACRYLAMIDE EXPOSURE ON ANIMALS

Routes of Exposure	Species	Dose and Duration	Observed Effects	References
Dermal	Rabbits	0.5 - 1.0 g/kg 24 hr	Edema, death 1/5	34
"	"	10% solution 3 d	On abraded skin, slight reddening, edema	34
"	"	10% solution 2 wk	On shaved skin, no effects	34
Ocular	"	10 and 40% 24 - 48 hr	Pain, conjunctival irritation	41
Oral	Rats	203 - 277 mg/kg 1 dose	LD50, death 5/5	27,28,34
"	"	50 - 126 mg/kg 1 - 15 d	Lethargy, weakness, bladder distension	29
"	"	100 mg/kg 2 - 3 d	Death of most animals	14,27,29
"	"	0.3 - 11 mg/kg 55 - 189 d	No effects	27,34
"	"	200 - 400 ppm 1 - 6 mo	Loss of motor control, ataxia, leg weakness, progressive paralysis	14,27,29,34,56
"	"	100 ppm 6 - 40 wk	Growth retardation, leg weakness	27,34
"	"	10 - 50 ppm 6 wk	No effects	14

TABLE III-2 (CONTINUED)

SUMMARY OF EFFECTS OF ACRYLAMIDE EXPOSURE ON ANIMALS

Routes of Exposure	Species	Dose and Duration	Observed Effects	References
Oral	Mice	170 mg/kg 1 dose	LD50	14
"	"	250 ppm 45 d	Weight loss, ataxic gait	33
"	Rabbits	252 mg/kg 1 dose	Death 4/4	34
"	"	126 mg/kg 1 dose	Death 1/4; tremors, pupil dilation	34
"	Guinea pigs	252 mg/kg 1 dose	Death 4/4	34
"	"	126 mg/kg 1 dose	No deaths, slight weight loss	34
"	Cats	1 - 20 mg/kg 53 - 367 d	Weakness, paralysis, twitching	35
"	"	0.03 - 0.3 mg/kg 367 d	No effects	34
"	Dogs	5 - 100 mg/kg 4 - 5 wk	Ataxia, sedation, weakness	14,21
"	"	1 - 8 mg/kg 4 - 19 wk	No effects	14
"	Monkeys	10 - 30 mg/kg 8 - 10 wk	Weakness, decreased nerve conduction velocity, myelin and axonal degeneration	34,35
"	"	0.03 - 3 mg/kg 51 wk	No effects	34
ip	Rats	50 - 100 mg/kg 4 - 6 wk	Weight loss, paralysis, bladder distension, myelin and axonal destruction	38,39

TABLE III-2 (CONTINUED)

SUMMARY OF EFFECTS OF ACRYLAMIDE EXPOSURE ON ANIMALS

Routes of Exposure	Species	Dose and Duration	Observed Effects	References
ip	Monkey	100 mg/kg 2 d	Lung and kidney congestion, liver necrosis, severe weakness, death	34
iv	"	50 mg/kg 4 d	Death within 4 d	34
Subcutaneous	Cats	10 mg/kg 21 - 61 d	Ataxia, absent Achilles tendon jerks, interruption of nerve function	45
Oral ip iv im Subcutaneous	"	1 - 50 mg/kg (duration not specified)	Ataxia, progressive weakness, gradual blood-pressure drop to shock level; death of some animals	41

IV. ENVIRONMENTAL DATA AND ENGINEERING CONTROLS

Sampling and Analytical Methods

During industrial operations, monomeric acrylamide may escape into the environment as both dust and vapor from the solid and as a mist from aqueous solutions [57]. Little or no information has been found in the published literature on sampling methods for either acrylamide dust or vapor. However, the major manufacturers and users of monomeric acrylamide have provided some insight into a few sampling procedures. A direct readout method for analysis of airborne monomeric acrylamide dust and vapor has not been found.

One method for the sampling of acrylamide dust involving the use of a portable pump with an 0.8-μm membrane filter (open face) at an air flowrate of 2-3 liters/minute has been recommended for breathing zone sampling [58]. The minimum sampling time at a concentration of 0.3 mg/cu m was 30 minutes. No information is available on different concentration ranges over which this method is applicable. Unless the membrane filter is properly stored after sampling either by refrigerating or in a sealed cassette, sample loss by sublimation [1] could cause an error. Also, sampling with a membrane filter does not collect the vapor portion of acrylamide in the air and tends to underestimate the total exposure.

Adsorption of acrylamide on silica gel has been used for personal and general air sampling [59]. Two silica gel tubes with small glasswool plugs on each end were connected in series to a sampling pump. The flowrate was adjusted at 0.05-0.20 liters/minute. Acrylamide collected on the silica gel was extracted with water [59] or methanol-water (80:20 V/V) solution

[58] for analysis. There is insufficient information regarding concentrations that were tested, the concentration ranges over which this method is applicable, and a minimum sampling time. Although this method can be used for collection of acrylamide vapor, it probably does not collect acrylamide particulates efficiently. In addition, glasswool plugs at both ends of the tube would probably collect some dust particles since they are inefficient filters. In any case, this system is not useful for collection of total acrylamide in air.

Another method of sampling for determination of acrylamide vapor in air was developed by using a midget fritted glass bubbler [60]. The bubbler was filled to the 20-ml mark with distilled water and air was passed at a flowrate of 1 liter/minute for 100 minutes. Data concerning concentrations of acrylamide in the air that were collected are not available. However, the sampling adsorption efficiency of one bubbler with a flowrate of 1 liter/minute and a sampling period of 100 minutes was reported to be 98%, but without supporting data.

Midget impingers, as well as silica gel tubes, have been used to sample airborne dust and vapor of acrylamide [58,61]. Two midget impingers, each containing 15 ml of distilled water, were connected in series. The recommended sampling time was a minimum of 60 minutes with an air pump adjusted to a flowrate of up to 1.75 liters/minute [58]. It was indicated that this sampling method is applicable to any acrylamide monomer which may be present in the air in an industrial environment [58]. It was also stated that, since the sample size is essentially unlimited, the limit of detection of acrylamide in air is determined by the amount of interference present. Details such as efficiency of collection by the

impingers and concentration ranges over which this sampling technique is valid were not given.

A variety of sampling methods have been discussed, such as the portable pump with a membrane filter, silica gel tube, midget fritted glass bubbler, and midget impingers. There is no one method that is uniquely applicable for collecting acrylamide aerosol and vapor. A membrane filter has been used to collect samples of acrylamide aerosol and the midget fritted glass bubbler has been used for determinations of acrylamide vapor in air. Silica gel tubes and midget impingers can be used to collect both dust and vapor with the latter method having less vapor loss. Therefore, despite the disadvantages of handling glassware and liquid solutions in field measurements, the sampling technique of using a midget impinger is recommended for personal breathing-zone sampling of airborne acrylamide dust and vapor to guard against losses attendant with filter sampling.

Samples of acrylamide in air have been analyzed by using spectrophotometry [62], gas chromatography [60,63], refractive index measurement [64], titration using bromate-bromide solution [65], thin-layer chromatography [63], direct current (DC) polarography [66], and differential pulse polarography (DPP) [67].

Mattocks [62] reported on spectrophotometric methods which involve the formation of pyrazoline by reacting monomeric acrylamide with diazomethane in a methanol-ether solution. The formed pyrazoline yields a bright yellow derivative with acidic Ehrlich reagent (4-dimethylaminobenzaldehyde) and a more stable, purple-colored complex with 4-dimethylaminocinnamaldehyde; the yellow and purple colors are measured at 440 and 538 nm, respectively. The working range for

both assays was 0.2-2.0 μg/ml of acrylamide. One disadvantage of these methods is working with diazomethane, a suspected carcinogen [62] which has to be redistilled shortly before use to eliminate impurities. In addition, the color formation in the reaction of pyrazoline and either 4-dimethylaminocinnamaldehyde or 4-dimethylaminobenzaldehyde is subject to interference from pyrroles, indoles and related compounds, aromatic amines, hydrazine, and carbonyl compounds.

Analysis of monomeric acrylamide solutions was also determined by measuring the refractive index of a sample solution at 35 C with an Abbe refractometer and converting the reading to percent acrylamide using a standard curve [64]. Duplicate determinations were within 0.4% and the method could be applied for an aqueous acrylamide solution range of 5-60%. The usual concentration range of acrylamide monomer solutions in previously discussed analytical procedures is much lower than 5% and lacks specificity and sensitivity for a determination of acrylamide at the environmental limit.

A more sensitive, but nonspecific, analysis of monomeric acrylamide solutions can be performed by a titrimetric method [65]. This method was based on the reaction of acrylamide with bromine which is obtained from an acidified bromate-bromide solution. The excess bromine was treated with potassium iodide which generates free iodine. The iodine was then titrated with thiosulfate to yield an indirect measure of acrylamide. Any reducible substance may interfere with this method. The titrimetric method gave a relative standard deviation of 0.1 and 0.01% for concentrations above and below 2% of acrylamide in solution, respectively.

Acrylamide vapor in air was collected with a bubbler and subsequently analyzed by gas chromatography after formation of a 1,2-dibromopropionamide derivative [60]. This method was used over a concentration range of 0.005-0.160 mg/cu m over a 100-liter air sample. Contents of a bubbler diluted with sulfuric acid solution from a fritted glass midget bubbler containing monomeric acrylamide were brominated with excess bromine water, irradiated with UV light, and an ether extract was injected into a gas chromatograph and detected by electron capture. No information was reported on interferences. The conversion efficiencies from the monomer to the derivative are unknown. However, the concentration range was well within limits to test adequately for the Threshold Limit Value of acrylamide (0.3 mg/cu m). Use of bromine water and UV irradiation to form the derivative along with the steps involved in sample preparation, such as the adjustment of pH and the extraction process, are disadvantages of this method, but they are within the technical capabilities of most laboratories.

Croll [63] determined the acrylamide content in polymers and copolymers by analyzing a methanol-water (80:20 V/V) extract with a gas chromatograph. A 20% W/W Carbowax 20 M on 60/80 mesh Chromosorb W-acid-washed, dimethyldichlorosilane column was used. The sensitivity of this method for acrylamide is 4 μg in 10 ml of methanol-water extract. Extracts from some of the polymers studied contained compounds (unspecified) which had similar retention times as acrylamide. Buildup of nonvolatile compounds in the injection zone affected the column performance. These compounds made discrete acrylamide determinations impossible without further purification of the extracts. Infrared spectroscopy and thin-layer chromatography were used to confirm that peaks from the gas chromatographic

analysis tentatively identified as acrylamide were in fact from acrylamide. To prepare for infrared spectroscopy, a portion of the polymer extract equivalent to about 2 mg of acrylamide was evaporated to dryness onto potassium bromide and pressed into a disc. The infrared spectrum of this sample was so intense that other contaminants were obviously interfering. After the sample was separated by thin-layer chromatography and the acrylamide portion of the chromatogram removed with methanol, the potassium bromide disc prepared from the extract gave an infrared spectrum identical to that of the pure acrylamide standard. Direct infrared analysis is subject to interferences from unspecified contaminants from the polymers. Another disadvantage of the method is the large amount of acrylamide required for measurement.

Thin-layer chromatography was used to evaluate the acrylamide content in polymers extracted with acetone or a chloroform-methanol (80:20 V/V) solution [63]. Acrylamide was determined chromatographically on silica gel plates. The spots on the plates representing acrylamide were made visible by spraying with either a fluorescein-bromine reagent or 0.01% potassium permanganate reagent which produced yellow spots on a pink background plates for samples containing as little as 0.25 μg of acrylamide. The eluates of the sample scraped from the plates were analyzed by gas chromatography giving a 90% recovery of the acrylamide standard.

MacWilliams et al [66] used direct current (DC) polarographic techniques for analysis of monomeric acrylamide in polyacrylamides. The procedure involved the use of a mixed methanol-water (80:20 V/V) solution for the extraction of the monomer from the polymer. The extract was then polarographically analyzed using the supporting electrolyte tetra-n-

butylammonium hydroxide. The concentration range over which this method is sensitive was 0.01-0.5% acrylamide in polyacrylamides. The authors were able to detect acrylamide concentrations as low as 100 ppm. As long as potentials were carefully corrected for cell resistance and the acrylamide concentration was kept below 0.5 mg/ml in the extract, the DC polarographic technique was reliably accurate. Low monomer concentrations made the acrylamide wave difficult to resolve from the background.

Betso and McLean [67] adopted the polarographic technique to detect and determine monomeric acrylamide in polyacrylamides by using differential pulse polarography. The extraction procedure was similar to that of MacWilliams et al [66] except that the electroanalytical chemical instrumentation has improved since 1965. A methanol-water solvent extract of the polyacrylamides was treated with an ion-exchange resin to remove interfering cationic and anionic species. After appropriate pH adjustments, the resin-treated extract was polarographically analyzed with the supporting electrolyte, tetra-n-butylammonium hydroxide. The polarographic cell consisted of a dropping mercury electrode as the cathode and a platinum wire auxiliary electrode as the anode. Recovery of acrylamide in the polyacrylamides was reported to be greater than 90%. The detection limit for acrylamide was less than 1 μg/ml. However, the presence of some nonionic species, substituted acrylamide, or acrylates would be electroactive in the same potential region as that of acrylamide and would thus interfere with polarographic acrylamide analysis. Acrylonitrile also interfered but, because of its high volatility, it was purged readily by nitrogen from the solution with no adverse effects on acrylamide concentration. Acrolein, acrylic acid, acetone, vinyl-benzyl

chloride, vinyl-benzyl alcohol, styrene, and beta-hydroxypropionitrile did not interfere in polarographic analysis of acrylamide. Resin treatment of the methanolic extract of polyacrylamide for 20 minutes removed the ionic species, such as sodium and potassium ions, without causing any detectable loss of acrylamide concentration.

The analysis of monomeric acrylamide by differential pulse polarography has been adapted for determining airborne acrylamide [58]. The sampling solution for dust and vapor from impingers was analyzed for acrylamide polarographically after ion-exchange resin treatment and the addition of the supporting electrolyte tetra-n-butylammonium hydroxide. No information on the accuracy or the precision for this analytical method was provided. The method was claimed to be reasonably specific for acrylamide and to have relatively few interferences. It was also reported that an acrylamide concentration as low as 0.5 μg/ml could be determined by analysis.

A major factor for identifying the most appropriate analytical technique for acrylamide is the sensitivity of the instrumentation. It appears that gas-chromatographic analysis [60,63] of acrylamide in a methanol-water extract and of 1,2-dibromoproprionamide (derivative of acrylamide) yields sensitivities of 0.400 μg/ml [63] and a working concentration range of 0.005-0.160 mg/cu m [60]. The sensitivity for differential pulse polarography was less than 1 μg/ml for the detection and determination of acrylamide in polyacrylamides [67]. The differential pulse polarography adopted for determining airborne acrylamide dust and vapor concentrations has a reported sensitivity of 0.5 μg/ml of impinger solution [58]. Since both the polarographic and chromatographic analyses

have sensitivities in the microgram range, these analytical methods are applicable to measure acrylamide air concentrations down to 0.15 mg/cu m of acrylamide. However, the gas-chromatographic method involves a complex number of steps for derivative formation and sample preparation, therefore reducing reliability and reproducibility. The efficiencies of bromination and subsequent irradiation are also unknown. Therefore, differential pulse polarography is recommended as the method of choice for the determination of acrylamide.

Environmental Levels

No published information has been found on atmospheric concentrations of acrylamide in industry. Two companies have supplied NIOSH with the results of air sampling data taken at their plants.

Clyne (written communication, July 1976) reported on sampling performed in the breathing zone of workers who wore respirators and were exposed in the acrylamide operation. The results of the 4-hour samples for two packers, the reactor operator, and the dryer operator were 0.22 ppm (0.76 mg/cu m), 0.15 ppm (0.52 mg/cu m), 0.14 ppm (0.48 mg/cu m), and 0.15 ppm (0.52 mg/cu m), respectively.

The Vistron Corporation (DR Brinkley, written communication, June 1976) supplied information on stationary sampling sites of an acrylamide manufacturing plant. Eight-hour samples were collected in water containing impingers and analyzed by a colorimetric method using a ferric chloride reagent. The sampling was begun in January 1971 for the control room and bagging room and in June 1974 for the second-floor processing area. The sampling continued until May 1975. The data were presented as weekly

averages and ranged from 0.1 to 0.4 mg/cu m for the control room, 0.1 to 0.9 mg/cu m for the bagging room, and 0.1 to 0.4 mg/cu m for the second-floor processing area. The stationary air monitoring was reported not to be representative of worker exposure and, therefore, exposure concentrations were estimated from the time each employee worked in the three areas where stationary air monitoring was done. These calculated concentrations usually did not exceed 0.3 mg/cu m during normal operation.

Limited personal monitoring was performed in one plant from late 1974 until June 1975. Two methods were used for collecting acrylamide samples, ie, an 0.8-μm cellulose acetate membrane filter and sodium carbonate. No other specific information was given. The limited personal monitoring data indicated that the actual exposure concentrations were two to three times higher than those of the stationary sites. Table XII-3 shows these data.

Engineering Controls

In the industrial manufacturing of monomeric acrylamide and in the production of its polymers and copolymers, both the solid and aqueous forms of acrylamide are encountered [1,68], the solid having a vapor pressure of 0.007 mmHg at 25 C [1]. The saturated vapor concentration in air for solid acrylamide monomer under standard conditions is estimated to be 27 mg/cu m. During industrial operations in which acrylamide is used for polymerization, both vapor and particulate forms of acrylamide are, and should be, monitored [57 (pp 47-48)]. Concentrations and relative percentage data are not available. The control of exposure to acrylamide should therefore emphasize engineering designs which prevent the escape of

both vapor and dust into the environment.

Any line system or storage vessel necessary for the transfer, maintenance, or manufacture of solid or aqueous acrylamide should be enclosed, ventilated, and have other engineering controls, preferably automated systems, to provide a healthful work environment to minimize worker exposure to acrylamide [57 (pp 133-36)]. In the handling of aqueous acrylamide, skin and eye contact must be prevented. A closed system may be the best way to accomplished this. The liquid should be transferred in a closed-line system from the storage vessel to the polymerization reactor [57 (p 133)]. Closed systems that are properly designed, operated, and maintained should be used, where practical, for the containment of vapor and dust from acrylamide. The conventional method of filling storage tanks or reactor vessels manually with the solid or aqueous acrylamide monomer should be replaced with an automated, enclosed, or ventilated system [57 (pp 133-36)]. Strict engineering controls should minimize skin contact and inhalation hazards associated with acrylamide exposure.

If closed systems are not feasible, local exhaust ventilation should be provided. Guidance for proper design can be obtained in Industrial Ventilation--A Manual of Recommended Practice [69], or more recent revisions, and in ANSI Z9.2-1971 [70]. All ventilation air that contains acrylamide vapor or dust or has contacted solid acrylamide shall be controlled to meet with EPA and local air standards; exhaust air shall not be recirculated into the workplace [57 (p 59)].

Engineering controls should be complimented with good work practices for more effective control of exposure to acrylamide. Respiratory

protective equipment should not be used as a substitute for proper engineering controls but must be worn when the worker is exposed to dust or vapor concentrations exceeding the environmental exposure limit.

V. DEVELOPMENT OF A STANDARD

Basis for Previous Standards

The acrylamide environmental limit was first introduced in 1966 in the United States by the American Conference of Governmental Industrial Hygienists (ACGIH) as a tentative Threshold Limit Value (TLV) of 0.3 mg of acrylamide/cu m of air with the notation "Skin" [71]. This designation is intended to suggest the need for appropriate measures for the prevention of dermal or other local contact or absorption. The tentative TLV of 0.3 mg/cu m was adopted as the recommended value by the ACGIH the following year [72], and has remained unchanged since 1967 [73].

According to the 1971 (third) edition of Documentation of the Threshold Limit Values for Substances in Workroom Air [74], the basis for the ACGIH TLV was extrapolation from long-term feeding experiments on cats reported by McCollister et al [34] in 1964. The oral LD50 for laboratory animals (rats, guinea pigs, and rabbits) was in the range of 150-180 mg/kg and the document [74] further stated that "toxic effects may be produced by any route of administration--ingestion, inhalation, injection, skin contact, or contact with the eye." The cat was described in this document as the most sensitive species. Cats given acrylamide at a dose of 1 mg/kg/day by iv or ip injection developed the neurologic effects in about 6 months; however, long-term feeding experiments (0.3 and 1 mg/kg/day, 5 days/week, for 1 year) in this same species apparently did not produce any ill effect. From the results of long-term feeding experiments in the most sensitive species, the cat, the ACGIH recommended "that no more than 0.05

mg/kg/day be absorbed by workmen" [74].

According to this 1971 ACGIH Documentation of TLV's [74], an absorption of 0.05 mg/kg/day, assuming a ventilation rate of 10 cu m of air for each 8-hour workday, corresponds to an environmental limit of 0.3 mg/cu m, or about 0.1 ppm. The present federal standard for acrylamide, 0.3 mg/cu m as a TWA concentration with the notation "Skin" (29 CFR 1910.1000), is based on the 1968 ACGIH Threshold Limit Value.

According to a 1968 joint report of the International Labour Office and the World Health Organization [75], no standards for acrylamide had been promulgated by countries other than the United States.

Basis for the Recommended Standard

The studies of human intoxication with acrylamide have indicated that dermal absorption [16-18,20,21,23] and ingestion [22] have been the main routes of exposure without, however, ruling out the possible contribution of inhalation of aerosol or vapor. In addition, the airborne form of acrylamide (vapor or aerosol) has not been positively identified. Little information has been found on the acrylamide concentrations to which people are occupationally exposed [16-21,23], much less the airborne concentrations of acrylamide that have caused adverse effects (DR Brinkley, written communication, June 1976). However, data obtained from Vistron Corporation (DR Brinkley, written communication, June 1976) showed that airborne concentrations of acrylamide ranged from 0.1 to 3.6 mg/cu m for personal monitoring and from 0.1 to 0.3 mg/cu m for stationary sites at an acrylamide manufacturing plant. No information was presented in this report to correlate personal monitoring data with the incidence of skin

peeling. The author indicated that a correlation existed between skin reactions and airborne acrylamide concentrations obtained from stationary site data in the plant. In addition to these airborne concentrations of acrylamide, Brinkley stated that two employees experienced neurologic symptoms and initial symptoms of erythema and skin peeling were noted in almost every employee who was working in the acrylamide plant.

Garland and Patterson [20] reported six human cases of occupational acrylamide intoxication. The duration of exposure before the onset of symptoms varied from 4 weeks to 13 months. Though no solid or aqueous acrylamide concentrations to which people were dermally exposed was reported, most of the patients showed excessive sweating, weakness, and skin peeling as initial signs of toxicity. In another occupational dermal exposure study, Auld and Bedwell [16] described a 21-year-old worker who came into contact with a 10% aqueous solution of acrylamide. The patient showed hand and leg muscle weakness as the first symptom of acrylamide intoxication. The authors [16] reported that another worker stopped work because of tiredness and skin rashes. After 2 weeks, he was able to return to work with no complaints. The other occupational incidents of monomeric acrylamide intoxication were reported by Cavigneaux and Cabasson [18], Graveleau et al [17], and Morviller [19] in France and by Fujita et al [23] and Takahashi et al [21] in Japan. However, all of these reports on human effects are qualitative and deal only with clinical signs and symptoms of acrylamide intoxication.

Igisu et al [22] described a nonoccupational exposure to monomeric acrylamide in a family of five persons who used acrylamide contaminated well water for cooking, drinking, washing, and bathing. Three adults in

the family showed signs of CNS toxicity manifested by ataxia. This was followed in 2-4 weeks by symptoms of peripheral neuropathy. The well water was analyzed by gas chromatography and shown to contain 400 ppm of acrylamide and a trace of dimethylaminoproprionitrile. Although slightly more quantitative information was presented in this report than in the reports on occupational exposures [16-21,23], no information is available which would allow estimation of dermal or airborne exposure limits from this report.

There is abundant documentation that experimental administration of acrylamide has produced peripheral neuropathy in many animal species: hens [56], rats [27,38,39], mice [33], cats [34-36,41], dogs [14,30], baboons [31,32], and monkeys [34]. There is some evidence that acrylamide, at a higher dose than that necessary to produce peripheral neuropathy, has caused damage to the CNS of a baboon [32]. Hamblin [14] reported that neurotoxic effects of acrylamide were dose dependent and cumulative, similarly Kuperman [41] found that the CNS effects of acrylamide depended on the dose magnitude, rate of administration, and the length of time during which it was administered in cats. The author [41] did not find any differences in the chronic effects of acrylamide when given by different routes. Kuperman [41] stated that whether the route was iv, ip, im, oral, or subcutaneous, the characteristic effects of chronic poisoning appeared at identical dose levels and after equivalent latencies.

Hashimoto and Ando [37] and McCollister et al [34] have described studies in which acrylamide was applied dermally. Hashimoto and Ando [37] demonstrated the dermal penetration of a 10-30% solution of acrylamide which subsequently appeared in the blood. In rabbits, application of

aqueous solutions of acrylamide (10 and 12.5%) killed one of two rabbits at a dose of 1 g/kg and resulted in slight toxicity at 0.5 g/kg [34]. McCollister et al [34] also studied the effects of 10 and 40% aqueous solutions of acrylamide instilled into the eyes of rabbits. The 10% aqueous solution caused signs of slight pain and slight conjuctival irritation, while the 40% aqueous solution caused moderate pain, slight conjunctival irritation, and marked corneal injury.

McCollister et al [34] found that acrylamide in the feed at 0.3 mg/kg/day, 5 days/week, for 1 year produced no adverse effect on cats. A dose of 1 mg/kg/day caused questionable effects, whereas the higher doses of 3 and 10 mg/kg/day resulted in definite signs of neurotoxicity. The authors [34] found that one monkey fed with 0.1 mg/kg/day, two with 0.3 mg/kg/day, and one with 1 mg/kg/day, 5 days/week, for one year also showed no adverse effects. However, 3 and 10 mg/kg/day levels did cause signs of neurotoxicity in monkeys. The authors [34] concluded that the "no adverse effect" level for monkeys on a diet containing acrylamide lay between 1 and 3 mg/kg/day. It was the authors' [34] suggestion that the summation of industrial exposures should be so controlled that it will be almost impossible for a worker to absorb more than 0.05 mg/kg/day of acrylamide on a day-to-day basis. As previously stated, studies of human intoxication with acrylamide have indicated that dermal contact and ingestion may have been the main routes of exposure without neglecting the possible contribution of inhalation of aerosol or vapor. Consequently, without knowing the airborne acrylamide concentrations at which skin and neurologic symptoms manifest themselves, and also in the absence of information as to the primary routes of exposure, ie, dermal, inhalation, or ingestion, by

which these symptoms may be produced, it is difficult to correlate dermal or neurologic symptoms with worker exposure to airborne acrylamide. The available human and animal studies do not provide enough information to alter the existing federal standard for acrylamide of 0.3 mg/cu m of air as a TWA value. NIOSH, therefore, recommends that the present federal standard be kept.

Several human [16-18,20,21,23] and animal [34,37] studies reported that dermal exposure of monomeric acrylamide produced skin peeling, eye irritation, and signs of neurotoxicity. Thus, a medical surveillance program should include preplacement and periodic medical examinations that give attention to nervous system, skin, and eyes. Medical attention should be provided to workers accidentally overexposed to acrylamide. Personnel occupationally exposed to acrylamide must be warned and advised of the adverse effects of accidental overexposure and must be informed of the symptoms of the disorders and that they may be delayed in onset. If eye contact occurs, the affected eye should be immediately flushed with water and examined by a physician. Each worker's fingers should be examined by medical, paramedical, or other properly trained personnel. Workers should be informed of the importance of this examination.

A continuing education program is an important fact of a preventive hygiene program for employees exposed to hazardous materials such as acrylamide. Workers should be periodically apprised by properly trained persons about the possible sources of acrylamide exposure, the adverse health effects associated with excessive exposure to acrylamide, the engineering and work practice controls in use and being planned to limit exposure to acceptable concentrations, and on environmental and medical

monitoring procedures used to check on control procedures and on the health status of employees. The types and functions of monitoring equipment, such as personal samplers, should be explained so that each employee understands his or her part in environmental monitoring.

Because dermal contact by acrylamide induced skin irritation and neuropathy in humans and animals, care must be exercised to ensure adequate protection against contact with acrylamide. Personal protective clothing and respiratory protective equipment should be available and worn where indicated. Work practices that prevent skin and eye contact must be followed. Showers and eyewash fountains must be available for immediate use if accidental contact occurs.

Engineering controls must be used whenever feasible to control airborne concentrations of acrylamide monomer within the recommended TWA limit. Where acrylamide monomer is present, a closed system of control should be used. During the time required to install adequate controls and equipments, to make process changes, to perform routine maintenance and operations, or to make repairs, overexposure to acrylamide can be prevented by the use of respirators and protective clothing and in some cases by administrative controls.

Because acrylamide produces delayed neuropathy, it is recommended that all medical and other pertinent records involving acrylamide exposure be maintained for 20 years after termination of employment. This will allow enough time for future detection of chronic neurotoxicity of acrylamide which may be related to the employee's known occupational exposure.

The technology is currently available to sample and analyze the present environmental limit to institute appropriate engineering controls. As was discussed in greater detail in Chapter IV, a midget impinger is recommended for personal breathing zone sampling of airborne acrylamide aerosol and vapor to guard against losses attendant with filter sampling. Current analytical techniques commonly used for the determination of acrylamide in the industrial environment are differential pulse polarography and gas chromatography. As was discussed in Chapter IV, differential pulse polarography is the analytical method of choice for airborne acrylamide since gas chromatography involves complex derivative formations of unknown efficiencies and sample preparation.

Concern for worker health requires that protective measures be instituted below the enforceable limit to ensure that exposures stay below that limit. An action level is set as a TWA concentration of one-half the environmental limit. It has been chosen on the basis of professional judgment rather than on quantitative data that delineate nonhazardous areas from areas in which a hazard may exist. However, in the case of acrylamide it is also recognized that many employees work with solid or liquid forms of the substance in situations where there may be skin contact with the substance resulting in dermal or systemic effects. Consequently, appropriate work practices, training, and other protective measures should be required regardless of concentrations of acrylamide in air. Therefore, occupational exposure to acrylamide has been defined as work in an area where acrylamide is stored, produced, processed, or otherwise used, except as an unidentified contaminant in other material at a concentration of less than 1% by weight. Under these conditions, all provisions of this

recommended standard except environmental monitoring and associated recordkeeping should be complied with; in work areas where the action level is exceeded, this requirement (Section 8) should also be complied with.

VI. WORK PRACTICES

Occupational exposures can occur in the manufacture of solid forms of acrylamide [19,23], in the preparation and utilization of aqueous solutions of acrylamide [16], in the polymerization process [20], and in the handling of polymerized products which contain the residual monomer [17,18].

The conventional way of cutting bags of solid monomeric acrylamide manually with a knife and dumping the pellets or flakes into the reactor for polymerization should be replaced with a method that limits exposure to acrylamide. One method that has been used is a mechanized, maximally enclosed, or ventilated system [57 (p 135)]. The only manual step in this process involves placing the bags on the cutter; the rest is handled mechanically. The bags are cut open automatically and the solid acrylamide is dropped by gravity into the hopper of a bin. Any dust or vapor may be controlled by a canopy-type local exhaust ventilation and trapped by a filter. The empty acrylamide bags are transferred on a moving conveyor to a compressor, where they are compacted and automatically inserted into plastic bags for disposal. There is less chance of acrylamide escaping in this system if the hopper is connected directly to the reactor.

The trend of some manufacturers to replace solid crystalline forms with aqueous solutions of monomeric acrylamide has warranted special work practices in handling the liquid form. Because of the high dermal hazard of the aqueous solution of acrylamide, liquid acrylamide should be transferred from the truck to the storage tank and from the tank to the reactor in closed-line systems [57 (pp 134-35)]. If pressure buildup is a problem, then the tank should be equipped with an alarm system to signal

any internal pressure buildup so that corrective measures or evacuation of the area may be accomplished as needed [57 (p 135)]. Filters installed on top of the storage tanks should be routinely checked and replaced as necessary. Safety features on the tanks should also be checked regularly and corrected when found defective. Precautions should be taken for line opening and tank entry [57 (pp 58-59),76]. Before opening up a line, the worker or workers should set up a barricade to isolate the area and check the condition and location of the nearest eyewash fountain and safety shower. All workers involved in this operation must be supplied with whole body protection, including air-supplied respirators (self-contained or airline). This protective equipment should be worn when entering the tank unless it is known that entry into the tank is safe. A second properly protected worker must be on standby outside the tank [76].

In addition to sound engineering controls, work practices should emphasize personal protective devices, good housekeeping, and personal hygiene. To minimize dermal contact with solid or liquid acrylamide, all workers and nonworkers entering work areas should wear protective clothing including long-sleeved coveralls, head covering including face shield (8-inch minimum), protective footwear, and impervious gloves or neoprene gloves with cotton liners [57 (p 6)]. Soiled protective clothing provided at the beginning of each work shift should be left in bins at the workplace for laundering after work. Protective and personal clothing should be kept in separate lockers [76].

If there is any chance of skin contact with acrylamide, then the protective clothing worn should be impervious to acrylamide. At the present time, the suitability of impervious clothing for the protection of

the worker has not been adequately established. In addition, it is difficult for workers to wear this clothing for extended periods of time. These factors emphasize the need for showers, eyewash fountains, and proper engineering controls.

Protective clothing and some polyvinyl chloride (PVC) coated gloves have shown a wide variation of permeability to acrylamide [77]. Of the different types of gloves tested for resistance to penetration in an 8-hour test period from a 50% acrylamide solution, the Edmond Snorkel Vinyl-coated glove has been reported to have low permeability to acrylamide, whereas PVC-coated gloves have proven to be more permeable to acrylamide. Therefore, to ensure employee protection against dermal acrylamide exposure, all protective clothing and glove types should be first tested for their permeability to acrylamide before being worn. For further dermal protection against acrylamide, all protective clothing should have a cotton lining for comfort.

Impervious gloves with separate cotton liners and impervious long-sleeve overalls must be worn when handling equipment or containers used in acrylamide operations. The gloves should be either gauntlet type or long enough to overlap the sleeve [57 (pp 48-51),78]. A supply of these gloves should be on hand in the workplace. After work, the outside of the gloves must be washed before removal from the hands; if contaminated on the inside, hands must be washed immediately and the gloves should be replaced by a clean pair. Since eye irritation has been reported in acrylamide operations [1] and acrylamide is volatile [1,3,4], chemical safety goggles [76] should be worn in operation areas. Face shields are required in addition to chemical safety goggles during line openings involving liquid

acrylamide [76]. Eyewash fountains and emergency showers also should be available in acrylamide work areas [57 (p 6)]. It has been reported [3] that acrylamide monomer is neither an explosion nor a fire hazard when stored at room temperature.

Solid acrylamide wastes, including compressed contaminated bags, drums, drum liners, or containers should be disposed of either by burial in an approved landfill away from drinking water sources or by burning in an approved industrial incinerator [76]. Decontaminated liquids or any aqueous acrylamide waste solutions should be drained to a sump for subsequent treatment by an approved facility.

Good housekeeping must be instituted to minimize the hazards of acrylamide inhalation. Floors constructed of concrete in operation areas should be sealed with a layer of impervious material to prevent the trapping of acrylamide that may otherwise occur and to facilitate the removal of spills [57 (p 135)]. Certain types of epoxy resin floors are the most impervious to acrylamide penetration [77]. Thorough testing should be conducted to investigate varying degrees of acrylamide penetration through the epoxy resin floor covering before any epoxy resin or other material is used as an impervious floor covering. Coroline 505 (an epoxy resin) is said to have a high degree of resistance to acrylamide penetration as a concrete floor covering. Other floor covering formulations may also be effective. When spilled, solid acrylamide should be either wet vacuumed or mopped up immediately and deposited in a covered drum [57 (p 135)]. One quart each of 1.6% potassium persulfate solution and 1.6% sodium metabisulfite solution should be mixed and used to decompose each pound of acrylamide in the drum [57 (p 22)]. After 30

minutes, the contents of the drum should be properly disposed of. The residual acrylamide on the floor should be mopped with a mixture of 3 gallons each of potassium persulfate and sodium metabisulfite for every 250 square feet of floor area and the liquid residue should be properly disposed of. Any acrylamide spilled on the surface of equipment should be removed and transferred to a covered drum and treated as described for floor spills. Contaminated equipment surfaces should be washed with a mixture of potassium persulfate (1.6%) and sodium metabisulfite (1.6%) solution by a worker wearing impervious long-sleeve overalls and rubber gloves. The floor area adjacent to contaminated equipment should be treated with the mixed solution.

Good sanitation and personal hygiene practices should minimize the risk of acrylamide ingestion. Hands should be washed before drinking, eating, or smoking. Food and beverages consumption or smoking should not be allowed in any acrylamide work or storage areas. Showering is recommended after each work shift [57 (pp 6,46)] before leaving the workplace where acrylamide is handled.

For emergency conditions such as spills and leaks, full body protection, including an air-supplied respirator, must be worn [76]. If the eyes come into contact with acrylamide, they should be immediately flushed with low-pressure flowing water for at least 15 minutes. Any skin contacting acrylamide should be immediately washed with soap and flowing water. Vomiting should be induced if acrylamide is ingested and the worker is conscious. A physician should be contacted immediately. Employees, physicians, and other medical attendants should be informed of the possibility of delayed neurologic effects. All employees should be trained

and verbally informed about accident and first-aid procedures and use of respirators. They should also be informed of the hazardous areas, with special instruction given to illiterate employees.

VII. RESEARCH NEEDS

Two routes of entry, dermal and inhalation, are of major concern in occupational exposure to acrylamide. Only two animal study reports have briefly described the absorption [37] and toxicity [34] aspects of acrylamide after dermal applications. No inhalation studies on humans or animals have been found to date. The toxicity in animals of acrylamide administered by dermal and inhalation routes should be investigated as this chemical exists as an aerosol or vapor in the industrial work environment. Such studies should involve investigation of both short- and long-term effects.

No epidemiologic report on acrylamide has been found in the literature to date. Such studies are needed to provide information on occupational exposures to acrylamide and to determine the relationship between airborne concentrations and observed effects on humans. No human or animal studies have been found in the literature regarding the possibility of carcinogenic, mutagenic, or teratogenic or other reproductive effects of acrylamide. However, Hashimoto and Aldridge [38] have observed a low level of incorporation of iv-administered 14C-acrylamide in the DNA and RNA of rat brain and liver. These observations and the fact that acrylamide bears a structural resemblance to other biologically active compounds, including a known carcinogen, vinyl chloride, would suggest that acrylamide may produce mutagenic or carcinogenic effects in mammaliam systems. However, there is insufficient information to draw any conclusion at this time. Research efforts should be initiated in these areas to answer these important questions. Studies

are now being conducted by NIOSH to investigate any mutagenic potential of acrylamide.

Although the effects of acrylamide on the CNS are suggested by the results of human [21,22] and animal [39,42,52] studies, the extent and reversibility of the changes after short-term exposure, and the structural damage after prolonged, low concentration exposure are not clear at this time. Further research is therefore indicated in this area. Except in a few studies [34,47,55], acrylamide has been used by various workers as a tool for investigating its mechanism of action in causing peripheral neuropathy in experimental animals. Toxicologic information on other physiologic systems (such as cardiovascular, renal, hepatic, and pulmonary) is lacking. Detailed investigations of the effects of acrylamide on these organ systems in animals need to be done.

Available information on the pharmacokinetics of acrylamide is inadequate. It is not known whether the toxicity of acrylamide is from the parent compound or its metabolite or metabolites. The half-life of acrylamide in the blood, plasma, and in various tissues along with fecal and urinary excretion rates should be investigated. Interdisciplinary studies are needed to determine the metabolic/biochemical basis for neurotoxicity and why the distal parts of central and peripheral nerve fibers are most vulnerable to systemic acrylamide intoxication.

At present, no sensitive tests are available for early diagnosis of adverse effects to acrylamide. There is a need to develop a sensitive, practical, and economical test for this purpose. Research efforts are in progress to develop such a test at Albert Einstein College of Medicine of Yeshiva University.

Tomcufcik et al [10] found that various acrylamide compounds inhibited the grcwth of tumors in mice. Ismaylova [11] also found the same inhibition property in tomato plant tumors and Ismaylova et al [12] in plant tissue cultures. This property might be interesting to investigate in mammals.

The recommended impinger sampling method for acrylamide has several disadvantages when used for personal monitoring. These include breakage of the glass impinger and spillage of the absorption solution during sampling and subsequent shipment to the laboratory unless extreme care is taken. A method of personal monitoring using a membrane filter followed by a silica gel tube or other adsorbent tubes should be evaluated. The efficiency of the method sought should apply equally to the collection of both acrylamide dusts and vapors. Differential pulse polarography and gas chromatography are the commonly used analytical techniques for the determination of acrylamide in the industrial environment. Differential pulse polarography requires validation of its reliability and reproducibility while gas chromatography needs the development of an improved derivatization technique.

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IX. APPENDIX I

METHOD FOR SAMPLING ACRYLAMIDE IN AIR

The recommended sampling method presented is a modification of that described in the Dow Chemical Company analytical method PAA No. 46 [58].

Collect breathing zone samples representative of the individual employee's exposure. Collect enough samples to permit calculation of a time-weighted average (TWA) concentration for every operation or location in which there is exposure to acrylamide. At the time of sample collection, record a description of sampling location and conditions, equipment used, time and rate of sampling, and any other pertinent information.

The midget impinger recommended must be operated in a uniform and consistent way if data obtained are to have meaning in the assessment of environmental conditions. The impinger should be made of glass in all portions that may contact the collection medium or the airstream before collection is effected. It should be emphasized that the distilled water used as a collection medium must be free of contaminating substances that produce interferences (see Appendix II) when analyzed by polarography.

Equipment

The sampling train consists of a sampling pump and an all-glass midget impinger filled with 10 ml of distilled water. The sampling pump is protected from splash-over or water condensation by an adsorption tube loosely packed with a plug of glasswool and inserted between the exit arm

of the impinger and pump or, preferably, by a water trap inserted in the same location.

Calibration

Since the accuracy of environmental monitoring can be no greater than the accuracy of the air volume measurement, the accurate calibration of a sampling pump is essential to the correct interpretation of the volume indicated. The frequency of calibration is dependent on the use, care, and handling to which the pump is subjected. Pumps should also be recalibrated if they have been misused or if they have just been repaired or received from a manufacturer. If the pump receives hard usage, more frequent calibration may be necessary. Regardless of use, maintenance and calibration should be performed on a regular schedule and records of these should be kept.

Ordinarily, pumps should be calibrated in the laboratory. The accuracy of calibration is dependent on the type of instrument used as a reference. The choice of calibration instrument will depend largely upon where the calibration is to be performed. For laboratory testing, primary standards, such as a spirometer or a soapbubble meter, are recommended, although other standard calibration instruments, such as a wet-test meter or dry gas meter, can be used. The actual setups will be similar for all instruments.

Instructions for calibration with the soapbubble meter follow. If another calibration device is selected, equivalent procedures should be used. Since the flowrate given by a pump is dependent on the pressure drop of the sampling device, in this case an impinger, the pump must be

calibrated while operating with a representative filled impinger in line. The calibration system should be assembled in series following this order: soapbubble meter, water manometer, midget impinger, and pump as shown in Figure XII-1.

(a) Check the voltage of the pump battery with a voltmeter to ensure adequate voltage for calibration and charge the battery if necessary.

(b) Turn on the pump and moisten the inside of the soapbubble meter by immersing the buret in the soap solution and drawing bubbles up the inside until they travel the entire buret length without bursting.

(c) Adjust the pump rotameter to provide the desired flowrate.

(d) Check the water manometer to ensure that the pressure drop across the sampling train does not exceed 13 inches of water at 1 liter/minute.

(e) Start a soapbubble up the buret and measure with a stopwatch the time required for it to move between calibration marks.

(f) Repeat the procedure in (e) above at least twice, average the results, and calculate the flowrate from the volume between the preselected marks divided by the time required for the soapbubble to traverse the distance.

(g) Record the volume measured, elapsed time, pressure drop, air temperature, atmospheric pressure, serial number of the pump, the date, time, and name of the person performing the calibration.

(h) The rotometer reading should be corrected for temperature and pressure, if necessary.

Sampling Procedure

Any air mover capable of drawing the desired flowrates through the impinger may be used, so long as flowrates do not vary more than ± 5% during the sampling period. The sampling pump must be capable of operating at a pressure drop of 13 inches of water while providing a flow of 1 liter/minute.

(a) For samples representative of an individual employee's exposure, place the midget impinger within the breathing zone of the exposed employee by inserting it into a holster for fastening to the employee's coat lapel or shirt collar, or hold the impinger near the face of the employee during the sampling period.

(b) Collect an air sample at a flowrate of 1 liter/minute. The flowrate of the pump must be calibrated and this calibration checked periodically to ensure that it has not changed.

(c) Transfer the contents of the impinger to a sample bottle for shipping. Wash the impinger, stem, and splash-over with 2-5 ml of distilled water, add the washing solution to the sample bottle, and record the exact amount of distilled water used. Seal the sample bottle tightly and place it upright in a carrying case. Every attempt should be made to prevent losses from spillage or evaporation.

The trapped acrylamide is analyzed as described in Appendix II. Other collection methods shown to be equivalent may be used.

X. APPENDIX II

ANALYTICAL METHOD FOR ACRYLAMIDE

The following analytical method for acrylamide is adapted from those described by Betso and McLean [67] and presented in the Dow Chemical Company analytical method PAA No. 46 [58].

Scope

This method is applicable to the determination of acrylamide monomer which may be present in the air in an industrial environment. The procedure is described for measuring potential employee exposure. Amounts of 5-200 μg of acrylamide/10 ml of aqueous solution can be determined; larger amounts of acrylamide may be determined by appropriate dilution [58].

Principle of the Method

A known volume of air is drawn through a midget impinger filled with distilled water to collect the acrylamide dust and vapor. Two ml of sample are mixed with 8 ml of methanol. An aliquot of the sample is treated with ion-exchange resin and a fraction is injected into a differential pulse polarograph. The response of the resulting peak is determined and compared with responses obtained from the addition of standards. Polarographic response is based on the electrochemical reduction of the acrylamide double bond.

Range and Sensitivity

The polarographic detection limit for acrylamide in a clean system is less than 1 μg of acrylamide/ml of acrylamide solution [67]. Even at this low concentration, the acrylamide reduction peak is well-defined and resolved from the background.

Interferences

Differential pulse polarography is reasonably specific and relatively free from interferences. In addition, the ion-exchange resin treatment removes most common interferences, such as acrylic acid, acrylonitrile, and sodium and potassium ions. However, any compounds which are reducible in the same potential region (-2.0 v) will interfere. Substituted acrylamides and acrylate esters are reducible in the same potential region and, if present, will interfere.

Apparatus

(a) Glass-fiber filter disc, or equivalent.

(b) Magnetic stirrer and bar.

(c) Differential pulse polarographic analyzer (Princeton Applied Research (PARC) Model 174 equipped with PARC droptimer or equivalent).

(d) Two dimensional (x-y) recorder, or equivalent.

(e) Polarographic cell, 10-ml, equipped with a dropping mercury working electrode, a platinum-wire counterelectrode, and a saturated calomel reference electrode connected to the cell via a tetra-n-butylammonium chloride bridge. The cell should be equipped for deaeration with solvent-saturated, oxygen-free nitrogen.

(f) A gas scrubbing tower filled with a methanol-water solution (80:20 V/V) for nitrogen scrubbing.

(g) Eppendorf pipet, 100-μl, or equivalent.

(h) Watch glass.

(i) Beakers, 10- and 20-ml.

(j) Volumetric flasks, 100- and 250-ml.

Reagents

(a) Methanol, ACS reagent grade.

(b) Methanol-water solution (80:20 V/V).

(c) Nitrogen, oxygen-free (prepurified).

(d) Mixed ion-exchange resin, Bio-Rad Analytical Grade Mixed Bed Resin Ag 501-X8 or equivalent.

(e) Tetra-n-butylammonium chloride, 1.0 M, polarographic grade.

(f) Tetra-n-butylammonium hydroxide, 1.0 M, polarographic grade.

(g) Acrylamide, purified.

(h) Acrylamide standard solution. Accurately weigh about 0.02 g of acrylamide, transfer it to a 100-ml volumetric flask, and dilute to volume with 80:20 methanol-water solution. The solution will contain approximately 200 μg of acrylamide/ml.

Preparation of Mixed Ion-Exchange Resin

Preextract and partially dry a 1-2 week supply as follows: fill a 16-oz bottle about half full of resin. Add about 200 ml of methanol and shake the tightly closed bottle for 8-24 hours. Decant the solvent through a suction filter and wash the resin twice (by decantation from the bottle)

using the methanol-water solution (80:20). Transfer the resin to the filter and wash twice more with the 80:20 solution. Air dry until the resin will fall off a tilted spatula. This washing procedure will give a resin which has an equal mixture of hydrogen and hydroxide ions.

Analytical Procedure

(a) Measure the volume of each sample to the nearest 0.1 ml. Record the volume as "V."

(b) Add methanol: four times the volume measured in (a).

(c) Place 15 ml of the solution in (b) into a 20-ml beaker and add 1 g of prepared resin and a miniature magnetic stirring bar. Cover the beaker with a watch glass, place on a magnetic stirrer, and stir for 20 minutes.

(d) Prepare a reagent blank as in (c) using 15 ml of methanol-water solution in place of the sample solution.

(e) Transfer 10 ml of the resin-treated extract of the reagent blank to the polarographic cell and add 0.5 ml of 1.0 M tetra-n-butylammonium hydroxide.

(f) Insert the electrodes into the cell and deaerate for 5 minutes by purging with nitrogen.

(g) Record the differential pulse polarogram from -1.6 to -2.4 v against the saturated calomel electrode and a full-scale current range of 2 μamp, a pulse height of 50 mv, and a drop time of 0.5 seconds.

(h) Repeat (e-g) employing 10 ml of the resin-treated sample.

(i) To the sample, add 0.1 ml of acrylamide standard solution (20 μg) with a 100-μl Eppendorf pipet to each of the samples and repeat (f) and (g). Record micrograms of acrylamide added.

(j) Measure the peak height of the sample at about -2.0 v, correcting for any blank reading, both before (value "A") and after (value "B") adding acrylamide (i).

Calculations

$$\text{Let } F = \frac{\text{micrograms of acrylamide added}}{B-A}$$

The total micrograms of acrylamide in the sample of air are calculated by the following equation:

$$\text{micrograms of acrylamide in the sample} = 5 \times \frac{(A) \times (F) \times (V)}{10}$$

$$= 0.5 \times (A) \times (F) \times (V)$$

The concentration of acrylamide in the air sampled can be expressed in mg/cu m:

$$\text{mg/cu m} = \frac{\text{total micrograms of acrylamide in sample}}{\text{total volume of air sampled in liters}}$$

XI. APPENDIX III

MATERIAL SAFETY DATA SHEET

The following items of information which are applicable to a specific product or material shall be provided in the appropriate block of the Material Safety Data Sheet (MSDS).

The product designation is inserted in the block in the upper left corner of the first page to facilitate filing and retrieval. Print in upper case letters as large as possible. It should be printed to read upright with the sheet turned sideways. The product designation is that name or code designation which appears on the label, or by which the product is sold or known by employees. The relative numerical hazard ratings and key statements are those determined by the rules in Chapter V, Part B, of the NIOSH publication, An Identification System for Occupationally Hazardous Materials. The company identification may be printed in the upper right corner if desired.

(a) Section I. Product Identification

The manufacturer's name, address, and regular and emergency telephone numbers (including area code) are inserted in the appropriate blocks of Section I. The company listed should be a source of detailed backup information on the hazards of the material(s) covered by the MSDS. The listing of suppliers or wholesale distributors is discouraged. The trade name should be the product designation or common name associated with the material. The synonyms are those commonly used for the product, especially formal chemical nomenclature. Every known chemical designation or

competitor's trade name need not be listed.

(b) Section II. Hazardous Ingredients

The "materials" listed in Section II shall be those substances which are part of the hazardous product covered by the MSDS and individually meet any of the criteria defining a hazardous material. Thus, one component of a multicomponent product might be listed because of its toxicity, another component because of its flammability, while a third component could be included both for its toxicity and its reactivity. Note that a MSDS for a single component product must have the name of the material repeated in this section to avoid giving the impression that there are no hazardous ingredients.

Chemical substances should be listed according to their complete name derived from a recognized system of nomenclature. Where possible, avoid using common names and general class names such as "aromatic amine," "safety solvent," or "aliphatic hydrocarbon" when the specific name is known.

The "%" may be the approximate percentage by weight or volume (indicate basis) which each hazardous ingredient of the mixture bears to the whole mixture. This may be indicated as a range or maximum amount, ie, "10-40% vol" or "10% max wt" to avoid disclosure of trade secrets.

Toxic hazard data shall be stated in terms of concentration, mode of exposure or test, and animal used, eg, "100 ppm LC50-rat," "25 mg/kg LD50-skin-rabbit," "75 ppm LC man," or "permissible exposure from 29 CFR 1910.1000," or if not available, from other sources of publications such as the American Conference of Governmental Industrial Hygienists or the American National Standards Institute Inc. Flashpoint, shock sensitivity,

or similar descriptive data may be used to indicate flammability, reactivity, or similar hazardous properties of the material.

(c) Section III. Physical Data

The data in Section III should be for the total mixture and should include the boiling point and melting point in degrees Fahrenheit (Celsius in parentheses); vapor pressure, in millimeters of mercury (mmHg); vapor density of gas or vapor (air = 1); solubility in water, in parts/hundred parts of water by weight; specific gravity (water = 1); percent volatiles (indicated if by weight or volume) at 70 degrees Fahrenheit (21.1 degrees Celsius); evaporation rate for liquids or sublimable solids, relative to butyl acetate; and appearance and odor. These data are useful for the control of toxic substances. Boiling point, vapor density, percent volatiles, vapor pressure, and evaporation are useful for designing proper ventilation equipment. This information is also useful for design and deployment of adequate fire and spill containment equipment. The appearance and odor may facilitate identification of substances stored in improperly marked containers, or when spilled.

(d) Section IV. Fire and Explosion Data

Section IV should contain complete fire and explosion data for the product, including flashpoint and autoignition temperature in degrees Fahrenheit (Celsius in parentheses); flammable limits, in percent by volume in air; suitable extinguishing media or materials; special firefighting procedures; and unusual fire and explosion hazard information. If the product presents no fire hazard, insert "NO FIRE HAZARD" on the line labeled "Extinguishing Media."

(e) Section V. Health Hazard Information

The "Health Hazard Data" should be a combined estimate of the hazard of the total product. This can be expressed as a TWA concentration, as a permissible exposure, or by some other indication of an acceptable standard. Other data are acceptable, such as lowest LC50 if multiple components are involved.

Under "Routes of Exposure," comments in each category should reflect the potential hazard from absorption by the route in question. Comments should indicate the severity of the effect and the basis for the statement if possible. The basis might be animal studies, analogy with similar products, or human experiences. Comments such as "yes" or "possible" are not helpful. Comments pertinent to acrylamide might be:

> Skin Contact--single short contact, no adverse effects likely; prolonged or repeated contact, possibly mild irritation, erythema, and skin peeling.
>
> Eye Contact--some pain and mild transient irritation; conjunctival injury.

"Emergency and First Aid Procedures" should be written in lay language and should primarily represent first-aid treatment that could be provided by paramedical personnel or individuals trained in first aid.

Information in the "Notes to Physician" section should include any special medical information which would be of assistance to an attending physician including required or recommended preplacement and periodic medical examinations, diagnostic procedures, and medical management of overexposed employees.

(f) Section VI. Reactivity Data

The comments in Section VI relate to safe storage and handling of hazardous, unstable substances. It is particularly important to highlight instability or incompatibility to common substances or circumstances, such as water, direct sunlight, steel or copper piping, acids, alkalies, etc. "Hazardous Decomposition Products" shall include those products released under fire conditions. It must also include dangerous products produced by aging, such as peroxides in the case of some ethers. Where applicable, shelf life should also be indicated.

(g) Section VII. Spill or Leak Procedures

Detailed procedures for cleanup and disposal should be listed with emphasis on precautions to be taken to protect employees assigned to cleanup detail. Specific neutralizing chemicals or procedures should be described in detail. Disposal methods should be explicit including proper labeling of containers holding residues and ultimate disposal methods such as "sanitary landfill" or "incineration." Warnings such as "comply with local, state, and federal antipollution ordinances" are proper but not sufficient. Specific procedures shall be identified.

(h) Section VIII. Special Protection Information

Section VIII requires specific information. Statements such as "Yes," "No," or "If necessary" are not informative. Ventilation requirements should be specific as to type and preferred methods. Respirators shall be specified as to type and NIOSH or US Bureau of Mines approval class, ie, "Supplied air," "Organic vapor canister," etc. Protective equipment must be specified as to type and materials of construction.

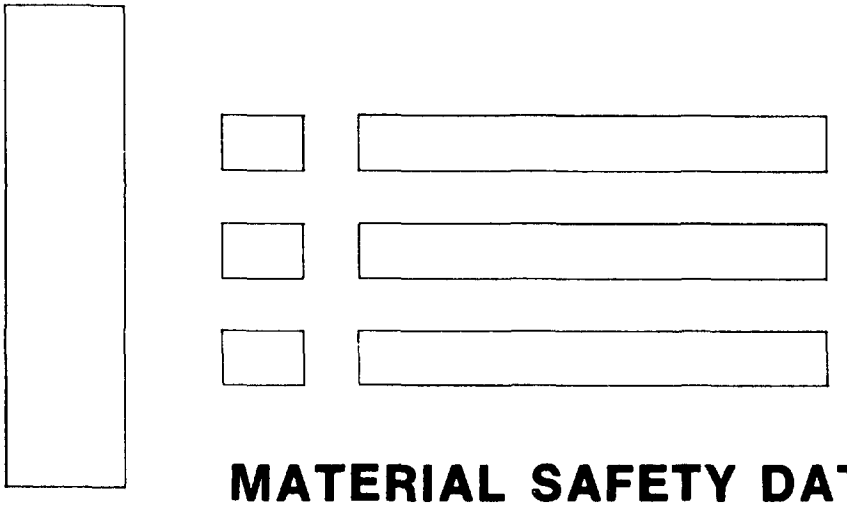
(i) Section IX. Special Precautions

"Precautionary Statements" shall consist of the label statements selected for use on the container or placard. Additional information on any aspect of safety or health not covered in other sections should be inserted in Section IX. The lower block can contain references to published guides or in-house procedures for handling and storage. Department of Transportation markings and classifications and other freight, handling, or storage requirements and environmental controls can be noted.

(j) Signature and Filing

Finally, the name and address of the responsible person who completed the MSDS and the date of completion are entered. This will facilitate correction of errors and identify a source of additional information.

The MSDS shall be filed in a location readily accessible to employees exposed to the hazardous substance. The MSDS can be used as a training aid and basis for discussion during safety meetings and training of new employees. It should assist management by directing attention to the need for specific control engineering, work practices, and protective measures to ensure safe handling and use of the material. It will aid the safety and health staff in planning a safe and healthful work environment and in suggesting appropriate emergency procedures and sources of help in the event of harmful exposure of employees.



MATERIAL SAFETY DATA SHEET

I PRODUCT IDENTIFICATION	
MANUFACTURER'S NAME	REGULAR TELEPHONE NO. EMERGENCY TELEPHONE NO.
ADDRESS	
TRADE NAME	
SYNONYMS	

II HAZARDOUS INGREDIENTS		
MATERIAL OR COMPONENT	%	HAZARD DATA

III PHYSICAL DATA			
BOILING POINT, 760 MM HG		MELTING POINT	
SPECIFIC GRAVITY (H_2O=1)		VAPOR PRESSURE	
VAPOR DENSITY (AIR=1)		SOLUBILITY IN H_2O, % BY WT	
% VOLATILES BY VOL		EVAPORATION RATE (BUTYL ACETATE=1)	
APPEARANCE AND ODOR			

IV FIRE AND EXPLOSION DATA

FLASH POINT (TEST METHOD)		AUTOIGNITION TEMPERATURE	
FLAMMABLE LIMITS IN AIR, % BY VOL.	LOWER		UPPER
EXTINGUISHING MEDIA			
SPECIAL FIRE FIGHTING PROCEDURES			
UNUSUAL FIRE AND EXPLOSION HAZARD			

V HEALTH HAZARD INFORMATION

HEALTH HAZARD DATA

ROUTES OF EXPOSURE

INHALATION

SKIN CONTACT

SKIN ABSORPTION

EYE CONTACT

INGESTION

EFFECTS OF OVEREXPOSURE

ACUTE OVEREXPOSURE

CHRONIC OVEREXPOSURE

EMERGENCY AND FIRST AID PROCEDURES

EYES

SKIN

INHALATION

INGESTION

NOTES TO PHYSICIAN

VI REACTIVITY DATA

CONDITIONS CONTRIBUTING TO INSTABILITY

INCOMPATIBILITY

HAZARDOUS DECOMPOSITION PRODUCTS

CONDITIONS CONTRIBUTING TO HAZARDOUS POLYMERIZATION

VII SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

NEUTRALIZING CHEMICALS

WASTE DISPOSAL METHOD

VIII SPECIAL PROTECTION INFORMATION

VENTILATION REQUIREMENTS

SPECIFIC PERSONAL PROTECTIVE EQUIPMENT

RESPIRATORY (SPECIFY IN DETAIL)

EYE

GLOVES

OTHER CLOTHING AND EQUIPMENT

IX SPECIAL PRECAUTIONS

PRECAUTIONARY
STATEMENTS

OTHER HANDLING AND
STORAGE REQUIREMENTS

PREPARED BY

ADDRESS

DATE

XII. TABLES AND FIGURE

TABLE XII-1

PHYSICAL AND CHEMICAL PROPERTIES OF ACRYLAMIDE

Molecular formula	$CH_2=CHCONH_2$
Formula 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/ml at 30 C
Solubility in g/100 ml of solvent at 30 C:	
acetone	63.1
benzene	0.346
chloroform	2.66
ethanol	86.2
ethyl acetate	12.6
n-heptane	0.0068
methanol	155
water	215.5

Adapted from Kirk-Othmer Encyclopedia of Chemical Technology [1]

TABLE XII-2

OCCUPATIONS WITH POTENTIAL EXPOSURE TO ACRYLAMIDE

Acrylamide manufacturing workers
Adhesive tape-making workers
Chemical grouting workers
Electrophoretic gel-making workers
Flocculator workers
Papermaking workers
Soil stabilization workers
Surface coating workers
Synthetic fiber-making workers
Textile workers
Well drillers

Adapted from Chemistry of Acrylamide [3]

TABLE XII-3

SAMPLING DATA FROM AN ACRYLAMIDE MANUFACTURING PLANT

Job Description	Date	Airborne Exposure to Acrylamide*	
		Personal Monitoring Data	Stationary Site Data
Supervisor, preparation and mixing of solution	4/29/75	0.5	0.2
	4/30/75	0.7	0.2
	"	0.6	0.2
	5/2/75	0.6	0.2
	"	0.5	0.2
	5/5/75	0.8	0.2
	5/6/75	0.2	0.1
	"	0.2	0.1
	5/7/75	1.5	0.2
Bagging	1/6/75	0.5	0.1
	1/7/75	3.6	0.1
	1/10/75	0.5	0.2
	1/14/75	0.6	0.1
	1/15/75	0.7	0.1
	1/16/75	2.0	0.1
	1/17/75	1.3	0.2
	2/7/75	0.3	0.1
	2/10/75	0.3	0.1
	2/11/75	2.3	0.3
	2/12/75	0.5	0.1
	2/14/75	0.3	0.2
	4/29/75	1.8	0.2
	5/28/75	0.8	0.2
General, solid only	9/5/74	0.5	0.1
	5/8/75	0.7	0.2
	5/12/75	0.4	0.2
	5/13/75	0.3	0.1
	5/15/75	0.5	0.2
	5/16/75	1.8	0.2
General, solutions only	5/8/75	0.7	0.2
	5/13/75	0.5	0.1
	5/15/75	0.2	0.2
	5/16/75	0.1	0.2

TABLE XII-3 (CONTINUED)

SAMPLING DATA FROM AN ACRYLAMIDE MANUFACTURING PLANT

Job Description	Date	Airborne Exposure to Acrylamide*	
		Personal Monitoring Data	Stationary Site Data
General, solutions and solid	5/7/75	0.4	0.2
	5/9/75	0.6	0.3
	"	0.8	0.3
	5/14/75	0.3	0.1
	"	1.0	0.1

*All concentrations are given in mg/cu m for 8-hr exposures.

Adapted from Brinkley (written communication, June 1976)

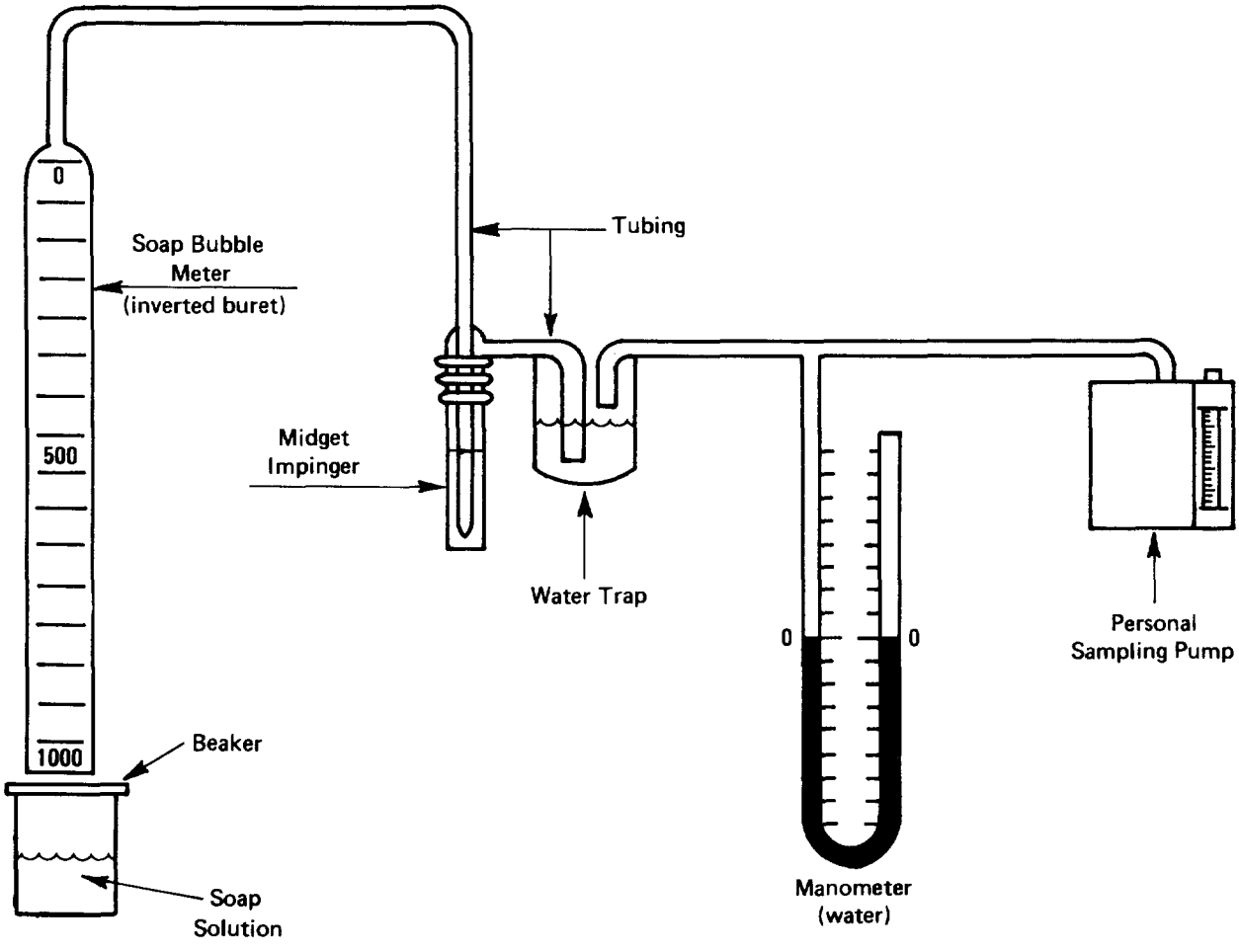


FIGURE XII–1 CALIBRATION SETUP FOR PERSONAL SAMPLING PUMP WITH MIDGET IMPINGER

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