NIOSH

CRITERIA FOR A RECOMMENDED STANDARD. . .

OCCUPATIONAL EXPOSURE TO

NITRILES

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health

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PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and provide for the safety of workers occupationally exposed to an ever-increasing number of potential hazards. The National Institute for Occupational Safety and Health (NIOSH) evaluates all available research data and criteria and recommends standards for occupational exposure. The Secretary of Labor will weigh these recommendations along with other considerations, such as feasibility and means of implementation, in promulgating regulatory standards.

NIOSH will periodically review the recommended standards to ensure continuing protection of workers and will make successive reports as new research and epidemiologic studies are completed and as sampling and analytical methods are developed.

The contributions to this document on nitriles by NIOSH staff, other Federal agencies or departments, the review consultants, the reviewers selected by the Society of Toxicology, and Robert B. O'Connor, M.D., NIOSH consultant in occupational medicine, are gratefully acknowledged.

The views and conclusions expressed in this document, together with the recommendations for a standard, are those of NIOSH. They are not necessarily those of the consultants, the reviewers selected by professional societies, or other Federal agencies. However, all comments, whether or not incorporated, were considered carefully and were sent with the criteria document to the Occupational Safety and Health Administration for consideration in setting the standard. The review consultants and the Federal agencies which received the document for review appear on pages v and vi.

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The Division of Criteria Documentation and Standards Development, National Institute for Occupational Safety and Health (NIOSH), had primary responsibility for the development of the criteria and recommended standard for nitriles. Sonia Berg of this Division served as criteria manager. Equitable Environmental Health, Inc. (EEH) developed the basic information for consideration by NIOSH staff and consultants under contract CDC 210-77-0148.

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I. RECOMMENDATIONS FOR A NITRILES STANDARD

NIOSH recommends that employee exposure to selected aliphatic saturated nitriles in the workplace be controlled by adherence to the following sections. The recommended standard is designed to protect the health and provide for the safety of employees for up to a 10-hour workshift, 40-hour workweek, over a working lifetime. Compliance with all sections of the recommended standard should prevent adverse effects of exposure on the health and safety of workers. Although NIOSH considers the recommended workplace environmental limits to be safe based on current information, the employer should regard them as the upper boundaries of exposure and make every effort to maintain any exposure as low as is technically feasible. These criteria and recommended standard will be reviewed and revised as necessary.

Nitriles are defined as organic compounds that contain a cyano group, C≡N, as the characteristic functional group. They may react to release cyanide. Ten nitriles are included in the recommended standard, namely, the mononitriles (acetonitrile, propionitrile, n-butyronitrile, and isobutyronitrile); the cyanohydrins (glycolonitrile and acetone cyanohydrin); and the dinitriles (malononitrile, succinonitrile, adiponitrile, and tetramethylsuccinonitrile). Their selection was based on the extent of production and use in industry and the degree of toxicologic hazard, but acrylonitrile was omitted because NIOSH recently recommended an Emergency Temporary Standard for the chemical. The term "selected nitriles" will be used to refer to these compounds. "Occupational exposure" to selected nitriles is defined as exposure to airborne concentrations at or above the action level. "Action level" is defined as one-half the time-weighted average (TWA) or ceiling workplace environmental limit, whichever is appropriate. The criteria and recommended standards apply to any area in which nitriles are produced, packaged, processed, mixed, blended, handled, or stored. If concomitant exposure to other chemicals occurs during the production and use of the selected nitriles, the employer shall comply also with the provisions of applicable standards for these other chemicals. Adherence to all provisions of the recommended standard is required if any employee is exposed to airborne nitriles at concentrations above the action level. If any employee is occupationally exposed at concentrations equal to or below the action level, then all sections of the recommended standard except Section 8(a) shall be complied with because adverse effects can be produced by skin and eye contact with nitriles.

The recommended standard is based on reports indicating that the selected nitriles are sources of cyanide ion, which interferes with basic cellular oxidative mechanisms, and that they have effects on the cardiovascular, renal, gastrointestinal, hepatic, and central nervous

systems. These nitriles exert their toxic actions after inhalation, dermal contact, or ingestion. Dinitriles, and possibly other nitriles, irritate the eyes, skin, and upper and lower respiratory tract. No carcinogenic, mutagenic, teratogenic, or reproductive effects in humans have been reported. However, acrylonitrile (vinyl cyanide) has been found to be carcinogenic in animal tests, and the recent NIOSH recommendation for an Emergency Temporary Standard was based on the serious suspicion that acrylonitrile may be a human carcinogen. The carcinogenicity of this compound may be associated with the vinyl component rather than with its identity as a nitrile. Compliance with the recommended standard should eliminate the hazards associated with the selected nitriles.

Section 1 - Environmental (Workplace Air)

(a) Concentration

Workplace exposure to nitriles shall be controlled so that employees are not exposed at concentrations greater than the limits, in milligrams per cubic meter (mg/cu m) of air, shown in Table I-1 as either TWA concentrations for up to a 10-hour workshift, 40-hour workweek, or as ceiling concentrations based on a 15-minute sampling period.

When there is simultaneous exposure to several nitriles or other sources of cyanide, the exposures shall be regarded as additive, and the environmental concentration limit for equivalent exposure to a mixture (E_m) shall be determined as follows:

$$E_m = C_1/L_1 + \ldots + C_n/L_n$$

where:

C_1 = the concentration of the main component of the mixture

C_n = the concentration of other constituents of the mixture, with n having values from 2 to n

L_1 = the permissible exposure limit for the main component

L_n = the permissible exposure limits for other constituents, with n having values from 2 to n

E_m shall not exceed 1.

Compounds with ceiling concentration limits are additive independently from those that have TWA exposure limits. When the additive formula exceeds 1, exposure to the mixture shall be reduced even if none of the individual TWA or ceiling concentration limits is exceeded.

TABLE I-1

RECOMMENDED WORKPLACE EXPOSURE LIMITS

Nitrile	mg/cu m	Approximate ppm Equivalents	Type of Limit
Acetonitrile	34	20	TWA
Propionitrile	14	6	"
n-Butyronitrile	22	8	"
Isobutyronitrile	22	8	"
Acetone cyanohydrin	4	1	Ceiling
Glycolonitrile	5	2	"
Malononitrile	8	3	TWA
Adiponitrile	18	4	"
Succinonitrile	20	6	"
Tetramethyl-succinonitrile	6	1	Ceiling

(b) Sampling and Analysis

Workplace air samples shall be collected and analyzed for nitriles as described in Appendix I or by any method shown to be at least equivalent in accuracy, precision, and sensitivity.

Section 2 - Medical

Medical surveillance shall be made available as specified below to all employees subject to exposure to the compounds covered by this standard.

(a) Preplacement medical examinations shall include at least:

(1) Comprehensive medical and work histories, with special emphasis directed to skin disorders and the cardiopulmonary and central nervous systems.

(2) A physical examination giving particular attention to the skin and the cardiovascular, pulmonary, and central nervous systems.

(3) Specific clinical tests including a 14- x 17-inch chest X-ray and tests of pulmonary function such as the forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1).

(4) An evaluation of the employee's physical ability to safely wear a positive pressure respirator. Factors such as age, evidence of obstructive lung disease or impairment, cardiopulmonary impairment, and level of activity required while wearing the device should be considered in evaluating the worker's ability to wear respirators.

(b) Periodic examinations shall be made available at least annually and shall consist of the following:

(1) Interim medical and work histories.

(2) Physical examination as described in (a)(2) and (3) above, with the exception of an annual chest X-ray.

(c) In view of the numerous body systems in which toxic effects of nitriles have been demonstrated, medical and work histories and physical examinations should be thorough and should give particular attention to combinations of signs or symptoms, including evidence of dermal contact, which may indicate toxicity.

(d) Employees with evidence of impaired pulmonary function or cardiovascular disease shall be counseled as to the possible increased risk of impairment to their health from working with selected nitriles.

(e) A responsible physician and the employer shall be aware of first-aid and treatment procedures and shall ensure that trained employees are on duty whenever there is a potential occupational exposure to these selected nitriles or their decomposition product, hydrogen cyanide.

(f) In addition to medical treatment kits, as described in Appendix III, first-aid kits shall be immediately available at workplaces where there is potential exposure to nitriles. Kits shall contain as a minimum two boxes of ampules (two dozen), each containing 0.3 ml of amyl nitrite. Ampules shall be replaced as often as necessary to ensure their potency.

The amyl nitrite ampules should be protected from high temperatures. In all cases, the contents of the first-aid kits shall be replaced before the manufacturer's assigned expiration dates.

(g) Pertinent medical records shall be kept for 30 years after employment has ended for all employees exposed to the selected nitrile in the workplace. Records of environmental exposures for an employee shall be included in the employee's medical records. These records shall be made available to the designated medical representatives of the Secretary of Health, Education, and Welfare, of the Secretary of Labor, of the employer, and of the employee or former employee.

Section 3 - Labeling and Posting

(a) Containers of nitriles used or stored in the workplace shall carry a label, in a readily visible location, that bears the chemical name of the nitrile contained therein, the trade name of the product, and information on the effects of the particular compound on human health. The trade name and/or other designation and other pertinent information shall be arranged as in the following example:

MALONONITRILE
(TRADE NAME OR OTHER DESIGNATION)

MAY BE HARMFUL IF INHALED, SWALLOWED,
OR ABSORBED THROUGH SKIN

IRRITATING TO SKIN AND EYES

Avoid contact with eyes, skin, and clothing.
Avoid inhaling vapor, aerosol, fumes, gases.
Use only with adequate ventilation.

First Aid: Remove victims to fresh air immediately. Apply artificial respiration if breathing stops. Wash exposed skin or eyes thoroughly with water and remove contaminated clothing and shoes. If material has been swallowed and the victim is conscious, induce vomiting. If the victim is unconscious but still breathing, administer vapor of amyl nitrite under the victim's nose for 15 seconds. Repeat five times at about 15-second intervals. Consult a physician as soon as possible.

(b) Posting

In areas where nitriles are used, signs containing information on the effects of the specific compounds on human health shall be posted in

readily visible locations. This information shall be arranged as in the following example:

MALONONITRILE
(TRADE NAME OR OTHER DESIGNATION)

MAY BE HARMFUL IF INHALED, SWALLOWED,
OR ABSORBED THROUGH SKIN

IRRITATING TO SKIN AND EYES

(c) If respirators are required, the following statement shall be added in large letters to the sign required in Section 3(b):

RESPIRATORY PROTECTION REQUIRED IN THIS AREA

(d) In any workplace or area where there is a likelihood of emergency situations, signs required by Section 3(b) shall be supplemented by additional signs giving emergency and first-aid instructions and procedures, the locations of first-aid supplies and emergency equipment, and the location of emergency showers and eyewash fountains.

(e) All warning signs shall be printed in English and in the predominant language of non-English-reading employees. Employers shall ensure that employees unable to understand these signs and labels also know the hazards associated with the selected nitriles and the location of areas in which there may be occupational exposures.

Section 4 - Personal Protective Equipment and Clothing

Engineering controls and safe work practices shall be used when needed to keep the concentration of airborne nitriles at or below the limits specified in Section 1(a). Protective clothing and equipment shall be provided by the employer and worn by the employee to prevent skin and eye contact with nitriles, particularly in the liquid form. Emergency equipment shall be located at clearly identified stations within the work area and shall be adequate to permit all employees to escape safely from the area. Protective equipment suitable for emergency use shall be located at clearly identified stations outside the work area.

(a) Protective Clothing

(1) The employer shall provide chemical safety goggles or face shields (20-cm or 8-inch minimum) and goggles, and shall ensure that

employees wear the protective equipment during any operation where eye contact with liquid nitriles is likely.

(2) The employer shall provide appropriate protective clothing made of material resistant to penetration by nitriles, including gloves, aprons, coveralls, and boots, and shall ensure that employees wear protective clothing when necessary to prevent skin contact. The employer shall ensure that personal protective clothing is regularly inspected for defects.

(b) Respiratory Protection

(1) Engineering controls shall be used whenever needed to maintain nitrile concentrations at or below the recommended workplace limits. The use of respiratory protective equipment is permitted only in the following circumstances:

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

(B) For operations such as maintenance and repair activities causing brief exposure at concentrations in excess of the recommended environmental limits.

(C) During sampling of process streams.

(D) During emergencies when concentrations of airborne nitriles might exceed the recommended environmental limits.

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

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

(B) The employer shall ensure that employees are properly instructed in the use of respirators assigned to them and in how to test for leakage, proper fit, and proper operation as judged by quantitative fit tests. Quantitative faceseal fit test procedures using sodium chloride, dioctyl phthalate, or the equivalent shall be used. For full-facepiece cartridge respirators, the maximum allowable leakage is 2% of the test atmosphere.

(C) The employer shall provide respirators in accordance with Tables I-2 and I-3, and shall ensure that employees use the respirators properly when they are required. The respiratory protective devices shall be approved by NIOSH and the Mine Safety and Health Administration (MSHA) as specified under the provisions of 30 CFR 11.

(D) Respirators specified for use in higher concentrations of a specific airborne nitrile may be used in atmospheres of lower concentrations.

(E) When a self-contained breathing apparatus is permitted in accordance with these tables, it shall be used pursuant to the following requirements:

(i) The employer shall provide initial training and refresher courses on the use, maintenance, and function of a self-contained breathing apparatus.

(ii) Whenever a self-contained breathing apparatus is supplied for escape purposes, the respirator shall be operated in the pressure-demand or continuous-flow mode.

TABLE I-2

RESPIRATOR SELECTION GUIDE FOR ACETONITRILE, N-BUTYRONITRILE, ISOBUTYRONITRILE, AND PROPIONITRILE

Concentration	Respirator Type Approved under Provisions of 30 CFR 11
Less than or equal to 100 ppm	(1) Chemical cartridge respirator with full facepiece and organic vapor cartridge (2) Supplied-air respirator with a full facepiece, helmet, or hood, operated in demand mode
Less than or equal to 1,000 ppm	(1) Supplied-air respirator with a full facepiece, helmet, or hood, operated in pressure-demand or continuous-flow mode (2) Self-contained breathing apparatus with a full facepiece operated in pressure-demand mode
Greater than 1,000 ppm or emergency (entry into area of unknown concentration)	(1) Self-contained breathing apparatus with a full facepiece operated in pressure-demand mode (2) Supplied-air respirator with a full facepiece, helmet, or hood, operated in pressure-demand or continuous-flow mode, with auxiliary self-contained breathing apparatus

TABLE I-3

RESPIRATOR SELECTION GUIDE FOR ACETONE CYANOHYDRIN, GLYCOLONITRILE, MALONONITRILE, SUCCINONITRILE, ADIPONITRILE, AND TETRAMETHYLSUCCINONITRILE

Concentration	Respirator Type Approved under Provisions of 30 CFR 11
Less than or equal to 50 ppm	(1) Supplied-air respirator with a full facepiece, helmet, or hood, operated in demand mode (2) Self-contained breathing apparatus with a full facepiece operated in demand mode
Less than or equal to 250 ppm	(1) Supplied-air respirator with a full facepiece, helmet, or hood, operated in pressure-demand or continuous-flow mode (2) Self-contained breathing apparatus with a full facepiece operated in pressure-demand mode
Greater than 250 ppm or emergency (entry into area of unknown concentration)	(1) Self-contained breathing apparatus with a full facepiece operated in pressure-demand mode (2) Supplied-air respirator with a full facepiece, helmet, or hood, operated in pressure-demand or continuous-flow mode, with auxiliary self-contained breathing apparatus

Section 5 - Informing Employees of Hazards from Nitriles

(a) The employer shall provide information at the beginning of employment and on a semiannual basis thereafter on the hazards, relevant symptoms, appropriate emergency procedures, and proper conditions and precautions for the safe handling or use of the selected nitriles to all employees working in the areas where exposure may occur. First-aid procedures shall be included. This information shall be readily available to all employees involved in the manufacture, use, transport, or storage of selected nitriles and shall be posted in prominent positions within the workplace.

(b) The employer shall institute a continuing education program, conducted by persons qualified by experience and training, to ensure that all employees have current knowledge of job hazards, proper maintenance and

cleanup methods, and proper respirator usage and maintenance. The instructional program shall include a description of the general nature of the medical surveillance procedures and of the advantages to the employee of undergoing these examinations. As a minimum, instruction shall include the information on the Material Safety Data Sheet (MSDS) in Appendix II.

(c) Required information shall be recorded on the MSDS specified in Appendix II or on a similar form approved by the Occupational Safety and Health Administration, US Department of Labor. The appropriate form shall be readily accessible to employees at all places of employment where exposure may occur.

Section 6 - Work Practices and Control Procedures

(a) Emergency Procedures

Employers shall take all necessary steps to ensure that employees are instructed in and follow the procedures specified below, and any others appropriate for the specific operation or process, for all work areas where there is a potential for emergencies involving nitriles.

(1) Instructions shall include prearranged plans for obtaining emergency medical care and for transporting injured employees.

(2) Eye, skin, and respiratory protection as specified in Section 4 shall be used by personnel engaged in emergency operations. Employees not essential to emergency operations shall be evacuated from hazardous areas where inhalation, ingestion, or direct skin or eye contact may occur. The perimeters of these areas shall be delineated, posted, and secured.

(3) Only personnel properly trained in the procedures and adequately protected against the attendant hazards shall shut off sources of nitriles, clean up spills, and repair leaks. Spills and leaks shall be attended to immediately to minimize the possibility of exposure.

(4) Any large spill of nitriles to be discarded shall be diluted with water, with sufficient alkali added to establish a pH of more than 9.5, and the neutralized spill drained to a chemical sewer system, which should not receive any influx of acids.

(5) Firefighting procedures shall be established for areas where flammable materials are used with nitriles. Chemical foam, dry chemical, carbon dioxide, or water spray shall be used to extinguish fires in areas where nitriles are present. Hydrogen cyanide and other toxic products may be released during a fire, and proper protective respirators and clothing shall be worn by all personnel in the hazard area until concentrations of airborne nitriles and hydrogen cyanide have been shown to be below the recommended concentration limits.

(6) Eyewash fountains and emergency showers shall be provided and readily accessible to employees in all areas where skin or eye contact with nitriles is possible.

(b) Control of Airborne Nitriles

Engineering controls, such as process enclosure and local exhaust ventilation, shall be used whenever needed to keep concentrations of nitriles within the recommended workplace limits. Ventilation systems shall be designed and operated to prevent the accumulation or recirculation of nitriles in the workplace environment and to effectively remove nitriles from the breathing zones of employees. Design of ventilation systems, as well as other equipment, shall conform to requirements for the appropriate flammability class for each nitrile (see Table V-1). Exhaust ventilation systems discharging to outside air shall conform to applicable local, state, and Federal air pollution regulations and shall not constitute a hazard to employees or the general public. Ventilation systems shall be subject to regular preventive maintenance and cleaning to ensure effectiveness, which shall be verified by airflow measurements taken at least every 3 months.

(c) Storage

Containers of nitriles shall be kept tightly closed at all times when not in use. Containers shall be stored in a safe manner to minimize accidental breakage or spillage, to avoid heat, and to prevent contact with acids and strong oxidizers.

(d) Handling and General Work Practices

(1) Before maintenance work is undertaken, sources of nitriles shall be shut off. If concentrations at or below the recommended workplace limits cannot be assured, respiratory protective equipment, as described in Section 4 of this chapter, shall be used during such maintenance work.

(2) In case of contact, the skin or eyes shall be flushed immediately with large amounts of water to remove all traces of nitriles. Contaminated clothing shall be removed immediately and disposed of or cleaned before reuse. Any contaminated clothing shall be stored, transported, or disposed of in a manner that prevents further dispersion of or exposure to nitriles. Personnel involved in cleaning contaminated clothing shall be informed about the hazards and appropriate precautions for the safe handling of these compounds. Contaminated leather shoes shall be discarded.

(3) Entry into confined spaces, such as tanks, pits, process vessels, tank cars, sewers, or tunnels, where there may be limited egress,

shall be controlled by a permit system. Permits shall be signed by an authorized employer representative certifying that preventive and protective measures have been followed.

Confined spaces that have contained nitriles shall be thoroughly ventilated to ensure an adequate supply of oxygen, tested for nitriles and other contaminants, and inspected for compliance with these requirements before each entry. Adequate ventilation shall be maintained while an employee or other individual is in the space. Leakage of nitriles or other contaminants into the confined space while work is in progress shall be prevented by disconnecting and blanking the supply lines for nitriles and other materials. An individual entering a confined space shall be furnished with appropriate personal protective clothing and devices and protected by a lifeline harness tended by another employee outside the space. The employee tending the lifeline shall also be equipped with personal protective clothing and devices approved for entry and shall have contact with a third party. Communication (visual, voice, signal line, telephone, radio, or other suitable means) shall be maintained by the standby person with the employee inside the confined or enclosed space. A third employee, equipped to proceed to the aid of the other two if necessary, shall be in a position to maintain a general surveillance of their activities.

Section 7 - Sanitation

(a) Consuming, preparing, or dispensing of food or beverages (including vending machines) shall be prohibited in nitrile work areas.

(b) Smoking shall not be permitted in areas where nitriles are manufactured, used, transferred, or stored.

(c) Employees who handle nitriles or equipment contaminated with nitriles shall be instructed to wash their hands thoroughly with soap or mild detergent and water before eating or using toilet facilities.

(d) Clothing that has been contaminated by nitriles shall be discarded or decontaminated by laundering or by an equivalent method.

(e) Waste material contaminated with nitriles shall be disposed of in a manner not hazardous to employees. The disposal method shall conform with applicable local, state, and Federal regulations and shall not constitute a hazard to the surrounding population or environment.

Section 8 - Monitoring and Recordkeeping Requirements

Employers shall conduct an industrial hygiene survey at locations where nitriles are released into workplace air to determine whether exposure to airborne concentrations of nitriles is in excess of the action level. The

employer shall keep records of these surveys. If the employer concludes that concentrations of airborne nitriles are at or below the action level, the records shall show the basis for this conclusion. Surveys shall be repeated at least annually and within 30 days of any process change likely to alter concentrations of any of these compounds in the workplace air. If it has been concluded that the environmental concentration of nitriles exceeds the action level, then the employer shall fulfill the following requirements:

(a) Personal Monitoring

(1) A program of personal monitoring shall be instituted to identify and measure, or permit calculation of, the exposure of each employee occupationally exposed to nitriles. Source and area monitoring may be used to supplement personal monitoring.

(2) Samples representative of the exposure to nitriles in the breathing zone of the employee shall be collected in all personal monitoring. Procedures for the calibration of equipment, sampling, and analysis of nitriles shall be as provided in Section 1(b).

(3) For each TWA concentration determination, a sufficient number of samples shall be taken to characterize the employee's exposure during each workshift. For determination of ceiling concentrations, employees shall be observed along with the operation in process to determine when maximum exposure is expected. A sufficient number of 15-minute samples taken during the time of such maximum exposure shall be used to determine the actual ceiling concentration to which an employee is exposed. Variations in the employee's work schedule, location, and duties and changes in production schedules shall be considered when samples are collected.

(4) If an employee is found to be exposed above the action level but below the recommended environmental limit, the exposure of that employee shall be monitored at least once every 3 months. If an employee is found to be exposed in excess of the recommended environmental limit, the exposure of that employee shall be measured at least once every 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 employee exposure no longer exceeds the recommended environmental concentration limit; quarterly monitoring shall then be resumed.

(b) Recordkeeping

Employers or their successors shall keep records of environmental monitoring for each employee for at least 30 years after the individual's

employment has ended. These records shall include an identification of the employee being monitored, duties and job locations within the worksite, dates of measurements, sampling and analytical methods used and evidence of their accuracy, duration of sampling, number of samples taken, results of analyses, TWA or ceiling concentrations based on these samples, and any personal protective equipment used. Records for each employee, indicating date of employment with the company and any changes in job assignment, shall be kept for the same 30-year duration. The employer shall make these records available upon request to authorized representatives of the Secretary of Labor and of the Secretary of Health, Education, and Welfare. Employees or authorized representatives shall have access to information on their own exposures, and they shall be given the opportunity to observe any measurement conducted in accordance with this section.

II. INTRODUCTION

This report presents the criteria and the recommended standard based thereon that were prepared to meet the need for preventing occupational disease or injury arising from exposure to selected aliphatic saturated nitriles. 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."

After reviewing data and consulting with others, NIOSH formalized a system for the development of criteria on which standards can be established to protect the health and provide for the safety of employees exposed to hazardous chemical and physical agents. Criteria for an environmental standard should enable management and labor to develop better engineering controls and work practices resulting in more healthful work environments; simply complying with the recommended standard should not be regarded as a final goal.

These criteria for a standard for selected aliphatic saturated nitriles are part of a continuing series of documents published by NIOSH. The recommended standard applies to workplace exposure to these selected nitriles resulting from manufacture, storage, handling, and use or release as intermediates, byproducts, or impurities. The standard was not designed for the population-at-large, and any extrapolation beyond the occupational environment is not warranted. It is intended to: (1) protect workers against skin and eye irritation and systemic effects; (2) be measurable by techniques that are available to industry and governmental agencies; and (3) be attainable with existing technology.

The selected nitriles included in this recommended standard are the mononitriles (acetonitrile, propionitrile, n-butyronitrile, and isobutyronitrile), the cyanohydrins (glycolonitrile and acetone cyanohydrin), and the dinitriles (adiponitrile, malononitrile, succinonitrile, and tetramethylsuccinonitrile).

Exposure to these nitriles occurs primarily by the dermal and inhalation routes, but there are also adverse effects from contact of these nitriles with the eyes. Depending on the amount absorbed, nitriles may cause central nervous system (CNS), hepatic, renal, cardiovascular, and gastrointestinal disorders, regardless of route of administration. These effects are attributed to the metabolic release of cyanide but may also be due in part to the intact molecule.

Development of the criteria for the recommended standard for occupational exposure to the selected nitriles indicates a need for further research in several areas, including: (1) comparative animal toxicity studies including exposure to mixtures known to occur in the workplace; (2) further research on sampling and analytical methods needed to characterize exposure; (3) epidemiologic studies to characterize the health effects produced by exposure to these nitriles in the occupational environment; (4) studies on potential carcinogenic, mutagenic, teratogenic, and reproductive effects; (5) studies on the rate of release of cyanide ion from various nitriles in mammalian systems; (6) further studies on reported health effects that may be attributed to the nitrile itself as well as to the release of cyanide; (7) the efficacy of emergency treatment of nitrile poisoning using sodium nitrite and sodium thiosulfate; and (8) the development of an improved analytical method for urinary thiocyanate. A more complete discussion of these research recommendations is presented in Chapter VII.

III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Nitriles are organic compounds that contain a cyano group, C≡N, as the characteristic functional group. Under selective hydrolysis conditions, nitriles may be hydrolyzed to the corresponding acid amides, whereas complete hydrolysis yields carboxcylic acids. The selective reduction of nitriles may yield imines, which can be hydrolyzed to aldehydes, and the complete reduction yields primary amines. In addition, selected nitriles, particularly cyanohydrins, will readily dissociate to form cyanide and the corresponding side chain derivative. Most nitriles are expressed by the general formula RC≡N in which R may be any saturated or unsaturated univalent organic radical. Nitriles in which an alpha-hydroxy group is bound to a carbon atom of the side chain are referred to as cyanohydrins [1].

Selected mononitriles, cyanohydrins, and dinitriles are included in this document. Their selection was based on the extent of production and use in industry and the degree of toxicologic hazard. The synonyms for selected nitriles are listed in Table XII-1.

The mononitriles selected for inclusion are acetonitrile, propionitrile, n-butyronitrile, and isobutyronitrile. These are saturated aliphatic nitriles with molecular weights ranging from 41.1 for acetonitrile to 69.1 for the butyronitriles. All are colorless liquids having varying solubilities in water. Vapor pressures for these nitriles at 20 C range from 14 mmHg for n-butyronitrile to 73 mmHg for acetonitrile [1].

The two cyanohydrins included are glycolonitrile and acetone cyanohydrin. Glycolonitrile, the alpha-hydroxy derivative of acetonitrile, has a molecular weight of 57.1; acetone cyanohydrin, the alpha-hydroxy derivative of isobutyronitrile, has a molecular weight of 85.1. Both glycolonitrile and acetone cyanohydrin are water-soluble colorless liquids. Acetone cyanohydrin has a vapor pressure of 0.8 mmHg at 20 C [2].

The dinitriles included are malononitrile, succinonitrile, adiponitrile, and tetramethylsuccinonitrile. The molecular weights for these dinitriles range from 66.1 for malononitrile to 136.2 for tetramethylsuccinonitrile. Three of these dinitriles are odorless solids; adiponitrile is a colorless and odorless oily liquid. Adiponitrile, malononitrile, and succinonitrile range from slightly soluble to soluble in water. Tetramethylsuccinonitrile is soluble in alcohol.

When heated to decomposition, nitriles emit toxic fumes containing cyanides [3]. Other physical and chemical properties of the mononitriles, cyanohydrins, and dinitriles are included in Table XII-2.

Nitriles can be synthesized by various processes; however, the following six processes provide examples of the most common methods used in industry.

(1) Dehydration of acid amides prepared by heating an equimolar mixture of a carboxylic acid and ammonia in the presence of a suitable catalyst:

$$(RCOOH + NH_3 \text{ ------> } RC{\equiv}N{+}2H_2O)$$

Acetonitrile can be prepared by reacting acetic acid and ammonia at 400-500 C in the presence of a dehydration catalyst consisting of 20% phosphoric acid and aluminum oxide [4]. Adiponitrile can be prepared by heating adipamide with acetic anhydride in the presence of cobalt [4].

(2) The dehydration of an ammonium salt of an organic acid with

$$(RCO_2NH_4 + P_2O_5 \text{ ----> } RCONH_2 + 2HPO_3)$$

heat plus a catalyst to produce an acid amide that is then dehydrated:

$$(RCONH_2 + P_2O_5 \text{ ----> } RC{\equiv}N + 2HPO_3)$$

Acetonitrile may also be prepared by heating ammonium sulfate or diammonium monohydrogen phosphate with acetic acid at 200 C.

(3) The reaction of alkylhalides with sodium or potassium cyanide in an aqueous-alcoholic solution:

$$(RX + NaCN \text{ ----> } RC{\equiv}N + NaX)$$

Propionitrile may be prepared by the reaction of ethyl chloride with potassium cyanide. Adiponitrile may be synthesized by reacting 1,4-dichlorobutane with sodium cyanide.

(4) Adiponitrile may be prepared by reacting butadiene with hydrogen cyanide:

$$CH_2 = CHCH = CH_2 + HCN \text{ ------> } (CH_2)4(CN)2$$

or by the electrodimerization of acrylonitrile:

$$2CH_2 = CHCN \xrightarrow{H_2} (CH_2)4(CN)2$$

(5) Malononitrile is prepared by continuous introduction of preheated acetonitrile and cyanogen chloride into a tube reactor until the reaction mixture reaches a temperature of approximately 780 C:

$$CH_3CN + ClCN \text{ ------> } CH_2(CN)2 + HCl$$

Published production estimates are available for acetonitrile, acetone cyanohydrin, and adiponitrile [5]. In 1962, 2.1 million pounds of acetonitrile were produced [6]. In 1964, 3.5 million pounds were consumed. In 1975, 573 million pounds of acetone cyanohydrin were produced, and its production is expected to increase at an average rate of 9% through 1980 [5]. In 1976, at least 150 million pounds of adiponitrile were produced [5]. Imports of malononitrile, which currently is not manufactured in the United States, are estimated at up to 60,000 pounds annually (I Gottleib, personal communication, February 1978).

Nitriles are adaptable to industrial applications because of their versatile chemical reactivity. The nitrile functional group can be converted to a primary amine; a carboxylic acid; or the corresponding amide, aldehyde, alcohol, or ester derivatives. Dinitriles can be converted to compounds with difunctional groups for use in a variety of processes and products, including plastics, dyestuffs, synthetic intermediates, and pharmaceuticals [7-9]. Industrial uses are listed in Table XII-3.

Industrial use for nitriles in the manufacture of plastics, synthetic fibers, elastomers, and solvents was stimulated by the growth of the petrochemical industry after World War II [10]. Acetonitrile was introduced to the commercial market in 1952 [11], but high-technology commercial development was inhibited for several years by economic factors. In 1967, new designs in the electrolytic synthesis of fine chemicals improved the efficiency of nitrile production, notably adiponitrile, and effectively increased the marketability of nitriles for industrial uses [12].

Acetonitrile is used as a solvent in extractive distillation that separates olefins from diolefins, butadiene from butylene, and isoprene from isopentane. Propionitrile is used as a solvent for the separation of hydrocarbons and in refining petroleum fractions. Isobutyronitrile is used as a catalyst in the polymerization of ethylene. Isobutyronitrile has been tested in the petroleum industry as a gasoline additive [13].

Glycolonitrile is an intermediate in the synthesis of bactericides and fungicides. Acetone cyanohydrin is used primarily in the preparation of methyl methacrylate, which is polymerized to form various plastics, including Plexiglas [4].

Adiponitrile is used as a raw material in the manufacture of synthetic fibers. The cyano groups of adiponitrile are hydrogenated to form hexamethylenediamine, a compound used in the production of nylon [14].

Malononitrile is used primarily as a chemical intermediate in the manufacture of thiamine and in the manufacture of pteridine-type anticancer agents; it also has application in the manufacture of photosensitizers, acrylic fibers, and dyestuffs and as an oil-soluble polar additive in lubricating oil [8,9].

The major occupational exposures to nitriles occur principally by inhalation of vapor or aerosols and by skin absorption. The likelihood of such exposures increases during the handling, transferring, and quality control sampling of nitriles. In addition, an increased risk of exposure is possible during maintenance operations and repair of equipment; on and after entry into tanks, vessels, or other confined spaces; or when emergency or nonroutine procedures are required [4].

Using data from a 1972-74 National Occupational Hazards Survey, NIOSH estimates that approximately 26,000 employees are potentially exposed to the selected nitriles in the occupational environment. It is estimated that acetonitrile exposures account for 24,000 of this figure. Occupations with the greatest potential for exposure to these selected nitriles are listed in Table XII-4.

Historic Reports

Several nitriles were discovered in the 19th century. Propionitrile was first prepared by Pelouze [13] in 1834. Malononitrile was synthesized by Henry in 1886 [15], and adiponitrile reportedly was identified by Henry in 1901 [16]. Naturally occurring nitriles were isolated from several plants in 1874 [17].

Giacosa [18], in 1883, mentioned that Pelikan and Maximowitsch had already investigated the toxic effects and possible therapeutic uses of nitriles. Giacosa was more interested in studying the transformation of such compounds by mammalian systems. He administered propionitrile subcutaneously (sc) to animals (species not mentioned). He observed the odors, colors, and precipitates of metabolites in exhaled air, urine, and feces. Some propionitrile was exhaled unchanged; some was metabolized and excreted in the urine as propionic acid. Giacosa gave a dog acetonitrile for a few days. It was first given in capsules with the food at doses up to 65 mg/kg/day and later by sc injection at doses up to 100 mg/kg/day. Other than the dog's refusal to eat the dosed food, no adverse effects were noted. From his own studies and reviews of those of other investigators, Giacosa concluded that the elimination of acetonitrile and its metabolic products was through the exhaled air and the urine.

Giacosa's discovery [18] of sulfocyanic acid in the urine of animals poisoned with acetonitrile or hydrogen cyanide led to the use of sulfur compounds as antidotes for hydrogen cyanide poisoning. In 1907, Hunt [19] wrote that Giacosa's discovery of sulfocyanic acid in the urine after administration of acetonitrile (and some other nitriles) was the beginning of pharmacologic knowledge of acetonitrile.

Meurice [20], in 1900, reported on the toxic effects of various nitriles in pigeons. Acetonitrile injected intramuscularly (im) caused no reaction at a dose of 500 mg/kg body weight, incomplete paralysis at 1,000 mg/kg, marked paralysis at 2,000-3,500 mg/kg, and death within 23 hours at 4,000 mg/kg. Propionitrile at 1,250 mg/kg caused death in 1.5 hours. At 1,100 mg/kg, n-butyronitrile caused convulsions and death in 1 hour. Isobutyronitrile at 2,500 mg/kg caused paralysis and death in 1.5 hours.

In 1906, Brissemoret [21] discussed some pharmacologic properties of several nitriles including acetonitrile and propionitrile. They were characterized as causing labored breathing, convulsions, asphyxia, and gastrointestinal irritation.

Hunt [22], in 1905-1906, while studying contemporary theories on thyroid function, injected acetonitrile sc into white mice that received powdered thyroid in the diet. Results indicated that the powdered thyroid modified metabolism so that the toxic effects of acetonitrile were not as severe as those seen in mice that were provided a diet without thyroid supplementation. This finding was the basis for what became known as the acetonitrile test for thyroid function in which the blood of patients with hyperthyroidism increases the resistance of mice to poisoning by acetonitrile [23].

In 1932, Marine et al [24] described experimental studies of nitriles that led to an initial understanding of the "essential" cause of thyroid hyperplasia. Further studies on acetonitrile by Marine and Rosen [25], in 1934, were significant in stimulating future inquiry into the cause of hyperthyroidism.

Hyden and Hartelius [26], in 1948, reported that malononitrile injected intravenously (iv) stimulated the formation of nucleoproteins in pyramidal cells of the cerebral cortex in rabbits. They also compared pyramidal cells of 11 "schizophrenic" persons with those of 4 "normal" persons, and they found that the pyramidal cells of schizophrenic persons were poorly developed compared with those of the other persons. Hyden and Hartelius also discussed previously unpublished clinical studies of Hyden and Reuterskiold on the use of malononitrile in the treatment of mental illness. Their work was followed by the clinical studies of MacKinnon et al [27] in 1949, Meyers et al [28] in 1950, and Hartelius in 1950 [29].

In 1964, Marigo and Pappalardo [30] described in detail the death of a patient who had received daily im injections of succinonitrile (200 mg) for

about 3 weeks as part of a therapeutic regimen for treatment of polyarthritis and bronchial inflammation. The 53-year-old man was hospitalized after he developed vomiting, psychomotor agitation, mental disorientation, and cold sweating; he died 2 hours later during one of many tonic-clonic convulsions.

A post-mortem examination revealed few abnormalities [30]. Unusual gross findings included cerebral and pulmonary edema and congestion in the brain, lungs, and gastrointestinal tract. Microscopic examination yielded evidence of fatty and vacuolar degeneration of the liver and marked tubulonephrosis. Recognition of the odor of bitter almonds when the brain was removed from the skull during the autopsy led to the initiation of a forensic toxicologic investigation of the man's death. The delayed onset of death made the possibility of primary poisoning from cyanide unlikely but suggested poisoning by a secondary source of cyanide, eg, a nitrile. The discovery that the patient had been undergoing therapy with succinonitrile for polyarthritis and bronchial inflammation, together with the presence of cyanide in the urine and various viscera, strengthened the conclusion that succinonitrile probably was the lethal agent. Marigo and Pappalardo proposed that detoxication of cyanide by the enzyme rhodanase in the patient failed to keep pace with the accumulation of cyanide.

This report [30] implicated succinonitrile as the responsible agent in a fatal poisoning. Using this information, the authors retrospectively analyzed three other observed fatal cases of sudden death from supposed toxic, but unspecified, agents. Because succinonitrile was involved in all three cases, two in therapeutic doses for mental depression (one following 6 days of 350 mg im injections and the other following 15 days of 200 mg/day im injections) and one as an accidental injection of 500-600 mg, the compound was considered to have contributed to the deaths. A fourth case, not personally observed by the authors but reported by them, was of an accidental ingestion of 400-500 mg of succinonitrile that led to death shortly thereafter. The symptoms were similar in all cases, with convulsions the common antecedent to death.

Effects on Humans

The effects of nitriles on humans (summarized in Table III-2) are described for compounds within three classifications: (a) mononitriles, (b) cyanohydrins, and (c) dinitriles. For each compound, workplace exposures or clinical cases are described first, followed by human experimental studies, when available.

(a) Mononitriles

In 1955, Grabois [31] described an incident in which 16 workers in a chemical manufacturing plant were accidentally exposed to ACETONITRILE

vapor while brush painting the inside walls of a storage tank with corrosion-resistant resinous primer paint. The paint consisted of an epoxy resin, a polysulfide resin, a polymerization catalyst, and an air inert filler. Acetonitrile was used as a thinner for the paint and was the only volatile solvent in the mixture. The paint was brushed on the inside of the tank by three workers at a rate of 2 gallons/hour.

On the 2nd day of the operation, about 7 gallons of paint were used. The paint was warmed to at least 25 C to facilitate application. In addition, the supply of fresh air to the compartments was reported to have been interrupted for about 15 minutes toward the end of the day. Fifteen workers, including 11 not involved in painting inside the tank, were exposed to the nitrile to some degree. The extent and duration of their exposure to acetonitrile during the operation were not specified.

One worker complained of chest pains and vomited, coughed, and expectorated blood. He developed convulsions and deep coma during the night and died the following morning. Two workers became seriously ill and were hospitalized the following morning; one of these workers was confused and lethargic. These three employees had worked together in brushing the primer resin paint on the inside of the tank. High concentrations of inorganic cyanide were present in the blood and urine of all three, but actual values were not reported. Thirteen other workers reported to a hospital; five were released after examination, and eight were admitted for overnight observation. No signs or symptoms for the eight workers were mentioned.

Amdur [32], in 1959, studied further the incident of exposure to acetonitrile reported by Grabois [31]. According to Amdur, the corrosion-resistant material consisted of the following four components: (1) a phenolic resin primer; (2) a catalyst containing diethylene triamine, sodium polysulfide (Thiokol), and 30-40% of acetonitrile; (3) a thinner containing 90-95% of acetonitrile; and (4) mica. After 1 day of attempted hand brushing of a mixture of these compounds on the walls of the tank, a modified procedure was adopted for the following days. The primer was heated to 25 C outside the tank before being mixed with the thinner, the catalyst, and a small amount of mica. Positive airflow through the tank was eliminated entirely, and exhaust air was operative for only 45 minutes late in the afternoon on the 2nd day of the operation. The worker who died had worked inside the tank for about 12 hours. Of the two other seriously affected workers, one had worked inside the tank for "about three hours...late in the afternoon," and the other had spent most of a 12-hour workday painting around the ports from the outside of the tank but had painted inside the tank for the last hour of the day. Two other men, less severely affected, had painted inside the tank for no more than 2.5 hours each on the 2nd day. Mixing the paint, sand blasting, and other activities in the work area for varying periods of time on the 2nd day accounted for the exposures of the 10 other workers who were evaluated. Following the

incident, the paint ingredients were not heated, adequate ventilation was provided, and the concentration of organic cyanide was kept below 17 ppm. There were no further incidents.

All workers who reported symptoms were affected within 3-12 hours after exposure on the 2nd day [32]. Their symptoms included chest pain, feelings of tightness in the chest and abdomen, palpitations, shortness of breath, nausea, vomiting, abdominal cramps, urinary frequency, headache, difficulty in swallowing, lassitude, and fatigue. One described his symptoms as being like those of "zinc chills." In a few cases, symptoms persisted for up to a month after the incident, and, in one case, urinary frequency was a continuing complaint. There were no preemployment physical data, but the authors noted that the condition resulting in complaints about urinary frequency may have preceded the exposures.

Signs observed among the exposed group included pale to ash-gray skin; vesicular eczema on the trunk and extremities; initial rapid pulse followed by slow, shallow, and irregular pulse; subnormal blood pressure; subnormal oral temperature; albuminuria; transient hepatomegaly; diminished deep tendon reflexes; transient paralysis of flexor muscles of the hands; stiff neck; and coma [32]. The author reported that 16 individuals were involved; however, only 15 cases were discussed in the report. Nine of these 15 cases were discussed in detail, and serum thiocyanate concentrations were reported for 6 additional workers.

Six workers, including the one who died, had elevated blood cyanide concentrations ranging from 33 to 970 µg% on the initial examination [32]. In the five survivors, these concentrations of cyanide decreased during the following 2 weeks. Seven of nine surviving workers had serum thiocyanate concentrations ranging from 6 to 23 mg% initially and showed a steady decrease in concentration during the next 48 hours. Six additional workers had initial serum thiocyanate values under 3 mg%. No serum thiocyanate value was reported for the worker who died. Gross post-mortem findings included cerebral, thyroidal, hepatic, splenic, and renal congestion.

Amdur [32] stated that the onset of symptoms was so delayed, by from 3 to 12 hours, as to be inconsistent with the well-known ability of cyanide to rapidly depress tissue oxidation by inhibition of the cytochrome oxidase system. He therefore concluded that acetonitrile could not have been the direct cause of the poisonous effects. The author related the signs and symptoms in these workers to thiocyanate, the detoxification product of cyanide, rather than to acetonitrile. He attributed the delayed response to slow release of cyanide and to its metabolism to thiocyanate. According to Amdur, this may have been due, at least in part, to the fact that the alkyl group of acetonitrile, ie, methyl, was less readily oxidized than higher members of the homologous series. He stressed the importance of safe handling of materials. Grabois [31] earlier had discussed

modifications in the ventilation of the tanks and work practices that reduced exposures. The painting of the tanks was completed without further incident.

Dequidt et al [33], in 1972, described the death of a 19-year-old male photographic laboratory worker after exposure to acetonitrile. The worker had handled acetonitrile in a closed vat for 2 days without incident. However, at the end of the 2nd day, he poured an unknown amount of acetonitrile and boiling water on the floor to clean it. The exact duration of his exposure was not determined. About 4 hours after leaving work and eating his evening meal, he experienced gastric distress with nausea and subsequently vomited during the night. When found the next morning, he was sweating profusely and alternately crying out sharply and lapsing into a comalike state. He was taken to a local hospital where he was given a sedative. Later he was transferred to a regional treatment center. There his heart and breathing ceased; he was revived with cardiac massage and an intracardiac injection of adrenalin. Blood examination revealed "large amounts" of cyanides and thiocyanates. He was given dicobalt tetracemate and hydroxycobalamine, neither of which relieved his symptoms. He died 6 days after the onset of poisoning by acetonitrile.

Blood, urine, and tissues (heart, lungs, liver, spleen, kidneys, brain, pancreas, and bladder were analyzed for acetonitrile and for free and combined cyanide [33]. At 44 µg/100 g of tissue, the spleen contained the largest amounts of free hydrogen cyanide, but only traces were found in the bladder. Combined hydrogen cyanide varied from 81 µg/100 g of tissue in the bladder to 1,112 µg/100 g of tissue in the lungs. The largest amounts of acetonitrile were found in the liver (1,184 µg/100 g of tissue) and kidneys (1,535 µg/100 g of tissue). On the 2nd and 3rd days after exposure, his blood contained free hydrogen cyanide, 112 and 87 µg/100 ml, respectively, and combined hydrogen cyanide, 376 and 1,038 µg/100 ml of blood, respectively. On the 3rd day after exposure, the acetonitrile concentration in the blood was 1,176 µg/100 ml and on the 4th day, the acetonitrile concentration in the urine was 311 µg/100 ml. The combined hydrogen cyanide concentration and free hydrogen cyanide concentration in the urine on the 2nd and 3rd days following exposure were 105 and 460 µg/liter, respectively. The authors found acetonitrile in most examined organs 6 days after poisoning, in spite of a large urinary excretion, and thus concluded that because acetonitrile remains in the body so long and releases cyanide so slowly, antidotes should be given slowly and continuously until the victim revives and the acetonitrile is no longer present in the blood.

In 1974, Dequidt et al [34] provided additional details on the acetonitrile exposure they had described in 1972 [33]. Other abnormalities after exposure were hypersalivation, conjunctivitis, totally suppressed or abnormally low output of urine, abnormally low blood pressure (systolic pressure between 70 and 100 mmHg), and albumin in the cerebrospinal fluid and urine.

In 1959, Pozzani and coworkers [35] studied the effects of acetonitrile vapor on 31- to 47-year-old men who inhaled acetonitrile vapor at 40, 80, and 160 ppm for 4 hours each on three separate occasions. Inhalation exposures took place inside a 7,900-liter chamber with a maximum ambient air temperature of 76 F (24 C) and an exhaust airflow of 1,400 liters/minute. Exposure of three men to acetonitrile vapor at 40 ppm was followed a week later by exposure of two of the same subjects at 80 ppm and, 9 days later, at 160 ppm. Blood cyanide and urine thiocyanate concentrations were measured at various times before and after all three exposures.

At 40 ppm, all three subjects recognized the odor of acetonitrile for the first 2-3 hours of the 4-hour inhalation period and then experienced some olfactory fatigue [35]. Throughout the night, following inhalation of acetonitrile at 40 ppm, the youngest subject reported a feeling of tightness in the chest and a sensation in the lungs similar to that experienced when inhaling menthol. The two older subjects exposed at 80 ppm reported no subjective response. After exposure at 160 ppm, one of the two subjects reported a slight transitory flushing of the face 2 hours after inhalation followed about 5 hours later by a feeling of bronchial tightness. These symptoms did not persist overnight.

Cyanide was not detected in the blood of any of the subjects [35]. Thiocyanate excretion in the urine did not correlate with exposure concentrations. The authors concluded that blood cyanide and urine thiocyanate concentrations were not reliable indicators of morbidity due to exposure to acetonitrile when exposures were at low concentrations for short periods of time.

Dalhamn et al [36], in 1968, reported on the absorption through the oral tissues of volatile and aerosolized components, including acetonitrile, found in cigarette smoke. Sixteen 20- to 65-year-old men and women who smoked from 0 to more than 30 cigarettes daily were studied. A smoke-dosage machine was used to blow cigarette smoke into the subjects' mouths; the smoke was never inhaled. After 2 seconds, the subjects blew the smoke (about 60 mm H_2O pressure) through precooled traps to remove water vapor and to collect the smoke component condensates.

From measurements of the amount of acetonitrile and other volatiles in the smoke that either passed through the mouth before condensation or was condensed directly from the smoking machine, it was possible to determine the amount retained in the mouth as a percentage of the amount initially present in the direct smoke [36]. This was done for each component. Of the smoke volatiles examined, acetonitrile was absorbed to the highest extent (74%). In similar experiments in which the smoke was inhaled, Dalhamn et al [37] found that the pulmonary retention of acetonitrile in smoke was 91 ±4.1%.

In 1962, McKee et al [38] reported that acetonitrile is present in the morning urine of smokers. This was confirmed by mass spectrometric analysis of the gas chromatographic fraction in a composite sample of the urine samples from 40 smokers. Acetonitrile concentrations ranged from 2.2 µg/100 ml urine for those smoking three cigarettes/day to values in excess of 20 µg/100 ml of urine for heavy smokers (up to 2.5 packs/day). An average value of 11.76 µg/100 ml urine was determined for the 40 smokers, with a correlation coefficient of 0.707 between the number of cigarettes smoked and the urinary excretion of acetonitrile. These results indicated that acetonitrile, once absorbed into the body, can be excreted unchanged in the urine. In contrast, the concentration of acetonitrile in a composite sample of the urine of 20 nonsmokers was not sufficient to permit a mass spectrometric analysis. The cigarette-smoking studies in humans by McKee et al and Dalhamn et al [36-38] demonstrated that acetonitrile was absorbed by oral tissues, retained by the lungs, and partly excreted unchanged in the urine.

Thiess and Hey [39], in 1969, described a workplace inhalation exposure to ISOBUTYRONITRILE of a 44-year-old man who was rendered unconscious, with convulsive movements of his upper limbs, while filling a tank. He had a soft and thready pulse, dilated pupils, shallow and gasping breathing, and secretion of viscous, glossy mucus from glands of the oropharyngeal area.

After admission to a hospital, the man's condition worsened and he had tonic-clonic movements of the upper extremities [39]. A powerful clenching of the teeth began, and cold sweat formed on the patient's forehead. He was cyanotic, and blood drawn for blood grouping was dark red. The pulse was small and thready, and its rate was 120/minute. The patient was given an iv injection of 1 mg of norepinephrine and was then treated with amyl nitrite, sodium nitrite, and sodium thiosulfate. The man's cyanotic condition diminished and his pulse became stronger, but he continued to have gasping breath and convulsive movements of the upper limbs. He was then given iv injections of lobeline and phenobarbital. Within the next 5-10 minutes, the patient's condition rapidly improved, and he was given a slow iv infusion of 300 ml of whole blood. Four hours after the initial exposure, the patient was fully conscious, although he remembered nothing after the ambulance entered the plant. During the following days, the patient complained often of headache but recovered gradually. He was able to leave the hospital symptom free on the 14th day after admission.

Two other apparently milder cases of isobutyronitrile inhalation exposure were reviewed by Zeller et al [10] in 1969. Details were not given, except that unknown concentrations of isobutyronitrile vapor reportedly produced headache, dizziness, and vomiting 10-60 minutes after exposure and that the intensity of the symptoms varied with the concentration and duration of exposure.

No reports of effects on humans following exposure to propionitrile or n-butyronitrile were found.

(b) Cyanohydrins

In 1960, Wolfsie [40] described an acute exposure of a 30-year-old worker to 70% aqueous GLYCOLONITRILE, in a chemical manufacturing plant. While the operator was filling 55-gallon drums with the solution, his clothing was contaminated because a leak occurred in the filling line that he held under his arm. Since the operator was unaware of his contact with the solution, the extent and duration of his exposure were unknown. The drumming station where he worked was described as a building equipped with adequate local exhaust ventilation. The operator complained of headache, dizziness, unsteady gait, and a sensation described as "rubbery legs," and he vomited within 5-10 minutes after leaving the operation. He was treated at the plant dispensary where he showered and received an unspecified injection from a physician. During the next 7 hours, he appeared to be pale and bewildered, perspired moderately, and had a pulse rate of 104/minute and a respiration rate of 24/minute. He vomited several times and experienced some memory loss. Later, he spoke irrationally, became increasingly unresponsive, and had an irregular rapid pulse. Supportive therapy included bed rest, intermittent inhalation of one ampule of amyl nitrite, 100% oxygen by face mask, and 30 cc of 25% sodium thiosulfate injected iv. Feeling well and apparently fully recovered, the worker was discharged from the hospital in less than 24 hours, without signs of illness. On his return to work the next day, he was assigned to a different job. He continued to feel weak and nauseated for 5 days after returning to work and to experience some congestion of his pharyngeal mucosa for a longer period of time.

A second acute exposure to glycolonitrile reported by Wolfsie [40] involved a 36-year-old worker who used the same kind of filling line and worked under the same environmental conditions as those just described. In this instance, the operator was aware that a 6- x 12-inch area of his clothing had been wet by an unknown quantity of the glycolonitrile solution during the course of the drumming, but it was almost dry by the end of the operation. In less than 1 hour after removing his clothing and taking a soap and water shower, he began to feel weak and dizzy. He drove home with difficulty. He had an unsteady gait and symptoms progressed to severe nausea, repeated vomiting, and severe vertigo; feeling chilled, he went to bed. When he awoke the next morning, his clothing was wet with perspiration, and he felt weak and "washed out." He had no appetite and still felt weak until he ate later in the day after returning to work.

Even though glycolonitrile appears from this study [40] to present a hazard by skin exposure, the possibility that exposure also occurred by inhalation cannot be ruled out. Although local exhaust ventilation equipment was operating, no evidence was provided to indicate that the system was operating efficiently. Wolfsie made two points in the report that suggest the possibility of concomitant inhalation exposure. First,

the subsequent abnormal finding of congested pharyngeal mucosa in the case of the first operator may be indicative of inhalation exposure. Second, glycolonitrile is odorless. Although neither worker reported detecting any odor, vapor and/or aerosol may have been present.

Sunderman and Kincaid [2], in 1953, reported on two fatalities from exposure to ACETONE CYANOHYDRIN. The first case was that of a plant worker whose clothing was splashed with an unknown quantity of acetone cyanohydrin when a tank overflowed. Three hours later, he complained of nausea and was referred to a hospital. On the advice of a physician, he returned to work, but he again felt nauseated. He became unconscious and convulsive and died 6.5 hours after initial exposure. His death was presumed to be associated with skin, and possibly respiratory, absorption of acetone cyanohydrin, although no autopsy record was available. Other details of the exposure were not reported.

The second fatality also involved a plant worker who purportedly drank an unknown quantity of unidentified alcohol obtained from a recovery tank containing traces of acetone cyanohydrin [2]. He lost consciousness and was given unspecified doses of sodium thiosulfate and sodium nitrite. Although he apparently regained consciousness, he died about 12 hours later. Again, no autopsy record was available. The effects produced by alcohol also may have contributed to the fatality.

Sunderman and Kincaid [2] also described nonfatal cases involving three operators who had dermal exposures to acetone cyanohydrin while packing pumps leading to and from storage tanks. The workers lost consciousness but revived when they were exposed to fresh air and their hands cleaned. They suffered no permanent injuries. The workmen stated that, ordinarily, when their hands were covered with grease, the effects of acetone cyanohydrin were minimal. The authors listed cardiac palpitation, headache, nausea, and vomiting as the effects of mild dermal exposure to acetone cyanohydrin.

In 1955, Krefft [41] cited an incident that occurred during a filling operation in a chemical factory. A glass flask containing acetone cyanohydrin burst, and 19 liters of the liquid splashed on the face and clothing of a 51-year-old worker. Her skin was partially washed, but her contaminated clothing was not removed. She was given milk about 5 minutes after the exposure; she subsequently vomited and became short of breath and unconscious. Ten minutes after the accident, tonic-clonic convulsions occurred. When she entered the hospital, her pulse was absent and Cheyne-Stokes respiration was present. She died 1 hour and 20 minutes after exposure, despite attempts to maintain vital functions. Autopsy findings included a bitter almond odor of the internal organs, particularly the brain; hyperemia of the brain and skin; dilatation of the right side of the heart; dark red blood; hyperemia and moderate edema of the lungs; and moderate gastric irritation.

The author [41] reported that death was caused by extensive skin exposure to acetone cyanohydrin over a period of time. Inhalation of an unknown concentration of free hydrocyanic-acid vapor was mentioned as an added factor based on a finding that the free hydrocyanic-acid content of the acetone cyanohydrin varied between 0.007% and 0.7%.

In 1960, Lang and Stintzy [42] reported an incident of acute occupational exposure to acetone cyanohydrin. A 19-year-old worker at a chemical synthesis plant had a portion of his pants wet with acetone cyanohydrin while he was dismantling a conduit containing residual acetone cyanohydrin. Although the quantity of acetone cyanohydrin to which he was exposed was unknown, it apparently did not exceed 30-40 ml. His skin reportedly had direct contact with his wet clothing for 40-60 minutes and with the dry residue for about 5.5 hours.

About 5 hours after initial exposure, the worker complained of headache, retching, a feeling of painful constriction of the throat, progressive weakness, numbness, and dizziness [42]. When he finished work, he changed his clothes and drove home with no apparent difficulty. Whether he washed or showered before changing clothes was not mentioned. After reaching home, the worker's gait was slow and unsteady; he vomited a small amount of bilelike material once; his headache and dizziness increased; and he retired without eating.

He was brought to a hospital approximately 8.5 hours after initial exposure in a state of deep coma [42]. His entire body was cyanotic and reflexes were absent, and he was short of breath. He underwent a period of transitory trismus and muscular fibrillations, followed by tonic-clonic convulsions. He awoke the next morning fully oriented though still tired and said that he remembered nothing that had happened after retiring on the previous evening. A diagnosis of slow intoxication by hydrogen cyanide was made after a review of a report describing the work clothes the patient had worn on exposure, which retained the characteristic odor of acetone cyanohydrin. The patient remained hospitalized for 10 days. He returned to work nearly a month after the incident.

The authors [42] considered this episode a rare example of delayed hydrogen cyanide poisoning resulting from the dissociation of acetone cyanohydrin into acetone and hydrogen cyanide. The dissociation of acetone cyanohydrin is favored by an alkaline medium, and this was considered to be present in the form of perspiration on the skin. The authors postulated that hydrogen cyanide easily permeated the vascular and lymphatic endothelium by the ability of acetone to dissolve lipid substances in these tissues.

Thiess and Hey [39], in 1969, described an exposure to acetone cyanohydrin involving a 23-year-old man who was filling large drums using a rubber hose connection from a tank car. Apparently this was not the usual

method, but it was employed because of a defective part. The affected worker was not wearing a face mask or rubber overalls, and the gloves he wore were made of cloth rather than rubber. During the operation, one glove got soaked; after completing the job, the man put the wet glove in his trouser pocket. Within 5 minutes he vomited. When he became unconscious 10 minutes later, he was taken to the company's infirmary. His breathing was difficult and irregular, and he was given artificial respiration. He regained consciousness after receiving amyl nitrite but lapsed again into unconsciousness and showed tonic-clonic convulsions of the extremities. After he was treated with sodium nitrite and sodium thiosulfate, his symptoms again subsided temporarily. When the soaked glove, which had served as a continuing source of exposure, was discovered in his trouser pocket, he was bathed and given a second course of sodium nitrite and sodium thiosulfate treatment. He improved quickly; he was hospitalized for 3 days and returned to work 8 days later.

Zeller et al [10], in 1969, described two cases of acetone cyanohydrin skin exposure and one of combined exposure to acetone cyanohydrin and isobutyronitrile but provided no details of exposure or effects. The authors did report that the effects of acetone cyanohydrin poisoning were generally like those of intoxication of isobutyronitrile. Thiess and Hey [39] also commented that, in the cases of acetone cyanohydrin skin exposure and isobutyronitrile inhalation exposure, the illnesses resulting from these two chemically related compounds were quite similar although the routes of exposure were different.

(c) Dinitriles

Hyden and Hartelius [26], in 1948, reported on the clinical use of MALONONITRILE in the treatment of various forms of mental illness. The authors found that administration of malononitrile to rabbits increased the concentration of protein and polynucleotides in slices of brain cortex, spinal cord, paravertebral ganglia, and other areas of the CNS examined by UV absorption spectroscopy. Using the same spectroscopic method, Hyden and Hartelius found that pyramidal cells of the frontal cortices of psychiatric patients contained less protein and nucleic acid than those of accident victims. Malononitrile was subsequently administered to 66 patients, most diagnosed as schizophrenic or depressed, as an experimental treatment based on the rationale that malononitrile might restore the cellular function by stimulating the production of protein and polynucleotides within the nerve cells. Fasted individuals were given malononitrile 5% solution iv during the course of treatment at doses ranging from 1.0 to 6.0 mg/kg of body weight. The number of doses given each patient ranged from 3 to 17. Infusions were given, on the average, 2 or 3 times a week with at least 1-day intervals. Each treatment lasted from 10 to 69 minutes. Tachycardia occurred 10-20 minutes after infusion of malononitrile in every case. Facial redness, headache, nausea, vomiting, shivering, cold hands and feet, muscle spasms, and numbness also were reported with varying frequency.

Convulsions were seen in two patients, neither of whom had a history of epilepsy, and cardiac collapse occurred in one patient with a congenital heart defect.

MacKinnon et al [27], in 1949, described side effects similar to those described by Hyden and Hartelius [26] in nine psychiatric patients given 2-4 mg/kg doses of malononitrile as a 5% solution. Patients received 10 iv administrations over a 2- to 3-week period. Toxic effects occurred 15 minutes after the injection. In contrast to the side effects reported by Hyden and Hartelius, no convulsions occurred in the group of patients; however, feelings of nausea often reappeared several hours after treatment.

In 1950, Hartelius [29] reported treating 40 psychiatric patients with malononitrile (5% solution). Doses averaging 2.4 mg/kg body weight were administered iv. Each patient received from 3 to 12 injections in 24 days. The average duration of each treatment was 48 minutes. Facial redness, tachycardia, and congestive flow of blood to the head were consistently observed throughout the treatment.

Meyers et al [28], as reported in 1950, treated six psychiatric patients with malononitrile (5% solution) at doses of 3-6 mg/kg of body weight administered iv. The patients, who were fasted before each treatment, were given infusions during a 21- to 60-minute period, with an average of about 30 minutes. Reactions during treatment included: flushing of the face, appearing 5 minutes after treatment began and increasing throughout treatment; onset of tachycardia in 10-15 minutes; feelings of nausea in 20-25 minutes; and vomiting in about 30 minutes. Patients became restless and acutely distressed. Veins of the head and neck became distended, and extremities were cold. In some cases, there was an increase in systolic blood pressure and a decrease in pulse pressure. The authors indicated that the dose at which toxic effects were produced and the time of their onset varied with the individual.

In 1955, Ghiringhelli [16] reported a case of acute accidental poisoning in which an 18-year-old man drank a few cc of ADIPONITRILE while at work. About 20 minutes after ingestion, he vomited and experienced tightness in the chest, headache, profound weakness with difficulty standing, and vertigo. On admission to the company infirmary, he was observed to be cyanotic. He had rapid heartbeats, rapid and raspy respirations, and a low blood pressure. His pupils were dilated and barely reacted to light. Tonic-clonic contraction of limb and facial muscles and mental confusion were also present. Initially, his stomach was pumped out; but when the symptoms did not subside, single doses of 15 cc of 25% sodium thiosulfate and 20 cc of 40% glucose were injected iv. The signs and symptoms subsided within 10 minutes after treatment began, and he appeared fully recovered for about 4 hours. Then his illness recurred and continued in greater severity for at least 2 hours. Following a second course of treatment with sodium thiosulfate and glucose, the patient slowly and completely recovered.

Zeller et al [10], in 1969, reviewed seven cases of skin exposure to adiponitrile. Six of the seven cases resulted in skin irritation and inflammation 5-15 minutes following exposure, but none required hospitalization. A seventh worker suffered extensive destruction of the skin of one foot after his shoe was drenched with adiponitrile. He required surgical treatment and was incapacitated for 117 days. No details of exposure or clinical manifestations were discussed for any of the cases.

In 1957, Reinl [43] reported on a study of 16 workers who were allegedly suffering ill effects from exposure to the vapor of TETRAMETHYLSUCCINONITRILE at an unknown concentration. The investigation began after five cases of convulsions and unconsciousness occurred during an 18-month period at one plant where workers used azo-isobutyronitrile as the propellant gas to produce polyvinyl chloride foam.

The workers, seven women and nine men, either had cut and welded slabs of newly expanded foam or operated presses and mixers, within poorly ventilated areas [43]. Their ages ranged from 18 to 58 years and their length of service from 2 months to 5 years. The tetramethylsuccinonitrile was released by thermal decomposition of the azo-isobutyronitrile. The study consisted of detailed medical histories and a physical examination, with a limited number of laboratory tests on only 3 of the 16 subjects. The results of the physical examinations and laboratory tests (serum protein electrophoresis and limited liver function tests) were inconclusive, and no characteristic or consistent abnormalities were noted.

The signs and symptoms reported at the time of the investigation [43] included headache (by 4) or a sensation of pressure within the head (by 12), dizziness (by 5), nausea (by 7), vomiting (by 5), a peculiar taste (by 3) and frothy spittle in the mouth (by 7), respiratory distress (by 4), fatigue (by 3), unconsciousness (by 2 women), and convulsions (by 5). Complaints were more prevalent among workers involved in the cutting, thermal welding, and storage of the foam than among press and mixer workers.

All signs and symptoms of overexposure subsided following the installation of improved ventilation in the work areas. All 16 workers were medically checked every 14 days for the year following the original investigation, and no further symptoms were found.

No environmental measurements of tetramethylsuccinonitrile or of any other airborne contaminant were reported. Since the workers were exposed not only to tetramethylsuccinonitrile but also to a number of other chemicals including vinyl chloride monomer and azo-isobutyronitrile, it is not possible to definitely ascribe the reported effects of exposure to tetramethylsuccinonitrile alone.

Epidemiologic Studies

No epidemiologic studies of workers at risk from selected nitriles were found in the literature.

Animal Toxicity

The animal toxicity data for individual species by various routes of administration for mononitriles, cyanohydrins, and dinitriles are presented in Table III-3. The LD_{50} values for mice, rats, guinea pigs, and rabbits are shown in Table III-4. Szabo (S Szabo, written communication, May 1978), using female rats (200 g) of the Sprague-Dawley-derived Charles River CD strain, determined approximate LD_{50} values for adiponitrile, n-butyronitrile, isobutyronitrile, propionitrile, malononitrile, and succinonitrile. These LD_{50} values by sc and ip administration are shown in Table VI-1 and provide a basis for quantitative comparisons of toxicity for some of the selected nitriles. The toxicities to animals of mononitriles, cyanohydrins, and dinitriles are discussed below.

(a) Mononitriles

Smyth and Carpenter [44], as reported in 1948, exposed Sherman rats, in groups of six each, to ACETONITRILE administered orally or by inhalation. Doses differing by a factor of 10 were used to estimate an LD_{50} value by oral administration, and exposure to acetonitrile at 8,000 ppm for 4 hours was used to assess the effects of inhalation. To evaluate dermal toxicity, the authors kept the clipped skin of rabbits in contact with acetonitrile for 24 hours by means of a rubber cuff surrounding the animals' abdomens.

Primary skin irritation and eye injury resulting from contact with acetonitrile were described as being comparable to that resulting from acetone exposure [44]. The single dose oral LD_{50} for acetonitrile was estimated to be 3.8 g/kg in Sherman rats. One of six rats died after inhaling acetonitrile at 8,000 ppm for 4 hours. The percutaneous LD_{50} for acetonitrile in rabbits was 3.9 g/kg.

In 1971, Kimura et al [45] presented the results of their studies concerning the effect of age on the acute oral toxicity of acetonitrile in rats. Test animals were newborn Sprague-Dawley rats (24-48 hours old, weighing 5-8 g), 14-day-old rats (weighing 16-50 g), young adult rats (weighing 80-160 g), and older adult rats (weighing 300-470 g). Analytical grade acetonitrile was administered orally via straight needle in undiluted form, and the nonfasted rats were observed for a week.

Observable signs of toxic action in the rats ranged from labored breathing to ataxia, cyanosis, and coma [45]. The acute oral LD_{50}'s for the 14-day-old, the young adult, and the adult rats were 0.16 g/kg, 3.1

g/kg, and 3.5 g/kg, respectively. Acetonitrile was significantly more toxic in the 14-day-old than in the adult rats ($P < 0.05$). The lowest dose of acetonitrile that produced any sign of toxicity in young adult rats was 1.6 g/kg. An accurate assessment of the LD_{50} of acetonitrile in newborn rats was not possible because of their extreme sensitivity to the compound.

In 1959, Pozzani et al [35] summarized investigations of the toxicity of acetonitrile administered by various routes to mice, rats, guinea pigs, rabbits, dogs, and monkeys. Twelve separate acute oral toxicity tests were performed over a 5-year period on an unspecified number of male and female rats (Carworth Farms-Wistar or Nelson albino strains), weighing 30-425 g. Acetonitrile was diluted in corn oil, water, or 1% aqueous Tergitol 7 for administration by gastric intubation. The LD_{50} values ranged from 1.3 to 6.7 ml/kg; male rats were about three times as susceptible as females. Guinea pigs, rabbits, dogs, and monkeys were similarly tested, and the LD_{50} values for the various species and routes of administration are given in Table III-2.

When two groups of six Carworth Farms-Wistar rats were exposed to acetonitrile vapor at approximately 53,000 ppm, three of six rats exposed for 30 minutes died and none of the rats exposed for 15 minutes died [35]. Twenty groups of 12 male or 12 female rats were exposed for 4 or 8 hours to acetonitrile vapor at concentrations ranging from 1,000 to 32,000 ppm. Calculated LC_{50}'s for the 8-hour exposures were 7,551 ppm (males) and 12,435 ppm (females); the 4-hour LC_{50} was 16,000 ppm (males and females). The 4-hour LC_{50}'s determined in three groups of six (male and female) guinea pigs each and three groups of four male rabbits each were 5,655 and 2,828 ppm, respectively. Exposure of three dogs for 4 hours at 16,000 ppm and above killed all dogs, whereas a 4-hour exposure at 8,000 ppm and below killed none of three dogs. Most resistant to acetonitrile vapor were the rats, followed in decreasing order by dogs, guinea pigs, and rabbits. Although male rats appeared to be more susceptible than females to 8-hour inhalation exposures to acetonitrile, no sex difference was observed in the 4-hour exposures.

Groups of 15 male and 15 female Carworth Farms-Wistar rats weighing about 140-200 g were exposed 7 hours/day, 5 days/week, for a total of 18 weeks, to acetonitrile at 166, 330, or 655 ppm [35]. Acetonitrile concentrations were checked four times/day with a portable Zeiss interferometer. Four groups of 15 male or 15 female rats under similar experimental conditions, but without exposure to acetonitrile, served as controls. No deaths and no significant differences between the test and control groups in growth rates or in relative liver and kidney weights were seen. Microscopic examination showed that, of the 28 rats inhaling 166-ppm vapor, 1 had macrophage clumps in the alveoli and another suffered lung collapse. Of the 26 rats inhaling 330-ppm vapor, only 3 rats showed lung abnormalities including bronchitis, pneumonia, atelectasis, and macrophage clumps in the alveoli. Rats that inhaled 655-ppm vapor had lung, kidney,

and liver damage. Also found were transitory lesions, such as alveolar capillary congestion and focal edema, often accompanied by bronchial inflammation, desquamation, and hypersecretion of mucus; cloudy swelling in kidney tubules; and central reversible osmotic swelling of mitochondria of liver cells.

Urine samples pooled (59-62 days) from the rats exposed to acetonitrile at 166 or 330 ppm were analyzed for thiocyanate [35]. Samples showed thiocyanate levels of 17-79 mg/100 ml, but there was no direct correspondence with exposure level. However, after a 3-day rest, the urine samples from both groups were free of thiocyanate.

Four rhesus monkeys were exposed to acetonitrile at 330, 660, or 2,510 ppm 7 hours/day, 5 days/week, for up to 99 days [35]. Three of the monkeys had received acetonitrile and sodium thiocyanate iv 3 months earlier, and one did not. None of the four monkeys had appreciable weight loss during the inhalation periods. The monkey exposed at 2,510 ppm appeared normal after the 1st day's exposure but died on the 2nd day during reexposure, following labored breathing and prostration. Autopsy revealed engorgement of the dural capillaries and pleural effusion. Two monkeys exposed at 660 ppm appeared normal for the 1st week of exposure, but they began to show poor coordination during the 2nd week. One of the monkeys died on the 23rd day of inhalation. The other died on the 51st day of exposure. The monkey exposed to acetonitrile at 330 ppm was killed after showing hyperextension reflexes and hyperexcitability toward the end of the 99-day exposure period. The three monkeys that died during the exposure period had dural venous sinus hemorrhages and occasional fibrous tissue proliferation in the lungs.

Three male rhesus monkeys and three male dogs were exposed to acetonitrile at a nominal concentration of 350 ppm for 7 hours/day, 5 days/week for 91 days [35]. A significant decrease in the mean body weight of the dogs was observed on 10 occasions during the first 72 days of the study, whereas no striking weight changes were seen in the monkeys. Other changes included a depression of the hematocrit and hemoglobin values of the dogs during the 5th week, whereas the erythrocyte count of one of the monkeys was significantly increased throughout the study. At autopsy, all monkeys showed slight to moderate hemorrhage in the dural venous sinuses. Microscopic examination of lung tissues showed focal emphysema, as well as fibrous tissue and macrophage proliferation. The dogs showed no gross macroscopic changes. Microscopic examination revealed some focal emphysema and alveolar septal proliferation.

Blood samples from the monkeys contained 4.7-5.4 µg of cyanide/100 ml following a 5-consecutive-day inhalation period and 1.8-2.9 µg/100 ml after 2 days of no exposure [35]. The dogs showed 7.6-9.2 µg cyanide/100 ml following a 5-day inhalation period, and no detectable cyanide after a 2-day rest. Both dogs and monkeys excreted thiocyanate in the urine during

exposure to acetonitrile, and detectable amounts were still present 2 days postexposure.

To measure how much cyanide was formed during inhalation of lethal amounts of acetonitrile, the authors [35] exposed three dogs at 16,000 ppm for 4 hours. Blood cyanide levels reached a peak of 305-433 (u)g/100 ml after 3 hours of exposure and then decreased during the final hour. All three dogs died within 14 hours after exposure.

Pozzani et al [46], in their comparison of the oral and inhalation toxicities of equivolume mixtures of several industrial chemicals, first determined single-dose oral LD_{50}'s and single 4-hour inhalation LC_{50}'s for each of seven chemicals: acetonitrile, acetone, dioxane, ethylacetate, carbon tetrachloride, toluene, and propylene oxide. Groups of six female Carworth Farms-Nelson rats of unspecified weights and age were used. For the oral LD_{50} determination, the rats in each group received single oral doses of undiluted acetonitrile or an equivolume mixture of acetonitrile and one of the chemicals in each of six tests. For the LC_{50} determinations, the rats were allowed to inhale vapor of acetonitrile alone or in a 50:50 vapor mixture with each of the six other chemicals, in turn, for 4 hours.

For acetonitrile, the experimental oral LD_{50} was 6.5 g/kg, and the single 4-hour inhalation LC_{50} was 26.9 mg/liter [46]. Of the mixtures tested, only the acetonitrile-acetone administration had a tendency to yield more than additive effects by inhalation (LC_{50}, 14.6 mg/liter) and by oral administration (LD_{50} = 2.2 g/kg), as compared with expected values of 39.7 ml/liter and 9.99 ml/kg, respectively. All the other chemical pairs including acetonitrile produced essentially additive effects when administered either orally or by inhalation. Smyth et al [47] also determined that an equivolume mixture of acetone and acetonitrile given orally to rats was more acutely toxic than would have been expected had their toxicities been additive.

In 1932, Marine et al [48] studied the production of goiter and exophthalmos in prepubertal rabbits following sc administration of acetonitrile for up to 63 days. Male and female rabbits of Dutch and Belgian breeds, aged 3-5 months and weighing 1,184-1,911 g, were given daily injections of 79-118 mg/cc of acetonitrile. Exophthalmos developed as early as day 20 in the 3-month-old rabbits that received daily injections of 79 mg of acetonitrile. According to the authors, this effect was seen only in the young Dutch rabbits and did not occur at all in the adult rabbits (6 months and older) of either strain.

Marine et al [48] noted a close relationship between exophthalmos and thyroid hyperplasia. Exophthalmos was absent in rabbits that showed little or no thyroid hyperplasia. When hyperplasia was more intense, exophthalmos appeared and was said to be proportional to the degree of hyperplasia.

Exophthalmos is commonly a symptom of hyperthyroidism, but the authors did not speculate as to whether its occurrence was a direct or thyroid-mediated effect.

In 1932, Spence and Marine [49] investigated the production of thyroid hyperplasia in rats given acetonitrile in small doses. Twelve female albino rats, six litter mates aged 3 months and six litter mates aged 5 months, were divided into three groups, two rats from each litter. The animals were fed a nongoitrogenic diet and received daily sc injections of acetonitrile in water at doses of 0.08 cc (62.4 mg), 0.04 cc (31.2 mg), and 0.02 cc (15.6 mg).

At the end of 21 days, one rat from each group was killed [49]. At autopsy all animals showed only slight thyroid hyperemia. After 28 days of treatment, the rats showed definite thyroid hypertrophy. During the next 8 days, the daily doses were gradually increased for the remaining nine rats until those initially on the smallest dose were receiving 0.05 cc (39 mg), and those initially on the largest dose were receiving as much as 0.15 cc (117 mg) of acetonitrile daily without any sign of cyanide poisoning. After 36 days of treatment, the thyroids were larger with increased hyperemia. In general, these changes were proportional to dose.

A similar study in mice was carried out by Spence and Marine [49]. Twelve mice, 3.5 weeks old, weighing an average of 13 g and on the same diet as the rats, were divided into three groups to receive daily sc injections of acetonitrile at doses of 0.005 cc (3.9 mg), 0.0025 cc (1.95 mg), and 0.00125 cc (0.975 mg). After 11-34 days, only a slight thyroid reaction was produced. From these results, the authors concluded that, because thyroid reactions obtained in rats and mice exposed to acetonitrile were far less than those reported [48] in rabbits receiving much smaller doses, rats and mice possess considerable resistance to goitrogenic substances.

In 1927, Crivellari [50] reported that removal of the adrenal glands of white rats resulted in a hundredfold increase in sensitivity to acetonitrile injected sc. In 1934, Degti [51] found that removal of the suprarenal gland capsules of albino rats resulted in a twofold increase in sensitivity to acetonitrile injected sc.

Dessau [52], in 1935, described the results of his investigations of the protective function of the adrenal gland in acute acetonitrile poisoning in rats. Acetonitrile, at a dose of 5.0 mg/g, was administered intraperitoneally (ip) to 164 adrenalectomized rats weighing 50-150 g. Ninety of the rats had received adrenal implantations in the peritoneal cavity or on the ovaries. At 24 hours after the acetonitrile injection, only 8 of the 74 nonimplanted rats were still alive, whereas 19 of the 90 adrenal-implanted animals survived. Microscopic examination of the implantation sites in the surviving rats showed only altered residues of

adrenocortical substance. In a separate experiment, epinephrine at 10 and 100 µg was said to be without influence on the acetonitrile resistance of nine rats, but no actual results were cited. In yet another experiment, adrenalectomized rats were reportedly one-sixth less resistant to acetonitrile (tested 4-5 days after surgery) than control rats. No further experimental details were provided for these observations. The author concluded that the adrenal gland protects against acetonitrile poisoning and that the resistance-increasing factor is associated with the adrenal cortex rather than the medulla.

In 1972, Dequidt and Haguenoer [53] described their preliminary investigation to determine the distribution, metabolism, and excretion of acetonitrile in rats, in order to find the best antidotes and treatment in humans who had been overexposed to this compound. Furthermore, they wanted to define safe limits for acetonitrile exposure in the occupational environment.

Initially, two groups of four rats each and one group of three rats were given a single ip injection of 780 mg/rat (average weight 330 g) [53]. All of the animals died in 3-12 hours. The liver, lungs, spleen, kidneys, heart, brain, muscle, intestines, stomach, testes, and skin of each animal were analyzed for acetonitrile and both free and combined hydrogen cyanide content. At 359 µg/100 g tissue, combined hydrogen cyanide concentration was lowest in the liver; the concentrations in the spleen, stomach, and skin were 1,347, 1,757, and 1,045 µg/100 g of tissue, respectively. Free hydrogen cyanide found in the organs varied from 17 µg/100 g of tissue in the liver to 347 µg/100 g for the spleen. Acetonitrile was found to be evenly distributed in various organs.

Haguenoer and colleagues [54], in 1975, reported on the distribution and metabolic fate of acetonitrile in white male Wistar rats. Each rat (housed in groups of three) was injected ip with acetonitrile at single doses of 2,340, 1,500, or 600 mg/kg. Rats given the two highest doses died as a result of exposure, whereas rats given 600 mg/kg survived with no apparent signs of toxicity but were killed for autopsy on the 11th day. The heart, lungs, liver, spleen, kidneys, stomach, intestines, skin, muscle, brain, and testes of each animal were examined for acetonitrile and for free and combined hydrogen cyanide. The combined hydrogen cyanide consisted essentially of thiocyanates, plus cyanohydrins and cyanocobalamine.

On each of the 11 days postexposure, urine was collected from the 600 mg/kg rats for measurements of free and combined hydrogen cyanide and acetonitrile [54]. On day 1, the urine contained an average of 92 µg free hydrogen cyanide, 5,391 µg combined hydrogen cyanide, and 20.3 mg acetonitrile. No acetonitrile was measured after day 4, and free hydrogen cyanide excretion averaged 5.3 µg/animal on day 11. Each control rat excreted from 1.5 to 5.2 µg of free hydrogen cyanide and from 9 to 40 µg

combined hydrogen cyanide each day. No acetonitrile was found in the urine of control rats at any time. Tissue analyses at autopsy showed no important differences between the treated and the control rats. There was a dramatic decrease in the excretion of both forms of hydrogen cyanide after day 4 when acetonitrile was no longer present in the urine.

The authors [54] concluded that acetonitrile was low in toxicity and that the amount of the cyanide ion present was dependent on the rate of release of cyanide from the parent molecule. Also, they postulated that the large amounts of hydrogen cyanide liberated at the high doses (2,340 and 1,500 mg/kg) were responsible for the rat deaths.

In 1975, Haguenoer et al [55] reported their observations on the distribution and metabolic fate of acetonitrile in the rat after inhalation of acetonitrile at 2,800 or 25,000 ppm. At 25,000 ppm, all three rats died 30 minutes after the start of the exposure, following difficult breathing and cyanosis. Chemical analysis of various organs (heart, lungs, liver, spleen, kidneys, stomach, intestines, skin, muscle, brain, and testes) were made. The mean concentrations of acetonitrile ranged from 136 to 2,438 µg/100 g of muscle and kidney, respectively, and of free hydrogen cyanide, from 27 to 402 µg/100 g of liver and spleen, respectively. The free hydrogen cyanide was more uniformly distributed, except in the spleen (402 µg/100 g) and in the brain (129 µg/100 g), where it was somewhat higher.

The authors [55] stated that the high concentrations of acetonitrile (2,438 µg/100 g) found in the kidneys may have been due to either very high excretion of the acetonitrile or renal blockage. Acetonitrile concentrations in all the organs of rats exposed by inhalation (25,000 ppm) were up to 16 times those observed in a similar ip study [54]. In contrast to the latter study in which ip administration of acetonitrile was associated with a latency period of 3-12 hours between dosing and death, the rats in the present study died immediately after inhalation.

In the second experiment, three rats inhaled acetonitrile at 2,800 ppm, 2 hours/day for up to 5 days [55]. All showed labored breathing, temporary anuria, and diarrhea. After the third exposure, one rat died with lung and brain hemorrhages. After the fourth exposure, the remaining two rats suffered paralysis and decreased urinary excretion. One died at the start of the fifth exposure, and the other died 2 hours after the exposure was completed. Both rats had lost about 45% of their body weight during 5 days of exposure. Autopsies of the rats revealed that all the organs examined contained concentrations of acetonitrile and free hydrocyanic acid in the range of 96.0-286.9 and 53-990 µg/100 g tissue, respectively. Organ concentrations of acetonitrile were high but variable in the three animals (highest in the kidneys, 286.9 µg/100 g tissue). These values were lower than those noted for the 25,000-ppm intoxications. The authors attributed this to a greater pulmonary elimination (exhaled air) of the acetonitrile between exposures. By comparison, the average organ concentrations of free

hydrocyanic acid were slightly higher than those for the 25,000-ppm group, particularly in the spleen (990 µg/100 g tissue). However, the relative increase was greatest in the heart (4.9 times) and stomach (5.6 times) compared with only 2.4-fold in the spleen.

The authors [55] stated that the organ concentrations of hydrogen cyanide in the animals that died from inhaling acetonitrile were similar to those found in the animals that died from ip doses of acetonitrile. Additionally, the results implied that there was no quantitative relationship between the organ concentrations of the free hydrogen cyanide and exposures to acetonitrile. At either concentration of acetonitrile, a lengthy and persistent anuria was always observed as one of the effects. Such signs varied with the amount of acetonitrile inhaled and with the sensitivity of the animal.

In 1972, Szabo and Selye [56] reported the ulcerogenic effect of PROPIONITRILE in female rats. Forty test animals were divided into 4 groups of 10 rats each. Twenty animals, 10 each with a mean body weight of either 200 or 100 g, were administered sc doses of propionitrile three times daily for 4 days. The daily dose was increased from 6 mg/100 g body weight on day 1 to 8 mg/100 g on day 2, 15 mg/100 g on day 3, and 20 mg/100 g on day 4. Twenty animals, 10 each with a mean body weight of 100 or 200 g, were given sc doses once a day for 4 days. The daily dose was increased from 15 mg/100 g body weight on day 1 to 20 mg/100 g on day 2, 40 mg/100 g on day 3, and 50 mg/100 g on day 4. Duodenal tissues from rats that died or were killed with overdoses of chloroform were prepared for microscopic examination. Other unspecified organs were examined for gross and microscopic changes.

Szabo and Selye [56] observed that female rats given propionitrile in single or multiple sc injections at 6-50 mg/100 g body weight for 4 days developed duodenal ulcers, often perforating, on the 4th or 5th day of the experiment. The ulcers developed on the antimesenteric mucosal surface of the duodenum about 5-8 mm caudal to the pylorus. An unstated number of rats administered propionitrile died on day 2 of exposure. Examination of the duodenum of these animals showed no occurrence of duodenal ulcers.

Eight of 10 rats (mean body weight of 200 g) that were administered propionitrile sc in doses of 6 mg/100 g, 8 mg/100 g, 15 mg/100 g, and 20 mg/100 g of body weight three times a day for 4 days developed lesions of the duodenal mucosa [56]. Four of these eight rats had deep erosions in the duodenum, which involved the muscularis mucosae in some animals. The four remaining rats developed perforation of the duodenum with subsequent ulcer penetration into the liver. One rat also showed a perforated gastric ulcer, accompanied by peritonitis. Four of 10 rats (mean body weight of 200 g), administered propionitrile sc in doses of 15 mg/100 g, 20 mg/100 g, 40 mg/100 g, and 50 mg/100 g of body weight once a day for 4 days, subsequently developed duodenal ulcers. One of the four animals had a

perforated duodenum and accompanying peritonitis. In groups (mean body weight of 100 g) treated once or three times daily, one rat in each of the single- and multiple-dose studies developed duodenal ulcers. No structural changes in other body organs (not specified) were observed following propionitrile administration; however, evidence of lung edema was reported in animals that received unspecified doses of propionitrile. Rats administered propionitrile developed prostration and dyskinesia (number of animals and dosage not specified). Mortality was 80-100% in the treated animals. Most of the rats died by the 4th day of dosing.

Szabo and Selye [56] concluded that susceptibility to the ulcerogenic potential of propionitrile was age and dose related. Adult rats (200 g) were more likely than young ones (100 g) to develop duodenal ulcers. Also, rats administered propionitrile once a day for 4 days showed a lower incidence of duodenal ulcers than did those rats receiving a similar dose three times a day. Szabo et al [57] reported similar results in 1977 as part of their study on the influence of propionitrile on gastric acid secretion in female rats.

In 1975, Giampaolo et al [58] reported on the cellular effects of propionitrile in the stomach and duodenum in female rats. Rats weighing 200 g were administered either a single sc dose of 6 mg/100 g body weight of propionitrile or two doses 3 hours apart. The animals were killed 2 hours following the single dose or 5 or 8 hours after the injection of the two doses. Portions of tissue from the stomach and duodenum were fixed in Karnovsky's fixative by luminal or aortic perfusion and prepared for examination by electron microscopy.

The authors [58] found that propionitrile induced structural changes in the cells of the duodenum and stomach in female rats. Morphologic changes observed in the duodenal cells included vacuolization and alteration of the nuclear chromatin pattern, disarray and clubbing of the microvilli, and a progressive necrosis of cells down the sides of the villiferous folds. Giampaolo et al also observed a dilation of the intracellular canaliculi in the acid-producing parietal cells of the gastric mucosa 5 hours following two injections of propionitrile. Structural changes in the duodenum were not reported 2 hours after a single injection. These findings generally concur with Szabo and Selye's earlier report [56] of propionitrile-induced duodenal lesions in rats.

Dzau and associates [59], in 1975, reported that the incidence and intensity of propionitrile-induced duodenal ulcers in female rats were reduced by 50% following administration of metiamide, a histamine antagonist. These findings are consistent with another report [60] of a reduction in ulcer formation following treatment with gastric antisecretory agents.

Haith and coworkers [61], in 1975, described preliminary investigations of the effects of bilateral vagotomy and hypophysectomy in female rats

treated with propionitrile. They reported that bilateral vagotomy completely inhibited the occurrence of duodenal ulcers in rats and that hypophysectomy significantly reduced the incidence and severity of duodenal lesions. The authors concluded that the CNS affected the ulcerogenic property of propionitrile.

In 1975, Robert et al [60], in a report on factors that influence the ulcerogenic effects of propionitrile in rats, observed a decrease in the frequency of duodenal ulcers in rats that were fasted throughout the experiment, as compared with those that were allowed to eat at will. Male rats were more resistant than females to the induction of duodenal ulcers by propionitrile; the incidence in males was 15% vs 80% in females. There appeared to be no significant differences among the toxicities of propionitrile administered by various routes.

In a second series of experiments, the occurrence of duodenal ulcers was prevented by methscopolamine bromide and 16,16-dimethyl prostaglandin E_2 [60]. The effects of these agents were dose dependent. Prednisolone increased the toxicity of propionitrile in rats: 83% of the animals administered prednisolone sc along with propionitrile died as compared with 8% of those administered only propionitrile (60 mg/kg sc twice a day). Propionitrile-induced ulcers were not significantly affected by adrenocorticotropin but, at the highest dose (12 USP units), the mortality decreased from 42 to 8%. Desoxycorticosterone did not significantly influence the toxicity or ulcerogenicity of propionitrile in rats.

In 1975, Szabo and Reynolds [62] reported on the ulcerogenic effect of propionitrile. Female Spraque-Dawley rats (200 g) were administered sc doses of propionitrile. The doses given were 60 mg/kg, 80 mg/kg, 100 mg/kg, and 100 mg/kg three times per day on days 1, 2, 3 and 4, respectively. All animals died as a result of exposure before the 5th day. The authors reported that 80% of the rats had developed duodenal ulcers, but they observed no adrenal necrosis. Szabo and Reynolds considered propionitrile and some structurally related compounds to be potent ulcerogens in rats.

Haguenoer et al [63], in 1974, published animal studies of n-BUTYRONITRILE. Eighteen male rats of unspecified strain were divided into four exposure groups of three rats and one exposure group of six rats. All rats in the first four groups were administered a single ip dose of pure n-butyronitrile and were observed until death. Autopsies were performed; and tissues from the heart, lungs, liver, spleen, kidneys, stomach, intestines, skin, muscle, brain, and testes were examined to determine average concentrations of n-butyronitrile and free and combined hydrogen cyanide.

The first group of three rats (average weight 260 g) received single ip doses of 1,440 mg/kg [63]. The rats became comatose and cyanotic, and all

died within 90 minutes. Evidence of cerebral hemorrhages was seen in one rat at autopsy. All organs contained n-butyronitrile, free hydrogen cyanide, and combined cyanides. The highest average concentration of n-butyronitrile was found in the lungs, whereas the highest free hydrogen cyanide concentrations were in the heart and brain.

The second group of three rats (average weight 323 g) received n-butyronitrile in single ip doses of 600 mg/kg [63]. The rats became convulsive, short of breath, and comatose; and all died within 75-120 minutes after exposure. Two rats also had excess salivation. Except for the lungs, where the average n-butyronitrile concentration was only about 20% of the average 1,440-mg/kg dose, organ concentrations of n-butryonitrile averaged about 50% less. Free hydrogen cyanide was present in all organs and at the same order of magnitude as found at doses of 1,440 mg/kg. Combined hydrogen cyanide was present in all organs at lower average concentrations than those found at doses of 1,440 mg/kg, except that in the brain it was almost twice as great.

The third group of three rats (average weight 300 g) received single ip doses of 300 mg/kg [63]. In this group, respiration rate increased, and the animals became comatose before death occurred 12-14 hours after injection. n-Butyronitrile was present in all organs examined, but at lower average concentrations than at previous doses (one-third to one-eighth of those found at doses of 600 mg/kg). Free hydrogen cyanide was present in all organs at average concentrations close to those found at both previous doses. Combined hydrogen cyanide average concentrations were two to eight times greater than those found at both previous doses.

The fourth group of three rats (average weight 285 g) received single ip doses of 150 mg/kg [63]. The rats suffered nasal hemorrhages, and cyanosis preceded their deaths 21 hours after exposure. As in the other groups, n-butyronitrile was present in all organs examined at lower average concentrations than those found at previous doses. Average concentrations of both free and combined hydrogen cyanide showed a general increase over those found at doses of 300 mg/kg.

The group of six rats (average weight 290 g) was administered a single ip dose of 100 mg/kg of n-butyronitrile solution [63]. The animals were observed until death or for 8 days; at that time the surviving rats were killed. Autopsies were performed on all rats, and n-butyronitrile and free and combined hydrogen cyanide concentrations were determined in the organs cited above. Two rats died within 24 hours of exposure, and four were killed after 8 days. In the two rats that died, average concentrations of n-butyronitrile in various organs were less than those found at previous doses. However, average concentrations of free and combined hydrogen cyanide were greater than those found at previous dose levels, especially in the heart, spleen, kidneys, stomach, and muscles. The animals that were killed after 8 days had only very small amounts or traces of

n-butyronitrile, as well as greatly reduced free and combined hydrogen cyanide concentrations, as compared with other doses.

Urinary excretion of n-butyronitrile and free and combined hydrogen cyanide also were measured over the 8-day period for the group of six rats [63]. n-Butyronitrile was still present in the urine through the 8th day. The authors believed that retention of n-butyronitrile was attenuated by pulmonary elimination, although it was still present in most of the organs after 8 days. In the third group, n-butyronitrile was found in the exhaled air, and 116 μg was found in the urine. The authors stated that pulmonary elimination was greater, although no data were given. Free and combined cyanides were eliminated in amounts greater than n-butyronitrile, especially during the first 2 days. The authors concluded that the slow urinary excretion and the relatively low solubility of n-butyronitrile in water were attributable to the number of carbon atoms in the aliphatic chain of the nitrile.

The lethal dose of n-butyronitrile for all the animals was 150 mg/kg [63]. As the size of the dose decreased, there was an increase in the time to death. There was a parallel increase in the ratios of the combined cyanides to the free cyanides with an increase in the time before death occurred. The authors concluded that the increase in the time before death allowed for more n-butyronitrile to be metabolized and transformed to free and combined cyanides. This was supported in the case of the second group with regard to the average concentrations of combined hydrogen cyanide, especially in the brain. What remains unclear, however, is which compound was responsible for toxic effects at the cellular level.

Szabo and Reynolds [62], in 1975, reported effects of n-butyronitrile on the duodenum and adrenal glands in rats. Female Sprague-Dawley rats (200 g) were given sc doses of n-butyronitrile three times a day at 100 mg/kg on days 1 and 2 and 200 mg/kg on days 3 and 4. The animals were autopsied soon after death or were killed and examined on the 5th day. Forty percent of the rats died as a result of the exposure. The authors reported that 80% of the rats had developed duodenal ulcers and 20% showed adrenocortical necrosis.

In 1971, Tsurumi and Kawada [64] reported on studies of the toxicity of ISOBUTYRONITRILE in animals. Acute toxicity studies were conducted using an ip route of administration in an unspecified number of male mice weighing 17-20 g each. Doses ranged from 0.4 to 0.8 g/10 g. Immediately following injection, the mice were considered to have signs of slight hyperkinesia. The frequency and amplitude of respiration also had increased. A few minutes after injection, they rolled to their sides. Clonic movements of the limbs were observed. The frequency of respiration decreased, and sensitivity to pain at an unspecified site diminished gradually and then disappeared. Corneal reflexes remained normal. Their respirations stopped altogether 20-30 minutes after injection, and

autopsies were performed. The hearts were in a state of general dilatation, no contraction of the ventricles was observed, but feeble contractions of the atria were still present. The authors concluded that, in mice, isobutyronitrile induced a central paralyzing effect and death by inhibition of respiration. The lethal dose of isobutyronitrile administered ip to mice was assumed to be below 38.6 mg/kg, but the exact lethal dose could not be determined due to the potency of the compound and the difficulty of administering a smaller dose.

Another study [64] of acute toxicity used an unspecified number of Wistar-strain female rats weighing 130-150 g. Apparently, a single dose of isobutyronitrile was administered either ip or orally at seven to eight different dose levels to groups of six animals. The LD_{50} values after 72 hours by both routes of administration were calculated. The signs observed in rats after ip or oral administration were similar to those observed in mice. The ip LD_{50} was calculated as 0.2 g/kg, and the oral LD_{50} was calculated as 0.98 ml/kg.

The acute toxicity of isobutyronitrile by inhalation also was studied in mice and rats [64]. Fifty milliliters of isobutyronitrile were placed in the bottom of an exposure chamber 18 cm in diameter, and the lid was closed. The isobutyronitrile vaporized naturally at a temperature of 20 C for 10 minutes, producing a chamber atmosphere nominally saturated with isobutyronitrile. Animals then were placed on a metal net above the liquid. Fifty mice and 50 rats of unspecified strain, sex, and weight were exposed in subgroups of 5 mice or 2 rats for various lengths of time. After exposure, the animals were returned to a normal environment and observed for 24 hours. The fraction of deaths occurring as a function of exposure time is shown in Table III-1. Signs similar to those described for ip and oral exposure were observed. The authors concluded that mice are more sensitive than rats to isobutyronitrile.

The effect of iv-administered isobutyronitrile on cardiac function was studied in 2.5-kg rabbits [64]. Information on age, sex, strain, or the number of animals used was not specified. At doses below 0.01 mg/kg, isobutyronitrile produced no remarkable effects. At doses higher than 0.01 mg/kg, there was a decrease in blood pressure, blood flow, and respiration. A further dose of 0.1 mg/kg resulted in death of all the animals. The authors observed a decrease in blood pressure, blood flow, and respiration rate and a decrease in the frequency of heartbeats. The heart ceased functioning after 30-40 minutes.

The authors [64] concluded that the direct cause of death after administration of isobutyronitrile was respiratory arrest from depression of the central mechanism of ventilatory activity. This conclusion was supported by recordings on the electrocardiogram (ECG) of continued heartbeats after respiration had ceased.

TABLE III-1

DEATHS WITHIN 24 HOURS OF EXPOSURE OF
MICE AND RATS TO ISOBUTYRONITRILE AT NOMINAL SATURATION IN AIR

Species	Exposure Time (minutes)	Deaths
Mice	2.0	10/10
"	1.5	7/10
"	1.0	5/10
"	0.5	3/10
"	0.25	0/10
Rats	10.0	10/10
"	8.0	6/10
"	6.0	4/10
"	5.0	1/10
"	4.0	0/10

Adapted from reference 64

Local effects of isobutyronitrile also were investigated in rabbits [64]. Isobutyronitrile was applied to the conjunctiva of one eye of each rabbit from a dropper and removed after 1 minute. Doses of 7.7 mg produced no remarkable effects, whereas doses of 15.5 mg produced reddening of the eyelids and conjunctiva, edema, and tearing. Increased doses of isobutyronitrile resulted in loss of the corneal reflex. Isobutyronitrile was injected sc into one ear of each rabbit with the opposite ear used as the control. Doses of 7.7 mg produced no remarkable abnormality, and doses of 15.5 mg produced reddening at the injection sites. Effects became more distinctive in proportion to increased doses of isobutyronitrile, and the injection site showed a whitened and damaged center surrounded by an erythematous periphery.

The effects of repeated exposure to isobutyronitrile were studied in blood and other tissues of 80 male and female Wistar rats, initially weighing approximately 160 g each [64]. The rats were divided into 8 groups of 10 animals of the same sex. For each sex, there were three exposure groups and one control group. Each exposure group received isobutyronitrile once daily for 14 days by one of the following doses and routes: 23.2 mg/kg or 38.6 mg/kg administered ip or 0.2 g/kg given orally.

No signs of toxic effects or deaths occurred during the course of administration [64]. Male rats receiving 0.2 g/kg orally had the lowest

mean body weights during the period of administration relative to the other male exposure groups and the male control group. From the data provided, this group also showed the least average increase in weight during the same period relative to each of the male groups. No significant changes in values for erythrocyte count, hematocrit, hemoglobin, specific gravity, or differential count were found in any of the exposed groups relative to their control group. Male and female groups receiving 0.2 g/kg orally did show lower leukocyte counts relative to their respective control groups. Male and female groups receiving either ip dose of isobutyronitrile did not show significant changes in leukocyte count relative to their controls. No significant changes were found in the serum enzyme studies--serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), and alkaline phosphatase--for any of the groups. No significant differences among organ weights were found in animals receiving either ip dose of isobutyronitrile. Male and female groups receiving 0.2 g/kg orally showed slight weight increases of the stomach, liver, and adrenal glands relative to the respective control group. No significant differences were found for other organ weights for the oral exposure groups. No light microscopic changes were detected in the thymus, heart, lungs, stomach, spleen, kidneys, adrenal glands, and testes or ovaries in animals receiving 50 µl/kg of isobutyronitrile. The authors reported that rats exposed at 38.6 mg/kg showed definite parenchymatous degeneration of the liver and that male rats showed a greater degree of degeneration than females. Considering the liver cell degeneration and the earlier mentioned findings of increased organ weight of the liver in both sexes, the authors concluded that isobutyronitrile caused liver damage.

(b) Cyanohydrins

In 1960, Wolfsie [40] reported the results of animal studies using 0.05% W/W aqueous solution of anhydrous GLYCOLONITRILE. An oral LD_{50} of 10 mg/kg was determined based on a single feeding of the solution to an unspecified number of male albino mice. Death occurred within 2 hours after exposure. Signs of intoxication resembled "those of cyanide poisoning." A dermal LD_{50} was determined to be between 105 and 130 mg/kg, based on the exposure of an unspecified number of albino rabbits. Some surviving rabbits showed mild skin irritation. In three albino rabbits, a single application of 0.05 ml of a 50% solution (26 mg) of glycolonitrile to the conjunctiva produced an immediate moderate local irritation, followed by convulsions and coma 15-30 minutes later. Within 68 minutes, all three animals were dead.

Wolfsie [40] also described a study in which seven mice, seven rats, and seven guinea pigs of unspecified strain, sex, or age were exposed in an unspecified manner to glycolonitrile at an average vapor concentration of 27 ppm in air for 8 hours. Six of seven mice and two of seven rats died. The remaining mouse and four more rats died within the next 18 hours. Other signs of toxicity included lethargy and slight eye tearing. No guinea pigs died during the 18 hours after the exposure.

Wolfsie [40] next described a study in which glycolonitrile was administered in the diet to an unspecified number of albino rats for 13 weeks. Male rats ingested up to 62 mg/kg/day and the females ingested up to 92 mg/kg/day with no observed effects. Rat serum thiocyanate concentrations were related to the dose of glycolonitrile, but usually no serum cyanide was present. In a separate experiment, cyanide was observed to appear in the serum soon after the ip injection of an unspecified amount of glycolonitrile into rats and was accompanied by an increase in serum thiocyanate concentrations. Cyanide and thiocyanate concentrations were said to be proportional to the injected doses of glycolonitrile. The author concluded that the toxicity of glycolonitrile in animals was related to the release of cyanide, with detoxification occurring by rapid conversion to thiocyanate.

An experimental investigation of ACETONE CYANOHYDRIN toxicity, by unstated routes of administration, in four animal species was conducted by Shkodich [65], in 1966, in conjunction with research intended for use in determining a maximum permissible concentration of acetone cyanohydrin in water basins. The mice showed the highest sensitivity to acetone cyanohydrin with an LD_{50} value of 2.9 mg/kg. The LD_{50} value for albino rats was 13.3 mg/kg; for guinea pigs, 9 mg/kg; and for rabbits, 13.5 mg/kg.

The possibility of cumulative effects by acetone cyanohydrin was studied using 20 white mice and 20 albino rats [65]. Acetone cyanohydrin was administered by an unspecified route in daily doses equivalent to one-fifth of the LD_{50} for the respective species over 20 days. Neither death nor other evidence of cumulative effects was found in either species during the experiment.

A study of chronic effects of acetone cyanohydrin at daily doses of 0.00005, 0.0005, 0.005, and 1.33 mg/kg for 6 months was conducted in 44 albino rats and 16 rabbits [65]. The number and frequency of doses and route of administration were not specified. At the termination of the study, the animals were killed, and weight coefficients and vitamin C concentration of internal organs and the content of -SH groups in the gray matter of the cerebral cortex were determined. At doses of 1.33 mg/kg, rats exhibited the following effects at $P < 0.01$: an increase in erythrocytes, reticulocytes, and hemoglobin; an increase in vitamin C in the liver and adrenals; a decrease in the content of -SH groups in the brain; and decreases in the activities of serum catalase and cholinesterase. Also, at doses of 1.33 mg/kg, rabbits showed what was described as a disturbance in glycogenic function in the liver indicated by the slower utilization of galactose ($P < 0.05$) and a decrease in the content of -SH groups in blood serum.

At doses of 1.33 mg/kg and 0.0005 mg/kg, functional changes in higher nervous activity (attenuation of the processes of internal inhibition and a certain intensification of the excitatory process) were observed in rats

[65]. Also at doses of 0.0005 mg/kg, rats showed changes in the morphologic composition of the blood, catalase and cholinesterase activities, and vitamin C content, although no quantities were mentioned. Rabbits did not show noticeable effects in any of the tissues that were examined after doses of 0.005 mg/kg or 0.0005 mg/kg were administered. At doses of 0.00005 mg/kg, neither species showed any significant effects in the tissues or systems observed.

Motoc and associates [66] administered 5 mg of acetone cyanohydrin orally twice a week for 3, 5, or 8 months or 1 ml of acetone cyanohydrin in 84 liters (10.2 g/cu m) by inhalation twice a week for 3, 5, or 8 months to white rats in groups of 50 at each dose level. After exposure, the animals were killed. Blood samples were obtained for analysis of serum enzymes including leucinaminopeptidase, SGOT, SGPT, and glucose-6-phosphate dehydrogenase (G-6-PD). Concentrations of total proteins, electrophoretic fractions, and glycoproteins in the serum also were determined. Microscopic examinations of sections of the liver and kidney were conducted in all the animals. In addition, the stomachs of the rats exposed orally, and the lungs of those exposed by inhalation were examined microscopically.

Acetone cyanohydrin, apparently administered orally, produced a decrease of about 15% in the serum total proteins, a decrease in the albumin/globulin ratio, and an increase in gamma globulins [66]. Serum glycoproteins increased after 3 months of exposure. This was followed by a decrease below the mean, and, after 8 months of exposure, by a gradual increase without a return to the normal concentration. Beta-glucuronidase enzyme activity increased initially but dropped after prolonged exposure. Transaminase, aldolase, and leucinaminopeptidase activities were stated to have increased after initial exposures although no values were given. Changes in hepatic protein metabolism after increased duration of exposure were preceded by increases in leucinaminopeptidase, glutamic oxaloacetic transaminase, and glutamic pyruvic transaminase activities.

Acetone cyanohydrin administered orally produced various lesions in the stomach, liver, and kidney [66]. Stomach lesions ranged from increased gastric gland secretions to ulcerations, which became deeper and more extensive with increased duration of exposure. In the liver, both reversible and irreversible dystrophic changes were present. Reversible lesions became less frequent with increased exposure. The liver lesions were briefly described and illustrated. The pictured hepatic cell abnormalities included karyopyknosis, anisokaryosis, abnormal fat deposits, patchy thinning of cytoplasm, and absence of cytoplasmic granules. The livers of those animals exposed to acetone cyanohydrin by inhalation also had some degree of necrosis. Kidney lesions became predominantly irreversible during the longest period of exposure but were not as severe as those found in the liver.

Inhalation of acetone cyanohydrin produced lesions in the lungs with desquamation of bronchial epithelium, progressing to superficial

ulcerations associated with inflammatory infiltrates. Kidney lesions that encompassed the entire nephron and became irreversible during the longest period of exposure were also evident.

The authors [66] found that acetone cyanohydrin administered to white rats orally and by inhalation caused serious hepatic and kidney lesions that became irreversible with prolonged duration of exposure. The oral route of administration produced the most marked hepatic lesions and the most significant biochemical changes. An association was found between the presence and severity of tissue lesions and the degree of change in the serum concentrations of glycoproteins and albumin and the activities of leucinaminopeptidase, SGOT, SGPT, G-6-PD, aldolase, and beta-glucuronidase. Motoc et al suggested that these may be useful as indicators of toxic effects. Microscopic findings of regenerative zones and reversible lesions led them to conclude that adaptation mechanisms could possibly exist. Finally, the authors found that biochemical changes occurred sooner than histologic lesions, especially with regard to hepatic effects. Thus, these biochemical tests may be useful for monitoring subclinical changes induced by acetone cyanohydrin exposure and for detecting the potential for future pathologic changes.

Sunderman and Kincaid [2] studied the toxicity of acetone cyanohydrin in animals in 1953. Twenty-eight albino guinea pigs were studied for acute toxicity by skin absorption of a commercially prepared mixture consisting of 94.7% acetone cyanohydrin and 0.25% hydrogen cyanide; the authors thought the balance was water. The mixture was pipetted onto cheesecloth patches, 2.5-cm-square, which were applied to shaved abdomens of guinea pigs. The thickness of the patches varied according to the dose. At doses of 0.1 ml or less, one thickness of cheesecloth was applied; at doses of 0.2 ml or 0.5 ml, three thicknesses of cheesecloth were applied. The patches were secured with a 5-cm-wide band of adhesive tape around the animal. Observations were continued until either death or complete recovery occurred. The percutaneous LD_{50} was 0.14 g/kg.

Initial attempts by Sunderman and Kincaid [2] to study the toxicity of acetone cyanohydrin in rats by inhalation exposure led to the conclusion that contamination of vapor with free hydrogen cyanide affected the results. Reproducible results were obtained after 250 ml of commercially prepared acetone cyanohydrin, similar to that used for the skin exposure study, was placed in a saturator maintained at 23 ±1 C. Air from a drying tower was passed through the saturator into the chamber. The authors stated that the following results should be regarded as range-finding values: Mortality occurred in 50% of the rats within approximately 10 minutes after exposure to the saturated, purified acetone cyanohydrin vapor; 15 rats died after an average exposure time of 11 minutes; the rats collapsed within an average time of 4 minutes, but death occurred at a later time; recovery often occurred if the rats were removed from the chamber before cessation of respiration; when acetone cyanohydrin was

purified by the described method and allowed to remain at room temperature for 3 days, the toxicity of its vapor did not increase. Thus, the authors concluded that acetone cyanohydrin was the toxic agent in the vapor phase rather than newly formed hydrogen cyanide.

Sunderman and Kincaid [2] studied the effectiveness of treating acetone cyanohydrin poisoning by an adaptation of the procedure described by Chen et al [67], in 1944, for treatment of cyanide poisoning. Groups of five rats were exposed to acetone cyanohydrin vapor until respiration stopped in one of the five rats. Of the remaining four in each group, two were kept as controls and two were given treatment. Amyl nitrite, sodium nitrite, or sodium thiosulfate was administered at doses calculated to be equivalent to those recommended for administration of these cyanide antidotes to humans on the basis of relative body weights. In the control groups, all 16 untreated rats died within 1 minute after exposure ended. Amyl nitrite, administered after exposure to acetone cyanohydrin vapor, increased the survival time of four rats by 10 or more minutes, but all except one died. When sodium nitrite and sodium thiosulfate were administered separately to a pair of rats after exposure, one of each pair survived. When a combination of sodium nitrite and sodium thiosulfate was administered to two rats after exposure, both survived. The administration of sodium nitrite and sodium thiosulfate separately or in combination prior to exposure resulted in no deaths in each group of two rats so treated.

The authors [2] concluded that nitrites and sodium thiosulfate were effective for treating acetone cyanohydrin vapor poisoning in rats. Further, the effectiveness of this mode of treatment supported the view that the toxic action of acetone cyanohydrin was associated with the in vivo release of hydrogen cyanide as acetone cyanohydrin dissociated into acetone and hydrogen cyanide. The authors inferred that the mode of treatment described by Chen et al [67] relative to hydrogen cyanide poisoning in humans should also be effective for treating acetone cyanohydrin poisoning in humans because its toxic effects were mediated by the release of cyanide.

Krefft [41], in 1955, compared the effects of skin exposure to acetone cyanohydrin and aqueous potassium cyanide solution in guinea pigs. Three male guinea pigs were dermally exposed to acetone cyanohydrin, and one female was dermally exposed to 10% aqueous potassium cyanide solution. Three test animals were each exposed to about 1.5-2 cc of acetone cyanohydrin either by painting both ears, painting a small area of the shaved back, or by application of a 2- x 5-cm gauze sponge to the shaved area of skin on the back. All three were restless initially; pulse and respiration rates increased within 1 minute; within 7 minutes, all the animals showed difficulty in breathing, and there was excretion of urine and feces; respiratory paralysis and snapping movements of the snout occurred within 31-40 minutes; death occurred in all three animals within 48-51 minutes. Restlessness and a slight increase in the respiration rate

were also observed in one male animal exposed to about 10 cc of acetone by application of a 2- x 4-cm gauze sponge to the shaved back.

The single guinea pig exposed to potassium cyanide solution by a 3- x 4-cm gauze sponge applied on the shaved skin of the back showed similar effects as those previously described for the animals exposed to acetone cyanohydrin [41]. Spasms attributed to anoxia were observed within 34 minutes, and death occurred within 60 minutes.

Autopsy on animals exposed to acetone cyanohydrin and potassium cyanide showed local hyperemia and swelling of exposed areas, lung edema, bright red blood, hyperemia and edema of the liver and the brain, severe dilatation of the right side of the heart, extensive subpleural and subepicardial echymoses, and acute venous blood obstruction in the major organs and exposed areas of the skin [41]. A distinct bitter almond odor was present in the viscera. The author indicated that the intoxication phenomena were the same with respect to acetone cyanohydrin and potassium cyanide solution, except that acetone cyanohydrin was apparently absorbed faster because of its lipid solubility. The clinical signs resembled those of delayed hydrocyanic acid intoxication. In addition, the author commented that these animal tests show extensive parallels to human cases of death as a result of acetone cyanohydrin exposure.

(c) Dinitriles

In 1969, Panov [68] reported the effects of MALONONITRILE administered by various routes in mice, rats, and rabbits. In the first experiment, five mice (18-20 g) were exposed to vapor of malononitrile for 2 hours in an exposure chamber maintained at 18-20 C. The concentration of malononitrile vapor was not stated, but it was implied that the air in the chamber had been allowed to come into equilibrium with molten malononitrile. Six additional mice (18-20 g) were exposed for 2 hours in an exposure chamber maintained at 29-30 C, at concentrations of malononitrile ranging from 8 to 300 mg/cu m of air. The actual concentrations of malononitrile during these dynamic trials were checked colorimetrically twice during each experiment. In a second study, a total of 100 white mice (18-20 g) and an unspecified number of rats (260-270 g) were administered oral doses of 5-50 mg/kg of malononitrile. In a third experiment, molten malononitrile was applied for 2 hours to the tail skin of healthy white mice and applied on the shaved thigh of four chinchilla rabbits. The skin was washed 1 hour later. Two to three drops of molten malononitrile were applied in the conjunctival sac of six additional rabbits. The animals were observed for 14 days and then killed. All animals were examined for morphologic changes in selected organs.

In the inhalation study, Panov [68] reported that the white mice receiving a single exposure of malononitrile developed signs of restlessness and an increse in the respiration rate in the early

posttreatment period followed by lassitude, decrease in respiration rate, cyanosis, incoordination of movements, trembling, convulsions, and, in some animals, eventual death. None of the five animals in the chamber maintained at 18-20 C died; however, two of six mice in the chamber maintained at 29-30 C died. Fifty percent of white mice and rats exposed at 200-300 mg/cu m of malononitrile died; furthermore, at a concentration of 240 mg/cu m, the mice developed hyperemia and had increased weight coefficients of the lungs (10.0 ±0.39), kidney (21.0 ±0.90), and brain (19.7 ±0.7), compared with those of the control group with weight coefficients of 7.8 ±0.4, 16.6 ±0.76, and 16.5 ±0.77, respectively. The liver showed a decrease in weight coefficient (21.0 ±0.90) in those treated, compared with that in the controls (60.2 ±3.2).

After single oral administrations of 5-50 mg/kg of malononitrile, general intoxication was observed [68]. At 5 mg/kg, no mice died; however, at doses of 20-30 mg/kg, 60-80% of the mice died, whereas a 100% mortality occurred in those animals administered doses of malononitrile ranging from 40 to 50 mg/kg body weight. Further, at higher doses, a moderate destruction of the mucosa of the stomach, a general hyperemia of all organs, and "dystrophy" of intracellular fats and proteins accompanied by leukocytic infiltration of the gastric mucosa were observed. At lower doses of 5-20 mg/kg, no morphologic changes were observed in the mice that survived the exposure period. The LD_{50} was 18.6 mg/kg for mice and about 25 mg/kg for rats.

Panov [68] reported that direct application of warm malononitrile produced the following effects in the eyes of all six rabbits: tearing, hyperemia of the conjunctiva, and spasm and swelling of the eyelids. Respiratory impairment, convulsions, and death occurred in four of the six rabbits.

After the tails of the mice were wet by malononitrile, the animals showed signs of restlessness, rapid respiration, and slight cyanosis of the mucosa of the lips and extremities [68]. The symptoms subsided following removal of the chemical by washing. Panov also observed trembling and skin redness following exposure of the skin of the thigh of the rabbit to malononitrile.

Panov [69], in 1970, reported the effects of exposing a group of 10 rats with an initial mean body weight of 276.5 g to malononitrile vapor. The exposures were at a concentration of 36 mg/cu m for 2 hours/day for 35 days in a dynamic chamber maintained at a temperature of 29-30 C. The malononitrile was analyzed at 2-day intervals by determining the amount of nitrogen with Nessler reagent. Ten additional rats were used as controls. Following exposures, the treated and control rats were examined for changes in body temperature, weight, blood counts, and hemoglobin levels. Selected organs also were removed and weighed at autopsy 7 days after the end of exposure. The author measured the consumption of pure oxygen before and

after carbon dioxide inhalation and the consumption of oxygen by homogenized lung tissue, as determined with the Warburg apparatus. The effects of malononitrile on the CNS were measured by "the index of summation threshold." Also, the author examined the effects of malononitrile on hepatic function by measuring the amount of hippuric acid excreted in a 24-hour period following ingestion of 400 mg/kg of sodium benzoate.

Panov [69] found that the body weight of the experimental rats did not differ significantly from those of the controls. However, the ratio of lung weight to body weight increased in the treated rats, compared with that in the controls. There was a minor change in body temperature from days 19 through 35 in the treated rats. On day 35, the temperature was 36.8 C in the treated rats, as compared with one of 35 C in the control rats. A slight decrease in the concentration in blood of hemoglobin and an increase in that of reticulocytes were also observed. The reticulocyte count was 34 in the treated rats and 14.1 in the controls on the 7th day of treatment. On the 35th day, the reticulocyte count was 27.9 in the treated group and 10.3 in the controls. A decrease in the amount of hippuric acid in 24-hour urine samples of the treated animals was observed. However, there was a concomitant decrease in volume of urine excreted; therefore, the author reported no significant difference in hippuric acid excreted per ml of urine. The author also noted no significant difference in the "index of summation threshold" of the CNS in treated and control rats. Furthermore, the rate of oxygen consumption did not vary significantly in the experimental animals, as compared with that in the controls. Panov concluded that 36 mg/cu m of malononitrile was slightly toxic to rats; this toxicity was manifested mostly by its effect on red blood cells, viz, the hemoglobin level was down and the reticulocyte count was elevated.

Van Breemen and Hiraoka [70], in 1961, described, in an abstract, preliminary investigations on the effects of malononitrile on the cells of the spinal ganglia of rats. Rats were administered, through unspecified routes, 6 to 8 mg/kg of malononitrile. The authors reported the following nuclear and cytoplasmic changes in nerve and satellite cells of spinal ganglia: (1) an increase in the size of the nuclear pore, (2) an increase in the breakdown of endoplasmic reticulum into microvesicular units and an increase in the amount of dense material within the endoplasmic reticulum, (3) an increase in number and size of the Golgi vesicles, (4) an increase in the cytoplasmic pigment granules in the bodies of the nerve cells of the spinal ganglia, and (5) an increase in dense cytoplasmic granules in the satellite cells.

Rats administered (route not specified) 1.2 mg/kg malononitrile for 8 days developed cytoplasmic changes in the neurons [70]. This was demonstrated by the presence of vacuoles containing short filamentous structures in the cytoplasm along the periphery of the cell body and the

development of open spaces between Nissl bodies, which gave the appearance of increased fluidity of the neuronal cytoplasm in the treated animals.

Hicks [71], in 1950, reported the effects of malononitrile on the brain and other tissues in rats. Twenty-six young adult rats were administered ip doses of 5-10 mg/kg of malononitrile at 2- to 4-hour intervals for 1-2 days. The animals were killed, and complete autopsies were performed. All major organs were prepared for examination by conventional histologic methods.

Hicks [71] reported that malononitrile induced brain lesions in rats. Four rats died during the acute phase of malononitrile treatment. Fifteen of the 22 rats that survived had brain lesions, but the other 7 survivors had no discernible damage. The results of the autopsies of four representative rats showed brain lesions in the corpus striatum involving both the gray and white matter. In "one or two" of these rats, necrosis occurred in the striatal neurons, with accompanying proliferation of microglia and oligodendroglia, 1-2 days following treatment. Some striatal neurons of the white matter showed no reaction. The author also observed demyelinating lesions of the optic tract and nerve, lesions of the cerebral cortex, involving the rhinal fissure and cortical areas 51a and 51b, and lesions of the olfactory bulb and substantia nigra.

Hicks [71] also reported visceral changes, such as ventricular myocardial changes, in most of the experimental rats. Moderate patchy renal tubular necrosis was evident, and a few animals that died during the acute phase of treatment had developed pulmonary edema. An unstated number of rats showed elongation and vacuolation of the thyroid acinar cells and mitotic figures in the parathyroid cells.

The author [71] concluded that to some extent malononitrile exerts tissue specificity in its action. He could not precisely explain the nature of the effects observed, but he postulated that the differential tissue susceptibility was due to varying factors: duration of action of the injected chemical, rate of detoxification and excretion, selective permeability of tissues, qualitative differences in tissue metabolism, and inhibition of cellular respiration due to a reaction of released cyanide with cytochrome oxidase.

Stern et al [72], in 1952, reported on two studies on the metabolism of malononitrile by rat brain, liver, and kidney tissue in vitro. In the first study, malononitrile at a concentration of 0.01 M was added to three incubation media (Krebs III, modified Krebs III, and bicarbonate) containing tissue slices of brain, liver, and kidney. Respiration and glycolysis were then determined. In addition, cozymase levels were determined by the apozymase test. Respiration was measured manometrically. In the second study, respiration and anaerobic glycolysis were simultaneously determined in the rat and guinea pig tissue by Warburg's

two-vessel method. Anaerobic glycolysis was determined manometrically for guinea pig brain slices. The tissue slices were incubated at 37 C for 2 hours.

In an additional experiment [72], homogenates and extracts of brain, liver, and kidney tissue were analyzed to determine thiocyanate formation in rat liver extract, effects of tissue homogenates and extracts on malononitrile in the presence or absence of thiosulfate, and the effect of malononitrile on rhodanase activity.

Stern and his associates [72] found that respiration of brain, kidney, and liver slices was inhibited by 0.01 M malononitrile. In a bicarbonate medium, brain and kidney respiration were not markedly inhibited by 0.01 M malononitrile during the 1st hour but decreased during the 2nd hour for both the rat and the guinea pig. Also, the 2nd hour anaerobic glycolysis in guinea pig brain tissue decreased to approximately 50% of the 1st-hour value. Thiosulfate did not prevent the inhibition of anaerobic glycolysis produced by malononitrile. Malononitrile increased the lactic acid content of rat brain slices within 1-2 hours but had no effect on the NAD concentration. The formation of thiocyanate from malononitrile and thiosulfate was highest in the presence of liver tissue, lowest with brain, and intermediate with kidney.

The enzyme rhodanase, which catalyzed the formation of thiocyanate from cyanide and thiosulfate, was ineffective for catalysis of thiocyanate formation from malononitrile. The observed thiocyanate formation in vivo, therefore, apparently came from an intermediate metabolite and not the parent malononitrile molecule itself. Malononitrile inhibited respiration and increased the relative ratio of aerobic to anaerobic glycolysis. The authors did not postulate a mechanism for the effect of malononitrile on cellular respiration.

In 1952, Macht [73] reported the effects of single or repeated injections of SUCCINONITRILE in mice, rats, guinea pigs, rabbits, and cats. In the first series of experiments, the author investigated the toxicity and mean lethal dose. An unspecified number of rats and cats, 200 mice, 10 rabbits, and 30 guinea pigs were administered single ip doses of 5% succinonitrile. Eight rabbits were administered iv or im doses of 50 mg of succinonitrile five times/week for 3 weeks. The author did not report the weights of the animals. Mean lethal doses of 50 mg/kg, 250 mg/kg, "60 and 50 mg/kg," 23 mg/kg, and 80 mg/kg were determined for mice, rats, guinea pigs, rabbits, and cats, respectively. In the mice, rats, and guinea pigs, convulsions and signs of asphyxia developed after administration of mean lethal doses of succinonitrile by various routes. No toxic effects on the neuromuscular apparatus were observed in rabbits. Macht concluded that the toxicity of succinonitrile was low in mice, rats, guinea pigs, and rabbits. No control animals were used, although their use would have been appropriate in the chronic study of rabbits.

The second series of experiments was conducted to determine the effects of succinonitrile on blood pressure, respiration, and hepatic and renal function [73]. An unspecified number of rabbits and cats were anesthetized with pentobarbital and administered 1 ml of succinonitrile iv. No effects on the blood pressure and heart rate were observed in the rabbits and cats, and no impairment of kidney or hepatic function was observed in four of the rabbits. A transient increase in the frequency of respiration was observed after administration of iv doses of 5% succinonitrile. Although the author reported no apparent toxic effects in the gastrointestinal tract and neuromuscular systems, some animals developed diarrhea after repeated injections of succinonitrile.

Contessa and Santi [74], in 1973, investigated the release of cyanide from succinonitrile in rats and rabbits in vivo and in vitro. In the in vivo studies, male rabbits weighing 2-3 kg and male rats weighing 400-450 g were administered succinonitrile in iv doses of 25-40 mg/kg and 25-50 mg/kg, respectively. Levels of cyanide and thiocyanate were determined in samples of urine from rabbits and rats. The total number of rats that were studied was not mentioned. In the in vitro studies, levels of cyanide and thiocyanate were determined in liver slices and homogenates of rat or rabbit liver or with isolated mitochondrial, microsomal, and soluble fractions. Samples (0.1-2.0 ml) of filtered 24-hour urine output were collected from groups of two rats and from each rabbit pre- and postadministration with succinonitrile to determine thiocyanate concentrations. In another study, rats were pretreated with 2 ml/kg of carbon tetrachloride sc 48 hours prior to succinonitrile administration. Filtered urine samples were collected, and cyanide concentrations were determined colorimetrically.

Contessa and Santi [74] reported a sixfold increase in urinary thiocyanate following iv-injected doses of 25 mg/kg of succinonitrile compared with the controls. Forty-eight to 120 hours postadministration of succinonitrile, thiocyanate levels approached control values. Pretreatment of rats by sc injection of 2 ml/kg carbon tetrachloride inhibited urinary thiocyanate excretion. Urinary excretion of cyanide increased over fivefold 48 hours posttreatment with succinonitrile. The values at 72-120 hours posttreatment approached normal values.

The authors also reported that rat and rabbit liver slices catalyzed the release of cyanide from succinonitrile [74]. However, 0.1-2.0 mg/g of Triton-X-100 strongly inhibited cyanide release from succinonitrile in rat liver slices. Liver slices of rats pretreated with carbon tetrachloride did not release detectable amounts of cyanide from succinonitrile.

Contessa and Santi [74] concluded that rabbits and rats converted about 60% of the administered succinonitrile to cyanide, which was excreted as thiocyanate. The release of cyanide was inhibited by carbon tetrachloride and Triton-X-100. The authors also postulated that disruption of the liver

cells, as by centrifugation to separate their contents, depressed or eliminated their ability to liberate cyanide ions or to form thiocyanate. The authors proposed that cellular membranes contain enzymes or enzyme complexes that are responsible for the conversion of succinonitrile to cyanide, which is excreted as thiocyanate. However, following homogenization, these enzyme or enzyme complexes may be destroyed or damaged by homogenization.

In 1972, Cavanna and Pocchiari [75] investigated the fate of ^{14}C-labeled succinonitrile in male mice. They reported that a mean of 53% of the total succinonitrile injected ip in each animal in single- and multiple-dose studies was eliminated in the first 24 hours posttreatment and 88% of this eliminated succinonitrile was excreted as metabolites. In a single-dose study, 7% of the ^{14}C-labeled succinonitrile was excreted as thiocyanate and 36% as intermediate metabolites in 24 hours. In the multiple-dose study, 18% thiocyanate and 24% intermediate metabolites were excreted.

Cavanna and Pocchiari [75] concluded that succinonitrile was either excreted unmetabolized or was metabolized to cyanide and excreted as thiocyanate in mice within 24 hours posttreatment. The authors postulated that the high percentage of metabolites excreted in 24-hour urine samples may be due to the presence of two reactive centers in the succinonitrile molecule, resulting in the formation of two intermediate metabolites, diethylene cyanohydrin and cyanoacetic acid.

In 1975, Curry [76] reported on his investigation of the excretion of succinonitrile and its metabolites in urine and feces of mice, following a single injection of succinonitrile. The cumulative excretion of succinonitrile and metabolites in urine and feces measured 60% by 24 hours and 83% by 72 hours. In the first multiple-dose experiment in which mice received three doses of unlabeled succinonitrile and one dose of radioactive succinonitrile, 52% of the radioactivity was excreted in urine in 24 hours. In the second multiple-dose experiment, in which mice received four doses of radioactive succinonitrile, 50% of the radioactivity was excreted in each 24-hour period.

Curry [76] concluded that a fraction of the succinonitrile was excreted unmetabolized or converted to cyanide and excreted as thiocyanate in the 24 hours following its administration. After 24 hours, virtually all the metabolites were excreted. The highest rate for thiocyanate excretion occurred 2-6 hours after administration. After 48 hours, most of the excreted material was not extractable from water with chloroform or amyl alcohol, which suggested that highly polar, perhaps ionizable metabolites were formed. Curry speculated that one of the metabolites was cyanoacetic acid, a compound known to be derived from succinonitrile in rats. He further suggested that metabolic hydroxylation of the methylene group would form an unstable cyanohydrin that in turn would release cyanide. The

release of cyanide from succinonitrile in vivo and in vitro [74-76] further supports the possibility that toxicity of nitriles may be due to release of a cyanide radical. When alpha-hydroxylation occurs, the resulting cyanohydrin can readily dissociate under biologic conditions to release C≡N ions.

Harger and Hulpieu [77], in a 1949 abstract, described the effects of TETRAMETHYLSUCCINONITRILE in rats, guinea pigs, rabbits, and dogs and the influence of thiosulfate, nitrite, and barbiturates on the toxicity of tetramethylsuccinonitrile. Animals treated with tetramethylsuccinonitrile developed violent convulsions and asphyxia, which eventually led to death of the animals from 1 minute to 5 hours following the convulsions. Oral administration of tetramethylsuccinonitrile at 49 and 56 mg/kg induced convulsions in rats after 5 hours, and they died several hours later. Rats that inhaled vapor of the chemical at 60 ppm for 2-3 hours died. At a lower concentration, 6 ppm for 30 hours, the animals also died.

Tetramethylsuccinonitrile LD_{50} values were determined in three animal species: 30 and 23 mg/kg for rats and guinea pigs, respectively, after sc administration [77], and 20 mg/kg for rabbits after iv injection. A dose of 20 mg/kg given sc was lethal to dogs. The authors reported no influence of unspecified doses of sodium thiosulfate and sodium nitrite on the toxicity of tetramethylsuccinonitrile; however, administration of a quick-acting barbiturate (identity of the compound and route not specified) followed by phenobarbital did reduce the toxicity of tetramethyl-succinonitrile given in doses up to 50 mg/kg. Sodium thiosulfate and sodium nitrite have been reported to be effective antidotes following other nitrile poisonings. The failure of the authors to observe a reduction in the toxicity of tetramethylsuccinonitrile may well have been due to the administration of an inadequate dose of the antidotes or to the failure to administer the antidote soon enough following exposure.

Svirbely and Floyd [78], in 1964, reported the results of a toxicologic study of ADIPONITRILE. Mongrel bitches fed "the equivalent of" 10, 100, 500, and 1,000 ppm of adiponitrile daily were tested for blood and urine abnormalities and for liver and kidney functions. Normal values were found for animals fed adiponitrile at 500 ppm or less, but those given 1,000 ppm daily were unable to consume the entire dose; the dogs either vomited the adiponitrile-containing food or failed to eat portions of it during the 1st week. Monitoring the thiocyanate excretion in the urine showed that the levels increased as the concentration of the ingested nitriles increased. Recovery of adiponitrile in the form of urinary thiocyanate averaged about 50%. Slight increases in the concentration of thiocyanate in the blood were found, and negligible amounts were found in feces.

In a 2-year study, male and female Carworth Farms-Wistar rats were given 0.5, 5.0, and 50 ppm of adiponitrile in their drinking water [78]. Daily water consumption was not affected by the different concentrations of

adiponitrile. No abnormalities were found after periodic hematologic studies with these rats. No appreciable differences in body weight were noted during the 2-year study. Advanced adrenal degeneration was found in female rats exposed at all three concentrations of adiponitrile and in males exposed at 50 ppm. Degeneration of other organs was noted but was attributed to aging of the rats. The ratios of organ weights (spleen, liver, and kidney) to total body weight at the conclusion of the study were not significant. Pregnant Sprague-Dawley rats were exposed to adiponitrile at 10, 100, and 500 ppm. Data reported from the first generation (two litters) did not indicate any decrease in fertility, gestation, or viability.

Ghiringhelli [16], in 1955, reported on the metabolism and toxicity of adiponitrile in guinea pigs and the effects of anticyanide treatment. Twenty guinea pigs, 4-8 months old and weighing 560-580 g, were administered sc unspecified quantities of a 5% aqueous solution of adiponitrile. In addition to observing the animals for toxic effects, blood hydrocyanic acid and urine (24-hour samples) thiocyanate levels were determined 1-3 days after injection. In a second study, 5 of 13 animals that survived adiponitrile administration were given a 25% solution of sodium thiosulfate at a dose of 2.5 ml/kg. Also, an unspecified number of guinea pigs were administered sodium nitrite sc at a dose of 70 mg/kg.

The author [16] reported that adiponitrile was toxic to guinea pigs. The lethal dose was estimated to be 50 mg/kg on the basis of 20 animals. Hydrogen cyanide concentrations in blood from the heart ranged from 0.12 to 1 mg% (mean of 0.68 mg%). The mean thiocyanate concentrations for the 24-hour urine samples on days 1, 2, and 3 following adiponitrile treatment were 4.6 mg/100 g, 3.5 mg/100 g, and 2.64 mg/100 g, respectively. The mean concentration of thiocyanate excreted in 24-hour urine samples from animals treated with adiponitrile and sodium thiosulfate were 5.23, 3.13, and 2.44 mg/100 g, respectively. Ghiringhelli concluded that adiponitrile was metabolized to hydrocyanic acid and excreted in urine as thiocyanate. He also stated that sodium thiosulfate was an effective antidote against adiponitrile poisoning, based on 92.8% survival of animals poisoned with a mean lethal dose of adiponitrile.

Correlation of Exposure and Effect

Humans absorb nitriles through the skin [2,10,40,42] and respiratory tract [10,31-33,35,37,38]. After absorption, nitriles may be metabolized to an alpha cyanohydrin or to inorganic cyanide, which is oxidized to thiocyanate and excreted in the urine. Nitriles also undergo other types of reactions, depending in part on the constitution of the moiety to which the C≡N group is attached. The C≡N group may be converted to a carboxylic acid derivative and ammonia or may be incorporated into cyanocobalamine.

Ionic cyanide reacts also with carboxyl groups and with disulfides. Nitriles and their metabolic products have been detected in urine, blood, and tissues [38].

Studies on the effects of the selected nitriles on humans, following exposure by various routes of administration, have revealed a variety of effects. These include constriction and numbness in the throat, increased salivation, nausea, anxiety, confusion, vertigo, giddiness, hyperpnea, labored breathing, and slow and irregular respiration. In some cases, palpitations, rapid, weak, and irregular pulse, coma, convulsions, trismus, and profuse sweating may occur. Depending on the extent of exposure, death by respiratory arrest may ensue [10,31,32]. These effects are similar to those associated with cyanide poisoning [86,87]. These observations of a close similarity to an underlying cyanide effect for acute poisoning by nitriles are further supported by the effectiveness of anticyanide therapy, sodium nitrite followed by sodium thiosulfate [67], in treatment of nitrile poisoning. There are no chronic effects associated with exposure of humans to cyanide [88]; but there is evidence of ulcerogenic effects in animals produced by sc injection of propionitrile and n-butyronitrile in rats [56,62], thyroid hyperemia and hyperplasia produced by sc injection of acetonitrile in rats [48,49], and CNS effects from therapeutic use of malononitrile and succinonitrile [26,27,30].

The effects produced by exposure to cyanide from a variety of sources, including nitriles, are respiratory difficulties, headache, muscular incoordination, varying degrees of mental confusion (progressing to deep coma), and either cyanosis or bright red color of the blood. Depending on the extent of poisoning, there may be convulsions of an anoxic nature, with involuntary urination and defecation. The circulation may be strong or weak, and the pupils are dilated. Vomiting frequently occurs before loss of consciousness, and the vomitus may have the odor of bitter almonds characteristic of cyanide. Pneumonia is a common sequela in nonfatal cases. In fatal cases of poisoning, death usually occurs during the first 30 minutes. Pathologic findings are those of asphyxia. The most affected tissues (stomach, mouth, and lungs) are often reddened. All portions of the CNS, including the corpus callosum and the substantia nigra, may show degenerative changes [71,87] (see Table III-2).

Although all the selected nitriles appear to have in common the release of cyanide for producing toxic effects, at least on an acute basis, there are substantial differences among nitriles in the amounts necessary to cause poisoning, in the durations of exposure, and in the time intervals between exposure and manifestation of these effects. These differences among the effects of the various nitriles may be partly related to the differences in the rate and extent of cyanide ion release.

The only mononitriles for which human exposure data are available [10,31,32,39] are acetonitrile and isobutyronitrile. The onset of illness

from an acute exposure of humans to isobutyronitrile appears to occur more rapidly [10,39] than that occurring from similar exposures to acetonitrile [31,32]. This may be explained by Amdur's suggestion [32] that the delayed effect of acetonitrile when compared with other members of the homologous series may be due, in part, to the more rapid rate of oxidation in vivo of the alkyl group of the higher homologs. The signs and symptoms of overexposure to these mononitriles include headache, dizziness, profuse sweating, vomiting, loss of consciousness, difficulty in breathing, and dilated pupils. In cases of severe exposure, coma followed by death has occurred [31,32]. Treatment for the acute effects includes use of sodium nitrite and sodium thiosulfate, the conventional therapy for cyanide poisoning.

The cyanohydrins can be absorbed through the skin or inhaled without the exposed individual being aware of exposure. The alpha-cyanohydrins will apparently dissociate readily to yield hydrogen cyanide and a ketone or aldehyde [2]. There is a delayed onset of illness, generally attributed to the time required for dissociation to produce free hydrogen cyanide. One investigation [39] suggested that the effects of exposure of humans to acetone cyanohydrin are similar to those produced by exposure to isobutyronitrile, a mononitrile. However, the amount of cyanohydrin and the time required for it to produce a toxic effect in humans appear to be less than those for exposure to a mononitrile.

A few cc of adiponitrile produced severe signs and symptoms in an 18-year-old man, requiring hospitalization [16]. Malononitrile has been used therapeutically at 2-4 mg/kg doses [26,27,29] for the treatment of certain mental disorders. Facial redness, tachycardia, and congestive flow of blood to the head were consistently observed during treatments [26]. Although the evidence is inconclusive, exposure to tetramethylsuccinonitrile at a low concentration in air may cause convulsions and loss of consciousness [43].

In the workplace, acute poisoning and death have been reported following inhalation of nitriles. Dequidt et al [33] reported a fatality in a man exposed to acetonitrile vapor (concentration and duration not known). Approximately 4 hours after leaving work, the worker experienced gastric and respiratory distress, vomiting, profuse perspiration, and coma. Death occurred 6 days after the onset of poisoning despite anticyanide therapy. Unmetabolized acetonitrile, free hydrogen cyanide, and combined cyanide were detected in the viscera, blood, and urine. Zeller et al [10] reported similar findings following a 10-minute exposure of a worker to isobutyronitrile vapor at an unknown concentration. However, the worker recovered following repeated doses of thiosulfate. Grabois [31] and Amdur [32] described the effects of exposure of approximately 15-20 workers to volatilized acetonitrile. One death and eight cases of intoxication were reported. Signs and symptoms following exposure were similar to those reported by Dequidt et al [33] and Zeller et al [10]. However, eight

survivors developed additional signs and symptoms including hypothermia, hypotension, and oliguria.

Dermal exposures to various nitriles have caused adverse reactions including death in some instances. Zeller et al [10] reported seven cases of minor skin irritation and inflammation developing about 5-15 minutes following exposure to adiponitrile. One of seven workers had serious skin destruction and required hospitalization for 117 days. In another incident [39], a worker had direct skin contact with acetone cyanohydrin (quantity unknown) for an unknown period of time while filling drums. He vomited within 5 minutes and became unconscious within 10 minutes. In these cases of skin contact [10,39], exposures also may have been by inhalation.

Wolfsie [40] reported two cases of skin exposure to unknown quantities of 70% aqueous solutions of glycolonitrile in an occupational setting. In addition to the characteristic signs and symptoms of cyanide poisoning, the author reported that there was incoherent speech. Sunderman and Kincaid [2] reported three cases of poisoning following direct skin contact with acetone cyanohydrin. One of the workers became nauseated, subsequently developed convulsions, and died 6.5 hours postexposure. Signs and symptoms observed in survivors were headache, nausea, vomiting, and cardiac palpitation. Lang and Stintzy [42] reported poisoning with acetone cyanohydrin following direct skin contact with the liquid for 40-60 minutes and with the dry residue for about 5.5 hours. Five hours after exposure, typical signs and symptoms of cyanide poisoning, including muscular spasm and a painful constriction of the throat, were observed.

Nitrile intoxication has been reported following ingestion in the workplace. Ghiringhelli [16] reported the poisoning of a worker who ingested a small amount of adiponitrile. Signs and symptoms were similar to those caused by nitrile intoxication dermally and by inhalation and included headache, dizziness, mental confusion, and loss of consciousness. In addition, both pupils were extremely dilated.

Only one report of long-term, low-level effects of occupational exposure to a nitrile has been found. Reinl [43] reported a study of 16 workers allegedly suffering ill effects from exposure to tetramethylsuccinonitrile vapor at an unknown concentration. The subjects complained of headache, dizziness, nausea, vomiting, a peculiar taste in the mouth, formation of excessive and frothy spittle, respiratory distress, insomnia, lapses of consciousness, and convulsions. The results of physical examination and limited laboratory tests of liver function and serum proteins revealed no consistent or characteristic abnormality. Two of the subjects examined had lost consciousness following acute exposures. The presence of tetramethylsuccinonitrile had not been proven in the work environment. However, the author conjectured that it was released as a thermal decomposition product of azo-isobutyronitrile, which was employed in the workplace as a polyvinyl chloride foaming agent.

One report, by Pozzani and associates [35], of experimental exposures of three men indicated the possibility of minor and transient effects from inhaling acetonitrile at relatively low concentrations for 4-hour periods. One of three volunteers exposed at 40 ppm described a slight tightness in the chest, which he characterized as a "cooling sensation" like that of menthol in the lungs. He also experienced a slight transitory flushing of the face 2 hours after inhalation and a slight feeling of bronchial tightness after 5 hours. No significant levels of cyanide were detected in the blood or urine of the subjects. All other volunteers exposed to acetonitrile at 40 or 80 ppm intermittently for up to 2 weeks showed no subjective responses. However, at 160 ppm one of two exposed volunteers had a slight flushing of the face, followed 5 hours later by a feeling of bronchial tightness.

Animal studies have been conducted to determine the effects of exposure to various nitriles by inhalation and dermal absorption. Inhalation studies with rats, monkeys, guinea pigs, and dogs consisted of exposing them to acetonitrile, propionitrile, n-butyronitrile, isobutyronitrile, glycolonitrile, acetone cyanohydrin, tetramethylsuccinonitrile, and malononitrile. These studies were at concentrations ranging from 6 to 53,000 ppm (Table III-3).

Pozzani et al [35] reported that rats exposed to acetonitrile at 53,000 ppm for 30 minutes died but survived at the same concentration when exposed for 15 minutes. Haguenoer and colleagues [55] reported that death of rats occurred 30 minutes after exposure to acetonitrile at 25,000 ppm. In dogs, death occurred within 14 hours from 4-hour exposures at 16,000 ppm [35]. In the same study, after 4-hour exposures, the LC_{50} values for rabbits and guinea pigs were 2,828 ppm and 5,655 ppm, respectively. Pozzani et al also reported hyperexcitability, incoordination, and subdural hemorrhages in monkeys following exposure to acetonitrile vapor at 330, 660, and 2,510 ppm for 7 hours/day until death.

Subchronic studies involving acetonitrile have been reported for a variety of animal species. Pozzani et al [35] described the results of exposing monkeys to acetonitrile at 330 and 2,510 ppm for 7 hours/day. The monkey exposed at 330 ppm died after 2 days of exposure; the other monkey was alive after 99 days of exposure. At 330 ppm, monkeys showed subdural hemorrhage, brain congestion, and pleural adhesions. In the same study, rats were exposed to acetonitrile for 7 hours/day, 5 days/week at 166 and 665 ppm. No effects were observed at 166 ppm; however, rats exposed at the higher dose developed lung edema and congestion, bronchial inflammation with hypersecretion of mucus, and kidney and liver damage. Dogs exposed to acetonitrile at 350 ppm for 91 days showed a reduction in hemoglobin and hematocrit [35].

Acute and subchronic animal studies indicate that the effects of acetonitrile are species specific and depend on dose and duration of

exposure. Among the species studied, dogs were most resistant followed in decreasing order by rats, guinea pigs, and rabbits. Inhalation of acetonitrile produced the characteristic signs and symptoms of cyanide intoxication as described previously. The signs and symptoms reported are similar for long- and short-term studies. However, at relatively small but nonetheless lethal doses, death was delayed in all species. As with human case studies, these effects have been attributed largely to the nitrile per se and metabolic release of hydrogen cyanide [35,55].

Acute inhalation studies have been performed to determine the effects of cyanohydrins, notably acetone cyanohydrin and glycolonitrile. Wolfsie [40] reported that exposure to glycolonitrile at 27 ppm for 8 hours caused death in 29% of rats and 86% of mice studied; however, none of the guinea pigs in the study died from exposure. In another study [2], 50% of the rats died within 10 minutes following exposure to saturated vapor of acetone cyanohydrin.

Acute and subchronic inhalation studies have been conducted on selected dinitriles, notably tetramethylsuccinonitrile and malononitrile. In acute studies, Harger and Hulpieu [77] reported death of rats following exposure to tetramethylsuccinonitrile for 30 hours at 6 ppm. Reinl [43] reported that the mean death times for mice exposed at 0.158 mg/liter and 0.125 mg/liter were 153 minutes and 175 minutes, respectively. All animals died within 200 minutes.

In subchronic studies, Panov [68] reported that mice and rats exposed to malononitrile at 200-300 mg/cu m for 2 hours showed restlessness, an initial increase in the respiration rate, and lassitude, followed by decreased rate of respiration, incoordination, and convulsions. Death occurred in 50% of the rats studied. Results of another study [69] showed that, in rats exposed to malononitrile at 36 mg/cu m for 2 hours/day for 35 days, a decrease in the concentration in blood of hemoglobin and an increase in that of reticulocytes occurred.

Results of acute dermal studies [2,35,40] show that selected mononitriles, cyanohydrins, and dinitriles produce adverse effects in laboratory animals. Acetonitrile has been reported to be absorbed through intact skin of rabbits yielding a dermal LD_{50} of 980 mg/kg. Acute studies with glycolonitrile showed that rabbits exposed dermally at 105-130 mg/kg developed mild skin irritation. The LD_{50} for guinea pigs dermally exposed to acetone cyanohydrin was calculated to be 0.15 ml/kg.

Although exposure to nitriles in the workplace occurs primarily through inhalation and skin contact, additional effects have been observed in humans and animals with other routes of exposure, notably ocular, sc, iv, and ip.

Szabo (S Szabo, written communication, May 1978), in comparative toxicity studies with female rats, determined approximate LD_{50} values for

several nitriles. These values ranged from 100 mg/kg for malononitrile to 300 mg/kg for isobutyronitrile. Other nitriles tested were adiponitrile, n-butyronitrile, propionitrile, and succinonitrile. When compared with data on acetonitrile [2,35], Szabo's data provide a quantitative base for developing recommended concentration limits (Table III-4).

Panov [68] reported severe eye irritation and death in four of six rabbits following instillation of two to three drops of malononitrile into the conjunctival sac. In another study [40], three rabbits showed local eye irritation and convulsions within 15-30 minutes of applying glycolonitrile to the eyes. Death occurred within 68 minutes.

Animal studies indicate additional effects of nitrile poisoning, including the development of duodenal ulcers in rats administered propionitrile sc at doses from 15 to 60 mg/100 g for 4 days [56]. Nuclear changes in neurons and satellite spinal ganglia were seen in rats administered single doses of malononitrile (route unspecified) of from 6 to 8 mg/kg [70]. Thyroid hyperemia and hyperplasia have been reported in rats and rabbits administered acetonitrile sc at daily doses of 0.02-0.08 cc for 28 days and of 0.1-0.15 cc for 63 days, respectively [48,49].

Since human and animal studies mainly report signs and symptoms characteristic of cyanide poisoning, it is reasonable that a portion of the toxic effects of exposure to selected mono- and dinitriles is due to the release of the cyanide ion from the parent compound. The graded severity of effects observed in both human and animal studies indicates that the toxic action of nitriles depends on the dose and duration of exposure. The route of administration does not appear to be a major factor contributing to toxicity in that similar symptoms were seen in humans regardless of the route of administration [2,10,28,29,31-33,35-38,42].

Cyanohydrins and dinitriles show signs and symptoms resembling those reported for mononitriles. However, the dinitriles and cyanohydrins appear to be more toxic in that adverse effects generally occurred at lower concentrations. In addition, on acute exposures the cyanohydrins reportedly produced effects within minutes. Dinitriles could presumably exert a greater effect due to more rapid release of C≡N from one of the two nitrile groups available. As with selected mononitriles, reported effects of cyanohydrins and dinitriles may be due to the nitrile itself, to metabolites other than free cyanide, and to release of free cyanide.

Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction

No reports have been identified that discuss possible carcinogenic, mutagenic, or teratogenic effects of the selected nitriles, except adiponitrile. Adiponitrile has been tested in *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, and TA 98 at concentrations up to 10,000

μg/petri plate [4]. No significant increase in the spontaneous (background) mutation rate was observed. Adiponitrile was not mutagenic in these microbial assays in either the presence or the absence of a liver microsomal enzyme preparation (5-g mixture). No adverse reproductive effects were found after one generation in rats exposed daily for two years to adiponitrile at concentrations up to 500 ppm [78].

A structurally related nitrile, acrylonitrile (vinyl cyanide) is suspected of inducing cancer in both animals and humans [89] (29 CFR 1910.1045). Since other vinyl derivatives containing electronegative groups, such as vinyl chloride and vinyl bromide, are also known to induce cancer, the adverse effects induced by acrylonitrile are probably more closely related to the vinyl moiety and not to the nitrile portion of the molecule. However, further scientific evaluation is necessary to confirm this conjecture.

TABLE III-2

EFFECTS OF SELECTED NITRILES ON HUMANS

Substance	Route and Duration of Exposure	Concentration or Dose	Number Exposed	Effects	Reference
Acetonitrile	inhalation, 4 hr	160 ppm (270 mg/cu m)	2	Bronchial tightness in 1	35
"	"	80 ppm (130 mg/cu m)	2	None	35
"	"	40 ppm (70 mg/cu m)	3	Slight bronchial tightness in 1	35
"	inhalation, unknown	Unknown	1	Gastric distress, respiratory distress, coma, death 6 d postexposure	33
"	inhalation, 2.5-5.0 hr	"	1	Hypotension, hypersecretion of saliva, conjunctivitis	34
"	"	"	15-20	9 became ill; 1 died; 1: chest pain, gastric distress, skin discoloration, tachypnea; 8: hypotension, general weakness, absence of deep reflexes, skin discoloration, tachypnea	31,32
Isobutyronitrile	inhalation, unknown	"	3	Dizziness, vomiting	10
Glycolonitrile	dermal,* unknown	"	2	General weakness; respiratory distress; unsteady gait; irregular, rapid pulse	40
Acetone cyanohydrin	"	"	4	1: nausea, convulsions, death 6.5 hr postexposure; 3: vomiting, cardiac palpitation	2
"	"	"	1	Vomiting, dyspnea, convulsions, coma	39
"	dermal,* 40-60 min wet and 5.5 hr dry	"	1	Constricting throat pain; slow, deep respiration; convulsions; cyanosis	42
"	oral, unknown	"	1	Death 12 hr postexposure	2
Adiponitrile	"	"	1	Vomiting, severe asthenia, tightening of the chest, tachypnea, raspy breathing, convulsions, cyanosis	16
"	dermal, unknown	"	7	1: skin inflammation, destruction, necrosis; 6: minor skin irritations	10
Malononitrile	iv, average of 48 min	2.4 mg/kg	40 (av 8 treatments each)	Tachycardia, congestive flow of blood to head	29
"	iv, 21-60 min	3-6 mg/kg	6	Tachycardia, vomiting, retching	28
"	iv	2-4 mg/kg	13 (9 had 10 or more treatments)	Tachycardia with palpitations, hypotension, gastric distress	27
"	"	1-6 mg/kg	66 (3-17 treatments)	Tachycardia, muscle spasms, gastric distress, convulsions in 2	26
Succinonitrile	im	200 mg	1 (19 daily treatments)	Convulsions followed by death	30
Tetramethyl-succinonitrile	inhalation, unknown	Unknown	16	CNS and gastrointestinal disturbances, convulsions in 5, unconsciousness in 2	43

* With possible inhalation

TABLE III-3

EFFECTS OF SELECTED NITRILES ON ANIMALS

Substance	Route and Duration of Exposure	Concentration or Dose	Species	Number Exposed	Effect	Reference
Acetonitrile	inhalation, 30 min	53,000 ppm (89,000 mg/cu m)	Rats	-	Death in 50%	35
"	"	25,000 ppm (42,000 mg/cu m)	"	3	Dyspnea, cyanosis, 100% mortality in 30 min	55
"	inhalation, 4 hr	32,000 ppm (53,760 mg/cu m)	"	30	Death in 57%	79
"	"	8,000 ppm (13,440 mg/cu m)	"	30	Death in 33%	79
"	"	4,000 ppm (6,720 mg/cu m)	"	30	Death in 10%	79
"	"	16,000 ppm (27,000 mg/cu m)	Dogs	3	Death 14 hr postexposure	35
"	inhalation, 2 hr/d for 5 d	2,800 ppm (4,700 mg/cu m)	Rats	3	Dyspnea; anuria; hemorrhages in brain and lungs; death in all 3 rats	55
"	inhalation, 7 hr/d	2,510 ppm (4,200 mg/cu m)	Monkeys	3	Death after second exposure	35
"	"	660 ppm (1,100 mg/cu m)	"	3	Death after 23 and 51 exposures	35
"	inhalation, 7 hr/d 5 d/wk for 90 d	655 ppm (1,100 mg/cu m)	Rats	30	Bronchial inflammation, desquamation and hypersecretion of mucus, hepatic and renal lesions	35
"	inhalation, 7 hr/d 5 d/wk for 91 d	350 ppm (590 mg/cu m)	Monkeys	3	Bronchitis, post mortem: moderate hemorrhage of superior and inferior sagittal sinuses of the brain	35
"	"	"	Dogs	3	Decreased hematocrit and hemoglobin	35
"	inhalation, 7 hr/d	330 ppm (550 mg/cu m)	Monkeys	1	Excitability, post mortem: subdural hemorrhage, chronic pneumonitis, pleural adhesions	35
"	"	"	Rats	30	Bronchitis, pneumonia, atelectasis	35
"	"	166 ppm (280 mg/cu m)	"	30	Histiocyte clumps in alveoli of lungs	35
"	sc, 34 d	0.98-3.93 mg	Mice	12	Slight thyroid reaction	49
"	sc, 36 d	15.7-796 mg	Rats	12	Thyroid hyperemia and hypertrophy	49
"	sc, 20-63 d	79.6-118 mg	Rabbits	11	Thyroid hyperplasia, exophthalmos	48
Propionitrile	inhalation, 4 hr	500 ppm (1,125 mg/cu m)	Rats	6	Death in 33% after 14 days	80
"	sc, 4 d	15-60 mg/100 g/d	"	40	Duodenal ulcers	56
"	sc	6 mg/100 g	"	Unknown	Duodenal ulcers, gastric cellular changes	58
"	sc, 3 x d	60 mg/kg on d 1, 80 mg/kg on d 2, 100 mg/kg on d 3 and d 4	"	10	Duodenal ulcers in 80%; death in 100%	62
n-Butyronitrile	inhalation, 4 hr	1,000 ppm (2,830 mg/cu m)	"	6	Death in 83% after 14 days	81,82
"	"	500 ppm (1,415 mg/cu m)	"	6	No deaths after 14 days	81,82

TABLE III-3 (CONTINUED)

EFFECTS OF SELECTED NITRILES ON ANIMALS

Substance	Route and Duration of Exposure	Concentration or Dose	Species	Number Exposed	Effect	Reference
Isobutyronitrile	inhalation, 4 hr	1,000 ppm (2,830 mg/cu m)	"	6	Death in 100% after 14 days	81
"	"	500 ppm (1,415 mg/cu m)	"	6	No deaths after 14 days	81
Glycolonitrile	inhalation, 8 hr	27 ppm (63 mg/cu m)	Mice	7	Death in 86%	40
"	"	"	Rats	7	Death in 29%	40
"	"	"	Guinea pigs	7	No deaths	40
"	dermal, single	105-130 mg/kg	Rabbits	Unknown	Mild skin irritation, death in 50%	40
"	oral, 13 wk	62-92 mg/kg/d	Rats	"	None	40
"	ocular, single	55 mg of 50% solution	Rabbits	3	Moderate eye irritation, convulsions and coma 15-30 min postexposure, death in 100% 68 min postexposure	40
Glycolonitrile, 70%	inhalation, 4 hr	250 ppm (5,825 mg/cu m)	Rats	6	Death in 66% after 14 days	81
Acetone cyanohydrin	inhalation 3, 5, 8 mo	1 ml/84 liters	Rats	50	Bronchial ulceration, renal and hepatic necrosis	66
"	inhalation, 4 hr	125 ppm (435 mg/cu m)	"	6	Death in 100% after 14 days	81
"	"	62.5 ppm (217.5 mg/cu m)	"	6	Death in 33% after 14 days	81
"	oral, 3, 5, 8 mo	5 mg/rat	"	50	Gastric ulceration, liver necrosis	66
Malononitrile	inhalation, 2 hr/d for 1 mo	36 mg/cu m	"	10	Increased respiration, increase in reticulocytes, increase in weight coefficient of lung	69
"	dermal, single	Unknown	Mice	Unknown	Tachypnea, cyanosis	68
"	"	"	Rabbits	4	Trembling, erythema	68
"	ocular, single	5%	"	6	Severe eye irritation, death in 67%	68
Adiponitrile	sc, single	50 mg/kg	Guinea pigs	20	Tachypnea, irregular respiration, paresis, tonic contractions of extremities	16
Tetramethyl-succinonitrile	inhalation, 98-164 min	159 mg/cu m	Mice	5	Muscle spasms, death 98 min postexposure, death in 100% 164 min postexposure	43
"	inhalation, 130-200 min	125 mg/cu m	"	"	Muscle spasms, death 130 min postexposure, death in 100% 200 min postexposure	43
"	inhalation	60 ppm (334 mg/cu m)	Rats	Unknown	Death after 2-3 hr	77,83
"	"	6 ppm (33 mg/cu m)	"	"	Death after 30 hr	77,83
"	oral, unknown	49-56 mg/kg	"	2	Convulsions 5 hr postexposure, death several hr later	77

TABLE III-4

LD_{50} VALUES FOR MICE, RATS, GUINEA PIGS, AND RABBITS

Substance	Species	Route of Exposure	Concentration or Dose	Reference
Acetonitrile	Rats	inhalation, 4 hr	16,000 ppm (26,880 mg/cu m)	35
"	"	oral	2,460 mg/kg	79
"	Mice	ip	520.79 mg/kg	84
"	Guinea pigs	inhalation, 4 hr	5,655 ppm (9,500 mg/cu m)	35
"	Rabbits	"	2,828 ppm (4,751 mg/cu m)	35
"	"	dermal	1.25 ml/kg undiluted, (980 mg/kg), 75% solution 0.50 ml/kg (390 mg/kg)	35
"	Rats	oral	1.7-8.5 ml/kg (1,340-6,680 mg/kg)	35
"	Guinea pigs	"	0.177 ml/kg (140 mg/kg)	35
Propionitrile	Mice	ip	33.73 mg/kg	84
"	Rats	oral	39 mg/kg	80
"	"	sc	150 mg/kg	*
"	Rabbits	dermal	160 mg/kg	80
"	Rats	oral	80 mg/kg	*
n-Butyronitrile	Mice	ip	45.75 mg/kg	84
"	Rats	oral	135 mg/kg as 0.5% in corn oil	81,82
"	"	sc	200 mg/kg	*
"	Rabbits	dermal	400 mg/kg	81,82
Isobutyronitrile	Mice	ip	<50 l/kg (38.6 mg/kg)	64
"	Rats	"	0.25 ml/kg (190 mg/kg)	64
"	"	oral	100 mg/kg	81
"	"	sc	300 mg/kg	*
"	"	oral	200 mg/kg	*
"	Rabbits	dermal	240 mg/kg	81
Glycolonitrile	Mice	oral	10 mg/kg	40
"	Rats	"	16 mg/kg	81
"	Rabbits	dermal	105-130 mg/kg	40
"	"	"	5.0 mg/kg	81

TABLE III-4 (CONTINUED)

LD_{50} VALUES FOR MICE, RATS, GUINEA PIGS, AND RABBITS

Substance	Species	Route of Exposure	Concentration or Dose	Reference
Acetone cyanohydrin	Mice	unknown	2.9 mg/kg	65
"	"	ip	8.39 mg/kg	84
"	Rats	oral	17 mg/kg	81
"	"	unknown	13.3 mg/kg	65
"	Guinea pigs	"	9 mg/kg	65
"	Rabbits	"	13.5 mg/kg	65
"	"	dermal	16 mg/kg	81
"	Guinea pigs	dermal	0.15 ml/kg (140 mg/kg)	2
Isobutyronitrile	Rats	oral	100 mg/kg	81
"	Rabbits	dermal	310 mg/kg	81
Malononitrile	Mice	oral	18.6 mg/kg	68
"	"	ip	12.9 mg/kg	85
"	Rats	"	25 mg/kg	68
"	"	oral	61 mg/kg	119
"	"	"	100 mg/kg	*
Succinonitrile	Mice	iv, im	50 mg/kg	73
"	Rats	"	250 mg/kg	73
"	Guinea pigs	iv	50 and 60 mg/kg	73
"	Rabbits	"	23 mg/kg	73
"	Rats	sc	250 mg/kg	*
Adiponitrile	Guinea pigs	"	50 mg/kg	16
"	Rats	"	200 mg/kg	*
"	"	oral	300 mg/kg	120,*
"	Mice	ip	40 mg/kg	118
Tetramethyl-succinonitrile	Rats	oral	30 mg/kg	43
"	Guinea pigs	"	17.5-25 mg/kg	43
"	Rabbits	iv	20 mg/kg	77
"	Rats	ip	17.5 mg/kg	43
"	"	sc	30 mg/kg	77
"	Guinea pigs	"	23 mg/kg	77

*S Szabo (written communication, May 1978)

IV. ENVIRONMENTAL DATA, SAMPLING, AND ANALYTICAL METHODS

Environmental Data

Data on workplace air concentrations for the various nitriles are limited. Air monitoring data for adiponitrile and acetonitrile were obtained during plant visits [4]. For adiponitrile monitoring, 43 samples (8-hour TWA's) for two field operators showed no detectable exposure (lower detection limit of 0.02 ppm). Of 12 stationary samples, 10 showed no detectable adiponitrile, whereas 1 sample indicated 0.25 ppm and another near a temporary high exposure source indicated 7.5 ppm. In a second plant, all samples for adiponitrile indicated TWA concentrations below 1 ppm. In a third plant using acetonitrile in a closed system, a single full-shift TWA concentration of 0.46 ppm was obtained. Several plants also monitor for the presence of hydrogen cyanide or total cyanide [4].

Sampling

Few papers discuss methods of collecting samples of nitriles in workplace air. Marich and Borskii [90] discussed a method of collecting succinonitrile by drawing 2 liters of air, during 10-15 minutes, through a porous plate absorber containing 2 ml of a nitrating mixture. Colorimetric determination of succinonitrile in the resulting solution was then performed. A syringe-type air sampler has been used to collect acetonitrile at a flowrate of 300 cc/minute [91]. This sampling procedure was used in conjunction with the potassium permanganate method of analysis.

Kondo et al [92] experimentally sampled for acetone cyanohydrin and acetonitrile and other organic cyanides in air using a glass and Teflon apparatus consisting of: (1) a charcoal Celite column for cleaning the air sample, (2) absorbent cotton soaked with a known quantity of an organic cyano compound, (3) a drying tube, (4) collecting tubes with an absorbing solution of deionized water, and (5) a pump. A flowrate of 500 ml/minute was used, and 100% recovery was found for acetone cyanohydrin and acetonitrile when up to 20 liters of air were drawn. Recovery sharply declined with air samples of over 20 liters. Experimentation with flowrates of from 345 ml/minute to 10 liters/minute, with a fixed sample volume of 10 liters, yielded total recovery of nearly 100% in all cases.

Charcoal tube sampling was found to be in use at various plants in the United States [4] for collection of acetonitrile, adiponitrile, and propionitrile. Methylene chloride or chloroform was used as a desorption solution for adiponitrile, and carbon disulfide plus 2% acetone was used for desorbing propionitrile. In a NIOSH health hazard evaluation and technical assistance report [93], acetonitrile was sampled with charcoal

tubes and desorbed with toluene. The NIOSH Manual of Analytical Methods [94] recommends sampling with charcoal tubes for acetonitrile and for tetramethylsuccinonitrile; acetonitrile is desorbed with benzene, and tetramethylsuccinonitrile is desorbed with carbon disulfide. A 10-liter air sample is obtained at a rate of 0.2 liter/minute or less. For sampling, the tubes are placed in a vertical position, and after sampling, the tubes are sealed at each end and submitted to a laboratory for analysis. This charcoal tube method has undergone a thorough laboratory evaluation by NIOSH, and the sampling method has been rated as "B," or "acceptable." A similar charcoal tube sampling method has been recommended for tetramethylsuccinonitrile [94]. A calibrated personal sampling pump with a flowrate that can be accurately determined at ±5% for 1.0 liter/minute is required, and a sample of 50 liters is recommended. A larger air sample than that required for estimation of acetonitrile is necessary to detect tetramethylsuccinonitrile in the range 1.80-8.20 mg/cu m (0.3-1.5 ppm).

A solid sorption tube containing sodium hydroxide flakes, developed for collection of concentrations of airborne hydrogen cyanide [95], is being considered by industry for collection of total cyanide in atmospheres where both hydrogen cyanide and a cyanohydrin are present (J Mair, personal communication, July 1978). Collection of acetone cyanohydrin in dilute sodium hydroxide has been attempted experimentally [96]. Complete dissociation of acetone cyanohydrin occurred during collection of air containing this compound at 0.8 liter/minute in absorption vessels containing 5 ml of 0.05 normal sodium hydroxide. Hydrogen cyanide was analyzed by colorimetric determination. Since acetone cyanohydrin is more stable in some acidic media [4], collection in an impinger containing an acid-absorbing solution may be necessary if the cyanohydrin is to be analyzed separately from hydrogen cyanide.

Because succinonitrile, malononitrile, and tetramethylsuccinonitrile exist as solids at room temperature (Table XII-2), sampling for particulates would be an appropriate additional method of nitrile collection. However, no such sampling data have been identified.

NIOSH recommends that tetramethylsuccinonitrile be sampled with charcoal tubes and desorbed with carbon disulfide. Because benzene has been shown to be quite toxic [97], it is recommended that toluene be substituted for it as a desorbing solution for acetonitrile following collection by charcoal tube. The use of charcoal tubes is preferable to alternate methods because the tubes are relatively simple to prepare, ship, and store; personal sampling is easily achieved; and sampling tubes and pumps are commercially available. Sampling with charcoal tubes may suffice for the collection of other mononitriles and dinitriles, but sorbent capacity for these compounds and effectiveness of desorbing solvents need to be determined. The recommended methods of sampling for acetonitrile and tetramethylsuccinonitrile are described in Appendix I. There are, at the

present time, no recommended sampling methods for n-butyronitrile, isobutyronitrile, propionitrile, adiponitrile, malononitrile, succinonitrile, acetone cyanohydrin, and glycolonitrile.

Analytical Methods

Several methods have been used to measure the selected nitriles in air samples. The two major analytical methods are based on colorimetry and gas chromatography.

A general colorimetric method for determination is based on the decomposition of nitriles in alkaline solution with liberation of free ammonia [98]. The free ammonia is determined colorimetrically using Nessler's reagent. However, this method is nonspecific for nitriles, and ammonia, formaldehyde, and hydrogen sulfide interfere. Marich and Borskii [90] developed a colorimetric method for analyzing samples of succinonitrile, utilizing the pink-violet reaction products of succinonitrile nitro derivatives with alkali in a toluene-acetone medium followed by acidification of the solution. The method is sensitive to less than a microgram of succinonitrile in the final solution and provides a stable color for up to 30 minutes; however, nitro and halogenated aromatic hydrocarbons interfere with the determination.

Collection and determination of acetonitrile by the permanganate oxidation method has been used [91]. This method was developed for acrylonitrile and was adapted for acetonitrile analysis. A sample of approximately 800 cc of air is required, and reduction of permanganate ions by the nitrile yields quadrivalent manganese ions, indicated by a change in the color of the solution from pink to blue green. The color change is rapid for acetonitrile concentrations in excess of 25 ppm (42 mg/cu m). It is possible to estimate concentrations down to 25 ppm, and the reduction of permanganate by acetonitrile may be useful in obtaining on-the-spot estimates for the concentration of acetonitrile [91]. However, acrylonitrile, ethyl acrylate, methyl methacrylate, methyl vinylpyridine, and similar compounds interfere in the analysis.

Acetonitrile has been detected alone at 125 ppm with 20% error using laser absorption spectroscopy [99]. In a prepared gas mixture, the minimum detectable concentration was 400 ppm.

A spot test for malononitrile [100], using benzofurazan oxide in an alkaline medium, yields an intense violet color. The color develops to a maximum in 20-30 minutes and then slowly fades to red. The reagent is also useful for detecting malononitrile on thin-layer chromatography plates or determining it colorimetrically in solutions.

Another spot test for malononitrile involves the reaction of nitroprusside with the nitrile in alkali hydroxide solution to yield a

blood-red color [101]. Use of such a reaction may allow a determination of malononitrile in submicrogram quantities in solution.

Several gas chromatographic techniques [98,102-106] have been described for analysis of nitriles. These techniques allow for the separation and identification of nitriles from other nitriles and related substances. Adiponitrile has been collected and determined in the presence of impurities associated with its production from adipic acid [102] or acrylonitrile [105]. Traces of acetonitrile and other impurities have been determined in acrylonitrile by gas chromatography using a flame-ionization detector [106]. A similar procedure allowed separation and determination of acetonitrile and propionitrile in the presence of unsaturated nitriles [103].

The solutions obtained by Kondo et al [92] in experimental air sampling were injected directly into a gas chromatographic column. Using 10-liter air samples collected at 760 mmHg and 25 C, the authors found that the minimum detectable concentrations of acetone cyanohydrin and acetonitrile were 2.15 and 4.46 ppm, respectively. It was determined that several organic solvents with boiling points above 100 C and deionized water gave excellent separation of the organic cyanides from the solvent peaks. The packing agent PEG 6000 proved best for stability and sharpness of peaks. A mixture of acrylonitrile, propionitrile, butyronitrile, succinonitrile, and adiponitrile in an aqueous solution containing hydrochloric acid and potassium chloride was successfully analyzed by gas chromatography using a hot wire detector [104]. However, gas chromatographic methods do not provide for specific determination of nitriles, and substances with similar retention times may interfere. In the absence of interfering substances, nitriles may be separated and determined by comparison with appropriate standards.

The use of a gas chromatograph equipped with a flame-ionization detector is recommended for analysis of acetonitrile and tetramethylsuccinonitrile in the NIOSH Manual of Analytical Methods [94]. Method S165 for acetonitrile was validated over the range 31.4-140.2 mg/cu m with a coefficient of variation of 0.072. Method S155 for tetramethylsuccinonitrile was found to have a coefficient of variation of 0.075 when validated over the range 1.80-8.20 mg/cu m. The same method, with appropriate modifications, may be applied to the determination of concentrations of other airborne mononitriles and dinitriles because of the similar physical and chemical properties of compounds in each category (Table XII-2). The plants visited in preparation of this document used gas chromatography with a flame-ionization detector for analysis of samples of propionitrile and adiponitrile [4]. However, the application of this method to n-butyronitrile, isobutyronitrile, propionitrile, adiponitrile, malononitrile, and succinonitrile has not as yet been tested or validated by NIOSH. There are, at the present time, no recommended methods for analyzing acetone cyanohydrin and glycolonitrile.

V. CONTROL OF EXPOSURES

Engineering Controls

In processes for the production, packaging, storage, and use of nitriles, the application of good chemical engineering principles and care in the selection of process equipment, particularly pumps and valves, are necessary to ensure that nitriles and cyanide-containing wastes are not released to the occupational or community environments [4]. The use of instrumentation and remote controls are recommended for monitoring processes and for allowing rapid and safe intervention for routine operations, as well as for emergencies that might develop from failures of the process or equipment. In general, use of a closed system to prevent the release of materials from a process is recommended. To maintain the integrity of a closed system, an engineering control program, including frequent inspections, preventive maintenance, and prompt repair of leaks, is essential.

When closed systems are not practical or leaks develop, exposure to nitriles in the occupational environment is possible. The likelihood of exposure increases during operations that require handling, transferring, or sampling of raw materials, nitrile products, or wastes. Exposure is also possible during required maintenance or repair of equipment, by entry into tanks, vessels, or other confined spaces, or when an emergency or a nonroutine situation develops. Therefore, a ventilation system such as a hood, glove box, or local exhaust system is necessary when nitriles are handled in an open system. In addition, a ventilation system is desirable as a standby, should a closed system fail. The principles set forth in Industrial Ventilation--A Manual of Recommended Practice [107] and in Fundamentals Governing the Design and Operation of Local Exhaust Systems [108] should be applied to control atmospheric concentrations and to prevent the release of raw materials, nitrile products, or wastes during those operations when exposure is possible. Fire hazard and explosion potential should be considered in designing ventilation systems as well as other equipment. See Table V-1 for fire hazard properties of the selected nitriles.

To ensure effective operation of ventilation systems, routine inspection should include face velocity measurements of the collecting hood, examination of the air mover and collection or dispersion system, and measurements of atmospheric concentrations of nitriles in the work environment. Any changes in the work operation, process, or equipment that may affect the ventilation system should be promptly evaluated to ensure that control measures provide adequate protection for employees. Because hydrogen cyanide may be present, all facilities require frequent inspection and preventive maintenance to ensure that leaks are readily detected and

TABLE V-1

FIRE HAZARD PROPERTIES OF SELECTED NITRILES*

Nitrile	Flashpoint (Closed Cup) F	(C)	Ignition Temperature F (C)	Flammable Limits (Percent by Volume) Lower	Upper	Flammability Class
Acetonitrile	42	(6)	975 (524)	3.0	16.0	I B
Propionitrile	36	(2)	-	3.1	-	I B
n-Butyronitrile	76	(24)	935 (501)	1.65	-	I C
Acetone cyanohydrin	165	(74)	1270 (688)	2.2	12.0	III B
Succinonitrile	270	(132)	-	-	-	III B
Adiponitrile	200	(93)	-	-	-	III B
Malononitrile	234	(112)	-	-	-	III B

*Similar data for isobutyronitrile, glycolonitrile, and tetramethylsuccinonitrile were unobtainable.

Adapted from references 4,109, and from 29 CFR 1910.106

repaired to avoid exposure of employees. Nitriles and materials used in manufacturing processes may be corrosive, and systems for such manufacturing should be constructed of corrosion-resistant materials such as stainless steel or other passivated metal. All exhaust gases from ventilation systems should be passed through a system operated to prevent release of raw materials, nitriles, and wastes at unacceptable concentrations into the occupational and community environments.

Contingency planning for emergencies, inadvertent release of materials, and breakdown of facilities is vital, and the planned procedures should be facilitated by the availability of appropriate equipment at proper locations and by trained personnel. In addition to overall contingency planning for the total plant site, contingency planning on a department or process basis within the plant is necessary. Such plans should be written out, well understood by the department's personnel, and updated as required. They should include provisions for satisfying the following requirements:

(a) Reporting requirements: how and whom to notify to obtain prompt and proper help, and how to document the incident later.

(b) Medical care: arrangements to secure prompt removal of injured personnel to local medical centers and to ensure professional triage and care in medical emergencies related to the workplace. First aid at the plant site should be integrated into the total program. There should be coordination among the medical, safety, fire, and guard departments of the industrial establishment; the local county and state police; and the participating administrative, medical, and surgical staff of external medical facilities.

(c) Steps to take to keep any spilled chemical from reaching a waterway, overloading a process waste water sewer, or creating an airborne cloud.

(d) Data on the toxicity, solubility, explosibility, flammability, and reactivity of materials being handled.

(e) Inventory of spill contingency equipment and where it is located.

(f) Procedures for handling water-soluble and insoluble chemicals, and other chemicals that require special consideration.

(g) Adequate containment structures (such as a dike) or devices around storage facilities for liquid nitriles.

(h) Tank-car and tank-truck loading and unloading facilities having a potential for serious spills require consideration of vehicle

positioning and inspections, procedures to keep equipment from being moved during loading or unloading, equipment design features, instrumentation, and employee monitoring of operations.

In addition to internal reporting procedures, plant management personnel should clearly understand the need for external reporting procedures, both those required by regulatory agencies and those to be followed in good community relations. Information on these requirements should be readily accessible to supervisors along with lists of appropriate names and telephone numbers. Each plant should also be prepared to assess the impact or hazards of a specific spill or release of material should it reach a waterway or create an airborne cloud. New facilities should be reviewed in the design phase and during construction to build in effective means of minimizing spills.

As a general approach, the employer should take necessary steps to review material-handling operations, maintenance and repair procedures, and process operations to identify areas and job locations where employees may come in contact with nitriles, hydrogen cyanide, other raw materials, and cyanide containing waste products. Factors to be considered include at least the following:

(a) Transfer, loading and unloading facilities, and related procedures for moving chemicals to and from storage tanks, trucks, railcars, and marine equipment.

(b) Sources of process upsets, and process startup, shutdown, and cleanup procedures.

(c) Equipment and storage tank diking, surface drainage routing, and sewer system layout.

(d) History of individual department spillages, clarity of operating procedures, availability of information regarding the characteristics of the chemicals handled, and their contingency planning.

(e) Mooring practices, booming, dock design, hose systems, catch or drip pans, collection systems, curbing, spill contingency equipment, preferred valve types, equipment blanking practices, lighting, barge design, loading logs, and communications systems for marine facilities.

(f) Operating procedure recommendations, piping and valve identification, capping or plugging of drain and vent valves, hose connection design, lighting, and winterizing practices for in-plant process and transfer equipment.

(g) Recommended practices for diking to contain the contents of the largest tank within the diked area, with dike valves maintained normally closed for storage tank areas.

Work Practices

Work practices appropriate to the manufacture, handling, storage, and use of nitriles are primarily concerned with preventing skin and eye contact with liquids, aerosols, and vapor of nitriles and preventing inhalation of nitriles, raw materials, and decomposition products. Acute exposure to nitriles produces signs and symptoms similar to those for exposure to cyanide [10,31,32,35].

There is evidence from case reports of industrial exposure that nitriles may be absorbed through the intact skin [2,10,16,40,42]. Systemic toxicity produced by skin absorption appears to be delayed, probably due to the low rate of metabolic release of cyanide. Prevention of exposure to nitriles in the occupational environment is also a primary goal of a work-practices program. Once exposure has occurred, prevention of adverse effects depends on early recognition of signs and symptoms and the taking of immediate countermeasures.

Areas of potential exposure by inhalation or skin contact should be posted, and the present practice is to restrict access to such areas to designated employees [4]. When skin contact with a nitrile occurs or is suspected, any contaminated clothing or personal protective equipment should be promptly removed and the affected area washed immediately with soap and water. Organic solvents should not be applied to the affected area because possible defatting of the skin or absorption of the solvent may result. Organic solvents may also enhance absorption of the nitrile. Mixtures that have more than additive toxic action, such as nitriles and acetone [46,47], may pose an additional risk to workers. Emergency showers should be available where exposures may occur. Where contact with the eyes is possible, emergency eyewash stations should be provided. Both emergency showers and eyewash facilities should be checked periodically to ensure that they are in good operating condition.

Washrooms and showers should be provided in convenient locations, and employees should be urged to wash or shower after each workshift. To minimize exposure time, whenever employees are exposed through skin contact they should be required to clean up immediately and change contaminated work clothes.

Work practices, handling procedures, and the use of protective devices should be developed to minimize contact with nitriles. The wearing of personal protective garments and equipment is necessary for additional positive protection during those activities and situations where exposures are likely.

Training

In all areas where nitriles are handled, written instructions informing employees of the particular hazards of the compounds, methods of handling the materials, procedures for cleaning up spills, personal protective equipment requirements, and procedures for emergencies should be on file and readily available to employees. The employer should establish a program of instruction to familiarize all potentially exposed employees with these procedures. A Material Safety Data Sheet (illustrated in Appendix II) should be used as a guide by employers in providing the necessary information, but this should be supplemented with specific instruction and training in work operations involving potential contact with or inhalation exposure to a nitrile.

Only properly trained individuals should be permitted access to areas in which exposures to nitriles are likely. This is particularly important in areas or during operations where cyanide may be released. All such areas and operations should be clearly identified by appropriate posted warnings (Chapter I, Section 3). In addition, an effective continuing education and training program should be organized and conducted [4]. Such a program should include at least the following:

(a) Standardized written procedures, with appropriate personnel training and periodic review, for all routine phases of plant operation.

(b) Identification of leak and spill potential through job procedure analysis.

(c) Unsafe condition reports by employees as a mechanism for pointing out spill potentials.

(d) Reporting forms for all leaks and spills of any materials, indicating whether or not they reach a waterway; investigation and review of all significant leaks and spills, with the objective of preventing recurrence.

(e) Periodic inspection procedures for dike valve conditions, transfer station valves, and material-handling procedues.

(f) Spill containment drills.

(g) Flyers or bulletins to publicize incidents, "near misses," or typical unsafe conditions.

(h) New ideas on health and safety aspects of the job.

(i) Slogans, posters, and other types of exhibits to maintain employee interest.

(j) Publicizing plant and department health and safety performance.

(k) Editorials by plant manager in plant newspaper or bulletins, and emphasis on their importance at employees' and supervisors' meetings.

For the prevention of injuries resulting from contact of nitriles with the eyes, skin, or other sensitive tissues, employees should wear and be trained in the use of personal protective garments and equipment as recommended in Chapter I, Section 4, in areas where exposure to nitriles is possible.

Good work practices, personal hygiene, and proper training of employees are necessary to control the hazards associated with workplace exposure to nitriles. Employees should be thoroughly trained in all work operations and emergency procedures and in how to use required equipment and protective devices. The effective use of good work practices to prevent exposures depends on the knowledge and cooperation of employers and employees. The employer should take all necessary steps to ensure that each employee:

(a) Receives adequate instruction and training in safe work procedures, the proper use of all operational equipment, the correct use of protective devices and practices, and all emergency procedures.

(b) Periodically attends refresher sessions and drills to maintain a high level of competence in safe work practices and emergency procedures.

(c) Is provided with proper tools, equipment, and personal protective clothing or devices.

(d) Is given adequate, responsible supervision to ensure that all safety requirements and practices are followed.

Protective Clothing, Devices, and Equipment

Gloves, boots, aprons, goggles, face shields, and other personal protective equipment should be made available for employee use. This equipment should be kept clean and in good condition. All personal protective equipment should be cleaned frequently, inspected regularly, and repaired or replaced as necessary. This equipment should be stored in appropriately designated containers or locations when not in use. Protective clothing (resistant to penetration by nitriles, raw materials, and wastes) should have all openings closed and fit snugly about the neck, wrists, and ankles whenever the wearer is in an exposure area. Clean work clothing should be put on before each workshift. At the end of the

workshift, the employee should remove soiled clothing and shower before putting on street clothing. Street and work clothing should be separated within the change area. Clothing or other material should not be blown with air under pressure because of the potential generation of airborne dust. Soiled clothing should be deposited in a designated, labeled container and appropriately laundered before reuse.

Each employee potentially exposed to nitrile vapor, or likely to come in contact with a nitrile in a solution or as a solid, should be provided with, and required to wear, adequate protective clothing and other equipment for the tasks and area of work. Adequate supervision should be exercised to ensure that the protective clothing and equipment are regularly and properly worn. The garments and equipment should be inspected and maintained on a regular basis. Items damaged by wear or abuse to the extent that the effectiveness of protection is impaired or doubtful should be repaired or replaced. All personal protective devices should be washed thoroughly after each wearing and before being reused. If any such item becomes contaminated with a nitrile during the workshift, it should be immediately flushed with a large amount of water; when such flushing makes the item unsuitable for continued wear, it should be removed and replaced by a clean one.

Respirators are not recommended as an alternative to engineering controls for routine use, but they may be needed during maintenance and repair operations that require opening of systems, during process sampling, and during emergencies or other nonroutine situations. A device-fitting program, including initial quantitative fit tests, is necessary to ensure that the respirator chosen provides sufficient protection to the wearer under conditions that may be expected during actual use. Procedures for quantitative faceseal testing and some types of systems available are described in A Guide to Industrial Respiratory Protection [110].

Eye protection is of particular importance because of the irritant effects of nitriles. Well-fitted chemical safety goggles should be worn as protection from irritating concentrations of nitrile vapor or aerosols, and as protection from mists, splashes, and spills of nitriles or other solutions. Full-length, plastic face shields may also be worn to protect the face from splashes and spills, but chemical safety goggles are still necessary to protect the eyes from vapor, mists, and splashes that may enter behind the edge of the shield [4]. A full-facepiece respirator will also provide the necessary eye protection.

Emergency and First-Aid Practices

Each plant should establish a program to meet any emergency that can reasonably be anticipated. The employees and emergency teams should be

thoroughly informed and trained in their responsibilities and actions in dealing with emergencies. Stations equipped with first-aid supplies and equipment, approved respiratory protective devices, protective garments, and other special equipment as needed should be established and maintained in readiness at easily accessible locations adjacent to areas of likely emergencies.

In emergency operations or other operations where airborne concentrations are unknown, respiratory protection should be provided to employees. Employees assigned to an operation requiring the use of respiratory protective devices should be examined to determine whether they are capable of performing the task while using the device. It is the employer's responsibility to inform employees of the necessity of using a respiratory protective device when the air concentration of a nitrile cannot be maintained at or below the limit. Respiratory protective devices should be kept clean and in good working order (29 CFR 1910.134), and should be cleaned and inspected after each use. Cleanliness of respirators is particularly important because of the hazard associated with skin exposure to nitriles. Respirators will often restrict the wearer's field of vision and perhaps mobility. This may pose additional safety hazards, so safety procedures appropriate to the job should be developed.

In areas where a high concentration of hydrogen cyanide is accidentally produced by decomposition of a nitrile, a self-contained breathing apparatus or a full-facepiece, air-supplied respirator of the pressure-demand type with auxiliary self-contained air supply should be available for employees engaged in emergency operations.

When employees are required to enter any room, equipment, or other confined space suspected of, or possibly subject to, contamination by a nitrile, tests should be made to determine the safety of the atmosphere before employees enter. The odor of certain nitriles may provide warning of high concentrations but does not necessarily indicate the extent of respiratory protection required (Chapter I, Section 4). Recommended procedures are as follows:

(a) No individual may enter any tank or equipment until it has been flushed free of nitriles, the atmosphere therein has been determined to contain the normal concentration of oxygen and not to contain dangerous concentrations of nitriles and other possible contaminants, and a permit has been issued by the responsible supervisor.

(b) No individual may enter any tank or confined space wherein the entrance is not large enough to admit an individual fitted with safety harness, lifeline, and an emergency respiratory protective device.

(c) An individual may work in a tank or confined space only with another person outside in constant contact and having rescue equipment and assistance available.

(d) Pipelines and hoses, if any, should be blanked off or disconnected to prevent inadvertent entry of a nitrile into a confined space wherein an individual is working [4].

Respiratory protective devices approved for escape or evacuation should be readily available at prominently and clearly identified locations throughout areas where excessive exposure to a nitrile is possible. The equipment is required in numbers sufficient for use by all operating and maintenance personnel likely to be present in an area.

Eye-flushing stations and safety showers are necessary in plant areas where splashes or spills of nitriles are possible. On any contact with a nitrile, flushing of the eyes or skin with water is necessary to prevent or to reduce local irritation and systemic poisoning [2,4,40,42.] Showers and eye flushing facilities should be clearly marked as to location and should have emergency and first-aid instructions posted nearby.

Employees should exercise care not to transfer nitriles from contaminated hands, gloves, or other protective garments or equipment to unprotected eye or skin surfaces.

Material Handling

The following practices and procedures are recommended whenever nitriles are handled:

(a) Enclosed process machinery and containers of nitriles or solutions containing nitriles should be kept closed or covered, except when operations require otherwise.

(b) Protective clothing and equipment should be supplied and worn when needed to prevent exposure to liquid or vapor containing a nitrile.

(c) Containers of nitriles should be securely closed during transport.

(d) Large containers (portable tanks, drums, etc) should be moved and handled by appropriate mechanical equipment.

(e) Transfer of a nitrile or solutions containing a nitrile to or from a container should be done with care to minimize any splashing and to prevent spills. Transfer by pumping through hermetically sealed lines is preferred. Lines should be flushed free of nitriles before breaking connections.

(f) Transfer of nitriles or solutions containing nitriles from tank cars or tank trucks should be done only by adequately trained employees following safe procedures.

(g) Tanks, machines, pumps, valves, and lines should be drained and flushed thoroughly with water and/or steam before maintenance or repair work is performed on them. Care should be exercised to avoid contact with the drained or flushed fluids.

(h) Containers and lines should be purged of nitriles before doing any external welding, grinding, or other operation that might provide a source of ignition for flammable vapors.

(i) Spills and leaks of nitriles or solutions should be immediately diluted with water and treated with an alkali. A decontamination procedure outlined for acetone cyanohydrin uses calcium hypochlorite and cautions to maintain a pH of 9.5 or more [4]. Employees can flush the neutralized spill to a chemical sewer system using an abundant flow of water. Employees should wear respiratory protective devices and protective garments during the cleanup of spills.

(j) Eyes and skin surfaces coming into contact with a nitrile should be immediately flushed with large amounts of water. In the case of contact with the eyes, a physician should be consulted as soon as possible.

(k) Ventilation, enclosures, remote controls, and other engineering controls or administrative procedures should be properly used or followed [4].

Sanitation

Food should not be stored, prepared, dispensed (including vending machines), or eaten in work areas where nitriles are manufactured, stored, or used. Employees should exercise great care not to transfer material from contaminated gloves, garments, or respirators to the eyes, mouth, or skin. Lunchroom or lounge areas, if provided, should be separate from work areas and protected from contamination by nitriles.

Spills and leaks of any nitrile should be cleaned up immediately, and employees engaged in cleanup should wear adequate personal protective garments and approved respiratory protective devices. Any employee whose skin or clothing becomes wetted with a nitrile should take a shower as soon as possible and change the contaminated clothing (including contaminated footgear).

Spills may be covered with sand or other suitable mineral aggregate. When the absorbed material can be handled safely, it should be removed from

the work area and disposed of in a suitable sanitary landfill. Storage facilities containing liquid nitriles should be appropriately diked to contain emergency spills.

Liquid wastes containing nitriles should not be flushed into a community sewer system unless such action neither interferes with sewage treatment nor violates applicable Federal, state, or local regulations and ordinances regarding water contamination. Disposal or treatment of solid or liquid wastes should not result in prohibited or undesirable contamination of water, air, or land. Organic components of waste water may be treated by either chemical or biologic oxidation processes. The latter processes usually involve impounding the waste liquor, in which case precautions must be taken to ensure that seepage or effluent from the impoundment does not contaminate ground water or adjacent watercourses. Recycling spilled material back into the process should be considered.

VI. DEVELOPMENT OF STANDARD

Basis for Previous Standards

Federal occupational standards presently exist for two of the selected nitriles, namely, acetonitrile and tetramethylsuccinonitrile. Both standards are based on the threshold limit values (TLV's) for workplace exposure previously adopted by the American Conference of Governmental Industrial Hygienists (ACGIH).

In 1960, the ACGIH proposed a tentative limit of 40 ppm (70 mg/cu m) for acetonitrile [111], and this limit was adopted in 1962 [112]. The proposed limit was based on an accidental group exposure reported by Grabois [31] and Amdur [32], and on human and animal studies conducted by Pozzani et al [35].

Grabois [31] reported an incident in which 16 chemical workers were accidently exposed to acetonitrile vapor while painting the inside walls of a storage tank. Acetonitrile was used as a thinner for the corrosion-resistant resinous paint. The workers became ill during the 2nd day of exposure, after the paint was warmed to facilitate application and ventilation was interrupted. One worker died, two were seriously ill when hospitalized, and eight others later were admitted to a hospital.

In a more detailed description of the same incident, Amdur [32] reported that the onset of illness was delayed 3-12 hours after exposure. The author attributed the toxicity to slow metabolic release of cyanide ions from acetonitrile. When ventilation was restored and the paint was used at room temperature, no incidents were observed at organic cyanide concentrations of 17 ppm or less.

Pozzani et al [35] exposed three subjects to acetonitrile vapor at 40 ppm for 4 hours, and two subjects were similarly exposed at 80 ppm and 160 ppm. One of the three subjects exposed at 40 ppm described a slight tightness of the chest and a "cooling sensation" in the lungs, similar to that produced by inhaling menthol, and he had increased thiocyanate concentrations in the urine. One of the two subjects exposed at 160 ppm had a slight flushing of the face after exposure, followed by a feeling of bronchial tightness.

Pozzani et al [35] suggested a standard of 40 ppm for acetonitrile on the basis of the 20-ppm standard for acrylonitrile set in 1942. This was supported by animal studies that showed that acetonitrile vapor had only a fraction of the toxicity of acrylonitrile but that both released cyanide in vivo and produced a varied species response. A standard of 40 ppm for acetonitrile was considered safe because it was shown to be less toxic than

acrylonitrile in rats, dogs, and monkeys. In 1959, the authors stated that "because of the above considerations and the fact that the permissible acrylonitrile concentration figure has withstood the test of time, it is reasonable to suggest an initial hygienic standard for acetonitrile vapor of no more than 40 ppm. This may be modified by human experience as data on acceptability and clinical evidence of safety are accumulated."

In 1965, the ACGIH proposed a tentative limit of 0.5 ppm (3 mg/cu m) for tetramethylsuccinonitrile [113], and this limit was adopted in 1967 [114]. This limit was intended to prevent systemic effects experienced by workers [115]. The recommended limit was based in part on the experience of workers in Europe who had headache, nausea, convulsions, and coma after working with vinyl foam or vinyl products [43], and was supported by the toxic effects observed in animals exposed to tetramethylsuccinonitrile [43,77]. The 1967 ACGIH listing [114] included the notation "skin" along with the recommended TLV, indicating that percutaneous absorption of tetramethylsuccinonitrile must be prevented if the limit is to protect employees from the toxic effects of exposure to the compound.

The current Federal occupational standards (ie, air contaminant limits) for acetonitrile and tetramethylsuccinonitrile were adopted from the 1968 ACGIH TLV listing by the Occupational Safety and Health Administration (OSHA) in 1971, under the provision of the Occupational Safety and Health Act of 1970. The standard for workplace exposure to acetonitrile is an 8-hour TWA concentration limit of 70 mg/cu m (40 ppm) and that for tetramethylsuccinonitrile is an 8-hour TWA concentration limit of 3 mg/cu m (0.5 ppm) with a "skin" notation. NIOSH/OSHA Draft Technical Standards have been developed as part of the Standards Completion Program to augment the current Federal limits for acetonitrile and tetramethylsuccinonitrile.

Permissible exposure levels have been established by foreign countries for four of the selected nitriles [116]. With respect to acetonitrile, Australia, Belgium, the Federal Republic of Germany, Finland, the Netherlands, Switzerland, and Yugoslavia established levels at 70 mg/cu m (40 ppm) determined as an 8-hour TWA, the USSR set a maximum allowable concentration (MAC) of 10 mg/cu m (6 ppm), and Rumania set an MAC of 50 mg/cu m (29 ppm) and an average concentration limit of 30 mg/cu m (18 ppm) with a "skin" notation. For acetone cyanohydrin, Hungary and the USSR established MAC levels of 0.9 mg/cu m (0.3 ppm). Italy set an 8-hour TWA limit of 70 mg/cu m (20 ppm), and Rumania established a TWA limit of 15 mg/cu m (4 ppm) and an MAC at 25 mg/cu m (7 ppm). Both the USSR and Rumania warned of possible skin absorption. With respect to adiponitrile, the USSR and Yugoslavia set MAC levels of 20 mg/cu m (5 ppm). With respect to tetramethylsuccinonitrile, Australia, Belgium, the Federal Republic of Germany, Finland, the Netherlands, and Switzerland established levels of 3 mg/cu m (0.5 ppm) determined as an 8-hour TWA. All but Australia and Switzerland had a "skin" notation in addition to the listed value.

Basis for the Recommended Standard

In general, acute exposure of humans to the selected nitriles can cause headache, dizziness, vomiting, profuse sweating, loss of consciousness, convulsions, coma, and death [2,10,31,32]. Autopsy findings in humans overexposed to acetonitrile indicate a general distribution in body tissues of acetonitrile and hydrogen cyanide, both free and combined [10,33]. The reported toxic effects after exposure to the selected nitriles resemble the toxic effects of cyanide [2,10,31,32]. Although cyanide is well known as an acute and fast-acting poison [88], the signs and symptoms of nitrile poisoning are characterized by a delayed onset generally attributed to the time required for metabolic release of cyanide [26-28,40,42,63]. Cyanide acts by inhibiting cytochrome oxidase and thus impairs cellular respiration [42]. At higher concentrations, cyanide may completely inhibit cellular respiration and produce histotoxic anoxia [117]. Evidence for the cyanide effect of various nitriles is supported further by the reported effectiveness of specific cyanide antidotes, such as sodium nitrite and sodium thiosulfate, in the treatment of acute overexposure [2,10,16].

A review of the human and animal toxicity information presented in Chapter III reveals that sufficient quantitative inhalation toxicity data needed for recommending workplace exposure limits for nitriles are available only for acetonitrile. Comparison of toxicity, therefore, is made with acetonitrile, either directly or indirectly, in developing the recommended standard for other nitriles.

The toxicity ratios of various nitriles injected by the sc route of administration in female rats are presented in Table VI-1. The LD_{50} values submitted by S Szabo (written communication, May 1978) are approximated values; however, the advantages of using these values for comparative toxicities of various nitriles are that these values were obtained by the same route of administration (sc), in the same species (rats), and in the same sex (female). The strain (CD rats) and weight (200 g) of the animals used were also comparable.

The LD_{50} values reported by Szabo are within the same range as those reported by other investigators using different parenteral routes of administration. Tsurumi and Kawada [64] reported an LD_{50} value of 0.25 ml/kg (193 mg/kg) for isobutyronitrile in ip-injected Wistar-strain female rats (130-150 g). The LD_{50} value reported by Szabo for isobutyronitrile injected sc was 300 mg/kg. Macht [73] reported an LD_{50} value of 250 mg/kg for succinonitrile in iv-injected rats, whereas Szabo reported an LD_{50} value of 250 mg/kg for succinonitrile in rats injected sc. However, the major difficulty in ranking this group of nitriles on the basis of relative toxicities from these data is that the few values obtained on relative toxicities by inhalation (Table VI-2) do not agree closely with those obtained by sc injection. For example, Table VI-1 indicates that n-butyronitrile is 1.5 times as toxic as isobutyronitrile in rats by sc injection. However, both of these nitriles had minimal lethal

TABLE VI-1

TOXICITY RATIOS OF VARIOUS NITRILES INJECTED SUBCUTANEOUSLY IN FEMALE RATS

Nitrile	LD_{50} (mg/kg)	LD_{50} (millimole/kg)	Molar LD_{50} Ratio with Respect to Isobutyronitrile
Isobutyronitrile	300	4.34	1.00
Propionitrile	150	2.72	1.60
n-Butyronitrile	200	2.89	1.50
Malononitrile	100	1.51	2.87
Adiponitrile	200	2.12	2.05
Succinonitrile	250	3.12	1.39

Adapted from S Szabo, written communication, May 1978

TABLE VI-2

MINIMUM LETHAL CONCENTRATIONS FOR RATS EXPOSED TO SELECTED NITRILES BY INHALATION*

Nitrile	Calculated MLC (mg/cu m)
Acetonitrile	3,857
Propionitrile	1,134
n-Butyronitrile	1,619
Isobutyronitrile	1,619
Tetramethyl-succinonitrile	235
Glycolonitrile	350
Acetone cyanohydrin	211

*The MLC is the lowest concentration that kills at least one rat when a group of rats is exposed to the airborne nitrile for 4 hours.

Adapted from references 79-83

concentrations for the rat during a 4-hour exposure of 1,619 mg/cu m [81,82]. Propionitrile is 1.6 times as toxic as isobutyronitrile by sc injection (Table VI-1), but 1.4 times as toxic by inhalation in the same species (Table VI-2). Although these three nitriles are the only ones among those studied by Szabo for which inhalation toxicities are apparently available, the difference between the relative toxicities of these compounds by these two routes of administration indicates that the workplace environmental concentration limits for the nitriles should be based on relative toxicities by inhalation when such data are available.

Table VI-3 relates the toxicities of other selected nitriles to those of acetonitrile by several routes of administration. The ratios indicate that the agreement between the comparative toxicities by different routes is poor in some cases.

On the basis of these figures, propionitrile is 3.4 times as toxic by inhalation as acetonitrile; n-butyronitrile and isobutyronitrile are 2.4 times as toxic; tetramethylsuccinonitrile is 16.5 times as toxic; glycolonitrile is 11.0 times as toxic; and acetone cyanohydrin is 18.3 times as toxic.

The toxicities of propionitrile, n-butyronitrile, isobutyronitrile, tetramethylsuccinonitrile, glycolonitrile, and acetone cyanohydrin have been related to that of acetonitrile because of the comparatively extensive information about the toxic properties of this nitrile. Since a similar basis of comparison by inhalation exposure does not exist for the remaining nitriles, the molar LD_{50} ratios for the subcutaneously administered nitriles presented in Table VI-1 are the primary basis for developing recommended workplace environmental limits for malononitrile, adiponitrile, and succinonitrile.

(1) Mononitriles

Acetonitrile, propionitrile, n-butyronitrile, and isobutyronitrile show similar toxic effects in animals [2,10,35]. These compounds may be inhaled, absorbed through the skin, or ingested. Acute toxic effects observed in animals include labored breathing, anuria, ataxia, cyanosis, coma, and death. Tissue distribution studies indicate that mononitriles are distributed uniformly in various organs [33,53] and that cyanide metabolites are found predominantly in the spleen, stomach, and skin, with smaller amounts present in the liver, lungs, kidneys, heart, brain, muscle, intestines, and testes [53]. Acetonitrile [54] and other mononitriles [36,37] are excreted partly unchanged in the urine or in exhaled air.

(A) Acetonitrile (1 ppm = 1.7 mg/cu m)

McKee et al [38] and Dalhamn et al [36,37] demonstrated that acetonitrile can be absorbed by oral tissues, retained by the lungs, and partly excreted unchanged in the urine of cigarette smokers.

TABLE VI-3

COMPARATIVE TOXICITIES OF ACETONITRILE AND OTHER SELECTED NITRILES

	Inhalation MLC (Rats)	Dermal LD_{50} (Rabbits)	Intraperitoneal LD_{50} (Mice)	Oral LD_{50} (Rats)
Acetonitrile/ Propionitrile	3.4	6.0	15.5	64.3
Acetonitrile/ n-Butyronitrile	2.4	2.5	11.4	18.5
Acetonitrile/ Isobutyronitrile	2.4	4.0	-	24.6
Acetonitrile/ Malononitrile	-	-	40.1	41.1
Acetonitrile/ Adiponitrile	-	-	13.0	8.4
Acetonitrile/ Tetramethyl-succinonitrile	16.5	-	-	100.3
Acetonitrile/ Glyconitrile	11.0	250.0	-	156.7
Acetonitrile/ Acetone cyanohydrin	18.3	73.5	62.0	147.2

Adapted from references 79-85,118-120

Amdur [32] and Grabois [31] described an accidental exposure to acetonitrile vapor in which 16 workers were exposed to acetonitrile at unknown concentrations for up to 12 hours. Nine of these workers who became ill reported symptoms of fatigue, nausea, chest pain, and headache and showed signs of hypothermia, hypotension, oliguria, coma, absence of deep reflexes, skin discoloration, and respiratory irregularities. One of the workers died within 24 hours of exposure.

Pozzani et al [35], in experiments with humans, found that one of three subjects, after inhaling acetonitrile at 40 ppm for 4 hours, experienced tightness of the chest that persisted for 24 hours. This subject also showed a slight increase in urinary thiocyanate concentration. Although these minimal effects were present in the youngest (age 31) of the three subjects, the other two showed no effects. Another subject exposed at 160 ppm experienced a slight flushing of the face and tightness of the chest after exposure but did not show significant changes in blood cyanide or urinary thiocyanate concentrations.

Pozzani et al [35] also studied the effects of inhaling acetonitrile on rats, dogs, and monkeys. Animals were exposed at 166-2,510 ppm acetonitrile 7 hours/day for up to 13 weeks (5 days/week). One monkey exposed at 2,510 ppm died on the 2nd day of exposure; two monkeys exposed at 660 ppm died in 23 and 51 days, respectively; and one monkey exposed at 330 ppm survived the duration of exposure. Monkeys exposed at 660 ppm showed poor coordination during the 2nd week of exposure, and the monkey exposed at 330 ppm showed hyperexcitability toward the end of the 13th week. Dogs exposed to acetonitrile at 350 ppm for 7 hours/day for 13 weeks (5 days/week) showed decreases in body weight and hemoglobin and hematocrit values.

Pozzani et al [35] reported LD_{50} values of 0.85 and 0.95 ml/kg (calculated from the author's data to be 707 mg/kg from a mean of 0.90 ml/kg) in female rats administered acetonitrile ip. Rats exposed to acetonitrile at 655 ppm for 7 hours/day, 5 days/week, for 13 weeks, had significant microscopic changes involving the kidneys, liver, and lungs. There were reversible lesions of the lungs, such as alveolar capillary congestion and focal edema, often accompanied by bronchial inflammation, desquamation, and hypersecretion of mucus. Osmotic swelling of mitochondria in tubular epithelial cells of the kidneys and in hepatocytes in the central portion of hepatic cords was also seen. Three of the 26 rats exposed at 330 ppm and 2 of the 28 exposed at 166 ppm for 13 weeks showed tissue abnormalities in the lungs.

In summary, exposure of humans to acetonitrile at 40 ppm for 4 hours [35] produced slight chest tightness in one of three experimental subjects. Amdur [32], in describing an incident of acute effects from exposure of workers to acetonitrile at high concentrations, commented that after controls that lowered the exposure to 17 ppm were instituted there were no

further complaints. Thus, it appears that exposure to acetonitrile at 40 ppm produced minimal effects, whereas no observable effects were produced in humans at 17 ppm. Therefore, NIOSH recommends that the current Federal standard of 40 ppm for acetonitrile be reduced to 20 ppm (33.6 mg/cu m) as a TWA limit for up to a 10-hour workshift in a 40-hour workweek.

(B) Propionitrile (1 ppm = 2.3 mg/cu m)

No human toxicity data were found for propionitrile. In animal studies, the prominent effect of propionitrile is the formation of duodenal ulcers in rats [56-61]. All these studies utilized the sc route of administration.

Comparison of the inhaled minimal lethal concentrations in Table VI-2 for propionitrile and acetonitrile shows that propionitrile was about 3.4 times as toxic as acetonitrile by this route of administration. On this basis, NIOSH recommends that employee exposure to propionitrile not exceed 6 ppm (14 mg/cu m) as a TWA concentration for up to a 10-hour workshift in a 40-hour workweek.

(C) n-Butyronitrile (1 ppm = 2.8 mg/cu m)

No human toxicity data were found for n-butyronitrile. Using sc administration in rats, Szabo and Reynolds [62] observed that n-butyronitrile had higher ulcerogenic and adrenocorticolytic potency than propionitrile. Haguenoer and Dequidt [63] found that the lethal dose for male rats by ip injection was about 150 mg/kg, whereas at 100 mg/kg only two of six rats died in 8 days.

According to the data presented in Table VI-2, inhaled n-butyronitrile is about 2.4 times as toxic as acetonitrile in rats. Thus, reduction of the TWA limit recommended for acetonitrile by this factor appears to be adequate to protect the heatlh of workers exposed to n-butyronitrile. NIOSH therefore recommends that employee exposure to n-butyronitrile not exceed 8 ppm (22 mg/cu m) as a TWA limit for up to a 10-hour workshift in a 40-hour workweek.

(D) Isobutyronitrile (1 ppm = 2.8 mg/cu m)

Zeller et al [10] and Thiess and Hey [39] reported three cases of inhalation exposure to isobutyronitrile. Symptoms of all three appeared 10-60 minutes after exposure. One worker was exposed at an unknown concentration for 10 minutes and reported dizziness and vomiting; he became unconscious and experienced circulatory collapse. He also had convulsions but recovered in a few days. The other two workers, also exposed at unknown concentrations, reported headache, dizziness, and vomiting. No other human toxicity data were found for isobutyronitrile.

The inhalation toxicity data for isobutyronitrile in mice and rats suggest that this chemical is rapidly toxic in both species [64]. All mice and rats died within 24 hours when exposed for 2 and 10 minutes, respectively, to atmospheres nominally saturated with isobutyronitrile. A significant number of deaths also occurred in both mice and rats when similarly exposed for 30 seconds and 6 minutes, respectively.

Isobutyronitrile has also been toxic by other routes of administration [64]. The lethal dose of isobutyronitrile administered to mice ip was less than 50 µl/kg (38 mg/kg), indicating a high toxicity for this species. The LD_{50} for female rats injected ip was calculated as 0.25 ml/kg (193 mg/kg).

In a subchronic study, no remarkable signs of toxicity, including deaths, occurred when male and female rats were injected ip with isobutyronitrile once daily for 14 days at 30 or 50 µl/kg or were administered 0.2 ml/kg orally. The only significant change observed was the parenchymatous degeneration of the liver in rats receiving 50 µl/kg. Male rats showed a greater degree of liver cell degeneration than did females.

According to the inhalation data presented in Table VI-2, the acute toxicity of isobutyronitrile appears to be about 2.4 times that of acetonitrile. NIOSH therefore recommends that employee exposure to isobutyronitrile not exceed 8 ppm (22 mg/cu m) as a TWA limit for up to a 10-hour workshift in a 40-hour workweek.

(2) Cyanohydrins

The principal route of exposure to cyanohydrins appears to be dermal [2,39,42], but these nitriles can also be inhaled. Because of the alpha-hydroxy group, these compounds will dissociate readily to yield hydrogen cyanide and the corresponding aldehyde or ketone [2]. The onset of toxicity is related to the time required for dissociation to produce free hydrogen cyanide.

Shkodich [65] reported that the stability of acetone cyanohydrin in solution was pH dependent, with stability being greater in an acid medium. Thus, at pH 7.4, alpha-cyanohydrins may spontaneously release cyanide ions. The rapid onset of toxicity further supports the ready release of cyanide ion from cyanohydrins.

(A) Acetone Cyanohydrin (1 ppm = 3.5 mg/cu m)

Sunderman and Kincaid [2] reported a case of exposure to acetone cyanohydrin in which a worker had skin exposure from a splash of the compound. He had symptoms of nausea 3 hours after exposure, lost consciousness, convulsed, and died 6.5 hours after exposure. The authors

also described three nonfatal cases involving operators who had dermal exposure to acetone cyanohydrin while packing pumps leading to and from storage tanks. The workers lost consciousness but revived after they were carried into fresh air and their hands were washed.

Krefft [41] reported two incidents of acute exposure involving fatalities that resulted from accidental spilling and splashing of acetone cyanohydrin on the face and clothing of workers. Other cases of acetone cyanohydrin intoxication have been reported [10,39,42]; however, no quantitative data for humans are available to enable correlation of exposure concentration with effect.

Shkodich [65] reported LD_{50} values in four animal species administered acetone cyanohydrin by an unspecified route. The mice showed the highest sensitivity to acetone cyanohydrin with an LD_{50} value of 2.9 mg/kg. The LD_{50} values for the other animals were: albino rats, 13.3 mg/kg; guinea pigs, 9 mg/kg; and rabbits, 13.5 mg/kg. Sunderman and Kincaid [2] reported an LD_{50} value of 120 mg/kg in albino guinea pigs by the dermal route. They also reported that 50% of rats died within approximately 10 minutes after exposure to saturated, purified acetone cyanohydrin vapor. These LD_{50} values suggest that acetone cyanohydrin is highly toxic in animals.

Motoc and associates [66] reported that acetone cyanohydrin administered orally to white rats (5 mg, twice a week for 3, 5, or 8 months) and by inhalation (1 ml in 84 liters of air, twice a week for 3, 5, or 8 months) caused serious liver and kidney lesions that became irreversible with prolonged duration of exposure. Inhalation of acetone cyanohydrin also produced lung damage. These lesions were degenerative with desquamation of bronchial epithelium progressing to superficial ulceration.

Because the data in Table VI-2 indicate that acetone cyanohydrin is about 18.3 times as toxic as acetonitrile by inhalation and because the alpha-cyanohydrins seem to dissociate readily to release hydrogen cyanide [2], NIOSH recommends a ceiling concentration limit no greater than 1 ppm (4 mg/cu m) for any 15-minute period for acetone cyanohydrin.

(B) Glycolonitrile (1 ppm = 2.3 mg/cu m)

Wolfsie [40] described two cases of human skin exposure to unknown quantities of 70% aqueous solution of glycolonitrile. Both workers experienced symptoms of headache, dizziness, unsteady gait, and general weakness within 1 hour after leaving work. They later experienced vertigo, respiratory distress, retching, and loss of appetite. The two workers initially recovered in 1 day, but feelings of nausea and weakness returned and persisted for 5 days in one worker. No other human toxicity data are available for glycolonitrile.

Wolfsie [40] also reported that six of seven mice, two of seven rats, and none of seven guinea pigs died when exposed to glycolonitrile at 27 ppm for 8 hours. The remaining mouse and four additional rats died within the next 18 hours.

In another study, Wolfsie [40] reported an oral LD_{50} of 10 mg/kg for male albino mice and a dermal LD_{50} value between 105 and 130 mg/kg for albino rabbits. These data indicate that glycolonitrile is significantly more hazardous than acetonitrile. As shown in Table VI-2, glycolonitrile was about 11 times as toxic to rats as acetonitrile by the inhalation route. A reduction of the limit recommended for acetonitrile by this factor, therefore, appears to be adequate to protect the health of workers exposed to glycolonitrile. However, because of the expected rapid onset of toxic action, NIOSH recommends that the occupational exposure limit for glycolonitrile not exceed a ceiling concentration of 2 ppm (5 mg/cu m) for any 15-minute period.

(3) Dinitriles

The effects of exposure to the selected dinitriles--malononitrile, adiponitrile, succinonitrile, and tetramethylsuccinonitrile--are similar. Effects on the respiratory, circulatory, and central nervous systems were observed after iv administration of malononitrile in humans [121,126-128] and following ingestion of adiponitrile in animals [16]. Tetramethylsuccinonitrile produced respiratory and CNS effects in animals [77]. Dinitriles have also produced irritation of the skin and eyes [10,68].

Malononitrile and succinonitrile released cyanide in vivo and were ultimately excreted as thiocyanate in urine [16,74-76]. Stern et al [72] also demonstrated the formation of thiocyanate from malononitrile and thiosulfate by liver and kidney tissues in vitro. The release of cyanide from dinitriles suggests that the mechanism of acute toxicity of dinitriles may be similar to that of mononitriles.

(A) Malononitrile (1 ppm = 2.7 mg/cu m)

The only human toxicity data on malononitrile found are those reported during the clinical use of the compound in the treatment of various forms of mental illness [26,27,29]. The treatment consisted of repeated administration of malononitrile (1-6 mg/kg, 3-12 doses in 2-5 weeks). Signs and symptoms of toxicity included tachycardia, facial redness, headache, nausea, vomiting, shivering, cold hands and feet, muscle spasms, and convulsions.

Panov [68] reported that mice subjected to a single 2-hour inhalation exposure to malononitrile showed signs of restlessness, increased rate of respiration in the early posttreatment period followed by lassitude, decrease in respiration rate, cyanosis, incoordination of movements,

trembling, convulsions, and eventual death in some animals. The concentration of malononitrile to which the mice were exposed was not mentioned. The author also reported tearing, blepharospasm, hyperemia of the conjuctiva, and swelling of the eyelids after the direct application of liquefied malononitrile to the eyes of rabbits.

Panov [69] found that repeated exposure to malononitrile (3.6 mg/liter, 2 hours/day for 35 days) was only slightly toxic to rats, the principal result of such exposures being a slight anaplasia of red bone marrow evidenced by a slight decrease in the concentration of the hemoglobin in the blood and by reticulocytosis.

Hicks [71] reported that malononitrile induced brain lesions in rats. These were characterized by necrosis in the striatal neurons accompanied by proliferation of microglia and oligodendroglia 1-2 days after treatment. The author also observed demyelinating lesions of the optic tract and nerve, the cerebral cortex, the olfactory bulb, and the substantia nigra.

Studies indicate that malononitrile can produce CNS, respiratory, and cardiovascular effects in humans and animals [26,27,29,68,69,71]. However, no quantitative inhalation data are available from human or animal studies and, thus, the recommended standard is based on a toxicity ratio calculated in Table VI-1. The data indicate that malononitrile is about threefold as toxic as isobutyronitrile by the sc route of administration. NIOSH therefore recommends that employee exposure to malononitrile not exceed 3 ppm (8 mg/cu m) as a TWA limit for up to a 10-hour workshift in a 40-hour workweek.

(B) Adiponitrile (1 ppm = 4.4 mg/cu m)

While reviewing cases of adiponitrile poisoning that occurred in the occupational setting over a 15-year period, Zeller et al [10] reported that six of the seven cases that they encountered resulted in skin irritation and inflammation 5-15 minutes after exposure to adiponitrile. A seventh worker suffered extensive destruction of the skin of one foot after his shoe was drenched with adiponitrile.

The only other human case report found was that of an 18-year-old man who drank a few cc of adiponitrile while at work. About 20 minutes after ingestion, he experienced tightness in the chest, headache, profound weakness with difficulty in standing, and vertigo.

Ghiringhelli [16] estimated that 50 mg/kg of adiponitrile was the "lethal" dose for guinea pigs and reported that adiponitrile was metabolized to hydrocyanic acid and excreted in urine as thiocyanate. Svirbely and Floyd [78] reported that no adverse reproductive effects were observed for the first generation in rats exposed to adiponitrile at up to 500 ppm in drinking water.

Since no quantitative data for toxicity of adiponitrile by any route of exposure in humans or animals are available on which to base an occupational exposure limit, the limit must be based on the comparative toxicity of isobutyronitrile and adiponitrile in animals. The data presented in Table VI-1 suggest that adiponitrile is about twice as toxic as isobutyronitrile administered sc in female rats. NIOSH therefore recommends that employee exposure to adiponitrile not exceed 4 ppm (18 mg/cu m) as a TWA limit for up to a 10-hour workshift in a 40-hour workweek.

(C) Succinonitrile (1 ppm = 3.3 mg/cu m)

Animal data on succinonitrile include one LD_{50} study [73] and three pharmacokinetic studies [74-76]. The latter studies demonstrated that cyanide ions are released from succinonitrile and subsequently excreted as thiocyanate. Macht [73], during his LD_{50} study in mice, rats, and guinea pigs, observed signs of asphyxia and convulsions after administration of mean lethal doses of succinonitrile by various routes. During repeated dosing experiments, Macht found no impairment of hepatic and renal functions in rabbits and no effect on blood pressure in rabbits or cats.

Since no quantitative data from inhalation exposures of humans or animals necessary for recommending an occupational exposure limit are available, the workplace environmental limit is based on the comparative toxicity of isobutyronitrile and succinonitrile. The latter compound is about 1.4 times as toxic as the former. NIOSH therefore recommends that employee exposure to succinonitrile not exceed 6 ppm (20 mg/cu m) as a TWA limit for up to a 10-hour workshift.

(D) Tetramethylsuccinonitrile (1 ppm = 5.6 mg/cu m)

The only human toxicity report on tetramethylsuccinonitrile found in a search of the literature is that of Reinl [43]. His report covered a period of about 18 months at a single plant where employees used azo-isobutyronitrile as a propellant gas to produce polyvinyl chloride foam. The exposure to tetramethylsuccinonitrile was at an unknown concentration. The symptoms reported were headache or a sensation of pressure on the head, dizziness, nausea, vomiting, a peculiar taste and frothy spittle in the mouth, respiratory distress, insomnia, unconsciousness, and convulsions. All symptoms subsided after the installation of improved ventilation in the work areas.

In animal toxicity experiments, rats exposed at 6 ppm died after 30 hours of continuous exposure, and rats exposed at 60 ppm died after 2-3 hours of continuous exposure [77]. Harger and Hulpieu [77] reported that rats, guinea pigs, rabbits, and dogs treated with tetramethylsuccinonitrile

developed violent convulsions and asphyxia, which led to their death within 1 minute to hours after the convulsions.

The work of Harger and Hulpieu [77], mentioned above, indicates that tetramethylsuccinonitrile, like the cyanohydrins, can be fatal quite rapidly. The data in Table VI-2 indicate that the inhalation toxicity of tetramethylsuccinonitrile in rats is about 16.5 times that of acetonitrile. Because of these two considerations, NIOSH recommends that the occupational exposure limit for tetramethylsuccinonitrile not exceed a ceiling concentration of 1 ppm (6 mg/cu m) during any 15-minute period in a 10-hour workday.

NIOSH-recommended workplace environmental limits for selected nitriles are summarized in Table VI-4. This table indicates that the occupational exposure limits recommended for some nitriles are less than those recommended for hydrogen cyanide and other inorganic cyanides (4.7 ppm or 5 mg/cu m of CN as a ceiling concentration limit for any 10-minute period) [88]. This does not necessarily mean that NIOSH considers these nitriles to be more acutely toxic than hydrogen cyanide but that the toxicity information available to NIOSH on these compounds allows no better estimates to be made. However, the evidence of delayed or chronic effects from exposure of experimental animals to certain nitriles [26,48,49,56,62] suggests that prolonged exposure to at least some of these compounds may actually be more hazardous than prolonged exposure to hydrogen cyanide or an inorganic cyanide.

TABLE VI-4

NIOSH-RECOMMENDED WORKPLACE ENVIRONMENTAL LIMITS FOR SELECTED NITRILES

Nitrile	ppm	mg/cu m	Type of Limit
Acetonitrile	20	34	TWA
Propionitrile	6	14	"
n-Butyronitrile	8	22	"
Isobutyronitrile	8	22	"
Acetone cyanohydrin	1	4	Ceiling
Glycolonitrile	2	5	"
Malononitrile	3	8	TWA
Adiponitrile	4	18	"
Succinonitrile	6	20	"
Tetramethyl-succinonitrile	1	6	Ceiling

Because nitriles release cyanide in vivo [16,53-55,63,74,75] and because major signs and symptoms of acute toxicity of nitriles are attributed to the release of cyanide, exposure to several of them may produce additive effects, even at or below the recommended workplace air concentration limits. These additive effects must be considered when simultaneous exposure to two or more nitriles or other cyano compounds may occur. The following formula (from 29 CFR 1910.1000) is to be used to calculate the equivalent exposure (E_m) when such simultaneous exposure occurs:

$$E_m = C_1/L_1+\ldots+C_n/L_n$$

where:

C_1 = the concentration of a particular substance
L_1 = the permissible exposure limit for that substance
E_m must be no greater than 1.

This formula cannot be applied to mixtures of nitriles with widely differing reactivities. The three substances in Table VI-4 for which ceiling concentration limits are recommended produce effects after brief exposure, whereas the other selected nitriles produce effects after more prolonged exposure. Where nitriles or other cyano compounds with widely different rates of toxic action occur in a mixture, the substances with the recommended TWA concentration limits and those with ceiling concentration limits may be entered into independent evaluations of equivalent exposure. The recommended limit for the mixed occupational exposure is exceeded when the E_m for either the nitriles with the recommended TWA concentration limits or those with ceiling concentration limits is greater than 1.

(b) Sampling and Analysis

Validated techniques are currently available to sample and analyze acetonitrile and tetramethylsuccinonitrile at the recommended environmental concentration limits. As discussed in Chapter IV and presented in greater detail in Appendix I, a charcoal tube method is recommended for personal breathing zone sampling of these two airborne nitriles and gas-liquid chromatography is recommended for analyzing them. These methods were selected because they have been shown to be sensitive, reproducible, and commercially available. The proposed methods allow for separation, detection, and quantitative determination of nitriles in the presence of other materials that could be encountered during their manufacture and use. Although the same general method may apply to the related mononitriles and dinitriles, until accurate methods have been validated, no sampling and analytical techniques for the eight remaining nitriles can be recommended.

(c) Medical Surveillance and Recordkeeping

Several human [2,16,26-29,33,34,38,40,80] and animal [22,23,49,53,54, 63-65,122] studies indicate that exposure to the vapor, aerosol, or liquid forms of these compounds produced skin, eye, and respiratory irritation; CNS disorders; systemic damage in various organs including the liver, kidneys, lungs, and heart; and death. Thus, a medical surveillance program should include preplacement and periodic medical examinations that focus attention on the nervous system, skin, lungs, and circulatory system. Because of the severity of possible acute effects, emergency medical attention should be provided for employees accidentally exposed to any nitrile included in this recommended standard. The therapeutic use of sodium nitrite and sodium thiosulfate for cyanide poisoning has been widely studied. Both agents increased the rate of detoxification of free cyanide ions, the former by increasing the amount of methemoglobin (a compound that avidly binds cyanide) and the latter by increasing the rate of enzymatic conversion of cyanide to thiocyanate. All medical and other pertinent records involving exposure to these nitriles should be kept for 30 years after employment ends to allow enough time for future detection of chronic sequelae that may be related to occupational exposure.

(d) Personal Protective Equipment and Clothing

Dermal [2,10,36,40] and ocular [68] contact with the liquid form or solutions of the nitriles included in the recommended standard may cause irritation of the skin and eyes in humans and animals. Zeller et al [10] reported seven cases of skin exposure to adiponitrile. One worker, whose shoe was soaked, suffered severe blistering and necrosis of the skin of the foot, which left him incapacitated for 117 days. The six remaining workers suffered minor skin irritation and inflammation that appeared 5-15 minutes after contact. Therefore, care should be exercised to ensure adequate protection against direct contact with liquid nitriles. Personal protective clothing, including eye protective devices and work clothes and shoes that prevent penetration of the nitriles, should be available and worn where exposure to these nitriles is likely [4]. Contaminated shoes and clothing should be removed immediately to prevent skin absorption. Any contaminated cloth or leather that cannot be adequately cleaned should be destroyed or discarded to prevent reuse. Work practices that prevent skin and eye contact with liquid nitriles should be followed. Emergency showers and eyewash fountains should be available for immediate use if accidental contact occurs.

Respirators may be needed by employees engaged in maintenance or repair operations that require opening of systems. Whenever respirators are provided, the employer should maintain an adequate respirator training and fitting program in accordance with 29 CFR 1910.134. In addition, a quantitative fit test of facepiece leakage is recommended because it provides a numerical index of respirator fit, does not rely solely on the

subjective response of the wearer, and therefore provides a more reliable means of protection than does qualitative fitting.

(e) Informing Employees of Hazards

At the beginning of employment, all employees should be informed of the hazards from exposure to these nitriles. Brochures and pamphlets can be effective as aids in informing employees of hazards. In addition, appropriate signs warning of the danger of exposure should be posted in any work area where there is a possibility of workplace exposure to these compounds.

A continuing education program is an important part of a preventive hygiene program for employees exposed in the workplace to hazardous materials such as mononitriles, cyanohydrins, and dinitriles. An education program, which includes training in the use of protective equipment, emergency procedures, first aid, and information about the advantages of medical examination, should be available to the employees. Trained persons should periodically apprise employees of possible sources of nitrile exposure, the potential adverse health effects associated with such exposure, the engineering controls and work practices in use to limit exposure, including those being planned, and the environmental and medical monitoring procedures used to check control procedures and the health status of employees. Personnel exposed to any of these nitriles should be warned of the potential adverse effects of accidental exposure and should be informed of the signs and symptoms of overexposure. Employees should be warned that the onset of these signs and symptoms may be delayed, particularly with exposures to mononitriles, and that their odor may not be detected.

(f) Work Practices

Processes should be designed and operated to minimize leaks of hazardous substances and to prevent spills during material handling, transfer, storage, and sampling. In addition, work practices for both routine operations and emergencies should be developed to ensure that direct contact with nitriles is avoided. When contact of liquid nitriles with the skin occurs, the affected area should be washed thoroughly with water and soap. When liquid nitriles or solutions containing nitriles are splashed into the eyes, they should be immediately flushed with a large amount of water (under low pressure). Medical attention should be promptly sought.

(g) Engineering Controls

The employer should use engineering controls and administrative procedures whenever possible to control exposures to airborne nitriles within the recommended environmental concentration limits. A closed system

of control is recommended for the nitriles included in this standard. Respiratory protective devices may be used during the time required to install adequate controls and equipment, to make process changes, to perform routine maintenance operations, or to make emergency repairs. However, respirators should not be used as a substitute for engineering controls for routine operations. The employer should prepare contingency plans for nonroutine operations, process upset, cold-weather operations, and emergencies. Facilities should be evaluated on a regular basis, and appropriate equipment and supplies should be available at proper locations to meet unusual conditions or emergencies. All such plans should be prepared in writing, understood by operating personnel and managers, and updated as required.

(h) Monitoring and Recordkeeping Requirements

Periodic sampling is needed to characterize each employee's exposure. This is accomplished with due consideration of environmental changes and changes in processes. Environmental, in addition to medical, records need to be retained primarily to provide a factual basis for the protection of an employee's health or for decisions related to an employee's health and legal rights. Such records need to be retained for 30 years after employment ends, and access to these records by the employer, employee, and designated representatives of the Department of Labor, and the Department of Health, Education, and Welfare is essential.

VII. RESEARCH NEEDS

(a) Epidemiologic Studies

Because no reports of epidemiologic studies on any of the 10 nitriles included in the recommended standard have been found and because very little is known concerning the health effects of long-term workplace exposure, such studies should be conducted. To the extent that there are records of environmental exposure, there should be an attempt to relate any such effects to exposures at specific concentrations. Longitudinal prospective studies of groups of workers exposed to nitriles at or below the recommended environmental limits would be useful to assess the validity of such limits. Because significant amounts of acetonitrile and possibly other nitriles are present in cigarette smoke, smoking histories should be taken into account in any epidemiologic studies of nitrile employees.

(b) Comparative Animal Toxicity Studies

As shown in the Basis for the Recommended Standard, the comparative animal toxicity data on which the environmental limits for the selected nitriles are based are minimal. In order to support or refute, and thus change, the environmental limits recommended in the standard, more complete comparative toxicity data are needed. Toxicities of the 10 compounds should be compared using the inhalation, oral, and percutaneous routes of administration in at least two species of experimental animals. The inhalation exposures should simulate probable schedules of workplace exposures as closely as possible. Animals exposed by the three routes for at least 18-20 months should be studied carefully after the exposures end to assess whether residual effects persist or appear despite withdrawal of the toxicant.

(c) Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction

Adiponitrile has been studied for mutagenicity using the Ames test [4]. A reproductive study of rats exposed to adiponitrile did not indicate any decreases in fertility, gestation, or viability in the first generation [78]. No report on investigations of the carcinogenic or teratogenic potential of any of the nitriles has been found. Studies, therefore, should be conducted into oncogenic and reproductive effects, preferably on mammals exposed to nitriles both by inhalation and dermally. Those nitriles most closely related to acrylonitrile in structure should be assigned the highest priority for testing.

(d) Metabolic Studies

Studies on the rate of release of cyanide ion from the various nitriles in mammalian systems should be pursued. Studies of the metabolism and detoxification of nitriles in the same animals also should be incorporated into such studies. The possibility that certain observed toxic effects of nitriles in animals may not be mediated by cyanide ions released from the nitrile should be investigated.

(e) Efficacy of Emergency Treatment

Administration of sodium nitrite and sodium thiosulfate appears to be an effective antidote for several nitriles [16,39,40]. However, this antidote has apparently not been tested for effectiveness in treating poisoning due to other nitriles. In addition, side effects from the administration of the antidote are not uncommon and, in several cases, have been severe. Therefore, research is recommended to develop effective emergency treatment less subject to risk from undesirable side effects.

(f) Biologic Monitoring

Research should be undertaken to develop and validate an improved analytical method for urinary thiocyanate for the purpose of assessing occupational exposure to nitriles. If it should prove possible to quantitate a relationship between urinary thiocyanate excretion (thiocyanate being a normal minor urinary metabolite) and exposure to nitriles, this could form the basis for biologic monitoring of nitrile exposure. The desirability of biologic monitoring as an adjunct to environmental control is emphasized by the probability that certain nitriles may be significantly absorbed through the skin [39,40,42].

(g) Sampling and Analysis

Validated methods are needed to collect and analyze eight of the selected nitriles. For the mononitriles and dinitriles, methods already available for acetonitrile and tetramethylsuccinonitrile, with appropriate modification, may be applied to the determination of n-butyronitrile, isobutyronitrile, propionitrile, adiponitrile, malononitrile, and succinonitrile. The cyanohydrins, acetone cyanohydrin and glycolonitrile, may pose a different chemical problem because of the relative ease with which they may decompose to yield cyanide and the presence of a second reactive group on the molecule. For these compounds, pH of the collection media is an important consideration, and analytical means of separation from other sources of cyanide in the same atmosphere need to be assessed. It is anticipated that work will be initiated by the Division of Physical Sciences and Engineering of NIOSH to address this requirement. Research and development of continuous monitors are also recommended.

(h) Personal Protective Equipment

Research is needed to identify or develop comfortable, lightweight materials impervious to the various nitriles for use in work clothing and personal protective equipment for workers.

(i) Combined Effects of Mixtures

In two studies [46,47] of combined toxicity of acetonitrile with other industrial chemicals, acetonitrile paired with acetone deviated most markedly from predicted additive action. Other nitriles that are used with industrial chemicals should be tested for combined effects.

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IX. APPENDIX I

SAMPLING AND ANALYTICAL METHODS

The recommended sampling and analytical methods for tetramethylsuccinonitrile and acetonitrile are adapted from Methods S155 and S165 of the NIOSH Manual of Analytical Methods [94]. Both methods utilize charcoal tubes for sampling and a gas chromatograph equipped with a flame-ionization detector for analysis. Other methods of analysis for these two nitriles may be used, provided their precision and sensitivity are determined to be at least equivalent to the recommended methods.

TETRAMETHYLSUCCINONITRILE

Principle of the Method

(a) A known volume of air is drawn through a charcoal tube to trap the organic vapors present.

(b) The charcoal in the tube is transferred to a small, stoppered sample container, and the analyte is desorbed with carbon disulfide.

(c) An aliquot of the desorbed sample is injected into a gas chromatograph.

(d) The area of the resulting peak is determined and compared with areas obtained for standards.

Range and Sensitivity

This method was validated over the range of 1.80-8.20 mg/cu m at an atmospheric temperature and pressure of 22 C and 760 mmHg, using a 55-liter sample. Under the conditions of sample size (55 liters), the probable useful range of this method is 0.5-10 mg/cu m. The method is capable of measuring much smaller amounts if the desorption efficiency (DE) is adequate. Desorption efficiency must be determined over the range used.

The upper limit of the range of the method is dependent on the adsorptive capacity of the charcoal tube. This capacity varies with the concentrations of tetramethylsuccinonitrile and other substances in the air. The first section of the charcoal tube was found to hold at least

0.78 mg of tetramethylsuccinonitrile when a test atmosphere containing 3.63 mg/cu m of tetramethylsuccinonitrile in air was sampled at 0.90 liter/minute for 240 minutes; breakthrough was not observed at this time since no tetramethylsuccinonitrile was detected in the backup section of the charcoal tube. (The charcoal tube consists of two sections of activated charcoal separated by a section of urethane foam.) If a particular atmosphere is suspected of containing a large amount of contaminant, a smaller sampling volume should be taken.

Interference

When the amount of water in the air is so great that condensation actually occurs in the tube, organic vapors will not be trapped efficiently. Preliminary experiments using toluene indicate that high humidity severely decreases the breakthrough volume.

When interfering compounds are known or suspected to be present in the air, such information, including their suspected identities, should be transmitted with the sample.

It must be emphasized that any compound that has the same retention time as the analyte at the operating conditions described in this method is an interference. Retention time data on a single column cannot be considered proof of chemical identity.

If the possibility of interference exists, separation conditions (column packing, temperature, etc) must be changed to circumvent the problem.

Precision and Accuracy

The coefficient of variation for the total analytical and sampling method in the range of 1.80-8.20 mg/cu m was 0.075. This value corresponds to a 0.23 mg/cu m standard deviation at 3 mg/cu m.

A collection efficiency of 1.0 was determined for the collecting medium; thus, no bias was introduced in the sample collection step. There was also no apparent bias in the sampling and analytical method for which a DE correction was made. Thus, coefficient of variation is a satisfactory measure of both accuracy and precision of the sampling and analytical method.

Advantages and Disadvantages

The sampling device is small and portable and involves no liquids. Interferences are minimal, and most of those that do occur can be

eliminated by altering chromatographic conditions. The tubes are analyzed by means of a quick instrumental method. The method also can be used for the simultaneous analysis of two or more substances suspected to be present in the same sample by simply changing gas chromatographic conditions.

One disadvantage of the method is that the amount of sample that can be collected is limited by the number of milligrams that the tube will hold before overloading. When the sample value obtained for the backup section of the charcoal tube exceeds 25% of that found on the front section, the possibility of sample loss exists.

Furthermore, the precision of the method is limited by the reproducibility of the pressure drop across the tubes. This drop will affect the flowrate and cause the volume to be imprecise because the pump usually is calibrated for one tube only.

Apparatus

(a) Calibrated personal sampling pump with a flowrate that can be accurately determined within ±5% at the recommended rate.

(b) Charcoal tubes: glass tube with both ends flame sealed, 7 cm long with a 6-mm OD and a 4-mm ID, containing two sections of 20/40 mesh activated charcoal separated by a 2-mm portion of urethane foam. The activated charcoal is prepared from coconut shells and fired at 600 C prior to packing. The adsorbing section contains 100 mg of charcoal, the backup section 50 mg. A 3-mm portion of urethane foam is placed between the outlet end of the tube and the backup section. A plug of silylated glass wool is placed in front of the adsorbing section. The pressure drop across the tube must be less than 1 inch of mercury at a flowrate of 1 liter/minute.

(c) Gas chromatograph equipped with a flame-ionization detector.

(d) Column (6-feet x 1/4-inch ID stainless steel) packed with 5% SE-30 on 80/100 mesh Chromosorb W DMCS.

(e) Electronic integrator or some other suitable method for measuring peak areas.

(f) Sample containers: 2-ml, with glass stoppers or Teflon-lined caps.

(g) Microliter syringes: 10-µl and other convenient sizes for making standards.

(h) Pipets: 1.0-ml delivery pipets.

(i) Volumetric flasks: 10-ml or convenient sizes for making standard solutions.

Reagents

(a) Chromatographic quality carbon disulfide.

(b) Tetramethylsuccinonitrile, reagent grade.

(c) Hexane, reagent grade.

(d) Acetone, reagent grade.

(e) Purified nitrogen.

(f) Prepurified hydrogen.

(g) Filtered compressed air.

Procedure

(a) Detergent wash and thoroughly rinse with tapwater and distilled water all glassware used for the laboratory analysis.

(b) Calibrate each personal pump with a representative charcoal tube in the line. This minimizes errors associated with uncertainties in the sample volume collected.

Collection and Shipment of Samples

(a) Immediately before sampling, break the ends of the tube to provide an opening at least one-half the internal diameter of the tube (2 mm).

(b) Use the smaller section of charcoal as a backup and position nearest the sampling pump.

(c) Place the charcoal tube in a vertical direction during sampling to minimize channeling through the charcoal.

(d) Do not pass air being sampled through any hose or tubing before it enters the charcoal tube.

(e) A sample size of 50 liters is recommended. Sample at a flow of 1.0 liter/minute or less. The flowrate should be known with an accuracy of at least ±5%.

(f) Record the temperature and pressure of the atmosphere being sampled. If pressure reading is not available, record the elevation.

(g) Cap the charcoal tubes with the supplied plastic caps immediately after sampling. Under no circumstances should rubber caps be used.

(h) With each batch of 10 samples, submit 1 tube from the same lot of tubes that is used for sample collection and is handled exactly the same as the samples except that no air is drawn through it. Label this as a blank.

(i) To minimize tube breakage during shipping, tightly pack and pad capped tubes before shipping.

Analysis of Samples

(a) Preparation of Samples

In preparation for analysis, each charcoal tube is scored with a file in front of the first section of charcoal and broken open. The glass wool is removed and discarded. The charcoal in the first (larger) section is transferred to a 2-ml stoppered sample container. The separating section of foam is removed and discarded; the second section is transferred to another stoppered container. These two sections are analyzed separately.

(b) Desorption of Samples

Prior to analysis, 1.0 ml of carbon disulfide is pipetted into each sample container. (All work with carbon disulfide should be performed in a hood because of its high toxicity.) Desorption should be done for 30 minutes. Tests indicate that this is adequate if the sample is agitated occasionally during this period.

(c) Gas Chromatographic Conditions

The typical operating conditions for the gas chromatograph are:

(1) 50 ml/minute (60 psig) nitrogen carrier gas flow.
(2) 65 ml/minute (24 psig) hydrogen gas flow to detector.
(3) 500 ml/minute (50 psig) airflow to detector.
(4) 230 C injector temperature.
(5) 255 C manifold temperature (detector).
(6) 90 C column temperature.

(d) Injection

The first step in the analysis is the injection of the sample into the gas chromatograph. To eliminate difficulties arising from blowback or distillation within the syringe needle, the solvent flush injection technique should be used. The 10-µl syringe is first flushed with solvent several times to wet the barrel and plunger. Three microliters of solvent are drawn into the syringe to increase the accuracy and reproducibility of the injected sample volume. The needle is removed from the solvent, and the plunger is pulled back about 0.2 µl to separate the solvent flush from the sample with a pocket of air to be used as a marker. The needle is then immersed in the sample, and a 5-µl aliquot is withdrawn, taking into consideration the volume of the needle, since the sample in the needle will be completely injected. After the needle is removed from the sample and prior to injection, the plunger is pulled back 1.2 µl to minimize evaporation of the sample from the tip of the needle. (Observe that the sample occupies 4.9-5.0 µl in the barrel of the syringe.) Duplicate injections of each sample and standard should be made. No more than a 3% difference in area is to be expected.

(e) Measurement of Area

The area of the sample peak is measured by an electronic integrator or some other suitable form of area measurement, and preliminary results are read from a standard curve prepared as discussed in the following sections.

Determination of Desorption Efficiency

(a) Importance

The DE of a particular compound can vary from one laboratory to another and also from one batch of charcoal to another. Thus, it is necessary to determine at least once the percentage of the specific compound that is removed in the desorption process, provided the same batch of charcoal is used.

(b) Procedure

Activated charcoal equivalent to the amount in the first section of the sampling tube (100 mg) is measured into a 2.5-inch, 4-mm ID glass tube, flame sealed at one end. This charcoal must be from the same batch as that used in obtaining the samples and can be obtained from unused charcoal tubes. The open end is capped with Parafilm (or equivalent). A known amount of a 20% (V/V) acetone-hexane solution of tetramethylsuccinonitrile containing 34.75 mg/ml is injected directly into the activated charcoal with a microliter syringe, and the tube is capped with more Parafilm. The amount injected is equivalent to that present in a 50-liter air sample at the selected level.

Six tubes at each of three levels (50%, 100%, and 200% of the standard) are prepared in this manner and allowed to stand, at least overnight, to assure complete adsorption of the analyte onto the charcoal. These tubes are referred to as the samples. A parallel blank tube should be treated in the same manner except that no sample is added to it. The sample and blank tubes are desorbed and analyzed in exactly the same manner as the sampling tube.

Two or three standards are prepared by injecting the same volume of compound into 1.0 ml of carbon disulfide with the same syringe used in the preparation of the samples. These are analyzed with the samples.

The DE equals the average weight in mg recovered from the tube divided by the weight in mg added to the tube, or

$$DE = \frac{\text{average weight recovered (mg)}}{\text{weight added (mg)}}$$

The DE is dependent on the amount of analyte collected on the charcoal. Plot the DE vs weight of analyte found. This curve is used to correct for adsorption losses.

Calibration and Standards

It is convenient to express concentration of standards in terms of mg/1.0 ml carbon disulfide because samples are desorbed in this amount of carbon disulfide. The density of the analyte is used to convert milligrams into microliters for easy measurement with a microliter syringe. A series of standards, varying in concentration over the range of interest, is prepared and analyzed under the same gas chromatographic conditions and during the same time period as the unknown samples. Curves are established by plotting concentration in mg/1.0 ml vs peak area.

Note: Since no internal standard is used in this method, standard solutions must be analyzed at the same time that the sample analysis is done. This will minimize the effect of known day-to-day variations and variations during the same day of the flame-ionization detector response.

Calculations

Read the weight, in mg, corresponding to each peak area from the standard curve. No volume corrections are needed because the standard

curve is based on mg/1.0 ml carbon disulfide, and the volume of sample injected is identical to the volume of the standards injected.

Corrections for the blank must be made for each sample.

$$mg = mg\ sample - mg\ blank$$

where:

mg sample = mg found in front section of sample tube
mg blank = mg found in front section of blank tube

A similar procedure is followed for the backup sections.

Add the weights found in the front and backup sections to get the total weight in the sample.

Read the DE from the curve for the amount found in the front section. Divide the total weight by this DE to obtain the corrected mg/sample.

$$\text{corrected mg/sample} = \frac{\text{total weight}}{\text{DE}}$$

The concentration of the analyte in the air sampled can be expressed in mg/cu m.

$$\text{mg/cu m} = \frac{\text{corrected mg} \times 1{,}000\ (\text{liter/cu m})}{\text{air volume sampled (liter)}}$$

Another method of expressing concentration is in ppm.

$$\text{ppm} = \text{mg/cu m} \times \frac{24.45}{MW} \times \frac{760}{P} \times \frac{T + 273}{298}$$

where:

P = pressure (mmHg) of air sampled
T = Temperature (C) of air sampled
24.45 = molar volume (liter/mole) at 25 C and 760 mmHg
MW = molecular weight (g/mole) of analyte

760 = standard pressure (mmHg)
298 = standard temperature (K)

ADIPONITRILE, MALONONITRILE, AND SUCCINONITRILE

These other dinitriles may be analyzed by gas chromatography [104]. Adiponitrile is monitored in industry by collection on charcoal and analyzed by gas chromatography with a flame-ionization detector using an SP1000 column at 220 C [4]. When these compounds are released as particulates, filter sampling should be considered. NIOSH has not tested or validated methods for these compounds, but the relatively similar physical and chemical properties of the dinitriles (Table XII-2) suggest that the recommended method for tetramethylsuccinonitrile can be adapted for use in the determination of concentrations of airborne adiponitrile, malononitrile, and succinonitrile.

ACETONITRILE

Principle of the Method

(a) A known volume of air is drawn through a large charcoal tube to trap the organic vapors present.

(b) The charcoal in the tube is transferred to a small, stoppered sample container, and the analyte is desorbed with toluene.

(c) An aliquot of the desorbed sample is injected into a gas chromatograph.

(d) The area of the resulting peak is determined and compared with areas obtained from the injection of standards.

Range and Sensitivity

This method was validated over the range of 31.4-140.2 mg/cu m at an atmospheric temperature and pressure of 22 C and 760 mmHg, using a 10-liter sample. Under the conditions of sample size (10 liters), the probable useful range of this method is 10-210 mg/cu m at a detector sensitivity that gives nearly full deflection on the strip chart recorder for a 2.1-mg sample. The method is capable of measuring much smaller amounts if the DE is adequate. The DE must be determined over the range used.

The upper limit of the range of the method depends on the adsorptive capacity of the charcoal tube. This capacity varies with the

concentrations of acetonitrile and other substances in the air. The first section of the charcoal tube held 5.2 mg of acetonitrile when a test atmosphere containing 140 mg/cu m of acetonitrile in air was sampled at 0.196 liter/minute for 190 minutes; breakthrough was observed at this time, ie, the concentration of acetonitrile in the effluent was 5% of that in the influent. (The charcoal tube consists of two sections of activated charcoal separated by a section of urethane foam.)

If a particular atmosphere is suspected of containing a large amount of contaminant, a smaller sampling volume should be taken.

Interference

When the amount of water in the air is so great that condensation actually occurs in the tube, organic vapors will not be trapped efficiently. Preliminary experiments using toluene indicate that high humidity severely decreases the breakthrough volume.

When two or more substances are known or suspected to be present in the air, such information, including their suspected identities, should be transmitted with the sample. When the desorbing solvent is present as a contaminant in the occupational environment, it cannot be effectively analyzed in the sample. If it is suspected that toluene is present, a separate sample should be collected for toluene analysis.

Any compound that has the same retention time as a nitrile of interest under the operating conditions described in this method is an interference. Retention time data on a single column cannot be considered proof of chemical identity.

When there is possible interference, separation conditions (column packing, temperature, etc) must be changed to circumvent the problem.

Precision and Accuracy

The coefficient of variation for the total analytical and sampling method in the range of 31.4-140.2 mg/cu m was 0.072. This value corresponds to a standard deviation of 5.0 mg/cu m at 70 mg/cu m.

On the average, the concentrations obtained at 70 mg/cu m using the overall sampling and analytical method were 5.3% higher than the "true" concentrations for a limited number of laboratory experiments. Any difference between the "found" and "true" concentrations may not represent a bias in the sampling and analytical method but rather a random variation from the experimentally determined "true" concentration. Therefore, no recovery correction should be applied to the final result.

Advantages and Disadvantages of the Method

The sampling device is small and portable and involves no liquids. Interferences are minimal, and most of those that do occur can be eliminated by altering chromatographic conditions. The tubes are analyzed by means of a quick instrumental method. The method can also be used for the simultaneous analysis of two or more substances suspected to be present in the same sample by simply changing gas chromatographic conditions from isothermal to a temperature-programmed mode of operation.

One disadvantage of the method is that the amount of sample that can be collected is limited by the number of milligrams that the tube will hold before overloading. When the sample value obtained for the backup section of the charcoal tube exceeds 25% of that found on the front section, the possibility of sample loss exists.

Furthermore, the precision of the method is limited by the reproducibility of the pressure drop across the tubes. This drop will affect the flowrate and cause the volume to be imprecise because the pump is usually calibrated for one tube only.

Apparatus

(a) A calibrated personal sampling pump with a flowrate that can be accurately determined within ±5% at the recommended rate.

(b) Charcoal tubes: glass tube with both ends flame sealed, 9 cm long with an 8-mm OD and a 6-mm ID, containing two sections of 20/40 mesh activated charcoal separated by a 2-mm portion of urethane foam. The activated charcoal is prepared from coconut shells and fired at 600 C prior to packing. The adsorbing section contains 400 mg of charcoal, the backup section 200 mg. A 3-mm portion of urethane foam is placed between the outlet end of the tube and the backup section. A plug of silylated glass wool is placed in front of the adsorbing section. The pressure drop across the tube must be less than 1 inch of mercury at a flowrate of 1 liter/minute.

(c) Gas chromatograph equipped with a flame-ionization detector.

(d) Column (4-feet x 1/4-inch stainless steel) packed with 50/80 mesh Porapak, Type Q.

(e) An electronic integrator or some other suitable method for measuring peak areas.

(f) Volumetric flasks: 10-ml or convenient sizes for making standard solutions and for desorbing the samples. If an automatic sample injector is used, aliquots of the samples may be transferred to the associated vials.

(g) Microliter syringes: 10-µl for injection of samples into the gas chromatograph.

(h) Pipets: 5-ml delivery pipets.

Reagents

(a) Chromatographic quality toluene.

(b) Acetonitrile, reagent grade.

(c) Purified nitrogen.

(d) Prepurified hydrogen.

(e) Filtered compressed air.

Procedure

(a) Detergent wash and thoroughly rinse with tap water and distilled water all glassware used for the laboratory analysis.

(b) Calibrate each personal pump with a representative charcoal tube in the line. This will minimize errors associated with uncertainties in the sample volume collected.

Collection and Shipment of Samples

(a) Immediately before sampling, break the ends of the tube to provide an opening at least one-half the internal diameter of the tube.

(b) Use the smaller section of charcoal as a backup and position it nearest the sampling pump.

(c) Place the charcoal tube in a vertical direction during sampling to minimize channeling through the charcoal.

(d) Do not pass air being sampled through any hose or tubing before it enters the charcoal tube.

(e) A sample size of 10 liters is recommended. Sample at a flow of 0.20 liter/minute or less. The flowrate should be known with an accuracy of at least ±5%.

(f) Record the temperature and pressure of the atmosphere being sampled. If pressure reading is not available, record the elevation.

(g) Cap the charcoal tubes with the supplied plastic caps immediately after sampling. Under no circumstances should rubber caps be used.

(h) One tube should be handled in the same manner as the sample tube (break, seal, and transport) except that no air is sampled through this tube. Label this tube as a blank.

(i) To minimize tube breakage during shipping, tightly pack and pad capped tubes before shipping.

(j) Submit a sample of the bulk material to the laboratory in a glass container with a Teflon-lined cap. Do not transport this sample in the same container as the charcoal tubes.

Analysis of Samples

(a) Preparation of Samples

In preparation for analysis, each charcoal tube is scored with a file in front of the first section of charcoal and broken open. The glass wool is removed and discarded. The charcoal in the first (larger) section is transferred to a 10-ml stoppered sample container. The separating section of foam is removed and discarded; the second section is transferred to another stoppered container. These two sections are analyzed separately.

(b) Desorption of Samples

Prior to analysis, 5 ml of toluene are pipetted into each sample container. (All work with toluene should be performed in a hood.) Desorption should be done for 30 minutes. Tests indicate that this is adequate if the sample is agitated occasionally during this period. If an automatic sample injector is used, an appropriate amount of the sample should be transferred to the automatic sample injector vials after desorption is complete. To minimize volatilization, the sample vials should be capped as soon as the sample is added.

(c) Gas Chromatographic Conditions

The typical operating conditions for the gas chromatograph are:

(1) 50 ml/minute (60 psig) nitrogen carrier gas flow.
(2) 65 ml/minute (24 psig) hydrogen gas flow to detector.
(3) 500 ml/minute(50 psig) airflow to detector.

(4) 270 C injector temperature.
(5) 285 C manifold temperature (detector).
(6) 180 C column temperature.

(d) Injection

The first step in the analysis is the injection of the sample into the gas chromatograph. To eliminate difficulties arising from blowback or distillation within the syringe needle, the solvent flush injection technique should be used. The 10-µl syringe is first flushed with solvent several times to wet the barrel and plunger. Three microliters of solvent are drawn into the syringe to increase the accuracy and reproducibility of the injected sample volume. The needle is removed from the solvent, and the plunger is pulled back about 0.2 µl to separate the solvent flush from the sample with a pocket of air to be used as a marker. The needle is then immersed in the sample, and a 5-µl aliquot is withdrawn, taking into consideration the volume of the needle, since the sample in the needle will be completely injected. After the needle is removed from the sample and prior to injection, the plunger is pulled back 1.2 µl to minimize evaporation of the sample from the tip of the needle. (Observe that the sample occupies 4.9-5.0 µl in the barrel of the syringe.) Duplicate injections of each sample and standard should be made. No more than a 3% difference in area is to be expected. An automatic sample injector can be used if it is shown to give reproducibility at least as good as the solvent flush method.

(e) Measurement of Area

The area of the sample peak is measured by an electronic integrator or some other suitable form of area measurement, and preliminary results are read from a standard curve prepared as discussed below.

Determination of Desorption Efficiency

(a) Importance

The DE of a particular compound can vary from one laboratory to another and also from one batch of charcoal to another. Thus, it is necessary to determine at least once the percentage of the specific compound that is removed in the desorption process, provided the same batch of charcoal is used.

(b) Procedure

Activated charcoal equivalent to the amount in the first section of the sampling tube (400 mg) is measured into a 9-cm x 6-mm ID glass tube, flame sealed at one end. This charcoal must be from the same batch as that used

in obtaining the samples and can be obtained from unused charcoal tubes. The open end is capped with Parafilm.

A known amount of acetonitrile in toluene containing 157 mg/ml is injected directly into the activated charcoal with a microliter syringe, and the tube is capped with more Parafilm.

The amount injected is equivalent to that present in a 10-liter air sample at the selected level. Six tubes at each of three levels (50%, 100%, and 200% of the standard) are prepared in this manner and allowed to stand for at least overnight to assure complete adsorption of the analyte onto the charcoal. These tubes are referred to as the samples. A parallel blank tube should be treated in the same manner except that no sample is added to it. The sample and blank tubes are desorbed and analyzed in exactly the same manner as the sampling tube.

Two or three standards are prepared by injecting the same volume of compound into 5.0 ml of toluene contained in a 10-ml volumetric flask. These are analyzed with the samples.

The DE equals the average weight in mg recovered from the tube divided by the weight in mg added to the tube, or

$$DE = \frac{\text{average weight recovered (mg)}}{\text{weight added (mg)}}$$

The DE is dependent on the amount of analyte collected on the charcoal. Plot the DE vs weight of analyte found. This curve is used to correct for adsorption losses.

Calibration and Standards

It is convenient to express concentration of standards in terms of mg/5 ml toluene because samples are desorbed in this amount of toluene. The density of the analyte is used to convert mg into microliters for easy measurement with a microliter syringe. A series of standards, varying in concentration over the range of interest, is prepared and analyzed under the same gas chromatographic conditions and during the same time period as the unknown samples. Curves are established by plotting concentration in mg/5.0 ml vs peak area.

Note: Since no internal standard is used in the method, standard solutions must be analyzed at the same time that the sample analysis is done. This will minimize the effect of known day-to-day variations and variations during the same day of the flame-ionization detector response.

Calculations

Read the weight, in mg, corresponding to each peak area from the standard curve. No volume corrections are needed because the standard curve is based on mg/5.0 ml toluene, and the volume of sample injected is identical to the volume of the standards injected.

Corrections for the blank must be made for each sample.

$$\text{mg} = \text{mg sample} - \text{mg blank}$$

where:

mg sample = mg found in front section of sample tube
mg blank = mg found in front section of blank tube

A similar procedure is followed for the backup sections.

Add the weights found in the front and backup sections to get the total weight in the sample.

Read the DE from the curve for the amount found in the front section. Divide the total weight by this DE to obtain the corrected mg/sample.

$$\text{corrected mg/sample} = \frac{\text{total weight}}{\text{DE}}$$

The concentration of the nitrile in the air sampled can be expressed in mg/cu m.

$$\text{mg/cu m} = \frac{\text{corrected mg} \times 1{,}000 \text{ (liter/cu m)}}{\text{air volume sampled (liter)}}$$

Another method of expressing concentration is in ppm.

$$\text{ppm} = \text{mg/cu m} \times \frac{24.45}{\text{MW}} \times \frac{760}{\text{P}} \times \frac{\text{T} + 273}{298}$$

where:

P = pressure (mmHg) of air sampled
T = temperature (C) of air sampled

24.45 = molar volume (liter/mole) at 25 C and 760 mmHg
MW = molecular weight (g/mole) of analyte
760 = standard pressure (mmHg)
298 = standard temperature (K)

n-BUTYRONITRILE, ISOBUTYRONITRILE, AND PROPIONITRILE

These other mononitriles may be analyzed by gas chromatography [103,104]. Evidence available for propionitrile indicates that it can be separated from other nitriles after collection on charcoal and analyzed at a column temperature of 80 C [4]. NIOSH has not tested or validated methods for n-butyronitrile, isobutyronitrile, and propionitrile, but the relatively similar physical and chemical properties of the mononitriles (Table XII-2) suggest that the recommended method for acetonitrile can be adapted for use in the determination of concentrations of airborne n-butyronitrile, isobutyronitrile, and propionitrile.

ACETONE CYANOHYDRIN AND GLYCOLONITRILE

There is no recommended method available to collect and determine concentrations of airborne acetone cyanohydrin and glycolonitrile.

X. APPENDIX II

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 that 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 that 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, whereas a third component could be included both for its toxicity and its reactivity. Note that an 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) that 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 LC_{50}-rat," "25 mg/kg LD_{50}-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 conventional millimeters of mercury (mmHg); vapor density of gas or vapor (air = 1); solubility in water by weight; specific gravity (water = 1); percent volatiles (indicated if by weight or volume) at 70 F (21.1 C); 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 LD_{50} 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. Typical comments might be:

Skin Contact--possible systemic poisoning through skin absorption.

Eye Contact--some pain, transient irritation; corneal scarring if prolonged contact.

"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 that 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 Mine Safety and Health Administration approval class, ie, "supplied air," "organic vapor canister," etc. Protective equipment must be specified as to type and materials of construction.

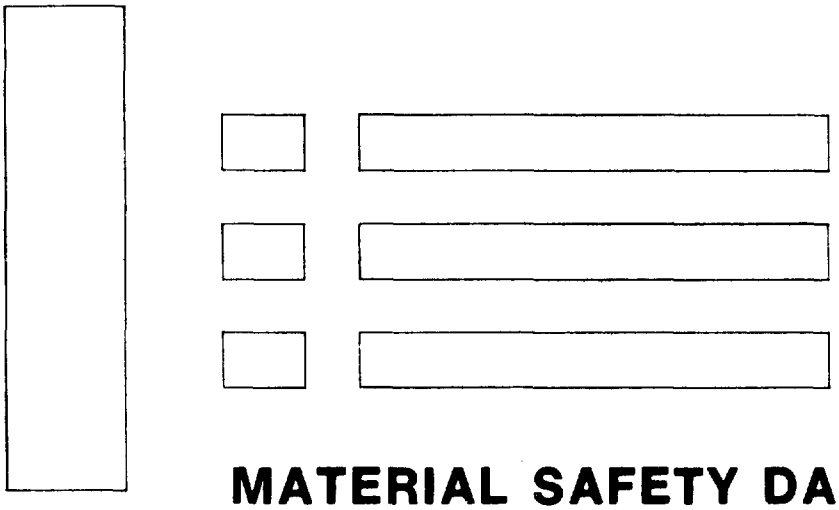
(i) Section IX. Special Precautions

"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 _____

XI. APPENDIX III

MEDICAL TREATMENT KITS AND FIRST-AID PROCEDURES

Medical Treatment Kits

Two physicians' treatment kits should be immediately available to trained medical personnel at each plant where there is a potential for the accidental release of, or other contact with, nitriles. One kit should be portable so that it may be carried by medical personnel while accompanying a patient to the hospital. The other kit should be kept under lock and key to ensure that it is intact and available when and if needed. The key should be readily available at all times to the work supervisor on duty, and the storage place should be of such construction as to allow accessibility in the event of loss of the key.

Both kits for use by the medical personnel servicing each firm should contain the following as a minimum:

(a) Two boxes of amyl nitrite (two dozen) ampules (each ampule containing 0.3 ml of amyl nitrite).

(b) Two ampules of sterile sodium nitrite solution (10 ml of a 3% solution in each).

(c) Two ampules of sterile sodium thiosulfate solution (50 ml of a 25% solution in each).

(d) Two sterile 10-ml syringes with intravenous needles.

(e) One sterile 50-ml syringe with intravenous needle.

(f) One tourniquet.

(g) One gastric tube (rubber).

(h) One nonsterile 100-ml syringe.

The medical personnel servicing a firm where there is a potential for exposure to nitriles should be familiarized with the use of these kits. First-aid kits should be immediately available at workplaces where there is a potential for the release, accidental or otherwise, of nitriles. This

kit should contain, as a minimum, two boxes of ampules (two dozen), each containing 0.3 ml of amyl nitrite. Ampules should be replaced biannually or sooner, if needed, to ensure their potency. The amyl nitrite ampules should be protected from high temperatures. In all cases, the contents of the medical and first-aid kits should be replaced before the manufacturers' assigned expiration dates.

First-Aid Procedures

Speed in the rendering of first-aid treatment is of the utmost importance. The patient should be removed at once to an area free from nitriles or hydrogen cyanide. The rescuer should wear respiratory protective equipment so as not to be overcome or weakened by the agent.

Many victims will have stopped breathing. In this case, it is imperative that efforts at resuscitation be instituted at once and continued without interruption even while other treatment is being administered.

A physician should be summoned immediately. First-aid kits should be readily available at all times. They should be quickly accessible and should be kept in all operating areas where they may be available in case of a spill.

(a) Contact with Skin and Mucous Membranes

(1) If the skin or clothing has become contaminated with nitriles, remove clothing and flush the skin with copious amounts of water. Pay careful attention to underwear, shoes, and socks.

(2) Carry out the specific actions recommended in (c) below.

(b) Internal Ingestion

(1) If the victim is conscious, induce vomiting by having the victim drink a glassful of lukewarm saltwater, soapy water, or mustard water. If the victim is unconscious, omit this step. NEVER GIVE ANYTHING BY MOUTH TO AN UNCONSCIOUS PERSON.

(2) Carry out the specific actions recommended in (a) and (c).

(c) Inhalation

(1) Administer amyl nitrite. If the ampule is not provided with a fabric sleeve, wrap it lightly in a handkerchief or gauze pad, break it, and hold it about 1 inch from the patient's mouth and nostrils for 15 seconds. Repeat five times at 15-second intervals.

Use a fresh ampule every 5 minutes until three or four ampules have been administered. Other drugs and stimulants are rarely necessary and should be administered only by a physician or trained medical personnel under the direction of a physician.

WARNING: First-aiders should keep the ampules away from their own mouths and noses lest they become weak and dizzy and unable to give proper assistance to the victim. Amyl nitrite is flammable, and mixtures with air may be explosive if a source of ignition is present.

(2) Begin resuscitation. Before instituting artificial resuscitation, remove dentures and foreign objects, such as gum and tobacco, and any accumulated oropharyngeal fluids (saliva, etc), from the patient's mouth and pharynx, and pull the tongue forward. If the patient's breathing is weak or has stopped, start artificial resuscitation at the earliest possible moment and continue without interruption until normal breathing has been established or the patient is pronounced dead.

Mouth-to-mouth resuscitation is the preferred method because of its simplicity and effectiveness. It is, however, impossible to administer amyl nitrite while using this method. Therefore, it is advisable to switch to other methods of artificial respiration, such as the Holger-Nielsen armlift, back-pressure method, during the periods when the amyl nitrite is being given.

If a mechanical resuscitator and personnel skilled in its use are available, this equipment may be used instead of other forms of resuscitation.

(3) Keep the patient comfortably warm but not hot.

XII. TABLES AND FIGURE

TABLE XII-1

SYNONYMS FOR SELECTED NITRILES

Acetone cyanohydrin	Adiponitrile
acetoncianidrina (Ita)	adipic acid dinitrile
acetoncyaanhydrine (Dut)	1,4-dicyanobutane
acetoncyanhydrin (Ger)	dinitrile hexanedioic acid
acetonecyanhydrine (Fre)	hexanedinitrile
acetonkyanhydrin (Cze)	hexanedioic acid, dinitrile
cyanhydrine d'acetone (Fre)	nitrile adipico (Ita)
acetoncianhidrinei (Rum)	tetramethylene cyanide
cyanohydrin-2-propanone	
2-cyano-2-propanol	
alpha-hydroxyisobutyronitrile	n-Butyronitrile
2-hydroxy-2-methylpropanenitrile	
2-methyllactonitrile	butanenitrile
oxyisobutyric nitrile	butyric acid nitrile
USAF RH-8	1-cyanopropane
	n-propyl cyanide
	propyl cyanide
Acetonitrile	
acetonitril (Ger)	Isobutyronitrile
cyanomethane	
cyanure de methyl (Fre)	isopropylcyanide
ethanenitrile	2-methylpropanenitrile
ethyl nitrile	2-methylpropionitrile
methane, cyano	
methanecarbonitrile	
methyl cyanide	
USAF EK-488	

TABLE XII-1 (CONTINUED)

SYNONYMS FOR SELECTED NITRILES

Glycolonitrile	Succinonitrile
formaldehyde cyanohydrin	butanedinitrile
glycolic nitrile	deprelin
glyconitrile	sym-dicyanoethane
	dinile
	ethane, 1,2-dicyano-
Malononitrile	ethylene cyanide
	ethylene dicyanide
cyanoacetonitrile	succinic acid dinitrile
dicyanomethane	succinic dinitrile
malonic dinitrile	succinodinitrile
methane, dicyano-	suxil
nitril kyseliny malonove (Cze)	USAF A-9442
USAF A-4600	
Propionitrile	Tetramethylsuccinonitrile
cyanoethane	succinonitrile, tetramethyl
ether cyanatus	tetramethylbutanedinitrile
ethyl cyanide	
hydrocyanic ether	
propanenitrile	
propionic nitrile	
propiononitrile	

Adapted from references 3,123,124

Table XII-2
PHYSICAL AND CHEMICAL PROPERTIES OF 10 NITRILES*

Substance	Molecular Formula	Molecular Weight	Specific Gravity	Melting Point (C)	Boiling Point (C)	Flashpoint (C)	Vapor Pressure (mmHg)	Vapor Density	Solubility	Odor	Form
					MONONITRILES						
Acetonitrile	CH_3CN	41.05	0.786	−43±2	81.6, 760 mmHg 13.0, 50 mmHg −15.0, 10 mmHg	48+7 (Cleveland open cup)	73.0 at 20 C 87.0 at 24 C 100.0 at 27 C 310.0 at 55 C	1.42	Miscible with water, methanol, ethyl alcohol, ether, chloroform, acetone, carbon tetrachloride, ethylene chloride	Ethereal	Liquid
Propionitrile	CH_3CH_2CN	55.08	0.782	−98 +6	97.1 - 97.4	61 (open cup)	35.2 at 20 C	1.90	Miscible with water, alcohol, ether	"	"
n-Butyronitrile	$CH_3(CH_2)_2CN$	69.11	0.793	−112.6	116–117, 760 mmHg	79 (open cup)	14.0 at 20 C	–	Sl sol in water; sol in benzene, miscible with alcohol, ether, dimethylformamide	Sharp, suffocating	"
Isobutyronitrile	$(CH_3)_2CHCN$	69.11	0.773	−75	107	–	–	–	Sl sol in water; sol in acetone; very sol in alcohol, ether	–	"
					CYANOHYDRINS						
Glycolonitrile	$CH_2(OH)CN$	57.05	1.104	–	183, 759 mmHg with slight decomposition	–	119 at 24 C	1.97	Sol in water, ethanol, ether	None	Oily liquid
Acetone cyanohydrin	$CH_3C(OH)CNCH_3$	85.11	0.932	−20	95, 760 mmHg 82, 23 mmHg 90, 20 mmHg 81, 15 mmHg	165	0.8 at 20 C 23.0 at 82 C	2.93	Sol in water, alcohol, ether, acetone, benzene; insol in petroleum ether, carbon disulfide	Bitter almond	Liquid
					DINITRILES						
Malononitrile	$NCCH_2CN$	66.06	1.049	30 - 31	218–220, 760 mmHg	234	–	–	Sol in water, acetone, benzene; very sol in alcohol, ether; insol in ethanol	None	Crystalline
Succinonitrile	$NC(CH_2)_2CN$	80.09	0.9867	57–57.5	265–267, 760 mmHg 158–160, 20 mmHg	270	2.0 at 100 C	2.10	Sol in water (12.8 g/100 ml); more sol in ethyl alcohol, acetone, benzene, ether; sl sol in carbon disulfide	"	Waxy solid
Adiponitrile	$NC(CH_2)_4CN$	108.14	0.967	1–3	295, 100 mmHg	199.4 – 200 (open cup)	2.0 at 119 C	3.73	Sl sol in water (6/1, 100 ml); sol in methanol, ethyl alcohol, chloroform; partly sol in carbon tetrachloride	Detectable, not charcterized	Oily liquid
Tetramethyl-succinonitrile	$NCC(CH_3)_2C(CH_3)_2CN$	136.20	1.070	169–170.5 (Sublimes)	–	–	–	–	Sol in alcohol	None	Solid

*Colorless, except malononitrile (yellow)

Adapted from references 3, 36, 40, 123, 125, 126, 128

TABLE XII-3

INDUSTRIAL USES OF SELECTED NITRILES

Mononitriles	Cyanohydrins	Dinitriles
Acetonitrile	Acetone cyanohydrin	Adiponitrile
Solvent	Intermediate for resins	Synthetic fiber synthesis
Hydrocarbon additive		Rubber accelerator manufacture
Acetophenone synthesis	Glycolonitrile	Corrosion inhibitor manufacture
1-Naphthaleneacetic acid synthesis		
Thiamine synthesis	Barrier resin additive	Malononitrile
	Bactericide and fungicide synthesis	
Propionitrile	Hydantoin synthesis	Lubricating oil additive
	Chloroacetonitrile synthesis	Thiamine synthesis
Solvent	Glycine synthesis	Pteridine-type anticancer agents synthesis
	Alpha-aminonitriles synthesis	Photosensitizer synthesis
n-Butyronitrile	Aminoethylpiperazines synthesis	Acrylic fibers synthesis
		Dyestuff synthesis
Specialty chemicals synthesis		
Pharmaceutical chemicals synthesis		Tetramethylsuccinonitrile
Isobutyronitrile		Decomposition product of azo-isobutyronitrile (used as a propellant gas in production of light polyvinyl foams
Catalyst		
Gasoline additive		

Adapted from references 3,8,13,14,127

TABLE XII-4

OCCUPATIONS WITH POTENTIAL EXPOSURE TO SELECTED NITRILES

Fibermakers	Maintenance workers
Organic nitrile synthesizers	Perfumemakers
Petroleum hydrocarbon purifiers	Thiaminemakers
Tank coaters	Laboratory technicians
Drugmakers	Firefighters
Plastic workers	Photographic workers
Animal and vegetable oil processors	Pipefitters
Drum fillers	Millwrights
Industrial laundry workers	

Adapted from references 3,8,127

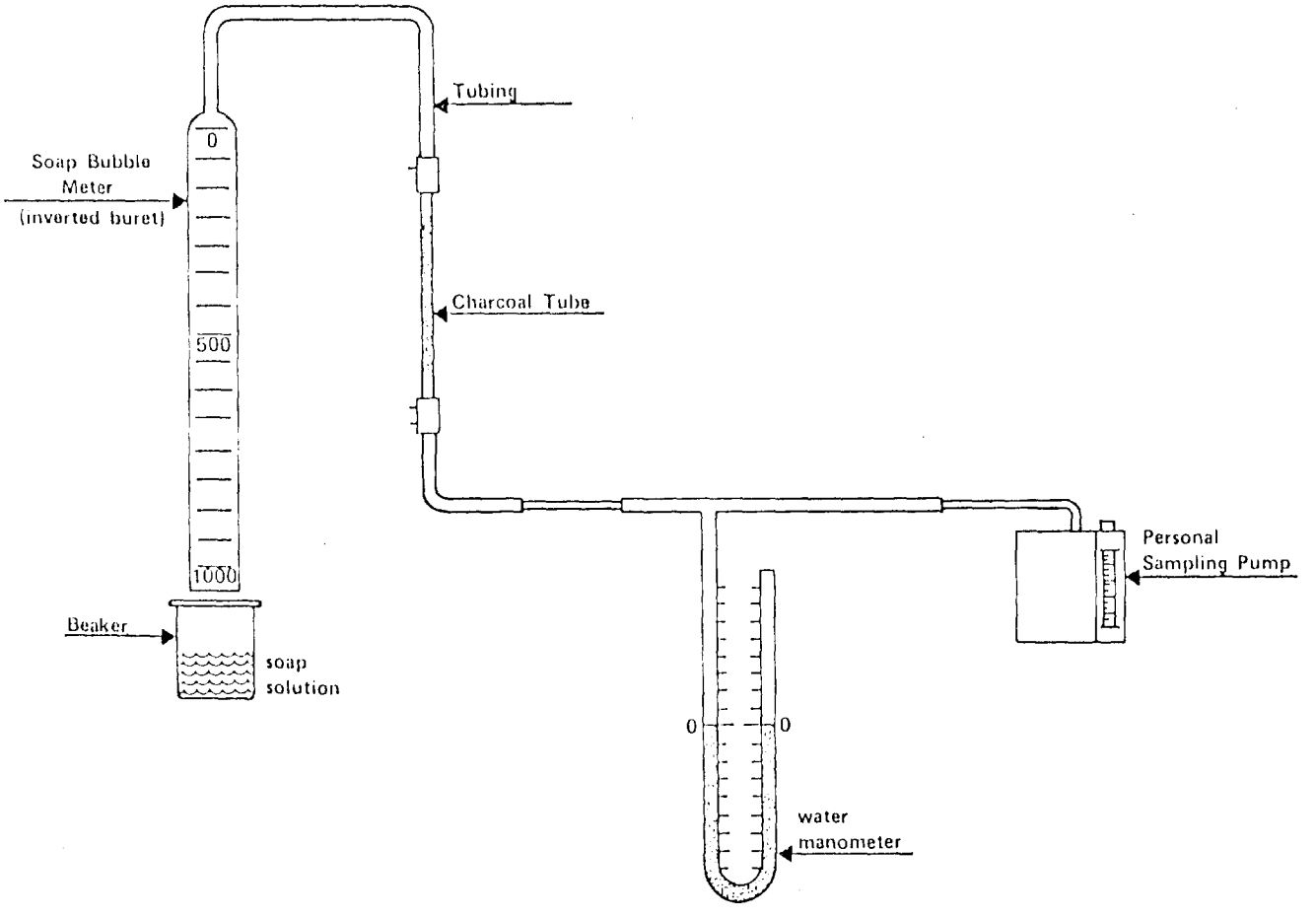


FIGURE XII-1

CALIBRATION SETUP FOR PERSONAL SAMPLING PUMP WITH CHARCOAL TUBE

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