FILE: VINYL CHLORIDE PANEL

CHEMICAL MANUFACTURERS ASSOCIATION

December 1, 1992

Dear Vinyl Chloride Panel Research Coordinators:

In August 1991, the ATSDR published a draft Priority Data Needs for Vinyl Chloride. I now have the final Priority Data Needs for Vinyl Chloride. Please let me know if the Vinyl Chloride Research Coordinators should consider any activities pertaining to the identification of final data needs in the attached profile.

A copy of the ATSDR "Revised Procedures for Conducting Voluntary Research" (57 FR 54160; November 16, 1992) also is enclosed for your information.

Sincerely,

Has Shah

Hasmukh C. Shah, Ph.D.
Manager, Vinyl Chloride Panel

Enclosure

DEC 4 1992

2501 M Street NW, Washington, DC 20037 202-887-1100 Panafax 202-887-1237 Telex 89617 (CMA WSH)

Substance-Specific Applied Research Program
Priority Data Needs for:
VINYL CHLORIDE

Prepared by: Agency for Toxic Substances and Registry/Division of Toxicology (ATSDR/DT)

Date prepared: September 1992

I. Executive Summary

Vinyl Chloride appeared on the first priority list of 100 hazardous substances identified by ATSDR and the Environmental Protection Agency (EPA) on April 17, 1987 (52 FR 12866). This list contains substances that have been identified at National Priorities List (NPL) sites and determined to pose a potential human health risk based on (1) known or suspected human toxicity, (2) frequency of occurrence at NPL sites or other facilities, and (3) potential for human exposure to the substance. The original Toxicological Profile for Vinyl Chloride was published by ATSDR in August 1989 (ATSDR 1989). An updated version of this profile is currently under development (ATSDR 1991).

Vinyl chloride, also known as chloroethene, chloroethylene, ethylene monochloride or monochloroethylene, is a colorless gas with a mild, sweet odor. It is a man-made chemical that does not occur naturally in the environment. Vinyl chloride is an important industrial chemical due to its wide variety of end-use products, and the low cost of producing polymers from it. Major end-use products include: polyvinyl chloride (PVC) products such as automotive parts and accessories, furniture, packaging materials, pipes; and vinyl chloride-vinyl acetate copolymer products such as films and resins. Vinyl chloride has been used in the past as a refrigerant, as an extraction solvent for heat-sensitive materials, and in the production of chloroacetaldehyde and methyl chloroform. In the United States, limited quantities of vinyl chloride were used as an aerosol propellant and as an ingredient of drug and cosmetic products; however, these practices were banned by the EPA in 1974.

In 1988 production of vinyl chloride in the United States was 9.1 billion pounds. Vinyl chloride has been identified in at least 245 of the 1,300 NPL hazardous waste sites in the United States. Vinyl chloride has been found in ambient air, water, soil and foodstuffs. The greatest potential for exposure to vinyl chloride for the general population is through inhalation and ingestion. The toxicity of vinyl chloride has been reported in humans and investigated in animals. It has been shown to cause suppression of the central nervous system and hepatotoxicity. Other evidence suggests that vinyl chloride causes developmental, reproductive, hematological, and musculoskeletal effects. The potential carcinogenicity and genotoxicity from exposure to vinyl chloride are well documented.

On the basis of the available data, ATSDR has identified the following priority data needs:

Exposure

- o Evaluation of existing data on concentrations of vinyl chloride in contaminated environmental media at hazardous waste sites (Group A)
- o Exposure levels in humans living near hazardous waste sites and other populations such as workers exposed to vinyl chloride (Group A)
- o Potential candidate for subregistry of exposed persons (Group A)

Toxicity

- o Dose-response data in animals for acute-duration exposure via inhalation (Group A)
- o Dose-response data in animals for chronic-duration exposure via inhalation (Group B)
- o 2-species multigeneration reproductive study via inhalation (Group A)
- o 2-species developmental study via inhalation (Group B)
- o Mitigation of vinyl chloride-induced toxicity (Group B)

II. Introduction: ATSDR's Substance-Specific Applied Research Program

A. Legislative

Section 104(i)(5) of the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of vinyl chloride is available. Where adequate information is not available, ATSDR, in cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine these health effects. Such program shall include, to the extent necessary to supplement existing information, but shall not be limited to--

- o laboratory and other studies to determine short, intermediate, and long-term health effects;
- o laboratory and other studies to determine organ-specific, site-specific, and system-specific acute and chronic toxicity;

- o laboratory and other studies to determine the manner in which such substances are metabolized or to otherwise develop an understanding of the biokinetics of such substances; and
- o where there is a possibility of obtaining human data, the collection of such information.

Section 104(i)(5)(C): In the development and implementation of the research program ATSDR is required to coordinate with EPA and NTP to avoid duplication of research being conducted in other programs and under other authorities.

Section 104(i)(5)(D): It is the sense of Congress that the costs for conducting this research program be borne by private industry, either under the Toxic Substances Control Act (TSCA), the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), or cost recovery under CERCLA.

B. Impact on Public Health

The major purpose of this research program is to supplement the substance-specific informational needs of the public and the scientific community. More specifically for ATSDR, this program will supply necessary information for conducting Health Assessments as more fully described in the ATSDR Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (54 FR 37618) [henceforth referred to as the ATSDR Decision Guide]. Experience from ATSDR Health Assessments indicates the need, for select substances, for additional information on both exposure and toxicity in order for the Agency to more completely assess human health effects. Exposure data collected from this substance-specific research effort will complement data being collected on a site-specific basis by the ATSDR Division of Health Studies and Division of Health Assessment and Consultation. More specifically, the exposure data will be used by the Agency to assist in identifying populations in need of follow-up exposure or health outcome studies. Regarding substance toxicity, the data collected will be used to characterize the toxicity of the substance for use by the public and the scientific community; for ATSDR, the data are necessary and essential to improve the design and conduct of follow-up health studies.

C. Procedures

Section 104(i)(2) of CERCLA, as amended, requires that ATSDR (1) with EPA develop a list of hazardous substances found at NPL sites (in order of priority), (2) prepare toxicological profiles of those substances, and (3) assure the initiation of a research program to fill identified data needs associated with the substances. To date, ATSDR has listed 275 hazardous substances and prepared 156 toxicological profiles, in draft or final, covering 215 substances.

The first step in implementing the ATSDR substance-specific research program for vinyl chloride occurred with the determination of the data needs in the ATSDR Toxicological Profile for Vinyl Chloride (ATSDR 1989). These data needs, determined as a subset of all information gaps

on vinyl chloride, were reviewed by scientists from the ATSDR, NTP, EPA, and the Centers for Disease Control; peer reviewed by an external review panel; and made available for public comment. All comments received by ATSDR on the identification of data needs for vinyl chloride were addressed prior to the finalization of the toxicological profile; thus, ATSDR believes that these are the data needs for vinyl chloride necessary to perform health assessments. An updated version of this toxicological profile is currently under development (ATSDR 1991).

The purpose of this paper is to take the data needs identified in the Toxicological Profile for Vinyl Chloride and subject them to further scientific evaluation leading to priorities and ultimately to ATSDR's substance-specific research agenda. In order to effect this step, ATSDR developed and presented a logical scientific approach to priority setting in its Decision Guide.

Briefly, data needs are categorized as exposure or toxicity and are then subcategorized across three levels (Tables 1 and 2) Level I research is defined as a base set of exposure and toxicity information for identifying basic characteristics of each substance. Level II research is conducted to confirm the toxicity and exposure indicated by Level I data; and Level III is defined as research to improve the application to humans of the results of Level II research.

The Decision Guide recognized three general principles for setting priorities:

- Not all information gaps identified in toxicological profiles are data needs.
- All data needs are not of the same priority.
- Substances should be considered individually but may be grouped because of structural similarity or other relevant factors.

Other considerations spelled out in the Decision Guide include:

- All levels of data should be considered in selecting priority data needs.
- Level I gaps are not automatically in the priority grouping. In general, Level I data have priority when there are no higher level data for the same category, and when data are insufficient to make higher level priority testing decisions. For example, priority would generally not be assigned multigeneration animal studies (Level II) if an adequate subchronic study (Level I) had not been conducted that evaluated reproductive organ histopathology.
- Priority for either exposure or toxicity data requires thorough evaluation of research needs in other areas to help achieve a balanced research program for each substance.

The Decision Guide listed the following 8 tenets for determining research priorities.

- Development and/or confirmation of appropriate analytical methods.

- o Determination of environmental and human exposure levels when analytical methods are available.
- o Bioavailability studies for substances with known significant toxicity and exposure.
- o Studies available to characterize target organs and dose response.
- o Disposition studies and comparative physiologically-based pharmacokinetic studies when a toxic endpoint has been determined and differences in species response have been noted.
- o Mechanistic studies on substances with significant toxicity and substantial human exposure.
- o Investigation of methods for mitigation of toxicity for substances where enough is known about mode of action to guide research.
- o Epidemiologic studies designed to link human disease with a substance of known significant toxicity.

These last three "prioritizing" tenets address Level III research. When Level III research is identified as priority, it will not be the practice of ATSDR to develop in detail the methods for successful fulfillment of the data needs. As there are no standard "testing guidelines" for Level III research, it is anticipated that considerable discussion is likely to take place by parties interested in conducting this research. Thus, ATSDR will go no further than to announce that it believes that the accumulation of Level III research is appropriate and a priority at this time and state the reasons why it believes this to be so.

D. Selection Criteria

ATSDR prepares toxicological profiles on substances that are most commonly found at facilities on the NPL and which, in its sole discretion, pose the most significant threat to human health due to their known or suspected toxicity and potential for human exposure. Support documentation for inclusion of vinyl chloride on this list can be found as part of the ATSDR Administrative Record (Docket # 1). Briefly, the rationale is as follows.

1. Frequency of Occurrence

Finding: Vinyl Chloride appeared in the ATSDR first priority list of 100 hazardous substances published in the Federal Register on April 17, 1987 (52 FR 12866). It was selected from a list of 717 hazardous substances currently identified under section 102 of CERCLA.

Vinyl chloride has been detected in at least 245 of 1,300 NPL hazardous waste sites in the United States (MIS 1990). Exposure to vinyl chloride at these sites may occur by contacting contaminated air, water, soil, sediment, and food products. ATSDR is presently evaluating the extent of media-specific contamination at these and other sites.

2. Potential for human exposure

Finding: ATSDR has determined that there has been significant past and

present human exposure to vinyl chloride via inhalation, ingestion, and limited dermal contact.

The following is a brief summary of the potential for human exposure to vinyl chloride. Please refer to the ATSDR Toxicological Profile for Vinyl Chloride, chapter on "Potential for Human Exposure" for a more detailed discussion of available information (ATSDR 1989, 1991).

Vinyl chloride, also known as chloroethene, chloroethylene, ethylene monochloride or monochloroethylene, is a colorless gas with a mild, sweet odor. It is a man-made chemical that does not occur naturally in the environment; and most of the vinyl chloride produced in the United States is used to make polyvinyl chloride (PVC). PVC is used to manufacture a variety of plastic and vinyl products including pipes, wire and cable coatings, furniture, automobile upholstery, housewares and automobile parts. Humans are exposed to vinyl chloride from environmental and occupational sources. Vinyl chloride is mainly released into the air, discharged as exhaust gases from factories that manufacture or process vinyl chloride, or evaporation from areas where chemical wastes are stored. Vinyl chloride enters drinking water from factories that release waste containing it into rivers and lakes and from its seepage into underground water in areas where chemical wastes are stored. The total release of vinyl chloride into the environment from point sources was reported to be 1,326,568 pounds in 1988 and 1,801,851 in 1987 (TRI 1990). Small amounts of vinyl chloride can enter the drinking water from contact with polyvinyl chloride pipes. In the past, higher than expected amounts were present in food packaged in plastic that contain vinyl chloride.

This colorless gas is an important substance for research because of its widespread environmental contamination. Vinyl chloride is a stable chemical that is degraded very slowly, so there has been a gradual accumulation of vinyl chloride in the environment as a consequence of releases from human activities. The general population living in the vicinity of emission sources are exposed to vinyl chloride by inhalation of contaminated air. The average daily intake of vinyl chloride by inhalation for these people ranges from trace amounts to 2,100 ug/day (Gordon and Meeks, 1977). The National Occupational Exposure Survey (NOES) conducted by NIOSH from 1981 to 1983, estimated that 81,314 workers employed at 3,711 plant sites were potentially exposed to vinyl chloride in the United States (NIOSH 1991). Exposure is believed to occur primarily through inhalation with some absorption via the oral route and limited dermal absorption (Sittig 1985). Vinyl chloride has been detected at varying concentrations in surface, ground and drinking waters throughout the U.S. (EPA 1985b). Concentrations as high as 9.8 ug/l (0.01 ppm) in surface water, 380 ug/l (0.38 ppm) in groundwater and 10 ug/l in drinking water have been reported (Dyksen and Hess 1982 and HSDB 1987).

Vinyl chloride has been detected in groundwater samples taken at an estimated 3% of the NPL hazardous waste sites included in EPA's Contract Laboratory Program Statistical Database (CLPSD) at a geometric mean

concentration of 0.102 ppm (CLPSD 1989). Vinyl chloride can be released into soil from leachates at hazardous waste sites. However, vinyl chloride was not listed in the EPA CLPSD of chemicals detected in soil samples taken at NPL sites.

3. Toxicity

Finding: ATSDR finds that short, intermediate, and long-term health effects can result from inhalation, ingestion, and limited dermal contact of vinyl chloride gas, liquid or vapor. Target organs or systems known to be affected include the central nervous system and the liver.

The following is a brief summary of the toxicology of vinyl chloride. Please refer to the ATSDR Toxicological Profile for Vinyl Chloride, chapter on "Health Effects" for a more detailed discussion of available information (ATSDR 1989, 1991).

The toxicity of vinyl chloride has been investigated in humans and demonstrated in animals. Most toxicity studies have focused on the central nervous system and hepatotoxicity. Central nervous system depression is the earliest symptom associated with acute vinyl chloride exposure in humans and animals. Workers exposed to vinyl chloride complained of dizziness, drowsiness, euphoria, nausea, headache, and occasional loss of consciousness (Juhe et al. 1974; Langauer-Lewowicka et al. 1976; Walker 1976; Lilis et al. 1975). Changes in the liver have been observed in humans exposed to vinyl chloride via inhalation. Some of the characteristic pattern of changes include hypertrophy and hyperplasia of hepatocytes and sinusoidal cell; focal areas of hepatocellular degeneration due to disruption of hepatic circulation; and fibrosis of portal tracts, and septa (Falk et al. 1974; Gedigke et al. 1975; Marsteller et al. 1975; Popper and Thomas 1975).

Studies in humans indicate that male reproductive function may be adversely affected and developmental effects may occur (Suciu et al. 1975; Veltman et al. 1975; Walker 1976). There are a number of studies on the carcinogenic effects of vinyl chloride in humans and animals following inhalation and oral exposure. Various types of cancers can occur in humans but angiosarcoma of the liver is strongly associated with chronic exposure to vinyl chloride (Bryen et al. 1976; Creech and Johnson 1974; Fox and Collier 1977; Infante et al. 1990; Smulevich et al. 1988).

Drugs and other chemicals that increase the metabolism of vinyl chloride can increase the toxicity of vinyl chloride. Thus, individuals who take phenobarbital for medicinal purposes are at a greatly increased risk of liver and/or central nervous system damage following exposure to vinyl chloride. In addition, exposure to trichloropropene oxide (TCPO) potentiates the toxicity of vinyl chloride; and individuals who are heavy drinkers of alcohol increase their risk of hepatic angiosarcomas, hepatomas, and lymphosarcomas (Hefner et al. 1975b and Hultmark et al. 1979). Other conditions such as poor nutritional status, preexisting liver disease or genetically-based high mixed function oxidase (MFO)

activity may predispose an individual to toxicity.

III. Identification of Data Needs

In evaluating the exposure and toxicity testing needs for vinyl chloride, ATSDR considered all available published and unpublished information that has been peer reviewed. From its evaluation of these data, ATSDR is recommending the conduct of specific research or testing.

A. Exposure Data Needs (Table 1)

Three of the eight "prioritizing" tenets presented in the Decision Guide directly address exposure data needs.

- o Development and/or confirmation of appropriate analytical methods.
- o Determination of environmental and human exposure levels when analytical methods are available.
- o Bioavailability studies for substances of known significant toxicity and exposure.

The progressive accumulation of exposure information begins with the development of suitable analytical methods for analysis of the compound in all relevant biological and environmental media, followed by confirmation of exposure information, prior to the conduct of any Level III research. However, in order to know what analytes are available for monitoring, some basic environmental fate information is generally required and becomes a priority if it is lacking. Bioavailability and food chain bioaccumulation studies are appropriately placed in Level II, and should be undertaken after analytical methods are developed and confirmation of the substance is achieved in numerous hazardous waste sites and media.

1. Levels I & II Data Needs

a. Analytical

Purpose: To determine if available methods are adequate for detecting and quantifying levels of vinyl chloride in environmental and biological matrices. The methods should be sufficiently specific and sensitive to measure (1) background levels in the environment and the population; and (2) levels at which biological effects might occur.

Finding: A data need has been identified. Reliable analytical methods are available for detecting and quantifying vinyl chloride in air, water, sediment and foodstuffs but more accurate and precise methods are need for detection of vinyl chloride in soil. The primary method of analyzing vinyl chloride in air is gas chromatography (GC) combined with either mass spectrometry (MS), electron capture detectors (ECD), or flame ionization detectors (FID). The limit of detection for GC/MS and GC/ECD is in the parts per billion (ppb) range; accuracy is generally adequate ranging from 5-20% (Bozzelli and Kabbekus 1979; Harsch et al.

1979; Krost et al. 1982; Rasmussen et al. 1977; McMurray and Tarr 1978). Trace amounts of vinyl chloride in air and water are detected by employing GC/ECD after derivatization to 1,2-dibromochloroethane (Wittisiepe et al. 1990). The detection limits for air and water samples are 50 ng/m^3 and 0.4 ng/L (0.4 parts per trillion), respectively. Vinyl chloride can be detected in drinking water, groundwater, waste water, and leachate from solid waste. The analytical methods employed are separation by GC combined with MS, ECD, FID, Hall's electrolytic conductivity detector (HECD), or another type of halogen specific detector (HSD). The limit of detection is in the ppb range for halogen specific detectors and in the low-ppb range for MS (American Public Health Association (APHA) 1985; EPA 1982d,1982e). Accuracy is greater than 98% and precision ranges from 11% to 25% for GC/HECD and GC/MS (EPA 1982d). Vinyl chloride has been measured in sediment using GC/ECD (Wang et al. 1985). GC/HSD of headspace gases is the EPA recommended method for solid matrices (which may not include soil) with sensitivity in the ppb range (EPA 1982d). Vinyl chloride levels in food have been determined using GC/FID. Headspace analysis is a common method of preparation for foodstuffs with sensitivity in the low-ppb. range (IARC 1978).

The analytical methods used to analyze vinyl chloride in environmental media are the same for biological media, i.e., GC combined with MS, FID or ECD. Vinyl chloride and/or its metabolite, thiodiglycolic acid, has been detected in breath, urine, blood, and tissues. Vinyl chloride was determined in exhaled air by preconcentration with a multistage-cryogenic trapping system followed by thermal desorption using GC/FID, GC/ECD, and GC/MS. Sensitivity of these methods is in the low-ppb range (Conkle et al. 1975). Vinyl chloride has been measured in rat blood and tissues using headspace GC/FID with accuracy ranging from 75% to 92% recovery. This method is sensitive to 5 ng/mL of vinyl chloride in blood and 30 ng/g in tissues. GC/MS is used as a biomonitoring method for the quantitative measurement of thiodiglycolic acid, a urinary metabolite of vinyl chloride with a reported sensitivity of 50 ng/ml (Muller et al. 1979; van Sittert and de Jong 1985). ATSDR Minimal Risk Levels (MRLs) for intermediate and chronic exposures have been established for vinyl chloride and these analytical methods are sufficiently sensitive to measure vinyl chloride levels at which adverse health effects might occur after short-term or long-term exposure and background levels in the general population.

Priority Recommendation: The identified data need is not considered priority. Reliable analytical methods for detecting and quantifying vinyl chloride in soil, while still a data need, is not priority at this time due to the high vapor pressure of vinyl chloride, which indicates that the compound should volatilize quite rapidly from dry soil surfaces (see section d).

b. Physical/Chemical Properties

Purpose: To determine whether adequate data on the chemical and physical properties of vinyl chloride are available to permit estimation

of its environmental fate under various conditions of release.

Finding: A data need has not been identified. Physical and chemical properties (K_{ow}, K_{oc}, Henry's Law Constant, vapor pressure, etc.) for vinyl chloride have been well studied and reliable values for key parameters are available for use in environmental fate and transport models.

Priority Recommendation: A data need has not been identified.

c. Exposure Levels

i. Environmental Media

Purpose: To determine whether adequate data are available on the levels of vinyl chloride in the ambient and contaminated environments for purposes of conducting meaningful follow-up exposure and health studies.

Finding: A data need has been identified. The evaluation of existing data on concentrations of vinyl chloride in contaminated environmental media at hazardous waste sites is needed.

Ambient air contains no detectable amount of vinyl chloride (Grimsrud and Rasmussen 1975a,1975b; Harkov et al. 1984; Stephens et al. 1986; Wallace et al. 1984). Limited air monitoring data indicates that in areas near vinyl chloride and polyvinyl chloride (PVC) manufacturers, the concentration of vinyl chloride typically ranges from 105 ug/m^3 (0.041 ppm) to 2,600 ug/m^3 (EPA 1979a; Gordon and Meeks 1977; Fishbein 1979). Vinyl chloride in air has been found in the vicinity of hazardous waste sites and municipal landfills. Concentrations ranging from 5-8 ug/m^3 have been measured in the air above some landfills (type of landfill not specified) (Baker and Mackay 1985; Stephens et al. 1986). Gaseous emissions from 20 Class II (nontoxic) landfills in southern California had concentrations of vinyl chloride ranging from 0.24 to 44 ppm (Wood and Porter 1987). Homes near a hazardous waste site were found to contain levels of vinyl chloride as high as 1,040 ug/m^3 (0.4 ppm) (Stephens et al. 1986).

Vinyl chloride has been detected in varying concentrations in surface, ground, and drinking waters throughout the United States. The level of vinyl chloride in groundwater was determined during the 1982 EPA Groundwater Supply Survey where water samples from 945 sites geographically located throughout the U.S. were studied. Vinyl chloride was positively identified in only 0.74% of the 945 samples (detection limit 0.001 ppm). The concentrations of vinyl chloride ranged from 1.1 ug/L (0.0011 ppm) to 8.4 ug/L (0.0084 ppm) at the various sites (Westrick et al. 1984). Monitoring studies in nine states have identified vinyl chloride as high as 9.8 ug/L (0.01 ppm) in surface water and 380 ug/L (0.38 ppm) in groundwater (Dyksen and Hess 1982; Coniglio et al. 1980). Vinyl chloride has been detected in groundwat r samples taken at an estimated 3% of the NPL hazardous waste sites included in the EPA's Contract Laboratory Program Statistical Database

(CLPSD) at a geometric mean concentration of 0.102 ppm for the positive samples (CLPSD 1989). Vinyl chloride was not listed in the CLPSD of chemicals detected in surface water samples collected at NPL sites. Concentrations of vinyl chloride in drinking water wells and surface water in New York were found to be 0.05 and 0.01 ppm, respectively (Burmaster 1982). Vinyl chloride has also been reported to leach into drinking water from PVC pipes. One study found that drinking water that ran through PVC pipes contained vinyl chloride at 1.4 ug/L (.0014 ppm), whereas water that ran through a 9 year old system without PVC piping contained 0.03-0.06 ug/L ($3x10^{-5}$-$6x10^{-5}$ ppm) (Dressman and McFarren 1978).

Monitoring data for vinyl chloride in soil were not located in the available literature. Vinyl chloride has been detected in other environmental media. In the past, vinyl chloride has been detected in various foods (i.e., in edible oils at 0.3-18.0 ppm) as a result of migration from PVC food wrappings and containers (Gilbert et al. 1980). At present, the Food Drug Administration (FDA) regulates the use of PVC polymers in food packaging materials and the amount of residual monomer in polymers. Today the migration of vinyl chloride monomer into foodstuffs is essentially zero (Kontominas et al. 1985)

Priority Recommendation: The identified data need is considered priority. Reliable and current monitoring data for the levels of vinyl chloride in ambient air, water, and soil for the general population is needed in order to estimate exposure from each of these sources. These data should be collected simultaneously with data on levels of vinyl chloride in human tissues and fluids. In particular, there is a need to collect this information for populations living in the vicinity of hazardous waste sites so that information obtained on levels of vinyl chloride in the environment and the resulting body burden of vinyl chloride can be used to assess the potential risk of adverse health effects in these populations. One effort currently underway at ATSDR will examine the extant data from the 245 NPL sites at which vinyl chloride has been found. When complete, this database will include concentrations of vinyl chloride in on-site and off-site media, the size of the potentially exposed population, and an indication of relevant routes of exposure. This database will be developed and evaluated before the need to collect additional media-specific data is assigned priority.

ii. Humans

Purpose: To determine whether adequate data are available on the levels of vinyl chloride in human tissues for the general population and exposed populations for purposes of conducting meaningful follow-up exposure and health studies. ATSDR does not consider that this information can be reliably predicted from modeling and other risk assessment procedures.

Finding: A data need has been identified. No data are available regarding the levels of vinyl chloride in body tissues or fluids for

populations living near hazardous waste sites.

Thiodiglycolic acid is a major metabolite of vinyl chloride and its measurement in biological tissues is used to monitor exposure to vinyl chloride because vinyl chloride metabolizes so rapidly in the body (Conkle et al. 1975; Baretta et al. 1969; Zuccato et al. 1979). However, there is one study which indicates ambient levels of thiodiglycolic acid in humans. Thiodiglycolic acid was detected in 34 urine samples from males between 20 and 55 years of age and from 14 females between 19 and 42 years of age who were not exposed to vinyl chloride or its precursors in their workplace. The average levels of thiodiglycolic acid were 0.64±0.32 μg/ml and 0.51±0.20 μg/ml in males and females, respectively (Muller et al. 1979). There is one occupational study which gives concentrations for unmetabolized vinyl chloride via inhalation. The mean concentration of vinyl chloride in expired air for humans exposed for 6 hours to 2.9-23.5 ppm of vinyl chloride ranged from 0.21 to 1.11 ppm, representing up to 3.6-4.73% of the inhaled concentration (Krajewski et al. 1980). There were no studies located regarding levels of vinyl chloride or its metabolite in human tissues or fluids after exposure to hazardous waste sites or other environmental media. Even though measurement of thiodiglycolic acid is used to monitor vinyl chloride exposures, its use is of limited utility because the amount of thiodiglycolic acid in the urine will vary according to individual metabolic idiosyncracies. The rate of metabolism of vinyl chloride to thiodiglycolic acid may be influenced by the presence of liver disease, ethanol, or certain other substances such as barbiturates (Hefner et al. 1975b). Additionally, excretion of thiodiglycolic acid is not unique to exposure to vinyl chloride (Norpoth et al. 1986; Pettit 1986).

As part of the Third National Health and Nutrition Evaluation Survey (NHANES III), the Environmental Health Laboratory Sciences Division of the Center for Environmental Health and Injury Control, Centers for Disease Control, is developing methods for the analysis of vinyl chloride in blood. These methods use purge and trap methodology and magnetic section mass spectrometry which gives detection limits in the low parts per trillion range. This methodology, once developed, will be more reliable because one would be able to measure the parent compound, vinyl chloride, and not the metabolites thereby determining more accurate exposure levels of vinyl chloride in populations living in the vicinity of hazardous waste sites.

Priority Recommendation: The identified data need is considered priority. Information on exposure levels in humans is needed to better define exposure estimates in the general population and workforce, and to examine the relationship between levels of vinyl chloride in the environment, human tissue levels, and the subsequent development of adverse health effects.

One effort is currently underway at ATSDR that will examine the extant data at the 245 NPL sites at which vinyl chloride has been found. When complete, this database will include concentrations of vinyl chloride

in on-site and off-site media, the size of the potentially exposed population, and an indication of relevant routes of exposure. This database will not, however, supply information on the levels of vinyl chloride (or its metabolites) in the tissues of individuals living near hazardous waste sites or other exposed populations, such as workers.

d. Environmental fate

Purpose: To determine whether the available data are adequate to estimate exposure to vinyl chloride under various conditions of environmental release for purposes of planning and conducting meaningful follow-up exposure and health studies.

Finding: A data need has been identified. The environmental fate of vinyl chloride in air and water is well studied but data are lacking regarding adsorption, transformation and degradation of vinyl chlorid in soil.

Essentially all vinyl chloride in the atmosphere is expected to exist in vapor form based on a vapor pressure of 2,660 mmHg at 25^0C. Consequently, removal from the atmosphere by dry deposition is not expected to be an important fate process. Vinyl chloride is transformed in the atmosphere by photooxidation. Reaction of vinyl chloride vapor with photochemically generated hydroxyl radicals is predicated to be the primary degradation mechanism. The half-life for this reaction in the atmosphere ranges from 1.2 to 1.8 days (Cox et al. 1974; Howard 1976; Perry et al. 1977). Under conditions of photochemical smog, the half-life of vinyl chloride would be reduced to a few hours (Carassitti et al. 1978). Reaction with ozone and direct photolysis are less important degradation mechanisms of vinyl chloride in the atmosphere (EPA 1985c; Hill et al. 1976; Zhang et al. 1983).

The primary removal process for vinyl chloride from natural water systems is volatilization into the atmosphere. Henry's law constant value of 1.2 atm-m^3/mol at 10^0C indicates that vinyl chloride should partition rapidly to the atmosphere. The half-life for vinyl chloride volatilization from a typical pond, river, and lake has been estimated to be 43.3, 8.7, and 34.7 hours, respectively (EPA 1982a). These predicted half-lives should be considered rough estimates since the presence of various salts in natural waters can increase the solubility of vinyl chloride in water (Callahan et al. 1979). The primary removal process for vinyl chloride from surface waters is volatilization into the atmosphere. Vinyl chloride in water does not absorb ultraviolet radiation above 218nm; therefore, direct photolysis in the aquatic environment is not expected to occur (Hill et al. 1976). In waters containing photosensitizers, such as humic material, photodegradation may be fairly rapid. The hydrolytic half-life of vinyl chloride has been estimated to be 10 years at 25^0C. Since the volatilization rate of vinyl chloride is more rapid than the predicated rate of hydrolysis, hydrolysis is not a significant aquatic fate (Hill et al. 1976; Callahan et al. 1979). Additionally, vinyl chloride is not oxidized chemically by reaction with photochemically generated molecular oxygen in natural

waters (Hill et al. 1976). There is limited data that indicates that vinyl chloride is resistant to microbial degradation. One study found that an isolated micobial culture containing two species of bacteria and three mixed fungal populations was unable to biodegrade vinyl chloride over a 5-week period at concentrations of 20-120 mg/L (20-120 ppm) (Hill et al. 1976). A second study also found that vinyl chloride was not degraded in the presence of raw sewage at 25^{0}C for a 25-day period (Helfgott et al. 1977).

The relatively high vapor pressure of vinyl chloride also indicates that the compound should volatilize quite rapidly from dry soil surfaces. The effective half-life of vinyl chloride placed 10 cm deep in dry soil is predicted to be 12 hours (Verschueren 1983; Jury et al. 1984). Experimental data regarding adsorption of vinyl chloride to soil were not located. However, the soil organic carbon adsorption coefficient (K_{oc}) for vinyl chloride was estimated to range from 14 to 131 (Lyman et al. 1982; Sabljic 1984; Kenaga and Goring 1980). These K_{oc} values suggest a very low sorption tendency and the potential of vinyl chloride to leach into soil and travel to groundwater before evaporation (Cowfer and Magistro 1983). There is no information on the transformation and degradation of vinyl chloride in soil. However, based on physical and chemical parameters and information from other studies the following predictions have been made. The majority of vinyl chloride present on soil surfaces will volatilize to the atmosphere. Vinyl chloride is mobile in soil and susceptible to leaching. Photodegradation on the surface of soils is expected since sensitized photodegradation in water occurs. Also, based on data in aquatic media, microbial degradation of vinyl chloride is not expected to occur in soil.

Priority Recommendation: The identified data need is not considered priority. The need to determine vinyl chloride fate in soil, while still a data need, is not assigned priority at this time because adequate data on the chemical and physical properties of vinyl chloride are available to permit estimation of its environmental fate in soil. Additionally, the primary release media for vinyl chloride at hazardous waste sites is expected to be air.

e. Bioavailability and Bioaccumulation Potential

Purpose: To determine whether adequate data are available to predict the potential of vinyl chloride to be taken up by individuals exposed via contaminated air, soil, water, and the food chain for purposes of planning and conducting meaningful follow-up exposure and health studies.

Finding: A data need has been identified. The environmental factors that may influence the bioavailability of vinyl chloride from contaminated air, water, soil and the food chain have been studied but data on bioaccumulation in the terrestrial food chain is not available. Vinyl chloride can be absorbed following inhalation and oral exposure but to a much lesser extent from dermal exposure. All of these routes

are of concern to humans because vinyl chloride has been shown to contaminate the air, drinking water, soil and food. Due to the relatively high vapor pressure of vinyl chloride, all vinyl chloride in the atmosphere exist in vapor form and vinyl chloride volatilizes quite rapidly from surface waters and dry soil surfaces. Vinyl chloride does not form particulates in the atmosphere and dry deposition is not expected to be an important fate process therefore, vinyl chloride is readily available in air. It is known that vinyl chloride is readily absorbed following inhalation exposure, which is the primary route of exposure for individuals living in the vicinity of hazardous waste sites.

It is predicted that vinyl chloride will not strongly absorb to soil due to its K_{oc} value (14 to 131) but leach through soil and travel to groundwater (Lyman et al. 1982; Sabljic 1984; Kenaga and Goring 1980). Vinyl chloride's low octanol/water partition coefficient (log K_{ow} = 1.23) indicates that it bioaccumulates to a limited extent (EPA 1982a).

The bioconcentration factor (BCF) of an organic chemical can be estimated from the K_{ow} or water solubility (EPA 1982a). Investigators in one study, estimated the BCF of vinyl chloride to be 5.1 in aquatic organisms, indicating limited potential for bioconcentration (Veith et al. 1980). The measured BCFs in algae, fish and activated sludge were 40, less than 10, and 1,100, respectively. The low tissue concentrations found in fish suggested that vinyl chloride is not biomagnified in aquatic food chains to any substantial degree (Frietag et al. 1985). The bioaccumulation of ^{14}C-vinyl chloride in a closed model aquatic ecosystem over a 3-day period was examined. The investigators found that the high volatility of vinyl chloride minimized any potential for bioaccumulation (Lu et al. 1977). No data were located on the bioaccumulation of vinyl chloride in terrestrial food chains.

Priority Recommendation: The identified data need is not considered priority. The need to conduct bioaccumulation studies of vinyl chloride in terrestrial food chains, while still a data need, is not assigned priority at this time because given the high vapor pressure of vinyl chloride, the compound will probably volatilize to the atmosphere before significant amounts can be taken up by the biota. Additionally, it is known that vinyl chloride is readily absorbed following inhalation exposure, which is the primary route of exposure for individuals living in the vicinity of hazardous waste sites.

2. Level III Data Needs

a. Registries of exposed persons

Purpose: To aid in assessing long-term health consequences of exposure to vinyl chloride in the environment. The ATSDR Division of Health Studies will be asked to consider this chemical for selection as a primary contaminant for the establishment of a vinyl chloride subregistry of the National Exposure Registry.

Finding: A data need has been identified. Vinyl chloride has been found in at least 245 NPL hazardous waste sites. At this time no formal subregistries exist that identify individuals known to have been exposed to vinyl chloride. The development of an exposure subregistry would provide an important reference tool to aid in assessing long-term health consequences of exposure to vinyl chloride. It would also facilitate the conduct of epidemiological or health studies to assess any increased incidences of chronic diseases or late-developing effects such as cancer. An effort is currently underway at ATSDR to characterize the potentially exposed populations at the 245 sites where known human exposure to site contaminants has occurred.

Priority Recommendation: The identified data need is considered priority. The development of an exposure registry would contribute to the current database due to the advanced stage of knowledge on exposure to vinyl chloride and the evidence that vinyl chloride exposure is associated with the development of chronic health effects including cancer. This recommendation will be provided to the ATSDR Division of Health Studies who will judge the extant information on vinyl chloride against their criteria for initiating an exposure subregistry.

B. Toxicity Data Needs (Table 2)

The five remaining "prioritizing" tenets presented in the Decision Guide address toxicity data needs.

- o Studies available for all toxicological profile substances to characterize target organs and dose response.
- o Disposition studies and comparative physiologically-based pharmacokinetics when a toxic endpoint has been determined and differences in species response have been noted.
- o Mechanistic studies on substances with significant toxicity and substantial human exposure.
- o Investigation of methods for mitigation of toxicity for substances where enough is known about mode of action to guide research.
- o Epidemiologic studies that will provide a direct answer on human disease for a substance of known significant toxicity.

The following is a brief summary of the toxicity data needs for vinyl chloride. Please refer to the ATSDR Toxicological Profile for Vinyl Chloride, chapter on "Health Effects" for a more detailed discussion of available information (ATSDR 1989,1991). Generally, ATSDR believes that the most relevant route of human exposure to vinyl chloride at waste sites is inhalation of contaminated media; thus, ATSDR believes that the proposed toxicity studies should be conducted via inhalation. Additionally, animal testing should be conducted on the species with metabolism most similar to man or the most sensitive species.

1. Levels I & II Data Needs

ATSDR is mandated to determine the levels of significant human exposure for each substance and the associated acute, subacute, and chronic

health effects. In order to accomplish this goal, ATSDR determines MRLs which are defined as estimates of daily human exposure to a chemical that are likely to be without appreciable risk of deleterious effects over a specified duration. In order to derive MRLs for acute, intermediate, and chronic exposure durations, ATSDR evaluates the substance-specific database to identify studies of the appropriate route and duration of exposure.

At this time, ATSDR does not extrapolate data across routes or durations of exposure. The scientific basis for this practice has recently been prepared and presented to the ATSDR Board of Scientific Counselors. However, ATSDR does acknowledge that such extrapolations may be done on a substance by substance basis after toxicokinetics information has been collected. Thus, in order to derive acute MRLs, ATSDR evaluates studies of less than 14 days durations that identify the target organs and levels of exposure associated with these effects. Similar studies are identified for intermediate and chronic duration exposures.

Currently, as reflected in the Decision Guide, it is the practice of ATSDR to assign priority to identified data needs for acute/intermediate (Level I) studies by the most relevant route of exposure at Superfund sites. Regarding the need to conduct studies by other routes of exposure, ATSDR will generally first require toxicokinetic studies for the three routes of exposure to determine the need for the additional route-specific information. Regarding chronic studies, ATSDR acknowledges that appropriately conducted 90-day studies can generally predict the target organs for chronic exposure, but may fall short in accurately predicting the levels of exposure associated with these effects. Although, ATSDR acknowledges this fact, it will generally await the results of prechronic (14-& 90-day) and toxicokinetic studies prior to assigning priority to chronic toxicity studies. Note: Chronic toxicity studies may be separated from bioassays and require an exposure duration of one year.

a. Acute-Duration Exposure

Purpose: To determine whether adequate data exist to identify target organs and levels of exposure which present a significant risk to human health of acute health effects.

Finding: A data need to conduct additional acute-duration animal studies via all routes of exposure has been identified. There were no studies located regarding acute oral exposure in humans and no studies for oral or dermal exposure in animals.

Available data on the acute effects of vinyl chloride exposure to humans and animals are limited. However, there are acute-duration inhalation exposure data that indicate that the central nervous system and the liver are the major target organs of vinyl chloride toxicity in humans and animals. The most commonly reported central nervous system effects are ataxia or dizziness, drowsiness or fatigue and loss of consciousness (Juhe et al. 1974; Langauer-Lewowicka et al. 1976; Walker 1976;

Waxweiler et al. 1977; Patty et al. 1930; Mastromatteo et al. 1960; Hehir et al. 1981; Lester et al. 1963). A threshold for central nervous system effects in humans appears to be in the range of 8,000 ppm (Lester et al., 1963). It was also noted that high (unspecified) concentrations of vinyl chloride causes respiratory, cardiovascular, gastrointestinal and hematological effects in humans (Juhe et al. 1974; Lloyd et al. 1984; LaPlanche et al. 1987; Lilis et al. 1975; Danziger 1960), similar effects have been reported in animals (Mastromatteo et al. 1960; Oster et al. 1960; Carr et al. 1949; Lester et al. 1963). The available data are insufficient to derive an inhalation MRL for acute duration because the lowest LOAEL identified was for death (John et al. 1977) and no sensitive endpoints have been detected thus far.

No studies were located in humans or animals after acute oral exposure to vinyl chloride; and no ATSDR MRL has been developed. However, pharmacokinetic data indicate that similar end points might be expected if sufficiently high doses could be consumed by the oral route (Watanabe et al. 1976a, 1976b; Buchter et al. 1977; Bolt et al. 1976). However, the solubility characteristics of vinyl chloride in aqueous media indicate that achieving concentrations of vinyl chloride in excess of 5,000 ppm may be extremely difficult.

No studies were located in humans or animals after acute dermal exposure to vinyl chloride. However, there was one report of an individual who developed second degree burns on his hands after they were sprayed with liquid vinyl chloride. At first, the man reported that his hands felt numb and within a short period, his hands had developed marked erythema and edema (Harris 1953). ATSDR presently has no methodology for deriving MRLs for dermal exposure.

Priority Recommendation: The identified data need to conduct additional acute-duration animal studies via inhalation exposure is considered priority. The primary route of exposure to vinyl chloride at hazardous waste sites is via inhalation; and additional inhalation studies in animals involving a range of exposure concentrations and employing sensitive histological and biochemical measurements of injury to a comprehensive set of endpoints, including the central nervous system, respiratory system, and hepatic system are needed for establishing dose-response relationships and identifying thresholds for these effects. This information is necessary for determining levels of significant exposure to vinyl chloride that do not result in death but are associated with other adverse health effects.

Data on acute oral and dermal exposure, while data needs, are not considered priority at this time because they are not considered major routes of exposure to vinyl chloride for populations living in the vicinity of hazardous waste sites. Additionally, toxicokinetic information indicates that absorption of vinyl chloride across the skin is very limited (Hefner et al. 1975a).

b. Intermediate-Duration Exposure

Purpose: To determine whether adequate data exist to identify target organs and levels of exposure which present a significant risk to human health of subacute health effects.

Finding: A data need to conduct additional animal studies via oral and dermal exposure has been identified. There were no studies located which specifically addressed intermediate-duration exposure by any route in humans, and no oral studies were located for animals.

There is a large database describing the effects of intermediate-duration inhalation exposures in animals. Animals exposed to vinyl chloride gas for more than 2 weeks and less than a year have experienced effects on the liver, kidney, lungs, and blood (Feron et al. 1975, Feron et al. 1981 and Til et al. 1983); and the data were sufficient to derive a MRL for intermediate-duration inhalation exposure of 0.002 ppm based on a LOAEL for hepatic effects observed in rats (Bi et al. 1985). There was only one oral study located for animals. Vinyl chloride was administered to Sprague-Dawley rats by gavage for 52 weeks. A statistically significant increase in the incidence of hepatic anigosarcomas was observed at doses as low as 16.65 mg/kg/day in females and 50 mg/kg/day in males. Zymbal gland tumors were also detected but the data were not statistically significant (Maltoni et al. 1981). The above study was the only identified intermediate study (364 days) and no oral MRL could be derived. There were no animal studies addressing intermediate-duration dermal exposures.

Priority Recommendation: The identified data need to conduct additional animal studies via the oral and dermal routes is not considered priority. Intermediate-duration oral and dermal studies, are not considered priority at this time because oral and dermal exposure routes are not the major routes of exposure for populations living in the vicinity of hazardous waste sites. Additionally, toxicokinetic data indicates that absorption of vinyl chloride across the skin is very limited (Hefner et al. 1975).

c. Chronic-Duration Exposure

i. Toxicity Assessment

Purpose: To determine whether adequate data exist to identify target organs and levels of exposure which present a significant risk to human health of chronic health effects.

Finding: A data need to conduct additional animal studies via the inhalation and dermal routes has been identified. No information was available regarding chronic-duration oral exposure in humans, and no studies were available for dermal exposure in humans and animals.

A large number of studies of workers exposed to vinyl chloride have identified a wide range of target organs that may be affected by

chronic-duration inhalation of vinyl chloride. The major target organs are the liver and the central nervous system but other affected organs include the lungs, blood, immune system, cardiovascular system, skin, bones, and the reproductive organs (Berk 1976; Lee et al. 1977b; Tamburro 1984; EPA 1985 a,b). A profile of vinyl chloride-induced liver damage for humans was compiled which includes the following features: hypertrophy and hyperplasia of hepatocytes; activation and hyperplasia of sinusoidal lining cells; fibrosis of portal tracts, septa and intralobular perisinusoidal regions; sinusoidal dilation; and focal areas of hepatocellular degeneration (Gedigke et al. 1975). In general studies in animals provide supportive evidence for these effects and give indications of the exposure levels that may be associated with them (Feron and Kroes 1979; Viola 1970; Viola et al. 1971). An ATSDR MRL for chronic-duration inhalation exposure was not determined from the database because the calculated chronic MRL value would have exceeded the intermediate MRL value.

No information was available regarding chronic-duration oral exposure in humans. However, studies in animals indicate that the liver, blood; and skin are target organs for oral exposure to vinyl chloride (Feron and Kroes 1979; Viola 1970; Viola et al. 1971); and a chronic-duration oral MRL of 0.00002 mg/kg/day has been calulated based on hepatic toxicity (Til et al. 1983).

No information was available regarding effects of chronic-duration dermal exposure in humans or animals.

Priority Recommendation: The identified data need to conduct additional animal studies via the inhalation route is considered priority. Additional animal studies are needed to determine exposure concentrations that establish a dose-response relationship and define threshold levels for chronic health effects. Additionally, ATSDR believes inhalation is the major route of exposure for populations living in the vicinity of hazardous waste sites. Studies on the dermal route are not needed because dermal exposure is not a major route of exposure at hazardous waste sites and toxicokinetic information indicates that absorption of vinyl chloride across the skin is very limited (Hefner et al. 1975).

ii. Cancer Assessment

Purpose: To determine whether populations potentially exposed to vinyl chloride are at an increased risk for developing cancer for purposes of conducting meaningful follow-up exposure and health studies. Similar to toxicity endpoint assessment, when bioassays are indicated because of the potential for substantial exposure and the lack of information on carcinogenicity, ATSDR will generally only assign priority to a bioassay conducted via the most relevant route of human exposure at Superfund sites. Comparative toxicokinetic information across routes as previously discussed will be assigned priority and conducted before assigning priority to any additional routes of exposure. In cases where the assessment of chronic toxicity and carcinogenicity can be combined,

they will.

Finding: A data to conduct additional animal studies for the carcinogenicity of vinyl chloride has not been identified.

A large number of studies have reported a greater than expected incidence of a rare type of cancer, angiosarcoma of the liver among workers exposed to vinyl chloride (Bryen et al. 1976; Creech and Johnson 1974; Fox and Collier 1977; Infante et al. 1976; Jones et al. 1988; Monson et al. 1975; Pirastu et al. 1990; Rinsky et al. 1988; Teta et al. 1990; Waxweiler et al. 1976; Weber et al. 1981; Wong et al. 1986; Wu et al. 1989). Other types of cancer that have shown a statistically significant increase in incidence among vinyl chloride workers include cancer of the brain and central nervous system, the lung and respiratory tract, and the lymphatic/hematopoietic system (Belli et al. 1987; Cooper 1981; Infante et al. 1976; Rinsky et al. 1988; Smulevich et al. 1988; Waxweiler et al. 1977; Weber et al. 1981; Wong et al. 1986). One study on Soviet males and females occupationally exposed to vinyl chloride indicated that females may have higher incidences of stomach and lung cancers, leukemias, and lymphomas than males (Smulevich et al. 1988).

Increased incidences of angiosarcoma of the liver have been found in a variety of animal species after inhalation of vinyl chloride gas (Maltoni et al. 1980 and 1981). Although no studies examining the incidence of carcinogenic effects in humans exposed to vinyl chloride by the oral route have been located, vinyl chloride incorporated into the diet of rats has been demonstrated to cause an increased incidence of hepatic angiosarcoma (Feron et al. 1981; Til et al. 1983). Based on these findings, the International Agency for Research on Cancer (IARC) has concluded that sufficient evidence for carcinogenicity in humans and animals exists and has placed vinyl chloride in carcinogenicity category 1, carcinogenic to humans (IARC 1979). EPA also has concluded that sufficient evidence of carcinogenicity exists in humans and animals and has classified vinyl chloride according to its classification scheme as a Group A carcinogen, (EPA 1980a). The National Toxicological Program (NTP) has classified vinyl chloride as a known carcinogen (NTP 1989).

Priority Recommendation: A data need has not been identified. Although no dermal studies have been conducted for the carcinogenicity of vinyl chloride, dermal exposure is not considered a major exposure route at hazardous waste sites. Additionally, toxicokinetic information indicates that absorption of vinyl chloride across the skin is very limited (Hofner, et al. 1975a)

d. Genotoxicity

Purpose: To evaluate the mechanism of vinyl chloride-induced toxicity for purposes of future mitigation activities. Generally, priority is assigned genotoxicity studies if information is lacking to assess the genotoxic potential of this substance both *in vivo* (mouse micronucleus) and *in vitro* (Ames *Salmonella*). This is particularly true if there are human data to suggest that the substance may act by a genotoxic

mechanism to cause cancer, reproductive toxicity, etc. or there exists "structural alerts" that suggest that the substance may be genotoxic. Additional studies will not be assigned priority simply to confirm or refute an equivocal database without justification.

Finding: A data need to conduct additional animal studies has not been identified.

There are substantial data on both clastogenesis and DNA alkylation in humans exposed to vinyl chloride that indicate that this chemical acts as a potent genotoxicant. Studies completed through the mid-1980s generally found a statistically significant increase in the frequency of chromosomal aberrations, usually of the chromatid type (i.e., affecting only one of the two strands formed upon deoxyribonucleic acid (DNA) replication) but also including some chromosomal-type defects such as inversions, rings, and translocations which affect the entire chromosome. Increased sister chromatid exchanges have also been reported in occupationally exposed workers (Kucerova et al. 1979; Hansteen et al. 1978; Purchase et al. 1978; Fucic et al. 1990). There are studies that indicate that the clastogenic effects of vinyl chloride exposure in humans are reversible. One study reported that the increase of chromosome aberrations observed in workers exposed to 50 ppm returned to normal within 42 months after exposure levels had been reduced to less than 5 ppm of vinyl chloride (Anderson et al. 1980).

The human findings are supported by both in vivo and in vitro animal studies that show positive genotoxicity in a variety of microbial organisms, cultured cell lines, and isolated nucleic acid assays (Laib et al. 1989; Gwinner et al. 1983; Styles 1077; Jenssen and Ramel 1980).

Priority Recommendation: A data need has not been identified.

e. Reproductive toxicity

Purpose: To determine whether populations potentially exposed to vinyl chloride are at an increased risk for developing reproductive effects for purposes of conducting meaningful follow-up exposure and health studies. The ATSDR places importance on the acquisition of reproductive toxicity data in its desire to consider the needs of susceptible populations. Additionally, it is desirable to have information on reproductive toxicity prior to the development of MRLs to ensure that target organs have been adequately evaluated.

Generally, when considering the need to assign priority, ATSDR will, in the absence of all information on this endpoint, assign priority to the conduct of 90-day studies with special emphasis on reproductive organ pathology. If (1) any indication is found in these studies that the reproductive system of either male or female animals is a target organ of substance exposure; or (2) there have been human anecdotal reports of reproductive effects following substance exposure; or (3) there are structurally similar compounds that affect reproduction, then ATSDR will consider assigning priority to multigeneration animal studies. As

before, priority will be assigned to studies conducted by the most relevant route of human exposure at Superfund sites; comparative toxicokinetic studies will be performed and evaluated prior to assigning priority to studies conducted via additional routes of exposure.

Finding: A data need to conduct additional animal reproductive studies via the inhalation, oral, and dermal routes has been identified.

A number of case reports of workers occupationally exposed to vinyl chloride provide suggestive evidence of adverse effects on male and female reproductive function. In males sexual impotence, decreased androgen levels, and loss of libido were reported in men exposed occupationally to vinyl chloride (Suciu et al. 1975; Veltman et al. 1975; Walker 1976). These studies are limited by the lack of quantification of exposure levels and possible concomitant exposures to other chemicals. In a vinyl chloride worker who died of angiosarcoma of the liver, decreased testicular size was observed. However, it is unclear whether this effect was a direct effect of the vinyl chloride exposure or due to wasting secondary to the angiosarcoma (Lee and Harry 1974). Males employed in PVC and acrylic glass industries also reported decreased testosterone levels and sexual function. However, concomitant exposure to methylmethacrylate also occurred in these workers (Makarov 1984).

In women exposed to vinyl chloride, there was an exposure-related decrease in sexual function in females between 41 and 50 years of age and in those who had been exposed to vinyl chloride for 21 or more years when compared to controls. An increase in menstrual activity followed by a hypomenstrual syndrome was reported to occur, but supporting data were not presented (Makarov et al. 1984). In another study, increased blood pressure and edema during pregnancy (preeclampsia) and decreased hemoglobin levels were found in females exposed to vinyl chloride when compared to unexposed workers (Bao et al. 1988).

No studies were located that documented the effects of vinyl chloride on reproductive performance when both parental animals were exposed. However, there were two dominant lethal studies which examined the reproductive performance of exposed males. Exposure to concentrations as high as 30,000 ppm of vinyl chloride in mice (5 days, 6 hours/day) had no effect on male fertility or pre- or post-implantation loss (Anderson et al. 1976). In contrast, exposure of male rats to concentrations as low as 250 ppm for 6 hours/day, 5 days a week, for 11 weeks caused a decrease in the ratio of pregnant to mated females, indicating a decrease in male fertility (Short et al. 1977). These results were supported by two other studies using rats in which adverse effects on the testes were observed; these effects included damage to the spermatogenic epithelium and seminiferous tubules, depletion of spermatocytes, and a decrease in testicular weight at concentrations of 100 ppm of vinyl chloride (Bi et al. 1985; Sokal et al. 1980). There were no indications of the effects on female rats in the latter two studies. There were no studies regarding reproductive effects in humans or animals following oral or dermal exposure to vinyl chloride. There

were no data on reproductive toxicity following dermal exposure.

Due to the suggestive evidence in humans that vinyl chloride causes reproductive effects this endpoint should be evaluated in future epidemiology studies.

Priority Recommendation: The identified data need to conduct additional animal reproductive studies via the inhalation route is considered priority. Reproductive toxicity assessment (i.e., 2 species multigenerational studies) using currently accepted protocols is necessary since there is suggestive human data and animal studies (dominant lethal) which indicates that exposure to vinyl chloride causes adverse reproductive effects. These studies should be conducted via the primary route of exposure at hazardous waste sites, inhalation.

Reproductive studies following the oral or dermal routes are not considered priority at this time because they are not the major routes of exposure for populations living in the vicinity of hazardous waste sites.

f. Developmental toxicity

Purpose: To determine whether populations potentially exposed to vinyl chloride are at an increased risk for developing developmental effects for purposes of conducting meaningful follow-up exposure and health studies. Similar to reproductive toxicity assessment, the Agency places importance on the assessment of developmental toxicity data, and does not consider an MRL to be of high confidence if this data is lacking.

In the absence of any reproductive or teratologic information, ATSDR will consider proposals to simultaneously acquire reproductive and teratological information. Additionally, ATSDR acknowledges that there will be some circumstances that require that separate conduct of classical teratology studies; these studies are generally assigned priority after the conduct of 90-day studies that assess reproductive organ pathology, the consideration of data generated on structurally similar compounds, or evidence from human anecdotal reports. As for reproductive toxicity, priority will be assigned to studies conducted by the most relevant route of human exposure at Superfund sites; comparative toxicokinetic studies will be performed and evaluated before assigning priority to the conduct of studies via additional routes of exposure.

Finding: A data need to conduct additional animal developmental studies via the inhalation, oral and dermal routes has been identified.

Epidemiology studies suggest that exposure to vinyl chloride may cause developmental effects. Although a statistically significant increase in congenital abnormalities has been observed in members of some communities located near a vinyl chloride processing facility, reports have failed to establish a statistically significant association between developmental toxicity and either parental occupation or proximity to

the facility (Edmonds et al. 1978; Infante et al. 1976a, 1976b; Rosenman et al. 1989; Theriault et al. 1983; Waxweiler et al. 1977). In another similar study, pregnancy outcomes of mothers occupationally exposed to vinyl chloride were compared to those of pregnant workers not exposed to vinyl chloride. The authors concluded that exposure to vinyl chloride did not correlate with involuntary infertility, pregnancy outcome, or the incidence of congenital abnormalities (Bao et al. 1988). Epidemiologic studies designed to examine this endpoint would be helpful due to the inconclusive human data.

In contrast, a number of inhalation studies using pregnant animals have shown developmental toxicity consisting of resorptions, decreased litter size and fetal weight, delayed ossification, and dilated ureters. These effects occurred when animals were exposed during the first trimester of pregnancy and at moderately high levels of vinyl chloride (500-2,500 ppm) (John et al. 1977, 1981; Ungvary et al. 1978). However, these levels also produced maternal toxicity characterized by increased liver weight, decreased body weight and food consumption, and increased mortality. Adverse postnatal effects have been observed in rats following in utero exposure to low levels of vinyl chloride. Pregnant rats were exposed to 0, 1.9, or 13.9 ppm vinyl chloride for 4 hours/day, and offspring examined 6 months postnatally. Rats at 6 months were found to have decreased hemoglobin and leukocytes and decreased organ weights (males: liver, kidney, spleen; females: lung, liver). In addition, exposure to 13.9 ppm in utero resulted in a decreased ability of the rats to orient themselves (Sal'nikova and Kotsovskaya 1980). In a similar study, pregnant rats were exposed continously throughout gestation to 2.4 ppm of vinyl chloride. This study reported decreased fetal weight and increased early post-implantation loss, hematomas, and hydrocephaly with intracerebral hematoma. Weanling rats had hepatotoxic effects and increased hexobarbital sleep time. No histological data on the livers of the pups or information regarding maternal health, or statistical analyses of the data were presented (Mirkova et al. 1978). Also, both this study and the report by Sal'nikova and Kotsovskaya (1980), failed to provide information on the number of animals in each test group. There were no studies located regarding developmental effects in humans or animals following oral or dermal exposure to vinyl chloride.

Priority Recommendation: The identified data need to conduct additional animal developmental studies via the inhalation route is considered priority. In view of the inadequate animal data and the suggestive human data, developmental toxicity should be assessed in future reproductive toxicology testing (i.e., two species developmental study). These studies should be conducted via the primary route of exposure at hazardous waste sites, inhalation. Data for oral and dermal routes of exposure are not considered priority at this time because these are not the major routes of exposure for populations living in the vicinity of hazardous waste sites.

g. Immunotoxicity

Purpose: To evaluate the mechanism of vinyl chloride-induced toxicity for purposes of defining target organs and future mitigation activities. There is increasing evidence to suggest that the immune system may be a susceptible target organ for many environmental contaminants. In the absence of any information on the immune system as a target organ, priority will be assigned evaluation of the immune system (lymphoid tissue, blood components) as an endpoint in 90-day studies (Level I) before assigning priority to an immunotoxicology battery as recently defined by the NTP. For those substances that either (1) show evidence of immune system effects in 90-day studies, (2) have human anecdotal data to suggest that the immune system may be affected, or (3) are structurally similar to known immunotoxicants, an immunotoxicology battery of tests will be assigned priority.

Finding: A data need to conduct animal immunotoxicty studies following oral and dermal exposure to vinyl chloride has been identified.

A number of studies have examined the immunologic profile of workers occupationally exposed to vinyl chloride. A statistically significant increase in circulating immune complexes and immunoglobulins were found in workers exposed to vinyl chloride when compared to levels in unexposed workers (Bodganikowa and Zawilska 1984; Wagnerova et al. 1986, 1988). The most frequent immunologic finding in workers with "vinyl chloride disease," was an increase in circulating immune complexes or cryoglobulinemia. As the severity of the clinical signs of vinyl chloride disease increased, there was an increase in B-cell proliferation, hyperimmunoglobulinemia, and complement activation (Grainer et al. 1980; Langauer-Lewowicka et al. 1976; Ward 1976).

Animal data following inhalation exposure to vinyl chloride support the findings seen in humans. A stimulation of the immune response has been observed in mice exposed to low to moderate levels of vinyl chloride via inhalation for 4 weeks: lymphocytes had increased spontaneous and lectin-stimulated transformation. This increase was not observed when lymphocytes from unexposed mice were cultured in the presence of vinyl chloride (Sharma and Gehring 1979).

There were no studies located regarding immunological effects in humans or animals after oral or dermal exposure to vinyl chloride.

Priority Recommendation: The identified data needs to conduct animal immunotoxicity studies following oral and dermal exposure to vinyl chloride are not considered priority because they are not the major routes of exposure for populations living in the vicinity of hazardous waste sites.

h. Neurotoxicity

Purpose: To evaluate the mechanism of vinyl chloride-induced toxicity for purposes of defining target organs and future mitigation activities.

Similar to immunotoxicity, there is a growing body of data to suggest that the nervous system is a very sensitive target organ for many environmental chemicals. In the absence of any information on the nervous system as a target organ, priority will be assigned evaluation of the nervous system as an endpoint in 90-day studies (Level I) before assigning priority to a neurotoxicology battery. Additionally, it may be possible to assign priority to evaluation of demeanor in 90-day studies along with neuropathology. For those substances that either (1) show evidence of nervous system effects in 90-day studies, (2) have human anecdotal data to suggest that the nervous system may be affected, or (3) are structurally similar to known neurotoxicants, a neurotoxicology battery of tests will be assigned priority.

Finding: A data need to conduct animal neurotoxicity studies following oral and dermal exposure to vinyl chloride has been identified.

The central nervous system is one of the major targets of vinyl chloride toxicity. Neurotoxicity in humans and animals have been well documented. Concentrations as low as 8,000 ppm may cause dizziness in humans exposed by inhalation (Lester et al. 1963). Workers exposed to vinyl chloride, before occupational standards were made more rigorous, complained of dizziness, drowsiness; euphoria, nausea, headache, and occasional loss of consciousness (Juhe et al. 1974; Langauer-Lewowicka et al. 1976; Lilis et al. 1975; Marsteller et al. 1975; Spirtas et al. 1975; Suciu et al. 1963, 1975; Veltman et al. 1975; Walker 1976). Similar neurological effects have been observed in animals as well as damage to nervous tissue. Histopathological examination revealed diffuse degeneration of gray and white matter, cerebellar degeneration in the purkinje cell layer, and peripheral nerve endings were surrounded and infiltrated with fibrous tissue (Viola 1970; Viola et al. 1971; Hehir et al. 1981; Jaeger et al. 1974; Mastromatteo et al. 1960).

No studies were located regarding neurological effects in humans or animals after oral or dermal exposure to vinyl chloride.

Priority Recommendation: The identified data need to conduct additional animal neurotoxicity studies following oral and dermal exposure to vinyl chloride is not considered priority because they are not the major routes of exposure for populations living in the vicinity of hazardous waste sites.

i. Toxicokinetics

Purpose: To evaluate the disposition of vinyl chloride across species and routes of exposure for purposes of elucidating target organs and mechanisms of toxicity, and to assess the need to conduct studies by other than the primary route of exposure.

Finding: A data need has not been identified. There are few data on humans for all toxicokinetic parameters across all exposure routes, and limited information is available regarding interspecies differences in kinetics. However, human and animal data indicate that similar target

organs (liver and the central nervous system) for the toxic effects of vinyl chloride exist, suggesting some similarities of kinetics.

There was one study located regarding absorption in humans. The authors reported that inhalation absorption is rapid in humans. Retention reached a maximum within 15 minutes and declined rapidly after 30 minutes of exposure. The authors did not report whether steady state had been achieved, and the data were inadequate to determine this point (Krajewski et al. 1980). There were no studies located regarding absorption in humans after oral or dermal exposure to vinyl chloride.

Animal data also indicated that inhalation and oral absorption of vinyl chloride occurs rapidly. Peak blood levels occurred at 30 minutes in rats exposed to 7,000 ppm; on removal from the vinyl chloride atmosphere, blood levels fell rapidly (Withey 1976). Several studies in rats indicated that vinyl chloride is rapidly and virtually completely absorbed from the gastrointestinal tract (Withey 1976; Watanabe et al. 1976a; Feron et al. 1981). Animal data suggest that dermal absorption of vinyl chloride is not likely to be significant. Dermal absorption in rhesus monkeys was estimated to be 0.031% and 0.023% of the total available vinyl chloride at 800 and 7,000 ppm, respectively. The investigators concluded that after short-term exposure to high concentrations, dermal absorption was far less significant than inhalation absorption (Hefner et al. 1975a).

There were no studies located regarding tissue distribution in humans after inhalation, oral, or dermal exposure to vinyl chloride. Data from rat studies suggest that the distribution of inhaled vinyl chloride is rapid and widespread, but storage of vinyl chloride in the body is limited by rapid metabolism and excretion. The highest levels of vinyl chloride were located in the liver and kidneys when metabolism was not blocked by chemical means (Buchter et al. 1977). The highest levels of vinyl chloride were also located in the liver after oral exposure in rats (Watanabe et al. 1976a). There were no studies located regarding tissue distribution in animals after dermal exposure.

Metabolism of vinyl chloride appears to be similar in humans and animals. In the only human study located, metabolism of vinyl chloride was attributed to the cytochrome P-450 monooxygenases obtained from liver specimens (Sabadie et al. 1980). Animal inhalation and oral studies indicated that the metabolism of vinyl chloride proceeds primarily through a mixed-function oxidase pathway which forms a highly reactive epoxide intermediate, 2-chloroethylene oxide (Bolt et al. 1980; Bolt et al. 1977; Jedrychowski et al. 1984, Hefner 1975b; Watanabe et al. 1978a; Green and Hathway 1975; 1977). Data from animal studies also indicated that the metabolism of vinyl chloride is a dose-dependent, saturable process. Metabolism, estimated by measuring the rate of disappearance of vinyl chloride from a closed system, followed first-order kinetics with a half-life of 86 minutes at less then 100 ppm. At greater than 200 ppm, metabolism was slowed to a half-life of 261 minutes, suggesting saturation of the pathway predominant at less than 100 ppm (Hefner et al. 1975b). Most toxicokinetics studies have been

conducted using rats, but one study in primates indicated that metabolism may saturate at lower concentrations in primates than rats (Buchter et al. 1980). There were no studies located regarding metabolism after dermal exposure in animals.

Toxicokinetic information indicated that the predominant route of excretion of vinyl chloride in humans and animals is urinary excretion (Krajewski et al. 1980; Watanabe and Gehring 1976; Watanabe et al. 1976b, 1978b). There were no studies located regarding excretion in humans after oral and dermal exposure and no studies in animals after dermal exposure.

Priority Recommendation: A data need has not been identified.

2. Level III Data Needs

a. Epidemiology Studies

Purpose: To evaluate the extant epidemiologic database and to propose the conduct of additional studies that may lead to cause and effect findings. The ATSDR Division of Health Studies will be informed of all candidate substances for future consideration.

Finding: A data need has been identified. Virtually all of the data on health effects in humans following inhalation exposure to vinyl chloride come from epidemiologic studies of workers exposed during the production of polyvinyl chloride. These studies have reported neurological, hepatic, immune and the carcinogenic effects of exposure to vinyl chloride (Lester et al. 1963; Grainer et al. 1980; Bryen et al. 1976; Teta et al. 1990). However, many of these studies are limited by the absence of information on individual exposure levels. While these studies contribute to an understanding of acute, subacute, and chronic health effects of vinyl chloride, studies are necessary on humans living in the vicinity of hazardous waste sites contaminated with vinyl chloride who may be exposed through unique pathways.

Priority Recommendation: The identified data need is not considered priority. A large number of people are potentially exposed to vinyl chloride at hazardous waste sites (vinyl chloride has been identified at 245 sites thus far) and the toxicity of vinyl chloride is well characterized. Therefore, if either worker or general population with appropriate exposures can be identified, epidemiologic studies could be undertaken with special emphasis placed upon evaluation of systemic toxicity (including immunotoxicity, neurotoxicity and renal toxicity), carcinogenicity, and reproductive/developmental toxicity.

There are two on-going epidemiologic studies. One will update epidemiologic studies on vinyl chloride and the other study will determine the effects of vinyl chloride on pregnancy, parturition and fetal development among female workers (ATSDR 1991).

The results of the on-going studies should be evaluated prior to the initiation of additional epidemiologic studies.

b. Mechanism of toxic action

Purpose: To evaluate the mechanism of vinyl chloride-induced toxicity for purposes of defining target organs and future mitigation activities.

Finding: A data need has been identified. Exposure to vinyl chloride results in hematological, musculoskeletal, reproductive, and developmental toxicity for which mechanisms of action have not been specifically determined. The intermediary metabolites of vinyl chloride appear to be responsible for many of the toxic effects observed. The highly reactive epoxide intermediate, 2-chloroethylene oxide, has been shown to bind to macromolecules including DNA, ribonucleic acid (RNA), and other protein molecules.

The central nervous system is one of the major targets of vinyl chloride toxicity. The most commonly reported central nervous system effects are ataxia or dizziness, drowsiness or fatigue, loss of consciousness, and headaches. Other effects that have been reported include euphoria and irritability, visual and hearing disturbances, nausea, memory loss, nervousness and cerebellar disturbances (Juhe et 1974; Marsteller et al. 1975; Spirtas et al. 1975; Langauer-Lewowicka et al. 1983; Suciu et al. 1963). Long term exposure to vinyl chloride causes peripheral neuropathy which is manifested as denervation-related fasciculations and fibrillations (indicating collateral sprounting) (Percotini et al. 1986; Magnavita et al. 1986). Peripheral neuropathy may be caused by tissue anoxia due to vascular insufficiency or the direct toxic effect of vinyl chloride on peripheral nerves. Histopathological examination of brain tissues from rats chronically exposed to vinyl chloride demonstrated damage to nervous tissue. There was degeneration of gray and white matter, cerebellar degeneration in the purkinje cell layer, and peripheral nerve endings were surrounded and infiltrated with fibrous tissue (Viola 1970; Viola et al. 1971).

The liver is the other major target of vinyl chloride toxicity. In humans, a profile of vinyl chloride-induced liver damage has been compiled which includes the following features: hypertrophy and hyperplasia of hepatocytes; activation and hyperplasia of sinusoidal lining cells; fibrosis of portal tracts, septa and intralobular perisinusoidal regions; sinusoidal dilation; and focal areas of hepatocellular degeneration. Similar symptoms of hepatoxicity have also been observed in animals, as well as changes in metabolic enzyme activities (Gedigke et al. 1975; Bi et al. 1985; Lester et al. 1963; Sokal et al. 1980 Torkelson et al. 1961; Wisniewska-Knypl et al. 1980). Long term exposure to vinyl chloride also causes a rare type of cancer, hepatic angiosarcoma. The causes for the induction of cancer is discussed below under genotoxicity and carcinogencity.

Mechanisms by which vinyl chloride may exert its carcinogenic effects have been elucidated from both in vitro and in vivo studies. Vinyl chloride is metabolized to chloroethylene oxide, which is the ultimate genotoxic intermediate of vinyl chloride. The clastogenic effects of vinyl chloride is believed to be due to these reactive metabolites. Animals exposed via inhalation to vinyl chloride have demonstrated increased alkylation of liver DNA and increased cell proliferation. Chloroethylene oxide has been identified as the compound that caused the hepatocellular ATPase-deficient foci and alkylation of liver DNA (Gwinner et al. 1983; Laib et al. 1989). Chloroethylene oxide forms adducts in vivo (such as the nucleoside, N-2,3-ethenoguanosine) which incorporate into DNA and causes base-pair (i.e., purine to purine or pyrimidine to pyrimidine exchange) transitions during transcription (Singer et al. 1987; Bolt et al. 1986; Ciroussel et al. 1990 Eberle et al. 1989). More recently it has been suggested that vinyl chloride or its metabolites interact more frequently with specific sites along the chromosome than would be expected. A cohort of 67 workers exposed to approximately 5 ppm of vinyl chloride for an average of 15 years was reported to have a nonrandom distribution of chromatid and biochromatid breaks. The most frequently affected areas of the genome were the terminal segments of the A, B, and C group chromosomes (Fucic et al. 1990).

Exposure to vinyl chloride causes various immunological effects known as "vinyl chloride disease". The most frequent immunologic findings are an increase in circulating immune complexes or cryoglobulinemia (Grainger et al. 1980; Languer-Lewowicka et al. 1976; Ward 1976). Based on the similarity of vinyl chloride disease and systemic sclerosis, which may be a genetically linked autoimmune disease, a genetic link has been proposed for vinyl chloride disease. Investigators have examined the human lymphocyte antigen (HLA) phenotypes of patients with vinyl chloride disease and showed statistically significant associations with certain HLA alleles. Among those patients with the disease, the severity of the symptoms was significantly related to the possession of the HLA-DR3 and B8 alleles. The authors concluded that susceptibility was increased in the presence of HLA-Dr5 or a gene in linkage disequilibrium with it, and progression was favored by HLA-DR3 and B8 (Black et al. 1983, 1986).

Other effects of exposure to vinyl chloride include hematological, musculoskeletal, reproductive and developmental toxicity for which mechanisms of action have not been specifically determined. However, the binding of vinyl chloride and/or its metabolites to macromolecules in cells may play a role in these observed effects. There are a number of on-going studies investigating the mutagenesis and carcinogenesis of vinyl chloride, and the mechanisms of hepatotoxicty. There are also two on-going epidemiologic studies (updating epidemiologic studies on vinyl chloride and the effects of vinyl chloride on pregnancy, parturition and fetal development among female workers) which may have valuable data on mechanism of action of vinyl chloride (ATSDR 1991).

Priority Recommendation: The identified data is not considered

priority. The results of the on-going studies should be evaluated prior to the initiation of additional research in the area of mechanism of action.

c. Biomarkers

Purpose: To evaluate the need to develop additional biomarkers of exposure and effect for purposes of future medical surveillance which can lead to early detection and treatment.

Finding: A data need has been identified to develop a sensitive and specific biomarker of exposure for vinyl chloride. Methods are available for measuring vinyl chloride and/or its metabolite, thiodiglycolic acid, in breath, urine blood, and tissue. The predominant excretion route for vinyl chloride is urinary, and thiodiglycolic acid in urine has been used to monitor workers occupationally exposed to vinyl chloride (Muller et al. 1979). However, measurement of this metabolite is of limited utility in estimating levels of exposure because the amount of thiodiglycolic acid in the urine will vary according to individual metabolic idiosyncracies. The rate of metabolism of vinyl chloride to thiodiglycolic acid may be influenced by the presence of liver disease, ethanol, or certain other substances such as barbiturates (Hefner et al. 1975b). Finally, excretion of thiodiglycolic acid is not unique to exposure to vinyl chloride (Norpoth et al. 1986; Pettit 1986).

Biomarkers of effect caused by exposure to vinyl chloride may be estimated from diagnosis of physiological effects known to be closely associated with it. A syndrome known as vinyl chloride disease has been identified in workers occupationally exposed to vinyl chloride. This syndrome includes Raynaud's phenomenon, acro-osteolysis of the distal phalanges of the fingers, and sclerodermal-like changes in the hands and forearms. Although this syndrome resembles systemic sclerosis, a differential diagnosis may be made based on the absence of antinuclear antibodies from the blood of those afflicted with vinyl chloride disease. The occurrence of vinyl chloride disease in exposed populations is about 3% and susceptibility appears to be genetically related (see section 2b). Therefore, absence of these symptoms would not eliminate the possibility of exposure, but their presence may be a good indicator of exposure.

Angiosarcoma of the liver has been identified in workers occupationally exposed to vinyl chloride. This type of tumor is extremely rare in the general population (Heath et al. 1975); therefore, its diagnosis may indicate vinyl chloride exposure. However, exposure to arsenicals and Thorotrast® (thorium dioxide; formerly used in arteriography) also causes angiosarcoma of the liver; these substances must be eliminated as causative agents before correlating hepatic angiosarcoma with vinyl chloride exposure (Gedigke et al. 1975; Marsteller et al. 1975).

Chromosomal aberrations found in lymphocytes may be indicative of the genotoxic effects of vinyl chloride (Anderson et al. 1980; Ducatman et

al. 1975; Fucic et al. 1990). The DNA adducts produced by the intermediary metabolites of vinyl chloride, 1,N^6-ethenoadenosine and 3,N^4-ethenocytidine, may be used as specific indicators of vinyl chloride's genotoxic potential.

Presently, the Environmental Health Laboratory Sciences Division of the Center for Environmental Health and Injury Control, Centers for Disease Control, is developing methods for the analysis of vinyl chloride in blood. These methods use purge and trap methodology and magnetic section mass spectrometry which gives detection limits in the low parts per trillion range. This methodology once developed will be more reliable because one would be able to measure the parent compound, vinyl chloride, and not the metabolites thereby determining more accurate exposure levels of vinyl chloride in populations living in the vicinity of hazardous waste sites.

Priority Recommendation: The identified data need is not considered priority. ATSDR will await the development of the new methodology to measure vinyl chloride in blood before assigning this data need priority.

d. Clinical methods of mitigating toxicity

Purpose: To determine whether any efforts are currently underway to mitigate the effects of exposure to vinyl chloride.

Finding: A data need has been identified. There are no efforts underway to specifically address this need at this time. The target organs for vinyl chloride-induced toxicity have generally been identified and limited data are available on the mechanisms of neurotoxicity and carcinogencity caused by vinyl chloride. Vinyl chloride is clastogenic and can alkylate DNA (Anderson et al. 1980) and histopathology has shown that vinyl chloride exposure leads to degeneration of gray and white matter (Viola 1970). Furthermore, vinyl chloride disease and angiosarcoma of the liver are associated with vinyl chloride exposure.

Priority Recommendation: The identified data need is considered priority. This is justified because a large number of people are potentially exposed to vinyl chloride at hazardous waste sites (vinyl chloride has been identified at 245 sites thus far), the advanced stage of knowledge exists on exposure to vinyl chloride and there are two unique diseases associated with vinyl chloride exposure.

IV. Summary: Prioritization of Data Needs for Vinyl Chloride

A. Exposure

Application of the hierarchy of research priorities presented in the Decision Guide begins with the evaluation of available analytical methods for vinyl chloride and proceeds through to assessing the need

for epidemiologic studies. As stated previously, much information is available on vinyl chloride, albeit some of it from studies done quite some time ago. This does not mean that data derived from older studies are not adequate. ATSDR agrees with the National Research Council in that it is not appropriate to judge the quality of past and future studies solely by the standards of today.

Building a sound basic data foundation for higher level environmental research via the Decision Guide requires the determination of human exposure levels and media-specific data on vinyl chloride. Although a considerable amount of information is available on vinyl chloride, a need to evaluate existing data on concentrations of vinyl chloride in contaminated enviromental media at hazardous waste sites has been identified. Furthermore, a need to collect data on levels of vinyl chloride in body tissues and fluids for populations living in the vicinity of hazardous waste sites has been determined.

One effort is currently underway at ATSDR that will examine the extant data at the 245 NPL sites at which vinyl chloride has been found. When complete, this database will include concentrations of vinyl chloride in on-site and off-site media, the size of the potentially exposed population, and an indication of relevant routes of exposure. This database will be developed and evaluated before the need to collect additional media-specific data is assigned priority. This database will not, however, supply information on the levels of vinyl chloride (or its metabolites) in the tissues of individuals living near hazardous waste sites or other exposed populations such as workers.

This information is necessary to establish a database that can be used to assess the need to conduct follow-up human health studies of populations exposed to vinyl chloride as mandated. In addition, vinyl chloride should be considered as a potential candidate for a subregistry of exposed persons due to the advanced stage of knowledge on exposure to vinyl chloride and the evidence that vinyl chloride exposure is associated with the development of chronic health effects including cancer. This recommendation will be provided to the ATSDR Division of Health Studies who will judge the extant information on vinyl chloride against its criteria for initiating an exposure subregistry.

There is a data need for clinical methods of mitigating vinyl chloride toxicity since a large number of people are potentially exposed to vinyl chloride at hazardous waste sites (vinyl chloride has been identified at 245 sites thus far), there exits an advanced stage of knowledge on exposure to vinyl chloride and there are two unique diseases associated with vinyl chloride exposure.

Thus, on the basis of the findings given in Section II and above, ATSDR is recommending the initiation of research or studies to fill the following exposure priority data needs (Table 3):

Exposure

- o Evaluation of existing data on concentrations of vinyl chloride in contaminated environmental media at hazardous waste sites (Group A)

- o Exposure levels in humans living near hazardous waste sites and other populations such as workers exposed to vinyl chloride (Group A)

- o Potential candidate for subregistry of exposed persons (Group A)

B. Toxicity

A considerable amount of toxicity information is available for vinyl chloride, and its targets of toxicity (i.e., the central nervous system and the liver). However, additional inhalation acute- and chronic-duration studies are necessary for determining thresholds for these effects so that levels of significant human exposure for these health effects can be identified. Even though there is evidence from animal data that exposure to vinyl chloride may cause developmental and reproductive effects, human studies are limited by the lack of quantification of exposure levels or fail to show a statistically significant correlation between developmental/reproductive effects and exposure to vinyl chloride. Additional research is necessary (e.g. continuous breeding studies) to fully assess the developmental and reproductive health effects to the human population living near hazardous waste sites or workers exposed to vinyl chloride. These nonhuman research needs are justified because of the widespread contamination of environmental media by vinyl chloride and the obvious impact of developmental and reproductive effects.

Furthermore, a priority data need for clinical methods of mitigating vinyl chloride toxicity has been identified. This is justified because a large number of people are potentially exposed to vinyl chloride at hazardous waste sites (vinyl chloride has been identified at 245 sites thus far), an advanced stage of knowledge exists on exposure to this chemical and there are two unique diseases associated with vinyl chloride exposure.

Thus, on the basis of the findings given in Section II and above, ATSDR is recommending the initiation of research or studies to fill the following toxicity priority data needs (Table 3):

- o Dose-response data in animals for acute-duration exposure via inhalation (Group A)

- o Dose-response data in animals for chronic-duration exposure via inhalation (Group B)

- o 2-species multigeneration reproductive study via inhalation (Group A)

- o 2-species developmental study via inhalation (Group B)
- o Mitigation of vinyl chloride-induced toxicity (Group B)

V. References

Anderson D, Hodge MCE, Purchase IFH. 1976. Vinyl chloride: Dominant lethal studies in male CD-1 mice. Mutat Res 40:359-370.

Anderson D, Richardson CR, Weight TM, et al. 1980. Chromosomal analyses in vinyl chloride exposed workers: Results from analysis 18 and 42 months after an initial sampling. Mutat Res 79:151-162.

APHA. 1985. Standard methods for the examination of water and wastewater, 16th ed. American Public Health Association, American Water Works Association and Water Pollution Control Federation. Washington, DC, 591-602.

ATSDR. 1989. Toxicological Profile for Vinyl Chloride. Agency for Toxic Substances and Disease Registry. Atlanta, Ga.

ATSDR. 1991. Toxicological Profile for Vinyl Chloride (Draft). Agency for Toxic Substances and Disease Registery. Atlanta, Ga.

Baker LW, MacKay KP. 1985. Hazardous waste management. Screening models for estimating toxic air pollution near a hazardous waste landfill. J Air Pollut Control Assoc 35:1190-1195.

Bao Y-S, et al. 1988. [The effects of vinyl chloride on pregnancy, parturition, and fetal development among female workers.] Chin J Prev Med 22:343-346. (Chinese) [Translation in progress]

Baretta ED, Stewart RD, Mutchler JE. 1969. Monitoring exposures to vinyl chloride vapor: Breath analysis and continuous air sampling. Am Ind Hyg Assoc J 30:537.

Belli S, Bertazzi PA, Comba P, et al. 1987. A cohort study on vinyl chloride manufacturers in Italy: Study design and preliminary results. Cancer Lett 35:253-261.

Berk PD. 1976. Vinyl chloride-associated liver disease. Ann Int Med 84:717-731.

Bi W, Wang Y, Huang M, et al. 1985. Effect of vinyl chloride on testis in rats. Ecotoxicol Environ Safety 10:281-289.

Black C, Pereira S, McWhirter A, et al. 1986. Genetic susceptibility to scleroderma-like syndrome in symptomatic and asymptomatic workers exposed to vinyl chloride. J Rheumatol 13:1059-1062.

Black CM, Welsh KI, Walker AE, et al. 1983. Genetic susceptibility to scleroderma-like syndrome induced by vinyl chloride. Lancet 1:53-55.

Bogdanikowa B, Zawilska J. 1984. Immune complexes in the serum of patients occupationally exposed to vinyl chloride. Przeglad Lekarski 41:253-257.

Bolt HM, Filser JG, Laib RJ, et al. 1980. Binding kinetics of vinyl chloride and vinyl bromide at very low doses. In: Quantitative aspects of risk assessment in chemical carcinogenesis. Arch Toxicol Suppl 3:129-142.

Bolt HM, Kappus H, Buchter A, et al. 1976. Disposition of (1,2^{14}C) vinyl chloride in the rat. Arch Toxicol 35:153-162.

Bolt HM, Laib RJ, Kappus H, et al. 1977. Pharmacokinetics of vinyl chloride in the rat. Toxicology 7:179-188.

Bolt HM, Laib RJ, Peter H, et al. 1986. DNA adducts of halogenated hydrocarbons. J Cancer Res Clin Oncol 112:92-96.

Bozzelli JW, Kebbekus BB. 1979. Analysis of selected volatile organic substances in ambient air, final report Apr-Nov 1978. NJ Institute of Technology, Newark, NJ, 80.

Bryen D, Engholm G, Englund A, et al. 1976. Mortality and cancer morbidity in a group of Swedish VCM and PCV production workers. Environ Health Perspect 17:167-170.

Buchter A, Bolt HM, Kappus H, et al. 1977. [Tissue distribution of 1,2-^{14}C-vinyl chloride in the rat.] Int Arch Occup Environ Health 39:27-32. (German) [Translation in progress]

Buchter A, Filser JG, Peter H, et al. 1980. Pharmacokinetics of vinyl chloride in the rhesus monkey. Toxicol Lett 6:33-36.

Burmaster DE. 1982. The new pollution groundwater contamination. Environ 24:6-13, 33-36.

Callahan MA, Slimak MS, Gabel NW, et al. 1979. Water-related environmental fate of 129 priority pollutants. Volume II. Environmental Protection Agency, Washington, DC. EPA-440/4-79-0298.

Carassiti V, Chiorboli C, Bignozzi CA, et al. 1978. Atmospheric photooxidation of vinyl chloride: A generalized treatment of the relative rates of product formation. Ann Chim 67:499-512.

Carr J, Burgison RM, Vitcha JF, et al. 1949. Anesthesia: XXIV. Chemical constitution of hydrocarbons and cardiac automaticity. J Pharmacol Expd Ther 97:1.

Ciroussel F, Barbin A, Eberle G, et al. 1990. Investigations on the relationship between DNA ethenobase adduct levels in several organs of vinyl chloride-exposed rats and cancer susceptibility. Biochem Pharmacol 39:1109-1113.

CLPSD. 1989. Contract Laboratories Program Statistical Database. U.S. Environmental Protection Agency, Washington, DC. July 1989.

Coniglio WA, Miller K, MacKeever D. 1980. The occurrence of volatile organics of in drinking water. Criteria and Standards Division. Science and Technology Branch. Exposure Assessment Project.

Conkle JP, Camp BJ, Welch BE. 1975. Trace composition of human respiratory gas. Arch Environ Health 30:290-295.

Cooper WC. 1981. Epidemiologic study of vinyl chloride workers: Mortality through December 31, 1972. Environ Health Perspect 41:101-106.

Cowfer JA, Magistro AJ. 1983. Vinyl chloride. In: Kirk-Othmer encyclopedia of chemical technology. Vol. 23. Wiley Interscience, New York, NY, 865-885.

Cox RA, Enggleton AEJ, Sandalls FJ. 1974. Photochemical reactivity of vinyl chloride. AERE-R7820. Are Harwell, Oxforshire, England. 16.

Creech JL, Johnson MN. 1974. Angiosarcoma of liver in the manufacture of polyvinyl chloride. J Occup Med 16:150-151.

Danziger H. 1960. Accidental poisoning by vinyl chloride: Report of two cases. Can Med Assoc J 82:828.

Dressman RC, McFarren EF. 1978. Determination of vinyl chloride migration from polyvinyl chloride pipe into water. Am Water Works Assoc Jour 70:29.

Ducatman A, Hirschhorn K, Selikoff IJ. 1975. Vinyl chloride exposure and human chromosome aberrations. Mutat Res 31:163-168.

Dyksen JE, Hess AF III. 1982. Alternatives for controlling organics in groundwater supplies. J Am Water Works Assoc 74:394-403.

Eberle G, Barbin A, Laib RJ, et al. 1989. 1,N6-etheno-2'-deoxyadenosine and 3,N4-etheno-2'-deoxycytidine detected by monoclonal antibodies in lung and liver DNA of rats exposed to vinyl chloride. Carcinogenesis 10:209-212.

Edmonds LD, Anderson CE, Flynt JW, et al. 1978. Congenital central nervous system malformations and vinyl chloride monomer exposure: A community study. Teratology 17:137-142.

EPA. 1979. Formulation of preliminary assessment of halogenated organic compounds in man and environmental media. Research Triangle Park, NC: U.S. Environmental Protection Agency. EPA/560/13-79-006.

EPA. 1980. Ambient water quality criteria for vinyl chloride. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office. EPA 440/5-80-078. NTIS PB 81-117889.

EPA. 1982a. Aquatic fate process data for organic priority pollutants. Washington, DC: U.S. Environmental Protection Agency, Office of Water Regulations and Standards.

EPA. 1982b. Emission standard for ethylene dichloride, vinyl chloride, and polyvinyl choride. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 61.65.

EPA. 1982c. Methods for organic chemical analysis of municipal andindustrial wastewater. Test method: Purgeable halocarbons - method 601 and Purgeable - Method 624. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Monitoring and Support Laboratory, EPA 600/4-82-057, 601-1 to 601-10 and 624-1 to 624-12.

EPA. 1982d. Test methods for evaluating solid waste. Physical/chemical methods. Method 8010 - Halogenated volatile organics. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, 8010-1 to 8010-12.

EPA. 1985a. Designation, reportable quantities, and notification. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 302.

EPA. 1985b. Drinking water criteria document for vinyl chloride. Washington, DC: U.S. Environmental Protection Agency, Office of Drinking Water. NTIS PB86-118320.

EPA. 1985c. Health and environmental effects profile for chloroethene. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office. ECAO-CIN-P155.

Falk H, Creech JL Jr, Heath CW Jr, et al. 1974. Hepatic disease among workers at a vinyl chloride polymerization plant. J Am Med Assoc 230:59-63.

Feron VJ, Kroes R. 1979. One-year time-sequence inhalation toxicity study of vinyl chloride in rats. II. Morphological changes in the respiratory tract, ceruminous glands, brain, kidneys, heart and spleen. Toxicology 13:131-141.

Feron VJ, Hendriksen CFM, Speek AJ, et al. 1981. Lifespan oral toxicity study of vinyl chloride in rats. Food Cosmet Toxicol 19:317-333.

Feron VJ, Speek AJ, Willems MI, et al. 1975. Observations on the oral administration and toxicity of vinyl chloride in rats. Food Cosmet Toxicol 13:633-638.

Fishbein L. 1979. Potential halogenated industrial carcinogenic and mutagenic chemicals. I. Halogenated unsaturated hydrocarbons. Sci Total Environ 11:111-161.

Fox AJ, Collier PF. 1977. Mortality experience of workers exposed to vinyl chloride monomer in the manufacture of polyvinyl chloride in Great Britain. Br J Ind Med 34:110.

Freitag D, Ballhorn L, Geyer H, et al. 1985. Environmental hazard profile of organic chemicals. Chemosphere 14:1589-1616.

Fucic A, Horvat D, Dimitrovic B. 1990. Localization of breaks induced by vinyl chloride in the human chromosomes of lymphocytes. Mutat Res 243:95-99.

Gedigke P, Muller R, Bechtelsheimer H. 1975. Morphology of liver damage among polyvinyl chloride production workers. A report on 51 cases. Ann NY Acad Sci 246:279-285.

Gilbert SG, Miltz J, Giacin JR. 1980. Transport considerations of potential migrants from food packaging materials. J Food Process Preserv 4:27-49.

Gordon SJ, Meeks SA. 1977. A study of gaseous pollutants in the Houston, Texas area. AICHE Symp Ser 73:84-94.

Grainger RG, Walker AE, Ward AM. 1980. Vinyl chloride monomer-induced disease: Clinical, radiological, and immunological aspects. In: Induced Disease, Drug Irradiation. Occupation. Preger L., ed. Grune and Stratton, New York, 191-214.

Green T, Hathway DE. 1975. The biological fate in rats of vinyl chloride in relation to its oncogenicity. Chem Biol Interact 11:545-562.

Green T, Hathway DE. 1977. The chemistry and biogenesis of the S-containing metabolites of vinyl chloride in rats. Chem Biol Interact 17:137-150.

Grimsrud EP, Rasmussen RA. 1975a. The analysis of chlorofluorocarbons in the troposphere by gas chromatography-mass spectrometry. Atmos Environ 9:1010-1013.

Grimsrud EP, Rasmussen RA. 1975b. Survey and analysis of halocarbons in the atmosphere by gas chromatography-mass spectrometry. Atmos Environ 9:1014-1017.

Gwinner LM, Laib RJ, Filser JG, et al. 1983. Evidence of chloroethylene oxide being the reactive metabolite of vinyl chloride towards DNA: Comparative studies with 2,2'-dichlorodiethyl ether. Carcinogenesis 4:1483-1486.

Hansteen IL, Hillestad L, Thiis-Evensen E, et al. 1978. Effects of vinyl chloride in man: A cytogenetic follow-up study. Mutat Res 51:271-278.

Harkov R, Kebbekus B, Bozzelli JW, et al. 1984. Comparison of selected volatile organic compounds during the summer and winter at urban sites in New Jersey. Sci Total Environ 38:259-274.

Harris DK. 1953. Health problems in the manufacture and use of plastics. Br J Ind Med 10:255.

Harsch DE, Cronn DR, Slater WR. 1979. Expanded list of halogenated hydrocarbons measurable in ambient air. J Air Pollut Control Assoc 29:975-976.

Heath CW Jr, Fable H, Creech JL Jr. 1975. Characteristics of cases of angiosarcoma of the liver among vinyl chloride workers in the United States. Ann NY Acad Sci 246:231-236.

Hefner RE Jr, Watanabe PG, Gehring PJ. 1975a. Percutaneous absorption of vinyl chloride. Toxicol Appl Pharmacol 34:529-532.

Hefner RE Jr, Watanabe PG, Gehring PJ. 1975b. Preliminary studies of the fate of inhaled vinyl chloride monomer in rats. Ann NY Acad Sci 246:135-148.

Hehir RM, McNamara BP, McLaughlin J, Jr, et al. 1981. Cancer induction following single and multiple exposures to a constant amount of vinyl chloride monomer. Environ Health Perspect 41:63-72.

Helfgott TB, Hart FL, Bedard RG. 1977. An index of refractory organics.. Ada, OK: U.S. Environmental Protection Agency. EPA-600/2-77-174.

Hill J IV, Kollig HP, Paris DF, et al. 1976. Dynamic behavior of vinyl chloride in aquatic ecosystems. EPA-600/3-76-00-1. (NTIS PB-249 302). Environmental Research Lab., Athens, GA.

Howard CJ. 1976. Rate constants for the gas-phase reactions of hydroxyl radicals with ethylene and halogenated ethylene compounds. J Chem Phys 65:4771-4777.

HSDB. 1987. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Information Program, Bethesda, MD. September 1987.

Hultmark D, Sundh K, Johansson L, et al. 1979. Ethanol inhibition of vinyl chloride metabolism in isolated rat hepatocytes. Chem Biol Interact 25:1-6.

IARC. 1978. Methods for the measurement of vinyl chloride in polyvinyl chloride, air, water, and foodstuffs. In: Egan H, Squireel DCM, Thain W, Davis W, eds. Environmental Carcinogens Selected Methods of Analysis. Lyons, France: World Health Organization, International Agency for Research on Cancer. IARC Sci Pub No 22.

IARC. 1979. Monographs on the evaluation of the carcinogenic risk of chemicals in humans. Vinyl chloride, polyvinyl chloride and vinyl chloride-vinyl acetate copolymers. Lyons, France: World Health Organization, International Agency for Research on Cancer. WHO, IARC 19:377-401; 419-438.

Infante PF. 1976. Oncogenic and mutagenic risks in communities with polyvinyl chloride production facilities. Ann NY Acad Sci 271:49-57.

Infante PF, Wagoner JK, McMichael AJ, et al. 1976a. Genetic risks of vinyl chloride. Lancet (April 3) 734-735.

Infante PF, Wagoner JK, Waxweiler RJ. 1976b. Carcinogenic, mutagenic, and teratogenic risks associated with vinyl chloride. Mutat Res 41:131-142.

Jaeger RJ, Reynolds ES, Conolly RB, et al. 1974. Acute hepatic injury by vinyl chloride in rats pretreated with phenobarbital. Nature 252:724-726.

Jedrychowski RA, Sokal JA, Chmielnicka J. 1984. Influence of exposure mode on vinyl chloride action. Arch Toxicol 55:195-198.

Jenssen D, Ramel C. 1980. The micronucleus test as part of a short-term mutagenicity test program for the prediction of carcinogenicity evaluated by 143 agents tested. Mutat Res 75:191-202.

John JA, Smith FA, Leong BKJ, et al. 1977. The effects of maternally inhaled vinyl chloride on embryonal and fetal development in mice, rats, and rabbits. Toxicol Appl Pharmacol 39:497-513.

Jones RD, Smith DM, Thomas PG. 1988. A mortality study of vinyl chloride monomer workers employed in the United Kingdom in 1940-1974. Scand J Work Environ Health 14:153-160.

Juhe VS, Lange CE, Stein G, et al. 1974. [On so-called vinyl chloride disease (a new occupational disease).] Berufsdermatosen 22:4-22. (German)

Jury WA, Spencer WF, Farmer WJ. 1984. Behavior assessment model for trace organics in soil: III. Application of screening model. J Environ Qual 13:573-579.

Kenaga EE, Goring CAI. 1980. Relationship between water solubility, soil-sorption, octanol-water partitioning, and concentration of chemicals in biota. In: Eaton JG, Parrish PR, Hendricks AC, eds. Aquatic Toxicology. American Society for Testing and Materials, 78-115.

Knight KR, Gibbons R. 1987. Increased collagen synthesis and cross-link formation in the skin of rats exposed to vinyl chloride monomer. Clin Sci 72:673-678.

Kontominas MG, Gupta C, Gilbert SG. 1985. Interaction of vinyl chloride with polyvinyl chloride in model food systems by HPLC chromatography: Migration aspects. Lebensm-Wiss u-Technol 18:353-356.

Krajewski J, Dobecki M, Gromiec J. 1980. Retention of vinyl chloride in the human lung. Br J Ind Med 37:373-374.

Krost KJ, Pellizzari ED, Walburn SG, et al. 1982. Collection and analysis of hazardous organic emissions. Anal Chem 54:810-817.

Kucerova M, Polivkova Z, Batora J. 1979. Comparative evaluation of the frequency of chromosomal aberrations and the SCE numbers in peripheral lymphocytes of workers occupationally exposed to vinyl chloride monomer. Mutat Res 67:97-100.

Laib RJ, Bolt HM, Cartier R, et al. 1989. Increased alkylation of liver DNA and cell turnover in young versus old rats exposed to vinyl chloride correlates with cancer susceptibility. Toxicol Lett 45:231-239.

Langauer-Lewowicka H, Dudziak Z, Byczkowska Z, et al. 1976. Cryoglobulinemia in Raymond's phenomenon due to vinyl chloride. Int Arch Occup Environ Health 35:197-207.

Langauer-Lewowicka H, Kurzbauer H, Byczkowska Z, et al. 1983. Vinyl chloride disease-neurological disturbances. Int Arch Occup Environ Health 52:151-157.

Laplanche A, Clavel F, Contassot JC, et al. 1987. Exposure to vinyl chloride monomer-report on a cohort study. Br J Ind Med 44:711-715.

Lee FI, Harry DS. 1974. Angiosarcoma of the liver in a vinyl chloride worker. Lancet 1:1316-1318.

Lee CC, Bhandari JC, Winston JM, et al. 1977. Inhalation toxicity of vinyl chloride and vinylidene chloride. Environ Health Perspect 21:25-32.

Lester D, Greenberg LA, Adams WR. 1963. Effects of single and repeated exposures of humans and rats to vinyl chloride. Am Ind Hyg Assoc J 24:265-275.

Lilis R, Anderson H, Nicholson WJ, et al. 1975. Prevalence of disease among vinyl chloride and polyvinyl chloride workers. Ann NY Acad Sci 246:22-41.

Lloyd MH, Gauld S, Copland L, et al. 1984. Epidemiological study of the lung function of workers at a factory manufacturing polyvinyl chloride. Br J Ind Med 41:328-333.

Lu PY, Metcalf RL, Plummer N, et al. 1977. The environmental fate of 3 carcinogens: Benzo(a)pyrene, benzidine and vinyl chloride evaluated in laboratory model ecosystems. Arch Environ Contam Toxicol 6:129-142.

Lyman WJ, Reehl WF, Rosenblatt DH. 1982. Handbook of chemical property estimation methods. Environmental Behavior of Organic Compounds. McGraw Hill Book Co., New York, NY, 4-9.

Magnavita N, Bergamaschi A, Garcovich A, et al. 1986. Vasculitic purpura in vinyl chloride disease: A case report. Angiology 37:382-388.

Makarov IA. 1984. [Sexual disorders in male workers occupationally exposed to methyl methacrylate and vinyl chloride.] Gig Tr Prof Zabol 6:19-23. (Russian)

Makarov IA, Solovyeva MS, Gnelitsky GI. 1984. [Sexual disorders in women chronically exposed to methylmethacrylate and vinyl chloride.] Gig Tr Prof Zabol 3:22-27 (Russian)

Maltoni C, Lefemine G, Ciliberti A, et al. 1980. Vinyl chloride carcinogenicity bioassays (BT project) as an experimental model for risk identification and assessment in environmental and occupational carcinogenesis. Epidemiol Anim Epidemiol Hum: Cas Chlorure Vinyle Monomere (Reun Club Cancerog Chim), 20th, Meeting Date 1979, 11-112. Publ Essent, Paris, France.

Maltoni C, Lefemine G, Ciliberti A, et al. 1981. Carcinogenicity bioassays of vinyl chloride monomer: A model of risk assessment on an experimental basis. Environ Health Perspect 41:329.

Marsteller HJ, Lelbach WK, Muller R, et al. 1975. Unusual splenomegalic liver disease as evidenced by peritoneoscopy and guided liver biopsy among polyvinyl chloride production workers. Ann NY Acad Sci 95-134.

Mastromatteo E, Fisher AM, Christie H, et al. 1960. Acute inhalation toxicity of vinyl chloride to laboratory animals. Am Ind Hyg Assoc J 394-398.

McMurry JR, Tarr J. 1978. Vinyl chloride in Texas' ambient air. Proc Ann Tech Meet - Inst Environ Sci. 149-155.

Mirkova E, Mihaylova A, Nosko M. 1978. [Embryotoxic and teratogenic effects in vinyl chloride.] Khig Zdraveopaz 21:440-443. (Bulgarian)

MIS. 1990. Management Information System (Release 1.0). Agency for Toxic Substances and Disease Registry, Atlanta, GA. September 24, 1990.

Monson RR, Peters JM, Johnson MN. 1975. Proportional mortality among vinyl chloride workers. Environ Health Perspect 11:75-77.

Muller G, Norpoth K, Wickrama-Singhe RH. 1979. An analytical method using GC-MS for the quantitative determination of urinary thiodiglycolic acid. Int Arch Occup Environ Health 44:185-191.

NIOSH. 1991. National Occupational Exposure Survey (NOES) (1981-1983). [Database]. Cincinnatic, Oh: National Institute of Occupational Safety and Health Department of Health and Human Services.

Norpoth K, Heger M, Mueller G, et al. 1986. Investigations on metabolism genotoxic effects and carcinogenicity of 2,2-dichlorodiethyl ether. J Cancer Res Clin Oncol 112:125-130.

NTP. 1989. National Toxicology Program. Fifth Annual Report on Carcinogens: Summary 1989. U.S. Department of Health and Human Services, Public Health Service. NTP 89-239.

Oster RH, Carr CJ, Krantz JC. 1947. Anesthesia XXVII. Narcosis with vinyl chloride. Anesthesiology 8:359-361.

Patty FA, Yapt WP, Waite CP. 1930. Acute response of guinea pigs to vapors of some new commercial organic compounds. V. Vinyl chloride. Pub Health Reports 45:1963-1971.

Perry RA, Atkinson R, Pitts JN Jr. 1977. Rat constants for the reaction of hydroxyl radicals with vinyl fluoride, vinyl chloride, and vinyl bromide over the temperature range 229-426°K. J Chem Phys 67:458-462.

Perticoni GF, Abbritti G, Cantisani TA, et al. 1986. Polyneuropathy in workers with long exposure to vinyl chloride. Electro-physiological study. Electromyog Clin Neurophysiol 26:41-47.

Pettit BR. 1986. The analysis of thiodiglycollic-acid by selected ion monitoring. Clim Chim Acta 156:85-90.

Pirastu R, Comba P, Reggiani A, et al. 1990. Mortality from liver disease among Italian vinyl chloride monomer/polyvinyl chloride manufacturers. Am J Ind Med 17:155-161.

Popper H, Thomas LB. 1975. Alterations of liver and spleen among workers exposed to vinyl chloride. Ann NY Acad Sci 246:172-194.

Purchase IFH, Richardson CR, Anderson D, et al. 1978. Chromosomal analysis in vinyl chloride exposed workers. Mutat Res 57:325-334.

Rasmussen RA, Harsch DE, Sweany PH, et al. 1977. Determination of atmospheric halocarbons by a temperature-programmed gas chromatographic freeze-out concentration method. J Air Pollut Control Assoc 27:579-581.

Rinsky RA, Ott G, Ward E, et al. 1988. Study of mortality among chemical workers in the Kanawha Valley of West Virginia. Am J Ind Med 13:429-438.

Sabadie N, Malaveille C, Camus AM, et al. 1980. Comparison of the hydroxylation of benzo(a)pyrene with the metabolism of vinyl chloride, n-nitrosonorpholine, and n-nitroso-n'methylpiperazine to mutagens by human and rat liver microsomal fractions. Cancer Res 409:119-126.

Sabljic A. 1984. Prediction of the nature and strength of soil sorption of organic pollutants by molecular topology. J Agric Food Chem 32:243-246.

Sal'nikova LS, Kotsovskaya IA. 1980. [Effect of vinyl chloride on embryogenesis of rats.] Gig Tr Prof Zabol 46-47. (Russian)

Sharma RP, Gehring PJ. 1979. Immunologic effects of vinyl chloride in mice. Ann NY Acad Sci 31:551-563.

Short RD, Minor JL, Winston JM, et al. 1977. A dominant lethal study in male rats after repeated exposures to vinyl chloride or vinylidene chloride. J Toxicol Environ Health 3:965-968.

Singer B, Spengler SJ, Chavez F, et al. 1987. The vinyl chloride-derived nucleoside, N2,3-ethenoguanosine, is a highly efficient mutagen in transcription. Carcinogenesis 8:745-747.

Sittig M. 1985. Handbook of toxic and hazardous chemicals and carcinogens. 2nd ed. Park Ridge, NJ: Noyes Publications, 918-921.

Smulevich VB, Fedotova IV, Filatova VS. 1988. Increasing evidence of the rise of cancer in workers exposed to vinyl chloride. Br J Ind Med 45:93-97.

Sokal JA, Baranski B, Majka J, et al. 1980. Experimental studies on the chronic toxic effects of vinyl-chloride in rats. J Hyg Epidemiol Microbiol Immunol 24:285-294.

Spirtas R, McMichael AJ, Gamble J, et al. 1975. The association of vinyl chloride exposures with morbidity symptoms. Am Ind Hyd Assoc J 36:779-789.

Stephens RD, Ball NB, Mar DM. 1986. A multimedia study of hazardous waste landfill gas migration. In: Pollutants in a Multimedia Environment. Cohen Y, ed. New York, NY: Plenum Press, 265-287.

Suciu I, Drejman I, Valeskai M. 1963. [Investigation of the diseases caused by vinyl chloride.] Med Intern 15:967-976. (Romanian)

Suciu I, Prodan L, Ilea E, et al. 1975. Clinical manifestations in vinyl chloride poisoning. Ann NY Acad Sci 246:53-69.

Teta MJ, Schnatter AR, Ott MG, et al. 1990. Mortality surveillance in a large chemical company: The union carbide corporation experience. Am J Ind Med 17:435-448.

Theriault G, Iturra H, Gingras S. 1983. Evaluation of the association between birth defects and exposure to ambient vinyl chloride. Teratology 27:359-370.

Til HP, Immel HR, Feron VJ. 1983. Lifespan oral carcinogenicity study of vinyl chloride in rats. Final report. Civo Institutes, TNO. Report No. V 93.285/291099.

Torkelson TR, Oyen F, Rowe VK. 1961. The toxicity of vinyl chloride as determined by repeated exposure of laboratory animals. Am Ind Hyg Assoc J 22:354-361.

TRI. 1990. Toxic Chemical Release Inventory. National Library of Medicine, National Toxicology Program, Bethesda, MD.

Ungvary G, Hudak A, Tatrai E, et al. 1978. Effects of vinyl chloride exposure alone and in combination with trypan blue-applied systematically during all thirds of pregnancy on the fetuses of CFY rats. Toxicology 11:45-54.

van Sittert NJ, de Jong G. 1985. Biomonitoring of exposure to potential mutagens and carcinogens in industrial populations. Food Chem Toxic 23:23-31.

Veith GD, Macek KJ, Petrocelli SR, et al. 1980. An evaluation of using partition coefficients and water solubility to estimate bioconcentration factors for organic chemicals in fish. In: Aquatic Toxicology, ASTM STP 707, JG Eaton, Parrish PR, Hendricks AC, eds. American Society for Testing and Materials. 116-1293.

Veltman G, Lange CE, Juhe S, et al. 1975. Clinical manifestations and course of vinyl chloride disease. Ann NY Acad Sci 246:6-17.

Verschueren K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. New York, NY: Van Nostrand Reinhold Company; 1185-1186.

Viola PL. 1970. Pathology of vinyl chloride. Med Lavoro 61:174-180.

Viola PL, Bigotti A, Caputo A. 1971. Oncogenic response of rat skin, lungs, and bones to vinyl chloride. Cancer Res 31:516-522.

Wagnerova M, Wagner V, Znojemska S, et al. 1988. Factors of humoral resistance in workers exposed to vinyl chloride with a view to smoking habits. J Hyg Epidemiol Microbiol Immunol 32:265-272.

Wagnerova M, Znojemska S, Wagner V, et al. 1986. Humoral factors of resistance in the cohort of workers exposed to vinyl chloride in the span of six years, concerning the influence of smoking. Czech Med 9:210-217.

Walker AE. 1976. Clinical aspects of vinyl chloride disease: Skin. Proc R Soc Med 69:286-289.

Wallace LA, Pellizzari E, Hartwell T, et al. 1984. Personal exposure to volatile organic compounds. Environ Res 35:293-319.

Wang T, Lenahan R, Kanik M. 1985. Impact of trichloroethylene-contaminated groundwater discharged to the main canal and Indian River Lagoon, Vero Beach, Florida. Bull Environ Contam Toxicol 34:578-586.

Ward AM. 1976. Clinical aspects of vinyl chloride disease: Evidence of an immune complex disorder in vinyl chloride workers. Proc R Soc Med; 69:289-290.

Watanabe PG, Gehring PJ. 1976. Dose-dependent fate of vinyl chloride and its possible relationship to oncogenicity in rats. Environ Health Perspect 17:145-152.

Watanabe PG, McGowan GR, Gehring PJ. 1976a. Fate of [^{14}C] vinyl chloride after single oral administration in rats. Toxicol Appl Pharmacol 36:339-352.

Watanabe PG, McGowan GR, Madrid EO, et al. 1976b. Fate of [^{14}C] vinyl chloride following inhalation exposure in rats. Toxicol Appl Pharmacol 37:49-59.

Watanabe PG, Zempel JA, Gebring PJ. 1978. Comparison of the fate of vinyl chloride following single and repeated exposure in rats. Toxicol Appl Pharmacol 44:391-399.

Waxweiler RJ, Falk H, McMichael A, et al. 1977. A cross-sectional epidemiologic survey of vinyl chloride workers. NTIS PB274193.

Waxweiler RJ, Stringer W, Wagner JK, et al. 1976. Neoplastic risk among workers exposed to vinyl chloride. Ann NY Acad Sci 271:40-48.

Weber H, Reinl W, Greiser E. 1981. German investigations on morbidity and mortality of workers exposed to vinyl chloride. Environ Health Perspect 41:95-99.

Westrick JJ, Mello JW, Thomas RF. 1984. The groundwater supply survey. J Am Water Works Assoc 76:52-59.

Wisniewska-Knypl JM, Klimczak J, Kolakowski J. 1980. Monooxygenase activity and ultrastructural changes of liver in the course of chronic exposure of rats to vinyl chloride. Int Arch Occup Environ Health 46:241-249.

Withey JR. 1976. Pharmacodynamics and uptake of vinyl chloride monomer administered by various routes to rats. J Toxicol Environ Health 1:381-394.

Wittsiepe J, Selenka F, Jackwerth E. 1990. Gas-chromatographic determination of trace amounts of vinyl-chloride in water and air after derivation to 1,2-bromochloroethane. Presenius Journal of Analytical Chemistry 336:322-327.

Wong O, Whorton MD, Ragland D, et al. 1986. An update of an epidemiologic study of vinyl chloride workers, 1942-1982. Prepared by Environmental Health Associates, Inc. for Chemical Manufacturers Association.

Wood JA, Porter ML. 1987. Hazardous pollutants in class II landfills. JAPCA 37:609-615.

Wu W, Steenland K, Brown D, et al. 1989. Cohort and case-control analyses of workers exposed to vinyl chloride: An update. J Occup Med 31:518-523.

Zhang J, Hatakeyama S, Akimoto H. 1983. Rate constants of the reaction of ozone with trans-1,2-dichloroethene and vinyl chloride in air. Int J Chem Kinet 15:655-668.

Zuccato E, Mancucci F, Fanelli R, et al. 1979. Head-space gas-chromatographic analysis of vinyl chloride monomer in rat blood and tissues. Xenobiotica 9:27-31.

Table 1. Exposure Data Needs

Exposure	Level I	Level II	Level III
Analytical	Methods for parent compound in REM*	Methods for degradation products in REM*	
	Methods for parent compound in blood or urine	Methods for parent compound/ metabolites/ biomarkers	
	Structure-Activity relationships (SAR)		
Physical Chemical Properties	Water solubility		
	Volatility/vapor pressure		
	K_{ow}		
	Henry's law		Registries of exposed persons
Exposure Levels	Production volume (may be used in lieu of monitoring data)	Monitoring in REM*	Human dosimetry studies
	Use (may be used in lieu of monitoring data)	Monitoring for human exposure (personal sampling, biomarkers of exposure, tissue levels)	Epidemiology
	Release/ disposal (may be used in lieu of monitoring data)		Disease registries
Environmental Fate	Aerobic/anaerobic Biodegradation in H_2O	Small field plot studies	
	Oxidation		
	Hydrolysis	Monitoring for products in REM*	
	Aerosolization		
	Photoreactivity		
	Volatilization		
	Soil adsorption/ desorption		
Bioavailability		Food chain bioaccumulation	
		Availability from REM* (analytical or toxicity) emphasize in vivo	

*REM = Relevant Environmental Media

Table 2. Toxicity Data Needs

Toxicity	Level I	Level II	Level III
Single dose exposure	Single dose disposition Skin/eye irritation Acute toxicity		
Repeated dose exposure	14-day by relevant route 90-day subchronic	Comparative toxicokinetics	
Chronic exposure	Structure-activity relationships (SAR)	1-Year chronic 2-Year bioassay	Epidemiology
Genotoxicity	Ames Micronucleus	Additional genotoxicity studies	Mechanism of toxic action
Reproductive toxicity	Extended repro workup in subchronic	2-Generation or continuous breeding	Biomarkers Clinical methods for mitigating toxicity
Developmental toxicity	Short term in vivo screen	2-Species developmental	
Immunotoxicity	Use subchronic results	Immunotox battery	
Neurotoxicity	Neuropath in subchronic Demeanor in subchronic	Neurotox battery	
Sensitization	Dermal sensitization		
Carcinogenicity	Use muta & subchronic results)	2-year bioassay	

Table 3. ATSDR Substance-Specific Applied Research Program for Vinyl Chloride

Data Needs

	EXPOSURE		
	Level I	Level II	Level III
Analytical	soil		
Physical Chemical Properties			
Exposure Levels		*EVALUATE EXISTING DATA ON LEVELS IN REM* *LEVELS IN TISS*	*POTENTIAL CANDIDATE FOR EXPOSURE REGISTRY*
Environment Fate	soil adsorp/ degradation/ transformation		
Bioavailability		food chain bioaccum (terrestrial)	

	TOXICITY		
	Level I	Level II	Level III
Acute	*INHALATION*, oral, dermal		
Repeated	oral, dermal		
Chronic		*INHALATION*, dermal	
Mutag			epidem studies on health effects
Repro		*2-SPECIES REPRO VIA INHALATION* (oral, dermal)	mechanistic studies
Develop		*2-SPECIES DEVELOP VIA INHALATION* (oral, dermal)	biomarkers
Immunotox	oral, dermal		*MITIGATION OF TOXICITY*
Neurotox	oral, dermal		
Carcinog			

UPPER CASE: Priority Data Needs identified for vinyl chloride.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Agency for Toxic Substances and Disease Registry

[ATSDR-61]

Revised Procedures For Conducting Voluntary Research

AGENCY: Agency for Toxic Substances and Disease Registry (ATSDR), Public Health Service (PHS), Department of Health and Human Services (HHS).

ACTION: Notice.

SUMMARY: This notice announces the revised procedures for volunteering to conduct research as part of the ATSDR Substance-Specific Applied Research Program authorized by the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA or Superfund), as amended. The procedures for conducting voluntary research were initially announced in the Federal Register on February 7, 1992 (57 FR 4758). The public was invited to comment on the procedures and the attendant Memorandum of Understanding (MOU). The voluntary research will be conducted by the private sector to fill priority data needs for hazardous substances that are the subjects of the ATSDR toxicological profiles. This notice describes the revised procedures.

DATES: The ATSDR considers this voluntary research effort to be of significant importance to the continuing development of the Substance-Specific Applied Research Program. Therefore, public comments concerning this Federal Register notice will be accepted throughout the Agency's involvement with voluntary research.

ADDRESSES: Comments on this notice should bear the docket control number ATSDR-61 and should be submitted to the Division of Toxicology, Research Implementation Branch, Agency for Toxic Substances and Disease Registry, Mailstop E-29, 1600 Clifton Road NE., Atlanta, Georgia 30333. Requests for a copy of the model Memorandum of Understanding should be addressed similarly.

Comments on this notice will be available for public inspection at the Agency for Toxic Substances and Disease Registry, Building 4, Suite 2400, Executive Park Drive, Atlanta, Georgia (not a mailing address), from 8 a.m. until 4:30 p.m., Monday through Friday, except for legal holidays.

FOR FURTHER INFORMATION CONTACT: Dr. William Cibulas, Division of Toxicology, Research Implementation Branch, Agency for Toxic Substances and Disease Registry, Mailstop E-29, 1600 Clifton Road NE., Atlanta, Georgia 30333, telephone 404-639-6306.

SUPPLEMENTARY INFORMATION:

Background

The Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA), as amended by the Superfund Amendments and Reauthorization Act of 1986 (SARA) [42 U.S.C. 9604(i)], requires that ATSDR: (1) Develop jointly with the Environmental Protection Agency (EPA) a list of hazardous substances found at National Priorities List (NPL) sites (in order of priority), (2) prepare toxicological profiles of these substances, and (3) assure the initiation of a research program to fill identified data needs associated with the substances.

The identification of the priority data needs for 38 priority hazardous substances was described in the Federal Register (56 FR 52178, October 17, 1991), public comments were invited, and companies were requested to volunteer to conduct research to fill specific priority data needs during the public comment period for that notice. The Federal Register notice, "Announcement of Final Priority Data Needs for 38 Priority Hazardous Substances", which includes a second call for private sector voluntarism, is being published in this issue of the Federal Register. Future Federal Register notices will announce the names of companies that have volunteered to fill specific priority data needs.

The major purpose of this ATSDR Substance-Specific Applied Research Program is to supplement the substance-specific information needs of the public and scientific community, and to supply necessary information for conducting comprehensive public health assessments for populations living in the vicinity of hazardous waste sites. This program will also provide data that can be generalized to other substances or areas of science, including risk assessments of chemicals, thus creating a scientific base for filling a broader range of data needs.

Procedure for Conducting Voluntary Research

CERCLA, as amended in section 104(i)(5)(D), states that it is the sense of Congress that the costs for conducting this research program be borne by the manufacturers and processors of the hazardous substances under the Toxic Substances Control Act (TSCA) and registrants under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), or by cost recovery from responsible parties under CERCLA. Furthermore, section 104(i)(5)(C) states that in developing and implementing the research program, the Administrator of ATSDR and the Administrator of EPA shall coordinate such program with the National Toxicology Program (NTP) and with programs of toxicological testing established under TSCA and FIFRA. To achieve this coordination, ATSDR established the Triagency Superfund Applied Research Committee (TASARC) as a forum for ATSDR, EPA, and NTP to discuss and coordinate use of potential mechanisms for developing and implementing this CERCLA Substance-Specific Applied Research Program. Meetings of the TASARC are not open to the public. The first meeting of TASARC was held on April 20, 1992, to inform the Committee on the Agency's progress in implementing the Substance-Specific Applied Research Program, and to seek the Committee's input in planning for the Agency's public meeting on voluntary research held on April 29, 1992.

The ATSDR encourages private sector organizations to conduct voluntary research to fill specific priority data needs identified in the Agency's Substance-Specific Applied Research Program. Toward that end, the procedures for conducting voluntary research, and the attendant Memorandum of Understanding, were developed by ATSDR and announced in the Federal Register on February 7, 1992 (57 FR 4758). The Agency is aware of concerns within some segments of the public regarding voluntary research conducted by companies with vested interests in the research. Therefore, the Agency encouraged the public to comment on ATSDR's procedure for conducting voluntary research. Additionally, for each research project conducted voluntarily, the MOU (signed by ATSDR and the interested company), the ATSDR approved study plan, peer reviewer's comments, and the final research report and supporting data will be available for public inspection at the location and times indicated in the ADDRESSES section of this notice.

ATSDR intends to enter into voluntary research projects in ways that lead only to high quality scientific work. This necessitates peer review of study protocols and results consistent with CERCLA section 104(i)(13). CERCLA requires the peer review panel to [illegible]

of three to seven peer reviewers who (a) are selected by the Administrator of ATSDR, (b) are disinterested scientific experts, (c) have a reputation for scientific objectivity, and (d) lack institutional ties with any person involved in the conduct of the study or research under review.

The ATSDR held a public meeting on April 29, 1992, to discuss the proposed procedures for voluntary research. Comments were received from industry groups, environmental groups and Federal agencies. As a result of discussions at these two meetings and other public comments received by the Agency, ATSDR has revised the voluntary research procedures. The major revisions and clarification of the procedures are described below.

ATSDR now believes that prior to negotiation of the study plan, it would be more appropriate to have a Letter of Intent submitted by the interested company, rather than to have the MOU signed by the interested company and the Agency as originally indicated. In the revised procedures, the interested company and ATSDR will enter into an MOU after the study plan has been approved by the Agency. Furthermore, the procedures will now indicate that ATSDR encourages innovative protocols, where appropriate. With respect to the role of peer review, ATSDR will continue to pursue its policy of peer review of both study protocols and results as mandated under CERCLA. However, to the extent that research protocols entail accepted test guidelines developed under TSCA, FIFRA or by organizations such as the Organization for Economic Cooperation and Development (OECD), less rigorous peer review of the study protocol may be required. Furthermore, the peer review process will not supersede the function of Institutional Review Board activities related to protection of human subjects or animals.

With respect to potential termination of the MOU at the convenience of either party, ATSDR intends that this action will be taken as a last resort, and that prior to such an action, all possible avenues of dialogue with the private sector organization would be pursued, within reasonable limits. However, decisions as to what constitutes a breach of the MOU will be at the discretion of ATSDR. Moreover, ATSDR recognizes that in the course of conducting research, unexpected and unanticipated delays may occur and wherever possible this will be negotiated with the private sector organization in the spirit of mutual cooperation.

The Agency is cognizant of the private sector's concern that EPA may require industry testing during or following a voluntary research effort with ATSDR which may be regarded as duplicative of that effort. There are several safeguards to prevent this from happening. First, ATSDR, EPA, and NTP are coordinating to conserve the testing resources of both the government and the private sector and avoid unnecessary or duplicative testing. This coordination occurs at many points: the review of ATSDR's toxicological profiles, review of ATSDR data needs documents, meetings of TASARC and the Interagency Testing Committee, and review of research proposals developed under ATSDR's voluntary research program. EPA intends to review research proposals developed under this program for conformity with basic testing concepts under TSCA, FIFRA, and the OECD.

Second, the Toxic Substances Control Act expressly requires EPA to find that data are inadequate to reasonably determine or predict the effects of a chemical substance. EPA has already interpreted this to mean that it cannot require duplicative testing. As a matter of policy EPA will not require testing in a rule which duplicates ongoing testing by government or the private sector pursuant to an MOU until the test data are submitted, reviewed and determined to be inadequate. There may be instances where research conducted under an industry/ATSDR MOU will yield results which indicate additional testing is necessary or where the testing under the MOU is not intended to address the endpoint of concern to EPA. In these cases, EPA may exercise its authority to require testing under TSCA or FIFRA.

It is generally the policy of ATSDR to rely on data and studies which are publicly available, with the exception of personally identifiable information on study projects. Therefore, research conducted under this program should be designed so as not to disclose Trade Secrets or other Confidential Business Information. If the company finds that such research is impossible to conduct under this restriction, ATSDR will enter into discussions of alternative solutions, or may choose to terminate negotiations.

Finally, in reference to research costs, the direct and indirect costs associated with the research program are those incurred by the research sponsor and not by ATSDR. The Agency will assume responsibility for administrative costs including the cost of peer review as part f its overall program.

The procedures for conducting voluntary research are described below.

Private sector organizations (companies) interested in volunteering to conduct research on priority data needs are asked to submit to ATSDR, in writing, a brief statement that addresses the priority data need(s) to be filled and the methods to be used. It should be noted that ATSDR encourages innovative protocols, where sppropriate. Therefore, the interested company should indicate when innovative protocols are being proposed. Interested companies may address substance-specific data needs or, where appropriate, propose to conduct research that will provide information relevant to classes of chemical substances or which may be generalized to other areas of science. It should be noted that all voluntary research conducted to fill ATSDR's priority data needs should comply with the Department of Health and Human Services' Laboratory Animal Welfare Act of 1966 (Pub. L. 89–544, as amended, 7 U.S.C. 2131 et seq.) or Protection of Human Subjects (45 CFR part 46).

The interested company's statement will be reviewed by TASARC. Based on TASARC's recommendations, ATSDR will determine which, and how, specific voluntary research projects will be pursued with volunteering companies. In instances where volunteered research initiatives are considered by TASARC to be more appropriate for EPA response, EPA may negotiate directly with the interested company.

If ATSDR decides to pursue a specific voluntary research project submitted by a company, the Agency will request the company to forward a Letter of Intent within four weeks of the approval of the company's statement. The Letter of Intent should indicate that the company is prepared to enter into discussion with ATSDR regarding the research plan to fill a specific data need identified by the ATSDR Substance-Specific Applied Research Program. Furthermore, the Letter of Intent will state that if the research plan is approved by ATSDR, the company will negotiate an MOU with ATSDR prior to initiation of the research.

The Agency recognizes that two or more companies or a consortium of interested firms may elect to enter into collaborative efforts in pursuing one or more research projects, therefore, where appropriate, a single MOU will be signed between ATSDR and multiple companies. Following the submission of the Letter of Intent and prior to the initiation of the research, the interested company will negotiate with ATSDR to agree upon an approved study plan including testing protocols and time schedules.

The company shall submit to ATSDR a study plan for each test six weeks after submitting the Letter of Intent. The study plan shall include test protocols and a schedule with reasonable timetable and deadlines for initiation and completion of each test and submission of interim and final reports. The test protocols will be reviewed by an ATSDR-appointed peer review panel. If ATSDR disapproves the study plan, it will inform the company of the deficiencies of the plan. The company may request reconsideration of the study plan, resubmit a modified study plan, or elect to terminate further discussion on the proposed research with no obligation of either party. In the event that the company resubmits a modified study plan and ATSDR disapproves it, the Agency may elect to terminate further discussion.

If the study plan is approved by ATSDR upon the recommendations of the peer reviewers, the company will enter into an MOU with the Agency. The content of the MOU is described below:

(1) Identification of the party or parties comprising the company which enters into the MOU—This section consists of the name and address of each party responsible for the conduct of the research.

(2) Identification of the substance(s) subject to research requirements under the MOU—This section consists of the name and Chemical Abstract Service (CAS) Number of the chemical substance(s) that is the subject of the MOU. The chemical substance(s) to be tested shall be as pure as reasonably can be attained. However, under certain circumstances, ATSDR recognizes that it may be more desirable to test mixtures or technical grade products. Furthermore, alternate language will be substituted when the subject of the research is a human population, as in epidemiologic studies.

(3) Identification of the effects or characteristics for which research is to be conducted—In this section, the health effects, environmental fate or other characteristics for which research is to be conducted under the MOU shall be listed.

(4) Initiation of Research and Submission of Interim and Final Reports—The starting date of the research project may be negotiated depending on the type of research being conducted. However, as a general guideline, the research effort shall be initiated within eight weeks of the approval of the study plan and attendant test protocols, and the signing of the MOU. Written notification of the starting date of the test will be submitted to ATSDR by the company. The testing schedule and completion date of the study will be established from the approved study plan. Interim progress reports shall be submitted to ATSDR within six months after the initiation of testing and thereafter within six months after submission of each previous interim report. The final report on the results of testing shall be submitted to ATSDR no more than 20 weeks following the end of the study. Final reports will not be accepted if the data are designated Confidential Business Information (CBI) or otherwise restricted from public disclosure, with the exception of personally identifiable information on study subjects. Moreover, ATSDR's acceptance of the final report will be contingent upon approval by ATSDR following the peer reviewers' recommendations, consistent with CERCLA section 104(i)(13) peer review requirements. All results of research conducted pursuant to the MOU and all supporting data associated with the research report will be provided to ATSDR and made available by the Agency to the public as part of its implementation of sections 104(i)(3) and (5) of CERCLA.

(5) Modifications of study plans, guidelines, and schedules—If a company intends to modify a study plan, protocol, or schedule that was approved by ATSDR, it must notify ATSDR in writing of the proposed modifications and reasons therefor. If ATSDR approves of the modifications, the time schedule established for completion of the tests shall be re-negotiated and appended to the existing MOU. If ATSDR disapproves the company's request and the company does not accept ATSDR's decision to disapprove the modified study plan, the company may terminate the MOU.

(6) Observance of Good Laboratory Practices—All research agreed to in the MOU shall be conducted in accordance with the Good Laboratory Practice (GLP) standards codified in 40 CFR part 792, to the extent that such GLP standards apply. Should Good Epidemiology Practices ("Guidelines for Good Epidemiology Practices for Occupational and Environmental Epidemiologic Research"—The Chemical Manufacturer Association's Epidemiology Task Group, Journal of Occupational Medicine, Volume 33, 1221–1229, 1991) be relevant to a research project, those Practices should be affixed to the study protocol.

(7) Inspections—The company shall ensure that authorized employees of ATSDR are permitted, at reasonable times and in a reasonable manner, to (i) inspect any research or testing facilities that is conducting research pursuant to the MOU, and (ii) inspect (and in the case of records, copy) any records or specimens required to be maintained in connection with research performed pursuant to the MOU.

(8) Submission and publication of data—All data and reports submitted to ATSDR pursuant to the MOU shall be sent to ATSDR, in duplicate, at the address indicated in the ADDRESSES section. Final reports will not be accepted if the data is designated Confidential Business Information (CBI) or otherwise restricted from public disclosure. Furthermore, acceptance of the final report is contingent upon approval by ATSDR following the peer reviewers' recommendations, consistent with CERCLA peer review requirements. The company maintains all rights to publication of data and results, however all results of research conducted pursuant to the MOU and all supporting data associated with the final research report will be provided to ATSDR and made available by the Agency to the public as part of its implementation of section 104(i)(5) of CERCLA.

(9) Payments of costs and expenses—Each company shall agree to pay all costs, direct and indirect, associated with the research programs. The Agency will assume responsibility for administrative costs including the cost of peer review as part of its overall program.

(10) Events constituting a breach of the MOU—Failure by the company to:

(a) Initiate any test agreed to in the MOU by the date established pursuant to the MOU;

(b) Adhere to GLP standards, established test procedures or accepted practices of good science to the extent that these standards and practices apply;

(c) Submit any interim report required under the MOU by the date established pursuant to the MOU; or

(d) Submit any final report that receives ATSDR's approval following peer review conducted by the Agency, shall constitute a breach of the MOU. In the event of a breach, ATSDR will not impose any claim to damages, but at the Agency's discretion may terminate the MOU.

For research completed subsequent to termination of an MOU, or termination of negotiations in anticipation of an MOU, companies may not represent endorsement of such research by ATSDR based on ATSDR's approval of a study protocol, plan or other aspect of the research.

(11) Termination—Since the MOU is entered into voluntarily by ATSDR and the company, termination by ATSD

not considered reviewable agency action pursuant to the Administrative Procedures Act or any other applicable Federal law, and there will be no appeal process beyond that set out in the MOU. The company may elect to terminate the MOU at any time.

(12) Statutory compliance—Consistent with section 104(i)(12) of CERCLA, as amended (42 U.S.C. 9604(i)(12)), nothing in the MOU shall be construed to delay or otherwise affect or impair the authority of the President, the Administrator of ATSDR or the Administrator of EPA to exercise any of their authority under any other provision of law, or the response and abatement authorities of CERCLA.

As previously stated, EPA is not currently planning to participate as a potential signatory in MOU negotiations arising from this Notice. However, if EPA were to participate, the contents described above would need to be appropriately revised to reflect commitments made by or to EPA, and other matters deemed appropriate by the parties.

The results of the research via this ATSDR Substance-Specific Applied Research Program will be used for public health assessment purposes and to reassess ATSDR's substance-specific priority data needs. It is the intention of the Agency, at this time, to re-evaluate the priority data needs for the listed hazardous substances every three years.

Dated: November 6, 1992.

William L. Roper,

Administrator, Agency for Toxic Substances and Disease Registry.

[FR Doc. 92-27639 Filed 11-13-92; 8:45 am]

BILLING CODE 4160-70-M