TOXICOLOGICAL PROFILE FOR
TETRYL

(2,4,6-Trinitrophenyl-N-methylnitramine)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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Agency for Toxic Substances and Disease Registry

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and the Environmental Protection Agency (EPA) and in support of Department of Defense information needs. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, when known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are significant to protect public health will be identified by ATSDR and the EPA. The focus of the profiles is on health and toxicologic information; therefore, we have included this information in the beginning of the document.

Each profile must include the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects.

(C) When appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that might present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public.

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). Section 211 of SARA also amended Title 10 of the U. S. Code, creating the Defense Environmental Restoration Program. Section 2704(a) of Title 10 of the U. S. Code directs the Secretary of Defense to notify the Secretary of Health and Human Services of not less than 25 of the most commonly found unregulated hazardous substances at defense facilities.

Section 2704(b) of Title 10 of the U. S. Code directs the Administrator of the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare a toxicological profile for each substance on the list provided by the Secretary of Defense under subsection (b).

Foreword

This profile reflects our assessment of all relevant toxicologic testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control and Prevention (CDC), and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Border review assures consistency with ATSDR policy.

2. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

3. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

4. Quality Assurance Review. The Quality Assurance Branch assures that consistency across profiles is maintained, identifies any significant problems in format or content, and establishes that Guidance has been followed.

PEER REVIEW

A peer review panel was assembled for tetryl. The panel consisted of the following members:

1. Dr. Tim Borges, Technical Information Analyst, Oak Ridge National Laboratories, Oak Ridge, Tennessee;

2. Dr. Lawrence Holland, Private Consultant, Los Alamos, New Mexico; and

3. Dr. Theodore Mill, SRI International, Menlo Park, California.

These experts collectively have knowledge of tetryl's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about tetryl and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,397 hazardous waste sites as the most serious in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal clean-up activities. Tetryl has been found in at least 12 of the sites on the NPL. However, the number of NPL sites evaluated for tetryl is not known. As EPA evaluates more sites, the number of sites at which tetryl is found may increase. This information is important because exposure to tetryl may cause harmful health effects and because these sites are potential or actual sources of human exposure to tetryl.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking substances containing the substance or by skin contact with it.

If you are exposed to a substance such as tetryl, many factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, gender, nutritional status, family traits, life-style, and state of health.

1.1 WHAT IS TETRYL?

Tetryl is a synthetic substance that was used to make explosives, mostly during World War I and World War II. It is no longer manufactured or used in the United States. The chemical name for tetryl is N-methyl-N,2,4,6-tetranitroaniline. Other commonly used names are 2,4,6-trinitrophenyl-N-methylnitramine, nitramine, tetralite, and tetril. Stocks of tetryl are

1.PUBLIC HEALTH STATEMENT

found in storage at military installations and are being destroyed by the Department of Defense. Tetryl was frequently manufactured as pellets or powder. Under certain manufacturing conditions, it could exist in the air as a dust. Tetryl is a yellow, crystal-like solid at room temperature. It dissolves slightly in water. It can also dissolve in other liquids, including benzene, alcohol, and acetone. At temperatures of 369 °F (187 °C) or higher, tetryl will explode. Tetryl has no odor, but some of its manufactured forms may have odors due to the presence of other chemicals. In addition, high concentrations of tetryl dust have an irritating effect on the nose that produces a sensation that might seem to be an odor. See Chapters 3 and 4 for more information on what tetryl is and how it is used.

1.2 WHAT HAPPENS TO TETRYL WHEN IT ENTERS THE ENVIRONMENT?

Tetryl may be released to the air, water, and soil when old stores of the explosive are destroyed by exploding or burning. However, tetryl has not been measured in air during any of these activities. Tetryl that was manufactured or stored at military installations, like Army ammunition plants, may still be present in the soil and water at or around these sites. Tetryl is not likely to evaporate into air from water or soil surfaces. However, tetryl may be present in air associated with dust from these sites. Tetryl appears to break-down rapidly in some soils. Picric acid, is one of the break down products of tetryl in soil. Tetryl probably does not easily travel from soil to groundwater. Erosion of soil from contaminated sites may release tetryl to nearby surface water. Once it is in the water, tetryl may dissolve or associate with small particles of suspended solids, sediments, or organic debris. Some of these particles will settle to the bottom. Tetryl breaks down rapidly in sunlit rivers and lakes but much more slowly in groundwater. It is not known whether tetryl will build up in fish, plants, or land animals. See Chapters 4 and 5 for more information on tetryl in the environment.

1.3 HOW MIGHT I BE EXPOSED TO TETRYL?

Most people are not exposed to tetryl because contamination is localized around military installations where it was manufactured, used, or stored. Tetryl can move through soil and enter underground water. If you live at or near one of these installations with tetryl contamination, you may be exposed to tetryl by drinking contaminated well water. You may also be exposed to tetryl by skin contact with contaminated soil or water. Workers who were previously involved in the processes of making, using, packing, or loading tetryl were probably exposed to tetryl by breathing contaminated dust and through skin contact. Workers currently involved in the clean-up, disposal, and destruction of tetryl may also be exposed by these routes. We do not know how many workers are exposed to tetryl.

Tetryl has been found in soil and water at some military installations, such as Army ammunition plants, and in underground water at one site located near a military installation. See Chapter 5 for more information on exposure to tetryl.

1.4 HOW CAN TETRYL ENTER AND LEAVE MY BODY?

Tetryl can enter your body if you breathe it in the air, drink it in water, or get it on your skin. We do not know the extent to which tetryl enters your body by these routes. Based on limited information from animal studies, tetryl probably leaves your body in urine after being broken down to other substances. See Chapter 2 for more information on how tetryl enters and leaves your body.

1.5 HOW CAN TETRYL AFFECT MY HEALTH?

Most of the information on the health effects of tetryl is from studies on workers employed in military facilities during World War I and World War II. These workers were involved in the production, use, packing, or loading of tetryl. The levels of tetryl in air at these facilities were often not measured. Many workers who breathed tetryl-laden dust complained of coughs, fatigue, headaches, eye irritation, lack of appetite, nosebleeds, nausea, and/or vomiting. Most workers who routinely handled tetryl powder and pellets in munitions factories developed a distinct yellow staining of the hands, neck, and hair. Workers with this staining were sometimes referred to as “canaries.” Many workers who had skin contact with tetryl dust or compounds containing tetryl also developed skin rashes (dermatitis). The rashes ranged from mild to severe and symptoms often included reddening, itching, swelling, and peeling of skin. Most of these health effects usually developed within a few days to a few weeks after exposure to tetryl. Some workers were more sensitive to tetryl exposure and developed allergies to tetryl. These often included severe asthma-like reactions that sometimes required medical attention or hospitalization. Workers who developed allergies to tetryl had reactions within a few hours after being exposed again to tetryl. Many of these workers were moved to work areas where there was no tetryl. Little is known about the longer term health effects in workers exposed to tetryl.

There is no information on health effects in humans exposed to drinking water contaminated with tetryl. Rabbits fed high doses of tetryl every day for 6 to 9 months developed degenerative lesions of the liver and kidney. Decreased blood-clotting capability and changes in the spleen were also noted. We do not know if tetryl causes cancer or birth defects, or if it affects reproduction in humans or animals. The Department of Health and Human Services, the International Agency for Research on Cancer, and the Environmental Protection Agency have not classified the carcinogenicity of tetryl. For more information on health effects, see Chapter 2.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO TETRYL?

During World War I and World War II, most workers who routinely handled tetryl powder and pellets in munitions factories developed a distinct yellow staining of the skin. Many workers also developed skin rashes. These workers were exposed to high concentrations of tetryl dust in the air and by direct contact with the explosives. There are no medical tests to show if you have been specifically exposed to tetryl. However, if the breakdown products of tetryl found in the urine of animals exposed to tetryl were also present in the urine of exposed humans, these breakdown products could be used to indicate exposure to tetryl or similar substances. The symptoms caused by exposure to tetryl can also occur for many other reasons; therefore, they cannot be used as proof of tetryl exposure. Refer to Chapters 2 and 6 for more information.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government has developed standards and guidelines to protect people from the health effects of tetryl. The Department of Transportation has many regulations for the transportation of explosives such as tetryl. Although tetryl is no longer being manufactured or used, the Occupational Safety and Health Administration (OSHA) has set a regulatory level for tetryl in the workplace. The maximum allowable amount of tetryl in workroom air during an 8-hour workday, 40-hour workweek, is 1.5 milligrams of tetryl per cubic meter of air (mg/m^3). This level may apply to workers engaged in destruction of tetryl explosives and those who work in locations where tetryl is stored. The National Institute for Occupational Safety and Health recommends that workers not be exposed to air containing more than 1.5 mg/m^3 during a 10-Hour workday. For more information on federal and state recommendations, see Chapter 7.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333
(404) 639-6000

This agency can also provide you with information on the location of the nearest occupational and environmental health clinic. These clinics specialize in the recognition, evaluation, and treatment of illness resulting from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of tetryl. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposureinhalation, oral, and dermal-and then by health effect-death, systemic, immunological/lymphoreticular, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods-acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

The existing database on tetryl is quite limited. Most of the information on health effects comes from case studies and reports on the health of workers employed in tetryl munitions plants during World War I and World War II. The levels of tetryl to which these workers were exposed were generally not reported. Few data exist from animal studies with tetryl. None of the data located were reliable enough to determine levels of significant exposure (LSE). Because of this, estimates of levels posing minimal risk to humans (Minimal Risk Levels, or MRLs) could not be derived.

2.2.1 Inhalation Exposure

The only studies located regarding health effects in humans after inhalation exposure to tetryl were case studies and other reports of workers exposed to tetryl dusts in manufacturing plants during World War I and World War II. Little information was available regarding the number of people exposed or the duration and level of exposure. Since exposure was to the tetryl-laden dusts, the effects could have been caused by inhalation, direct skin contact, or by swallowing. The dermal effects noted in these studies were most likely caused by direct skin contact and are described in Section 2.2.3. It is unknown whether the other effects were caused by inhaling or by swallowing tetryl; therefore, in this profile, it is assumed that the primary route of exposure was inhalation.

One study, which investigated skin and anaphylactic reactions of guinea pigs sensitized by inhalation of tetryl smoke (Gel1 1944), is discussed below. No other health effects were studied in animals.

2.2.1.l Death

Only two studies reporting death in humans were located. One study reports about two men who died approximately 3-5 years after exposure to tetryl dusts in a manufacturing plant (Hardy and Maloof 1950). Air samples taken in 1942, the only period for which exposure data were provided, ranged from 1 to 18 mg/m^3. The period of exposure for the 2 men ranged from 1 to 4 years. Both men complained of general symptoms, such as cough, fatigue, and weight loss, during and after the time they worked with tetryl. In both cases, death was attributed to liver failure, but the specific cause of the liver failure was difficult to determine. In one case, the liver failure was considered to be due to advanced hepatitis or cirrhosis, but rheumatic heart disease was also present. In the other case, symptoms were consistent with chemically-induced cirrhosis. A hepatoma that was observed at autopsy was considered a possible result of the cirrhosis. Neither subject had a history of excessive alcohol intake. One woman employed for approximately 2 years in a munitions factory in England died following clinical symptoms of toxic jaundice (Troup 1946). Autopsy revealed atrophy of the liver with distortion of the upper parts of the liver. Work subsequent to leaving the munitions factory and prior to death involved handling of closed containers of chlorinated naphthalenes. None of these deaths can be unequivocally attributed to tetryl; the possibility of complicating medical conditions and/or exposure to other toxic chemicals could also have been contributing factors in the deaths.

One of eight guinea pigs exposed to a tetryl smoke died of an anaphylactic reaction when later challenged with a picrylgelatin antigen which had a structure similar to suspected tetryl metabolites (Gel1 1944).

2.2.1.2 Systemic Effects

No studies were available regarding cardiovascular, musculoskeletal, renal, dermal or ocular effects in humans after inhalation exposure to tetryl. Dermal effects, presumably from direct skin contact, are described in Section 2.2.3.2. No studies were located regarding systemic effects in animals after inhalation exposure to tetryl. The systemic effects that have been observed after inhalation exposure in humans are described below.

Respiratory Effects. Workers exposed to tetryl dusts often complained of throat and nasal irritation consisting of dryness, burning, sneezing, nosebleeds, and coughing (Bergman 1952; Cripps 1917; Eddy 1943; Fischer and Murdock 1946; Hardy and Maloof 1950; McConnell et al. 1946; Murray et al. 1944; Probst et al. 1944; Smith 1916; Witkowski et al. 1942). In susceptible individuals, these symptoms were reported to occur within a few hours to a few weeks (Probst et al. 1944; Witkowski et al. 1942). Coughing generally occurred during exposure to tetryl but also occurred at night in some workers. In most cases, the symptoms disappeared within a few days after removal from tetryl exposure (Hardy and Maloof 1950; Probst et al. 1944; Witkowski et al. 1942). The throat and nasal symptoms were probably due to the irritating effect of inhaled dust particles on mucosal membranes (McConnell et al. 1946; Probst et al. 1944; Witkowski et al. 1942).

Two workers developed an asthma-like condition within a few weeks of being exposed to tetryl (Eddy 1943). Asthma-like symptoms (severe spasmodic coughing and wheezing) were reported in 6 of 11 workers involved in the manufacture of tetryl explosives (Hardy and Maloof 1950). Similar symptoms have been reported by other investigators (Cripps 1917; Smith 1916). Some workers complained of difficulty breathing after leaving the workplace (Cripps 1917). One of 11 workers in a munitions factory was diagnosed as having emphysema and fibrosis of the lungs several years after leaving the manufacturing plant, but the disease in this worker could not be clearly linked to tetryl exposure (Hardy and Maloof 1950). X-ray examinations revealed no evidence of lung damage in 4,000 workers exposed to tetryl (Hatch and Probst 1945). The authors attributed this to the large size of the airborne particles of tetryl in their facility. No pulmonary pathology was observed in chest X-rays of approximately 981 workers employed in a shell loading plant, although these subjects were exhibiting respiratory symptoms (cough, nasal and throat irritation, epistaxis) believed to be associated with tetryl exposure (Fisher and Murdock 1946). X-ray examinations of about 800-900 workers employed in the tetryl area of a manufacturing plant revealed no pulmonary conditions att'ributable to tetryl powder (Probst et al. 1944).

Gastrointestinal Effects. Workers exposed to unspecified levels of tetryl dusts in the workplace for unspecified durations occasionally complained of nausea, vomiting, or abdominal cramps (Bergman 1952; Cripps 1917; Fischer and Murdock 1946; Hardy and Maloof 1950; Hilton and Swanston 1941; Murray et al. 1944; Troup 1946; Witkowski et al. 1942). These effects may have been due to direct gastric irritation from swallowing tetryl-laden dusts. These effects generally occurred within the first two weeks of exposure and, according to some reports, were more common in workers who had not eaten adequately (Bergman 1952; Witkowski et al. 1942). No other information was available.

Hematological Effects. There are a few studies that examined hematological effects in workers exposed to tetryl dusts. Examinations of an unspecified number of operators engaged in the making and cleaning of tetryl pellets revealed many cases of slight leukocytosis and increased levels of lymphocytes (incidences not reported) and two cases of decreased red blood cells (Cripps 1917). Other symptoms exhibited by the subjects and the total number of subjects involved in the study were not specified. Three of 37 workers exposed to tetryl had slight variations in the size of red corpuscles, and an additional three had an increase in polymorphonuclear white blood cells when blood films were examined (Ruxton 1917). The author did not consider these changes to be related to tetryl exposure. Slight decreases in hemoglobin concentration and white blood cell counts were also reported in exposed workers (number exposed and exposure details not reported) who complained of loss of appetite, slight nausea, malaise, and sleeplessness (Brabham 1943). A later study of 800-900 workers reported that incidences of leukocytosis and leukopenia were not related to type or duration of tetryl exposure, symptoms, or complaints (Probst et al. 1944). The 4% incidence of anemia found in the study was considered to be within normal limits by the autnors, although no control values were used for comparison. Moderate secondary anemia was diagnosed in a small number of workers exhibiting tetryl dermatitis (<l% of 3,807 cases), but this incidence did not differ from that found in tetryl workers exhibiting symptoms other than dermatitis (<1% of 1,962 cases) or from that found in unexposed workers (Fischer and Murdock 1946). Anemia was diagnosed in a female tetryl operator following nine days of hospitalization for treatment of a severe tetryl-induced dermatitis (Witkowski et al. 1942). These authors stated that anemia was a common effect of tetryl exposure in munitions plants but presented no incidence data. An increased incidence of anemia was not observed in workers employed at Picatinny Arsenal (Dover, New Jersey) during 1941-1950 (size of the study population was not reported) (Bergman 1952). These studies are limited by the lack of control groups and/or values, incomplete hematological data, possible concomitant exposure to other chemicals, and the subjective nature of the reports. None of the studies examined changes in blood-clotting ability. The limitations and the differences in end points examined in the studies make it difficult to determine which hematological effects are most likely to occur in humans. There is no conclusive evidence to associate anemia with exposure to tetryl.

Hepatic Effects. Liver failure was reported in two of thirteen workers who died several years following exposure to tetryl dust in a plant that manufactured explosives (Hardy and Maloof 1950). In one case, the liver showed signs of advanced hepatitis or cirrhosis on autopsy. No history of excessive alcohol intake was noted, but evidence of rheumatic heart disease was present. The second subject had cirrhosis of the liver, and a hepatoma was found at autopsy. The authors considered the findings to be consistent with repeated chemical intoxication leading to cirrhosis and development of hepatoma. No history of excessive alcohol intake was noted in this subject. Jaundice, possibly toxic in origin, was reported in two women who worked in a munitions factory in England (Troup 1946). The total number of people exposed to tetryl in this factory was estimated to be about 5,000. In both cases, the period of exposure was slightly less than 2 years. In one of the subjects, excess urobilinogen, urobilin, and bile pigment were found in the urine. In the second case, which resulted in death, atrophy of the liver and distortion of the upper parts of the liver were found at autopsy. Subsequent to her employment as a tetryl worker, the subject was employed in a factory in which she handled closed containers of chlorinated naphthalene. In a third study, workers exposed over a 35-month period to tetryl dusts showed no evidence of liver injury, but details regarding the tests conducted were not provided (McConnell et al. 1946).

Body Weight Effects. Weight loss was reported in three workers exposed to tetryl for 14 years during the manufacture of explosives (Hardy and Maloof 1950). Anorexia was reported in three of eight workers similarly exposed to tetryl for a year or more (Hardy and Maloof 1950). Anorexia and weight loss have been reported by other authors as well (Brabham 1943; Fischer and Murdock 1946; Troup 1946; Witkowski et al. 1942) and may affect as many as 10% of exposed workers (Witkowski et al. 1942). Any role of tetryl in causing these effects could not be determined because details of exposure, past medical histories, and exposure to other chemicals were not reported.

2.2.1.3 Immunological and Lymphoreticular Effects

No studies which specifically examined immunologic end points in humans exposed to tetryl were located. However, asthma-like symptoms (severe spasmodic coughing, wheezing, and difficulty breathing) and a reaction similar to hay fever observed in susceptible individuals exposed during the manufacture of tetryl-containing explosives indicate that an immunologic response may occur following inhalation of tetryl-contaminated dust (Cripps 1917; Eddy 1943; Smith 1916). Although the respiratory effects have generally been attributed to the local irritative properties of tetryl dust (Bergman 1952; Cripps 1917; McConnell et al. 1946), in some cases the symptoms seemed to be associated with hypersensitivity to tetryl (Fischer and Murdock 1946; Probst et al. 1944). Acute asthma-like attacks have been controlled by administration of adrenalin (Eddy 1943). In one study, sympathomimetic drugs (e.g., ephedrine or amphetamine sulfate) were reported to control the respiratory effects associated with tetryl exposure better than an antihistamine (Bain and Thomson 1954). In the absence of definitive immunologic studies, it is difficult to determine the specific role of the immune system in tetryl toxicity.

Eight guinea pigs were exposed to a particulate smoke of tetryl made by blowing air over a 10% solution of tetryl in acetone (Gel1 1944). The estimated tetryl concentration in the exposure chamber was about 400 mg/m^3 and the animals were exposed 30 minutes per day for 6 days out of 14. Total absorption was estimated to be about 7-10 mg per animal. Six of the guinea pigs developed anaphylactic sensitivity to picrylgelatin antigen (Gel1 1944). Picrylgelatin was chosen as the antigen because prior testing with different possible metabolites of tetryl (picric acid among them) and protein analogs of tetryl and its metabolites indicated that the 2,4,6-trinitrophenylamino group (present in both tetryl and picric acid) was the primary antigenic determinant in the immune response to tetryl. Induced tetryl sensitivity in females exposed by inhalation was tested using an *in vitro* challenge method, and three of four responded positively in this test. Three of four males exposed to tetryl vapors and challenged with an intravenous dose of the antigen showed signs of anaphylaxis. In one, the reaction was severe enough to cause death. The experiment was limited by the use of whole-body animal exposure, the use of only a small number of exposed animals and the absence of a control group, the use of acetone as the solvent in the generation of the tetryl smoke, and the imprecise methods used to generate and measure the tetryl smoke. The overall evidence indicates that inhaled tetryl may initiate an immune response.

2.2.1.4 Neurological Effects

Workers exposed to unspecified levels of tetryl dusts for unspecified durations occasionally complained of increased irritability, headaches, nausea, vomiting, fatigue, or insomnia (Bergman 1952, Brabham 1943; Cripps 1917; Hardy and Maloof 1950; Murray et al. 1944; Witkowski et al. 1942). No other information was available.

2.2.1.5 Reproductive Effects

Only two reports were located that discussed possible effects of tetryl on the reproductive system. Two women employed in a plant that manufactured explosives containing tetryl during World War II (concentrations of tetryl dust and exposure duration were not given) reported increased durations between menstrual cycles and amenorrhea (Hardy and Maloof 1950). In contrast, decreased intervals between menstrual cycles and/or increased duration of flow were reported in women who worked with tetryl powder or pellets (Cripps 1917). The total population examined and the incidence within this population were not reported; however, of 30 individual cases discussed, four individuals reported excessive menstruation. It is not possible to draw conclusions regarding the effect of tetryl on the menstrual cycle because these reports described opposite effects, had few subjects, failed to describe pertinent health histories or exposure to other chemicals, and provided few details. No other data on effects to the reproductive system were located.

No studies were located regarding the following health effects in animals or humans after inhalation exposure to tetryl:

2.2.1.6 Developmental Effects

2.2.1.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

2.2.2 Oral Exposure

No studies were located regarding effects in humans after exposure to tetryl in food or drinking water. However, workers exposed to tetryl dusts in the air may have swallowed some of the larger particles. Because the primary exposure route for these workers was considered to be inhalation, these studies were discussed in Section 2.2.1.

A limited number of studies in animals exposed to tetryl via the oral route were located. These describe the acute effects of tetryl on rats (Parmeggiani et al. 1956) and rabbits (Wells et al. 1920), the effects in rabbits administered tetryl by gavage for 2 months (Guarino and Zambrano 1957) or 6-9 months (Daniele 1964; Fati and Daniele 1965), and the carcinogenicity of tetryl in rats treated by gavage for 30 days (Griswold et al. 1968).

2.2.2.1 Death

Groups of rats administered 1 or 2 g/kg/day by gavage died between 10 and 18 days after dosing started (Parmeggiani et al. 1956); the specific cause of death was not provided. Rabbits given 1,000 mg/kg/day in milk by gavage died after l-3 doses (Wells et al. 1920). This study was limited by the lack of a control group, use of only a single exposure concentration, and absence of microscopic data. No other details were provided. An additional study in rabbits reported that the mean survival time of 20 rabbits treated orally with 25 mg/kg/day was 2 months (Guarino and Zambrano 1957). No controls were used and no information was provided regarding the cause of death.

2.2.2.2 Systemic Effects

No studies were located regarding musculoskeletal, or ocular effects in animals after oral exposure to tetryl. The systemic effects that have been observed in animals after oral exposure are described below.

Respiratory Effects. Edema of the lungs and bronchi were observed in rabbits treated orally with l-3 doses of 1,000 mg/kg (Wells et al. 1920). This dose level was lethal and no other dose level was tested. Rabbits treated with daily doses of 25 mg/kg/day for up to 3 months exhibited gross and microscopic signs of congestion in their lungs (Guarino and Zambrano 1957). In contrast, no.gross or histological alterations were observed in the lungs of 12 rabbits treated orally with doses of 125 mg/kg/day for 6-9 months (Fati and Daniele 1965). In both studies, a control group was not used and no other dose level was tested. No other respiratory end points were assessed. The reason for the discrepancy between the results from Guarino and Zambrano (1957) and those from Fati and Daniele (1965) is unknown. Dyspnea was reported in rats treated orally with 1 or 2 g/kg/day; these doses killed the rats in 10-18 days (Parmeggiani et al. 1956).

Cardiovascular Effects. No gross or histological alterations were noticed in the hearts of rabbits treated orally with doses of 125 mg/kg/day for 6-9 months (Fati and Daniele 1965). A control group was not used, and no other dose level was tested. No other cardiovascular end points were monitored. No gross alterations, and no significant histological alterations were observed in rats treated with 25 mg/kg/day for up to 3 months (Guarino and Zambrano 1957), but moderate vascular congestion was noted. This study did not examine a control group and only one dose level was tested.

Gastrointestinal Effects. No gross or histological alterations were seen in the gastrointestinal mucosa of rabbits treated orally with 25 mg/kg/day for up to 3 months (Guarino and Zambrano 1957) or with 125 mg/kg/day for 6-9 months (Fati and Daniele 1965). Neither study used a control group and in both studies only one dose level was tested. No further details were provided.

Hematological Effects. Administration of 125 mg/kg/day to 12 rabbits for 120 days resulted in some statistically significant changes in blood parameters compared to controls (3 rabbits) (Daniele 1964). These changes, which suggested a coagulation disorder, were inconsistent and showed no increase in severity with time. The small numbers of animals used and the inconsistent results make i difficult to unequivocally attribute the observed effects to tetryl exposure. Accumulation of hematic pigments in the spleen was noted in rabbits administered a lethal dose of 1,000 mg/kg/day for l-3 doses (Wells et al. 1920) and rabbits administered 125 mg/kg/day for 6 months (Fati and Daniele 1965).

Hepatic Effects. The cytoplasm of the hepatocytes of rats that received 1 or 2 g/kg/day by gavage (death occurred in 10-18 days) had a granular appearance and the nuclei were polymorphous and pyknotic (Parmeggiani et al. 1956); frequent activation of Kupffer cells was also observed. Rabbits that received 1,000 mg/kg/day for l-3 days had normal livers at necropsy. No other relevant information was provided (Wells et al. 1920). The livers of rabbits treated with 25 mg/kg/day (a dose that was lethal to 18 of 20 rabbits) for up to 3 months were congested and yellowish in color (Guarino and Zambrano 1957). Microscopic examination revealed swelling of the epithelium, fatty infiltration, and necrotic foci. Similar observations were made in the livers of 12 rabbits administered 125 mg/kg/day for 6 months (Fati and Daniele 1965). In 4 of the rabbits treated for an additional 3 months, there was congestion of the liver. Microscopic examination revealed more severe damage of the hepatocytes than was observed at 6 months, including necrosis and hyperplasia of the Kuppfer cells. These studies in rabbits were limited by the small number of animals used in the treated groups, the absence of a control group, and by the use of only one dose level.

Renal Effects. Rats that received 1 or 2 g/kg/day (death occurred in 10-18 days) had frank kidney lesions which included swollen tubular epithelium, unrecognizable cytoplasmic structures, pyknotic nuclei, and obliterated tubular lumen (Parmeggiani et al. 1956). Rabbits that received 1,000 mg/kg/day for l-3 days had swelling and degeneration of the epithelium of the kidneys. No other relevant information (e.g., number of animals and whether or not controls were used) was provided (We& et al. 1920). Rabbits treated with 25 mg/kg/day for up to 3 months (this dose killed 18 of 20 rabbits before 3 months) showed renal congestion, lesions to the parenchymal tissue, and swelling and vacuolar degeneration of the convoluted tubules (Guarino and Zambrano 1957). Three of 4 rabbits administered 125 mg/kg/day for 9 months had slight congestion of the kidneys with cloudy swelling and vacuolar degeneration of the convoluted tubules on microscopic examination (Fati and Daniele 1965). Six rabbits treated similarly, but for only 6 months, showed no signs of toxicity; this is in conflict with the results of Guarino and Zambrano (1957), but no explanation is apparent from data presented in these studies. The studies in rabbits were limited by the absence of a control group, and by the use of only one dose.

Dermal Effects. The only information regarding dermal effects after oral administration of tetryl to animals is that rats treated with 1 or 2 g/kg/day by gavage exhibited rough coat and a yellow pigmentation in the nose, ears, and tail (Parmeggiani et al. 1956). These dose levels caused death in 10-18 days.

Body Weight Effects. Rats that received 1 or 2 g/kg/day by gavage experienced a steady and significant body weight loss accompanied by anorexia until death occurred 10-18 days after dosing began (Parmeggiani et al. 1956). No further information was available.

2.2.2.3 Immunological and Lymphoreticular Effects

Rats given 2 g/kg/day by gavage for up to 18 days had moderate hemosiderosis in the spleen and also exhibited atrophy of lymphatic follicles (Parmeggiani et al. 1956). It should be mentioned, however, that 2 g/kg/day was a lethal dose. In rabbits treated with 25 mg/kg/day for up to 3 months the spleen generally appeared congested with free erythrocytes in the splenic sinuses (Guarino and Zambrano 1957). Similar results were observed in rabbits given 125 mg/kg/day for 6 months (Fati and Daniele 1965). In some cases, atrophy of the lymph nodes and moderate splenic hemosiderosis were found. The study was limited by the small number of animals used in the treated groups, the absence of a control group, the use of only one dose, and the failure to report the incidence of effects.

2.2.2.4 Neurological Effects

The only information located regarding neurological effects in animals following oral exposure to tetryl is that rats treated with 1 or 2 g/kg/day by gavage had paralysis of the hind limbs, sometimes front limbs, and suffered tonic-clonic convulsions before death occurred lo-18 days after dosing began (Parmeggiani et al. 1956). Because the dose levels used were relatively high and lethal, the effects observed may represent general signs of deterioration that preceded death.

No studies were located regarding the following health effects in animals after oral exposure to tetryl:

2.2.2.5 Reproductive Effects

2.2.2.6 Developmental Effects

2.2.2.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

One study was located regarding cancer in rats following treatment with tetryl (Griswold et al. 1968). Twenty female Sprague-Dawley rats received 40 mg tetryl by gavage every 3 days for 30 days for a total dose of 400 mg of tetryl. The rats were examined for up to 9 months from initiation of exposure. Statistical analyses were not performed on the data from this study which was designed to survey the carcinogenicity of a large number of chemicals. Carcinomas, fibroadenomas, and hyperplasia were found in the mammary tissues of 5 of 132 control rats and in 1 of 19 of the tetryltreated rats. No stomach tumors were found in the controls, but an adenoma was found in 1 of 19 of the tetryl-treated rats. Several design limitations rendered the study inadequate to evaluate the carcinogenicity of tetryl. Limitations included an insufficient number of animals used, only females were tested, an insufficient follow-up period, and the use of only a single dose.

2.2.3 Dermal Exposure

Several studies are available regarding health effects in humans exposed to tetryl in munitions manufacturing plants. In most studies, the number of workers or the duration and level of exposure were not provided. These studies were conducted during World War I and World War II when tetryl was being manufactured in large quantities. The workers were exposed by both dermal and inhalation routes, and it is possible that some of the dusts were swallowed. The toxic effects, other than dermal and ocular effects, are described in Section 2.2.1, Inhalation Exposure.

One study, which showed no sensitization reactions in guinea pigs following dermal application of tetryl (Gel1 1944), is discussed below. No other health effects were studied in animals.

2.2.3.1 Death

No studies were located regarding death in humans or animals following dermal exposure to tetryl.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects in humans or animals after dermal exposure to tetryl. The systemic effects that have been observed after dermal exposure are described below.

Dermal Effects. Workers handling tetryl powder often developed a yellow staining on the hands, face, and hair (Bergman 1952; Cripps 1917; Hilton and Swanston 1941; Murray et al. 1944; Probst et al. 1944; Smith 1916). The terms “canary” or “tetryl blonde” were frequently used to describe the affected workers. Staining occurred in most workers and was not indicative of systemic effects or dermatitis. Discoloration was due to surface reactions and deepened with continued exposure. Persons with oily skin or those who perspired profusely were usually more susceptible to discoloration (Bergman 1952; Cripps 1917). Fading of the color occurred once workers were removed from the contaminated areas, but it often took several months before skin color returned to normal (Bergman 1952). Workers exposed to unspecified levels of tetryl dusts often complained of dermatitis (Bergman 1952; Cripps 1917; Fischer and Murdock 1946; Hilton and Swanston 1941; McConnell et al. 1946; Murray et al. 1944; Parmeggiani et al. 1956; Probst et al. 1944; Ruxton 1917; Schwartz 1944; Smith 1916; Witkowski et al. 1942). The dermatitis ranged from mild to severe and was characterized by itching or burning, redness, papular eruptions, and facial edema particularly on the eyelids, nasal folds, cheeks, forehead, and neck. Exfoliation usually occurred after the edema subsided. Dermatitis generally affected areas with more sebaceous glands, and persons with oily skin were generally more frequently and seriously affected (Cripps 1917; Fischer and Murdock 1946; Murray et al. 1944; Schwartz 194.4). The effects began within a few days to a few weeks of initial exposure to tetryl. Estimates of workers exposed to tetryl affected by dermatitis varied greatly. Figures such as 6% of 20,451 (Bergman 1952), 19% of 5,000 (Witkowski et al. 1942), 30% of 6,364 (Schwartz 1944), and 32% (number of exposed workers not reported) (Ruxton 1917) have been reported. Some workers were reported to become tolerant to continued exposure to tetryl and no longer exhibited dermatitis (Bergman 1952; Fischer and Murdock 1946; Schwartz 1944). Other workers, however, became sensitized by exposure and developed a rash whenever they were reexposed to even very small amounts of the substance (Bergman 1952; Cripps 1917; Probst et al. 1944). Hair loss has also been reported (Bergman 1952; Cripps 1917; Hardy and Maloof 1950; Smith 1916).

No studies were located regarding death in animals following dermal exposure to tetryl.

Ocular Effects. Conjunctivitis has been observed in workers exposed to tetryl (Brabham 1943; Hilton and Swanston 1941; Ruxton 1917; Troup 1946). It may have resulted from direct contact of airborne tetryl particles with the conjunctiva or from rubbing the eyes. According to the reports, the response varied from mild to marked conjunctivitis with purulent secretion followed by irido-cyclitis and keratitis.

No studies were located regarding death in animals following dermal exposure to tetryl.

2.2.3.3 Immunological and Lymphoreticular Effects

Reports of workers involved in the manufacture of tetryl during World War I and World War II described hypersensitivity-like reactions (dermatitis, facial edema, asthma) in some workers upon reexposure to even small amounts of tetryl (Bergman 1952; Cripps 1917; McConnell et al. 1946; Murray et al. 1944; Probst et al. 1944). In one case, dermatitis developed in a woman who had worked 4 months in an ammunition factory manufacturing 2,4,6-trinitrotoluene (TNT), tetryl, and hexahydro-1,3,5-trinitro-1,3,5triazine (RDX). Patch testing with 0.05-0.5% tetryl in petroleum ointment produced a positive response (Goh 1984). The response was negative when similar concentrations in olive oil or acetone were tested. Patch testing on 20 controls with 0.1% tetryl in petroleum ointment was negative. Although it was clear that the vehicle played a role in the manifestation of the response, no apparent explanation was offered regarding the mechanism involved. Only 3 out of approximately 200 workers employed in charging boosters with tetryl showed a positive response to the patch application of pure tetryl (Parmeggiani et al. 1956). A study in which individuals exhibiting symptoms of tetryl dermatitis were treated with an antihistamine lends support to an immune response in tetryl dermatitis (Bain and Thomson 1954). Twenty-six of 28 men given the antihistaminic treatment were able to continue work with tetryl compared to only 4 of 16 who received standard topical treatments. Problems with this study include bias in assignment of subjects to treatment groups, lack of a placebo control group, and inconsistent treatment in both experimental and control groups.

Limited information in animals was available. No sensitization occurred when guinea pigs had unspecified amounts of tetryl applied to normal or burned skin (Gel1 1944). A positive reaction to dermal challenge was observed when the tetryl was initially administered intravenously or by subcutaneous implantation of a tetryl pellet. In contrast, negative results were obtained in rats to which a compress of tetryl solution was applied 10 days after repeated intracutaneous inoculations of 1% tetrylin propylene glycol (Parmeggiani et al. 1956).

No studies were located regarding the following health effects in humans or animals after dermal exposure to tetryl:

2.2.3.4 Neurological Effects

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

2.3 TOXICOKINETICS

Data regarding the toxicokinetics of tetryl in humans are limited to information from cases of occupational exposure by the inhalation and dermal routes. These data provide qualitative evidence that tetryl may be absorbed in humans by these routes. There are no data regarding oral absorption of tetryl in humans. There is qualitative evidence that tetryl is absorbed when administered to animals by the oral route, but there is no information regarding absorption after inhalation or dermal exposure. The mechanism by which tetryl or its metabolites are transported to the tissues is unknown. There are no data regarding distribution patterns for tetryl or putative metabolites in humans or animals. No information is available regarding the metabolism of tetryl in humans. In animal studies, limited data suggest the existence of nitro reduction and sulfoconjugation reactions. There is no information on how tetryl or its metabolites might be excreted in humans. Urinary excretion of possible metabolites was reported in animals. The mechanism of tetryl toxicity is not known.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Workers exposed to tetryl-laden dusts, primarily by the inhalation and dermal routes, occasionally complained of systemic effects such as nausea, vomiting, and headaches, indicating possible absorption from the respiratory tract into the bloodstream (Cripps 1917; Hardy and Maloof 1950; Hilton and Swanston 1941; Ruxton 1917; Troup 1946; Witkowski et al. 1942). No information is available on rates or extent of exposure. No animal data are available.

2.3.1.2 Oral Exposure

No human data are available regarding absorption after oral exposure. Studies in rats (Griswold et al. 1968; Parmeggiani et al. 1956) and rabbits (Daniele 1964; Fati and Daniele 1965; Guarino and Zambrano 1957; Wells et al. 1920) showed adverse health effects following gavage exposure, indicating that gastrointestinal absorption occurs. In addition, appearance of picramic acid, a metabolite of tetryl, in the urine of rabbits fed the chemical provides evidence that tetryl is absorbed following ingestion (Zambrano and Mandovano 1956). No information is available on rates or extent of absorption.

2.3.1.3 Dermal Exposure

Workers exposed to tetryl dusts, primarily by the inhalation and dermal routes, occasionally complained of systemic effects such as nausea, vomiting, and headaches, indicating possible absorption through the skin (Cripps 1917; Hardy and Maloof 1950; Hilton and Swanston 1941; Ruxton 1917; Troup 1946; Witkowski et al. 1942). No information is available on rates or extent of exposure. No animal data are available.

2.3.2 Distribution

No information is available regarding the distribution of tetryl in humans. In animals, however, the appearance of liver and kidney damage following oral exposure to tetryl (Fati and Daniele 1965) implies that tetryl (or its metabolites) is distributed to these organs.

2.3.3 Metabolism

No information is available regarding the metabolism of tetryl in humans. Seven rabbits orally administered 36 mg/kg/day (range of 32.3-40.0 mg/kg/day) for up to 30 days excreted picramic acid in their urine (Zambrano and Mandovano 1956). Picramic acid was not detected in the urine of two control rabbits (the detection limit was 0.05 mg/L). In addition, the ratio of sulfoconjugates to total sulfates increased with duration of treatment in the treated rabbits, but not in the controls. These data support the hypothesis that tetryl is metabolized to pick acid by removal of the methylnitramine complex, and further metabolized to picramic acid by reduction of a nitro group (Zambrano and Mandovano 1956). The increased sulfoconjugates may be caused by conjugation of picramic acid to sulfates. No further data on the metabolic pathway for tetryl were located.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

No information is available regarding the excretion of tetryl in humans or animals following inhalation exposure.

2.3.4.2 Oral Exposure

No human data are available regarding excretion after oral exposure. Seven rabbits administered 100 mg tetryl daily for up to 30 days excreted picramic acid in their urine (Zambrano and Mandovano 1956). No picramic acid was detected in the urine of two control rabbits. Urinary excretion of sulfoconjugates was also increased in the treated rabbits.

2.3.4.3 Dermal Exposure

No information is available regarding the excretion of tetryl in humans or animals following dermal exposure.

2.3.5 Mechanisms of Action

No information was located regarding the mechanism by which tetryl enters the blood stream from the lungs, skin, or gastrointestinal tract, the mechanism by which tetryl is transported in the blood stream, or the mechanism of toxicity for tetryl. Earlier studies suggested that the cause of tetryl-induced dermatitis, which is the most common and widely studied adverse effect, may be both physical (direct irritation by sharp tetryl crystals) and chemical (by reacting with components of the skin) (Ruxton 1917). The chemical hypothesis was later advanced by others as well (Bain and Thompson 1954; Brownlie and Cumming 1946). Bain and Thompson (1954) specifically suggested that histamine release may result from a tetryl-induced sensitization reaction or from direct tetryl-induced release from mast cells.

The chemical structure of tetryl suggests that tetryl, like many amino and nitro aromatic compounds, has the potential to induce the formation of methemoglobin in red blood cells, which could lead to cyanosis and eventually death (Beard and Noe 1981). Methemoglobin results from iron in the ferrous state being oxidized to the ferric state. Methemoglobin is unable to reversibly combine with oxygen and carbon dioxide. This causes a shift in the oxygen dissociation curve which tends to prevent the transfer of oxygen from the blood to the tissues. The many occupational studies did not report increased incidence of methemoglobinemia or secondary anemia among the exposed workers. This may indicate either that the response was not observed or that it was not tested appropriately. No further information was located regarding the mechanism of tetryl toxicity.

2.4 RELEVANCE TO PUBLIC HEALTH

To help public health officials and others address the needs of persons living or working near hazardous waste sites, this section evaluates and interprets the significance of existing toxicity data with regard to human health. Because no reliable levels of exposure have been reported for human or animal studies, no MRLs were calculated for tetryl for any route or duration of exposure. Most of the human studies were from the time periods of World War I or World War II and often did not provide adequate information on number of people exposed, duration and levels of exposure, incidence of effects, and coexposure to other chemicals, and were deficient in clinical investigations. In spite of these limitations, the general effects (skin discoloration, dermatitis, coughing, sneezing, epistaxis, headache, dizziness, nausea and vomiting, and epigastric pain) have been consistently reported and attributed to tetryl exposure.

Very little information was located regarding health effects in humans or animals following exposure to tetryl by the inhalation, oral, or dermal routes. In reports of workers exposed while manufacturing munitions during World War I and World War II, the route of exposure was not well defined, but because exposure was primarily to tetryl-laden dusts, the main route of exposure is considered to have been inhalation. In most of these studies, the exposure concentration was not known, the duration of exposure was not well defined, and concomitant exposure to other chemicals was likely. Based on these reports, it is possible that inhalation exposure to tetryl may cause respiratory problems (nosebleeds, coughs, and difficulty breathing), gastrointestinal disturbances (nausea, vomiting, and abdominal cramps), weight loss and anorexia, and neurological effects (irritability, headaches, nausea, vomiting, fatigue, and insomnia). Mild to severe dermatitis (redness, itching, discoloration) affecting the eyes, eyelids, nasal folds, cheeks, neck, and hands has been linked to dermal exposure to tetryl. In addition to the dermatitis, skin discoloration, conjunctivitis, and hair loss have also been attributed to direct contact with tetryl-laden dust or tetryl-containing compounds. In most cases, workers became tolerant to exposure within a few weeks. However, some individuals became sensitized and developed a rash in response to recontact with even small amounts of the compound. Animals administered tetryl orally showed adverse effects of the liver, kidneys, and spleen.

Although most human exposure to tetryl was believed to have occurred by inhalation, this is not considered the most likely route of exposure for populations living near tetryl-contaminated waste sites. The low vapor pressure of tetryl makes partitioning of the compound to the atmosphere unlikely. Tetryl does partition to soil and water and has been detected in these media in and around sites where tetryl was manufactured, used, stored, or disposed. The most likely route of exposure for populations living near sites contaminated with tetryl is ingestion of contaminated drinking water. Dermal contact with contaminated water or soil is a possible secondary route.

Minimal Risk Levels for Tetryl.

Inhalation MRLS.

No MRLs have been derived for inhalation exposure to tetryl because human and animal data for all durations are insufficient or lacking. Insufficiencies in the human inhalation data include mixedchemical and unquantified exposures. The animal inhalation database is limited to one early study by Gel1 (1944).

Oral MRLs.

No MRLs have been derived for oral exposure to tetryl because of lack of human data and insufficient animal data. The few animal studies available (Daniele 1964; Fati and Daniele 1965; Guarino and Zambrano 1957; Parmeggiani et al. 1956; Wells et al. 1920) suffer from severe limitations such as small number of animals, lack of control groups, and use of only one dose level.

Death. The only reports of death in humans are case studies of two workers who died of liver failure 3 or 5 years after exposure to tetryl dust in a manufacturing plant (Hardy and Maloof 1950). Although cirrhosis was reported in both cases, neither worker had a history of excessive alcohol intake. These men worked with tetryl for l-4 years and were exposed primarily by inhalation of tetryl-laden dust. Limited air monitoring, conducted in 1942, reported concentrations of tetryl ranging from 1 to 18 mg/m^3 (Hardy and Maloof 1950). These deaths, however, cannot be unequivocally attributed to tetryl; complicating medical conditions and/or coexposure to other toxic chemicals could be contributing factors in the deaths. Available animal data report death in rats following gavage with 1 or 2 g/kg/day for about 2 weeks (Parmeggiani, et al. 1956), in rabbits following gavage with 1,000 mg/kg/day for l-3 days and 25 mg/kg/day for about 2 months (Guarino and Zambrano 1957) and in dogs following subcutaneous injection of 100 mg/kg/day for 5 days (Wells et al. 1920).

Systemic Effects.

Respiratory Effects. Respiratory symptoms, consisting of nasal and throat irritation, sneezing, epistaxis, coughing, wheezing, and difficulty breathing, have been associated with exposure of workers to tetryl-laden dust (Cripps 1917; Eddy 1943; Fischer and Murdock 1946; Hardy and Maloof 1950;

McConnell et al. 1946; Murray et al. 1944; Probst et al. 1944; Smith 1916; Witkowski et al. 1942). Some individuals were especially susceptible to exposure and developed symptoms similar to hay fever or asthma (Cripps 1917; Eddy 1943; Fischer and Murdock 1946; Hardy and Maloof 1950; McConnell et al. 1946; Probst et al. 1944; Smith 1916). Most authors attribute these symptoms to the irritating nature of the tetryl particles; however, a hypersensitivity reaction is suggested in some severe cases (Bergman 1952; Cripps 1917; Fischer and Murdock 1946; McConnell et al. 1946; Probst et al. 1944). It is clear from the epidemiological data that the respiratory system is a target organ for inhaled tetryl in humans. Lethal oral doses of tetryl induced lung congestion in rabbits (Guarino and Zambrano 1957) and dyspnea in rats (Parmeggiani et al. 1956).

Gastrointestinal Effects. Workers inhaling tetryl dusts during the manufacture of tetryl-containing explosives complained of abdominal pain, nausea, and vomiting (Bergman 1952; Cripps 1917; Fischer and Murdock 1946; Hardy and Maloof 1950; Hilton and Swanston 1941; Troup 1946; Witkowski et al. 1942). While the primary route of exposure for these populations is considered to be inhalation, it is possible that some of the tetryl-laden dusts were swallowed. Swallowing of tetryl may be the result of direct contamination of the mouth and pharynx and secondary exposure from tetryl that is coughed up and then swallowed. Not all workers exposed to the chemical exhibited these symptoms, suggesting that there are individuals who are susceptible to the gastrointestinal effects of tetryl. In some studies, gastrointestinal effects appeared to be more common in workers who had not eaten adequately prior to beginning their workshift (Bergman 1952; Witkowski et al. 1942). These data suggest that the gastrointestinal tract may be a target organ for tetryl toxicity, although the route of exposure and circumstances under which this toxicity may be exhibited are unclear.

Hematological Effects. Some studies have reported mild blood effects in workers exposed to tetrylladen dust and tetryl-containing compounds during the manufacture of explosives (Bergman 1952; Brabham 1943; Cripps 1917; Fischer and Murdock 1946; Probst et al. 1944; Ruxton 1917; Witkowski et al. 1942). These’effects included slight leukocytosis, increased lymphocytes, and slight anemia. Most authors did not find these effects to be associated with tetryl exposure as the incidence was comparable to that found in control subjects (Bergman 1952; Fischer and Murdock 1946; Probst et al. 1944; Ruxton 1917). However, picric acid, a suspected metabolite of tetryl (Gel1 1944; Zambrano and Mandovano 1956), has been suggested to cause destruction of red blood cells (Army 1987d), and could be involved in the anemia observed in some exposed workers. In addition, changes suggestive of a coagulation disorder and hemosiderin deposition in the spleen were observed in rabbits administered 125 mg/kg/day for 6 months (Daniele 1964; Fati and Daniele 1965). It is not possible to determine from these data if the hematopoietic system and/or the blood are targets of tetryl toxicity.

Hepatic Effects. There are only isolated reports of workers exhibiting liver effects following exposure to tetryl-containing compounds during employment in plants manufacturing explosives. The deaths of two men who died several years after exposure were attributed to liver failure (Hardy and Maloof 1950); however, there was no conclusive evidence that exposure to tetryl was a contributing factor. Two women who worked in factories that manufactured tetryl explosives were hospitalized with jaundice and one died (Troup 1946). While liver pathology was noted in three of these cases and functional indications of liver damage were found in the fourth, the hepatic symptoms could not be unequivocally attributed to their exposure to tetryl. In contrast with the results reported by Troup (1946), McConnell et al. (1946) found no evidence of liver injury in workers exposed to tetryl dusts over a 35-month period; however, no information was provided regarding the tests that were conducted. Rabbits administered 25 mg/kg/day for up to 3 months (Guarino and Zambrano 1957) or 125 mg/kg/day for 6-9 months had liver damage ranging from mild (swollen hepatocytes, cytoplasmic changes) to severe (hyperplasia and necrosis) (Fati and Daniele 1965). Dogs administered 100 mg/kg/day subcutaneously for 5 days had liver lesions consisting of necrosis and fatty degeneration (Wells et al. 1920). The animal data suggest that the liver may be a target organ for tetryl toxicity; however, the small number of cases of liver effects reported in humans makes it difficult to determine if it is a target organ in humans. No epidemiological studies of hepatic function in exposed workers exist to support or refute the case for hepatic toxicity in humans. However, picric acid, a suspected metabolite of tetryl (Gel1 1944; Zambrano and Mandovano 1956), has been associated with functional and clinical indications of liver impairment (elevated bilirubin and urobilinogen and jaundice) following inhalation or oral exposure of humans (Army 1987d).

Renal Effects. The limited data on renal effects of tetryl shows pathological changes (swelling and degeneration) in the kidneys of rabbits orally administered 1,000 mg/kg/day for l-3 days, 25 mg/kg/day for 3 months or 125 mg/kg/day for 9 months (Fati and Daniele 1965; Guarino and Zambrano 1957; Wells et al. 1920). Dogs given subcutaneous doses of 100 mg/kg/day for 5 days also exhibited kidney damage (swelling of the tubular epithelium with albuminuria and fatty deposits and necrosis) (Wells et al. 1920). Rats that received 1 or 2 g/kg/day for about 2 weeks also had signs of kidney damage (Parmeggiani et al. 1956). No supporting data in humans were located, but picric acid, a possible metabolite of tetryl (Gel1 1944; Zambrano and Mandovano 1956), produced hematuria in humans following ingestion (Army 1987d). It cannot be determined with certainty from these data if the kidneys are a target of tetryl toxicity in humans.

Dermal Effects. The most common effects (e.g., skin discoloration and dermatitis) observed in workers exposed to tetryl-laden dust were believed to have been caused by dermal exposure to the compound. Workers that handled tetryl in manufacturing plants frequently developed a yellow staining of the hands, face, and hair (Bergman 1952; Brabham 1943; Cripps 1917; Hilton and Swanston 1941; Murray et al. 1944; Probst et al. 1944; Smith 1916). The terms “canary” and “tetryl blond” were often used to describe .workers who developed this staining. This discoloration was not indicative of systemic effects or dermatitis. Fading of the color occurred once workers were removed from the tetryl areas, but it often took several months for skin color to return to normal (Bergman 1952). Dermatitis was also commonly observed in workers exposed to tetryl dusts in the workplace (Bergman 1952; Cripps 1917; Fischer and Murdock 1946; Hilton and Swanston 1941; McConnell et al. 1946; Murray et al. 1944; Probst et al. 1944; Ruxton 1917; Schwartz 1944; Smith 1916; Troup 1946; Witkowski et al. 1942). Dermatitis ranged from mild to severe and was characterized by itching, burning, redness, papular eruptions, and facial edema. The most severe cases sometimes required hospitalization. Dermatitis generally affected the areas with more sebaceous glands, such as the eyelids, nasal folds, cheeks, forehead, and neck, and persons with oily skin were generally more frequently and seriously affected (Cripps 1917; Fischer and Murdock 1946; Murray et al. 1944; Schwartz 1944). The reported incidence of dermatitis among exposed workers ranged from 6% to 32% (Bergman 1952; Ruxton 1917; Schwartz 1944; Witkowski et al. 1942). Some workers became tolerant to tetryl (Bergman 1952; Fischer and Murdock 1946; Schwartz 1944), while other workers were hypersensitive and developed a rash whenever reexposed to even very small amounts of tetryl (Bergman 1952; Brabham 1943; Cripps 1917; Probst et al. 1944). The levels of exposure that caused this dermatitis were not reported, but onset of symptoms generally occurred within a few days to a few weeks of initial exposure.

Ocular Effects. Conjunctivitis has been reported in workers exposed to tetryl dusts (Brabham 1943; Hilton and Swanston 1941; Ruxton 1917; Troup 1946). This condition results from either direct exposure to airborne tetryl particles or from rubbing of the eyes. Reports of conjunctivitis were less frequent than reports of dermatitis.

Body Weight Effects. Weight loss and anorexia have been reported in some workers exposed to tetryl (Brabham 1943; Fisher and Murdock 1946; Hardy and Maloof 1950; Troup 1946; Witkowski et al. 1942) and may have affected as many as 10% of the exposed workers (Witkowski et al. 1942). The role of tetryl in causing these effects could not be determined because of the lack of details of exposure.

Immunological and Lymphoreticular Effects. Dermatitis and symptoms similar to hay fever and asthma have been observed in susceptible individuals exposed to tetryl-laden dust (Bergman 1952; Cripps 1917; Eddy 1943; Goh 1984; Smith 1916). Some workers exhibited severe reactions that recurred upon reexposure to even small amounts of the chemical. The hypersensitivity observed in these workers indicates that exposure to tetryl may initiate an allergic immune response in some people. The successful use of epinephrine to control asthma-like respiratory symptoms (spasmodic cough, restricted breathing) (Bergman 1952; Eddy 1943) and antihistamines to control dermatitis (Bain and Thomson 1954) also suggests that these effects are an allergic reaction to tetryl. In addition, patch testing on a woman who worked around tetryl and developed dermatitis produced a positive response when concentrations of tetryl $\geq 0.05\%$ in petroleum ointment were used (Goh 1984). A study in guinea pigs supports the case for an immune involvement in the observed respiratory effects (Gell 1944). The anaphylactic reaction observed in these animals on challenge with a picrylgelatin antigen following initial sensitization via inhalation of a tetryl smoke is indicative of an allergic response to a metabolite-protein analog of tetryl. These studies implicated the N,2,4,6-trinitrophenylamino group as the primary antigenic determinant in the immune response to tetryl. Results from an in *vitro* study showed tetryl bound to egg albumin and amino acids when incubated together for 14 days at 37.5 ºC in a neutral or acid solution (Brownlie and Cumming 1946). The authors suggested that similar binding of tetryl to skin protein generated a product that elicited an immune response resulting in dermatitis. Together, these data indicate that tetryl elicits an immune response in susceptible individuals.

Neurological Effects. Epidemiological data show that workers exposed to tetryl during the manufacture of explosives in the workplace occasionally developed irritability, headaches, fatigue, and insomnia (Bergman 1952; Cripps 1917; Hardy and Maloof 1950). These effects suggest that tetryl may affect the nervous system. However, these symptoms have many other possible origins (e.g., loss of sleep could be caused by the intense itching of dermatitis or respiratory difficulties and could result in irritability and headaches) and cannot be unequivocally attributed to a direct effect of tetryl on the nervous system. Possible neurological effects have also been observed following dermal application of picric acid in humans and oral administration of picric acid to cats and mice (Army 1987d). Picric acid is a suspected metabolite of tetryl (Gel1 1944; Zambrano and Mandovano 1956). In the absence of more definitive studies, it is difficult to determine the nature of the neurologic response observed in exposed workers.

Reproductive Effects. Only two reports were located that discussed possible effects of tetryl on the reproductive system (Cripps 1917; Hardy and Maloof 1950). Both described changes in the menstrual cycle in a small number of female workers employed in tetryl munitions factories. It should be noted that some women had diminished menstrual flow, while others had increased bleeding. However, these studies have a number of limitations: very few women were studied, other medical history was not provided, possible exposures to other substances were not accounted for, and controls were not used. No animal data were available for any route of exposure.

Developmental Effects. No information was available regarding developmental effects in humans or animals after inhalation, oral, or dermal exposure to tetryl.

Genotoxic Effects. No studies were available regarding the genotoxicity of tetryl in either humans or animals. Bacterial and fungal assays for gene mutations, deoxyribonucleic acid (DNA) damage, gene conversion, and recombination comprise the available information for tetryl genotoxicity. Tetryl was shown to induce gene mutations in *Salmonella typhimurium* strains TA1535 (Whong et al. 1980a), TAlOO (Kawai et al. 1987; McGregor et al. 1980; Whong et al. 1980a), TA1537, TA1538 (McGregor et al. 1980), and TA98 (Kawai et al. 1987). In all cases in which the *S. typhimurium* studies were performed with and without metabolic activation, the absence of metabolic activators produced stronger positive results (Kawai et al. 1987; McGregor et al. 1980; Whong et al. 1980a). One possible conclusion is that the mutagenicity of tetryl is direct; that is, metabolic breakdown of tetryl may not be required to produce gene mutations (Whong et al. 1980a). However, all these *S. typhimurium* strains possess nitroreductase activity (Ames et al. 1979), suggesting that bacterial nitroreductase activity may directly activate tetryl to a mutagen. Two strains of the fungus *Neurospora crassa* were also tested for gene mutations following treatment with tetryl. Strain N23 was positive for gene mutations while strain 12-9-17 was not. N. crussu 12-9-17 is used to detect frameshift mutations. These results suggest that tetryl is a base-pair substitution mutagen (Whong et al. 1980a). In contrast, the positive results observed in the *S. typhimurium* strains TA1537, TA1538, and TA98 suggest that tetryl is a frameshift mutagen (Kawai et al. 1987; McGregor et al. 1980). Escherichia coli was used to test for tetryl-induced DNA damage. Positive results were observed both with and without metabolic activation (McGregor et al. 1980). The effects of tetryl on mitotic gene conversion were investigated using *Saccharomyces cerevisiae* D_4. As the dose of tetryl increased, the number of conversions at the *ade*$^+$ and *trp*$^+$ loci increased. Metabolic activation was not used in this study (Whong et al, 1980a). In another experiment, S. *cerevisiae* D_5 was used to test the effects of tetryl on mitotic recombination. With metabolic activation, the numbers of recombinants were not significantly increased. However, when metabolic activators were not used, the number of recombinants and other genetic aberrations did significantly increase (McGregor et al. 1980). Together, these *in vitro* studies support the hypothesis that tetryl is a direct-acting genotoxin. Refer to Table 2-l for a further summary of these results.

Cancer. No information is available regarding cancer in humans exposed to tetryl. The only animal carcinogenicity study found that 1 of 19 female rats treated orally with 40 mg of tetryl every 3 days for 30 days developed stomach adenomas (Griswold et al. 1968); males were not tested. The lack of human data and the limitations of the single animal study (small numbers of animals, insufficient duration of exposure and follow-up, use of only a single dose, and lack of statistical analyses) do not permit an assessment of the potential carcinogenicity of tetryl.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the

TABLE 2-1. Genotoxicity of Tetryl *In Vitro*

Species (test system)	End point	Results With activation	 Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium (TA1535, TA100)	Gene mutation	(+)[a]	+	Whong et al. 1980a
S. typhimurium (TA1537, TA1538, TA98)	Gene mutation	No data	–	Whong et al. 1980a
S. typhimurium (TA1537, TA1538, TA98, TA100)	Gene mutation	(+)	+	McGregor et al. 1980
S. typhimurium (TA1535)	Gene mutation	–	–	McGregor et al. 1980
S. typhimurium (TA100, TA98)	Gene mutation	+[b]	+	Kawai et al. 1987
Escherichia coli (W3110/pol A^+, p 3478/pol A^-)	DNA damage	+	+	McGregor et al. 1980
Eukaryotic organisms:				
Fungi: *Saccharomyces cerevisiae* (D_4)	Mitotic gene conversion	No data	+	Whong et al. 1980a
S. cerevisiae (D_5)	Mitotic recombination	–	+	McGregor et al. 1980
Neurospora crassa (N23)	Gene mutation	No data	+	Whong et al. 1980a
N. crassa (12-9-17)	Gene mutation	No data	–	Whong et al. 1980a

[a] Metabolic activation only tested for strain TA100

[b] The presence of metabolic activators reduced the toxicity

– = negative result; + = positive result; (+) = weakly positive result; DNA = deoxyribonucleic acid properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to tetryl are discussed in Section 25.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by tetryl are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, Populations That Are Unusually Susceptible.

2.5.1 Biomarkers Used to Identify or Quantify Exposure to Tetryl

Picric acid and picramic acid have been identified as possible metabolites of tetryl exposure (Zambrano and Mandovano 1956). Picramic acid has been detected in rabbits fed 32.3-40.0 mg/kg/day for up to 30 days. The concentrations of picramic acid in the urine of these animals were estimated to be between 0.05 and 0.33 Mg/L; however, the calorimetric assay used to detect the metabolite was only semiquantitative. Picric acid could not be detected in the treated animals, possibly because of the high detection limit of the calorimetric assay used (1 mg/L). Sulfoconjugates were also detected in the urine and were found to increase with duration of exposure. These would only be useful biomarkers of exposure if they could be identified and quantitated. No other biomarkers to identify or quantify exposure to tetryl were located. No studies have been designed to identify interactions between tetryl (or its metabolites) and target molecules or cells within exposed humans or animals.

2.5.2 Biomarkers Used to Characterize Effects Caused by Tetryl

Many of the potential effects of tetryl exposure are very general (headaches, coughs, nausea, or dermatitis) and can be associated with numerous other chemically or biologically induced disease states. These factors limit the use of these effects as biomarkers for tetryl. Dermatitis is more specific to tetryl exposure, although other nitro compounds-mercury fulminate, ammonium picrate, and picric acid-may also produce this effect (Army 1987d; Goh 1984; Schwartz 1944). Persons exhibiting dermatitis of unknown origin and with possible exposure to tetryl (e.g., through proximity to a hazardous waste site, explosives storage area, or site of demolition activity) could be suspected of exhibiting signs of tetryl toxicity. Patch testing with tetryl could be used to determine if sensitivity to tetryl was exhibited in these individuals. No specific biomarkers are known.

For more information on biomarkers for renal and hepatic effects of chemicals see *ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage* (1990) and for information on biomarkers for neurological effects see OTA (1990).

2.6 INTERACTIONS WITH OTHER CHEMICALS

No information was located regarding interactions between tetryl and other chemicals in humans or animals. There are no known chemicals that influence the toxicity of tetryl in the body.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to tetryl than will most persons exposed to the same level of tetryl in the environment. Reasons include genetic make-up, developmental stage, health and nutritional status, and chemical exposure history. These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic and renal) or the pre-existing compromised function of target organs. For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, Populations With Potentially High Exposure.

Some people who developed dermatitis following exposure to tetryl dusts in the workplace became hypersensitive to subsequent exposure to even very small amounts of tetryl (Bergman 1952; Brabham 1943; Cripps 1917; McConnell et al. 1946; Probst et al. 1944). Those with oily or sweaty skin were more susceptible to dermatitis than those with dry skin (Bergman 1952; Cripps 1917). Some workers were especially sensitive to irritation of the respiratory tract and developed symptoms similar to hay fever and/or severe, asthma-like coughs (Bergman 1952; Cripps 1917; Eddy 1943; Fischer and Murdock 1946; Hardy and Maloof 1950; McConnell et al. 1946; Probst et al. 1944; Smith 1916). There are no other populations that are known to be unusually susceptible to the toxic effects of tetryl.

2.8 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to tetryl. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to tetryl. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

2.8.1 Reducing Peak Absorption Following Exposure

Current information about reducing absorption of tetryl is limited. People who are exposed by inhaling tetryl dusts should be removed from the site of exposure and allowed to breathe fresh air (Mackison et al. 1978). In cases where tetryl has been swallowed, large amounts of water should be administered and, if the person is conscious, vomiting should be induced (HSDB 1994). Exposed areas of the skin should be treated by washing the affected areas with soap and water. Washing with soap containing sodium sulfite has been recommended because it will turn a purple color until the tetryl is washed away (Bergman 1952; Schwartz 1944).

2.8.2 Reducing Body Burden

There are no known specific methods for reducing tetryl body burden.

2.8.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanism of tetryl toxicity is not completely understood. The primary response to tetryl exposure is dermatitis and irritation of mucous membranes in general (see Section 2.2). These responses, which appear to have an immunological component, have been successfully treated with epinephrine and antihistamines (Bain and Thompson 1954; Bergman 1952; Eddy 1943). Although not widely reported, secondary anemia has been observed after exposure to tetryl (Brabham 1943; Witkowski et al. 1942). Although no concrete evidence exists, secondary anemia may have resulted from increased formation of methemoglobin, a common response to exposure to amino and nitro aromatic compounds (Beard and Noe 1981). Ferrous sulfate was used to treat secondary anemia in exposed workers (Brabham 1943; Witkowski et al. 1942). It is possible that other antidotes used to treat methemoglobinemia and/or anemia, such as methylene blue, will also be effective after tetryl exposure (Beard and Noe 1981). Calamine lotion and zinc oxide ointments and lotions have been used to treat tetryl dermatitis (Bain and Thompson 1954; Bergman 1952; Cripps 1917; Eddy 1943; Ruxton 1917; Smith 1916; Troup 1946; Witkowski et al. 1942). Aluminum acetate or boric acid dressings also have been used to treat dermatitis and eye irritation (Bergman 1952; Brabham 1943; Eddy 1943; Schwartz 1944; Troup 1946; Witkowski et al. 1942).

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, 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 tetryl is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of tetryl.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will ‘be evaluated and prioritized, and a substance-specific research agenda may be proposed.

2.9.1 Existing Information on Health Effects of Tetryl

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to tetryl are summarized in Figure 2-l. The purpose of this figure is to illustrate the existing information concerning the health effects of tetryl. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as “data needs.” A data need, as defined in ATSDR’s Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Information on the health effects of tetryl is limited. The information on humans consists of a number of studies on workers exposed to tetryl dusts in the workplace during World War I and World War II. The reported effects were general, and limited information was provided on duration or levels of exposure. The workers were most likely exposed primarily by the inhalation route, although they probably had some direct skin contact and may have swallowed some of the dusts. The dermal effects (skin discoloration, dermatitis) observed in workers were attributed to dermal exposure; other effects (respiratory, gastrointestinal, neurological, etc.) were believed to be due to inhalation exposure. One animal study gave information on the possible immunological effects following inhalation exposure. There are no human studies on the effects of tetryl ingested in the drinking water. There are only a few animal studies in which tetryl was administered by the oral route. These provide data on effects of acute- and intermediate-duration exposure in a small number of rabbits and rats, and data on cancer effects following intermediate-duration exposure of rats. The one dermal study in animals gives information on possible adverse immunological effects. There are no studies in humans or animals regarding developmental or genotoxic effects after inhalation, oral, or dermal exposure.

2.9.2 Identification of Data Needs

Although most human exposure to tetryl was believed to have occurred by inhalation, this is not considered the most likely route of exposure for populations living near tetryl-contaminated waste sites. The low vapor pressure of tetryl makes partitioning of the compound to the atmosphere unlikely. Tetryl does partition to soil and water and has been detected in these media in and around

FIGURE 2-1. Existing Information on Health Effects of Tetryl

		SYSTEMIC								
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	●	●	●	●	●	●	●			
Oral										
Dermal		●	●	●	●					

Human

		SYSTEMIC								
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation					●					
Oral	●	●	●		●					●
Dermal					●					

Animal

● Existing Studies

sites where tetryl was manufactured, used, stored, or disposed of. The most likely route of exposure for populations living near sites contaminated with tetryl is ingestion of contaminated drinking water. Dermal contact with contaminated water or soil is a possible secondary route. Exposed populations need to be better identified and the extent of exposure quantitated.

Acute-Duration Exposure. Studies in workers exposed to tetryl indicate that the target organ following acute dermal exposure is the skin (Bergman 1952; Brabham 1943; Cripps 1917; Hilton and Swanston 1941; McConnell et al. 1946; Murray et al. 1944; Probst et al. 1944; Schwartz 1944; Smith 1916; Troup 1946; Witkowski et al. 1942). Dermal and ocular effects (yellow staining, dermatitis, hair loss, conjunctivitis) were generally observed within a few days to a few weeks of initial exposure. The incidence of dermatitis among exposed workers ranged from 6% to 32% (Bergman 1952; Ruxton 1917; Schwartz 1944; Witkowski et al. 1942). Humans exposed primarily by inhalation have exhibited respiratory (irritation, coughs, epistaxis), gastrointestinal (stomach cramps, nausea, vomiting), and neurological (irritability, headaches, nausea, vomiting, fatigue, insomnia) effects (Bergman 1952; Cripps 1917; Eddy 1943; Fischer and Murdock 1946; Hardy and Maloof 1950; Hilton and Swanston 1941; McConnell et al. 1946; Murray et al. 1944; Probst et al. 1944; Ruxton 1917; Smith 1916; Troup 1946; Witkowski et al. 1942). The target organs following acute oral exposure in humans are not known, but animals exposed by gavage have developed adverse hepatic and renal effects (Parmeggiani et al. 1956; Wells et al. 1920). Methodological problems with these studies, such as lack of control animals, lack of supporting histopathological data, and/or lack of exposure data, prevent their use in development of acute-duration MRLs. No pharmacokinetic data were available. Acute-duration studies in animals following oral or dermal exposure would help define target organs and levels of exposure that may be harmful to populations near hazardous waste sites.

Intermediate-Duration Exposure. Studies of workers exposed to tetryl indicate that the skin is most likely the target organ following dermal exposure for an intermediate duration (Bergman 1952; Brabham 1943; Cripps 1917; Hilton and Swanston 1941; McConnell et al. 1946; Murray et al. 1944; Probst et al. 1944; Schwartz 1944; Smith 1916; Troup 1946; Witkowski et al. 1942). Dermal and ocular effects (yellow staining, dermatitis, hair loss, conjunctivitis) were generally observed within a few days to a few weeks of initial exposure. Staining was observed in most workers who were routinely exposed to tetryl. The incidence of dermatitis among exposed workers ranged from 6% to 32% (Bergman 1952; Ruxton 1917; Schwartz 1944; Witkowski et al. 1942). Workers exposed primarily by inhalation for unspecified periods of time have exhibited respiratory (irritation, coughs, epistaxis), gastrointestinal (stomach cramps, nausea, vomiting), anorexia and weight loss, and neurological (irritability, headaches, nausea, vomiting, fatigue, insomnia) effects (Bergman 1952; Brabham 1943; Cripps 1917; Eddy 1943; Fischer and Murdock 1946; Hardy and Maloof 1950; Hilton and Swanston 1941; McConnell et al. 1946; Murray et al. 1944; Probst et al. 1944; Ruxton 1917; Smith 1916; Troup 1946; Witkowski et al. 1942). Menstrual irregularities have also been reported in some women workers exposed to tetryl for intermediate and chronic durations (Cripps 1917; Hardy and Maloof 1950). Most of these studies failed to provide adequate information on duration or levels of exposure. No human data are available regarding effects following intermediate-duration oral exposure, although this is considered the most likely route of exposure for people living near tetryl contaminated hazardous waste sites. Intermediate-duration oral studies in rabbits have shown liver and kidney lesions, hemosiderin deposition in the spleen, and, possibly, reduced blood-clotting (Daniele 1964; Fati and Daniele 1965; Guarino and Zambrano 1957). No studies are available regarding effects in animals following intermediate-duration inhalation or dermal exposure. The data are insufficient to develop any intermediate-duration MRLs. No pharmacokinetic data were available. Intermediateduration studies of humans or animals following oral and dermal exposures would help define target organs and levels of exposure that may be harmful to populations near hazardous waste sites.

Chronic-Duration Exposure and Cancer. There are several studies that describe health effects in persons exposed to tetryl in the workplace (Bergman 1952; Brabham 1943; Cripps 1917; Hilton and Swanston 1941; McConnell et al. 1946; Murray et al. 1944; Probst et al. 1944; Schwartz 1944; Smith 1916; Troup 1946; Witkowski et al. 1942). However, levels and durations of exposures were often not defined. The exposure route was considered to be primarily inhalation. The target organs of humans exposed for chronic periods are not known, but the effects appear to be similar as those observed for acute- and intermediate-duration exposures. No information on chronic oral exposure via drinking water was available for humans, although this is a likely route of exposure. No chronic animal studies were available. Because exposure levels were not determined in human studies, no chronic MRLs were developed. Chronic-duration studies in animals following oral exposure are needed since contamination through drinking water is the major route of concern for populations living around tetryl-contaminated sites. Such studies would help define target organs of effect and would be useful in developing MRLs in order to protect the health of people living near these sites. There were no suitable studies for evaluating the risks of cancer from tetryl. No human data were available, and the only animal data were from an oral study that was limited by a short exposure duration (30 days), a short post-exposure monitoring period (up to 9 months), and small group size (19 rats) (Griswold et al.

1968). Chronic-duration oral studies in a sufficient number of animals would need to be conducted to determine if humans living near hazardous waste sites have an increased risk of cancer from exposure to tetryl. Dermal studies may also be useful if absorption via this route is found to be significant.

Genotoxicity. There were no available human or animal studies regarding the genotoxicity of tetryl. In vitro studies suggest that tetryl is a direct-acting genotoxin for certain strains of S. *typhimurium, E. coli, S. cerevisiae,* and *N. crassa* (Kawai et al. 1987; McGregor et al. 1980; Whong et al. 1980a). These data suggest a potential for genotoxic effects that requires further evaluation. *In vivo* animal studies and epidemiological studies of tetryl-exposed workers and/or Army personnel would be especially useful for evaluating the genotoxicity of tetryl in humans.

Reproductive Toxicity. Information regarding reproductive effects in humans comes primarily from two studies that indicated that a small number of women workers exposed to unspecified levels of tetryl dusts in factories developed menstrual irregularities (Cripps 1917; Hardy and Maloof 1950). The probable route of exposure for these women was inhalation of tetryl-laden dusts. It is not clear that exposure to tetryl caused these irregularities. No other information for humans or animals was available. In order to assure that humans living near tetryl-containing hazardous waste sites are not adversely affected by this substance, oral animal reproductivity studies would need to be performed, since the most likely route of exposure for humans is through contaminated drinking water. Dermal studies may be useful if dermal absorption is found to be significant.

Developmental Toxicity. No information was available regarding developmental effects in humans or animals following exposure to tetryl by any route. In order to assure that humans living near hazardous waste sites containing tetryl are not adversely affected by this substance, oral studies examining developmental end points would need to be performed in animals. If dermal absorption proves to be significant, dermal studies in animals that examine developmental end points may also be relevant.

Immunotoxicity. The information located regarding immunological effects in animals and humans following exposure to tetryl is limited. Some workers exposed to tetryl developed hypersensitivity-like reactions (dermatitis, facial edema, asthma) (Bergman 1952; Cripps 1917; McConnell et al. 1946; Murray et al. 1944; Probst et al. 1944). Amelioration of these effects by epinephrine and antihistaminic treatment suggest that they were due to an immunological effect (Bain and Thomson

1954; Bergman 1952; Eddy 1943). In addition, a positive reaction to a skin patch test was observed in a worker who had developed dermatitis (Goh 1984). Limited animal data also suggest that tetryl is allergenic (Gel1 1944). However, unequivocal data demonstrating the immune system to be a target for tetryl are not available. Further studies examining potential antibody formation in response to tetryl and the determination of the type of hypersensitivity reaction would be useful in defining possible immunological effects for people exposed to tetryl at hazardous waste sites.

Neurotoxicity. The only available information regarding neurotoxicity of workers exposed to tetryl dusts, primarily via inhalation, were occasional irritability, headaches, nausea, vomiting, fatigue, and insomnia (Bergman 1952; Brabham 1943; Cripps 1917; Hardy and Maloof 1950; Hilton and Swanston 1941; Murray et al. 1944; Smith 1916; Witkowski et al. 1942). No other data in humans or animals were available. Because the effects noted in workers were minor and relatively nonspecific, it is not likely that the nervous system was a target of toxicity. Further studies in animals would be useful in understanding the neurotoxicity of tetryl.

Epidemiological and Human Dosimetry Studies. Although there are several studies reporting health effects in groups of people exposed in the workplace (Bergman 1952; Hilton and Swanston 1941; Probst et al. 1944; Schwartz 1944; Troup 1946; Witkowski et al. 1942), most of these studies were missing critical data on incidences, exposure concentration, and exposure durations. In several cases, control populations were not well defined or were absent. Because tetryl was manufactured primarily during World Wars I and II, it is unlikely that a suitable population can be identified that is currently exposed to measurable amounts of tetryl. However, retrospective cohort mortality studies of ' exposed workers would be useful in assessing possible causes of death in workers previously employed in tetryl manufacturing plants. There are currently no techniques for measuring tetryl in human tissues or body fluids. Therefore, dosimetry studies of populations living near hazardous waste sites cannot be conducted until appropriate analytical methods are developed.

Biomarkers of Exposure and Effect.

Exposure. Picramic acid has been detected in the urine of rabbits fed tetryl (Zambrano and Mandovano 1956). No other studies suggested possible biomarkers of exposure to tetryl. Further information on the metabolism of tetryl and excretion of metabolites is needed to establish biomarkers of exposure for tetryl. This information is needed so that medical surveillance of potentially exposed populations can be conducted.

Effect. There are no specific biomarkers for the effects of tetryl. The toxic effects of tetryl, such as headaches, coughs, nausea, and dermatitis, are too general to be used to characterize exposure to this substance. Patch tests can be conducted in individuals who appear to be sensitive to tetryl (i.e., those who exhibit hypersensitivity-like reactions). Further studies are necessary to determine which types of biomarkers can be used to indicate effects caused by tetryl.

Absorption, Distribution, Metabolism, and Excretion. One study was available that investigated the metabolism of tetryl in rabbits (Zambrano and Mandovano 1956). This experiment showed that ingested tetryl was absorbed and metabolized and that picramic acid was excreted in the urine. Systemic effects in humans following exposure to tetryl dust support that the chemical is absorbed by humans. Further studies on the toxicokinetics of tetryl following oral or dermal exposure would help determine the relative importance of these two routes of exposure for populations located near tetryl-contaminated waste sites. These would also help to determine the most important route to use in studies examining the health effects of tetryl exposure.

Comparative Toxicokinetics. One study in rabbits fed tetryl showed that the chemical is absorbed and metabolized (Zambrano and Mandovano 1956). Picramic acid was detected in the urine of these animals. Since there were no other studies available, the toxicokinetics cannot be compared. The best animal models for studying the health effects of the chemical are not known. Further studies would be useful to determine if the target organs are likely to be the same in humans and animals.

Methods for Reducing Toxic Effects. Limited information is available on treatments to alleviate the symptoms of tetryl exposure. These include treatment of the dermatitis with calamine lotion and/or zinc oxide preparations, treatment of dermatitis and ocular irritation with aluminum acetate or boric acid compresses, and treatment of hypersensitivity-like symptoms (including severe dermatitis and asthma-like symptoms) with epinephrine or antihistamines (Bain and Thomson 1954; Bergman 1952; Cripps 1917; Eddy 1943; Ruxton 1917; Smith 1916; Troup 1946; Witkowski et al. 1942). The data on the pharmacokinetics of tetryl are also limited (Zambrano and Mandavana 1956). In order to develop mitigating agents, further studies are needed on its kinetics and mechanisms of action.

2.9.3 Ongoing Studies

There are no known ongoing studies on the health effects of tetryl.

3. CHEMICAL AND PHYSICAL INFORMATION

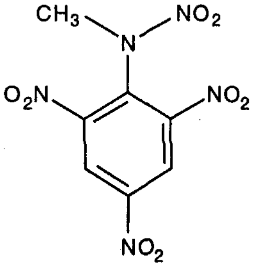
3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of tetryl is located in Table 3-l.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of tetryl is located in Table 3-2.

TABLE 3-1. Chemical Identity of Tetryl

Characteristic	Information	Reference
Chemical name	N-methyl-N,2,4,6-tetranitroaniline	HSDB 1994
Synonym(s)	2,4,6-trinitrophenyl-N-methylnitramine; N-methyl-N,2,4,6-tetranitrobenzenamine; N-picryl-N-methyl-nitramine; tetralit; tetralite; tetril; tetryl; trinitrophenyl-methylnitramine; nitramine; CE	HSDB 1994
Registered trade name(s)	No data	
Chemical formula	$C_7H_5N_5O_8$	HSDB 1994
Chemical structure		Merck 1989
Identification numbers:		
CAS Registry	479-45-8	HSDB 1994
NIOSH RTECS	BY6300000	HSDB 1994
EPA Hazardous Waste	No data	
OHM/TADS	No data	
DOT/UN/NA/IMCO	UN0208	HSDB 1994
HSDB	2857	HSDB 1994
NCI	No data	

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substance Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

TABLE 3-2. Physical and Chemical Properties of Tetryl

Property	Information	Reference
Molecular weight	287.15	Lide 1991
Color	Yellow	Sax and Lewis 1987
Physical state	Solid crystals	Sax and Lewis 1987
Melting point	130–132 °C 129.5 °C	Lide 1991 Meyers 1987
Boiling point	187 °C (explodes)	Lide 1991
Density at 19 °C	1.57	Lide 1991
Odor	Odorless	HSDB 1994
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Fresh water at 20 °C	75 mg/L	Army 1987d
Salt water at 25 °C	26 mg/L	Hoffsommer and Rosen 1973
Organic solvent(s)	Soluble in acetone, alcohol, ether, benzene, glacial acetic acid	Merck 1989
Partition coefficients:		
Log K_{ow}	2.4^{a}	Army 1987d
Log K_{oc}	$3.13–3.47^{b}$	Army 1987d
Vapor pressure at 20 °C	$4x10^{-10}$ $torr^{a}$	Army 1987d
Henry's law constant:		
at 25 °C	$2.0x10^{-12}atm–m^{3}/mol^{a}$	Army 1987d
Autoignition temperature	No data	
Flashpoint	Explodes	Mackison et al. 1978
Flammability limits at 25 °C	No data	
Conversion factors at 25 °C	1 ppm = 11.74 mg/m^{3}	HSDB 1994
Explosive limits	Explodes at 187 °C; impact sensitive	HSDB 1994

[a] Calculated values
[b] Estimated values

HSDB = Hazardous Substance Data Bank

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Tetryl has been produced in a batch process by dissolving dimethylaniline in an excess of concentrated sulfuric acid at 20-30 ºC to give dimethylaniline sulfate (Kirk-Othmer 1980). The solution was nitrated with a mixture of nitric and sulfuric acids to produce 2,4-dinitrodimethylaniline and eventually crude tetryl. The crude product was filtered, washed with water, and dissolved in acetone. The acetone was evaporated and the product filtered to yield purified tetryl. In a second production process 2,4- or 2,6-dinitrochlorobenzene was reacted with methylamine to form dinitrophenyl methylamine, which was nitrated to form tetryl (Gibbs and Popolato 1980).

Tetryl is not produced commercially in the United States (Army 1984c, 1989b; HSDB 1994). Prior production was limited to Army ammunition plants such as Joliet Army Ammunition Plant (Illinois), which produced tetryl until 1973 (HSDB 1994). Data on past production volumes for tetryl are not available. Other Army ammunition plants that have handled tetryl include Alabama (Alabama), Anniston (Alabama), Crane (Indiana), Fort Wingate (New Mexico), Hawthorne (Nevada), Letterkenny (Pennsylvania), Lexington (Kentucky), Louisiana (Louisiana), McAlester (Oklahoma), Milan (Tennessee), Navajo (Arizona), Pine Bluff (Arkansas), Pueblo (Colorado), Red River (Texas), Savanna (Illinois), Seneca (New York), Sierra (California), Tooele (Utah), and Umatilla (Oregon) (Army 1986a, 1986b).

Because tetryl releases are not required to be reported under SARA Section 313, there are no data on tetryl in the Toxics Release Inventory (TRI 1993).

4.2 IMPORT/EXPORT

Current import and export data for tetryl are not available.

4.3 USE

The primary use of tetryl from 1916-1979 was as a common component of military explosives (Jenkins and Walsh 1994). It has been largely replaced by RDX in modem explosive formulations

(Army 1984c, 1989b; Gibbs and Popolato 1980; Jenkins and Walsh 1994). Tetryl was used as an explosive in detonators and primers, as a detonating agent for other less sensitive high explosives, and as a booster charge for military devices (HSDB 1994; Sax and Lewis 1987). As a component in binary explosives, tetryl was used with 2,4,6-trinitrotoluene (TNT) to form tetrytols (80% tetryl, 20% TNT) that were used as a base charge in detonators (Army 1986b; Gibbs and Popolato 1980). Tetryl has also been used as a chemical indicator in the pH range between 10.8 (colorless) and 13.0 (redbrown) (Merck 1989).

4.4 DISPOSAL

Beginning in 1963, the U.S. Navy loaded munitions on obsolete liberty ships and sank them at selected oceanic sites (CEQ 1970; Hoffsommer and Rosen 1972). Tetryl was one of the most common and abundant explosives dumped in this manner (Hoffsommer and Rosen 1972), but ocean dumping has not been used since 1970 (CEQ 1970). Waste waters from tetryl manufacture were passed to holding lagoons for primary settling of solid materials before being released to rivers and streams (Harvey et al. 1993). Tetryl is completely deactivated into nonexplosive, water-soluble products by the action of sodium sulfite, and this reaction was used for the disposal of waste material (Bergman 1952). The deactivation was accomplished by adding the explosive to an aqueous solution containing 13% by weight of hydrated sodium sulfite. By-products, such as those created during the manufacture of tetryl, were openly burned or detonated at many Army ammunition plants. As much as 80% of waste munitions and propellants that have been disposed of in recent years have been incinerated (Army 1986d).

Wastes containing tetryl have been incinerated by grinding and spraying the ground material with water to form a slurry. The types of incineration that have been used to destroy waste munitions such as tetryl include rotary kiln incineration, fluidized bed incineration, and pyrolitic incineration (Army 1986d). The primary disadvantage of open burning or incineration is that explosive contaminants are often released into the air, water, and soils (Army 1986b). Wastes generated in the manufacturing of tetryl are classified as EPA hazardous wastes and any stored tetryl or tetryl-containing wastes from hazardous waste sites must be disposed according to EPA regulations (EPA 1990b). For more information on hazardous waste regulations that apply to tetryl, see Chapter 7.

Over 90% of tetryl wastes found in soils were transformed to non-carbon dioxide products in testing composts using substances such as hay-horse feed and sewage sludge-wood shavings (Army 1986a). The chemical has been destroyed from contaminated lagoon sediments using aqueous thermal decomposition (heating under pressure to 200-250 ºC in an aqueous medium) (Army 1985). Tetryl waste munitions have also been removed from waste waters by activated carbon columns (Army 1986b, 1987a). Once carbon columns were saturated with the explosive, they were traditionally destroyed by open burning. Since this practice is no longer allowed in many areas, other alternatives of disposing of spent carbons, such as thermal reactivation for reuse, oxidative incineration and burial, or thermal deactivation and carbon burial, have been investigated (Army 1987a). A method for removing tetryl from contaminated waste water and lagoons using a chemical reaction with a surfactant containing a quaternary ammonia group under basic conditions (pH 1l-l1.5) followed by filtration to remove the precipitate has been tested (Army 1984c).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Tetryl is a synthetic compound that does not occur naturally. It was once widely used as a military explosive but is no longer manufactured or used in the United States (see Chapter 4). Effluents and emissions from Army ammunition plants were responsible for the release of tetryl into the environment. When released to the atmosphere, tetryl is expected to react and undergo transformation with sunlight and it will be removed from the atmosphere by wet and dry deposition. When released to water, tetryl is subjected to hydrolysis and photolysis, but photolysis will be more important in surface water. Hydrolysis and photolysis products include picrate ion, N-methylpicramide, methylnitramine, nitrite ion, and nitrate ion. Tetryl is not mobile in soil and leaching into groundwater is not likely. Biodegradation studies suggest that tetryl may undergo biotransformation under certain environmental conditions.

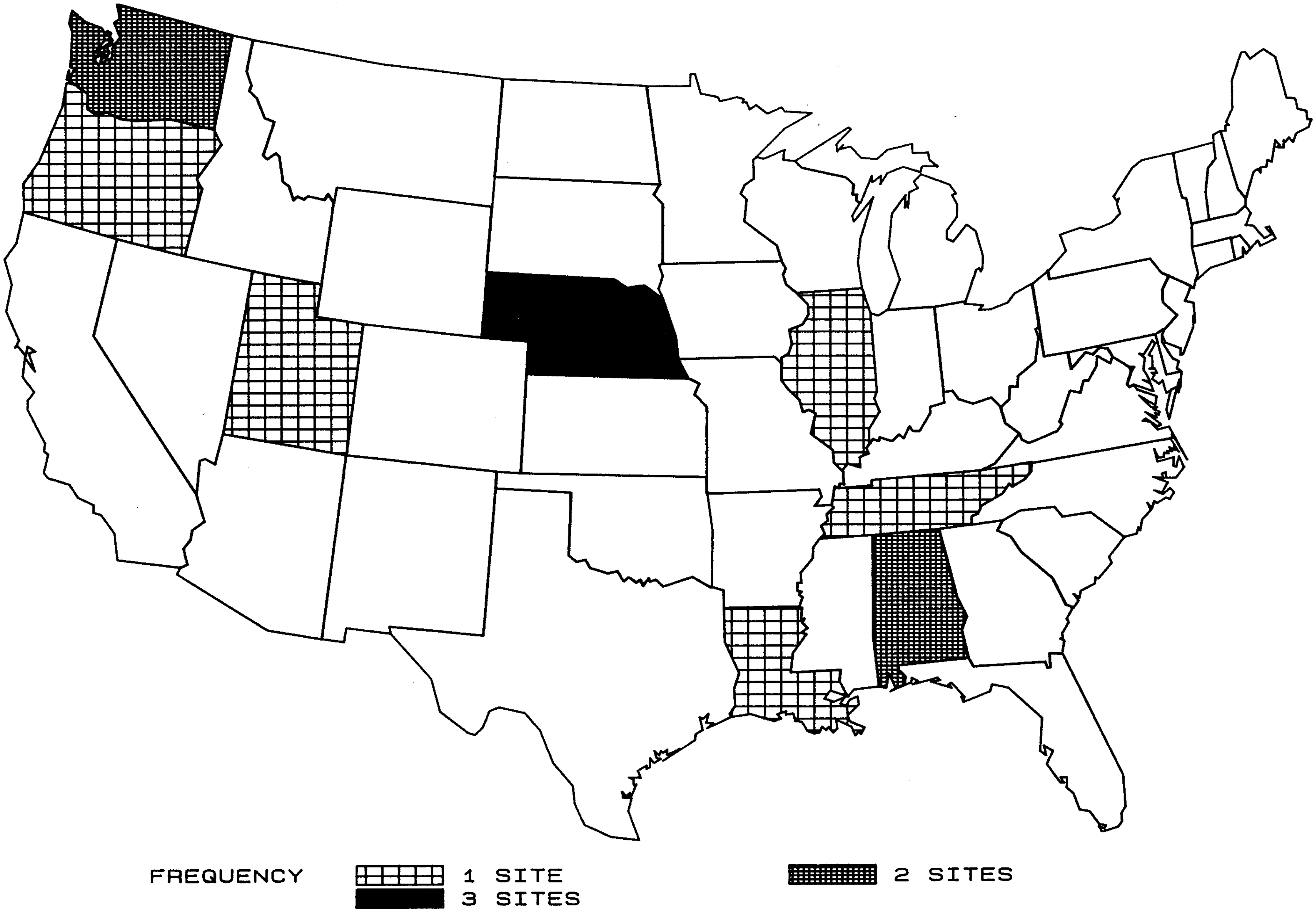
The general population is not likely to be exposed to tetryl. During World War I and World War II, occupational exposure to tetryl was confined to workers in munition plants. For these workers, exposure occurred primarily by inhalation of tetryl-laden dusts, although some dermal and oral exposure probably occurred. Current exposure to tetryl is likely limited to areas around military installations, such as Army ammunition plants, where it was manufactured, converted to munitions, packed, loaded, or released through the demilitarization of antiquated munitions. The probable route of exposure for populations living near contaminated facilities or waste sites is ingestion of contaminated drinking water. Dermal exposure via contaminated water and soil may also occur. Occupational exposure to tetryl may occur in workers handling tetryl at Army ammunition plants during disposal operations.

Tetryl has been identified in 12 of the 1,397 hazardous waste sites on the NPL (HazDat 1994). The frequency of these sites within the United States can be seen in Figure 5-1.

5.2 RELEASES TO THE ENVIRONMENT

Since tetryl releases are not required to be reported under SARA Section 3 13, there are no data on tettyl in the Toxics Release Inventory (TRI 1993).

FIGURE 5-1. FREQUENCY OF NPL SITES WITH TETRYL CONTAMINATION *


FREQUENCY
1 SITE
3 SITES
2 SITES

*Derived from HazDat 1994

5.2.1 Air

No data were located regarding releases of tetryl to air. A report on emissions from the Joliet Army Ammunition Plant (Joliet, Illinois), based on samples of effluent gases taken in 1967, showed only nitrogen oxides and sulfuric acid mist released to the air from the bubble tower and fume recovery facilities of tetryl manufacturing operations (Army 1976). Because tetryl is no longer manufactured or used in the United States, releases from these sources no longer occur. It is possible that some tetryl could be released to air during detonation, open-air burning, or incineration of the explosive during disposal operations (Army 1976, 1986b, 1986d). The by-products that have been reported to be produced when these methods are used include carbon monoxide, carbon dioxide, nitrogen oxides, nitrogen, water, and particulate carbon. The reported releases did not include tetryl, but it is unclear if tetryl was included in the analyses.

5.2.2 Water

Tetryl was released to water in waste discharge effluents from Army ammunition plants or through leaching from contaminated soil deposits. For example, the Joliet Army Ammunition Plant (Joliet, Illinois) produced tetryl until July 1973, releasing it via waste water into drainage ditches. Waste water streams discharged into drainage ditches typically containing 400,000-600,000 µg/L tetryl, corresponding to a daily discharge of 769 pounds from the tetryl nitration and refining houses (Army 1976). Even after production of tetryl at the Army ammunition plant ceased, tetryl releases to surface water and groundwaters were still possible via runoff and leaching from contaminated soils at the plant site (Army 1974, 1976). A 1988 survey showed tetryl was present at a concentration of 67 µg/L in a sample from a groundwater monitoring well installed in an area where highest soil contamination had been detected in 1981. However, tetryl was not detected in surface water, groundwater and sediment samples taken from other areas during 1981-1988 (detection limit of 1.8-100 µg/L for surface water and 2.86 µg/L for sediment) (Army 1990b). A monitoring study conducted at the ammunition plant during 19851986, detected tetryl in several groundwater samples at concentrations of 67 µg/L in the tetryl production area, 34.5 µg/L in the TNT production area, and 13.7 µg/L in a waste water area (Army 1990b). The other possible sources of water contamination with tetryl are from runoff and leaching of the material at dump sites containing tetryl and at sites of demilitarization activities. No specific data on these potential sources were located.

5.2.3 Soil

Tetryl was released to the soil in waste-discharge effluents from the manufacture of tetryl at Army ammunition plants and as a result of its use as an explosive (Army 1981b). Because tetryl is no longer manufactured or used in the United States (Army 1984c, 1989b), new releases from manufacturing sources will not occur. However, contamination from past releases may still exist. In addition, tetryl may be released to soil from demolition landfills or during demilitarization operations (open detonation or open burning) (Army 1981b, 1986b). Tetryl was detected at concentrations of <1,000 µg/gram in 4.8% of soil samples taken from open-burning grounds at selected military installations; none of the samples contained >1,000 µg tetryl/gram of soil (Army 1986b). In a 1981 survey of contamination at the Joliet Army Ammunition Plant (Joliet, Illinois), tetryl was found in two of five surface soil samples. Measured levels were 38,500 µg/gram in the surface soil near the tetryl production area and at a concentration 23.5 µg/gram in a location removed from this area. Tetryl was not detected in five soil core samples taken from the same area in 1988 (detection limit of 1.86µg/gram) (Army 1990b). No other specific data on releases to soil were located.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Neat tetryl is chemically stable and only slightly hygroscopic. It has remained stable for as long as 20 years during storage at ordinary temperatures (Bergman 1952). Although nitrated compounds are expected to exist in both the vapor phase and particulate form (Eisenreich et al. 1981), based on a vapor pressure of 4×10^{-10} mmHg (Army 1987d), it is unlikely that tetryl will partition to air. It is possible that tetryl might exist in the air as a particulate under certain conditions (i.e., following detonation or open-air burning), although no data were located. Tetryl present in the air as particulate would likely be deposited to land and water through wet and dry deposition. Tetryl is slightly soluble in water (75 mg/L in 20 ºC fresh water; 26 mg/L in 25 ºC salt water) (Army 1987d; Hoffsommer and Rosen 1973) but is soluble in alcohol, ether, benzene, acetone, and glacial acetic acid (Merck 1989). The calculated Henry's law constant for tetryl is 2.0×10^{-12} atm-m^3/mol (Army 1987d). Based on this value of Henry's law constant, tetryl is considered essentially nonvolatile (Lyman et al. 1982); therefore, volatilization is not expected to be an important fate process.

The mobility of tetryl through soil may be determined based on its K_{oc} value. A K_{oc} value of 406 has been calculated for tetryl based on a water solubility of 75 mg/L (HSDB 1994); however, a K_{oc} of 1,357-2,948 was estimated for tetryl based on measured water-soil partition coefficients (Army 1979, 1987d). The higher measured value may result from the binding of tetryl and its decomposition products to humic matter in soil (Army 1987d; Bongiovanni et al. 1984; Harvey et al. 1992). These higher K_{oc} values suggest that tetryl is slightly mobile in soil (Swarm et al. 1983); therefore, tetryl is not expected to leach substantially into groundwater, particularly if the soil has a high organic content. Monitoring studies have indicated that the movement of tetryl through soil to groundwater may be influenced by other factors. These factors include its rapid hydrolysis in soil which may, in some cases, prevent tetryl reaching the underlying groundwater (Kayser and Burlinson 1988). Alternatively, the presence of other solvents at contamination sites may increase the mobility of tetryl through the soil (Army 1974, 1990b). Tetryl has been detected in water collected in seepage holes and groundwater monitoring wells dug at contaminated soil sites, indicating some leaching does occur (Army 1974, 1990b).

The logarithm of the *n*-octanol/water partition coefficient (log K_{ow}) is a useful preliminary indicator of potential bioaccumulation of a compound. The log K_{ow} for tetryl was calculated to be 2.4 (Army 1987d), indicating a low potential for bioaccumulation. The bioconcentration factor (BCF) for tetryl was calculated to be 54 from a recommended regression-derived equation (HSDB 1994; Lyman et al. 1982). This BCF value does not suggest a potential for significant bioconcentration in aquatic organisms (HSDB 1994). Using an alternate regression-derived equation, a BCF of 15 was calculated (Army 1987d), which supports the low bioaccumulation potential of tetryl. However, the estimated BCF value based on K_{ow} is highly uncertain since it does not adequately take in account the interaction of tetryl with protein and other compounds present in fish tissues. Partition coefficients for plant/soil and beef fat/diet of 1 and 3.7×10^{-3}, respectively, were also calculated (Army 1987d). However, during attempts to develop a method of analyzing for tetryl in biological tissues (animal plasma, kidney, muscle/fat, and liver, as well as plant stems), tetryl could not be extracted from the samples even when intentionally spiked (Army 1981a). The authors concluded that tetryl was irreversibly adsorbed to macromolecules in the plant and animal tissues by binding of the methylnitroamino group (Army 1981a). The impact of macromolecular binding on the bioconcentration of tetryl in aquatic and terrestrial organisms is not known. No experimental bioconcentration data were located.

In a plant uptake study with bush bean plants maintained on tetryl-amended hydroponic cultures for exposure periods of up to 7 days, all but a small amount (3%) of tetryl was rapidly converted to polar metabolites. The majority of the tetryl metabolites (89% to 96%) were located within the root tissues. An intermediate amount of metabolites (3%-7%) was found in the stem tissues; the leaf tissues contained the smallest quantity (1%-4%) (Harvey et al. 1993).

Picric acid, one of the breakdown products of tetryl, is soluble in water and is expected to leach through soil to groundwater in substantial amounts (Army 1987d). It is expected to dissociate in water, especially when present in low concentrations. Picric acid may also form complexes with metal ions in soil, causing some of the chemical to remain bound (Army 1987d). Picric acid that is bound to soil may- be transformed via photolysis if present at the soil surface (Army 1987d).

5.3.2 Transformation and Degradation

5.3.2.1 Air

Tetryl (vapor phase) in the air may react with photochemically formed hydroxyl radicals. The half-life for this reaction was estimated to be >> 10 days assuming a normal atmospheric concentration of 5×10^5 hydroxyl radicals per cm^3 and a gas phase reaction rate of << $1\times10^{-12}cm^3$/molecule-second (Atkinson 1987; HSDB 1994). However, because tetryl has a very low vapor pressure and Henry's law constant (see Table 3-2), only a small amount of tetryl is expected to exist in the atmosphere in the vapor phase (Eisenreich et al. 1981) and be available for transformation via reaction with hydroxyl radicals. In the atmosphere, tetryl is expected to be more prevalent in the particulate form. The hydroxyl radical reaction rate for particulate tetryl would be much slower than the vapor phase reaction rate. Therefore, the transformation of tetryl in air due to reaction with OH radicals may not be important. No data were located on direct photolysis of tetryl in the atmosphere, but tetryl is expected to undergo direct photolytic degradation in the atmosphere because it undergoes this reaction in water (Army 1984d). Based on a pure water photolysis half-life of 20-40 hours for TNT, a structurally similar compound (Mabey et al. 1983), it is likely that photolysis will dominate the degradative fate of tetryl in air.

5.3.2.2 Water

If released to water, tetryl may be degraded by hydrolysis. Based on experimentally-derived pH (range of 4-9) versus rate profiles for tetryl at 40, 72, and 85 ºC and a range of activation energies, the hydrolysis half-life of tetryl at 20 ºC and pH 6.8 was crudely estimated to be 302 ± 76 days. Since the estimated half-life has a maximum uncertainty factor of 3, the hydrolysis half-life at 20 ºC! and pH 6.8 may be as high as 900 days. The hydrolysis rate is expected to increase with increasing temperature and pH (Navy 1984b). Hydrolysis products include picrate ion, N-methylpicramide, methylnitramine, nitrite ion, and nitrate ion. In the dark and under buffered, alkaline conditions (pH 9), methylnitramine formation dominated (66%); picrate ion (28%), nitrite (4.1%), nitrate (3.1%), and N-methylpicramide (4.1%) were also formed. Under laboratory light and more acidic conditions (pH 4-6), N-methylpicramide (41%) and nitrate (35.2%) were the major products; picrate ion (3.9%), nitrite (9.4%), and methylnitramine (0.01%) were also formed (Navy 1984b). In sea water at 25 ºC and pH 8.1, 88% of initial tetryl hydrolyzed in 101 days, yielding picric acid as a hydrolysis product. This hydrolysis rate corresponds to a first-order half-life of 33 days (Hoffsommer and Rosen 1973; HSDB 1994).

Under ambient lighting conditions and pH 6, the photolysis rate has been observed to be at least an order of magnitude faster than hydrolysis, with a hydrolysis half-life of approximately 302 days (Navy 1984b). After 20 minutes of incubation in the light, more than 95% of the initial concentration of tetryl (l-20 mg/L) had reacted, but only 3.2% had reacted in the dark. Therefore, photolysis may be the dominant degradation process in sunlit water (Navy 1984b). The photolysis study of a structurally similar compound (TNT) conducted by Mabey et al. (1983) tends to confirm this conclusion. The major detectable photolytic product of tetryl in aqueous solution was reported to be N-methylpicramide (Navy 1984b).

Insufficient data are available to predict the relative importance of biodegradation in water.

5.3.2.3 Soil

Based on effects observed in water (Navy 1984b), tetryl released to soil is expected to be susceptible to slow hydrolysis in acidic and neutral soils and to relatively rapid hydrolysis in highly alkaline soils (HSDB 1994). Samples of water collected from lysimeters containing tetryl-contaminated soil indicated that the major transformation products were picric acid (5-14%) and other polar, watersoluble decomposition products; no tetryl was detected in the water, or in the soil at the end of the study, suggesting complete hydrolysis (Kayser and Burlinson 1988; Navy 1982). The specific reaction leading to these products was not determined. Because tetryl is subject to photolysis in water, it may be susceptible to photolysis on sunlit soil surfaces (HSDB 1994).

Data from composting experiments suggest that biodegradation of tetryl may occur under some conditions (Army 1986a). When tetryl-contaminated sediment was added to hay-horse feed or sewage sludge-wood chip compost, 90% of the tetryl was removed after 44 days. A first-order half-life of 1.2 weeks was calculated for tetryl in a manure-hay-sawdust compost. In a biodegradation study with two types of soils (silt-loam and sandy loam), tetryl was found to undergo rapid biotransformation via two principal pathways (Harvey et al. 1992). The principal product of biodegradation was identified as N-methyl-2,4,6-trinitroaniline. Aminodinitrophenylmethylnitramine and other unidentified polar metabolites were identified as secondary biodegradation products. Mineralization of tetryl to carbon dioxide accounted for 9% of total degradation over a 60-day incubation period. However, the authors did not provide conclusive evidence that the primary degradation product N-methyl-2,4,6-trinitroaniline was not an artifact of methanolic Soxhlet extraction of soil. This may cast doubt on the validity of the conclusions of this soil biodegradation study (Jenkins and Walsh 1994).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

No data were located regarding the levels of tetryl in air.

5.4.2 Water

Seepage water collected in a hole dug at the Joliet Army Ammunition Plant (Joliet, Illinois) in August 1973 contained tetryl at a concentration of 44,000 µg/L (Army 1974, 1990b). Later surveys conducted between 1985 and 1986 showed tetryl was present in groundwater samples taken from monitoring wells around the plant site; it was detected at 67 µg/L in a sample from the tetryl production area, at 34.5 µg/L in samples from the TNT production area, and at 13.7 µg/L in a waste water area (Army 1990b). The groundwater beneath the tetryl manufacturing area of the Alabama Army Ammunition

Plant (Talladega County, Alabama) contained 72.8 µg/L tetryl (ATSDR 1987). Tetryl has been detected in groundwater beneath artificial leaching pits located at the Louisiana Army Ammunition Plant at concentrations ranging from 1.4 to 53 µg /L (Army 1988).

No tetryl was detected (detection limit of 20 µg /L) in samples from 44 groundwater sites, 23 surface water sites, or 5 treatment lagoons located at the Milan Army Ammunition Plant in Tennessee (Army 1980). In addition, sediment samples from the 5 lagoons did not show tetryl to be present (detection limit of 90 µg /L). Tetryl was detected in groundwater samples taken at the Iowa Army Ammunition Plant at a maximum concentration of 49 µg /L; it did not exceed the level of detection (2.9 µg /L) in any surface water samples (Army 1982c).

Sea water samples taken in 1971 from two munitions dumping areas (at depths of 0-20 meters above the bottom and at the centers of the dumping areas) located in the Pacific Ocean (85 miles west of Cape Flattery, Washington) and the Atlantic Ocean (172 miles south-southeast of Charleston, South Carolina) were analyzed for tetryl (Navy 1972). No tetryl was found in any of the samples examined (detection limit of 20 ng/L).

5.4.3 Soil

Analysis of surface soil collected from the Joliet Army Ammunition Plant (Illinois) from 1973 to 1981 showed tetryl levels ranging from 23.5 to 84,400 µg /gram. Analysis of subsurface soil detected levels of 1,450-84,400 µg /gram tetryl. It was estimated that the soil at the Joliet Army Ammunition Plant (Illinois) contained approximately 31,000 pounds of tetryl in August 1973, less than 1 month after tetryl production had been terminated (Army 1974, 1990b). In a 1981 survey of contamination at the Joliet Army Ammunition Plant (Joliet, Illinois), tetryl was found in 2 of 5 samples from the tetryl production area at levels of 23.5-38,500 µg /gram in an old drainage ditch and in a location removed from the ditch, but none was detected in 5 soil samples taken from the same area in 1988 (detection limit of 2.86 µg /gram) (Army 1990b). One of 49 surface soil samples collected from 11 sites at the Milan Army Ammunition Plant (Milan, Tennessee) contained approximately 1.8 µg /gram of tetryl (Army 1980).

At the Louisiana Army Ammunition Plant (a shell manufacturing and explosives loading, assembly, and packing facility near Shreveport, Louisiana), waste waters were trucked to and discharged into on-site artificial leaching pits from 1951 to 1980 (Army 1986a, 1988). Tetryl in surface soil samples taken from the lagoons in 1984 ranged from below detectable levels (detection limit of 0.3 µg /grarn) to 42,217 µg /gram, while tetryl concentrations in the underlying soil cores ranged from below the detection limit to 7,113 µg /gram.

At the Alabama Army Ammunition Plant, tetryl was measured in the soil of the tetryl manufacturing area (13,600 µg /gram) and in the flashing ground (for flash burning of equipment and demolition materials to remove explosive residues) (6,620 ppm) (ATSDR 1987). At the same site, tetryl levels were also reported as <257-6,624 ppb in the flashing ground, >500 ppb in the rifle powder flashing area, and 554 ppb in the demolition landfill (Army 1981b). In the tetryl manufacturing area, a crystalline material suspected of being tetryl was visible in the soil.

Tetryl was detected in sediment samples taken at the Iowa Army Ammunition Plant at a maximum concentration of 33 µg /gram (Army 1982c). However, all soil samples were below the level of detection (2 µg /gram).

Ocean floor sediment samples taken in 1971 from two munitions dumping areas located in the Pacific Ocean (85 miles west of Cape Flattery, Washington) and the Atlantic Ocean (172 miles southsoutheast of Charleston, South Carolina) were analyzed for tetryl (Navy 1972). No tetryl was found in any of the sediment samples analyzed (no detection limit reported).

5.4.4 Other Environmental Media

Samples from ocean floor fauna (rat tail fish and sea cucumbers) taken in 1971 from two munitions dumping areas located in the Pacific Ocean (85 miles west of Cape Flattery, Washington) and the Atlantic Ocean (172 miles south-southeast of Charleston, South Carolina) were analyzed for tetryl (Navy 1972). No tetryl was found in any of the fauna samples analyzed (detection limit of 740 ppt).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population is not likely to be exposed to tetryl. Exposure to tetryl is likely to be limited to areas around military installations, such as Army ammunition plants (where tetryl was manufactured and converted to munitions), around storage and waste sites, and around sites of demilitarization and disposal operations. The most likely route of exposure for populations living near these areas is ingestion of contaminated drinking water: However, no data regarding estimated daily intakes of tetryl through drinking water were found for such populations. Inhalation of contaminated particulate matter produced during incineration, open-air burning, and detonation of tetryl-containing waste material is a possible route of exposure. However, since no monitoring data were located regarding levels of tetryl in air, the extent of exposure by this route is not known. Dermal contact with contaminated soil is also a possible route of exposure. However, no data concerning extent of absorption following dermal contact with tetryl-contaminated soil were located.

Inhalation, dermal, and some oral exposure to tetryl has occurred in workers involved in production and use of tetryl compounds. In the past, workers in munitions plants were exposed to tetryl dust released into workroom air (Cripps 1917; Hardy and Maloof 1950; Hilton and Swanston 1941; Probst et al. 1944; Troup 1946; Witkowski et al. 1942). In one study, air samples taken in 1942 from a small powder house where exploder bags were loaded with weighted tetryl, stemmed, tied, and inspected had tetryl levels ranging from 1 to 18 mg/m^3 (Hardy and Maloof 1950). Workers in these plants were exposed via inhalation of the tetryl dust and by dermal contact with the tetryl powder and pellets. Today, workers engaged in demilitarization operations involving detonation, open-burning, or incineration of tetryl explosives are likely to be exposed to tetryl. The extent of exposure in these workers has not been adequately determined.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Workers who were involved in the production and use of tetryl at Army ammunition plants were exposed to tetryl. Persons living near military installations, such as Army ammunition plants, may be exposed to tetryl from ingestion of drinking water or contact with soil contaminated by past manufacture and use. Persons involved in demilitarization operations or in the clean-up of contaminated sites may be exposed to high levels of tetryl.

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, 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 tetryl is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of tetryl.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda may be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of tetryl as shown in Table 3-2 are not sufficiently characterized to permit estimation of its environmental fate (Army 1987d; HSDB 1994; Navy 1984b). It would be helpful to develop experimental K_{ow} and K_{oc} data for tetryl.

Production, Import/Export, Use, and Release and Disposal. Tetryl is no longer produced in the United States (Army 1984c, 1989b). Production in the United States was limited to Army ammunition plants such as the Joliet Army Ammunition Plant (Illinois), which produced tetryl until 1973 (HSDB 1994). Several other Army ammunition plants that have handled tetryl in the past include Anniston (Alabama), Crane (Indiana), Fort Wingate (New Mexico), Hawthorne (Nevada), Letterkenny (Pennsylvania), Lexington (Kentucky), Louisiana (Louisiana), McAlester (Oklahoma), Milan (Tennessee), Navajo (Arizona), Pine Bluff (Arkansas), Pueblo (Colorado), Red River (Texas), Savanna (Illinois), Seneca (New York), Sierra (California), Tooele (Utah), and Umatilla (Oregon) (Army 1986a, 1986b). Past production and import/export data for tetryl were not available. Tetryl has primarily been used as an explosive (Gibbs and Popolato 1980; HSDB 1994), although it has also been used as a chemical indicator in the pH range between 10.8 and 13.0 (Merck 1989). Tetryl was primarily released to soil, surface water, and groundwater around military installations, such as Army ammunition plants (Army 1974, 1981b, 1987b, 1988; ATSDR 1987), and contamination still remains in some of these areas. Current releases probably occur at waste sites where tetryl is stored and at sites of demilitarization activities. More data on possible releases from these sources are needed in order to better determine populations at risk of exposure to tetryl. Data on the most commonly used disposal methods are sufficient (Army 1986b, 1986d, 1987a); however, more data on amounts of tetryl being disposed of and on alternative disposal methods would be useful. Wastes generated in the manufacturing of tetryl are classified as EPA hazardous wastes and must be disposed of according to EPA regulations (EPA 1990b).

Environmental Fate. Tetryl released to the environment partitions mainly to water and soil (Army 1987d; Lyman et al. 1982; Navy 1984b). Tetryl is transported in soil, surface water, and, rarely, in groundwater (Army 1987d; Swann et al. 1983). Because of its very low vapor pressure, it is unlikely to partition to air (Army 1987d). No data were located regarding atmospheric transport of tetryl. Experimental data are needed regarding photolysis of tetryl in the atmosphere so that the relative contributions of photochemical degradation can be determined. Photolysis and hydrolysis are the primary mechanisms that degrade tetryl in water (HSDB 1994). It would be helpful to develop reliable data for photoreaction, hydrolysis and biodegradation rates of tetryl in natural water, and biodegradation rates of tetryl in natural soils.

Data on the rates of biodegradation, photolysis and hydrolysis of tetryl in natural waters and the rate of biodegradation of tetryl in natural soil would help to estimate more accurately the persistence of tetryl in the environment. Additional data on the nature and fate of transformation products of tetryl in air, water, and soil are also needed.

Bioavailability from Environmental Media. Indirect evidence for absorption of tetryl is provided by the adverse health effects observed in exposed workers (Cripps 1917; Hardy and Maloof 1950; Hilton and Swanston 1941; Troup 1946; Witkowski et al. 1942). However, the relative contribution by the three possible routes (inhalation, oral, and dermal) is not known. Rabbits fed tetryl excreted picramic acid, a metabolite of tetryl, in their urine, showing that tetryl is absorbed following ingestion (Zambrano and Mandovano 1956). The oral and dermal routes of exposure, in particular, may be of concern to humans because of the potential for tetryl to contaminate drinking water and soil. Information regarding absorption of tetryl following ingestion of contaminated drinking water and dermal contact with contaminated water or soil would be useful in characterizing the bioavailability of tetryl from these media.

Food Chain Bioaccumulation. Since tetryl is likely to be bound strongly to fish tissues, the estimated BCF values based on K_{ow} (Army 1987d; HSDB 1994; Lyman et al. 1982) is likely to be questionable. Therefore, it would be useful to develop experimental data for BCF in aquatic organisms. Based on estimated plant-soil and beef fat-diet partition coefficients, bioaccumulation in plants and animals is expected to be low (Army 1987d). However, data exist to suggest that tetryl may bind to macromolecules in plant and animal tissues (Army 1981a), implying that bioconcentration is possible. No experimental data were located that would support either possibility. Experimental data are needed regarding the biomagnification potential of tetryl in both aquatic and terrestrial food chains. Primary emphasis needs to be given to development of a method that will enable tetryl to be extracted from plants and animal tissue. Metabolism data could also provide useful information that would help in determining the potential for bioaccumulation within organisms.

Exposure Levels in Environmental Media. Tetryl has been detected in seepage water, groundwater, and surface and subsurface soil at military installations (Army 1980, 1981b, 1986a, 1988, 1990b; ATSDR 1987; HazDat 1994). More data are needed regarding levels of tetryl in surface water, groundwater, soil, and air in and around these sites. Quantitative information is needed to assess the potential for human exposure and to better identify exposed populations.

Exposure Levels in Humans. Biomarkers for exposure to tetryl, especially metabolic products need to be identified so that biological monitoring studies can be conducted. Data are needed both for occupationally exposed populations and for populations living in the vicinity of Army ammunition plants and hazardous waste sites. These data would aid in evaluating the extent of human exposure.

Exposure Registries. No exposure registries for tetryl were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this substance.

5.7.2 Ongoing Studies

No ongoing studies on tetryl were located.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring tetryl in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify tetryl. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect tetryl in environmental samples are the methods approved by federal organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL SAMPLES

No analytical methods specifically used for the determination of tetryl in biological fluids and tissues were located. One attempt to develop a method for detecting tetryl in animal tissues using highperformance liquid chromatography (HPLC) with ultraviolet (UV) detection was unsuccessful because of suspected metabolism and binding of the parent compound and/or metabolites to macromolecules (Army 1981a). However, methods were located for the detection of the tetryl metabolites, picric acid and picramic acid, in urine and for the analysis of tetryl in hand swabs. Table 6-l is a summary of methods used to determine tetryl metabolites in urine and tetryl in hand swabs.

Methods to detect picric acid and picramic acid in rabbit urine using calorimetric assays have been reported (Zambrano and Mandovano 1956). The detection limits were in the sub- to low ppm range, but no information on recovery or precision was given.

Methods for the analysis of tetryl in hand swabs are used in forensics, but they could also be used to determine if dermal exposure of workers has occurred. The methods that have been used for the determination of trace amounts of tetryl on hands include high resolution gas chromatography (HRGC) with electron capture detection (ECD) or thermal energy analyzer (TEA), or HPLC with TEA or electrochemical detection (ED) (Douse 1982, 1985; Fine et al. 1983, 1984; Lloyd 1983a, 1983b). Thin-layer chromatography (TLC) has also been tested, but because of the large amounts of sample

TABLE 6-1. Analytical Methods for Determining Tetryl in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine (picric acid)	Add lead acetate to sample; filter and add sulfuric acid; filter and extract with chloroform; filter organic phase; add ammonia to an aliquot of the extract; add Grinbert reagent (ferrous sulfate/tartaric acid/water) to bottom of test tube	Colorimetric	1 mg/L	NR	Zambrano and Mandovano 1956
Urine (picramic acid)	Add sulfuric acid and sodium nitrate to sample; cool and add ammonia saturated with β-naphthol	Colorimetric	0.05 mg/L	NR	Zambrano and Mandovano 1956
Hand swabs	Wipe hand with swab soaked in ether; extract with ether; centrifuge to remove debris; decant supernatant and evaporate; redissolve in pentane; clean up on Amberlite XAD-7® beads, elute with ethyl acetate; evaporate; redissolve in pentane and repeat Amberlite XAD-7® clean-up	HRGC/ECD	50 ng/swab (1.7 ng/inj)	25	Douse 1982
		TLC	60 ng/swab	NR	
Hand swabs	Wipe hand with dry swab; extract with methanol/potassium phosphate; directly inject standards	HPLC/ED (PMDE)	24 pg/inj	44–91	Lloyd 1983a, 1983b
Hand swabs	Wipe hand with swab soaked in acetone; squeeze out acetone and concentrate	HPLC/TEA; HRGC/TEA	Low pg	NR	Fine et al. 1984

ECD = electron capture detection; ED = electrochemical detection; HPLC = high-performance liquid chromatography; HRGC = high resolution gas chromatography; inj = injection; NR = not reported; PMDE = pendant mercury drop electrode; TEA = thermal energy analyzer; TLC = thin-layer chromatography

required for the analysis, it is useful only as a confirmatory test (Douse 1982). Both HPLC and HRGC can rapidly separate tetryl from other explosive compounds, but HPLC has the advantage of being run at ambient temperature. This decreases temperature-related breakdown of the analyte and yields higher recoveries. The type of detector seems to be the most important factor in determining which of the reported methods is most useful in the analysis of tetryl in hand swabs. ECD appears to be less sensitive (ng amounts) than either TEA or electrochemical detection using pendant mercury drop electrode (PMDE) (pg amounts) (Douse 1982; Fine et al. 1983; Lloyd 1983a, 1983b). In addition, a clean-up step using ECD is usually required to prevent matrix interference (Douse 1982, 1985). Both TEA and PMDE appear to have greater selectivity than ECD, and because of the selectivity of the detector, a clean-up step was not required (Fine et al. 1983; Lloyd 1983b). Both TEA and PMDE methods are rapid, selective, and have high precision (Fine et al. 1983; Lloyd 1983b).

6.2 ENVIRONMENTAL SAMPLES

A variety of methods have been described for the detection of tetryl in environmental samples, including air, fresh water and sea water, soil, sediment, ocean floor fauna, and explosives. Table 6-2 is a summary of several representative methods for determining tetryl in environmental media.
A single method of analyzing tetryl in air was located (NIOSH 1977). The method utilized spectrophotometric analysis. Air samples were collected on a cellulose membrane filter and then extracted with N,N-diethylethanolamine.

The primary analytical methods for determining tetryl in water are gas chromatography (GC), GC/ECD, HRGC/ECD, HPLC/ED, HPLCKJV, and mass spectrometry (MS) (Army 1981c, 1984c, 1986c, 1988, 1989a; Belkin et al. 1985; Feltes and Levsen 1989; Hoffsommer and Rosen 1972; Yinon and Laschever 1982). These methods have been used to determine tetryl in sea water, well water, surface water, groundwater, and drinking water. Both GC and HPLC methods have been applied to the analysis of tetryl. One drawback with GC analysis is that thermally labile chemicals, such as tetryl, are subject to a significant amount of heating. This introduces the likelihood of partial degradation (Army 1986c). Liquid chromatographic methods, by contrast, do not volatilize the sample; therefore, thermal degradation was not a complication (Army 1986c). Following concentration of samples by liquid-liquid extraction or by solid phase extraction with C-18 adsorbents, HPLCAJV method can attain a detection limit of 0.05 ppb for tetryl in water samples (Levsen et al. 1993).

TABLE 6-2. Analytical Methods for Determining Tetryl in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collect sample on a cellulose membrane filter; extract with N,N-diethylethanolamine	Spectrophotometry	0.15 mg/m^3	NR	NIOSH 1977 (Method S225)
Water	Filter and extract sample with toluene	GC/ED	23.9 mg/L	NR	Army 1981c
Water	Inject sample directly into instrument	MS (CI)	40 mg/L	NR	Yinon and Laschever 1982
Water	Dilute aqueous sample 1:1 with acetonitrile; filter; inject into instrument	HPLC/UV	26 µg/L	96.7	Army 1988
Sea water	Add internal standard to sample; extract with benzene; evaporate; redissolve in benzene	GC/ECD	≈20 ng/L	70	Hoffsommer and Rosen 1972
Well water, surface water	Collect sample on Amberlite XAD-4® resin; rinse sorbent with distilled water and elute with acetone; concentrate; add methanol/water	HPLC/ED	2 µg/L	30–120	Army 1986c
Surface water (brooks, ponds)	Collect sample on Amberlite XAD-2/4/8® resin; dry; desorb with dichloromethane; dry over anhydrous sodium sulfate; solvent exchange to methanol and concentrate; elute from reversed phase column with methanol/water	HPLC/UV	50 ng/L	85–105	Feltes and Levsen 1989
Drinking water	Extract with toluene; inject into instrument	HRGC/ECD	1 ppb	100–107	Belkin et al. 1985

TABLE 6-2. Analytical Methods for Determining Tetryl in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Groundwater	Collect sample on Hayesep-R® solid sorbent cartridge; elute with acetone and concentrate; add internal standard; solvent exchange to methanol/water	HPLC/UV/PC	5–14 µg/L	62–82	Army 1989a
Water	Analyze tetryl using a monoclonal antibody with the required reactivity and specificity	Immunoassay	2 ppm	NR	Krogsrud and Lang 1990
Soil	Air dry, grind, and homogenize sample; extract with acetonitrile in ultrasonic bath; flocculate with aqueous $CaCl_2$ and filter clarified solution; elute from reverse phase column with methanol/water	HPLC/UV	0.12 µg/g	83	Jenkins et al. 1989 (Proposed AOAC method)
			0.12 µg/g	96.8	Army 1990a
			NR	70–100	Bauer et al. 1990
Soil	Stabilize soil samples at 20–30% moisture; homogenize; extract in acetonitrile with sonication; filter; elute from reverse-phase column with methanol/water	HPLC/UV	4.59 µg/g	103.5	Bongiovanni et al. 1984
Soil	Air dry, grind, and homogenize; extract with acetonitrile in ultrasonic bath; filter; elute from reversed-phase column with methanol/water	HPLC/UV	5.5 µg/g	97.1	Army 1987b
Soil	Air dry and sieve sample; extract with toluene; clean up on Florisil	GC/ECD	1.5 µg/g	NR	Army 1981a

TABLE 6-2. Analytical Methods for Determining Tetryl in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Sediment	Extract with benzene; centrifuge; evaporate; redissolve in benzene; clean-up with TLC; extract with benzene; evaporate; redissolve in benzene	GC/ECD	NR	NR	Navy 1972
Ocean floor fauna (rat tail fish, sea cucumber)	Homogenize sample in benzene; centrifuge; filter supernatant; clean up with TLC; extract with benzene; evaporate; redissolve in benzene	GC/ECD	≈740 pg/g	NR	Navy 1972
Explosives	Dissolve sample in acetone; dilute in methanol	HRGC/TEA HPLC/TEA	25 pg low pg	NR NR	Fine et al. 1984
Explosive debris	Extract sample with acetone; clean up on cyclohexyl column; wash with acetonitrile/water; elute with methylene chloride/hexane onto a cyanopropyl column; wash with hexane; elute with acetonitrile/water	HPLC/UV	NR	96	Strobel and Tontarski 1983
Explosives, explosive residues	Dissolve in acetone or methanol; elute from HPLC column with methanol/ammonium acetate	HPLC/TSP/MS	Low pg	NR	Berberich et al. 1988
Explosives	NR	HRGC/ECD	40 pg	NR	Douse 1981
Tetryl, picric acid, and 2,4,6-trinitroanisol	Irradiate single crystals of explosives with high-power laser pulses	MS	NR	NR	Bhasu et al. 1991

$CACl_2$ = calcium chloride; CI = chemical ionization; ECD = electron capture detector; ED = electrochemical detection; GC = gas chromatography; HPLC = high performance liquid chromatography; HRGC = high resolution gas chromatography; MS = mass spectrometry; NR = not reported; PC = photo-conductivity detector; TEA = thermal energy analyzer; TLC = thin-layer chromatography; TSP = thermospray; UV = ultraviolet detection

6. ANALYTICAL METHODS

GC/ECD has been used to analyze tetryl in sea water with sensitivity in the ppt range (Hoffsommer and Rosen 1972). Recovery of tetryl was adequate (70%) (Hoffsommer and Rosen 1972). The sensitivity of the HRGC/ECD method for analysis of tetryl in drinking water was in the low ppb range (Belkin et al. 1985). The sample preparation was simple and yielded recoveries of 100% (Belkin et al. 1985). Precision was very good, as shown by the relative standard deviation (RSD) range of 5.4- 7.5% for tetryl (Belkin et al. 1985).

Tetryl has also been measured in well water and surface water by HPLC/ED, using a gold-mercury electrode (Army 1986c). The technique provides a higher degree of selectivity than either UV or ECD. Sensitivity is in the low ppb range, but precision was not reported. Tetryl was best recovered using the Amberlite XAD-4® resin. A limitation with this method was that tetryl was not stable in acetone; therefore, the acetone eluates from the resin must be analyzed as quickly as possible (Army 1986c). Reversed-phase HPLC/UV is a highly selective technique that yields excellent recovery (Army 1988; Feltes and Levsen 1989). It can be used as an alternative method to gas chromatography (Feltes and Levsen 1989). Sensitivity was in the ppb-to-ppt range, and the precision was acceptable (<5-21% RSD) (Army 1988; Feltes and Levsen 1989). Tetryl was found to be unstable in a methanol-water matrix if left for an extended period of time, but was stable in a water-acetonitrile matrix. Therefore, dilution with acetonitrile prior to filtration was recommended (Army 1988). Tetryl has also been analyzed in groundwater by HPLC using UV and photo-conductivity (PC) in tandem (HPLC/UV/PC) (Army 1989a). This method allowed a solid sorbent cartridge to be used to collect the sample, which improved selectivity (Army 1989a), The serial use of the detectors effectively differentiated tetryl from other explosives and from contaminants in the solid sorbent cartridge. Sensitivity was in the low ppb range. Of all the explosives studied, tetryl was the only compound that showed evidence of chemical decomposition. Harsh conditions during the Hayesep-R® treatment were reflected in reduced recoveries (62-82%) and precision (7-47% RSD) (Army 1989a). To prevent negative baseline drift and random spikes in the PC, only highly purified water must be used and the eluent must be exhaustively degassed.

Other methods that have been used to determine tetryl in water are MS and immunoassays (Krogsrud and Lang 1990; Yinon and Laschever 1982). MS with chemical ionization (CIMS) permits direct injection of the water sample into the analytical instrument, but sensitivity was substantially less (ppm range) than with GC/ECD (ppt range) (Yinon and Laschever 1982). However, its selectivity makes it a good method for screening samples for further analysis (Yinon and Laschever 1982). A method has been developed for the analysis of tetryl in water using monoclonal antibodies (Krogsrud and Lang 1990). Because the detection limit achieved by the tetryl immunoassay was significantly higher (2 ppm) than that obtainable by more conventional methods such as HPLC, the assay will more likely be used as a field screen rather than a quantitative laboratory method (Krogsrud and Lang 1990).

Tetryl can be analyzed in soil using HPLC/UV (Army 1987b, 1990a; Bauer et al. 1990; Bongiovanni et al. 1984; Jenkins et al. 1989). It has also been qualitatively analyzed using HPLCAJV, GCYECD, and GC/MS (Army 1980, 1981c). The preparation steps for HPLC analysis generally involved drying, grinding, homogenizing, and extracting with acetonitrile in an ultrasonic bath (Army 1987b; Bauer et al. 1990; Bongiovanni et al. 1984; Jenkins et al. 1989). The method was rapid and selective and generally gave high recoveries from complex samples (Army 1987b; Bongiovanni et al. 1984; Jenkins et al. 1989). Supercritical carbon dioxide extraction also provides high recovery (Engelhardt et al. 1993). The lower recovery (≈70%) and precision (≈18% RSD) that were found in some laboratories were attributed to thermal degradation of tetryl (Bauer et al. 1990). The problem was corrected when the sonic bath temperatures were maintained near ambient levels (Bauer et al. 1990). Similarly, tetryl is not stable during methanolic Soxhlet extraction (Jenkins and Walsh 1994). Sensitivity in the low ppm to low ppb range has been reported and precision was excellent (0.1-6% RSD) (Army 1987b; Bauer et al. 1990; Bongiovanni et al. 1984; Jenkins et al. 1989).

GC/ECD has been used to measure tetryl in ocean floor sediment and fauna (Navy 1972). Preparation steps generally involved homogenization and extraction with benzene, filtering, clean-up with TLC, and concentration. The sensitivity for detecting tetryl in ocean floor fauna using this method was estimated to be in the ppt range. Precision and accuracy were not reported (Navy 1972).

An attempt to develop an HPLC/UV method for detecting tetryl in plant stems was unsuccessful because of binding of the compound to macromolecules in the tissue (Army 1981a). A methodology based on solvent extraction of plant tissues followed by silica gel fractionation and HPLCKJV detection was used for the determination of tetryl in plant tissues (Harvey et al. 1993). This method allowed 82.7% recovery of tetryl from fortified bush bean leaves.

Several methods have been used to detect and measure tetryl in explosive materials or mixtures and in debris from explosions. The most common separation procedures used are HPLC and HRGC. These methods have been paired with TEA, UV, ECD, and MS (Army 1988; Douse 1981; Fine et al. 1984;

Strobe1 and Tontarski 1983; Tamiri and Zitrin 1986). Several of the methods used were similar to those used to analyze for tetryl in hand swabs. The identification of tetryl in explosive debris usually involves extracting the debris with a suitable polar solvent such as acetone or methanol. TEA was very selective for nitroso compounds and nitramines (e.g., tetryl) and when paired with either HPLC or HRGC gave excellent selectivity, precision (2.6% RSD when paired with HRGC), and high sensitivity (low pg) (Fine et al. 1984). Because of the selectivity of this technique, there was no need for sample clean-up before analysis (Fine et al. 1984). The use of a dual column clean-up technique using both polar and nonpolar sorbents gave excellent recovery (96%) with HPLC/UV (Strobel and Tontarski 1983). Sensitivity and precision were not reported (Strobe1 and Tontarski 1983). With HPLC, tetryl elutes very near TNT, but a separation of TNT and tetryl may be achieved using a methanol/water (50/50) mobile phase (Army 1977). The level of sensitivity for the HPLC/UV method permits a lower limit of detection in the ppb range (Army 1977). The sensitivity of ECD was comparable to TEA (pg amounts) and precision was very good (5% RSD) (Douse 1981). A sophisticated method linking HPLC, thermospray (TSP), and MS (with both positive and negative chemical ionization) has also been proposed as a sensitive (low pg range) and selective method for detecting tetryl in explosives and explosive debris (Berberich et al. 1988). Other methods include photochemical decomposition, followed by ion-pair chromatography with electrochemical detection (Engelhardt et al. 1993) and micellar electrokinetic capillary chromatography (Kleiboehmer et al. 1993).

HRGC/MS has been used to identify tetryl in explosive debris (Tamiri and Zitrin 1986). Tetryl was reported to decompose by hydrolysis during the analysis, but its decomposition product, N-methylpicramide, was well defined and served as evidence for the presence of tetryl (Tamiri and Zitrin 1986). The authors of this report concluded that the hydrolysis of tetryl during the GC analysis could take place at the injector, which was held at relatively high temperatures (Tamiri and Zitrin 1986). MS can be used by itself for the identification of tetryl and its decomposition products, picric acid and 2,4,6-trinitroanisol, generated by laser irradiation (Bhasu et al. 1991). Chemical ionization mass spectrometry (CIMS) has also been successfully used to identify tetryl (Zitrin and Yinon 1976).

Other methods that have been used to determine tetryl in explosive material and debris from explosions are thin layer chromatography (TLC), supercritical fluid chromatography (SFC)AJV, and nuclear magnetic resonance (NMR) spectrometry (Griest et al. 1989; Margalit et al. 1986; Parker et al. 1975). TLC has been used to confirm the presence of tetryl in explosive residues using various solvent systems (Parker et al. 1975). The TLC method is suited to the analysis of bomb scene residues (Parker et al. 1975). SFC is complementary to GC and HPLC because of its ability to mobilize compounds not readily chromatographed by GC and because it can be interfaced with GC-like ionization detectors and mass spectroscopy more easily than can HPLC (Greist et al. 1989). The precision for the standard solutions was very good (2.8% RSD) with sensitivity in the low-ppm range (Griest et al. 1989). However, more work is needed to improve the mobile phase and column packing material before samples in complex matrices can be analyzed by this method. NMR spectrometry has also been applied to the analysis of explosive samples (Margalit et al. 1986). For unexploded samples, NMR was found to be a simple, fast, and reliable method, allowing for identification of mixtures without preseparation. Some of the postexplosion samples, which required sample preparation, were also successfully analyzed by NMR. Although sensitivity problems still exist, NMR shows promise for the difficult field of postexplosion analysis (Margalit et al. 1986).

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, 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 tetryl is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of tetryl.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda may be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Methods have been developed for detecting tetryl metabolites (picric and picramic acid) in urine (Zambrano and Mandovano 1956) and analyzing hand swabs for explosives (Douse 1982; Fine et al. 1984; Lloyd

1983b), including tetryl. The calorimetric assays for tetryl metabolites in urine have been used only in animal studies and lack sensitivity. In addition, they are only semiquantitative, and no data on recovery or precision were provided. Analysis methods for tetryl in hand swabs have been used primarily in forensics and not on workers or the general population. No methods for measuring tetryl or its metabolites in the tissues, fluids, or excreta of humans or animals were located. One attempt to develop a method failed because of suspected binding of tetryl to macromolecules in the animal tissue (Army 1981a). There are no known sensitive biomarkers of exposure or effect for tetryl. More sensitive methods for analyzing tetryl metabolites in urine are needed in order to assess the utility of urinary metabolites in monitoring human exposure. Development of a method for extracting tetryl and metabolites from biological samples are needed so that important information on tetryl metabolism and bioconcentration can be obtained and so that biomarkers of tetryl exposure can be better defined.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. One spectrophotometric method for detecting tetryl in air was located (NIOSH 1977). Methods exist to detect and quantify tetryl and/or its degradation products in water (Army 1986c, 1988, 1989a; Belkin et al. 1985; Feltes and Levsen 1989; Hoffsommer and Rosen 1972; Yinon and Laschever 1982), soil and sediments (Army 1987b, 1990a; Bauer et al. 1990; Bongiovanni et al. 1984; Jenkins et al. 1989; Navy 1972), ocean floor fauna (Navy 1972), and explosive materials and debris from explosions (Army 1988; Douse 1981; Fine et al. 1984; Griest et al. 1989; Strobe1 and Tontarski 1983; Tamiri and Zitrin 1986). These methods are relatively sensitive, selective, and reliable, and can be used to detect low levels of the compound in the environment (specifically water and soil). The most sensitive and selective methods for detecting tetryl in water and soil are HPLC-based with detection by UV and ECD (Army 1986c, 1987b, 1988, 1989a; Bongiovanni et al. 1984; Feltes and Levsen 1989; Lyter 1983). However, precision data are needed to assess the reproducibility of these methods. Methods are needed to detect and measure tetryl in fish, plants, and other aquatic and terrestrial organisms. One attempt to develop an HPLC/UV method for determining tetryl in plant tissue was unsuccessful because of binding of the compound to macromolecules in the plant tissue (Army 1981a). A method reportedly used to determine tetryl in ocean floor fauna did not give recovery data (Navy 1972). A reliable, well-characterized method for extracting and measuring tetryl in biological tissue is needed in order to investigate bioaccumulation in aquatic and terrestrial species. The most sensitive and selective methods for detecting tetryl in explosive materials and debris from explosions are HPLC/TEA and HPLC/ECD (Army 1977; Douse 1981; Fine et al. 1984). Recovery and precision data are needed in order to adequately assess the reproducibility of these methods.

Improvements that have been made in current methods and the improvements proposed for newer methods (Griest et al. 1989; Krogsrud and Lang 1990) will be useful in monitoring environmental contamination from manufacture and disposal of tetryl and in forensics.

6.3.2 Ongoing Studies

No ongoing analytical methods studies were located.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding tetryl in air, water, and other media are summarized in Table 7- 1.

ATSDR has not derived MRLs for tetryl because of the lack of reliable human or animal studies which identify levels of exposure associated with adverse health effects. In addition, EPA has not verified a reference dose (RfD) for oral exposure or a reference concentration (RfC) for inhalation exposure to tetryl.

The transportation of explosives including tetryl must be in accordance with the Department of Transportation hazardous material regulations (49 CFR 171-190) and the motor carrier safety regulations (49 CFR 390-398). Numerous states have established regulations on explosives for air quality control, solid waste disposal, storage, manufacture, and use.

Table 7-1. Regulations and Guidelines Applicable to Tetryl

Agency	Description	Information	Reference
NATIONAL			
Regulations: a. Air:			
OSHA	PEL TWA (skin designation)	1.5 mg/m^3	OSHA 1989a (29 CFR 1910.1000) OSHA 1989b
b. Other			
DOT	Class A explosive (high explosive domestic transportation limited to road and water)(cargo only, in magazines)	Yes	DOT 1989a (49 CFR 172.101) DOT 1989b
Guidelines: a. Air			
ACGIH	TLV TWA	1.5 mg/m^3	ACGIH 1991
NIOSH	REL (10-hour TWA) (skin designation)	1.5 mg/m^3	NIOSH 1990
STATE			
Regulations and Guidelines: a. Air:			
	Acceptable Ambient Air Concentrations		NATICH 1991
CT	8 hr avg. time	30.0 μg/m^3	
FL-Pinellas	8 hr avg. time	15.0 μg/m^3	
FL- Pinellas	8 hr avg. time	3.6 μg/m^3	
MD		0.00	
ND	8 hr avg. time	15 μg/m^3	
NV	8 hr avg. time	36 μg/m^3	
TX	30 min avg. time	1.0 μg/m^3	
TX	30 min. avg. time	0.1 μg/m^3	
VA	24 hr avg. time	25 μg/m^3	
KY	Significant emission levels of toxic air pollutants	3.827×10^{-4} pounds/hour	NREPC 1986 (KAR 401 63:022)

Table 7-1. Regulations and Guidelines Applicable to Tetryl (continued)

Agency	Description	Information	Reference
STATE (cont.)			
b. Other	Transportation of explosives is in accordance with the U.S. Department of Transportation hazardous materials regulations (49 CFR 171-190) and the motor carrier safety regulations (49 CFR 390-398) with some exceptions or additional requirements that vary from state to state. "Yes" in the Information column indicates that provisions for 49 CFR 171-170 and 49 CFR 390-398 exist in the specified state.		CELDs 1991
AL		Yes	
AK		Yes	
AZ		Yes	
CA		Yes	
CT		Yes	
CO		Yes	
DE		Yes	
FL		Yes	
GA		Yes	
HI		Yes	
ID		Yes	
IN		Yes	
IA		Yes	
LA		Yes	
MD		Yes	
MA		Yes	
MI		Yes	
MN		Yes	
MS		Yes	
MO		Yes	
MT		Yes	
NE		Yes	
NJ		Yes	
NM		Yes	
NC		Yes	
ND		Yes	

Table 7-1. Regulations and Guidelines Applicable to Tetryl (continued)

Agency	Description	Information	Reference
STATE (cont.)			
NY		Yes	
OH		Yes	
OR		Yes	
RI		Yes	
SD		Yes	
TN		Yes	
TX		Yes	
UT		Yes	
VA		Yes	
VT		Yes	
WA		Yes	
WA-DC		Yes	
WV		Yes	
WI		Yes	
WY		Yes	
	Rules and regulations for air quality control and/or solid waste disposal have been established for explosives in general. The regulations vary from state to state.		CELDs 1991
AL	Pretreatment standards for discharge Hazardous waste: Thermal treatment	Yes Yes	
AZ	Solid waste collection	Yes	
AR	Solid waste storage and collection	Yes	
CO	Fugitive dust	Yes	
CT	Hazardous waste: Thermal treatment	Yes	
FL	Hazardous waste: Thermal treatment	Yes	
GA	Open burning	Yes	
IL	Sewer discharge	Yes	
IN	Open burning	Yes	
KY	Hazardous waste management	Yes	
LA	Open burning	Yes	
MN	Hazardous waste management	Yes	

Table 7-1. Regulations and Guidelines Applicable to Tetryl (continued)

Agency	Description	Information	Reference
STATE (cont.)			
NH	Open burning	Yes	
NJ	Hazardous waste management	Yes	
NM	Hazardous waste management	Yes	
NV	Hazardous waste management	Yes	
NC	Hazardous waste: Thermal treatment	Yes	
ND	Fugitive emissions	Yes	
PA	Fugitive emissions	Yes	
SC	Open burning	Yes	
TN	Hazardous waste: Thermal treatment	Yes	
UT	Hazardous waste management	Yes	
VT	Open burning	Yes	
VA	Solid waste management	Yes	
WI	Open burning and malodorous emissions	Yes	
WV		none	
WI		none	
	Explosive control laws regulate storage, manufacture, and use. The regulations vary from state to state.		CELDs 1991
AK		Yes	
CA		Yes	
CT		Yes	
GA		Yes	
HI		Yes	
IN		Yes	
IA		Yes	
KS		Yes	
NJ		Yes	
MS		Yes	
NB		Yes	
NJ		Yes	
OK		Yes	
OR		Yes	

Table 7-1. Regulations and Guidelines Applicable to Tetryl (continued)

Agency	Description	Information	Reference
STATE (cont.)			
WA-DC		Yes	
WV		Yes	
WI		Yes	

NOTE: Units in table reflect values and units of measure designated by each agency in its regulations or advisories.

[a] Not classifiable as to human carcinogenicity.

ACGIH = American Conference of Governmental and Industrial Hygienists; CELDs = Comprehensive Environmental Legislative Database; CFR = Code of Federal Regulations; DOT = Department of Transportation; NATICH = National Air Toxics Information Clearinghouse; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = *Permissible exposure limit*; REL = Recommended Exposure Limits; TLV = Threshold limit value; TWA = Time weighted average

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9. GLOSSARY

Acute Exposure - Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{OC}) - The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd) - The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) - The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL) - The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen - A chemical capable of inducing cancer.

Ceiling Value - A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure - Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity - The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity - Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory - An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH) - The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure - Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

9. GLOSSARY

Immunologic Toxicity - The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro - Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo - Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC$_{LO}$) - The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC$_{50}$) - A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD$_{(LO)}$ - The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD$_{(50)}$) - The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT$_{(50)}$) - A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) - The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations - Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level - An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen - A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity - The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) - The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K$_{OW}$) - The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL) - An allowable exposure level in workplace air averaged over an 8-hour shift.

q1* - The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The ql* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually pg/L for water, mg/kg/day for food, and pg/m^3 for air).

Reference Dose (RfD) - An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) - The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 3 11 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity - The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL) - The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity - This term covers a broad range of adverse effects on target orgatis or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen - A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) - A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) - An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50}) - A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF) - A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.
The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-l and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer endpoints, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-l and Figure 2-l are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-l) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures,

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 " 18r" data points in Figure 2-l).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.4, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAFLs and LOAELs from different studies. In this case (key number lS), rats were exposed to toxaphene via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in chapter 8 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "c" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.0006 ppm.

LEGEND

See Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.0006 ppm (see footnote "c" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → **TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
3 → Systemic	5 ↓	6 ↓	7 ↓	8 ↓	9 ↓		10 ↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer						11 ↓	
38	Rat	18 mo 5d/wk 7hr/d				20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d				10 (CEL, lung tumors, *nasal tumors)*	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 2-1.

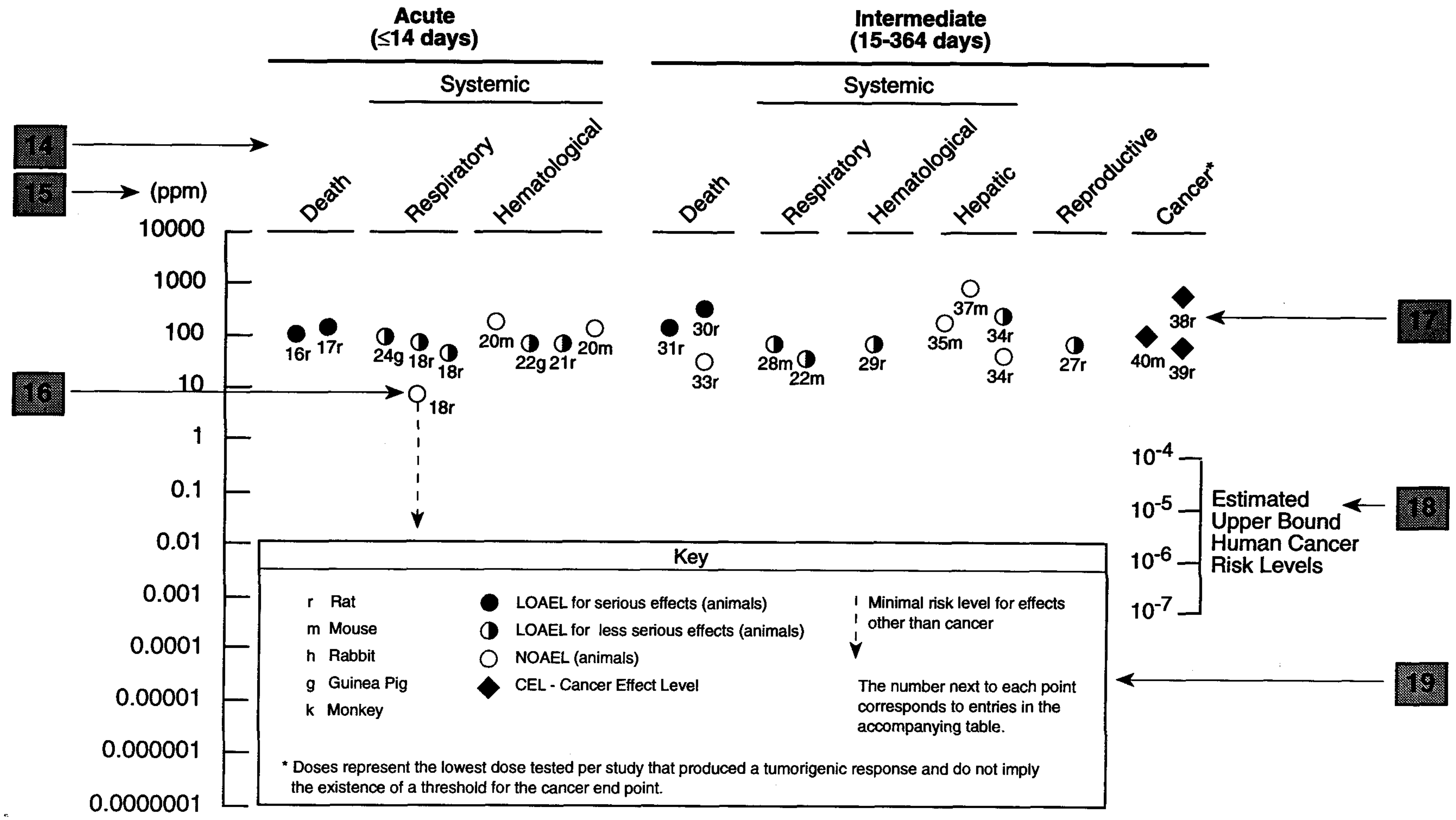
12 → [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = days(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

SAMPLE

13

Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation



* Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.

Chapter 2 (Section 2.4)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers endpoints in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer endpoints (if derived) and the endpoints from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.4, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.6, “Interactions with Other Substances,” and 2.7, “Populations that are Unusually Susceptible” provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOD	Department of Defense
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient

L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
RDX	hexahydro-1,3,5-trinitro-1,3,5-triazine
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification

APPENDIX B

SMR	standard mortality ratio
STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TNT	2,4,6-trinitrotoluene
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
µm	micron
µg	microgram

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