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 (Gell 1944), is discussed below. No other health effects were studied in animals.

2.2.1.1 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 (Gell 1944).

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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. HEALTH EFFECTS

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.

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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. HEALTH EFFECTS

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.

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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.

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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.

2. HEALTH EFFECTS

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).

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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. HEALTH EFFECTS

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.

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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.

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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.

2. HEALTH EFFECTS

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;

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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 (Gell 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.

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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 (Gel1 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	Results: 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. HEALTH EFFECTS

2.9.1 Existing Information on Health Effects of Tetryl

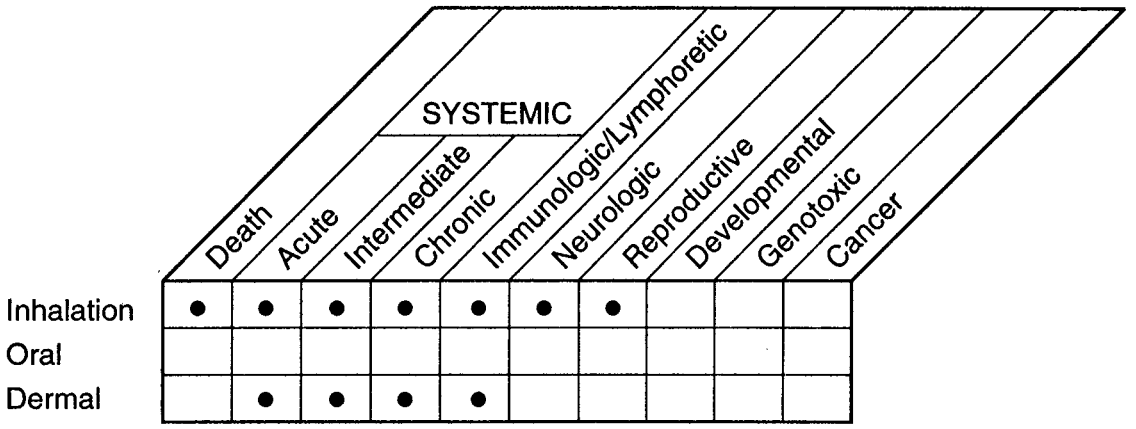
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to tetryl are summarized in Figure 2-l. The purpose of this figure is to illustrate the existing information concerning the health effects of tetryl. Each dot in the figure indicates that one or more studies 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.

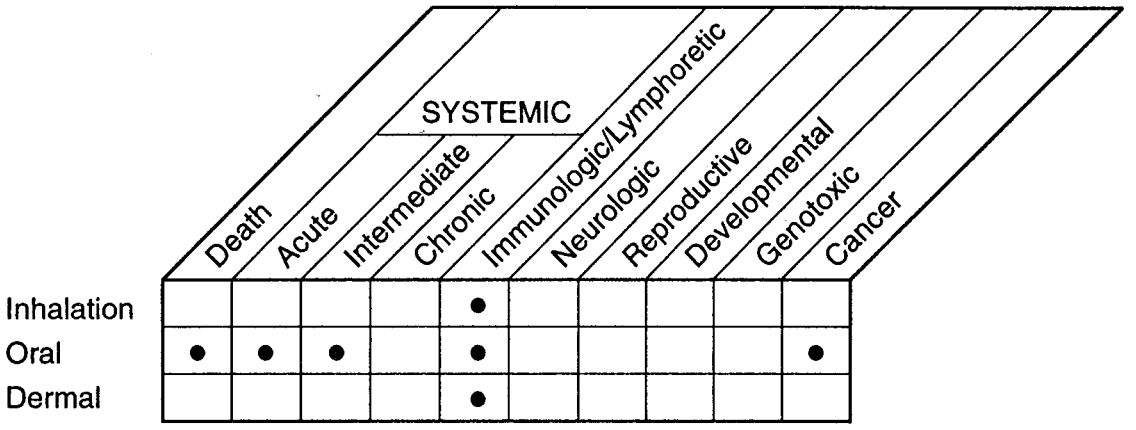
2.9.2 Identification of Data Needs

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



Human



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.