

U.S. Army Center for Health Promotion  
and Preventive Medicine

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**Wildlife Toxicity Assessment for  
N-Methyl-N,2,4,6-Tetranitroaniline  
(Tetryl)**

**JULY 2002**

**Prepared by  
Health Effects Research Program  
Environmental Health Risk Assessment Program**

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## Wildlife Toxicity Assessment for Tetryl

CAS No. 479-45-8

July 2002

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### 1. INTRODUCTION

Tetryl (CAS No. 479-45-8) is one of several compounds that have been released to the environment during the manufacture, load, and assembly and pack (LAP) activities at U.S. Army ammunition plants (AAPs) and other military installations. Structurally, the compound resembles picric acid with an additional N-methylnitramine substituent group (C<sub>7</sub>H<sub>5</sub>N<sub>5</sub>O<sub>8</sub>). In addition to “tetryl” it is known as N-picryl-N-methyl-nitramine, N-methyl-N-2,4,6-tetranitrobenzamine, and nitramine, among others (ATSDR, 1995). This Wildlife Toxicity Assessment summarizes current knowledge of the likely harmful impacts of tetryl on wildlife, with emphasis on identifying levels that may adversely affect wildlife species. Evaluating the toxicity of this compound will facilitate the derivation of toxicity reference values (TRVs) that could serve as protective exposure standards for wildlife species living in the vicinity of affected sites. The protocol for the performance of this assessment is documented in the U.S. Army Center for Health Promotion and Preventive Medicine Technical Guide 254, the *Standard Practice for Wildlife Toxicity Reference Values* (USACHPPM 2000).

### 2. TOXICITY PROFILE

#### 2.1 Literature Review

Relevant biomedical, toxicological and ecological databases were electronically searched May 5, 2000, using Dialog to identify primary reports of studies and reviews on the toxicology of tetryl. Separate searches were carried out linking the compound to either laboratory mammals, birds, reptiles and amphibians (combined) and wild mammals. In general, a two-tiered approach was used in which all citations were first evaluated as titles and “key words in context.” All available abstracts of those articles that were selected in the first tier as possibly relevant to TRV development were further evaluated for relevancy and retained for evaluation in the second tier. For tetryl, 11 articles were marked for retrieval from 31 initial hits. Details of the search strategy and the results of the search are documented in Appendix A.

In addition to a Dialog search, a number of U.S. Army reports were identified in the Defense Technical Information Center (DTIC). Secondary references and sources of information on tetryl included an Agency for Toxic Substances and Disease Registry (ATSDR) *Toxicological Profile for Tetryl*

(ATSDR,1995), the National Library of Medicine's Hazardous Substances Database (HSDB, 2000), and the U.S. Environmental Protection Agency's (U.S. EPA) Health Effects Assessment Summary Tables (HEAST) (U.S. EPA, 1997).

## 2.2 Environmental Fate and Transport

Tetryl is an explosive chemical that was formally used as a detonator and propellant in military ordnance. While the use of tetryl as a military propellant or detonator has been superseded by other formulations, spills and discharges to waste streams have resulted in contamination of environmental media at or near installations where the compound was manufactured and/or where it was used in load, assembly and pack (LAP) activities. For example, the maximum detected concentration of tetryl in soil at Joliet AAP has been reported to be 84,000 mg/kg, with concentrations in groundwater up to 67 µg/L. Other locations where tetryl was manufactured or handled are contaminated with the compound to varying extents (Talmage et al. 1999). Physicochemical data on tetryl that relate to the environmental fate and transport characteristics of the compound are listed in Table 1.

**Table 1. Summary of Physical-Chemical Properties of Tetryl**

Molecular weight	287.15
Color	yellow
Physical state	crystalline solid
Melting point	129–132 °C
Boiling point	187 °C (explodes)
Odor	odorless
Solubility	Sparingly soluble in water (75–80 mg/L at 20–25 °C), soluble in acetone, alcohol, ether, benzene, glacial acetic acid
Partition coefficients:	
Log K <sub>ow</sub>	2.4, 2.0, 1.65
Log K <sub>oc</sub>	3.13–3.47, 2.6, 1.69
Vapor pressure at 25 °C	$4.0 \times 10^{-10}$ , $5.7 \times 10^{-9}$ , $1 \times 10^{-8}$ mm Hg
Henry's Law constant at 25 °C	$2.0 \times 10^{-12}$ , $1.0 \times 10^{-11}$ atm.m <sup>3</sup> /mole
Conversion factors	1 ppm = 11.74 mg/m <sup>3</sup> 1 mg/m <sup>3</sup> = 0.085 ppm

Sources: ATSDR 1995, Talmage et al. 1999, HSDB 2000

The estimated values for vapor pressure and Henry's Law constants are sufficiently low to indicate that tetryl is unlikely to be released to the air as vapor. However, aerial dispersion of the compound adhering to soil or dust particles is a possible mechanism by which tetryl can be released to the

atmosphere (ATSDR 1995). Although low to moderately soluble in water, there is empirical evidence for the compound's mobilization from soil to groundwater. Thus, tetryl has been detected in groundwater in the parts per billion (ppb) range at a number of AAPs (Talmage et al. 1999).

Kayser et al. (1984) showed photolysis and hydrolysis to be significant processes by which tetryl can be broken down in the environment. The former process is dominant in sunlit waters, with N-methylpicramide, nitrate, picrate and methylnitramine among the primary products. Formation of most of these products proceeds at a much slower rate in the dark, and N-methylpicramide appears to be solely a product of photolysis rather than thermal degradation or abiotic transformation in the absence of light. However, biotransformation also may be a viable mechanism for the breakdown of the compound since microbial reduction of organic nitro-groups to amines has been demonstrated (Talmage et al. 1999).

## **2.3 Summary of Mammalian Toxicity**

### **2.3.1 Mammalian Toxicity**

#### **2.3.1.1 Mammalian Oral Toxicity - Acute**

In a series of experiments carried out for the U.S. Army Medical Research and Development Command by Toxikon Corporation, FitzGerald et al. (1991, 1992) reported data obtained from various short-term toxicological tests on tetryl. These included eye and skin irritation studies in rabbits, dermal lethality in rabbits, sensitization tests in guinea pigs and acute oral lethality studies. In the acute study, 10 each of F344 rats and Swiss mice were given 5 g/kg tetryl suspended in corn oil. For both the rats and the mice, only one animal died as a result of the exposure. Other effects noted in rats included lethargy, piloerection and loss of body weight. In mice, effects of tetryl exposure were tachypnea, catalepsy, piloerection and unusual locomotion. FitzGerald et al. (1991, 1992) concluded that tetryl was non-toxic at 5 g/kg in these animal models.

Reddy et al. (1997) conducted an acute toxicity study on male Fischer 344 rats. Four rats/sex/group were given a single oral dose of 0, 500 or 1000 mg/kg body weight tetryl in corn oil via gavage. Twenty-four hours after dosing, drug metabolizing enzymes, hematological and histological changes were studied. No mortality occurred, however, there were significant effects of tetryl on O-dealkylation activity (Ethoxyresorufin and Pentoxyresorufin) of liver microsomes. Gross necropsy examination revealed several tetryl-related effects including red to dark-brown blood in the stomach and small intestine, and food containing a yellow granular substance in the stomach. Histological examination showed focal coagulative necrosis at the junction of the stomach and duodenum of tetryl-treated rats (Reddy et al. 1997).

### **2.3.1.2 Mammalian Oral Toxicity – Subacute**

Reddy et al. (1994a, 1999) conducted a 14 day study where both male and female rats (5/sex/group) were fed laboratory chow containing 0, 500, 1250, 2000, 2500, and 5000 mg tetryl/kg feed and reported that these levels approximated average doses of 0, 31.8, 80, 121, 170.5 and 349.7 mg/kg-day in males and 0, 32.1, 82.5, 130.3, 178.9 and 374.4 mg/kg-day in females. Animals were observed daily for clinical signs of toxicity, food and water consumption was monitored twice weekly, and body weights were recorded at 7-day intervals. Blood samples for routine clinical chemistry and hematological parameters were obtained immediately prior to termination. Animals were subject to a gross necropsy and the weights of brain, kidneys, liver, spleen, adrenals, lungs, thymus, gonads, and heart were noted. Excised pieces of a wide range of organs and tissues were fixed and processed for histopathological examination. Sections of all tissues from the high-dose and control groups were examined under the microscope, while sections from certain likely target organs such as kidney, spleen and testis were examined in all groups.

There were few if any clinical signs of toxicity displayed by the animals under test, and all rats survived to term. Similarly, there were essentially no compound-related changes in food and water consumption among the groups. However, the high-dose males displayed a reduction in body weight compared to controls after 14 days. There were no statistically significant changes in organ weights, but some relative organ weights such as liver and spleen in females and kidneys in males were increased in high-dose rats compared to controls. While some sporadic differences in hematological parameters were observed, the only compound-related change appeared to be the dose-dependant increase in the concentration of methemoglobin (metHb), an effect that was statistically significant at doses of 121 mg/kg-day and above in male rats. Similarly, some clinical chemistry parameters appeared to fluctuate as a result of tetryl administration. For example, there was a dose-dependant reduction in plasma alkaline phosphatase activity in males receiving 80 mg/kg-day and above. Necropsy findings and histopathological changes induced by tetryl were sparse other than an increased incidence of cytoplasmic droplets in the proximal renal cortical tubular epithelial cells of male rats. Since these protein-containing droplets were apparent at all dose levels but not controls, this suggests a lowest observed adverse effect level (LOAEL) of 31.86 mg/kg-day (Table 2.).

### **2.3.1.3 Mammalian Oral Toxicity – Subchronic**

Reddy et al. (1994b, 1999) also provided data from a study in F344 rats in which the same parameters were monitored after a 90-day dietary exposure to tetryl. The compound was mixed with laboratory chow to concentrations of 0, 200, 1000 and 3000 mg/kg feed, amounts calculated by the authors to be equivalent to average daily doses of 0, 13, 62.43 and 179.63 mg/kg-day in males and 0, 14.2, 68.87 and 199.06 mg/kg-day in females.

Statistically significant reductions in body weight compared to controls were evident in both high-dose groups and in the mid-dose females, while changes in absolute and relative organ weights were noted, including increases in kidney, liver and spleen and reductions in brain, adrenals and thymus. Similar to the body weight changes, these deviations in organ weights were most evident in the high- and mid-dose groups, although the differences in relative kidney weight were also significantly different from controls in low-dose females. Food consumption in all dose groups for both males and females was significantly lower than corresponding controls. Water consumption was significantly higher in females at the high dose. A number of compound-related hematological changes were noted, including reductions in red blood cell count, hematocrit and hemoglobin concentration, and concomitant increases in reticulocytes, platelets and (especially) metHb. Dose-related changes in clinical chemistry parameters due to tetryl included reductions in alkaline phosphatase activity and increases in plasma cholesterol levels. The latter was statistically significant in all dosed groups. Necropsy findings were unremarkable, but histopathological changes were observed in stained sections of spleen (probable hemosiderin) and kidney. Thus, both sexes of high-dose rat had excess deposition of pigment in the spleen, whereas both sexes of high- and mid-dose animals displayed excess pigment deposition in kidneys. There was also some evidence for the formation of  $\alpha_2\mu$ -globulin-containing hyaline droplets in the kidneys of male rats, a feature that appeared to be dose-related. Reddy et al. (1994b, 1999) considered the kidney effects to be the most sensitive indicator of tetryl toxicity and suggested a no observed adverse effect level (NOAEL) of 13 mg/kg-day and a lowest observed adverse effect level (LOAEL) of 62.43 mg/kg-day. Also, Tetryl had a significant deleterious effect on growth rate in female rats with an associated NOAEL of 14.2 mg/kg-day and a LOAEL of 68.87 mg/kg-day (Table 2.).

Tetryl was one of a series of compounds tested for tumor induction in the mammary gland of female Sprague-Dawley rats (Griswold et al. 1968). In an unusual protocol, 20 animals received a total of 10 doses of the compound by gavage in sesame oil during a 30-day period at the previously determined maximum tolerated dose (400 mg tetryl). Animals were observed for 9 months, then necropsied, at which time histopathological mounts were made of a number of organs and tissues including the mammary gland. There was no increased incidence of tumor formation due to tetryl, although a number of the other compounds, including 7,12-dimethylbenz(a)anthracene (positive control), were positive for tumor formation.

#### **2.3.1.4 Mammalian Oral Toxicity – Chronic**

One study was identified that explored the toxicity of tetryl through chronic exposure. ATSDR (1995) summarized an Italian study in which 12 rabbits were orally dosed with 125 mg/kg-day tetryl for 6 to 9 months (Fati and Daniele 1965). No controls were used and no other doses were administered. Results indicated some statistically significant changes in blood parameters suggesting a coagulation disorder.

However, the effects were inconsistent and did not increase in severity with time. U.S. EPA (1997) used data from the Fati and Daniele (1965) study to derive human health chronic and subchronic reference doses (RfD) of  $1 \times 10^{-2}$  and  $1 \times 10^{-1}$  mg/kg-day, respectively, based on the onset of histopathological effects in the kidney, liver and spleen. However, as pointed out in ATSDR (1995), the value of these observations is limited by the use of small number of test animals, few doses and the lack of a control group in the study.

#### **2.3.1.5 Studies Relevant for Mammalian TRV Development for Ingestion Exposures**

The data on toxicity of tetryl is primarily limited to acute and subchronic oral exposures in F344 rats and are presented in Table 2 and Figure 1. Recent toxicological studies involving tetryl have employed either Swiss mice or F344 rats, the latter representing the animal model for which most of the toxicity data on the compound have been derived. No reliable chronic data are available and no studies have been found pertaining to mammalian wildlife. The parameters relevant to tetryl toxicity were changes in hematological, clinical chemistry and histological parameters, and reduction in body weight (Reddy et al. 1999).

The changes in hematological parameters included significant alterations in hemoglobin, platelets, reticulocytes, hematocrit (males only) and methemoglobin. However, values for these parameters fell within the normal range for these animals (Wolford et al, 1986), hence, it is difficult to discern a clear pathological condition associated with these changes. The biological significance of  $\alpha_2\mu$ -globulin-mediated hyaline droplet formation in males remains uncertain, considering no other adverse kidney effects were found. The biological relevance of tetryl-induced changes in hematological parameters, clinical chemistry parameters and hyaline droplet formation in the kidneys remains uncertain and hence, these parameters cannot be used for TRV determination.

As outlined in Technical Guide 254, TRV derivation should be based on an ecologically relevant endpoint. Decreased growth indicates an alteration in the overall energy balance of an organism, suggesting that the affected organism obtains and/or allocates energy differently than a control organism (Calow 1991, Congdon et al. 2001). Alterations in energy acquisition and/or processing may in turn cause changes in reproductive schedules or leave the affected organism more susceptible to predators for a longer time period. Data on the growth effects of tetryl were obtained from Reddy et al. (1994b, 1999).

**Table 2. Summary of Relevant Mammalian Data for TRV Derivation**

Study	Test Organism	Test Duration	Test Results		
			NOAEL (mg/kg/d)	LOAEL (mg/kg/d)	Effects Observed at the LOAEL
Reddy et al. (1994a,1999)	Rat (F344)	14-d	80	121.1	Methemoglobinemia in males.
			NA	31.86	Protein droplet-related nephropathy in males.
Reddy et al. (1994b, 1999)	Rat (F344)	90-d	13	62.43	Nephropathy/ $\alpha$ 2 <sub>μ</sub> -globulin-associated hyaline droplet formation in males at all doses. Increased kidney, liver and spleen weight in both sexes. Methemoglobinemia, lower hemoglobin and rbc count in both sexes. Decreased adrenal and thymus weights in both sexes.
			14.2	68.87	Reduced body weight in females at mid and high doses.

NA = Not applicable

### 2.3.2 Mammalian Oral Toxicity – Other

No other data relevant to oral exposures for mammals were found.

### 2.3.3 Mammalian Inhalation Toxicity

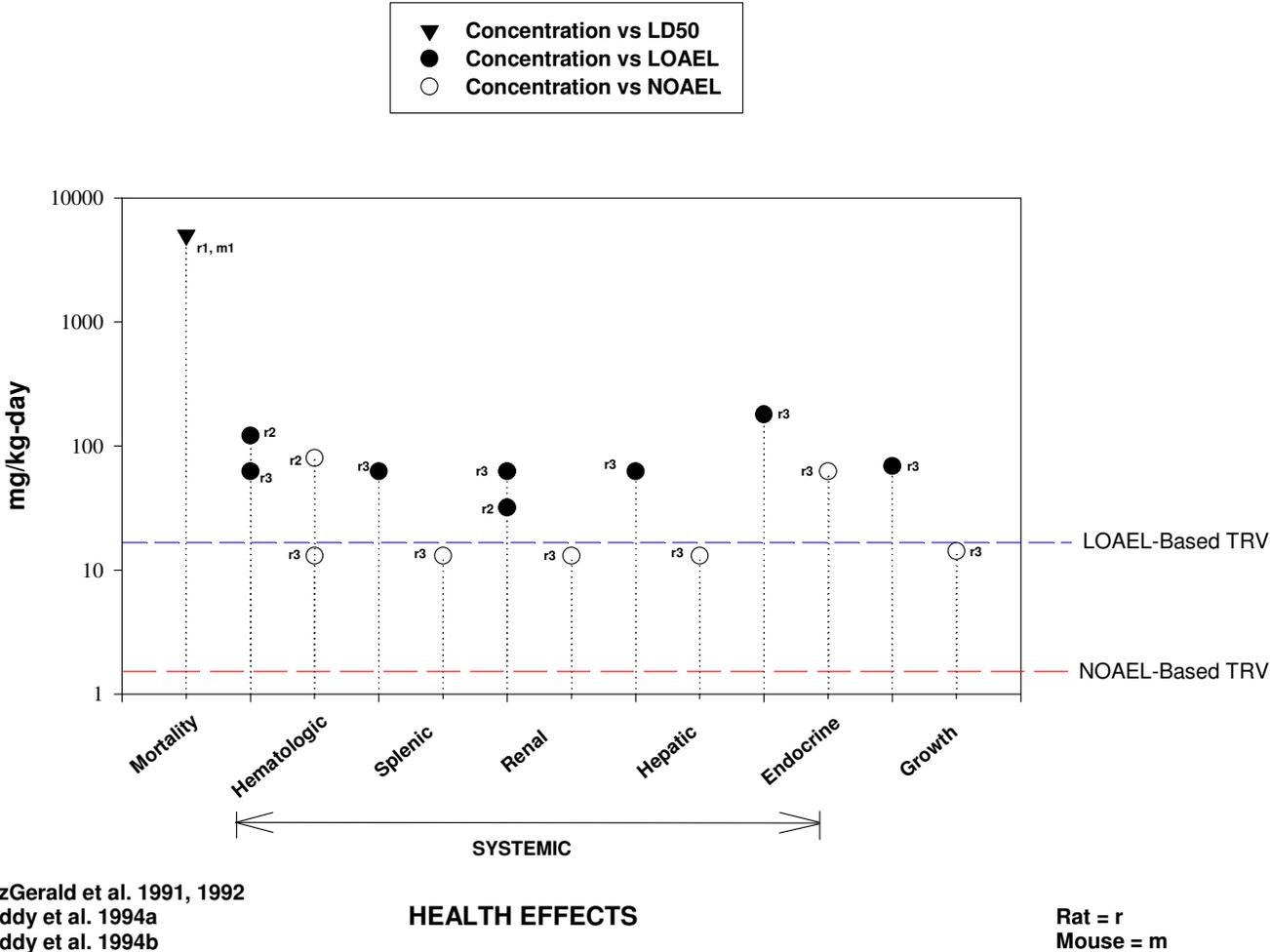
No inhalation studies conducted using mammals were found.

### 2.3.4 Mammalian Dermal Toxicity

No dermal studies conducted using mammals were found.

# TETRYL HEALTH EFFECTS TO MAMMALS

Figure 1.



## **2.4 Summary of Avian Toxicology**

Toxicological data for the effects of tetryl in avian species was not located. Ecotoxicological research on the effects of this compound in birds is recommended.

## **2.5 Amphibian Toxicology**

Toxicological data for the effects of tetryl in amphibian species was not located. Ecotoxicological research on the effects of this compound in amphibians is recommended.

## **2.6 Reptilian Toxicology**

Toxicological data for the effects of tetryl in reptilian species was not located. Ecotoxicological research on the effects of this compound in reptiles is recommended.

# **3. RECOMMENDED TOXICITY REFERENCE VALUES**

## **3.1 Toxicity Reference Values for Mammals**

### **3.1.1 TRVs for Ingestion Exposures for the Class Mammalia**

Data on reduced body weight in rats was used to derive the TRV (Reddy et al. 1994b, 1999). Data on female body weight was used for the TRV, as it was more sensitive and hence protective of males. Decreased body weight, an indication of a lower growth rate was used to determine the TRV because alterations in this endpoint are likely to affect fitness. For example, alterations in energy acquisition or allocation patterns may impair reproductive function and/or schedules (Callow 1991, Congdon et al. 2001). In addition, sustaining a smaller body size for longer time periods may increase risk of predation. All data concerning the toxicity of tetryl has been generated from studies on laboratory rats; data from tetryl investigations for wildlife species were not found. No reliable chronic studies were identified so the TRV was derived from a subchronic study on F344 rats (Reddy et al. 1999). Based on the available data and in accord with procedures outlined in TG 254, the approximation approach was used to derive the TRV for tetryl (USACHPPM, 2000). An uncertainty factor of 10 was used to derive the NOAEL-based approximate TRV from a subchronic NOAEL of 14.2 mg/kg/day. An uncertainty factor of 4 was used to derive the LOAEL-based approximate TRV from a subchronic LOAEL of 68.87 mg/kg/day. The minimum data requirements for a high confidence rating were not met, however, sufficient data is available to assign a medium confidence rating to the TRV for tetryl (USACHPPM 2000).

**Table 4. Selected Ingestion TRVs for the Class Mammalia**

<b>TRV</b>	<b>Dose</b>	<b>Confidence</b>
NOAEL-based	1.42 mg/kg/d	Medium
LOAEL-based	17.2 mg/kg/d	Medium

**3.1.2 TRVs for Inhalation Exposures for the Class Mammalia**

Not Available at this time.

**3.1.3 TRVs for Dermal Exposures for the Class Mammalia**

Not available at this time

**3.2 Toxicity Reference Values for Birds**

Not available at this time

**3.2 Toxicity Reference Values for Amphibians**

Not Available at this time.

**3.4 Toxicity Reference Values for Reptiles**

Not Available at this time.

**4. IMPORTANT RESEARCH NEEDS**

The limited availability of data on the toxicity of tetryl to wildlife species precludes the development of a high-confidence TRV. Hence, more studies on the toxicity of tetryl to wildlife species are required, especially chronic toxicity studies and studies on non-mammalian wildlife such as birds, reptiles and amphibians. Additional studies on mammalian species other than rats is also warranted and would likely allow the derivation of a high confidence TRV

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## APPENDIX A

### LITERATURE REVIEW

The following files were searched in Dialog:

File 155 MEDLINE; File 156, TOXLINE, File 5 BIOSIS, File 10 AGRICOLA, File 203 AGRIS, File 399 Chemical Abstracts, File 337 CHEMTOX, File 77 Conference Papers Index, File 35 Dissertation Abstracts, File 40 ENVIRONMENTAL, File 68 Environmental Bibliography, File 76 Life Sciences Collection, File 41 Pollution Abstracts, File 336 RTECS, File 370 Science, File 143 Wilson Biological & Agricultural Index, File 185 Zoological Record, File 6 NTIS, File 50 CAB, File 144 PASCAL, File 34 SCISEARCH.

The search strategy for **Amphibians & Reptiles**:

- ◆ Chemical name, synonyms, CAS numbers
- ◆ AND (amphibi? or frog or frogs or salamander? or newt or newts or toad? or reptil? or crocodil? or alligator? or caiman? snake? or lizard? or turtle? or tortoise? or terrapin?)
- ◆ RD (reduce duplicates)

The search strategy for **Birds**:

- ◆ Chemical name, synonyms, CAS numbers
- ◆ And chicken? or duck or duckling? or ducks or mallard? or quail? or (japanese()quail?) or coturnix or (gallus(domesticus) or platyrhyn? or anas or aves or avian or bird? or (song()bird?) or bobwhite? or (water()bird) or (water()fowl)
- ◆ RD

The search strategy for **Laboratory Mammals**:

- ◆ Chemical name, synonyms, CAS numbers
- ◆ AND (rat or rats or mice or mouse or hamster? or (guinea()pig?) or rabbit? or monkey?)
- ◆ AND (reproduc? or diet or dietary or systemic or development? or histolog? or growth or neurological or behav? or mortal? or lethal? or surviv? or (drinking()water))
- ◆ NOT (human? or culture? or subcutaneous or vitro or gene or inject? or tumo? or inhalation or carcin? or cancer?)/ti,de
- ◆ NOT ((meeting()poster) or (meeting()abstract))
- ◆ NOT (patient? or cohort? or worker? or child? or infant? or women or men or occupational)
- ◆ RD

The search strategy for **Wild Mammals**:

- ◆ Chemical name, synonyms, CAS numbers
- ◆ And(didelphidae or opossum? or soricidae or shrew? Or talpidae or armadillo? or dasypodidae or ochotonidae or leporidae)or canidae or ursidae or procyonidae or mustelidae or felidae or cat or cats or dog or dogs or bear or bears or weasel? or skunk? or marten or martens or badger? or ferret? or mink? Or aplodontidae or beaver? or sciuridae or geomyidae or heteromyidae or castoridae or equidae or suidae or dicotylidae or cervidae or antilocapridae or bovidae arvicolinae or myocastoridae or dipodidae or erethizontidae or sigmodon? or (harvest()mice) or (harvest()mouse) or microtus or peromyscus or reithrodontomys or onychomys or vole or voles or lemming?
- ◆ AND (reproduc? or diet or dietary or systemic or development? or histolog? or growth or neurological or behav? or mortal? or lethal? or surviv? or (drinking()water))
- ◆ RD

All abstracts from the DIALOG search were reviewed and encoded in ProCite. When the search retrieved an appreciable number of hits, *keywords in context* were reviewed to minimize costs before any abstracts were downloaded (Tier 1). However, when only a limited number of studies were identified by the search, the abstracts were downloaded at the time of the search (Tier 2).

As noted in Section 2.1, 31 hits on tetryl were obtained in the initial search, all of which were selected for abstract evaluation. Eleven of these articles and reviews were retrieved for this survey.