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# Chlorophacinone

Human Health and Ecological Risk Assessment  
Final Report

Submitted to:

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## Note on 508 Compliance

This report is compliant with Section 508 of the Rehabilitation Act of 1973 as amended by the Workforce Investment Act of 1998. The compliance report is attached to the PDF copy of this report.

## ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
AEL	adverse-effect level
a.e.	acid equivalent
a.i.	active ingredient
a.k.a.	also known as
a.s.	active substance
APHIS	Animal and Plant Health Inspection Service
ATSDR	Agency for Toxic Substances and Disease Registry
ASAE	American Society of Agricultural Engineers
BCF	bioconcentration factor
bw	body weight
calc	calculated value
CBI	confidential business information
CI	confidence interval
cm	centimeter
CNS	central nervous system
COC	crop oil concentrates
DAA	days after application
DAT	days after treatment
DER	data evaluation record
d.f.	degrees of freedom
EC	emulsifiable concentrate
EC <sub>x</sub>	concentration causing X% inhibition of a process
EC <sub>25</sub>	concentration causing 25% inhibition of a process
EC <sub>50</sub>	concentration causing 50% inhibition of a process
ECOTOX	ECOTOXicology (database used by U.S. EPA/OPP)
EFED	Environmental Fate and Effects Division (U.S. EPA/OPP)
ExToxNet	Extension Toxicology Network
F	female
FH	Forest Health
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FQPA	Food Quality Protection Act
g	gram
GLP	Good Laboratory Practices
ha	hectare
HED	Health Effects Division (U.S. EPA/OPP)
HQ	hazard quotient
HRAC	Herbicide Resistance Action Committee
IARC	International Agency for Research on Cancer
IREL	Interim Reregistration Eligibility Decision
IRIS	Integrated Risk Information System
k <sub>a</sub>	absorption coefficient
k <sub>e</sub>	elimination coefficient
kg	kilogram
K <sub>o/c</sub>	organic carbon partition coefficient

K <sub>o/w</sub>	octanol-water partition coefficient
K <sub>p</sub>	skin permeability coefficient
L	liter
lb	pound
LC <sub>50</sub>	lethal concentration, 50% kill
LD <sub>50</sub>	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LOC	level of concern
LR <sub>50</sub>	50% lethal response [EFSA/European term]
m	meter
M	male
mg	milligram
mg/kg/day	milligrams of agent per kilogram of body weight per day
mL	milliliter
mM	millimole
mPa	millipascal, (0.001 Pa)
MOS	margin of safety
MRID	Master Record Identification Number
MSDS	material safety data sheet
MSO	methyated seed oil
MW	molecular weight
NAWQA	USGS National Water Quality Assessment
NCI	National Cancer Institute
NCOD	National Drinking Water Contaminant Occurrence Database
NIOSH	National Institute for Occupational Safety and Health
NIS	nonionic surfactant
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level
NOS	not otherwise specified
N.R.	not reported
OM	organic matter
OPP	Office of Pesticide Programs
OPPTS	Office of Pesticide Planning and Toxic Substances
OSHA	Occupational Safety and Health Administration
Pa	Pascal
PBPK	physiologically-based kinetic
ppm	parts per million
RBC	red blood cells
RED	re-registration eligibility decision
RfD	reference dose
SERA	Syracuse Environmental Research Associates
TEP	typical end-use product
T.G.I.A.	Technical grade active ingredient
TRED	Tolerance Reassessment Eligibility Decision
UF	uncertainty factor



U.S.	United States
USDA	U.S. Department of Agriculture
U.S. EPA	U.S. Environmental Protection Agency
USGS	U.S. Geological Survey
VMD	volume median diameter (for droplet size distributions)
WHO	World Health Organization
WWSA	Weed Science Society of America

## COMMON UNIT CONVERSIONS AND ABBREVIATIONS

To convert ...	Into ...	Multiply by ...
acres	hectares (ha)	0.4047
acres	square meters (m <sup>2</sup> )	4,047
atmospheres	millimeters of mercury	760
centigrade	Fahrenheit	1.8°C+32
centimeters	inches	0.3937
cubic meters (m <sup>3</sup> )	liters (L)	1,000
Fahrenheit	centigrade	0.556°F-17.8
feet per second (ft/sec)	miles/hour (mi/hr)	0.6818
gallons (gal)	liters (L)	3.785
gallons per acre (gal/acre)	liters per hectare (L/ha)	9.34
grams (g)	ounces, (oz)	0.03527
grams (g)	pounds, (oz)	0.002205
hectares (ha)	acres	2.471
inches (in)	centimeters (cm)	2.540
kilograms (kg)	ounces, (oz)	35.274
kilograms (kg)	pounds, (lb)	2.2046
kilograms per hectare (kg/ha)	pounds per acre (lb/acre)	0.892
kilometers (km)	miles (mi)	0.6214
liters (L)	cubic centimeters (cm <sup>3</sup> )	1,000
liters (L)	gallons (gal)	0.2642
liters (L)	ounces, fluid (oz)	33.814
miles (mi)	kilometers (km)	1.609
miles per hour (mi/hr)	cm/sec	44.70
milligrams (mg)	ounces (oz)	0.000035
meters (m)	feet	3.281
ounces (oz)	grams (g)	28.3495
ounces per acre (oz/acre)	grams per hectare (g/ha)	70.1
ounces per acre (oz/acre)	kilograms per hectare (kg/ha)	0.0701
ounces fluid	cubic centimeters (cm <sup>3</sup> )	29.5735
pounds (lb)	grams (g)	453.6
pounds (lb)	kilograms (kg)	0.4536
pounds per acre (lb/acre)	kilograms per hectare (kg/ha)	1.121
pounds per acre (lb/acre)	mg/square meter (mg/m <sup>2</sup> )	112.1
pounds per acre (lb/acre)	µg/square centimeter (µg/cm <sup>2</sup> )	11.21
pounds per gallon (lb/gal)	grams per liter (g/L)	119.8
square centimeters (cm <sup>2</sup> )	square inches (in <sup>2</sup> )	0.155
square centimeters (cm <sup>2</sup> )	square meters (m <sup>2</sup> )	0.0001
square meters (m <sup>2</sup> )	square centimeters (cm <sup>2</sup> )	10,000
yards	meters	0.9144

Note: All references to pounds and ounces refer to avoirdupois weights unless otherwise specified.

## CONVERSION OF SCIENTIFIC NOTATION

Scientific Notation	Decimal Equivalent	Verbal Expression
$1 \cdot 10^{-10}$	0.0000000001	One in ten billion
$1 \cdot 10^{-9}$	0.000000001	One in one billion
$1 \cdot 10^{-8}$	0.00000001	One in one hundred million
$1 \cdot 10^{-7}$	0.0000001	One in ten million
$1 \cdot 10^{-6}$	0.000001	One in one million
$1 \cdot 10^{-5}$	0.00001	One in one hundred thousand
$1 \cdot 10^{-4}$	0.0001	One in ten thousand
$1 \cdot 10^{-3}$	0.001	One in one thousand
$1 \cdot 10^{-2}$	0.01	One in one hundred
$1 \cdot 10^{-1}$	0.1	One in ten
$1 \cdot 10^0$	1	One
$1 \cdot 10^1$	10	Ten
$1 \cdot 10^2$	100	One hundred
$1 \cdot 10^3$	1,000	One thousand
$1 \cdot 10^4$	10,000	Ten thousand
$1 \cdot 10^5$	100,000	One hundred thousand
$1 \cdot 10^6$	1,000,000	One million
$1 \cdot 10^7$	10,000,000	Ten million
$1 \cdot 10^8$	100,000,000	One hundred million
$1 \cdot 10^9$	1,000,000,000	One billion
$1 \cdot 10^{10}$	10,000,000,000	Ten billion

## EXECUTIVE SUMMARY

Chlorophacinone is an anticoagulant rodenticide registered for the control of several rodent pests including various species of rats, mice, voles, squirrels, rabbits, muskrat, chipmunks, gophers, and prairie dogs. Based on Forest Service direction, the current risk assessment is focused on the control of the black-tailed prairie dog (*Cynomys ludovicianus*) using Rozol Prairie Dog Bait, a 0.005% a.i. formulation of chlorophacinone.

Under normal and anticipated circumstances, the use of Rozol Prairie Dog Bait (i.e., a 0.005% formulation of chlorophacinone) in below-ground applications for the control of the black-tailed prairie dog should pose minimal risks to workers and members of the general public. Substantial reservations accompany the risk characterization for workers because of the lack of data on the extent of worker exposures during applications of chlorophacinone. Nonetheless, the exposure assessment for workers is based on a set of conservative assumptions which should overestimate exposures. There are also uncertainties in the dose-response assessment for workers. These uncertainties, however, focus on the reasonable supposition that dermal exposures are likely to be less hazardous than oral exposures. Since the dose-response assessment is based on oral toxicity, risks to workers are likely to be overestimated.

The upper bound hazard quotients for workers involved in the normal and proper application of chlorophacinone are below the level of concern by a factor of about 14 based on the chronic RfD and 1000 based on the acute RfD. The risk characterization for non-accidental and expected exposures to members of the general public suggests that risks are negligible.

One very extreme accidental exposure scenario, in which a child consumes bait accidentally deposited on the ground surface, is a modest concern. While there is no indication that the child would become seriously ill, the consumption of any rodenticide should be viewed with serious concern and warrants aggressive measures to ensure prompt medical care.

As would be expected from a rodenticide, applications of chlorophacinone for the control of the black-tailed prairie dog are likely to lead to adverse effects, including death, in other rodents and perhaps other mammals that consume substantial amounts of bait. The prevalence of lethal exposures to nontarget rodents will be reduced but not completely eliminated by subsurface applications to burrows of the black-tailed prairie dog. Birds are less sensitive than mammals to chlorophacinone. While adverse effects to some species of birds cannot be excluded, it appears that effects on birds will be less common and less severe, relative to effects on mammals. Almost all the uncertainty associated with the nature of or limitations in the risk characterization for chlorophacinone are related to the exposure assessments. Most exposures of nontarget species to chlorophacinone should be incidental. Nonetheless, misapplications of chlorophacinone could lead to wider exposures and effects in both primary consumers of the bait (mammals and birds) as well as predators that might consume contaminated prey.

For nontarget wildlife, all exposures associated with the consumption of contaminated water are far below the level of concern for both terrestrial organisms and aquatic organisms.

# 1. INTRODUCTION

## 1.1. Chemical Specific Information

This risk assessment document evaluates the human health effects and ecological effects associated with the use of chlorophacinone in Forest Service programs. Chlorophacinone is an anticoagulant rodenticide used in Forest Service programs for the control of the black-tailed prairie dog (*Cynomys ludovicianus*). More specifically, the Forest Service uses the 0.005% a.i. Rozol formulation from Liphatech Inc. (2012), which is labelled only for the control of the black-tailed prairie dog by subsurface (burrow) application.

The database for chlorophacinone is modest relative to most pesticides considered in Forest Service risk assessments. Numerous unpublished studies were submitted to regulatory agencies in both the United States and Europe in support of the registration of chlorophacinone. The registrant-submitted studies are classified as Confidential Business Information (CBI) and are not publically available. Studies classified as CBI were not available during the preparation of the current risk assessment. Nonetheless, as summarized in Table 1, reasonably detailed summaries of registrant-submitted studies are available from the U.S. EPA/OPP. These available summaries pertain to human health effects (U.S. EPA/OPP 1998a) and ecological effects (U.S. EPA/OPP/EFED 2008a, 2010a, 2011a) associated with chlorophacinone. Furthermore, much of the open literature regarding the effects of chlorophacinone on nontarget species is addressed in U.S. EPA/OPP/EFED (2011a) and FWS (2012a). Additional summaries of unpublished studies on chlorophacinone are provided in the WHO (1995) assessment of rodenticides and Colvin et al. (1988).

Along with the reviews from the U.S. EPA, the Agency has released more detailed summaries of several registrant-submitted studies at an EPA web site (<http://iaspub.epa.gov/apex/pesticides>). As detailed in Section 5 (References), these more detailed summaries are used in the current risk assessment. Several of these summaries are in the form of Data Evaluation Records (DERs). The nature and usefulness of DERs is addressed further in Section 1.2.

Table 2 provides an overview of the open literature on chlorophacinone. Consistent with the limited use of chlorophacinone as a rodenticide, the available data are also highly focused on species most likely to be exposed to chlorophacinone, including humans, other nontarget mammals, and birds. The literature on the effects of chlorophacinone on terrestrial invertebrates, reptiles, amphibians, and aquatic organisms is sparse. As discussed in the ecological risk assessment (Section 4), the limited amount of information on the effects of chlorophacinone on these groups of species somewhat constrains the current risk assessment. These limitations are common with most rodenticides, as illustrated in the Forest Service risk assessment on strychnine (SERA 2005).

The U.S. EPA registration review program operates on a 15-year cycle. The registration review for chlorophacinone has not been initiated and is not scheduled for completion until 2017 (U.S. EPA/OPP 2013a, p. 23). Consequently, it is unlikely that the EPA registration review will contribute to the current Forest Service risk assessment.

## 1.2. General Information

This document has four chapters, including this introduction (Section 1), a program description (Section 2), a risk assessment for human health effects (Section 3), and a risk assessment for ecological effects (Section 4). Each of the two risk assessment chapters has four major sections, including an identification of the hazards, an assessment of potential exposure to this compound, an assessment of the dose-response relationships, and a characterization of the risks associated with plausible levels of exposure.

This is a technical support document which addresses some specialized technical areas. Nevertheless an effort was made to ensure that the document can be understood by individuals who do not have specialized training in the chemical and biological sciences. Certain technical concepts, methods, and terms common to all parts of the risk assessment are described in plain language in a separate document (SERA 2014a). The human health and ecological risk assessments presented in this document are not, and are not intended to be, comprehensive summaries of all of the available information. Nonetheless, the information presented in the appendices and the discussions in chapters 2, 3, and 4 of the risk assessment are intended to be detailed enough to support an independent review of the risk analyses.

As noted in Section 1.1, studies submitted by registrants in support of the registration of chlorophacinone are used in this risk assessment based on summaries publically available from the U.S. EPA. The registrant-submitted studies are particularly important for aquatic organisms which are not covered well in the open literature. In any risk assessment using registrant-submitted studies, the Forest Service is sensitive to concerns of potential bias. The general concern might be expressed as follows:

*If the study is paid for and/or conducted by the registrant, the study may be designed and/or conducted and/or reported in a manner that will obscure any adverse effects that the compound may have.*

This concern is largely without foundation. While any study (published or unpublished) can be falsified, concerns with the design, conduct and reporting of studies submitted to the U.S. EPA for pesticide registration are minor. The design of the studies submitted for pesticide registration is based on strict guidelines for both the conduct and reporting of studies. These guidelines are developed by the U.S. EPA and not by the registrants. Full copies of the guidelines for these studies are available at <http://www.epa.gov/ocspp/pubs/frs/home/guidelin.htm>. Virtually all studies accepted by the U.S. EPA/OPP are conducted under Good Laboratory Practices (GLPs). GLPs are an elaborate set of procedures which involve documentation and independent quality control and quality assurance that substantially exceed the levels typically seen in open literature publications. As a final point, the EPA reviews each submitted study for adherence to the relevant study guidelines. These reviews most often take the form of Data Evaluation Records (DERs). While the nature and complexity of DERs varies according to the nature and complexity of the particular studies, each DER involves an independent assessment of the study to ensure that the EPA Guidelines are followed and that the results are expressed accurately. In many instances, the U.S. EPA/OPP will reanalyze raw data from the study as a check or elaboration of data analyses presented in the study. In addition, each DER undergoes internal review (and sometimes several layers of review). The DERs prepared by the U.S. EPA form the

1 basis of EPA risk assessments and, when available, DERs are used in Forest Service risk  
2 assessments.

3  
4 Despite the real and legitimate concerns with risk assessments based largely on registrant-  
5 submitted studies, data quality and data integrity are not substantial concerns. The major  
6 limitation of risk assessments based substantially on registrant-submitted studies involves the  
7 nature and diversity of the available studies. The studies required by the U.S. EPA involve a  
8 relatively small subset of species and follow standardized protocols. The relevance of this  
9 limitation to the current risk assessment on chlorophacinone is noted in various parts of this risk  
10 assessment as appropriate. Overall and as discussed in Section 1.1, the open literature on  
11 chlorophacinone for human, nontarget mammals, and birds is substantial and this literature is  
12 used quantitatively in the current risk assessment as needed and as appropriate.

13  
14 The Forest Service periodically updates pesticide risk assessments and welcomes input from the  
15 general public and other interested parties on the selection of studies included in risk  
16 assessments. This input is helpful, however, only if recommendations for including additional  
17 studies specify why and/or how the new or not previously included information would be likely  
18 to alter the conclusions reached in the risk assessments.

19  
20 As with all Forest Service risk assessments, almost no risk estimates presented in this document  
21 are given as single numbers. Usually, risk is expressed as a central estimate and a range, which  
22 is sometimes quite large. Because of the need to encompass many different types of exposure as  
23 well as the need to express the uncertainties in the assessment, this risk assessment involves  
24 numerous calculations, most of which are relatively simple. Simple calculations are included in  
25 the body of the document [typically in brackets]. The results of some calculations within  
26 brackets may contain an inordinate number of significant figures in the interest of transparency  
27 (i.e., to allow readers to reproduce and check the calculations). In all cases, these numbers are  
28 not used directly but are rounded to the number of significant figures (typically two or three) that  
29 can be justified by the data.

30  
31 Some of the calculations, however, are cumbersome. For those calculations, an EXCEL  
32 workbook (i.e., a set of EXCEL worksheets) is included as an attachment to this risk assessment.  
33 The workbook included with the current risk assessment is discussed in Section 2.4. The  
34 worksheets in this workbook provide the detail for the estimates cited in the body of the  
35 document. Documentation for the use of these workbooks is presented in SERA (2011a).

36  
37 The EXCEL workbook is integral part of the risk assessment. The worksheets contained in this  
38 workbook are designed to isolate the numerous calculations from the risk assessment narrative.  
39 In general, all calculations of exposure scenarios and quantitative risk characterizations are  
40 derived and contained in the worksheets. In these worksheets as well as in the text of this risk  
41 assessment, risks are characterized using the hazard quotient, the ratio of the estimated exposure  
42 to a toxicity value, typically a no adverse effect level or concentration (i.e., NOAEL or NOAEC).  
43 Both the rationale for the calculations and the interpretation of the hazard quotients are contained  
44 in this risk assessment document.

## 2. PROGRAM DESCRIPTION

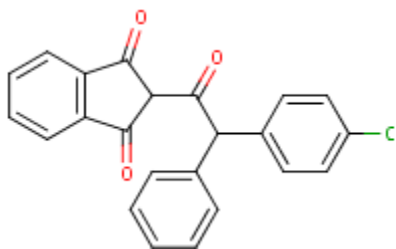
### 2.1. Overview

Chlorophacinone is an anticoagulant rodenticide registered for the control of several rodent pests including various species of rats, mice, voles, squirrels, rabbits, muskrat, chipmunk, gophers, and prairie dogs. Based on Forest Service direction, the current risk assessment is focused on the control of the black-tailed prairie dog (*Cynomys ludovicianus*) using Rozol Prairie Dog Bait, a 0.005% a.i. formulation of chlorophacinone. Based on estimates from U.S. EPA/OPP, a maximum application rate of 0.000625 lb a.i./acre is explicitly considered. For a 0.005% a.i. formulation, this application rate is equivalent to 12.5 lbs formulation/acre. Applications of chlorophacinone baits are made at least 6 inches down into the prairie dog borrows. The use other formulations for the control of other rodent species are encompassed to the extent that only subsurface baits are used, and any necessary adjustments to application rates are made.

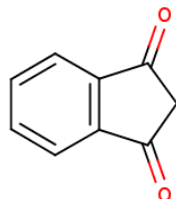
By definition, the areas in which chlorophacinone will be used in Forest Service programs are limited to the range of the black-tailed prairie dog. This range includes the west-central plains extending from parts of Montana to parts of Texas and encompassing parts of Colorado, Kansas, Nebraska, New Mexico, North Dakota, Oklahoma, South Dakota, and Wyoming. No use statistics or estimated amounts of chlorophacinone to be used in Forest Service programs are available. Detailed use statistics from California suggest that agricultural uses of chlorophacinone are much higher than uses related to forestry applications. The relevance of these data to Forest Service applications outside of California may be marginal. The available use data do not support a direct assessment of the use chlorophacinone by the Forest Service, relative to other uses.

### 2.2. Chemical Description and Commercial Formulations

Chlorophacinone is the common name for 2-[2-(4-chlorophenyl)-2-phenylacetyl]indan-1,3-dione:



Structurally, chlorophacinone as well as other similar rodenticides (i.e., diphacinone) are classified as 1,3-indandione rodenticides (U.S. EPA/OPP/HED 1997; Braselton et al. 1992; Watt et al. 2005):



These 1,3-indandione rodenticides along with 4-hydroxycoumarin rodenticides (e.g., brodifacoum, bromadiolone, difethialone, difenacoum, flocoumafen) are commonly referred to



1 as superwarfarins (Banks and Davies 2007; Katona and Wason 1989; Papin et al. 2007; Piatkov  
2 et al. 2010; Waddell et al. 2013; Wong 2006).

3  
4 Chlorophacinone, which is classified as a first-generation rodenticide, was developed by Lipha  
5 S.A., a subdivision of Merck, and was registered in the United States in 1971 (CDPR 2013a;  
6 Tomlin 2004; U.S. EPA/OPP/EFED 2012b; U.S. EPA/OPP 2013a). As discussed further in  
7 Section 3.2, chlorophacinone is an uncoupler of oxidative phosphorylation which inhibits the  
8 production of blood clotting factors (i.e., it acts as an anticoagulant). More than 50 formulations  
9 of chlorophacinone are currently registered in the United States (Kegley et al. 2014) for the  
10 control of numerous rodent pests including various species of mice, rats, voles, gophers,  
11 squirrels, chipmunks, rabbits, and muskrats (U.S. EPA/OPP/EFED 2011a). The open literature  
12 on chlorophacinone involves several formulations that range from 0.005 to 0.25% a.i. As  
13 discussed below, the current risk assessment is concerned only with a specific 0.005% a.i.  
14 formulation.

15  
16 A substantial simplification in the current risk assessment involves the limited use of  
17 chlorophacinone by the Forest Service. The Forest Service will use chlorophacinone, formulated  
18 as Rozol Prairie Dog Bait, for the control of the black-tailed prairie dog (*Cynomys ludovicianus*).  
19 Rozol Prairie Dog Bait is a 0.005% a.i. formulation of chlorophacinone, and although the MSDS  
20 does not specifically identify the other ingredients in the formulation, the EPA risk assessment of  
21 Rozol suggests that the primary inactive ingredient is a grain (U.S. EPA/OPP/EFED 2008a, p.  
22 13).

23  
24 By definition, the areas in which chlorophacinone will be used in Forest Service programs are  
25 limited to the range of the black-tailed prairie dog. As illustrated in Figure 1, this range is in the  
26 west-central plains extending from parts of Montana to parts of Texas. More specifically, as  
27 detailed in U.S. EPA/OPP/EFED (2010a, p. 32), concern for the use of chlorophacinone for the  
28 control of the black-tailed prairie dog is limited to parts of Colorado, Kansas, Montana,  
29 Nebraska, New Mexico, North Dakota, Oklahoma, South Dakota, Texas, and Wyoming.

30  
31 The regulatory status of Rozol Prairie Dog Bait is somewhat unclear. In 2011, use of  
32 formulations of Rozol Prairie Dog Bait packages labeled prior to August 8, 2011 was banned in  
33 Montana, New Mexico, North Dakota, and South Dakota (U.S. EPA/OPP 2011a). Based on the  
34 August 24, 2012 EPA label (U.S. EPA/OPP 2012b), this ban does not apply to formulations with  
35 later label dates. Nonetheless, the August 24, 2012 label indicates that it is valid only until  
36 March 15, 2014. A more recent label for Rozol Prairie Dog Bait is not available at the EPA web  
37 site for pesticide labels (<http://www.epa.gov/pesticides/ppls/>). The June 2012 label for Rozol  
38 Prairie Dog Bait from Liphatech Inc. (2012) does not note the March 15, 2014 date on the  
39 product label from the EPA web site. The Registration Division of OPP has indicated that a  
40 label amendment would lift the ban of applications of Rozol Prairie Dog Bait in Montana, New  
41 Mexico, North Dakota, and South Dakota (U.S. EPA/OPP/RD 2012b).

42  
43 The EPA appears to be in the process of canceling registrations for some other rodenticides,  
44 including warfarin, brodifacoum, and difethialone (U.S. EPA/OPP 2008a, 2013b). This activity,  
45 however, appears to be independent of and will not impact the registration status of  
46 chlorophacinone.

1  
2 The black-tailed prairie dog is sometimes classified as a pest species (Witmer and Fagerstone  
3 2003), and the USDA's Animal and Plant Health Inspection Service has initiated an eradication  
4 program for this this species (BLM 2007). In addition, the black-tailed prairie dog is a host for  
5 bubonic plague (the bacterium, *Yersinia pestis*) (St. Romain et al. 2013). Thus, populations of  
6 prairie dogs may pose potential public health risks (Andelt and Hopper 2012; Barnes 1993;  
7 Oldemeyer et al. 1993). As summarized by the Centers for Disease Control, plague cases in the  
8 United States are most prevalent in the western states, particularly in Utah, Colorado, Arizona,  
9 and New Mexico, and the number of cases reported annually in the United States from 1970 to  
10 2013 ranged from 1 to about 40 (CDC 2013) with a mortality rate of about 7% (Raoult et al.  
11 2013). Estimates of the number of cases of plague in the United States specifically associated  
12 with black-tailed prairie dog populations are not addressed in the available literature.  
13 Notwithstanding concerns for public health and excessive populations of the black-tailed prairie  
14 dog, the Forest Service is involved in efforts to sustain black-tailed prairie dog populations to  
15 support recovery of the endangered black-footed ferret in some areas of South Dakota,  
16 Wyoming, New Mexico, and Texas (Andelt and Hooper 2012; USDA/FS 2014).

17  
18 Selected chemical and physical properties of chlorophacinone are summarized in Table 3. As  
19 discussed in U.S. EPA/OPP/EFED (2011a), chlorophacinone is bound tightly to and is  
20 moderately persistent in soil. Other than the consumption of chlorophacinone bait, the primary  
21 route of dissipation and degradation appears to be aerobic soil metabolism. Chlorophacinone is  
22 subject to rapid soil photolysis (i.e., 4-day half-life), but this should not be a major route of  
23 degradation for subsurface applications. As discussed further in Section 2.3, Rozol Prairie Dog  
24 Bait is labeled only for subsurface applications. Similarly, chlorophacinone is subject to rapid  
25 aqueous photolysis (half-life of 37 minutes), but this may not be a major route of degradation  
26 due to light attenuation in aquatic sediments (U.S. EPA/OPP/EFED 2008a, p. 9).

27  
28 Some of the reported properties of chlorophacinone are, or at least appear to be, discordant. For  
29 example, Tomlin (2004) reports a water solubility of 100 mg/l (20 °C), U.S. EPA/OPP (1998a, p.  
30 74) reports a water solubility of 34 mg/L (at 25°C), and U.S. EPA/OPP/EFED (2011a, MRID  
31 42237401) reports a water solubility of 3.43 mg/L (at 25°C). The value from Tomlin may reflect  
32 the lower temperature at which the water solubility was determined. The 34 mg/L value from  
33 U.S. EPA/OPP/EFED (2011a) appears to be a typographical error. The reported  $K_{oc}$  values for  
34 chlorophacinone range from 15,556 to 135,976 with both extremes reported by Tomlin (2004).  
35 While these differences are substantial, they are not uncommon with  $K_{oc}$  values for compounds  
36 that may bind to soil based on factors in addition to organic carbon. The estimated  $K_{ow}$  of about  
37 316,000 from EPI Suite (2011) is substantially higher than the experimental value of about 94  
38 reported by U.S. EPA/OPP/EFED (2011a, MRID 42237401). The EPI Suite (2011) is based on  
39 quantitative structure-activity relationships and it is not unusual for estimates to differ  
40 substantially from experimental values. The estimate from EPI Suite (2011) is include in Table 3  
41 only for the sake of completeness and transparency but is not otherwise used in the current risk  
42 assessment.

### 43 **2.3. Application Methods**

44 Rozol Prairie Dog Bait may be applied only in subsurface applications to active prairie dog  
45 borrows. The June 2012 label from Liphatech, Inc. addresses only hand applications in which  
46 the bait is placed at least 6 inches down into the prairie dog borrows. The label also indicates

1 that applications should be made only between October 1 and March 15 (i.e., fall to early spring).  
2 For each burrow, the label specifies that 53 grams of the bait should be applied. This amount is  
3 equivalent to about 0.00265 g a.i./burrow [53 grams formulation/burrow x 0.005% a.i./formulation =  
4 53 g formulation/burrow x 0.00005<sub>a.i./formulation</sub> = 0.00265 g a.i./burrow].

5  
6 Rozol Prairie Dog Bait is a restricted use pesticide and may be applied only by certified pesticide  
7 applicators or individuals working under the direct supervision of a certified pesticide applicator.  
8 Four days after application and at 1- to 2-day intervals after this period, applicators are required  
9 to return to the application area to remove dead organisms. Specifications for the carcass search  
10 are given on the product label. The period of search for carcasses must be at least 2 weeks and  
11 may be longer if carcasses are still being found at 2 weeks after application. Any dead animals  
12 found must be buried or otherwise disposed of in a manner that will prevent scavengers from  
13 consuming the carcasses.

14  
15 The U.S. EPA/OPP label dated August 24, 2012 also allows for mechanical applications (U.S.  
16 EPA/OPP 2012b). The label specifies but does not detail the nature of the mechanical bait  
17 placement machine. As with manual applications, the label specifies that the bait must be placed  
18 at least 6 inches down the burrow hole and that no bait can be left on the soil surface. The  
19 follow-up removal of carcasses is identical to that for manual applications. The Liphatech, Inc.  
20 web site provides links to mechanical baiters (<http://www.liphatech.com/partners>) .

#### 21 **2.4. Mixing and Application Rates**

22 As discussed in Section 2.2, Rozol Prairie Dog Bait comes as a 0.005% formulation and no  
23 additional mixing is required. Nonetheless, applicators will need to handle the pre-mixed bait in  
24 either manual or mechanical applications. Worker exposures in handling and applying  
25 chlorophacinone formulations are considered in Section 3.2.2 (Exposure Assessment for  
26 Workers).

27  
28 Several exposure scenarios considered in the current risk assessment (Sections 3.2 and 4.2)  
29 require application rates expressed in units of lb a.i./acre. The amount of bait applied per acre  
30 will depend on the number of prairie dog burrows. As noted in Section 2.3, the amount applied  
31 per prairie dog burrow is specified as 53 grams formulation or 0.00265 g a.i./burrow. One pound  
32 is equivalent to about 454 grams. Thus, each prairie dog burrow is treated with about  
33 0.00000584 lb a.i. [0.00265 g a.i./burrow ÷ 454 g/lb = 0.000005837 lb a.i./burrow].

34  
35 U.S. EPA/OPP/EFED (2008a, p. 9) estimates an application rate of 0.000625 lb a.i./acre. This  
36 application rate implies about 117 burrows per acre [0.000625 lb a.i./acre ÷ 0.00265 g  
37 a.i./burrow ≈ 117.1 burrows/acre]. U.S. EPA/OPP/EFED (2010a, p. 11) estimates an application  
38 rate of 0.00058 lbs a.i./acre, which is equivalent to 100 holes/acre [0.00058 lbs a.i./acre ÷  
39 0.0000058 lb a.i./burrow]. In the latter estimate, U.S. EPA/OPP/EFED (2010a, p. 11) notes that  
40 the application rate is based on the assumption of 100 burrows per acre from King (1959). The  
41 paper by King (1959, p. 128), however, indicates the number of burrow entrances is 20 - 40 per  
42 acre. Hygnstrom and Virchow (1994) indicate that dense populations of the black-tailed prairie  
43 dog may involve 20 - 35 colonies per acre; however, the correspondence between colonies/acre  
44 and burrows/acre is unclear.

1 The current Forest Service risk assessment bases exposure estimates on a functional application  
2 rate of 0.000625 lb a.i./acre, which is the higher application rate from U.S. EPA/OPP/EFED  
3 (2010a, p. 11). For a 0.005% a.i. formulation, this application rate is equivalent to 12.5 lbs  
4 formulation/acre [ $0.000625 \text{ a.i./acre} \div 0.00005 \text{ a.i./formulation}$ ]. The EXCEL workbook that  
5 comes with this risk assessment may be modified as needed to accommodate different densities  
6 of prairie dog populations.

7  
8 Most Forest Service risk assessments consider broadcast applications. Because the current risk  
9 assessment considers only subsurface burrow applications, the EXCEL workbook that comes  
10 with this risk assessment is customized to include the limited set of exposure assessments similar  
11 to the Forest Service risk assessment on strychnine, another rodenticide used by the Forest  
12 Service only in subsurface applications (SERA 2005). For example, exposures scenarios for the  
13 consumption of contaminated vegetation are not included because these scenarios are not  
14 relevant to burrow applications. As with the strychnine risk assessment, the workbook that  
15 accompanies the current risk assessment on chlorophacinone includes some elaborated exposure  
16 scenarios that are unique to bait applications such as secondary and tertiary exposures (i.e., the  
17 consumption of organisms contaminated with the rodenticide).

18  
19 While this risk assessment is focused on the control of the black-tailed prairie dog using Rozol  
20 Prairie Dog Bait (Liphatech Inc. 2012), it could support the use of additional chlorophacinone  
21 formulations to control other rodent pests. These uses would most likely involve minor  
22 modifications to the EXCEL workbook relating to application rates. The extension in the use of  
23 this risk assessment would be limited, however, to grain bait formulations used only in  
24 subsurface applications. As discussed by the U.S. EPA, some above ground applications of  
25 chlorophacinone including aerial applications ... *would vastly increase exposure and risk to*  
26 *listed and non-listed non-target animals* (U.S. EPA/OPP/EFED 2011a, p. 24). Above ground  
27 applications of chlorophacinone are not anticipated in Forest Service programs and cannot be  
28 supported by the current risk assessment.

## 29 **2.5. Use Statistics**

30 Forest Service risk assessments attempt to characterize the use of the pesticide under  
31 consideration in Forest Service programs relative to the uses of the pesticide in agricultural  
32 applications. Forest Service pesticide use reports up to the year 2004 are available on the Forest  
33 Service web site (<http://www.fs.fed.us/foresthealth/pesticide/reports.shtml>); however, no uses of  
34 chlorophacinone are recorded.

35  
36 Another common source of pesticide use statistics is from the U.S. Geological Survey (USGS  
37 2013). This source of information, however, is focused on insecticides and herbicides used in  
38 agriculture. No records for the use of chlorophacinone are included in the USGS (2013)  
39 statistics.

40  
41 Detailed pesticide use statistics are compiled by the state of California. The use statistics from  
42 California for 2011, the most recent year for which statistics are available, indicate that a total of  
43 about 28.6 lbs of chlorophacinone was used in California (CDPR 2013, p. 220). The major uses  
44 relevant to Forest Service programs appear to be pasture land (0.09 lbs), rights-of-way  
45 management (2.33 lbs), uncultivated non-agricultural applications (0.02 lbs), and vertebrate  
46 control (1.4 lbs). The total of these uses (3.84 lbs) accounts for about 13.4% of the total

1 chlorophacinone use in California during 2011 [ $3.84 \div 28.6 \approx 0.1343$ ]. Since black tailed prairie  
2 dog populations are not found in California, the relevance of these data to the current risk  
3 assessment is marginal.

4

5 The limited amount of information on the uses of chlorophacinone precludes a direct assessment  
6 of chlorophacinone use by the Forest Service, relative to other uses.

7

### 3. HUMAN HEALTH

#### 3.1. HAZARD IDENTIFICATION

##### 3.1.1. Overview

As with most anticoagulant rodenticides, the acute toxicity of chlorophacinone is well characterized in rodents. In addition to standard toxicity studies, there is an abundant literature involving field applications of chlorophacinone to control rodent populations. Except for studies that are relevant to the human health risk assessment, most of the literature involving field applications of chlorophacinone is covered in Section 4 (Ecological Risk Assessment).

At least in Europe, chlorophacinone was used in several apparent suicide attempts; thus, the toxicity of chlorophacinone to humans is also relatively well characterized. Chlorophacinone interferes with the formation of vitamin K<sub>1</sub> and several other clotting factors, which accounts for its anticoagulant effect. The most common signs of toxicity in both mammals and humans are delayed clotting times and hemorrhaging. These effects are not seen immediately but are typically delayed by several days. This delay is probably associated with the depletion of endogenous vitamin K<sub>1</sub>. Another well-documented characteristic of chlorophacinone, at least in humans, is that the anticoagulant effect is often prolonged. Even in cases of single dose exposures, medical intervention may be needed for several weeks. The basis for this prolonged toxicity is not clear but is probably related to sequestration of chlorophacinone in some tissues, particularly the liver.

Based on EPA's standard system for classifying the acute toxicity of pesticides, chlorophacinone is highly toxic by oral, dermal, and inhalation routes. In experimental mammals, acute oral LD<sub>50</sub> values from well-documented studies are on the order of 1 to 10 mg/kg bw with no clear or consistent pattern of sensitivity among species. Some older and less well-documented LD<sub>50</sub> values in mammals range up to 50 mg/kg bw. These higher LD<sub>50</sub> values are possibly associated with studies involving relatively short observation periods. Approximate lethal doses in humans cannot be estimated reliably from the available literature, most of which involves suicide attempts, because all reported cases involve medical intervention. Nonetheless, it is clear that doses as low as 250 mg lead to severe and potentially lethal hemorrhaging in the absence of medical intervention. Based on reasonable estimates of adult human body weights of 60 - 70 kg, 250 mg corresponds to doses of about 3.6 - 4.2 mg/kg bw, which are in the range of reported LD<sub>50</sub> values in experimental mammals. In an experimental study involving three humans, a dose of 20 mg (corresponding to about 0.3 mg/kg bw) caused a transient decrease in clotting times but no overt toxic effects requiring medical intervention.

Based on both acute gavage and acute dietary studies, chlorophacinone is classified as *Very Highly Toxic* to mammals.

While the acute toxicity of chlorophacinone is well characterized, relatively little information is available on the longer-term toxicity of chlorophacinone. No chronic toxicity, reproduction, or carcinogenicity studies have been conducted. Longer-term studies are limited to one subchronic toxicity study in rats as well as developmental studies in rats and rabbits. As discussed further in Section 3.3, the lack of chronic toxicity studies limits the dose-response assessment for chlorophacinone.

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### 3.1.2. Mechanism of Action

Both the indandione rodenticides (including chlorophacinone) and the 4-hydroxycoumarin rodenticides are anticoagulants. These compounds interfere with the vitamin K cycle by inhibiting vitamin K<sub>1</sub>-2,3 epoxide reductase, thus blocking the production of vitamin K from vitamin K epoxide (Lawley et al. 2006; Papin et al. 2007; Watt et al. 2005). Chlorophacinone also uncouples oxidative phosphorylation which reduces the synthesis of prothrombin (clotting factor II) and proconvertin (clotting factor VII), an antihemophilic factor (clotting factor IX), and the Stuart-Prower factor (clotting factor X) (Burucoa et al. 1989; Hoffbrand and Moss 2011; Lagrange et al. 1999; Papin et al. 2007; WHO 1985). As reviewed by van den Berg and Nauta (1975), the uncoupling of oxidative phosphorylation is common in many 1,3-indandiones. The anticoagulant activity of chlorophacinone and other anticoagulant rodenticides leads to internal hemorrhaging and death, as discussed in Section 3.1.4 (Acute Toxicity).

Several reviews (HSDB 2003; U.S. EPA/OPP/EFED 2010a; WHO 1985) indicate that chlorophacinone may cause neurological and cardiopulmonary effects in rodents, which do not appear to be directly attributable to and may precede hemorrhage. Moreover, these effects, which seem to be specific to rodents and are not observed in humans (WHO 1985), as discussed further in Section 3.1.6, are not associated in the primary literature with the effects of chlorophacinone. Other than to note that neurological and cardiopulmonary effects in rodents are not directly related to hemorrhaging, the mechanisms of action for neurological and cardiopulmonary effects have not been characterized. Bromethalin (a 4-hydroxycoumarin anticoagulant) is clearly a direct neurotoxin (U.S. EPA/OPP 1998a); however, the direct neurotoxicity of chlorophacinone has not been demonstrated (Section 3.1.6).

### 3.1.3. Pharmacokinetics and Metabolism

#### 3.1.3.1. Metabolism

For pesticide registration, the U.S. EPA/OPP generally requires a relatively standard metabolism study in rats in which the compound is administered by both intravenous and oral routes. For chlorophacinone, however, the EPA notes that only one metabolism study is available (MRID 00155540), and this study involves only oral exposure. While a DER for this study is not available, the study is described in reasonable detail in U.S. EPA/OPP (1998a, pp. 40-41). The study involved groups of four rats receiving a 1 mg oral dose of <sup>14</sup>C-labeled chlorophacinone as well as a second group of two rats receiving oral doses of 1.43 mg <sup>14</sup>C-labeled chlorophacinone per day for 3 days. The EPA summary does not specify the body weights of the rats. Assuming a relatively standard weight of 250 g, the doses correspond to about 4 mg/kg bw in the single dose component of the study and about 6 mg/kg bw in the multiple component of the dose study. Other groups were assayed for excretion as discussed further in Section 3.1.3.3. No metabolites were characterized, and the EPA summary notes that ...*chlorophacinone remained unchanged in plasma*. The EPA reports that less than 1% of the administered oral doses were recovered as CO<sub>2</sub>. Four hours after exposure, chlorophacinone residues were found primarily in the liver (31.1 µg/g), kidney (6.6 µg/g), and lung (4.5 µg/g). At 48 hours after exposure, the highest concentrations of radioactivity were found in the liver (2.9 µg/g), kidney (1.2 µg/g), and fat tissue (0.7 µg/g).

1 In a feeding study in rats (see Appendix 1, Table A1-2 for details), Vein et al. (2013) report that  
2 about 52% of the administered chlorophacinone was metabolized. While the metabolites are not  
3 identified, they are characterized as hydroxyl-metabolites which would be consistent with  
4 metabolism by cytochrome P450. As discussed further in Section 3.1.3.3 (Excretion), Buroca et  
5 al. (1989) noted that dosing with phenobarbital (a potent inducer of cytochrome P450) increased  
6 the rate of chlorophacinone elimination in humans and speculated that this could be due to  
7 cytochrome P450 induction. The recent study by Vein et al. (2013) clearly supports this  
8 hypothesis, and the P450-mediated metabolism of chlorophacinone is consistent with the  
9 metabolism of other anticoagulants such as warfarin (e.g., Piatkov et al. 2010).

10  
11 Vein et al. (2013) assayed concentrations of about 10 to over 200 µg/whole liver of the rats.  
12 While these residues are characterized by Vein et al. (2013) as *liver accumulation*,  
13 concentrations of chlorophacinone in the blood or plasma are not reported.

14  
15 Environmental metabolites of chlorophacinone, specifically soil degradates, have been  
16 characterized and are discussed in Section 3.1.15.1.

### 17 **3.1.3.2. Absorption**

#### 18 **3.1.3.2.1. Oral Absorption**

19 Based on the limited data on the time course of chlorophacinone concentrations in various tissues  
20 of rats following oral administration (MRID 00155540 discussed in Section 3.1.3.1), the  
21 absorption of chlorophacinone from the gastrointestinal tract appears to be rapid, with peak  
22 tissue concentrations occurring at 4 hours after exposure. The extent of absorption, however,  
23 cannot be determined from this study except to note that 26% of the administered dose was  
24 subject to biliary elimination; hence, at least 26% of the administered dose was absorbed.  
25 Reported mean blood concentrations of chlorophacinone peaked at 4 -6 hours in the single dose  
26 component of this study. Nevertheless, in a 4-day dosing of 1.43 mg/day using only one rat,  
27 concentrations of chlorophacinone in the blood continued to increase for up to 8 hours following  
28 the last dose.

29  
30 Consistent with the estimates of oral absorption in standard laboratory mammals, an oral  
31 bioavailability of 92% for chlorophacinone has been reported in sheep (Berny et al. 2006).

#### 32 **3.1.3.2.2. First-Order Dermal Absorption**

33 The dermal absorption of chlorophacinone is not addressed in the available literature. In the  
34 absence of information on first-order dermal absorption rates, quantitative structure activity  
35 relationships (QSAR) are used to estimate these rates (SERA 2011a, Section 3.1.3.2.2, Equation  
36 3). As detailed in Worksheet B03b of the EXCEL workbook that accompanies this risk  
37 assessment, this equation estimates a first-order dermal absorption rate of about 0.0007 (0.00025  
38 – 0.0019 hour<sup>-1</sup> based on a K<sub>ow</sub> value of 94.5 and a molecular weight of 374.83 g/mole (Table 3).  
39 These properties are within the range of values on which the algorithm is based—i.e., K<sub>ow</sub> values  
40 ranging from 0.0015 to 3,000,000 and molecular weights ranging from 60 to 400 g/mole. As  
41 discussed in SERA (2014), the QSAR method is based exclusively on dermal absorption data  
42 from studies in humans using a skin loading of 0.004 mg/cm<sup>2</sup>.



### 3.1.3.2.3. Zero-Order Dermal Absorption

In the absence of experimental data, Forest Service risk assessments generally use a QSAR algorithm developed by the EPA (U.S. EPA/ORD 1992, 2007). This approach is discussed in further detail in SERA (2011a, Section 3.1.3.2.1). As with the algorithm for estimating the first-order dermal absorption rate constant, the EPA algorithm is based on molecular weight and  $K_{ow}$  (U.S. EPA/ORD 1992, 2007). The molecular weight and  $K_{ow}$  values used for estimating the  $K_p$  are identical to those used in the estimate of the first-order dermal absorption rate constants (i.e., a  $K_{ow}$  of 94.5 and a molecular weight of 374.83 g/mole). The EPA algorithm is derived from an analysis of 95 organic compounds with  $K_{ow}$  values ranging from about 0.0056 to 309,000 and molecular weights ranging from approximately 30 to 770 (U.S. EPA/ORD 1992, 2007). These ranges of  $K_{ow}$  and molecular weight values encompass the estimates of the corresponding values for chlorophacinone.

Details of the implementation of the algorithms are given in Worksheet B03a in the EXCEL workbook that accompanies this risk assessment. Using the EPA algorithm results in an estimated dermal permeability ( $K_p$ ) of about 0.0002 (0.0001 - 0.0004) cm/hour.

Because chlorophacinone is used only as a granular formulation, the use of both the first-order and zero-order dermal absorption rates is somewhat atypical of most Forest Service risk assessments of liquid formulations. These differences are discussed in more detail in Section 3.2.2.2 (Accidental Exposures of workers) and Section 3.2.3.6 (Dermal Exposure from Swimming in Contaminated Water).

### 3.1.3.3. Excretion

Excretion half-lives can be used to infer the effect of longer-term exposures on body burden, based on the *plateau principle* (e.g., Goldstein et al. 1974). The chemical concentration in the body after a series of doses ( $X_{Inf}$ ) over an infinite period of time can be estimated based on the body burden immediately after a single dose,  $X_0$ , by the relationship:

$$\frac{X_{Inf}}{X_0} = \frac{1}{1 - e^{-kt^*}} \quad (1)$$

where  $t^*$  is the interval between dosing and  $k$  is the first-order excretion rate.

In the standard metabolism study (MRID 00155540) summarized in U.S. EPA/OPP (1998a, pp. 40-41), the half-life of chlorophacinone in whole blood was about 10 hours. In an elimination component of this study, about 90% of the administered dose (i.e., 1.43 mg in one rat and 1.28 mg in the other rat) was excreted in the feces in the first 2 days following dosing. Similarly, in a secondary poisoning study involving voles, Askham (1988) estimated that voles excreted or metabolized about 82% of ingested chlorophacinone. Details supporting this estimate, however, are not given in the DER for the Askham (1988) study. In a subsequent publication, Askham and Poche (1992) indicate that voles fed chlorophacinone to the point of lethality eliminate or excrete 90% of ingested chlorophacinone prior to death.

1 The pharmacokinetics of chlorophacinone in mice were assayed in an open literature study by  
2 Vandembroucke et al. (2008) using groups of 12 male and 12 female mice orally dosed at 0.336  
3 mg/mouse. Vandembroucke et al. (2008) report an average body weight of 32.2 g bw /mouse.  
4 Thus, the dose of chlorophacinone used in this study was about 10 mg/kg bw [0.336 mg/mouse ÷  
5 0.0322 kg bw /mouse ≈ 10.435 mg/kg bw]. Following dosing, blood and liver samples were  
6 collected on days 1, 2, 3, 5, 7 and 21 after dosing from groups of four mice. Chlorophacinone  
7 evidenced a biphasic pattern of elimination from both the plasma and liver; however, the half-  
8 lives of 11.7 days from plasma and 35.4 days from liver are reported as a *noncompartmental*  
9 *analysis* (Vandembroucke et al. 2008). Based on the illustrations of chlorophacinone  
10 concentrations in the plasma (Figure 1) and liver (Figure 2) of the paper, it appears that a  
11 compartmental analysis would indicate much shorter initial half-lives and much longer terminal  
12 half-lives. Vandembroucke et al. (2008) note that 7 of the 24 mice died during the study due to  
13 extensive internal hemorrhaging.

14  
15 In patients recovering from suicide attempts, Buroca et al. (1989) reports plasma half-lives of  
16 about 6.5 days in one patient and 9.2 and 11 days in a second patient who had consumed  
17 chlorophacinone on two occasions. Buroca et al. (1989) specifically note that the half-life of 6.5  
18 days is the apparent terminal half-life. In a third patient, Buroca et al. (1989) determined half-  
19 lives for chlorophacinone prior to treatment with phenobarbital (22.8 days) and after treatment  
20 with phenobarbital (6.5 days) and speculate that the increased rate of elimination with  
21 phenobarbital treatment could be due to the induction of cytochrome P450. Mura et al. (1992)  
22 report plasma half-lives of 6.5 - 22.8 days in three patients with slower elimination in the early  
23 phases of poisoning in at least one patient (Mura et al. 1992, Figure 3). As discussed in Section  
24 3.1.3.1 (metabolism), the subsequent study by Vein et al. (2013) clearly supports this  
25 speculation. Arditti et al. (1997) report a whole blood half-life of 7.6 days in a young woman  
26 following a suicidal ingestion of chlorophacinone. A pharmacokinetic study in sheep reports a  
27 terminal plasma half-life of 30 hours or 1.25 days (Berny et al. 2006).

28  
29 For the application of the plateau principle, whole body half-lives are more relevant than plasma  
30 half-lives because the latter often reflect redistribution rather than excretion. Based on a  
31 standard first-order elimination model, the proportion ( $M_t$ ) of a compound remaining (i.e., not  
32 excreted) by a given time ( $t$ ) is:

$$M_t = e^{-kt} \quad (2)$$

34  
35 where  $k$  is the first-order elimination rate in units of reciprocal time. Taking the estimate of 90%  
36 whole-body elimination (i.e., 10% not eliminated) over a 2-day period from MRID 00155540,  
37 the first-order elimination constant can be estimated as:

$$k = \frac{-\ln(1-0.9)}{2 \text{ days}} = 1.15 \text{ days}^{-1} \quad (3)$$

40  
41 Substituting this estimate of  $k$  into the above equation for the plateau principle, the estimated  
42 plateau for chlorophacinone is about 1.5—i.e., long-term exposures to chlorophacinone would  
43 lead to body burdens that are a factor of about 1.5 higher than the body burden following a single  
44 dose.

45

1 As noted by U.S. EPA/OPP, a comparison of the acute to subchronic toxicity values for  
2 chlorophacinone suggests that repeated doses are more toxic than would be expected from the  
3 above relationship (U.S. EPA/OPP 1998a, p. 42). For example, the gavage LD<sub>50</sub> study in black-  
4 tailed prairie dogs by Yoder (2008) notes delayed mortality which occurred at 9 - 20 days post-  
5 dosing. The U.S. EPA DER for this study offers the following interpretation: *That deaths*  
6 *occurred more than 2 weeks after a single administration suggests that chlorophacinone remains*  
7 *in the body and pharmacologically active for 20 days or more* (p. 7 of DER for Yoder 2008). As  
8 discussed further in Section 3.1.4, delayed mortality is a common observation in mammals  
9 following poisoning with chlorophacinone as well as other anticoagulant rodenticides (e.g.,  
10 Andre and Guillaume 2004). As suggested by Papin et al. (2007), delayed mortality following  
11 exposures to chlorophacinone could be due, at least in part, to the time required to diminish  
12 normal reserves of prothrombin. Moreover, as discussed further in Section 3.1.4.1.2, acute  
13 dietary studies in mice covering periods of 1 - 21 day do not suggest a substantial relationship  
14 between the duration of daily doses and time to death. In the rat feeding study by Vein et al.  
15 (2012), the time course of chlorophacinone in the liver (expressed as µg/whole liver) does not  
16 indicate any systematic increase in the amount of chlorophacinone in the liver over the 14-day  
17 exposure period (see Figure 3 of publication). This observation is consistent with the above  
18 application of the plateau principle indicating that substantial and increasing accumulation of  
19 chlorophacinone in mammals is unlikely over repeated dosing. Thus, while repeated dosing of  
20 chlorophacinone does not lead to a substantial increase of chlorophacinone in the body, the  
21 delayed mortality suggests that effects on blood clotting processes do appear to accumulate,  
22 mostly likely due to a gradual depletion of prothrombin.

### 23 **3.1.4. Acute Oral Toxicity**

#### 24 **3.1.4.1. Experimental Mammals**

##### 25 **3.1.4.1.1. Gavage Dosing**

26 Because chlorophacinone has been used as a rodenticide for many years (Section 2), there is a  
27 relatively robust literature on the toxicity of chlorophacinone to several species of wildlife;  
28 however, much of this literature is focused on efficacy or potential toxicity to nontarget species.  
29 These studies are discussed in Section 4.1.2.1 (toxicity to mammalian wildlife) and are noted in  
30 the following discussion only to the extent that they are relevant to the human health risk  
31 assessment.

32  
33 The standard acute oral gavage studies are typically used to determine LD<sub>50</sub> values—i.e., the  
34 dose estimated to be lethal to 50% of the animals. These standard studies involve a single  
35 gavage dose followed by a 14-day observation period. LD<sub>50</sub> values as well as other measures of  
36 acute toxicity discussed in following sections are used by the U.S. EPA/OPP to categorize  
37 potential risks. U.S. EPA/OPP uses a ranking system for response ranging from Category I  
38 (most severe response) to Category IV (least severe response). Details of the EPA classification  
39 system are provided in SERA (2011a, Table 4) as well as the U.S. EPA's Label Review Manual  
40 (U.S. EPA/OPP 2010c, p. 7-2). As summarized in Appendix 1, Table A1-1), a standard gavage  
41 study in Sprague-Dawley rats (MRID 41875301) yielded an LD<sub>50</sub> of 6.26 mg/kg bw for male and  
42 female rats combined. Based on this study, the U.S. EPA/OPP (1998a) classifies  
43 chlorophacinone as Category 1 for acute oral toxicity. Based on the relatively detailed summary  
44 of this study in U.S. EPA/OPP (1998a), male rats are more sensitive than female rats by a factor

1 of over 3—i.e., an LD<sub>50</sub> of 3.15 mg/kg bw in males and 10.95 mg/kg bw in females [10.95 ÷ 3.15  
2 ≈ 3.48]. In all rats, mortality was delayed, occurring from Day 4 to Day 13 after dosing. As  
3 discussed below, delayed death is a common observation in chlorophacinone poisoning. As  
4 would be expected for an anticoagulant, the primary sign of toxicity was internal bleeding.

5  
6 Two other gavage studies in rats are reported. WHO (1985) makes a brief reference to an LD<sub>50</sub>  
7 of 20.5 mg/kg bw. This LD<sub>50</sub> is cited in several reviews (WHO 1995; HSDB 2004; and  
8 Vandembroucke et al. 2008), all of which reference other secondary sources. The original study  
9 that reported this LD<sub>50</sub> was not identified in the available literature. In the absence of additional  
10 information on the study, most importantly the period of observation, this LD<sub>50</sub> cannot be  
11 evaluated further.

12  
13 As summarized in Appendix 1, Table A1-1, Ashton et al. (1986) report LD<sub>50</sub> values of 0.13 - 0.2  
14 mg/kg bw/day for 5 days in Sprague-Dawley and Norway rats. Significant differences between  
15 male and female as well as Sprague-Dawley and Norway rats were not observed, although male  
16 rats appeared to be somewhat more sensitive than female rats. In mice, however, Ashton et al.  
17 (1986) observed substantial differences between male and female mice with males being more  
18 sensitive by a factor of about 9 [3.48 mg/kg bw/day ÷ 0.38 mg/kg bw/day ≈ 9.157] .

19  
20 Gavage toxicity studies also were conducted in the black-tailed prairie dog (Yoder 2008) and  
21 rabbits (Giban 1974; WHO 1985). The study by Yoder (2008) is a well-documented registrant-  
22 submitted study that reports an LD<sub>50</sub> of 1.8 mg/kg. The major signs of toxicity noted by Yoder  
23 (2008) included external bleeding and blood in the feces.

24  
25 An LD<sub>50</sub> of 50 mg/kg bw in rabbits reported in WHO (1985) and HSDB (2003) is not well  
26 documented and is referenced to other secondary sources. As with the LD<sub>50</sub> of 20.5 mg/kg bw in  
27 rats from WHO (1985), the lack of additional information, particularly the period of observation,  
28 prevents a further assessment of the LD<sub>50</sub> of 50 mg/kg bw in rabbits.

29  
30 The study by Giban (1974) reports 20% to 100% mortality in rabbits after doses of 2 to 10 mg/kg  
31 bw. Giban (1974), however, reports these data from a previous unpublished report, and few  
32 experimental details are provided.

33  
34 On balance, the two best documented gavage LD<sub>50</sub> studies are reasonably consistent—i.e., an  
35 LD<sub>50</sub> of 6.26 mg/kg bw in Sprague-Dawley rats (MRID 41875301) and an LD<sub>50</sub> of 1.8 mg/kg bw  
36 in the black-tailed prairie dog (Yoder 2008). The higher LD<sub>50</sub> values reported from secondary  
37 sources are questionable. These higher LD<sub>50</sub> values might possibly be associated with relatively  
38 brief periods of observation following the administration of chlorophacinone.

39  
40 Based on acute gavage studies in rats (MRID 41875301) and black-tailed prairie dogs (MRID  
41 47333601), chlorophacinone is classified as *Very Highly Toxic* to mammals.

#### 42 **3.1.4.1.2. Dietary Exposures**

43 Data on acute dietary exposures to chlorophacinone are summarized in Appendix 1, Table A1-2.  
44 Most of these studies are focused on efficacy in rats as well as other species of mammalian  
45 wildlife; therefore, doses in terms of mg/kg bw cannot be estimated directly. One notable  
46 exception is the study by El Bahrawy and Morsy (1990) which provides information on the

1 amount of chlorophacinone bait consumed by Norway rats. Based on these data, the calculated  
2 LD<sub>50</sub> values for chlorophacinone are about 1.1 mg/kg bw for male rats and 3.2 mg/kg bw for  
3 female rats. As with the gavage study in Sprague-Dawley rats (MRID 41875301), the data from  
4 El Bahrawy and Morsy (1990) indicate that male rats are more sensitive than female rats by  
5 about a factor of 3 [3.2 mg/kg bw ÷ 1.1 mg/kg bw ≈ 2.9]. The dietary LD<sub>50</sub> values are somewhat  
6 lower than the gavage LD<sub>50</sub> values from MRID 41875301 (i.e., ≈3 mg/kg bw for males and 11  
7 mg/kg bw for females). This difference is probably attributable to the 2-week dietary exposure  
8 period used in the El Bahrawy and Morsy (1990), compared with the single dose gavage  
9 exposure in MRID 41875301.

10  
11 The only other dietary study from which reliable LD<sub>50</sub> values can be estimated is the study by  
12 Giban (1974) in two populations of pine voles, one of which was resistant to endrin. The  
13 reported LD<sub>50</sub> for chlorophacinone in the population susceptible to endrin is 3.58 mg/kg bw,  
14 while the strain tolerant to endrin was somewhat more susceptible to chlorophacinone with an  
15 LD<sub>50</sub> of 1.06 mg/kg bw. These LD<sub>50</sub> values for voles are similar to the LD<sub>50</sub> values for rats from  
16 El Bahrawy and Morsy (1990), discussed above.

17  
18 Virtually all of the dietary studies reporting time-to-death summarized in Appendix 1, Table  
19 A1-2, indicate that death in fatally exposed animals is delayed by periods of about 3 - 20 days.  
20 Many of the studies suggest an inverse relationship between time-to-death and concentration of  
21 chlorophacinone in the diet. This relationship, however, is not consistent, which may be due to a  
22 decrease in food consumption over time, as documented in the study by Schafer and Bowles  
23 (1985).

24  
25 While all of the studies in Appendix 1, Table A1-2, are classified as acute, several of the studies  
26 involve multiple days of dietary exposure. The feeding study by Lund (1971) offers the most  
27 detailed examination of the relationship of exposure duration to response. In this study,  
28 individually caged mice were fed a chlorophacinone diet (0.025% a.i.) for 1 - 21 days, and the  
29 amount of food consumed was recorded and used to estimate cumulative doses in units of mg/kg  
30 bw for both fatally exposed animals and animals that survived, and the data are given by Lund  
31 (1971, Table 2, p. 70) as both lower and upper bound doses. For the current analysis, the dose  
32 data on fatally exposed animals are used to calculate average daily doses (i.e., mg/kg bw/day),  
33 as detailed in the supplemental table at the end of Appendix 1, Table A1-2. The upper bound  
34 doses do not differ remarkably between the 1-day exposure group (65 mg/kg bw/day) and the 21-  
35 day exposure group (55.6 mg/kg bw/day). The lower bound doses, however, show a marked  
36 difference with generally decreasing lower bound doses with increasing durations of exposure.  
37 For example, the lower bound fatal dose following a single day exposure is 23 mg/kg bw/day but  
38 the corresponding daily dose for a 21-day exposure is only 6 mg/kg bw/day. Although this  
39 difference might suggest a decrease in food consumption associated with longer term exposures,  
40 it is not reflected in the mean body weights. For example, the mean body weight for the single  
41 day exposure group is 13.2 g while the mean body weight for the 21-day exposure group is only  
42 modestly less at 12.5 g.

43  
44 As would be expected, the most obvious signs of toxicity are associated with anticoagulant  
45 indicators—i.e., extensive hemorrhaging as noted by Nikodémusz et al. (1981). A more unusual  
46 observation by Nikodémusz et al. (1981) involves cardiac pathology characterized by

1 ...*dissolution of cross-striation*. As discussed by Nikodémusz et al. (1981), the effect on the  
2 heart may have been secondary to hypoxia rather than a direct effect of chlorophacinone. As  
3 discussed further Section 3.1.4.2, this supposition is supported by a relatively large number of  
4 human poisoning incidents which fail to note a consistent indication of direct cardiotoxicity. As  
5 discussed in Section 4.1.2.2 (hazard identification for birds), hemorrhaging in the hearts of birds  
6 was noted following poisonings with some anticoagulants; however, these effects were not noted  
7 for chlorophacinone (Mendenhall and Pank 1980, p. 313). Radvanyi et al. (1988) notes  
8 hemorrhaging in the hearts of some kestrels following oral exposure to chlorophacinone;  
9 however, the hemorrhaging occurred in numerous tissues, and a direct cardiotoxic effect was not  
10 observed

11  
12 Based on acute dietary studies in rats and mice from Ashton, et al. (1987), chlorophacinone is  
13 classified as *Very Highly Toxic* to mammals (U.S. EPA/OPP/EFED 2011a, Appendix D, p. D-5).

### 14 **3.1.4.2. Data on Humans**

#### 15 **3.1.4.2.1. Poisonings**

16 As summarized in Appendix 1, Table A1-3, 19 case reports of human poisoning with  
17 chlorophacinone have been published. Of these, 18 cases involve oral exposures, and all but one  
18 of these cases (a case reported Burucoa et al. 1989) appears to involve attempted suicides. The  
19 case by Burucoa et al. (1989) is somewhat unusual in that the individual voluntarily consumed  
20 chlorophacinone on two occasions possibly in an attempt to avoid military service. Blood in the  
21 urine (i.e., hematuria), decreases in prothrombin concentrations in the blood, prolonged  
22 prothrombin times, and other signs of abnormal bleeding (particularly in the mouth) are the most  
23 commonly reported sign of toxicity. As noted in the discussion of experimental mammals  
24 (Section 3.1.4.1), signs of toxicity are commonly delayed for 3 - 7 days after exposure. This  
25 delay is probably due to the time required to diminish normal reserves of prothrombin (Papin et  
26 al. 2007).

27  
28 Of the 19 cases summarized in Appendix 1, Table A1-3, 15 cases occurred in France, 2 in  
29 England, and 1 in Spain. The cases summarized in Appendix 1 appear to represent only a small  
30 subset of the total cases of human poisoning with chlorophacinone, at least in France. This  
31 assessment is based on the survey of human poisonings with rodenticides in France from 2004 to  
32 2007 (Berny et al. 2010), which identifies 165 cases of chlorophacinone poisoning in France.

33  
34 Berny et al. (2010) also notes that none of the 165 cases involved fatal exposures; however, the  
35 survey apparently does not include the case of fatal poisoning in France reported by Papin et al.  
36 (2007). In any event, only 2 of the 19 case reports summarized in Appendix 1, Table A1-3,  
37 involved fatal exposures—i.e., the case reported by Papin et al. (2007) in France and the case of  
38 fatal poisoning in Spain reported by Garci-Repetto et al. (1998). The amount of chlorophacinone  
39 consumed is not reported in either of these two cases.

40  
41 In the case reports involving nonfatal exposures which report the amount of chlorophacinone  
42 consumed, the estimated doses range from 250 to 1875 mg. None of the case reports specifies  
43 body weights, and they all involve substantial medical intervention. Consequently, the doses of  
44 250 - 1875 mg would not be regarded as “non-lethal.” Because medical intervention was  
45 required, these doses should be viewed as potentially lethal. Assuming a standard 70 kg body

1 weight (SERA 2014a), the estimated doses in units of mg/kg bw are about 3.6 - 27 mg/kg bw.  
2 These estimated doses are in the range of reported single dose LD<sub>50</sub> values in rats—i.e., 3.15  
3 mg/kg bw (MRID 41875301) and 20.5 mg/kg bw (WHO 1985; HSDB 2004).

4  
5 The case reported by Binks and Davies (2007) is unusual in that it involves dermal exposure to a  
6 0.25% (2.5 mg/mL) formulation of chlorophacinone in paraffin. Since, however, the Forest  
7 Service will not be using a liquid formulation, this incident is only marginally relevant to the  
8 current risk assessment.

9  
10 No cases of chlorophacinone poisoning in the United States were identified in the available  
11 literature. The U.S. EPA/OPP/HED specifically reviewed incident reports of poisonings  
12 associated with chlorophacinone and other rodenticides (U.S. EPA/OPP/HED 2001). While  
13 poisonings of domestic animals or wildlife are reported (as discussed further in Section 4.1.2.1),  
14 no human poisoning associated with chlorophacinone are identified in the EPA review. As noted  
15 in Section 2, chlorophacinone is a restricted use pesticide in the United States. It is possible that  
16 the limitations on the distribution and use of chlorophacinone in the United States accounts, at  
17 least in part, for the lack of reports of human poisonings in the United States.

#### 18 **3.1.4.2.2. Experimental**

19 As also summarized in Appendix 1, Table A1-3, one experimental study on the toxicity of  
20 chlorophacinone in humans was conducted. This study is reported briefly in both WHO (1995)  
21 and Watt et al. (2005) and entails the administration of 20 mg of chlorophacinone to three  
22 volunteers. Details regarding the gender and body size of the volunteers are not provided. Using  
23 70 kg as a standard estimate of an adult male body weight, the dose would be equivalent to about  
24 0.3 mg/kg bw. The only reported sign of toxicity is a transient decrease in prothrombin  
25 concentrations (Watt et al. 2005). The WHO (1995, p. 39) summary states that the effect was a  
26 33-38 % decrease in prothrombin times, which would not make sense for an anticoagulant. The  
27 review by Watt et al. (2005) clarifies that the statement concerning prothrombin times was an  
28 error and that the effect involved a transient decrease in prothrombin concentrations that returned  
29 to normal or near normal values by Day 8 after dosing.

#### 30 **3.1.5. Subchronic or Chronic Systemic Toxic Effects**

31 The U.S. EPA/OPP waived the requirement for chronic toxicity studies in mammals because  
32 chlorophacinone as well as other rodenticides are not registered for application to crops (U.S.  
33 EPA/OPP 1998a, p. 27). As discussed further in the dose response assessments for human health  
34 (Section 3.3) and mammalian wildlife (Section 4.3.2.1), the longer-term risks associated with  
35 exposures to chlorophacinone are based on a NOAEL from a developmental study.

36  
37 As summarized in Appendix 1, Table A1-4, one registrant-submitted subchronic study is  
38 available in which Sprague-Dawley rats were given gavage doses for periods of 0, 5, 10, 20, or  
39 40, µg/kg/day for 77 days (lower dose only) to 113 days (all other doses). At all except the  
40 lowest dose, increases in clotting times were observed. Consistent with some acute toxicity  
41 studies (i.e., MRID 41875301 and Ashton et al. 1986), survival patterns as well as the magnitude  
42 of increased in clotting times at the doses of 10, 20, or 40 µg/kg bw/day suggest that males are  
43 more sensitive than females. Higher doses of 80 or 160 µg/kg bw/day resulted in complete  
44 mortality by 3 to 13 days—i.e., these were essentially acute rather than subchronic exposures.  
45 The dose of 5 µg/kg bw/day for 77 days caused no signs of toxicity (including no change in

1 coagulation times). As discussed further in Section 3.1.9, the dose of 5 µg/kg bw/day is also a  
2 NOAEL in a standard developmental study in rabbits.

### 3 **3.1.6. Effects on Nervous System**

4 In severely poisoned animals, virtually any chemical may cause gross signs of toxicity which  
5 might be attributed to neurotoxicity—e.g., incoordination, tremors, or convulsions. A direct  
6 neurotoxicant, however, is defined as a chemical that interferes with the function of nerves,  
7 either by interacting with nerves directly or by interacting with supporting cells in the nervous  
8 system. This definition of a direct neurotoxicant distinguishes agents that act directly on the  
9 nervous system (direct neurotoxicants) from those agents that might produce neurological effects  
10 secondary to other forms of toxicity (indirect neurotoxicants). U.S. EPA has developed a battery  
11 of assays to test for neurotoxicity (Group E in U.S. EPA/OCSPP 2013), and U.S. EPA/OPP  
12 requires neurotoxicity studies for pesticides when standard toxicity studies or other  
13 considerations such as chemical structure suggest that concerns for effects on the nervous system  
14 are credible.

15  
16 WHO (1985) notes the following concerning indandione anticoagulants: *In rodents, indandlones*  
17 *also cause neurologic and cardiopulmonary injuries which often lead to death before*  
18 *haemorrhage occurs.* This statement is repeated in U.S. EPA/OPP/EFED (2010a, p. 11): *In*  
19 *rodents, this type of rodenticide [referring to chlorophacinone] also causes neurologic and*  
20 *cardiopulmonary injuries which often lead to death before hemorrhage occurs.* Concern for  
21 neurological effects is also noted in U.S. EPA/OPP/EFED (2011a, p. 92 and elsewhere). The  
22 U.S. EPA/OPP documents reference WHO (2010) as the source for this statement. This  
23 reference, however, is to Data Sheets on Pesticides No. 62: Chlorophacinone, which is the WHO  
24 (1985) document. HSDB (2003) also notes that ... *the indandiones also cause neurologic and*  
25 *cardiopulmonary injuries* but does not provide any primary or secondary reference for this  
26 statement. Reigart and Roberts (1999) also note that ... *some indandiones cause symptoms and*  
27 *signs of neurologic and cardiopulmonary injury in laboratory rats leading to death before*  
28 *hemorrhage occurs* but no literature is cited to support this statement.

29  
30 WHO (1985) does not cite published studies supporting the statement concerning neurotoxicity.  
31 The current review of chlorophacinone did not identify studies suggesting that chlorophacinone  
32 is a neurotoxin. While the detailed review of anticoagulant rodenticides by Watt et al. (2005)  
33 notes that hemorrhaging in central nervous system tissue occurs following intoxication with  
34 anticoagulants, no specific signs of neurotoxicity are identified.

35  
36 As noted above, almost all toxins can cause gross signs of toxicity that could resemble  
37 neurotoxicity. Given the reasonably robust mammalian data on chlorophacinone and the lack of  
38 documented observations of neurotoxicity, the rationale for the statement that chlorophacinone  
39 may cause neurological effects prior to effects on blood clotting is not apparent.

### 40 **3.1.7. Effects on Immune System**

41 There are various methods for assessing the effects of chemical exposure on immune responses,  
42 including assays of antibody-antigen reactions, changes in the activity of specific types of  
43 lymphoid cells, and assessments of changes in the susceptibility of exposed animals to resist  
44 infection from pathogens or proliferation of tumor cells. In addition to these specific assays for  
45 immunotoxicity, typical subchronic or chronic animal bioassays conduct morphological



1 assessments of the major lymphoid tissues, including bone marrow, major lymph nodes, spleen  
2 and thymus (organ weights are sometimes measured as well), and blood leukocyte counts. These  
3 assessments can detect signs of inflammation or injury indicative of a direct toxic effect of the  
4 chemical on the lymphoid tissue. Changes in morphology/cellularity of lymphoid tissue and  
5 blood, indicative of a possible immune system stimulation or suppression, can also be detected.  
6 While the U.S. EPA/OPP developed guidelines for immunotoxicity testing (e.g., U.S.  
7 EPA/OPP/HED 2013), the available literature, including the reviews summarized in Table 1,  
8 does not address the immunotoxicity of chlorophacinone.

9  
10 Waddel et al. (2013) reviewed veterinary records of 123 dogs with reported poisonings by  
11 anticoagulant rodenticides and found no association between immune-mediated diseases and  
12 confirmed anticoagulant poisonings.

### 13 **3.1.8. Effects on Endocrine System**

14 The direct effects of pesticides on endocrine function are most often assessed in mechanistic  
15 studies of estrogen, androgen, corticosteroid, or thyroid hormone systems (i.e., assessments on  
16 hormone synthesis, hormone receptor binding, or post-receptor processing). As noted in U.S.  
17 EPA/OPP/HED (2013), the EPA developed a battery of screening assays for endocrine  
18 disruption (U.S. EPA/OCSPP 2013). Neither the open literature nor the registrant-submitted  
19 studies include specific assays of chlorophacinone for endocrine disruption. The effects of  
20 chlorophacinone on endocrine function are not addressed in the reviews of chlorophacinone  
21 summarized in Table 1, and no data suggestive of effects on the endocrine system were identified  
22 in the open literature.

### 23 **3.1.9. Reproductive and Developmental Effects**

#### 24 ***3.1.9.1. Developmental Studies***

25 Developmental studies are used to assess whether a compound has the potential to cause birth  
26 defects—also referred to as teratogenic effects—as well as other effects during development or  
27 immediately after birth. These studies typically entail gavage administration to pregnant rats or  
28 rabbits on specific days of gestation. Teratology assays as well as studies on reproductive  
29 function (Section 3.1.9.2) are generally required for pesticide registration. Specific protocols for  
30 developmental and reproduction studies are established by EPA (U.S. EPA/OPPTS 2000).

31  
32 As summarized in Appendix 1, Table A1-5, two standard developmental studies are available on  
33 chlorophacinone, one in rats (MRID 43349501) and the other in rabbits (MRID 43570801).  
34 While DERs on these studies are not available, the studies are well described and discussed in  
35 U.S. EPA/OPP (1998a). As would be expected, increases in prothrombin time were observed in  
36 both species. In rats, a dose-related increase in ureter anomalies was noted over the range of  
37 doses assayed—i.e., from 12.5 to 100 µg/kg bw/day (U.S. EPA/OPP 1998a, Table 21, p. 32). As  
38 reviewed by Watt et al. (2005), anticoagulant exposures may lead to hemorrhaging in the bladder  
39 which may lead to obstruction of ureters. Whether or not the ureter malformations in rats were  
40 secondary to hemorrhaging, however, is not clear in the summary of the developmental study in  
41 rats (MRID 43349501). No malformations were observed in the developmental study in rabbits  
42 at doses of 5 to 75 µg/kg bw/day (MRID 43570801).

1 At 5 µg/kg bw/day, no effects (including clotting times) were observed in female rabbits. As  
2 discussed further in Section 3.3 (dose-response assessment), this NOAEL in rabbits supported by  
3 the subchronic NOAEL of 5 µg/kg bw/day in rats is the basis for the longer-term RfD for  
4 chlorophacinone.

5  
6 In addition to these registrant-submitted studies, Mesban et al. (2003) exposed pregnant mice to  
7 chlorophacinone at dietary concentrations of 0, 10, or 20 mg/kg chow for 20 days. Although  
8 extensive maternal hemorrhaging was observed in the pregnant mice, fetal abnormalities were  
9 not observed

### 10 **3.1.9.2. Reproduction Studies**

11 Reproduction studies involve exposing one or more generations of the test animal to a chemical  
12 compound. Typically, the EPA requires one acceptable multi-generation reproduction study for  
13 pesticide registration (U.S. EPA/OCSPP 2013). For chlorophacinone, however, no reproduction  
14 studies appear to have been submitted to the U.S. EPA. In addition, no reproduction studies on  
15 chlorophacinone were identified in the open literature.

16  
17 One ecological risk assessment from EPA notes the lack of a reproduction study in mammals as  
18 a data gap (U.S. EPA/OPP/EFED 2004a, p. 30). In a more recent ecological risk assessment, the  
19 EPA notes the following: *Mammalian toxicity data do not characterize growth and reproduction*  
20 *effects because mortality effects occur before these effects are seen in mammals* (U.S.  
21 EPA/OPP/EFED 2010a, p. 14).

22  
23 A publication from the Hungarian literature (Nehez et al. 1985) notes that Redentin (which  
24 appears to be a formulation of chlorophacinone) did not induce pathological changes in the  
25 sperm of mice exposed to a single dose of 20 mg/kg bw, which is characterized as one-quarter of  
26 the LD<sub>50</sub>.

### 27 **3.1.10. Carcinogenicity and Mutagenicity**

28 As noted in Section 3.1.5 (Subchronic or Chronic Systemic Toxic Effects), the U.S. EPA/OPP  
29 did not require chronic toxicity studies or standard chronic carcinogenicity bioassays on  
30 chlorophacinone, because it is not registered for food uses (U.S. EPA/OPP 1998a, p. 27).  
31 Several standard *in vitro* bioassays for mutagenicity—i.e., assays with *Salmonella typhimurium*,  
32 Chinese hamster cells, and human lymphoma cells—failed to demonstrate mutagenic effects  
33 (U.S. EPA/OPP 1998a, p. 35).

### 34 **3.1.11. Irritation and Sensitization (Effects on the Skin and Eyes)**

35 The U.S. EPA/OPP requires standard studies with pesticide formulations for skin and eye  
36 irritation as well as skin sensitization (U.S. EPA/OCSPP 2013). The available studies on these  
37 endpoints are summarized in Appendix 1, Table A1-6. Chlorophacinone is classified as  
38 Category IV (the least severe category) for both skin and eye irritation and was found not to be a  
39 skin sensitizer. The rankings for skin irritation and sensitization are consistent with the MSDS  
40 for Rozol Prairie Dog Bait. The MSDS, however, does indicate that Rozol Prairie Dog Bait may  
41 cause transient eye irritation. This effect is not reported in an eye irritation study for  
42 chlorophacinone (MRID 41874001). As discussed in Section 2.2, Rozol Prairie Dog Bait is a  
43 0.005% chlorophacinone formulation in grain. Perhaps, the MSDS refers to a study conducted

1 with the formulation rather than the a.i., and the transient eye irritation was caused by the grain  
2 and not chlorophacinone.

3  
4 Mild hemorrhage of the eyes was observed in one bird with documented exposure to  
5 chlorophacinone (3.19 µg/g residues in the liver); however, this effect appears to be an incidental  
6 finding, probably secondary to the anticoagulant action of chlorophacinone rather than an irritant  
7 effect on the eyes (Sarabia et al. 2008, Table 1).

### 8 **3.1.12. Systemic Toxic Effects from Dermal Exposure**

9 As summarized in Appendix 1, Table A1-7, one standard dermal toxicity study in rabbits (MRID  
10 41702801) is summarized in U.S. EPA/OPP (1998a). In this study, rabbits were exposed for 24  
11 hours to doses of 0.25, 0.5 or 0.75 mg/kg and observed for 21 days. The LD<sub>50</sub> is reported as  
12 0.329 mg/kg bw with deaths occurring from Days 5 to 19. Signs of toxicity are consistent with  
13 those seen in oral exposures—i.e., hemorrhaging associated with the anticoagulant activity of  
14 chlorophacinone. Based on this study, U.S. EPA/OPP (1998a) classifies chlorophacinone as  
15 Category I (the most hazardous level) for acute dermal toxicity.

16  
17 As discussed in Section 3.1.4.1.1, a standard acute gavage toxicity study in rats yielded an LD<sub>50</sub>  
18 of 6.26 mg/kg bw (MRID 41875301), higher than the dermal LD<sub>50</sub> in rabbits by a factor of about  
19 19 [6.26 mg/kg ÷ 0.329 mg/kg ≈ 19.03]. This observation is quite unusual, in that oral LD<sub>50</sub>  
20 values are typically lower and often much lower than dermal LD<sub>50</sub> values (e.g., Gaines 1969).  
21 While the study by Gaines (1969) involved oral and dermal studies in rats, it does not seem  
22 likely that substantial differences in sensitivity between rabbits and rats would account of the  
23 unusual relationship for chlorophacinone. Secondary sources (WHO 1985; HSDB 2003) report  
24 an oral LD<sub>50</sub> of 50 mg/kg bw for rabbits, which is a factor of about 130 above the dermal LD<sub>50</sub>  
25 noted above [50 mg/kg ÷ 0.329 mg/kg ≈ 127.6]. As discussed in Section 3.1.4.1.1, several of the  
26 oral LD<sub>50</sub> values reported in secondary sources are poorly documented and appear to be aberrant,  
27 which is true also for dermal toxicity with WHO (1985) reporting a dermal LD<sub>50</sub> of 200 mg/kg  
28 bw in rabbits. While high confidence can be placed in the in U.S. EPA/OPP summary of MRID  
29 41702801 (U.S. EPA/OPP 1998a), the LD<sub>50</sub> of 200 mg/kg bw in WHO (1985) is not referenced.

30  
31 The validity of the acute dermal LD<sub>50</sub> of 0.329 mg/kg bw (MRID 41702801) is questionable,  
32 based on comparison of this study to the subchronic dermal toxicity study in rabbits (MRID  
33 42237402). As summarized in Table A1-7, this study involved doses of 0.08, 0.4, or 2.0 mg  
34 a.i./kg bw for 6 hours/day, 5 days/week, for 3 weeks. The NOAEL was 0.08 mg/kg bw. At a  
35 dose of 0.4 mg/kg bw/day, modestly higher than the reported acute dermal LD<sub>50</sub> in rabbits, no  
36 mortality occurred. This lack of mortality is clearly not consistent with or supportive of the LD<sub>50</sub>  
37 of 0.329 mg/kg bw (MRID 41702801). The apparent discrepancy between the acute and  
38 subacute toxicity data in rabbits is not discussed in U.S. EPA/OPP (1998a) or other EPA  
39 documents on chlorophacinone (Table 1).

40  
41 As discussed in Section 3.1.4.2.2, there is one case report for chlorophacinone poisoning  
42 involving dermal exposure (Binks and Davies 2007). This case report is, however, of limited use  
43 in the current risk assessment for assessing systemic effects from dermal exposure to  
44 chlorophacinone based on the lack of an estimated dose and the fact that the incident involved a  
45 liquid formulation rather than a granular formulation such as Rozol.

### 3.1.13. Inhalation Exposure

As summarized in Appendix 1, Table A1-8, one standard registrant-submitted inhalation study is available in which rats were exposed (nose-only) to chlorophacinone at concentrations of 1.33, 10.3, 11.5 or 14.5 µg/L for 4 hours with a 21-day observation period (MRID 41981102). As with other several other acute toxicity studies, males (LC<sub>50</sub>=7 µg/L) were more sensitive than females (LC<sub>50</sub>=12 µg/L). As with acute oral and dermal toxicity studies, mortality was delayed, occurring on Days 3 to 8 post-exposure. Based on this study, the U.S. EPA/OPP (1998a, p. 10) classifies chlorophacinone as Category I (the most hazardous category) for acute inhalation exposures.

Given the uses of chlorophacinone in Forest Service programs (Section 2), inhalation exposures to toxicologically significant amounts of chlorophacinone seem unlikely. This is a common pattern with anticoagulants for which adverse effects typically occur following oral exposures (Watt et al. 2005). For chlorophacinone, no cases of toxic effects from inhalation exposures are documented in the open literature.

### 3.1.14. Adjuvants and Other Ingredients

As discussed in Section 2, Rozol Prairie Dog Bait is a 0.005% a.i. formulation in grain bait. The product label for Rozol does not recommend the use of any adjuvants. While adjuvants may be a significant consideration in the risk assessment of some pesticides, this is not the case for Rozol Prairie Dog Bait.

### 3.1.15. Impurities and Metabolites

#### 3.1.15.1. Metabolites

As discussed in Section 3.1.3.1, only limited information is available on the metabolism of chlorophacinone in mammals indicating unidentified hydroxyl metabolites probably mediated by cytochrome P450 isozymes. Similarly, little information is available on the environmental metabolites of chlorophacinone—i.e., metabolites due to chemical or microbial metabolism in the environment. Based on an aerobic soil metabolism study (MRID 42452301), o-phthalic acid and p-chlorophenylphenyl acetic acid have been identified as minor degradates (U.S. EPA/OPP/EFED 2010a, Table 2.2, p. 21), accounting for about 15% of the applied chlorophacinone. Based on the structure of these compounds, EPA/OPP/EFED (2010a, p. 20) suggests that *...the toxic moiety is no longer present in these degradates*. As discussed further by EPA, two additional degradates (other than CO<sub>2</sub>) accounting for somewhat over 22% of the applied chlorophacinone were detected but not identified in the soil metabolism study. Because these compounds were not identified, no inferences concerning the toxicity of these compounds can be made.

#### 3.1.15.2. Impurities

There is no information in the published literature or the summaries of registrant-submitted studies from EPA documents (Table 2) concerning the impurities in chlorophacinone.

Virtually no chemical synthesis yields a totally pure product. Registrants disclose the nature of impurities in their formulations to the U.S. EPA; however, the identities of the impurities are not disclosed to the public, because that information may provide insight into the manufacturing process, which is considered proprietary and is protected under FIFRA (Section 10). Proprietary

1 information on the identities of these impurities was not available for the preparation of the  
2 current Forest Service risk assessment.

3  
4 To some extent, concern for impurities in technical grade chlorophacinone is reduced because  
5 most of the existing toxicity studies were conducted with the technical grade product or bait  
6 products containing technical grade chlorophacinone. Thus, any toxic impurities present in the  
7 technical grade product are likely to be encompassed by the available toxicity studies.

### 8 **3.1.16. Toxicological Interactions**

9 As discussed in Section 3.1.3.1, chlorophacinone appears to be metabolized by mixed-function  
10 oxidase, also known as the cytochrome P450 enzyme system. The cytochrome P450 enzyme  
11 system consists of many different specific enzymes (referred to as isozymes) involved in the  
12 metabolism of many naturally occurring and man-made chemicals (Coon 2005; Lynch and Price  
13 2007). While P450 status may be an important factor in sensitivity to some anticoagulants such  
14 as warfarin (Piatkov et al. 2010; Watt et al. 2005), the data on the role of P450 in response to  
15 chlorophacinone are limited. There is no direct evidence that the induction of cytochrome P450  
16 will interfere with the anticoagulant action of chlorophacinone (e.g. Papin et al. 2007);  
17 nonetheless, phenobarbital (a potent inducer of cytochrome P450) increased the rate of  
18 chlorophacinone elimination in one patient suffering from chlorophacinone poisoning after an  
19 apparent suicide attempt (Buroca et al. 1989). Another characteristic of the cytochrome P450  
20 enzyme system is that isozymes are often induced by the substrates that the enzyme system can  
21 metabolize. For strychnine (a non-anticoagulant rodenticide), there are some data indicating that  
22 cytochrome P450 induction may lead to acquired resistance/tolerance. No such information has  
23 been encountered on chlorophacinone. As detailed further in Section 4.1.2.1, rodent resistance to  
24 anticoagulant rodenticides appears to involve selection pressure leading to genetic resistance.

25  
26 As discussed in Section 3.1.4.2, there is ample literature on human poisonings from  
27 chlorophacinone and other anticoagulants. A standard treatment for such poisonings involves  
28 the administration of vitamin K<sub>1</sub> (Watt et al. 2005). Therapeutic treatment with vitamin K<sub>1</sub>,  
29 while diminishing the impact of chlorophacinone poisoning, would not generally be viewed as a  
30 toxicological interaction and has no substantial relevance in terms of environmental exposures to  
31 chlorophacinone that do not involve medical intervention.

1 **3.2. EXPOSURE ASSESSMENT**

2 **3.2.1. Overview**

3 Details of the exposure assessments for workers and members of the general public are provided  
4 in the EXCEL workbook that accompanies this risk assessment. These workbooks contain sets  
5 of worksheets on strychnine that provide details for each exposure scenario discussed in this risk  
6 assessment. In addition, the workbooks include summary worksheets for worker exposures  
7 (Worksheet E01) and exposures to members of the general public (Worksheet E02). The  
8 documentation for these worksheets is provided in SERA (2009a).

9  
10 Standard methods used in most Forest Service risk assessments to assess worker exposures (i.e.,  
11 SERA 2014a) do not accommodate bait applications of burrows. Consequently and as with the  
12 Forest Service risk assessment on strychnine (SERA 2005), the current Forest Service risk  
13 assessment on chlorophacinone relies on the Pesticide Handler's Exposure Database typically  
14 used by the U.S. EPA's Office of Pesticide Programs. Because proper worker hygiene is an  
15 important part of the label instructions for chlorophacinone applications, a separate accidental  
16 exposure scenario is given for workers who do not follow label directions in terms of washing  
17 shortly after chlorophacinone applications are completed.

18  
19 For members of the general public, most exposures to chlorophacinone are associated with  
20 below-ground applications are likely to be insignificant. One extreme accidental exposure  
21 scenario is developed for a young child who might consume bait accidentally deposited on the  
22 surface of the ground, which is unanticipated and has not been observed in below-ground  
23 applications of chlorophacinone.

24 **3.2.2. Workers**

25 **3.2.2.1. General Exposures**

26 As described in SERA (2014b), worker exposure rates in Forest Service risk assessments are  
27 expressed in units of mg of absorbed dose per kilogram of body weight per pound of chemical  
28 handled. Based on analyses of several different pesticides using a variety of application  
29 methods, default exposure rates are normally estimated for several different types of application  
30 methods (SERA 2014b, Table 14). The application method relevant to chlorophacinone—i.e.,  
31 hand baiting of burrows—is not included in the application methods covered in SERA (2014b).

32  
33 As also discussed in SERA (2014a), the U.S. EPA's Office of Pesticide Programs employs a  
34 deposition based approach using data from the Pesticide Handler's Exposure Database (PHED  
35 Task Force 1995). In this type of model, the exposure dose is estimated from air concentrations  
36 and skin deposition monitoring data. These estimates can be used to calculate the absorbed dose  
37 when estimates are available on absorption rates for inhalation and dermal exposure. As  
38 summarized in Table 4, standard exposure rates were developed for 37 application methods  
39 (Keigwin 1998). These application rates involve three different types of dermal exposures—no  
40 clothing, a single layer of clothing with no gloves, and a single layer of clothing with gloves—as  
41 well as estimates of inhalation exposure. Note that Scenario 17 in Table 4 applies to *Granular*  
42 *bait dispersed by hand*; however, the bait used in this scenario is an insecticide, not a  
43 rodenticide. The Pesticide Handlers Exposure Database (PHED) contains data on insecticides,

1 fungicides, herbicides, fumigants, and plant growth regulators but does not contain any data on  
2 rodenticide applications (PHED Task Force 1995).

3  
4 Occupational exposure rates for hand baiting are derived in the Forest Service risk assessment on  
5 strychnine (SERA 2005), another rodenticide applied by hand baiting of burrows, and this  
6 approach is adopted in the current risk assessment on chlorophacinone. Because the process of  
7 hand-baiting with chlorophacinone is essentially identical to that for strychnine, the amount of  
8 formulation handled per day is taken as 1.5 (0.75 to 3) lb formulation, identical to the amounts  
9 used in the Forest Service risk assessment on strychnine. In Worksheet A01 of Attachment 1,  
10 these formulation values are converted to active ingredient based on the 0.005% a.i. content of  
11 Rozol Prairie Dog Bait—i.e., 0.000075 (0.0000375-0.00015) lb a.i./day. In Worksheet C01a,  
12 these amounts are combined with the work exposure rates in Table 4 for dermal application (71  
13 mg per lb a.i. handled) and inhalation exposure (0.47 mg/lb handled). Following the standard  
14 practice in EPA risk assessments, 100% inhalation absorption is assumed. For the dermal  
15 component of the exposure, the absorbed dose is based on the first-order dermal absorption rate  
16 coefficients derived in Section 3.1.3.2.2.

### 17 **3.2.2.2. Accidental Exposures**

#### 18 **3.2.2.2.1. Standard Accidental Exposure Scenarios**

19 Two types of accidental exposure scenarios are considered: contamination of gloves with  
20 chlorophacinone and the failure to follow prudent personal hygiene practices after completing  
21 applications of chlorophacinone. Although the latter type of exposure may be better viewed as a  
22 misapplication rather than an accidental event, it is considered in this section on accidental  
23 exposures because the failure to follow proper hygiene practices is a substantial deviation from  
24 label instructions. In other words, failure to follow prudent personal hygiene practices is not an  
25 expected event.

26  
27 Contaminated glove scenarios are typically included in Forest Service risk assessments involving  
28 liquid formulations (SERA 2007a). For granular formulations, no standard methods for  
29 estimating exposure are available. Nonetheless, dust from chlorophacinone treated bait on the  
30 surface of the skin might be regarded as analogous to exposure to a neat (undiluted) solution.  
31 For such exposures, the EPA recommends using the solubility of the compound in water as an  
32 approximation of the chemical concentration on the surface of the skin (U.S. EPA/ORD 1992).  
33 The apparent rationale for this approach is that the amount of the chemical on the surface of the  
34 skin will saturate the pore water of the skin, and the factor limiting the chemical concentration in  
35 pore water will be the water solubility of the chemical. As indicated in Table 1, the water  
36 solubility of chlorophacinone is 3.43 mg/L (Tomlin 2001), which is equivalent to 0.00343  
37 mg/mL. Thus, accidental exposures to gloves contaminated with chlorophacinone dust are  
38 considered equivalent to dermal exposures to a saturated aqueous solution of chlorophacinone.

39  
40 The contaminated glove scenario encompasses three exposure periods: 1 minute (Worksheet  
41 C02a), 1 hour (Worksheet C02b) and 8 hours (Worksheet C02c). The first two duration periods  
42 are standard in Forest Service risk assessments. The 8-hour period of exposure is included to  
43 illustrate the consequences of a worker applying chlorophacinone over the course of a day with  
44 grossly contaminated gloves—i.e., equivalent to handling chlorophacinone without using gloves.  
45 Because the concentration of chlorophacinone is considered constant—i.e., at the water

1 solubility—zero-order kinetics are used with the estimates of dermal permeability ( $K_p$  in cm/hr)  
2 as discussed in Section 3.1.3.2.

### 3 **3.2.2.2.2. Poor Worker Hygiene**

4 The other type of quasi-accidental exposure involves the failure of the worker to wash after  
5 applications of chlorophacinone are complete. For general or expected exposures in Section  
6 3.2.2.1 and Worksheet C01a, the exposure duration is assumed to be 8 hours. If a worker does  
7 not change into clean clothing and wash, the functional exposure period could be longer.  
8 Worksheet C01b implements this scenario by assuming a functional exposure period of 24 hours.  
9 This exposure duration may be grossly conservative, because the underlying scenario involves  
10 the worker not only failing to wash but also not changing clothes for a 16-hour period post  
11 application.

12  
13 On the other hand, concern may be expressed for the efficacy for washing. As discussed in  
14 SERA (2014a), dermal absorption is a complex process in which the binding of chemicals to  
15 various constituents of the skin can result in both lag periods as well as reservoir effects. As  
16 summarized in Appendix 1, Table A1-3, a potential lag period is illustrated in the study by Binks  
17 and Davies (2007) in which the individual washed shortly after dermal contact but did not  
18 develop symptoms for several days. This exposure, however, involved a liquid solution of  
19 chlorophacinone. Based on the reported concentration of chlorophacinone in the solution  
20 (0.25%), it seems likely that the solution consisted of an organic solvent. Thus, it is reasonable  
21 to suppose that the chlorophacinone penetrated into the skin and that most of the  
22 chlorophacinone was not effectively removed by washing. For bait formulations, however, the  
23 skin of the worker will be contaminated with dust that contains chlorophacinone. While some  
24 residual skin contamination may remain after washing, most of the chlorophacinone will be on  
25 the surface of the skin in the form of dust, and it seems likely that washing will effectively  
26 remove most of the chlorophacinone and substantially diminish exposure.

## 27 **3.2.3. General Public**

### 28 **3.2.3.1. General Considerations**

29 As with strychnine (SERA 2005), the likelihood of any significant exposures to members of the  
30 general public is remote, because chlorophacinone is limited to underground applications only.  
31 The exposure scenarios developed for chlorophacinone are identical to those used in the Forest  
32 Service risk assessment on strychnine (SERA 2005).

33  
34 Forest Service risk assessments routinely include accidental exposure scenarios as well as a  
35 general set of extremely conservative non-accidental exposure scenarios. With some exceptions,  
36 these scenarios are used in the current Forest Service risk assessment. Three sets of standard  
37 exposures which are not considered for chlorophacinone involve the consumption of  
38 contaminated vegetation, dermal contact with contaminated vegetation, and direct spray  
39 scenarios.

40  
41 As discussed below (Section 3.2.3.6), chlorophacinone is not applied to vegetation and does not  
42 appear to translocate from soil to vegetation. Thus, scenarios for the consumption of or dermal  
43 contact with contaminated vegetation are not relevant. Similarly, chlorophacinone is not  
44 broadcast. While some bizarre scenarios might be constructed for dermal contact with the bait,



1 they would not be instructive or of substantial use in this risk assessment. Section designations  
2 for these excluded scenarios are given below as a matter of convenience for individuals who  
3 regularly use many different Forest Service risk assessments—i.e., the section designations in all  
4 Forest Service risk assessments are consistent or nearly so.

5  
6 All standard exposure scenarios, both accidental and non-accidental, involving exposures to  
7 contaminated water are considered. One exposure scenario not usually considered in Forest  
8 Service risk assessment involves the direct consumption of bait by a small child (Section  
9 3.2.3.2). This is an admittedly extreme exposure scenario developed as a replacement for the  
10 equally extreme scenario concerning the direct spray of a naked child, included in most Forest  
11 Service risk assessments.

12  
13 The exposure scenarios developed for the general public are summarized in Worksheet E03 of  
14 the EXCEL workbook that accompanies this risk assessment. As with the worker exposure  
15 scenarios, details about the assumptions and calculations used in these assessments are given in a  
16 series of worksheets, D01 to D08b, in this EXCEL workbook.

### 17 ***3.2.3.2. Consumption of Bait by a Child***

18 The scenario concerning the accidental consumption of chlorophacinone treated bait by a child is  
19 detailed in Worksheet D01 and is quite simple. The scenario assumes that a young child ingests  
20 a mouthful of chlorophacinone treated bait. The amount of bait consumed is taken as 8.2 (5.5 to  
21 10.9) grams, based on the estimated volume of a mouthful for a young (13.5 kg) child  
22 (Ratnapalan et al. 2003). The scenario is intended to illustrate the consequences of a child  
23 consuming a substantial but plausible amount of bait. This accidental exposure scenario is only  
24 modestly more conservative than the accidental exposure scenario developed in U.S. EPA/OPP  
25 (1998a, p. 47) involving the consumption of 5 grams of rodenticide bait.

26  
27 The probability of this scenario is low, given that chlorophacinone bait is applied below ground.  
28 As described in Section 2.3, each burrow hole is baited with about 53 grams of formulation.  
29 Thus, the mouthful of bait used in this scenario would be equivalent to about 20% of the amount  
30 used to bait one burrow hole [ $10.9 \div 53 \approx 0.2057$ ].

### 31 ***3.2.3.3. Dermal Exposure from Contaminated Vegetation***

32 Scenarios involving dermal contact with contaminated vegetation are based on data from  
33 applications to vegetation. These scenarios are not relevant to subsurface applications of  
34 chlorophacinone.

### 35 ***3.2.3.4. Contaminated Water***

#### 36 ***3.2.3.4.1. Accidental Spill***

37 The accidental spill scenario is presented for the acute consumption of contaminated water after  
38 an accidental spill into a small pond (1000 m<sup>2</sup> or about 0.25 acres in surface area and 1 meter  
39 deep). The actual concentrations in the water would depend heavily on the amount of compound  
40 spilled, the size of the water body into which it is spilled, the time at which water consumption  
41 occurs relative to the time of the spill, and the amount of contaminated water consumed. This  
42 scenario is based on the assumption that exposure occurs shortly after the spill; hence no  
43 dissipation or degradation is considered.

1  
2 All Forest Service risk assessments consider some type of accidental spill scenarios. For  
3 applications involving a solution of either a granular or liquid formulation, the accidental spill  
4 scenarios are generally based on spills of a field solution, specifically 100 (20-200) gallons of the  
5 pesticide after dilution to the concentration recommended for application. This scenario is  
6 obviously not relevant to chlorophacinone. For granular formulations that are not pre-mixed  
7 prior to application, the typical assumption is that 40 (16 - 80) pounds of the active ingredient are  
8 spilled into the small pond. For both the liquid and granular applications, the amounts spilled are  
9 intended to represent a batch of material that might be assembled in a single place and  
10 subsequently spilled into a small body of water. These assumptions, which are reasonable for  
11 most herbicides and some insecticides applied to relatively large areas, are not plausible for  
12 chlorophacinone.

13  
14 Chlorophacinone applications will involve a 0.005% formulation. Thus, a spill of 40 (16 - 80)  
15 pounds of the active ingredient would involve 800,000 (320,000 - 1,600,000) pounds of a  
16 formulation. For hand baiting, this amount is clearly inappropriate. Hand baiting burrows is  
17 labor intensive; consequently, an individual worker is expected to apply only about 1.5 (0.75 - 3)  
18 lbs of formulation per day. In the current Forest Service risk assessment on chlorophacinone, an  
19 accidental spill is based on 30 (20 - 40) pounds of a 0.005% formulation, which corresponds to  
20 the amount that might be handled by a large group of workers (i.e., about 30).

21  
22 As detailed in Worksheet B04b of the EXCEL workbook that accompanies this risk assessment,  
23 the accidental spill scenario described above leads to surface water concentrations of about 0.68  
24 (0.45 - 0.91) ppb.

#### 25 **3.2.3.4.2. Accidental Direct Spray/drift for a Pond or Stream**

26 Forest Service risk assessments concerned with broadcast applications of pesticides typically  
27 include estimates of surface water contamination associated with drift of the pesticide into small  
28 ponds and small streams (SERA 2014a, Section 3.2.3.4). These types of estimates are not  
29 appropriate for below-ground applications of chlorophacinone and are not included in the current  
30 risk assessment.

#### 31 **3.2.3.4.3. GLEAMS Modeling**

32 The Forest Service developed a program, Gleams-Driver, to estimate expected peak and longer-  
33 term pesticide concentrations in surface water. Gleams-Driver serves as a preprocessor and  
34 postprocessor for GLEAMS (Knisel and Davis 2000). GLEAMS is a field scale model  
35 developed by the USDA/ARS and has been used for many years in Forest Service and other  
36 USDA risk assessments (SERA 2007b; SERA 2011b). Gleams-Driver offers the option of  
37 conducting exposure assessments using site-specific weather files from Cligen, a climate  
38 generator program developed and maintained by the USDA Agricultural Research Service  
39 (USDA/NSERL 2005). Gleams-Driver was used in the current risk assessment to model  
40 chlorophacinone concentrations in a small stream and a small pond.

41  
42 Table 5 summarizes the chemical-specific values used in GLEAMS. The notes to Table 5  
43 indicate the sources of the chemical-specific values used in the GLEAMS modeling effort, most  
44 of which are based on the physical and chemical properties and the environmental fate data on  
45 chlorophacinone summarized in Table 3.

1  
2 GLEAMS and Gleams-Driver are not designed to model below-ground applications of bait.  
3 GLEAMS does have an input parameter for depth of incorporation—i.e., the depth in which the  
4 chemical is incorporated into soil during the application process—as well as soil injection.  
5 Deeper incorporation or injection depths will reduce the amount of the chemical available for  
6 loss due to runoff or sediment transport. In below-ground applications of chlorophacinone,  
7 however, the chemical is not incorporated or injected into the soil; instead, it is placed beneath  
8 the soil surface in the burrow. Following the approach used by EPA, the GLEAMS-Driver  
9 modeling uses an incorporation depth of 4 inches under the assumption ... *that some of the bait*  
10 *would be moved up to the surface through bioturbation* (U.S. EPA/OPP/EFED 2008a, p. 8). As  
11 with most Forest Service risk assessments, GLEAMS-Driver modeling is conducted for nine  
12 sites and three soil textures (clay, loam, and sand), as detailed in SERA (2014a, Tables 8 and 9).  
13

14 Details of the results for the Gleams-Driver simulations are provided in Appendix 3. A summary  
15 of the results for the Gleams-Driver runs are presented in Table 6, along with a summary of the  
16 spill scenarios discussed in Section 3.2.3.4.1 and other modeling efforts discussed further in the  
17 following subsections. For the small stream and the small pond, separate sets of values are given  
18 for clay, loam, and sand soil textures for peak and longer-term concentrations. For both peak  
19 and longer-term exposures, the highest WCR values are associated with the small stream in areas  
20 with predominantly clay soil textures. As discussed further in Section 3.2.3.6, these WCR values  
21 for clay soils are used in the EXCEL workbook that accompanies this risk assessment.

#### 22 **3.2.3.4.4. Other Modeling Efforts**

23 The U.S. EPA's risk assessment for the use of Rozol for the control of the black tailed prairie  
24 dog (U.S. EPA/OPP/EFED 2008a) addresses the same exposure scenarios as those in the current  
25 risk assessment. While the EPA does not provide a detailed discussion of surface water  
26 modeling, the report indicates that GENEEC, a Tier 1 surface water model, was used to model  
27 subsurface applications of chlorophacinone at an application rate of 0.000625 lb a.i./acre. The  
28 estimated peak concentration was 0.0009 µg/L, which corresponds to a Water Contamination  
29 Rate of 1.44 µg/L per lb a.i./acre [ $0.0009 \mu\text{g/L} \div 0.000625 \text{ lb a.i./acre}$ ]. As summarized in Table  
30 6, this WCR value is virtually identical to the central estimate of the WCR for streams in areas  
31 with predominately clay soils (i.e., 1.66 µg/L per lb/acre).  
32

33 Tier 2 modeling using PRZM/EXAMS was not identified in the available literature on  
34 chlorophacinone.

#### 35 **3.2.3.4.5. Monitoring Data**

36 Monitoring data for chlorophacinone were not identified in the open literature. Furthermore, the  
37 lack of monitoring data is noted in EPA's most recent ecological risk assessment on  
38 chlorophacinone (U.S. EPA/OPP/EFED 2011a, p. 8).

#### 39 **3.2.3.4.6. Concentrations in Water Used for Risk Assessment**

40 Table 7 summarizes the surface water concentrations of chlorophacinone used in this risk  
41 assessment. The concentrations are specified as water contamination rates (WCRs)—i.e., the  
42 concentrations in water expected at a normalized application rate of 1 lb a.i./acre, converted to  
43 units of ppm or mg/L per lb a.i./acre. In Table 6, units of exposure are expressed as ppb or µg/L,  
44 as a matter of convenience. In Table 7, however, ppb is converted to ppm because ppm and

1 mg/L are the units of measure used in the EXCEL workbook for contaminated water exposure  
2 scenarios in both the human health and ecological risk assessments. The water contamination  
3 rates are entered in Worksheet B04Rt in the EXCEL workbook that accompanies this risk  
4 assessment. The values in Worksheet B04Rt are linked to the appropriate scenario-specific  
5 worksheets in the EXCEL workbooks.  
6

7 Given the absence of monitoring data (Section 3.2.3.4.5) and the consistency of the GLEAMS-  
8 Driver with the modeling from EPA (Section 3.2.3.4.4), the selection of WCR values is  
9 straightforward. The WCR values are taken from the GLEAMS-Driver modeling of a small  
10 stream in an area with predominately clay soil textures (Table 6). The only modification is that  
11 the concentrations are rounded to one significant figure, a standard practice in Forest Service risk  
12 assessments.

### 13 **3.2.3.5. Oral Exposure from Contaminated Fish**

14 This risk assessment includes three sets of exposure scenarios for the consumption of  
15 contaminated fish, and each set includes separate estimates for the general population and  
16 subsistence populations. These exposure scenarios consist of one set for acute exposures  
17 following an accidental spill (Worksheets D03a and D03b), another set for acute exposures based  
18 on expected peak concentrations (Worksheets D06a and D06b), and the third set for chronic  
19 exposures based on estimates of longer-term concentrations in water (Worksheets D08a and  
20 D08b). The two worksheets in each of these three sets are intended to account for different rates  
21 of wild-caught fish consumption in both general and subsistence populations. Details of  
22 exposure scenarios involving the consumption of contaminated fish are provided in  
23 Section 3.2.3.5 of SERA (2014a).  
24

25 The concentration of the pesticide in fish ( $C_F$ ) is taken as the product of the concentration of the  
26 chemical in water ( $C_W$ ) and the bioconcentration factor ( $BCF$ ):  
27

$$28 \quad C_{Fish_{mg/kg}} = C_{W_{mg/L}} \times BCF_{L/kg}$$

29  
30 Bioconcentration is measured as the ratio of the concentration in the organism to the  
31 concentration in the water. For example, if the concentration in the organism is 5 mg/kg and the  
32 concentration in the water is 1 mg/L, the BCF is 5 L/kg [5 mg/kg ÷ 1 mg/L]. As with most  
33 absorption processes, bioconcentration depends initially on the duration of exposure but  
34 eventually reaches steady state.  
35

36 As summarized in Table 3, two substantially different estimates of the BCF are available,  
37 including a BCF of 510.9 from EPI Suite (2011) and 2.408 from U.S. EPA/OPP/EFED (2011a,  
38 p. 56). The reason for this difference is that the EPI Suite (2011) estimate is based on a  $K_{ow}$  of  
39 about 316,000. This  $K_{ow}$ , in turn, is estimated from a QSAR algorithm used by EPI Suite (2011).  
40 The much lower BCF of 2.408 from U.S. EPA/OPP/EFED (2011a, p. 56) is based on an  
41 experimental  $K_{ow}$  of 97 from MRID 42237401. For the current Forest Service risk assessment,  
42 the BCF of 2.408 estimated from the experimental  $K_{ow}$  is used for all exposure scenarios  
43 involving the consumption of contaminated fish.

1                   **3.2.3.6. Dermal Exposure from Swimming in Contaminated Water**

2 To assess the potential risks associated with swimming in contaminated water, an exposure  
3 assessment is developed for a young woman swimming in surface water for 1 hour (Worksheet  
4 D04).

5  
6 Conceptually and computationally, this exposure scenario is virtually identical to the  
7 contaminated gloves scenario used for workers (Section 3.2.2.2)—i.e., a portion of the body is  
8 immersed in an aqueous solution of the compound at a fixed concentration for a fixed period of  
9 time. The major differences in the two scenarios involve the pesticide concentration in water and  
10 the exposed surface area of the body. For the worker wearing contaminated gloves, the  
11 assumption is made that both hands are exposed. For the swimmer, the assumption is made that  
12 the entire surface area of the body is exposed to the expected peak concentrations in ambient  
13 water (Table 11). Also, like the exposure scenario involving contaminated gloves, the swimming  
14 scenario is conservative in that it assumes zero-order absorption directly from the water to the  
15 systemic circulation. While the swimmer will not be immersed for 1 hour, the entire body  
16 surface is used both as a conservative approximation and to consider intermittent episodes during  
17 which the whole body might be immersed or at least wet.

18  
19 Periods of exposure longer than 1 hour are possible. The 1-hour period is intended as a unit  
20 exposure estimate. In other words, the exposure and consequently the risk will increase or  
21 decrease linearly with the duration of exposure, as indicated in Worksheet D04. Thus, a 2-hour  
22 exposure would lead to a hazard quotient that is twice as high as that associated with an exposure  
23 period of 1 hour. In cases where this or similar exposures approach a level of concern, further  
24 consideration is given to the duration of exposure in the risk characterization (Section 3.4). For  
25 chlorophacinone, the levels of exposure are far below a level of concern.

26                   **3.2.3.7. Oral Exposure from Contaminated Vegetation**

27 Most Forest Service risk assessments as well as risk assessments conducted by the U.S.  
28 EPA/OPP estimate pesticide concentrations in terrestrial vegetation following foliar applications  
29 based on empirical relationships developed by Fletcher et al. (1994) between application rates  
30 and residues in various types of vegetation. For subsurface applications, however, this type of  
31 exposure assessment is not appropriate. This approach is consistent with the approach taken in  
32 in the EPA Reregistration Eligibility Decision for rodenticides (U.S. EPA/OPP 1998a, p. 46).

33

### 1 3.3. DOSE-RESPONSE ASSESSMENT

#### 2 3.3.1. Overview

3 The toxicity values used in the human health risk assessment are summarized in Table 8.  
4 Neither acute nor chronic RfDs for chlorophacinone were derived by the U.S. EPA/OPP, other  
5 governmental agencies, or international organizations. Following standard procedures (SERA  
6 2014a, Section 3.3), the current risk assessment derives a surrogate acute toxicity value of 0.003  
7 mg/kg bw and a chronic toxicity value of 0.00005 mg/kg bw/day.

#### 8 3.3.2. Acute RfD

9 In the absence of an acute RfD from U.S. EPA, a surrogate acute RfD is based on the  
10 experimental studies in humans summarized in in both WHO (1995) and Watt et al. (2005). As  
11 discussed in Section 3.1.4.2.2, this study involved three volunteers given a single oral dose of 20  
12 mg and evidenced a transient decrease (33-38 %) in prothrombin concentrations (relative to pre-  
13 exposure values) which returned to pre-exposure values by about 8 days after exposure. The  
14 summaries of this study do not specify the body weights of the subjects. Taking a standard body  
15 weight of 70 kg, the dose of 20 mg/person corresponds to 0.29 mg/kg bw (20 mg dose ÷ 70 kg  
16 bw ≈ 0.2857 mg/kg bw). While the observed endpoint is not severe, the dose of 0.29 mg/kg bw  
17 is taken as a LOAEL, because the decrease in prothrombin concentrations is clearly a sign of  
18 anticoagulant effects. Following the standard practice for the application of uncertainty factors  
19 (SERA 2014a, Section 3.3 and Table 15), an uncertainty factor of 100 is used—i.e., a factor of  
20 10 for sensitive individuals and a factor of 10 to approximate a NOAEL from a LOAEL. Thus,  
21 the surrogate acute RfD is taken as 0.003 mg/kg bw.

22  
23 No alternative approaches to deriving a surrogate acute RfD were identified in the  
24 chlorophacinone literature.

#### 25 3.3.3. Subchronic RfD

26 In the absence of a chronic RfD from the Health Effects Division of the U.S. EPA/OPP, the  
27 current risk assessment derives a longer-term subchronic surrogate RfD from the 77-day  
28 subchronic study in rats (MRID 92018013). As summarized in Appendix 1, Table A1-4, this is  
29 the only subchronic study on chlorophacinone. This study yields a NOAEL of 0.005 mg/kg  
30 bw/day with a corresponding LOAEL of 0.01 mg/kg bw/day, based on increases in coagulation  
31 times—i.e., 28% in male rats and 6% in female rats. Again following the standard practice for  
32 the application of uncertainty factors (SERA 2014a, Section 3.3 and Table 15), an uncertainty  
33 factor of 100 is used—i.e., a factor of 10 for sensitive individuals and a factor of 10 extrapolating  
34 from experimental mammals to humans. Thus, the surrogate subchronic RfD is taken as 0.00005  
35 mg/kg bw/day.

36  
37 U.S. EPA/OPP/EFED 2011a (p. 71) uses a somewhat higher NOAEL of 0.01 mg/kg bw/day  
38 from a reproductive study in rabbits (MRID 43570801) for risk characterization. This dose is a  
39 developmental NOAEL—i.e., a NOAEL for fetal effects. The dams used in this study evidenced  
40 increased clotting times, as in the subchronic study discussed above. Thus, the fetal NOAEL of  
41 0.01 mg/kg bw/day is not considered an appropriate basis for the derivation of a subchronic  
42 surrogate RfD.

1        **3.3.4. Dose-Severity Relationships**

2        As discussed in Section 3.4 (Risk Characterization), the only hazard quotients to exceed the level  
3        of concern involve the accidental consumption of bait by a small child. As discussed in Section  
4        3.3.2, the acute RfD of 0.003 mg/kg bw/day is based on an experimental study in three  
5        volunteers in which decreases in prothrombin concentrations occurred following single oral  
6        doses of about 0.3 mg/kg bw. This level of exposure would be considered clearly adverse but  
7        did not lead to overt signs of toxicity. As discussed in Section 3.1.4.2.1, potentially lethal doses  
8        in humans range from about 3.6 to 27 mg/kg bw, similar to oral LD<sub>50</sub> values in rats.  
9

## 3.4. RISK CHARACTERIZATION

### 3.4.1. Overview

Under normal and anticipated circumstances, the use of Rozol Prairie Dog Bait (i.e., a 0.005% formulation of chlorophacinone) in below-ground applications to control the black-tailed prairie dog should pose minimal risks to workers and members of the general public.

Substantial reservations accompany the risk characterization for workers because of the lack of data on the extent of worker exposures during applications of chlorophacinone. Nonetheless, the exposure assessment for workers is based on a set of conservative assumptions which should overestimate exposures. There are also uncertainties in the dose-response assessment for workers. These uncertainties, however, focus on the reasonable supposition that dermal exposures are likely to be less hazardous than oral exposures. Since the dose-response assessment is based on oral toxicity, risks to workers are likely to be overestimated.

The upper bound hazard quotients for workers involved in the normal and proper application of chlorophacinone are below the level of concern by a factor of about 14 based on the chronic RfD and 1000 based on the acute RfD. The risk characterization for non-accidental and expected exposures to members of the general public suggests that risks are negligible.

One very extreme accidental exposure scenario, in which a child consumes bait accidentally deposited on the ground surface, is a modest concern. While there is no indication that the child would become seriously ill, the consumption of any rodenticide should be viewed with serious concern and warrants aggressive measures to ensure prompt medical care.

### 3.4.2. Workers

As summarized in Worksheet E02, none of the general exposures for workers exceeds the level of concern (HQ=1). The highest HQ is 0.07, the upper bound of the HQ for hand-baiting based on the surrogate chronic RfD of 0.00005 mg/kg bw/day. This HQ is below the level of concern by a factor of about 14 [ $1 \div 0.07 \approx 14.2857$ ]. As discussed in Section 3.2.2.1, the exposure estimate for this scenario is based on the assumption that a worker may handle up to 3 lbs of Rozol Prairie Dog Bait (0.005% a.i.) per day. Thus, for this scenario to reach a level of concern, a worker must handle about 42 lbs of Rozol Prairie Dog Bait per day over a prolonged period.

Based on the surrogate acute RfD, the upper bound HQ for a worker is 0.001. For this scenario to reach a level of concern, the worker must handle 3000 lbs of Rozol Prairie Dog Bait in a single day. Handling this amount of the formulation in a single day is clearly not feasible.

### 3.4.3. General Public

The only exposure scenario that exceeds the level of concern (HQ=1) involves the consumption of bait by a small child—i.e., HQ = 10 (7-13). This is an extreme event in which a small child would have access to a baited burrow and consume up to 10.9 grams of Rozol Prairie Dog Bait (Section 3.2.3.1). As detailed in Worksheet D01, the upper bound dose associated with this scenario is about 0.04 mg/kg bw. As discussed in the dose-severity assessment (Section 3.4), this dose is a factor of 7.5 below the dose associated with a decrease of prothrombin in volunteers [ $0.3 \text{ mg/kg bw} \div 0.04 \text{ mg/kg bw}$ ] and a factor of 90 below the lower range of the potentially fatal dose for humans [ $3.6 \text{ mg/kg bw} \div 0.04 \text{ mg/kg bw}$ ]. Notwithstanding these



1 considerations, the accidental consumption of any anticoagulant warrants aggressive measures to  
2 ensure prompt medical care.

3  
4 None of the non-accidental exposure scenarios exceeds the level of concern. The highest non-  
5 accidental HQ is 0.0002, which is the upper bound of the HQ for a small child consuming  
6 contaminated surface water. This HQ is below the level of concern by a factor of 5000, and no  
7 further elaboration is required.

#### 8 **3.4.4. Sensitive Subgroups**

9 As discussed in Section 3.1.3, chlorophacinone is metabolized by liver mixed-function  
10 oxidases—i.e., the cytochrome P450 enzyme system—and this metabolism involves  
11 detoxification and excretion. Consequently, individuals with impaired liver function may be at  
12 greater risk than other members of the population.

13  
14 It may seem intuitive to view individuals with hemophilia as a sensitive subgroup.  
15 Chlorophacinone, however, disrupts clotting factors that may be essentially dysfunctional in  
16 some hemophiliacs. Thus, it is not clear that exposures to chlorophacinone would substantially  
17 aggravate this condition.

#### 18 **3.4.5. Connected Actions**

19 The Council on Environmental Quality (CEQ), which provides the framework for implementing  
20 NEPA, defines connected actions (40 CFR 1508.25) as actions which occur in close association  
21 with the action of concern; in this case, the use of a pesticide. Actions are considered to be  
22 connected if they: (i) Automatically trigger other actions which may require environmental  
23 impact statements; (ii) Cannot or will not proceed unless other actions are taken previously or  
24 simultaneously, and (iii) Are interdependent parts of a larger action and depend on the larger  
25 action for their justification. Within the context of this assessment of chlorophacinone,  
26 “connected actions” include actions or the use of other chemicals which are necessary and occur  
27 in close association with use of chlorophacinone. Other than grain, the only other ingredient in  
28 Rozol Prairie Dog Bait, no connected actions associated with the below-ground use of  
29 chlorophacinone for black-tailed prairie dog control are apparent.

#### 30 **3.4.6. Cumulative Effects**

31 Cumulative effects may occur with repeated exposures to a pesticide, co-exposures to other  
32 chemicals with similar mechanisms of action, or exposures to other agents which may impact the  
33 toxicity of the pesticide.

34  
35 Repeated exposures to chlorophacinone are explicitly considered in the exposure and dose-  
36 response assessments.

37  
38 Cumulative effects involving compounds that affect the toxicity of chlorophacinone are possible;  
39 however, the likelihood and nature of such interactions are unclear. As discussed in Section  
40 3.1.16, chlorophacinone is metabolized by mixed-function oxidase, and there are numerous  
41 chemicals that could potentially diminish the toxicity of chlorophacinone (by inducing mixed-  
42 function oxidase) or enhance the toxicity of chlorophacinone (by competing with  
43 chlorophacinone as a substrate for mixed-function oxidase). The potential significance of such

- 1 interactions would depend on the doses of chlorphacinone and any other agent to which an
- 2 individual might be exposed as well as the timing of the exposures.
- 3

## 4. ECOLOGICAL RISK ASSESSMENT

### 4.1. HAZARD IDENTIFICATION

#### 4.1.1. Overview

The acute toxicity of chlorophacinone to mammals and birds is well documented. In both groups of organisms, chlorophacinone acts as an anticoagulant, and exposures are associated primarily with hemorrhaging. The longer-term toxicity of chlorophacinone to mammals and birds, however, is not well documented. In mammals, long-term toxicity studies are limited to one subchronic toxicity study in rats and two developmental studies in rats and rabbits. In birds, the only longer-term data involve a reproduction study in quail. Based on case reports involving applications of chlorophacinone for rodent control, adverse effects in nontarget mammals and birds may occur due either to primary exposures (the consumption of chlorophacinone bait) or secondary exposures (the consumption of prey previously poisoned with chlorophacinone).

Little information is available on the toxicity of chlorophacinone to terrestrial invertebrates, fish, and aquatic invertebrates. The studies in terrestrial invertebrates are limited to a standard subchronic study in earthworms and bioassays in burying beetle larvae and adults. Toxicity data in aquatic organisms are limited to acute bioassays in two species of fish and one acute bioassay in *Daphnia magna*.

Based on acute toxicity studies, chlorophacinone is classified as *Very Highly Toxic* to mammals and *Highly Toxic* to birds, fish, and aquatic invertebrates. No data are available on the toxicity of chlorophacinone to reptiles, amphibians (aquatic- or terrestrial-phase), and plants (aquatic or terrestrial).

#### 4.1.2. Terrestrial Organisms

##### 4.1.2.1. Mammals

The mammalian toxicity studies used to assess the potential hazards of chlorophacinone to humans, discussed in Section 3.1, are applicable to the risk assessment for mammalian wildlife. In addition to these studies, additional information is available on the efficacy of chlorophacinone for controlling populations of target mammals as well as reported incidents of chlorophacinone poisoning of nontarget mammals.

##### 4.1.2.1.1. Secondary Toxicity

As summarized in the bottom section of Appendix 1, Table A1-2, four studies address the issue of secondary toxicity—i.e., adverse effects in predator species associated with the consumption of prey species poisoned with chlorophacinone. These studies demonstrate adverse effects in ferrets (Ahmed et al. 1996; Fisher and Timm 1987), mongoose (MRID 2467), and coyote (MRID 42760902). Information on the amount of chlorophacinone consumed by the predators, however, is not available. Hence, the secondary feeding studies are used only qualitatively to suggest that chlorophacinone may cause adverse effects in predators. As detailed further in Section 4.1.2.1.3, adverse effects in predator species are documented in several case reports.

#### 4.1.2.1.2. Efficacy Studies

As discussed in Section 2.4, the U.S. EPA's ecological risk assessments on chlorophacinone consider application rates of about 0.0006 lb a.i./acre for the control of the black-tailed prairie dog. As summarized in Appendix 1, Table A1-9, several efficacy studies document adequate control (i.e., efficacy rates in the range of 70 to 95%) of several species of target mammals following chlorophacinone applications ranging from about 0.0005 to 0.0009 lb a.i./acre (Askham 1985a; Byers and Carbaugh 1989; Merson and Byers 1985; Vyas et al. 2012). Some studies conducted in Europe use slightly higher application rates of about 0.00135 lb a.i./acre (Giban 1974; Vidal et al. 2009).

Two efficacy studies characterize exposures in terms of liver residues, with all reports given in terms wet weight. In a study conducted in the United States at an application rate of 0.00056 lb a.i./acre, initial residues in the liver of black-tailed prairie dog were about 7.6 µg/g and fell gradually to <0.5 µg/g by Day 29 after treatment (Vyas et al. 2012). In a study conducted in Spain at a higher application rate of 0.00133 lb a.i./acre, the geometric mean of liver residues in voles was 0.65 µg/g with a range of 0.082 - 3.8 µg/g (Vidal et al. 2009). Whereas, Vyas et al. (2012) provide detailed information on the time-course of the residues; Vidal et al. (2009) do not. These two studies are also the only efficacy studies that provide any detail on the observed adverse effects (other than death) in the target animals. In both cases, the predominant adverse effect from chlorophacinone poisoning was hemorrhaging. Vidal et al. (2009) note that: *Hemorrhages were present in voles with (67%) and without CP [chlorophacinone] residues (75%) (p=0.7)*. This somewhat unusual observation is not discussed in detail by Vidal et al. (2009); therefore, it is not possible to determine from the data presented in the publication whether the voles without detectable levels of chlorophacinone had been poisoned by chlorophacinone prior to death. As discussed in Section 3.1, chlorophacinone is eliminated relatively quickly from mammals (Section 3.1.3.3); however, there is a delay prior to the anticoagulant effect (Section 3.1.4). The presence of chlorophacinone residues in the liver of some animals may be due to repeated ingestion of bait following initial exposure but prior to mortality.

Vidal et al. (2009) also notes that a bacterial pathogen in voles, *Francisella tularensis*, was a significant cause of death in voles in the area where chlorophacinone was applied, and that voles infected with *Francisella tularensis* had lower concentrations of chlorophacinone than uninfected voles. The authors suggest an interaction between the pathogen and chlorophacinone, but do not elaborate. The pattern in the residues suggests that the apparent interaction may reflect competing mortality.

Resistance to anticoagulant rodenticides, including chlorophacinone, is a general problem and is one of motivators for the development of second generation rodenticides (Buckle 2013). While resistance to chlorophacinone in some rodent populations is reported, the magnitude of resistance (e.g., ratios of equitoxic doses in resistant and susceptible populations) is reported (e.g., Byers 1976; Hadler 1990; Lund 1967). Vein et al. (2013) observed that resistant populations of rats appear to accumulate chlorophacinone to the same extent as sensitive strains; however, the resistant strains survive longer than the sensitive strains. The mechanism for the longer period of survival, however, is not characterized. As discussed in Section 3.1.4.2, Papin et al. (2007) suggest that delayed mortality, a common feature of chlorophacinone poisoning, may be due to

1 the time required to diminish normal reserves of prothrombin. Theoretically, a longer period of  
2 survival in apparently resistant populations might be associated with higher levels of  
3 prothrombin.

#### 4 **4.1.2.1.3. Case Reports**

5 Case reports of potential effects in nontarget domestic and wildlife mammals associated with  
6 chlorophacinone applications are summarized in Appendix 1, Table A1-10. As with similar case  
7 reports in humans (Section 3.1.4.2.1, Appendix 1, Table A1-3), a major limitation in these  
8 studies is the lack of quantitative estimates of exposure.

9  
10 Most of the studies in Appendix 1, Table A1-10, involve effects associated with field  
11 applications of chlorophacinone. The one exception is the report from Del Piero and Poppenga  
12 (2006) in which lambs consumed bait that had been stored in a holding facility. These  
13 investigators note a very rapid onset of death (1 - 2 hours) following the first signs of  
14 intoxication. The time between the consumption of the chlorophacinone and the development of  
15 the overt signs of toxicity, however, is not clear from the publication. The primary sign of  
16 toxicity in the lambs—i.e., hemorrhaging—is consistent with chlorophacinone poisoning.

17  
18 The remaining studies in Appendix 1, Table A1-10, all involve applications of chlorophacinone  
19 for rodent control. Some of the studies from Europe and Canada involve surface applications  
20 (Sanchez-Barbudo et al. 2012; Proulx 2011); however, the nature of the applications in other  
21 studies is not clear (e.g., Berny et al. 2010; Fournier-Chambrillon et al. 2004; Stone et al. 1999).  
22 In cases of fatal poisonings associated with chlorophacinone, hemorrhage is the major sign of  
23 toxicity, and reported concentrations in the liver range from <1 µg/g (Gabriel et al. 2012; Stone  
24 et al. 1999) to 8.5 µg/g (Fournier-Chambrillon et al. 2004).

25  
26 In one study, chlorophacinone exposures are clearly not associated with mortality (Berny et al.  
27 2010). In terms of mortality, the study by Fournier-Chambrillon et al. (2004) is somewhat  
28 difficult to interpret. This is a survey study involving several species of nontarget mammals in  
29 areas of France where eight anticoagulant rodenticides were applied. Chlorophacinone was  
30 found in four mink and one otter with liver concentrations ranging from 3.4 to 8.5 µg/g.  
31 Although these liver concentrations might easily be associated with mortality, the authors report  
32 that the cause of death was not attributable to chlorophacinone. Moreover, hemorrhaging in  
33 these animals is not reported in the study, and the authors specifically state that the animals were  
34 *...without apparent lesions.*

35  
36 U.S. EPA/OPP/EFED maintains a database of incident reports involving effects in nontarget  
37 organisms caused by or reported to be associated with pesticides (U.S. EPA/OPP/EFED 2011a,  
38 Table 4-7, pp. 74-75). These incident reports do not appear to overlap with the incidents  
39 reported in the open literature. Several species of mammals cited in these incident reports had  
40 detectable levels of chlorophacinone in the liver. These mammals include the San Juan kit fox  
41 (0.03-1.24), grey squirrel (0.29-0.465), badger (2.0 to 4.4 ppm), bobcat (0.34 to 0.4 ppm),  
42 raccoon (liver concentration not available), and coyote (0.36 to 1.2 ppm). Deaths were or appear  
43 to be attributable to chlorophacinone for one badger (4.4 ppm in liver) and one bobcat (0.4 ppm  
44 in liver). As in many of the open literature reports, these incidents often note exposures to more  
45 than one rodenticide.

1 In a recent survey conducted in California, Quinn et al. (2012) did not detect chlorophacinone in  
2 the liver of free-ranging badgers.

### 3 **4.1.2.2. Birds**

#### 4 **4.1.2.2.1. Gavage Studies in Birds**

5 Avian studies involving the acute gavage administration of chlorophacinone are summarized in  
6 Appendix 2, Table A2-1. Two standard registrant-submitted studies are available in bobwhite  
7 quail, one reporting an LD<sub>50</sub> of 258 mg a.i./kg bw (MRID 41513101) and the other reporting an  
8 LD<sub>50</sub> of 495 mg a.i./kg bw (MRID 39233). These LD<sub>50</sub> values in quail are remarkably higher  
9 than the gavage LD<sub>50</sub> values in mammals. As discussed in Section 3.1.4.1.1, the well  
10 documented acute gavage toxicity studies in mammals report LD<sub>50</sub> values of about 1 - 10 mg  
11 a.i./kg bw. The quail LD<sub>50</sub> of 495 mg a.i./kg bw (MRID 39233) involved a 14-day observation  
12 period in which all deaths occurred within the first 10 days. While the lower LD<sub>50</sub> of 258 mg  
13 a.i./kg bw (MRID 41513101) involved a longer exposure period (30 days), all of the mortalities  
14 were noted within the first 5 days. Based on the lower LD<sub>50</sub> of 258 mg a.i./kg bw, quail may be  
15 less sensitive than mammals to chlorophacinone by factors of about 26 - 260.

16  
17 Observations of sublethal effects in MRID 41513101 included internal hemorrhaging, as seen in  
18 many studies in mammals (Section 3.1). As discussed below, hemorrhaging is commonly seen  
19 in birds exposed to chlorophacinone, which is to be expected. The clotting factors in birds are  
20 similar to those of mammals except that birds do not have clotting factor XII (Doolittle 2010).  
21 As discussed in Section 3.1.2, clotting factor XII is not one of the clotting factors impacted by  
22 chlorophacinone.

23  
24 An additional study involving gavage administration of chlorophacinone in birds is available  
25 from the open literature. Radvanyi et al. (1988) dosed small groups (n=4) of both juvenile and  
26 adult kestrels with a 2% chlorophacinone concentrate (not otherwise specified). Based on  
27 reported body weights and amounts of concentrate administered to the kestrels, doses ranging  
28 from 3 to about 30 mg a.i./kg bw caused 25 to 100% mortality over 20- to 27-day observation  
29 periods. As detailed in Appendix 2, Table A2-1, mortality in adult kestrels was not dose-related,  
30 which is not an unusual observation in studies conducted with small numbers of animals per dose  
31 group. As with mammalian studies, hemorrhaging was commonly observed in both adult and  
32 juvenile kestrels. While the dose-response data from Radvanyi et al. (1988) are limited by small  
33 sample size and only two doses, this study suggests that kestrels are more sensitive than quail to  
34 chlorophacinone and may be about equally sensitive as some mammals.

35  
36 Another sign of toxicity in kestrels noted by Radvanyi et al. (1988) was wing-drooping. In the  
37 gavage studies, wing-drooping occurred only in the birds dosed with chlorophacinone and was  
38 not observed in control birds. As noted by Radvanyi et al. (1988), wing drooping in birds can be  
39 a sign of heat stress. As discussed in Section 3.1.2, one purported mechanism for  
40 chlorophacinone is the uncoupling of oxidative phosphorylation which can lead to increased  
41 body temperature—e.g., increased body temperature in birds following administration of 2,4-  
42 dinitrophenol (a well-known uncoupler of oxidative phosphorylation). In the absence of panting,  
43 which is not reported by Radvanyi et al. (1988), the association between wing-drooping and an  
44 impact on body temperature seems tenuous at best.

#### 4.1.2.2.2. Acute Dietary Studies in Birds

Two acute dietary toxicity studies are available in bobwhite quail, one reporting an LC<sub>50</sub> of 56 mg a.i./kg diet (MRID 41513102) and the other reporting an LC<sub>50</sub> of 242 mg a.i./kg diet (MRID 29144). The U.S. EPA summary of the higher LC<sub>50</sub> does not specify the observation period. The lower LC<sub>50</sub> is associated with a 30-day observation period in which the mortalities occurred during the first 9 days of the study. Acute dietary toxicity studies in birds are summarized in Appendix 2, Table A2-2. Test guidelines for acute dietary toxicity studies in birds typically require a 5-day period of exposure and an additional 3-day observation period (U.S. EPA-OCSPP 2012a). Thus, it does not seem likely that the discrepancies between these two studies can be attributed to differences in the observation periods. Nonetheless, the lower LC<sub>50</sub> of 56 mg a.i./kg diet in bobwhite quail (MRID 41513102) is supported by a virtually identical LC<sub>50</sub> of 60 mg a.i./kg diet in Japanese quail (Reidel et al, 1990, MRID 47323201).

The only other study in quail is the open literature study by Blus et al. (1985) in California quail. This study is not comparable to any of the other dietary studies in that the chlorophacinone was fed in paraffin pellets. This study was motivated by an incident in which a dead California quail was found following applications of paraffin pellets containing chlorophacinone for the control of voles (Section 4.1.2.2.4). In both the case report and the laboratory study, the gastrointestinal tract of the quail appears to have been obstructed with the paraffin pellets, essentially resulting in starvation. Effects on blood clotting were not observed in either the laboratory or field study. This study is noted for the sake of completeness but does not appear to be relevant to the risk assessment of chlorophacinone.

The two short-term dietary studies available in mallard ducks report LC<sub>50</sub> values of 172 mg a.i./kg diet (MRID 41513103) and 426 mg a.i./kg diet (MRID 29143). These LC<sub>50</sub> values are in the range of the LC<sub>50</sub> of 242 mg a.i./kg diet in quail (MRID 29144) discussed above. In the absence of additional details on these studies as well as the studies in quail, a clear interpretation of species sensitivity in birds cannot be made. As discussed further in Section 4.3.2.2 (dose-response assessment for birds), the lower toxicity values are used quantitatively in the current document for risk characterization.

The U.S. EPA summaries of the standard acute dietary studies in quail and mallards do not provide information on body weights and food consumption. As indicated in a previous Forest Service risk assessment for which both body weights and food consumption rates in standard acute dietary studies were available for quail and mallards (SERA 2007a), approximate food consumption rates in acute dietary studies are about 0.4 kg food/kg bw for mallards and 0.3 kg food/kg bw for quail. Based on these estimates of food consumption, the lowest LC<sub>50</sub> of 56 mg a.i./kg diet for quail corresponds to a daily dose (LD<sub>50</sub>) of about 16.8 mg a.i./kg bw/day. As discussed in Section 3.1.4.1.2 and summarized in Appendix 1, Table A1-2, acute dietary LD<sub>50</sub> values for mammals range from about 1 to 3 mg/kg bw. Based on these standard dietary studies in birds and mammals, birds appear to be less sensitive than mammals by factors of about 5 - 20.

Giban (1974) provides a brief report on a study from the French literature involving 5- to 30-day feeding studies with 0.0075% chlorophacinone in grain. The study was conducted with two species of partridge, the red-legged partridge which consumed 3 mg of chlorophacinone for 5 or 15 days and the grey partridge which consumed 2.25 mg for 15 or 30 days and 4.5 mg of

1 chlorophacinone per day for 15 days. A dose of 3 mg/day for 15 days caused mortality in half  
2 (5/10) of the red-legged partridges. Giban (1974) does not provide body weights for the  
3 partridges. Using a reference body weight of 0.5 kg for the red-legged partridge (Dunning  
4 1993), the approximate LD<sub>50</sub> may be crudely estimated at about 6 mg a.i./kg bw/day. The grey  
5 partridge was somewhat less sensitive with about 30% (3/10) of the birds dying following 15  
6 days exposure to a dose of 2.25 mg. Taking a reference body weight of about 0.4 kg for the grey  
7 partridge (Dunning 1993), this corresponds to a lethal dose of about 6 mg a.i./kg bw/day. Again,  
8 these data suggest that birds are less sensitive than mammals to chlorophacinone, although the  
9 estimated lethal doses for partridges are closer to the mammalian acute dietary LD<sub>50</sub> values (1 to  
10 10 mg/kg bw/day) than the doses for quail and mallards.

11  
12 Details on sublethal effects in the acute dietary studies with birds are available only from MRID  
13 41513102, the study reporting the LC<sub>50</sub> of 56 mg a.i./kg diet in bobwhite quail. Consistent with  
14 observations from studies in mammals and other birds, hemorrhaging is noted as the  
15 predominant sign of toxicity. Based on the acute dietary studies (MRIDs 41513102, 41513103,  
16 Reidel et al. 1990), the EPA classifies chlorophacinone as *Highly Toxic* to birds (U.S.  
17 EPA/OPP/EFED 2011a, Appendix D, p. D-3).

#### 18 **4.1.2.2.3. Secondary Toxicity Studies in Birds**

19 Within the context of the current risk assessment on chlorophacinone, considerations of  
20 secondary toxicity focus on the potential of predatory birds to be poisoned following the  
21 consumption of mammalian prey contaminated with (i.e., poisoned by) chlorophacinone. In  
22 terms of practical benefit to the risk assessment, the demonstration of secondary poisoning is  
23 useful for assessing the potential for nontarget effects in birds.

24  
25 The available studies on secondary poisoning in birds are summarized in Appendix 2,  
26 Table A2-3. In all studies, the predatory birds were fed rodents (mice, rats, or voles) poisoned  
27 with chlorophacinone. Two of the studies, Askham (1988) and Mendenhall and Pank (1980)  
28 allow for estimates of dosing. Mendenhall and Pank (1980) provide information on both the  
29 amount of chlorophacinone consumed and the body weights of the birds (barn owls). Doses of  
30 about 1.2 - 1.7 mg/kg bw/day for 10 days caused no signs of toxicity and had no effect on  
31 coagulation times. Askham (1988) assayed red-tailed hawks (three female and two male) and  
32 one great horned owl by feeding them with contaminated voles at a level equivalent to a  
33 cumulative dose of 8.05 mg over a period of 6 days. Using an approximate body weight of 1.1  
34 kg for red-tailed hawks from Dunning (1993), the dose can be estimated at about 1.2 mg/kg  
35 bw/day. As in the study by Mendenhall and Pank (1980), no overt signs of toxicity and no effect  
36 on coagulation times were observed. The only effect possibly attributed to treatment is lethargy  
37 in one bird (not otherwise specified) on Days 24 and 25 of the study during the 37-day  
38 observation period. As noted in discussion of acute dietary studies (Section 4.1.2.2.2), the doses  
39 of 1.2 - 1.7 mg/kg bw/day are below (and in many cases substantially below) the daily doses in  
40 direct feeding studies associated with adverse effects in birds.

41  
42 Only one secondary exposure study (Radvanyi et al. 1988) noted signs of anticoagulant effects—  
43 i.e., hemorrhaging in multiple organs of American kestrels. The dosing used in this secondary  
44 feeding study cannot be estimated. As discussed in Section 4.1.2.2.1, Radvanyi et al. (1988)  
45 conducted gavage studies in kestrels in which hemorrhaging was noted at doses ranging from 3  
46 to 30 mg a.i./kg bw/day.



1  
2 Despite the limitations in the secondary toxicity studies in predatory birds, they suggest that  
3 secondary exposures to predatory birds are a legitimate concern. Hence, these exposures are  
4 considered explicitly in the exposure assessment for birds (Section 4.2.3).

#### 5 **4.1.2.2.4. Case Reports in Birds**

6 As with mammals (Section 4.1.2.1.2), several case reports involving applications of  
7 chlorophacinone and potential effects on wild birds are available in the open literature. These  
8 studies are summarized in Appendix 2, Table A2-4.  
9

10 Three of the reports are general surveys involving several anticoagulants—i.e., Albert et al.  
11 (2010) from Canada and Stone et al. (1999, 2003) from New York. Adverse effects from  
12 chlorophacinone are not clearly documented, although low levels of exposure to chlorophacinone  
13 are documented in the report from Albert et al. (2010)—i.e., <0.005 ppm—and Stone et al.  
14 (2003)—i.e., 0.18 ppm. In these studies, toxicity to birds was more clearly related to  
15 brodifacoum or bromadiolone than chlorophacinone.  
16

17 Several other reports do specifically link applications of chlorophacinone with adverse effects in  
18 birds. Relatively high concentrations of chlorophacinone in the liver of birds are reported in two  
19 studies from Spain—i.e., up to 3.8 µg/g (Lemus et al. 2011) and up to 50.1 µg/g (Sarabia et al.  
20 2008). The signs of toxicity primarily involved hemorrhaging, characteristic of chlorophacinone  
21 poisoning. While both of these studies clearly document the potential for chlorophacinone  
22 poisoning in birds, both of these studies also involved surface applications which are not directly  
23 relevant to the types of applications planned by the Forest Service. Sarabia et al. (2008) note that  
24 birds poisoned with chlorophacinone and evidencing signs of hemorrhage had concentrations of  
25 chlorophacinone in the liver of 11.2 (1.48 - 50.1) µg/g. Four additional birds with no signs of  
26 hemorrhaging had concentrations of chlorophacinone in the liver of 5.66 - 34.97 µg/g. This type  
27 of observation might possibly be associated with recent exposures in which the signs of  
28 chlorophacinone poisoning had not yet developed.  
29

30 The most directly relevant case report is from Ruder et al. (2011) in which chlorophacinone was  
31 found at concentrations of 0.4 and 0.69 µg/g in the liver of two wild turkeys. Both turkeys  
32 evidenced signs of moderate hemorrhaging. In this incident, chlorophacinone had been applied  
33 locally for the control of the black-tailed prairie dog. In the same paper, Ruder et al. (2011)  
34 report on a “large group” of turkeys (NOS) that also appeared to have been poisoned.  
35 Examination of six carcasses from this group, however, detected no chlorophacinone in the liver,  
36 although chlorophacinone was detected (NOS) in the crop of one of the turkeys. In this second  
37 group of turkeys, neither the involvement of chlorophacinone nor the potential sources of  
38 chlorophacinone is clear. At least with respect to the two turkeys with detectable levels of  
39 chlorophacinone in the liver, Ruder et al. (2011) demonstrate an association between  
40 chlorophacinone applications for the control of the black-tailed prairie dog and mortality in  
41 turkeys.  
42

43 Burrowing owls (*Athene cunicularia*) live in close association with prairie dogs (e.g., Butts and  
44 Lewis 1982). Nonetheless, the available literature on the use of chlorophacinone for the control  
45 of prairie dogs does not address the effects of chlorophacinone on burrowing owls. While Proulx  
46 (2011) specifically examines the impact of rodenticide treatments with both chlorophacinone and

1 strychnine for the control of ground squirrels on burrowing owl populations, the study clearly  
2 notes the potential for exposure to poisoned rodents, but does not report overt signs of toxicity in  
3 burrowing owls associated with rodenticide use.

4  
5 Also as with mammals (Section 4.1.2.1.2), the U.S. EPA/OPP/EFED (2011a, Table 4-7, pp. 74-  
6 75) summarizes several additional incident reports involving potential poisoning of birds with  
7 chlorophacinone. Species of birds (with concentration of chlorophacinone in the liver) include  
8 wild turkey (0.4 and 0.69  $\mu\text{g/g}$  in one case and 5.5  $\mu\text{g/g}$  in another) and red-tailed hawk (0.18  
9  $\mu\text{g/g}$ ). The EPA also summarizes another incident (Incident ID) that involved several species of  
10 birds; however, the incident also involved exposures to other rodenticides. Thus, the role of  
11 chlorophacinone in this incident cannot be clearly assessed. The incident involving wild turkeys  
12 with concentrations of chlorophacinone in the liver of 0.4 and 0.69  $\mu\text{g/g}$  clearly is from the  
13 report by Ruder et al. (2011). The other incidents do not appear to overlap with the open  
14 literature.

#### 15 **4.1.2.2.5. Longer-term Toxicity in Birds**

16 The U.S. EPA/OPP typically requires reproduction studies in both ducks and quail. These  
17 studies must provide all raw data to the EPA and follow GLP (Good Laboratory Practices)  
18 standards. As discussed in U.S. EPA/OPP/EFED (2011a), these studies were not submitted for  
19 chlorophacinone. Since these studies were not waived by the U.S. EPA, their lack of availability  
20 is viewed as a data gap.

21  
22 One reproduction study in Japanese quail (Riedel et al. 1990) has been published in the open  
23 literature. This study is reviewed in U.S. EPA/OPP/EFED (2011a, Table 4-3, p. 68) and  
24 classified as *Supplemental* because (as with most open literature publications) it does not provide  
25 raw data and does not (at least explicitly) follow GLP standards.

26  
27 As summarized in Appendix 2, Table A2-5, the study by Riedel et al. (1990) entailed 13-week  
28 exposures to Japanese quail at dietary concentrations of 1, 2, 4, or 8 mg a.i./kg diet. The dietary  
29 concentration of 1 mg a.i./kg diet caused no adverse effects on adults or offspring. Higher  
30 dietary concentrations were associated with increased mortality ( $\geq 2$  mg a.i./kg diet) as well as  
31 increased coagulation times ( $\geq 4$  mg a.i./kg diet). In the absence of information on food  
32 consumption, the NOAEL is estimated as 0.07 mg a.i./kg bw/day, based on food consumption  
33 rates in a quail reproduction study from a previous Forest Service risk assessment (see  
34 Appendix 2, Table A2-5 for details).

#### 35 **4.1.2.3. Reptiles and Amphibians (Terrestrial-phase)**

36 As noted by Lee and Hyngstrom (2007) burrow applications of chlorophacinone as well as other  
37 rodenticides could lead to exposures of predators and scavengers, such as snakes. Little specific  
38 information, however, is available on the potential exposures to or effects from exposures to  
39 chlorophacinone in terrestrial-phase amphibians or reptiles. In a general survey of exposures of  
40 nontarget organisms to anticoagulant rodenticides in Spain, Sánchez-Barbudo et al. (2012) note  
41 one instance of a documented exposure in snakes out of a total of 153 documented exposures in  
42 nontarget animals (i.e., about 0.25%). This exposure, however, involved flocoumafen rather  
43 than chlorophacinone. Flocoumafen is an anticoagulant rodenticide registered in Europe but not  
44 in the United States (Kegley et al. 2014).

1 No information is available on the toxicity of chlorophacinone to reptiles or amphibians;  
2 furthermore, chlorophacinone is not included in the Database of Reptile and Amphibian  
3 Toxicology Literature (Pauli et al. 2000). The lack of toxicity data on reptiles and amphibians is  
4 common even for pesticides with a substantial open literature. The lack of information on  
5 toxicity to reptiles and amphibians is noted in the most recent EPA ecological risk assessment on  
6 chlorophacinone which also notes that birds are used as a surrogate for reptiles and terrestrial-  
7 phase amphibians (U.S. EPA/OPP/EFED 2011a, p. 45).

8  
9 A concern with using birds as a surrogate for amphibians relates to the permeability of  
10 amphibian skin to pesticides and other chemicals. Quaranta et al. (2009) indicate that the skin of  
11 the frog *Rana esculenta* is much more permeable than pig skin to several pesticides and that  
12 these differences in permeability are consistent with differences in the structure and function of  
13 amphibian skin, relative to mammalian skin.

#### 14 **4.1.2.4. Terrestrial Invertebrates**

15 U.S. EPA/OPP/EFED (2010a; 2011a) summarizes two toxicity studies in terrestrial  
16 invertebrates, a standard subchronic bioassay in an earthworm, *Eisenia foetida* (MRID  
17 47383002) and a bioassay in the burying beetle, *Nicrophorus orbicollis* (MRID 47383001).

18  
19 A full DER for the study in earthworms is not available; nonetheless, the summary of the study  
20 in the U.S. EPA/OPP/EFED risk assessments (U.S. EPA/OPP/EFED 2010a; 2011a) indicates  
21 that the study follows normal EPA guidelines for the conduct of subchronic toxicity studies in  
22 earthworms (U.S. EPA/OCSPP 2012b). The subchronic LC<sub>50</sub> is reported as >1000 mg a.i./kg  
23 soil with an NOAEC for mortality of 309 mg a.i./kg soil. In terms of sublethal effects, the EPA  
24 summaries note that decreased body weights were observed at concentrations as low as 95 mg  
25 a.i./kg soil, which, presumably, is the lowest concentration assayed. The magnitude of the body  
26 weights are not specified in the EPA summaries of this study. The only reservation with this  
27 study is that EPA had not reviewed the full study at the time that the most recent EPA risk  
28 assessment was completed (U.S. EPA/OPP/EFED 2011a, Appendix D, p. D-6).

29  
30 Although the study on toxicity to the burying beetle is a not a standard study, it is described in  
31 U.S. EPA/OPP/EFED (2011a, pp. 72-73; 2010a, p. 71). This study involved feeding beetle  
32 larvae for 5 - 10 days on carcasses of rats poisoned with a 0.005% chlorophacinone bait as well  
33 as evaluating reproduction in adult beetles fed chlorophacinone contaminated ground beef at a  
34 concentration of 3 mg a.i./kg diet for 28 days. Following this exposure, the beetles were  
35 transferred to an untreated quail carcass for brooding. No effects were observed on  
36 reproduction; however, the investigators observed a decrease in larval emergence.

37  
38 The toxicity of chlorophacinone to terrestrial invertebrates is not addressed in the open literature.  
39 As noted in U.S. EPA/OPP/EFED (2010a, p. 76), an open literature study found no effects on  
40 reproduction in *Hemideina crassidens* (Orthoptera: Anostomatidae) following a 64-day  
41 exposure to a rodenticide bait containing diphacinone (Fisher et al. 2007), another indandione  
42 rodenticide (Section 2).

#### 43 **4.1.2.5. Terrestrial Plants (Macrophytes)**

44 Information regarding the toxicity of chlorophacinone to terrestrial plants was not identified in  
45 the available literature. As noted in the EPA risk assessments on chlorophacinone, exposures

1 and risks to terrestrial plants are likely to be minimal (U.S. EPA/OPP/EFED 2010a, 2011a).  
2 Nonetheless, the most recent EPA ecological risk assessment on chlorophacinone indicates that  
3 seedling emergence and vegetation vigor studies have been requested (U.S. EPA/OPP/EFED  
4 2011a, p. 53). The rationale for these requests, however, is not discussed.

#### 5 **4.1.2.6. Terrestrial Microorganisms**

6 As noted in the WHO environmental health criteria for anticoagulant rodenticides, information  
7 regarding the effect of these compounds, including chlorophacinone, on microorganisms is not  
8 available (WHO 1995). Other reviews and risk assessments on chlorophacinone and related  
9 anticoagulant rodenticides (Table 1) do not address risks to microorganisms.

10  
11 More recently, Berny et al. (2006) noted that bacteria in ruminant extracts do not appear to be  
12 adversely affected by anticoagulants including chlorophacinone. The concentrations of  
13 chlorophacinone used in this study ranged from about 45 to 50 mg/L (Berny et al. 2006,  
14 Figure 1, p. 365). Vidal et al. (2009) note that the control of vole populations with  
15 chlorophacinone may enhance the spread of *Francisella tularensis*, a pathogen among voles in  
16 fields. The likely mechanisms for this spread (i.e., an increase in the abundance of rotting  
17 corpses and cannibalism) would not suggest an adverse effect on the bacteria.

### 18 **4.1.3. Aquatic Organisms**

#### 19 **4.1.3.1. Fish**

20 As noted by WHO (1985), the open literature on chlorophacinone does not address toxicity to  
21 fish. This lack of information remains the case, based on the updated review of the literature in  
22 support of the current risk assessment.

23  
24 The U.S. EPA/OPP/EFED (2011a, Appendix D, p. D-2) notes that two 96-hour LC<sub>50</sub> values are  
25 available in freshwater fish—i.e., an LC<sub>50</sub> of 0.71 mg a.i./L in bluegill sunfish (MRID 43256102)  
26 and an LC<sub>50</sub> of 0.45 mg a.i./L in rainbow trout (MRID 43256103). The only details on these  
27 studies reported in the EPA appendix are that both studies involve flow-through exposures with  
28 100% a.i. and both studies are classified as *Acceptable*. Based on these LC<sub>50</sub> values, the EPA  
29 classifies chlorophacinone as *Highly Toxic* to fish. These studies are also summarized in the  
30 U.S. EPA database of ecotoxicity studies (ECOTOX 2014) which provides some additional  
31 details. The most important information from EXCOTOX is that the NOAEC for bluegills was  
32 0.36 mg a.i./L and the NOAEC for trout was 0.12 mg a.i./L.

33  
34 No information is available on the longer-term toxicity of chlorophacinone to fish, and the lack  
35 of a freshwater fish early life-stage study is identified as data that the EPA is requesting (U.S.  
36 EPA/OPP/EFED 2011a, p. 53).

#### 37 **4.1.3.2. Amphibians (Aquatic-phase)**

38 As with terrestrial-phase amphibians, there are no data regarding the toxicity of chlorophacinone  
39 to aquatic-phase amphibians. The most recent EPA ecological risk assessment on  
40 chlorophacinone recognizes the lack of data and indicates that fish are used as a surrogate for  
41 aquatic-phase amphibians (U.S. EPA/OPP/EFED 2011a, p. 67).

1                   **4.1.3.3. Aquatic Invertebrates**

2 Also, there is very little information available on the toxicity of chlorophacinone to aquatic  
3 invertebrates. U.S. EPA/OPP/EFED (2011a, Appendix D, page D-2) cites a single 48-hour EC<sub>50</sub>  
4 for immobility of 0.64 mg a.i./L for *Daphnia magna* from a flow-through study using 100%  
5 chlorophacinone (MRID 42356101). Based on this study, the EPA classifies chlorophacinone as  
6 *Highly Toxic* to aquatic invertebrates. As with the fish studies, ECOTOX (2014) provides some  
7 additional details, the most important of which is an NOAEC of 0.28 mg a.i./L. from the *Daphnia*  
8 study.

9  
10 ECOTOX (2014) cites another study involving a static exposure with *Daphnia magna* in which  
11 the EC<sub>50</sub> based on immobility was 0.426 mg a.i./L with a NOAEC of 0.13 mg a.i./L. The only  
12 other relevant detail is that the study involved technical grade chlorophacinone of unspecified  
13 purity. ECOTOX does not provide a specific reference for this study.

14  
15 No information is available on the longer-term toxicity of chlorophacinone in aquatic  
16 invertebrates and the lack of a freshwater invertebrate life cycle study is identified as data that  
17 the EPA is requesting (U.S. EPA/OPP/EFED 2011a, p. 53).

18                   **4.1.3.4. Aquatic Plants**

19 No information has been identified on the toxicity of chlorophacinone to aquatic macrophytes  
20 and algae. As with fish and aquatic invertebrates, the most recent EPA ecological risk  
21 assessment notes this lack of data and indicates that toxicity studies on a *Lemna* species (aquatic  
22 macrophyte) and algae are requested (U.S. EPA/OPP/EFED 2011a, p. 53).

## 4.2. EXPOSURE ASSESSMENT

### 4.2.1. Overview

The exposure scenarios for terrestrial species are summarized in Worksheet G01 of the Excel workbook that accompanies this risk assessment. The exposures to aquatic species are summarized in Worksheet G03 of this workbook.

Forest Service risk assessments generally employ a relatively standard set of exposure scenarios which are applied uniformly to herbicides and insecticides. While not all scenarios are included for all types of pesticides, the structures of the exposure assessments are similar. As with the Forest Service risk assessment on strychnine (SERA 2005), this approach is not taken for below-ground applications of chlorophacinone because the nature and details of potential exposures differ substantially from those of other pesticides. The field data on strychnine are much more extensive than the data on chlorophacinone; thus, the scenarios developed for chlorophacinone are adapted with little modification to the exposure scenarios used in Forest Service risk assessment on strychnine (SERA 2005).

The literature on chlorophacinone and other rodenticides generally classifies exposures as primary, secondary, or tertiary, and this convention is adopted in the current Forest Service risk assessment. *Primary exposures*, which involve the direct consumption of bait, are developed for small mammals as well as some types of birds. *Secondary exposures* involve the consumption of chlorophacinone-contaminated prey (i.e., prey poisoned as a result of primary exposure, like pocket gophers). Secondary exposure scenarios are developed for predatory mammals, birds (i.e., raptors), and reptiles. *Tertiary exposures* involve the consumption of prey containing chlorophacinone as a result of feeding on a primary consumer—e.g., the consumption of an insect that had fed on a poisoned carcass. Tertiary exposure scenarios are developed for an insectivorous mammal, bird, and terrestrial-phase amphibian. Other standard exposure scenarios include the consumption of contaminated water as well as the consumption of contaminated fish.

The exposure assessments for primary, secondary, and tertiary exposures of nontarget organisms are based largely on the corresponding exposure assessments in the Forest Service risk assessment on strychnine (SERA 2005). The exposure assessments for strychnine are well documented and based on an extremely rich and detailed body of field studies on the use of strychnine for the control of pocket gophers. Corresponding data for chlorophacinone are sparse. Thus, the strychnine data are used to develop the exposure scenarios, and that adds substantial uncertainty to the current risk assessment on chlorophacinone. For some scenarios, as discussed below, the assumptions are modified to reflect differences in the size of the target mammals—i.e., a small pocket gopher for strychnine and the much larger black-tailed prairie dog for chlorophacinone.

The animals used in the exposure assessments (i.e., ecological receptors) are listed as receptors in Table 9. Most Forest Service risk assessments use a relatively small number of receptors intended to represent worst-case exposures. In the current ecological risk assessment of chlorophacinone, the standard set of receptors is used for exposure scenarios involving the consumption of contaminated water—i.e., a small mammal (20 g mouse), a large mammal (70 kg deer), as small bird (20 g passerine), and a large bird (4 kg Canada goose), as discussed in

1 Section 4.2.2. For other exposure scenarios involving chlorophacinone, the receptors are  
2 elaborated. For mammals, primary exposure scenarios include the standard mouse and deer as  
3 well as the prairie dog and ground squirrel.

#### 4 **4.2.2. Primary Exposures**

##### 5 **4.2.2.1. Primary Exposures, Accidental Spill**

6 All Forest Service risk assessments include exposure scenarios involving some sort of accidental  
7 spill. The usual concern for an accidental spill is the contamination of surface water—e.g., a  
8 spill into a small pond, which is considered below for both terrestrial species (Sections 4.2.5) and  
9 aquatic species (Section 4.2.6). For chlorophacinone, however, an accidental spill could also  
10 involve a large spill of bait onto the ground, which is then consumed by terrestrial organisms.  
11 Primary exposures involve the consumption of contaminated bait. These exposure scenarios are  
12 detailed in Worksheet F01a through F01f of the EXCEL workbook that accompanies this risk  
13 assessment.

14  
15 Superficially, this is a simple scenario in which the amount of bait consumed might be estimated  
16 from the food consumption rates of the receptor. As in all Forest Service risk assessments, food  
17 consumption rates are estimated from allometric relationships developed by U.S. EPA/ORD  
18 (1993)—i.e., the Wildlife Exposure Factors Handbook. Allometric relationships scale the  
19 amount of food consumed per day to the body weight of the animal—i.e.,  $FC = aW^b$ —where  $FC$   
20 is the food consumption in grams,  $W$  is the body weight in grams, and  $a$  and  $b$  are coefficients.  
21 Different allometric relationships are developed for different groups of organisms. For example,  
22 the allometric equations for rodents is given as  $FC = 0.621W^{0.584}$  (U.S. EPA/ORD 1993, Eq. 3-8,  
23 p. 3-6).

24  
25 A critical input for this exposure scenario is the proportion of the diet constituted by  
26 contaminated bait. As discussed in the Forest Service risk assessment on strychnine (SERA  
27 2005, Section 4.2.2.1), the proportion of the contaminated diet was taken as 0.02 (0.002 - 0.2) as  
28 a model calibration based on data for the pocket gopher. Thus, these values are not applicable to  
29 the use of chlorophacinone for the control of the black-tailed prairie dog. An analogous  
30 approach, however, may be developed based on the study by Baroch (1998) involving above  
31 ground baiting for the control of ground squirrels. Using a 0.005% oat bait, essentially  
32 equivalent to a Rozol formulation, Baroch (1998) found mean residues of 0.19 mg/squirrel in  
33 carcasses recovered from bait station plots. Taking a body weight of about 0.15 kg for a squirrel  
34 (Table 9), the residue corresponds to about 1.3 mg/kg bw [ $0.19 \text{ mg/squirrel} \div 0.15 \text{ kg/squirrel} =$   
35  $1.3 \text{ mg a.i./kg bw}$ ]. Similar residues in squirrels are cited in U.S. EPA/OPP/EFED (2010a, p. 67,  
36 Table 3.3) and are attributed to Baroch, but the EPA document does not provide a full citation.  
37 As detailed in Worksheet F01b, the central estimate of the dose to a squirrel is approximately 1.2  
38 mg/kg bw using a value of 0.3 for the proportion of the diet that is contaminated. Based on this  
39 calibration and analogous to the approach used for strychnine, the proportion of the diet that  
40 might be contaminated in the event of an accidental spill is taken as 0.3 (0.03 - 1.0). The upper  
41 bound of the range is simply a worst-case assumption, and the lower bound yields an estimated  
42 dose of about 0.16 mg/kg bw, which is only modestly below the lowest residue for ground  
43 squirrels cited in U.S. EPA/OPP/EFED (2010a, p. 67, Table 3.3)—i.e., 0.264 mg/kg bw.

1 There are clear uncertainties in applying the proportions of 0.3 (0.03 -1.0) to other species;  
2 however, data are not available to justify species-specific elaborations of this assumption.  
3 Nonetheless, it is worth noting that the upper bound dose for a small (20g) bird in Worksheet  
4 F01c is about 12.7 mg/kg bw which is virtually identical to the estimated dose of 11.1 mg/kg for  
5 a 20 g bird from U.S. EPA/OPP/EFED (2011a, Table 3.6).

#### 6 **4.2.2.2. Primary Exposures, Misapplication**

7 Typically, chlorophacinone treated bait will be deposited directly into burrows, and it seems  
8 reasonable to assume that very little bait will be available to receptors who might consume bait  
9 but do not enter burrows—i.e., all primary consumers, except fossorial mammals. In below-  
10 ground hand baiting, the available field studies give no indication that misapplications would  
11 lead to potentially hazardous amounts of bait on the soil surface. Thus, with the exception of  
12 gross mishandling, it does not appear that misapplication scenarios are applicable to hand  
13 baiting.

14  
15 While misapplications are of concern in this risk assessment, data to directly support such an  
16 exposure assessment are not available. No studies are available with applications that give a  
17 quantitative estimate of the amount of spilled during application and the amount remaining after  
18 typical clean-up measures. For the misapplication scenario, the consumption factors of 0.03  
19 (0.003 - 0.1) are applied to all groups of nontarget primary consumers—i.e., one-tenth the values  
20 used for an accidental spill.

#### 21 **4.2.2.3. Primary Exposures, Typical Applications**

22 Exposure assessments are provided for each of three primary scenarios involving typical  
23 applications of chlorophacinone bait: the foraging of black-tailed prairie dog dens by fossorial  
24 mammals (Section 4.2.2.3.1), the consumption of incidental above-ground spillage by birds  
25 (Section 4.2.2.3.2), and foraging of black-tailed prairie dog burrows by larger omnivorous  
26 mammals (Section 4.2.2.3.3).

##### 27 **4.2.2.3.1. Fossorial Mammals**

28 It is likely that fossorial mammals, like mice and squirrels, will enter baited dens and directly  
29 consume treated bait. As summarized in the previous section and consistent with the Forest  
30 Service risk assessment on strychnine (SERA 2005), consumption factors for fossorial mammals  
31 in typical below-ground applications of chlorophacinone are assumed to be 0.002 (0.0002 -  
32 0.02). Exposure estimates are made for three receptors, a very small mammal (i.e., a mouse, in  
33 Worksheet F05a), a somewhat larger fossorial mammal (i.e., a ground squirrel, in Worksheet  
34 F05b), and substantially larger fossorial mammal (i.e., a skunk, in Worksheet F05c).

##### 35 **4.2.2.3.2. Ground Surface Feeders**

36 Unlike the case with fossorial mammals, data to support a calibration of consumption factors for  
37 surface dwelling mammals as well as birds that might feed on incidental surface deposits of bait  
38 are extremely limited. Other than small mammals and ground squirrels, the groups of vertebrates  
39 that might consume incidental amounts of chlorophacinone treated bait on the ground surface are  
40 birds. As discussed in the Forest Service risk assessment on strychnine (SERA 2005), some  
41 birds will avoid bait (e.g., grouse) while others will freely consume and may be attracted to bait.  
42



1 Because of the lack of adequate monitoring data, the risk characterization for the primary  
2 consumption of bait in typical below-ground applications of chlorophacinone is based primarily  
3 on field studies for strychnine (i.e., SERA 2005, Section 4.4.2.2). As with strychnine,  
4 consumption factors of  $2 \times 10^{-5}$  ( $2 \times 10^{-6}$  -  $2 \times 10^{-4}$ ) are used for birds that might consume incidental  
5 amounts of treated bait from the ground surface. As with the other primary exposure scenarios,  
6 the birds specifically used in exposure assessments are the small passerine (Worksheet F05d),  
7 mallard (Worksheet F05e), pigeon (Worksheet F05f), and quail (Worksheet F05g).

#### 8 **4.2.2.3.3. Bears Foraging on Caches**

9 As with the exposure scenarios for misapplications (Section 4.2.2.2), large grazing mammals,  
10 such as deer, are not included in the exposure scenarios for primary consumption. While deer  
11 and other mammals might consume incidental amounts of bait, there is no basis for asserting that  
12 these exposures might be toxicologically significant.

13  
14 As discussed in SERA (2005), bears do feed on pocket gopher food caches—i.e., below-ground  
15 areas where gophers store food. It is not clear that grizzly or other species of bears will forage for  
16 black-tailed prairie dog food caches; nevertheless, this exposure scenario is included in the  
17 current risk assessment as a precautionary approach. As with the risk assessment on strychnine,  
18 this exposure scenario involves what is likely to be a very rare event and is depicted primarily to  
19 illustrate the potential hazards of using chlorophacinone in grizzly bear habitat, as well as to  
20 encompass incidents in which other mammals might occasionally forage on food caches of the  
21 black-tailed prairie dog. As detailed in Worksheet G08, the assumptions concerning the amount  
22 of contaminated bait that might be consumed by a grizzly bear are identical to those used in the  
23 risk assessment for strychnine (SERA 2005).

#### 24 **4.2.3. Secondary Exposures**

25 As with the Forest Service risk assessment on strychnine (SERA 2005), the predator species used  
26 in the exposure scenario are a 13 kg coyote (Worksheet F09a), a 7 kg badger (Worksheet F09b),  
27 a 1 kg mink (Worksheet F09c), a 1.5 kg great horned owl (Worksheet F09d), and a 0.5 kg  
28 rattlesnake (Worksheet F09e). Note that the species used in these exposure scenarios are  
29 adopted from strychnine risk assessment (SERA 2005) and are intended to represent a plausible  
30 range of predator body weights. Not all of the species used in these examples (e.g., mink) are  
31 likely predators of the prairie dog.

32  
33 Field data regarding chlorophacinone residues in poisoned black-tailed prairie dogs were not  
34 identified in the available literature. Thus, the exposure assessment for secondary exposures  
35 assumes that the effect of baiting of burrows will lead to doses that approximate the  $LD_{50}$  for the  
36 black-tailed prairie dog—i.e., 1.8 (1.35 - 5.29) mg/kg bw from the study by Yoder (2008), as  
37 summarized in Appendix 1, Table A1-1.

38  
39 The most difficult aspect of the exposure assessment involves the proportion of prey to be  
40 consumed by the predator. In the absence of data specific to chlorophacinone, the amounts  
41 consumed by the predator are taken from the risk assessment on strychnine (SERA 2005), with  
42 the following exceptions. For the 1 kg mink and the 1.5 kg owl, it is not reasonable to assume  
43 that the predator will consume a large portion of the 1 kg black-tailed prairie dog. Thus, the  
44 proportion of the black-tailed prairie dog consumed by the predator is taken as 0.03 (0.01 - 0.08).

1 The central estimate and upper bounds are one-tenth those used for the mink in the risk  
2 assessment on strychnine.

#### 3 **4.2.4. Tertiary Exposures**

4 Tertiary exposures refer to the consumption of a lower order of contaminated prey (e.g., a mink  
5 that ate a poisoned gopher—i.e., *secondary exposure*) by a higher order of prey (e.g., a coyote or  
6 raptor—i.e., *tertiary exposure*). Any number of tertiary exposure scenarios could be developed.  
7 As in the Forest Service risk assessment on strychnine (SERA 2005), the current risk assessment  
8 focuses on small predators that consume contaminated insects and develops exposure scenarios  
9 for a small mammal (Worksheet 10a), a small bird (Worksheet 10b), and a bullfrog (Worksheet  
10 10c). Prairie dogs do not inhabit moist areas (e.g., Shefferly 1999); thus, they may not  
11 commonly occur in the same habitat as bullfrogs. As discussed below, bullfrogs are used as a  
12 representative of a small amphibian because estimates of food consumption by a bullfrog are  
13 readily available.

14  
15 For Forest Service risk assessments on insecticides and herbicides, pesticide residues on insects  
16 are based on the empirical relationships between broadcast application rates and pesticide  
17 residues on insects recommended by Fletcher et al. (1994). These methods are not applicable to  
18 applications of chlorophacinone for rodent control. As detailed in the Forest Service risk  
19 assessment on strychnine (SERA 2005), pesticide residues in insects feeding on the carcasses of  
20 poisoned gophers are estimated at 0.2 (0.07 - 0.6) µg/g. In the absence of data specific for  
21 chlorophacinone, the residues for strychnine are used in the current risk assessment.

22  
23 The mass of the insects which the receptors might consume is based on allometric relationships  
24 from the EPA for the small mammal (U.S. EPA/ORD 1993, Eq. 3-8, p. 3-6) and small bird (U.S.  
25 EPA/ORD 1993, Eq. 3-3, p. 3-3). The EPA has not developed an allometric relationship for the  
26 bullfrog, but provides sufficient information to do so. Consequently, an allometric relationship is  
27 developed for the bullfrog, as summarized in the risk assessment on strychnine (SERA 2005,  
28 Section 4.2.4). For a small (20 g) bullfrog, the estimated food consumption is 1.82 g or about  
29 9% of body weight.

#### 30 **4.2.5. Consumption of Contaminated Water and Fish**

31 The exposure assessments associated with the consumption of contaminated surface water and  
32 contaminated fish parallel those used in the human health risk assessment. Exposure scenarios  
33 are presented for the consumption of contaminated surface water or fish following an accidental  
34 spill as well as the consumption of water or contaminated fish associated with peak and longer-  
35 term concentrations of chlorophacinone in surface water which might be expected from runoff,  
36 sediment loss, and percolation. The exposure scenario for the accidental spill is detailed in  
37 Section 3.2.3.4.1.

38  
39 The receptors used in these exposure assessments include a small mammal (20 g), a canid (5 kg),  
40 a large mammal (70 kg), a small bird (20 g), and a large bird (4 kg). These are standard  
41 receptors used in all Forest Service risk assessments for the exposure scenarios associated with  
42 the consumption of contaminated water.

1        **4.2.6. Aquatic Organisms**

2        The exposure assessment for aquatic organisms parallels the exposure assessment for the  
3        consumption of surface water by nontarget terrestrial species. As discussed in the previous  
4        subsection, exposure scenarios are presented for the consumption of contaminated surface water  
5        following an accidental spill as well as expected peak and longer-term concentrations of  
6        chlorophacinone in surface water.  
7

## 4.3. DOSE-RESPONSE ASSESSMENT

### 4.3.1. Overview

Table 10 summarizes the toxicity values used in the ecological risk assessment. The derivation of each of these values is discussed below. The available toxicity data support separate dose-response assessments in mammals, birds, fish, and aquatic invertebrates. The units of measure are different for the various groups of organisms, depending on the nature of exposure and the way in which the toxicity data are expressed.

Forest Service risk assessments usually defer to the U.S. EPA in both study selection and general methods for developing dose-response assessments. The major common exception is that Forest Service risk assessments prefer to use NOAEC values rather than LD<sub>50</sub> or other estimates of lethal doses for acute dose-response assessment. For the dose-response assessment of mammals and birds, however, the current risk assessment differs substantially from dose-response assessments in recent EPA risk assessments. The EPA assessments use allometric relationships for estimating toxicity values for mammals and birds. An examination of these methods in the current Forest Service risk assessment, however, indicates that the methods used by EPA are not consistent with the available data, overestimating toxicity to mammals and underestimating toxicity to birds.

The data supporting dose-response assessments in aquatic species are limited. Accordingly, following standard practice, the dose-response assessments for fish and aquatic invertebrates are adopted from the most recent EPA ecological risk assessments.

### 4.3.2. Toxicity to Terrestrial Organisms

#### 4.3.2.1. Mammals

### 4.3.2. Toxicity to Terrestrial Organisms

#### 4.3.2.1. Mammals

In characterizing risk to mammalian wildlife, Forest Service risk assessments generally consider the NOAELs on which the acute and chronic RfDs used in the human health risk assessment are based. As summarized in Section 3.3, however, the U.S. EPA has not derived acute or chronic RfDs for chlorophacinone.

As discussed in Section 3.3, the current risk assessment derives a surrogate acute RfD 0.003 mg/kg bw from a 0.29 mg/kg bw LOAEL in humans and using an uncertainty factor of 100, a factor of 10 for sensitive individuals and a factor of 10 for LOAEL-to-NOAEL. Following the standard approach used in most Forest Service risk assessments, the acute NOAEL for mammalian wildlife is estimated at 0.03 mg/kg bw. Similarly, the surrogate longer-term RfD is 0.00005 mg/kg bw/day, based on a NOAEL of 0.005 mg/kg bw/day (Table 8).

An issue with the above and admittedly simple approach, involves consistency with the dose-response assessment in the EPA risk assessment on chlorophacinone for the control of the black-tailed prairie dog (U.S. EPA/OPP/EFED 2010a). As detailed in the EPA's dose-response

1 assessment (U.S. EPA/OPP/EFED 2010a, Section 5.1.2, Table 5.2, p. 82), the Agency elected to  
2 estimate species specific LD<sub>50</sub> values based on the following allometric relationship:  
3

$$4 \quad LD_{50} = 0.16 \text{ mg / kg bw} \times \left( \frac{20 \text{ g}}{BW(g)} \right)^{0.25} \quad (4)$$

5  
6 where 0.16 mg/kg bw is the LD<sub>50</sub> of a 20 grams mouse and BW is the body weight in grams of  
7 the animal of concern. As summarized in Table 5.2 of U.S. EPA/OPP/EFED (2010a, p. 82), the  
8 above relationship is used to estimate LD<sub>50</sub> values of 0.02 mg/kg bw (for a 102,000 g grizzly  
9 bear) to 0.07 mg/kg bw (for a 635 g black-footed ferret).

10  
11 The EPA does not provide a reference for the above equation; however, the form of this  
12 allometric relationship is commonly used in toxicology (e.g., Calabrese 1991; Sharma and  
13 McNeill 2009; SERA 2014a, Section 4.3.6).

14  
15 In terms of a practical significance to the current Forest Service risk assessment on  
16 chlorophacinone, the approach used by EPA would lead to an estimated NOAEC for the grizzly  
17 bear of 0.002 mg/kg bw (i.e., the estimated LD<sub>50</sub> of 0.02 mg/kg bw divided by 10), which is  
18 substantially below the 0.03 short-term NOAEL for mammals discussed above. In general,  
19 Forest Service risk assessments will be at least as conservative as EPA risk assessments unless  
20 there is a compelling reason to do otherwise.

21  
22 As discussed in the Forest Service risk assessment on strychnine (SERA 2005, Figure 8), there  
23 are adequate experimental data on strychnine to support the use of an allometric relationship for  
24 assessing interspecies relationships in the toxicity of strychnine, and these relationships suggest  
25 that larger mammals are more sensitive than smaller mammals. No such data are available for  
26 chlorophacinone. To the contrary, as summarized in Table 11, the available data do not support  
27 the EPA approach. As summarized in Table 11, the allometric relationship proposed by EPA  
28 substantially overestimates the LD<sub>50</sub> values for several species—i.e., factors of about 30 for  
29 prairie dogs, 17 for meadow voles, 115 for pine voles, and 15 for the Norway rat. Similarly, the  
30 EPA algorithm estimates an LD<sub>50</sub> of about 0.021 for both sheep and humans; however, there are  
31 experimental studies indicating that doses substantially higher than the LD<sub>50</sub> causes no overt  
32 toxicity effects in sheep (Teeters 1981) or humans (Watt et al. 2005).

33  
34 Given that the EPA does not offer a rationale for their algorithm, and given the experimental data  
35 on chlorophacinone which contradicts the EPA algorithm, the acute NOAEL of 0.03 mg/kg bw  
36 and the chronic NOAEL of 0.005 mg/kg bw/day (as discussed above and summarized in Table 8)  
37 are used in the current Forest Service risk assessment to characterize risks in mammals exposed  
38 to chlorophacinone.

#### 39 **4.3.2.2. Birds**

40 As with mammals, the EPA uses estimates of species-specific LD<sub>50</sub> values based on an  
41 allometric relationship (U.S. EPA/OPP/EFED 2011a, Table 5-3, p. 80):  
42

$$LD_{50} = 258 \text{ mg / kg bw} \times \left( \frac{178 \text{ g}}{BW(\text{g})} \right)^{1-SF} \quad (5)$$

The value of 258 mg/kg bw is the LD<sub>50</sub> for bobwhite quail from MRID 41513101, as summarized in Appendix 2 (Table A2-1), and 178 grams is presumably the body of the quail from this study. The term *SF* is designated as 1.15 and referenced as the “*EFED default*” Mineau scaling factor. While not specifically cited by EPA, the above equation as well as the scaling factor of 1.15 is from Mineau et al. (1996, p. 27).

The study by Radvanyi et al. (1988) can be used to assess the utility of the above relationship. This study is cited but not otherwise discussed in U.S. EPA/OPP/EFED (2011a, Appendix F). As summarized in Appendix 2 (Table A2-1), Radvanyi et al. (1988) noted mortality in three of four American kestrels (*Falco sparverius*) weighing an average 119 g each following a dose of 3 mg/kg bw and four of four birds of this species weighing an average of 129 g each following a dose of 8.2 mg/kg. Based on the above equation used by EPA, the expected LD<sub>50</sub> for these birds would be about 244 mg/kg bw. Thus, the allometric relationship for birds appears to underestimate the toxicity of chlorophacinone substantially.

As discussed in Section 4.1.2.2.2 and detailed in Appendix 2 (Table A2-2) several acute dietary studies in birds are available. The lowest estimated LD<sub>50</sub> from standard registrant-submitted toxicity studies is 16.8 mg a.i./kg bw/day (for bobwhite quail from MRID 41513102). The open literature study by Giban (1974), however, suggests that partridges may be more sensitive. In the red legged partridge (*Alectoris rufa*), Giban (1974) noted mortality in 1/10 birds following a 5-day dietary exposure to a dose of about 6 mg/kg bw/day and mortality in 5/10 birds following a 15-day dietary exposure to the same dose. The study by Giban (1974) is not discussed in U.S. EPA/OPP/EFED (2011a).

The current Forest Service risk assessment bases the dose-response assessment for birds on the LOAEL of 6 mg/kg bw/day from Giban (1974). Following standard practice (SERA 2014a, Section 3.3.2 and Table 15), the LOAEL of 6 mg/kg bw/day is divided by a factor of 10 to estimate a NOAEL of 0.6 mg/kg bw/day. The primary concern with this estimated NOAEL is that the corresponding LOAEL is based on mortality. Thus, the estimated NOAEL may be viewed as possibly insensitive and not protective of other sublethal effects.

For longer-term exposures, U.S. EPA/OPP/EFED (2011a, p. 69) uses the dietary NOAEC of 1 mg/kg diet from MRID 47323201. As indicated in Appendix 2, Table A2-5, this study is published in the German literature as Riedel et al. (1990), and the estimated daily dose associated with the NOAEC is a NOAEL of 0.07 mg a.i./kg bw/day. This NOAEL is used to characterize risks associated with longer-term exposures in birds.

#### **4.3.2.3. Reptiles and Amphibians (Terrestrial-Phase)**

The lack of toxicity data for terrestrial-phase reptiles or amphibians (Section 4.1.2.3) precludes the development of a dose-response assessment these groups of organisms.

1                   **4.3.2.4. Terrestrial Invertebrates**

2 As discussed in Section 4.1.2.4, the information on the toxicity of chlorophacinone to terrestrial  
3 invertebrates is limited to brief summaries in U.S. EPA/OPP/EFED (2010a; 2011a) of acute  
4 studies in earthworms and burying beetles. Hazard quotients for these species are not derived in  
5 either EPA or Forest Service risk assessments. Nonetheless, these studies are discussed further  
6 in a qualitative risk characterization in Section 4.4.2.4.

7                   **4.3.2.5. Terrestrial Plants (Macrophytes)**

8 No data are available on the toxicity of chlorophacinone to terrestrial plants. Potential risks to  
9 terrestrial plants are addressed qualitatively in Section 4.4.2.5.

10                   **4.3.2.6. Terrestrial Microorganisms**

11 As summarized in Section 4.1.2.6, little information is available on the effects of  
12 chlorophacinone on terrestrial microorganisms; accordingly, a dose-response assessment for this  
13 group of organisms is not warranted.

14                   **4.3.3. Aquatic Organisms**

15                   **4.3.3.1. Fish**

16 Because of the sparse toxicity data on fish (Section 4.1.3.1), the dose-response assessment for  
17 fish is relatively simple. The most recent EPA ecological risk assessment on chlorophacinone  
18 uses the 96-hour LC<sub>50</sub> of 0.45 µg/L in trout for risk characterization (MRID 42356103, U.S.  
19 EPA/OPP/EFED 2011a, p. 67). The Forest Service prefers to use NOAECs rather than LC<sub>50</sub>  
20 values. As summarized in Section 4.1.3.1, the NOAEC for the trout study is 0.12 mg a.i./L, and  
21 this value is used for risk characterization in presumably sensitive species of fish.

22  
23 When possible, Forest Service risk assessments attempt to identify tolerant as well as sensitive  
24 species of fish. For chlorophacinone, the only other toxicity value is an LC<sub>50</sub> of 0.71 mg a.i./L  
25 with a corresponding NOAEC of 0.36 mg a.i./L in bluegill sunfish (MRID 43256102). This  
26 somewhat higher NOAEC of 0.36 mg a.i./L is used for presumably tolerant species of fish.

27  
28 Given that data are available only on two species of fish, there is no expectation that the narrow  
29 range of NOAECs—i.e., 0.12 - 0.36 mg a.i./L—will encompass the true NOAECs for the  
30 numerous fish species that might be exposed to chlorophacinone. Nonetheless, as discussed in  
31 Section 4.4.3.3, plausible levels of exposures to chlorophacinone are far below the NOAECs for  
32 fish. Consequently, the limited data on fish do not contribute substantially to uncertainties in the  
33 overall risk assessment for chlorophacinone.

34  
35 As noted in Section 4.1.3.1 as well as U.S. EPA/OPP/EFED (2011a, p. 9), chronic toxicity data  
36 are not available for fish. Consequently, a dose-response assessment for longer-term exposures  
37 of fish to chlorophacinone is not developed.

38                   **4.3.3.2. Amphibians (Aquatic-Phase)**

39 Because toxicity data on the effects of chlorophacinone in aquatic phase-amphibians are not  
40 available, a dose-response assessment for this group of organisms is not proposed.

1                   **4.3.3.3. Aquatic Invertebrates**

2 As summarized in Section 4.1.3.3, two EC<sub>50</sub> values in *Daphnia magna* are available for  
3 chlorophacinone. U.S. EPA/OPP/EFED uses the EC<sub>50</sub> of 0.64 mg a.i./L (U.S. EPA/OPP/EFED  
4 2011a, p. 67, MRID 42356101). As noted in Section 4.1.3.3, the NOAEC for this study (taken  
5 from ECOTOX) is 0.28 mg a.i./L. ECOTOX (2014) also contains a brief summary of another  
6 toxicity study in *Daphnia magna* with a reported EC<sub>50</sub> of 0.426 mg a.i./L and an NOAEC of 0.13  
7 mg a.i./L. In the absence of fuller documentation on this somewhat lower EC<sub>50</sub>, the current  
8 Forest Service risk assessment defers to the EPA assessment and uses the NOAEC of 0.28 mg  
9 a.i./L to characterize risk to aquatic invertebrates. Because data are available on only a single  
10 species, there is no objective basis for asserting that *Daphnia magna* is a sensitive or tolerant  
11 species. Thus, the NOAEC is applied to presumably tolerant species as a precautionary  
12 approach.

13  
14 No longer-term studies are available on the effects of chlorophacinone on aquatic invertebrates.  
15 Consequently, no dose-response assessment is proposed for longer-term exposures.

16                   **4.3.3.4. Aquatic Plants**

17 Because no toxicity data are available on the effects of chlorophacinone on aquatic plants  
18 (Section 4.1.3.4), no dose-response assessment is proposed. As with terrestrial plants, potential  
19 risks to aquatic plants are addressed qualitatively in the risk characterization (Section 4.4.3.4).  
20



## 4.4. RISK CHARACTERIZATION

### 4.4.1. Overview

The risk characterizations for terrestrial species are summarized in Worksheet G02, and the risk characterizations for aquatic species are summarized in Worksheet G03 of the EXCEL workbook that accompanies this risk assessment.

All exposures associated with the consumption of contaminated water are far below the level of concern for both terrestrial organisms and aquatic organisms. This assessment is consistent with the EPA risk assessment for the use of chlorophacinone to control the black-tailed prairie dog (U.S. EPA/OPP/EFED 2010a) as well as the somewhat more recent EPA risk assessment on other uses of chlorophacinone (U.S. EPA/OPP/EFED 2011a).

As would be expected from a rodenticide, applications of chlorophacinone to control the black-tailed prairie dog are likely to lead to adverse effects, including death, in other rodents and perhaps other mammals that consume substantial amounts of bait. The prevalence of lethal exposures to nontarget rodents will be reduced but not completely eliminated by subsurface applications to burrows of the black-tailed prairie dog. Birds are less sensitive than mammals to chlorophacinone. While adverse effects to some species of birds cannot be excluded, it appears that effects on birds will be less common and less severe than effects on mammals. Almost all the uncertainty in the risk characterization for chlorophacinone is associated with the exposure assessments. Most exposures of nontarget species to chlorophacinone should be incidental. Nonetheless, misapplications of chlorophacinone could lead to wider exposures and effects in both primary consumers of the bait (mammals and birds) as well as predators that might consume chlorophacinone contaminated prey.

### 4.4.2. Terrestrial Organisms

#### 4.4.2.1. Mammals

As summarized in Worksheet G02 of the EXCEL workbook that accompanies this risk assessment, the hazard quotients exceed the level of concern (HQ=1) for mammals in both accidental and non-accidental primary, secondary, and tertiary exposure scenarios. Qualitatively, this risk characterization is identical to the risk characterization from the EPA risk assessment on the use of chlorophacinone to control of black-tailed prairie dog (U.S. EPA/OPP/EFED 2010a, Section 5.1.2, pp. 82-83).

The risk characterization for mammals is, in some respects, intuitive. As discussed in Section 4.3.2.1, the available toxicity data clearly indicate that chlorophacinone is highly toxic to rodents. While the toxicity data on other groups of mammals are sparse, these data suggest that chlorophacinone may be somewhat but not remarkably less toxic to other groups of mammals. Thus, if chlorophacinone is applied in a manner that is effective for the control of the black-tailed prairie dog and if the chlorophacinone is consumed by nontarget mammals, rodents as well as non-rodents, it is reasonable to anticipate that adverse effects in populations of nontarget mammals could occur.

The major reservation with the risk characterization for mammals involves the possible levels of exposure. As discussed in Section 4.2.2, some field data are available to essentially calibrate

1 “worst case” accidental exposures in nontarget mammals. These data, however, are sparse,  
2 relative to other rodenticides such as strychnine (SERA 2005). Other exposure scenarios (e.g.,  
3 misapplication and normal application) are essentially conservative; however, less severe  
4 modifications to the accidental exposure scenario are not supported by field studies useful for  
5 verifying the exposure estimates. Nonetheless, incident data and case reports (Section 4.1.2.1.3)  
6 qualitatively support the assessment that adverse effects, including mortality, may occur in small  
7 mammals and perhaps some larger mammals following applications of chlorophacinone.

#### 8 **4.4.2.2. Birds**

9 The risk characterization for birds is substantially less severe than that for mammals. This  
10 follows from the lower toxicity of chlorophacinone to birds relative to mammals. As  
11 summarized in Table 10, the acute NOAEL for birds is estimated at 0.6 mg/kg bw, which is a  
12 factor of 20 higher than the corresponding NOAEL for mammals. As summarized in Worksheet  
13 G02 of the EXCEL workbook that accompanies this risk assessment, the level of concern  
14 (HQ=1) is exceeded for accidental spills and misapplications but not for non-accidental  
15 applications of chlorophacinone. As with mammals, this risk characterization is consistent with  
16 the risk characterization in U.S. EPA/OPP/EFED (2010a, Section 5.1.1, p. 80).

17  
18 Vyas and Rattner (2012) expressed concern that standard gavage bioassays on birds could  
19 underestimate the risks to birds exposed to first generation anticoagulants including  
20 chlorophacinone. As discussed at some length in Section 3.1.3.3, this concern is based on the  
21 delayed mortality associated with oral doses of chlorophacinone. While this concern is  
22 reasonable, the dose-response assessment for birds used in the current Forest Service risk  
23 assessment is based on the 5-day dietary study in partridges by Giban (1994). Similarly, the U.S.  
24 EPA/OPP/EFED (2010a) uses a 5-day dietary study in quail (MRID 41513102) noting that the  
25 dietary studies present lower (i.e., more conservative) estimates of potency, compared with  
26 gavage studies.

27  
28 As with the risk characterization for mammals, the greatest uncertainties in the risk  
29 characterization for birds are associated with the exposure assessment, and biomonitoring data  
30 from field applications of chlorophacinone are of limited use in defining plausible levels of  
31 exposures of birds to chlorophacinone. As discussed in Section 4.1.2.2.4 (Case Reports in  
32 Birds), incidents of poisoning are reported in the European literature; however, these appear to  
33 be related to surface applications. In the context of the current Forest Service risk assessment,  
34 surface applications would be regarded as a misapplication. The study by Ruder et al. (2011)  
35 involving a chlorophacinone application in Kansas implicates chlorophacinone in the deaths of  
36 two turkeys; however, few details are available on the specific applications associated with the  
37 deaths of the two turkeys.

#### 38 **4.4.2.3. Reptiles and Amphibians (Terrestrial Phase)**

39 As discussed in Section 4.1.2.3, toxicity data are not available on terrestrial phase amphibians;  
40 consequently, an explicit risk characterization for this group of organisms is not proposed. The  
41 U.S. EPA/OPP typically uses birds as a surrogate for reptiles and terrestrial phase amphibians  
42 (e.g., U.S. EPA/OPP/EFED 2011a, p. 45). Somewhat atypically, the U.S. EPA/OPP/EFED  
43 developed toxicity values for a 50 and 500 gram snake based on allometric relationships using  
44 the acute oral LD<sub>50</sub> of 258 mg/kg bw in quail (U.S. EPA/OPP/EFED 2010a, p. 81, MRID  
45 41513101). Based on this approach, the risk quotients for snakes were below the level of

1 concern. Given the limitations in the use of allometric relationships for birds (Section 4.3.2.2),  
2 the EPA approach is not adopted in the current Forest Service risk assessment. Nonetheless, the  
3 lack of direct effects on snakes noted in the EPA risk assessment (U.S. EPA/OPP/EFED 2011a,  
4 p. 20) is consistent with the risk characterization for birds discussed in the previous section.

#### 5 **4.4.2.4. Terrestrial Invertebrates**

6 As with reptiles and amphibians, the current Forest Service risk assessment does not develop a  
7 quantitative risk characterization for terrestrial invertebrates. As discussed in Section 4.1.2.4,  
8 U.S. EPA/OPP/EFED (2010a, 2011a) provides a brief summary of a registrant toxicity study on  
9 the burying beetle, *Nicrophorus orbicollis*, in which decreased larval emergence was noted after  
10 the adult beetles fed on rodent carcasses poisoned with chlorophacinone (MRID 47383001).

11 Based on this study, the EPA expresses concern that beetles, including some beetles classified as  
12 endangered species, might be adversely impacted by the use of chlorophacinone to control the  
13 black-tailed prairie dog. Given that only a brief summary of the study on burying beetles was  
14 available for the preparation of the current Forest Service risk assessment, the conclusions from  
15 EPA are adopted in the current risk assessment.

#### 16 **4.4.2.5. Terrestrial Plants**

17 As discussed in Section 4.1.2.5, no data are available on the toxicity of chlorophacinone to  
18 terrestrial plants. The EPA notes: “*Given the mode of action of chlorophacinone, toxicity to*  
19 *plants is expected to be low*” (U.S. EPA/OPP/EFED 2011a, p. 9). In addition, as discussed in  
20 Section 2.2, chlorophacinone has been used as a rodenticide since 1971. Thus, there is a  
21 substantial body of experience with chlorophacinone, and it seems only modestly speculative to  
22 suggest that adverse effects on plants would have been noted if chlorophacinone was phytotoxic.

#### 23 **4.4.3. Aquatic Organisms**

24 As discussed in Section 4.4.1, none of the hazard quotients for aquatic organisms approach a  
25 level of concern, and a further elaboration of the risk characterization for aquatic species is not  
26 warranted.

## 5. REFERENCES

NOTE: The initial entry for each reference in braces {} simply specifies how the reference is cited in the text. The final entry for each reference in brackets [] indicates the source for identifying the reference.

ClRev	Cleared reviews from <a href="http://iaspub.epa.gov/apex/pesticides">http://iaspub.epa.gov/apex/pesticides</a> for chlorophacinone [N=16]
E-Docket01	EPA-HQ-OPP-2013-0049: Notice of cancellation for rodenticides other than chlorophacinone. [N=0]
E-Docket02	EPA-HQ-OPP-2012-0365, Approval for Rozol Label [N=5]
E-Docket03	EPA-HQ-OPP-2011-0718, Review of Scientific Conclusions Supporting EPA's FIFRA Section 6(b) Notice of Intent to Cancel Twenty Homeowner Rodenticide Bait Products. Includes Brodifacoum, Difethialone, and Warfarin. (N=2)
E-Docket04	EPA-HQ-OPP-2010-0584: Proposed use: California ground squirrel. No supporting documents. (n=0)
E-Docket05	EPA-HQ-OPP-2006-0955: Rodenticide cancelations. Does not include chlorophacinone. (N=1)
FS	Papers provided by the Forest Service.
PrRv	Papers added during peer review.
SET00	Papers from preliminary scoping.
SET01	Preliminary TOXLINE literature search.
SET02	Supplemental citations from screening of SET01.
SET03	Supplemental citations from screening of SET01 and SET02.
Sec	Summary of citation from a secondary source.
Std	Standard references used in most Forest Service risk assessments.

{Advani and Prakash 1987} Advani R; Prakash I. 1987. Variations in the Rodent Populations in Response to Four Anticoagulant Rodenticides in the Residential Habitat of the Indian Desert. Pesticides (Bombay). 21 (5): 18-22. [Set01]

{Ahmed et al. 1996} Ahrned MS; Baroch J; Carlet L; Whaley D. Secondary hazard study using chlorophacinone-killed laboratory rats fed to domestic Ferrets (*Mustela putorius furo*). DER from U.S. EPA/EFED 2001. MRID 44631401. [ClRev]

{Albert et al. 2010} Albert CA; Wilson LK; Mineau P; Trudeau S; Elliott JE. 2010. Anticoagulant Rodenticides in Three Owl Species from Western Canada, 1988-2003. Archives of Environmental Contamination and Toxicology. 58(2):451-9. [Set01]

{Andelt and Hopper 2012} Andelt WF; Hopper SN. 2012. Managing Prairie Dogs. Colorado State University Extension. Fact Sheet No. 6.506 dated December, 2012. Available at: <http://www.ext.colostate.edu/pubs/natres/06506.pdf>. [Set00]

{André and Guillaume 2004} André C; Guillaume Y-C. 2004. Anti-coagulant rodenticide binding properties of human serum albumin: a biochromatographic approach. Journal of Chromatography B. 801(2): 221-227. [Set02a]

{Andre et al. 2005} Andre C; Guyon C; Thomassin M; Barbier A; Richert L; Guillaume YC. 2005. Association Mechanism Between a Series of Rodenticide and Humic Acid: A Frontal Analysis to Support the Biological Data. Journal of Chromatography B, Analytical Technology in the Biomedical and Life Sciences. 820(1):9-14. [Set01]

{Arditti et al. 1997} Arditti J; Hayek M; Bourdon JH; Lachatre G; Masset D; David JM; Jouglard J. Self poisoning by chlorophacinone: Clinical and analytical data. [Intoxication volontaire à la Chlorophacinone : Suivi clinique et analytique]. Toxicorama 9: 266-270. (Cited in Papin et al. 2007) [Set02a]

## Appendix 1: Toxicity to Mammals (*continued*)

{Ashton et al. 1986} Ashton AD; Jackson WB; Peters H. 1986. Comparative evaluation of LD<sub>50</sub> values for various anticoagulant rodenticides in Control of Mammal Pests. *Tropical Pest Management*. 32(supplement) 1: 187-197. (Summarized in U.S. EPA/OPP/EFED 2011a and WHO 1995) [Set02a]

{Askham 1985a} Askham LR. 1985a. Effectiveness of Two Anticoagulant Rodenticides (Chlorophacinone and Bromadiolone) for Columbian Ground Squirrel (*Spermophilus columbianus*) Control in Eastern Washington USA. *Crop Protection*. 4 (3): 365-371. [Set01]

{Askham 1985b} Askham LR. 1985b. Mechanical Evaluation of the Weatherability of Pelletized Rodenticides. *International Pest Control*. 27 (6): 138-140. [Set01]

{Askham 1988} Askham L. 1988. Chlorophacinone – Secondary Hazard Evaluation of chlorophacinone in raptors. Submitted by Chempar, Lilpha Chemicals, Inc., Milwaukee, WI. Conducted by Washington State University, Pullman, WA. Laboratory Study No. 88-1. MRID 407514-02. DER from U.S. EPA/EFED 2001. [CIRev]

{Askham and Poche 1992} Askham LR; Poche RM. 1992. Biodeterioration of Chlorophacinone in Voles, Hawks and an Owl. *Mammalia*. 56 (1): 145-150. [Set01]

{Azoury and Levin 1998} Azoury M; Levin N. 1998. Identification of Zinc Phosphide in a Falsely Labeled Rodenticide Bait. *Journal of Forensic Sciences*. 43 (3): 693-695. [Set01]

{Baldwin et al. 2014} Baldwin RA; Quinn N; Davis DH; Engeman RM. 2014. Effectiveness of Rodenticides for Managing Invasive Roof Rats and Native Deer Mice in Orchards. *Environmental Science and Pollution Research International*. 21(9):5795-802. [Set01]

{Barnes 1993} Barnes AM. 1993. A Review of Plague and Its Relevance to Prairie Dog Populations and the Black-footed Ferret. In: *Proceedings of the Symposium on the Management of Prairie Dog Complexes for the Reintroduction of the Black-footed Ferret*. Fish and Wildlife Service, Biological Report 13, pp 28-37. [Set00]

{Baroch 1997} Baroch J. 1997. Secondary hazard study using chlorophacinone-killed laboratory rats fed to black-billed magpies (*Pica pica*). DER from U.S. EPA/EFED 2001. MRID 44631402. [CIRev]

{Baroch 1998} Baroch J. 1998. An Overview of Recent Ground Squirrel Bait Registration Research Supported By the California Bait Surcharge Program. *Proceedings of the Eighteenth Vertebrate Pest Conference (1998)*. Paper 30. Available at: <http://digitalcommons.unl.edu/cgi/viewcontent.cgi?article=1029&context=vpc18>. [Set03]

{Berny et al. 1997} Berny PJ; Buronfosse T; Buronfosse F; Lamarque F; Lorgue G. 1997. Field evidence of secondary poisoning of foxes (*Vulpes vulpes*) and buzzards (*Buteo buteo*) by bromadiolone, a 4-year survey. *Chemosphere*. 35(8):1817-29. [Set03]

{Berny et al. 2006} Berny PJ; De Oliveira LA; Videmann B; Rossi S. 2006. Assessment of Ruminal Degradation, Oral Bioavailability, and Toxic Effects of Anticoagulant Rodenticides in Sheep. *American Journal of Veterinary Research*. 67(2):363-71. [Set01]

{Berny et al. 2010} Berny P; Velardo J; Pulce C; D'amico A; Kammerer M; Lasseur R. 2010. Prevalence of Anticoagulant Rodenticide Poisoning in Humans and Animals in France and Substances Involved. *Clinical Toxicology (Philadelphia)*. 48(9):935-41. [Set01]

{Binks and Davies 2007} Binks S; Davies P. 2007. Case of the Month: "Oh! Drat! - Case of Transcutaneous Superwarfarin Poisoning and its Recurrent Presentation". *Emergency Medicine Journal*. 24(4):307-8. [Set01]

{BLM 2007} BLM (Bureau of Land Management). 2007. Statewide Programmatic Black-Tailed Prairie Dog (*Cynomys Ludovicianus*) Biological Evaluation. BLM Wyoming State Office. Available at: <http://www.blm.gov/pgdata/etc/medialib/blm/wy/wildlife/bt-prdog.Par.74785.File.dat/BTPDbio-eval.pdf>. [Set00]

## Appendix 1: Toxicity to Mammals (*continued*)

- {Blus et al. 1985} Blus LJ; Henny CJ; Grove RA. 1985. Effects of Pelletized Anticoagulant Rodenticides on California Quail. *Journal of Wildlife Diseases*. 21(4):391-5. [Set01]
- {Braselton et al. 1992} Braselton WE, Jr; Neiger RD; Poppenga RH. 1992. Confirmation of Indandione Rodenticide Toxicoses by Mass Spectrometry/mass Spectrometry. *Journal of Veterinary Diagnostic Investigation*. 4(4):441-6. [Set01]
- {Brooks et al. 1992} Brooks FE; Dolbeer RA; Angaya M; McConnel JE; LaVoie GK. 1992. The Toxicity and Efficacy of Several Rodenticides to Sahelian Rodent Species in Chad. Technical Report No. 3, Chad Rodent Control Research Project, November 1992. Available at: [http://pdf.usaid.gov/pdf\\_docs/PNABP425.pdf](http://pdf.usaid.gov/pdf_docs/PNABP425.pdf). [Set00]
- {Buckle 2013} Buckle A. 2013. Anticoagulant Resistance in the United Kingdom and a New Guideline for the Management of Resistant Infestations of Norway Rats (*Rattus norvegicus* Berk.). *Pest Management Science*. 69(3):334-41. [Set01]
- {Bullard et al. 1975} Bullard RW; Holguin G; Peterson JE. 1975. Determination of Chlorophacinone and Diphenadione Residues in Biological Materials. *Journal of Agricultural and Food Chemistry*. 23(1):72-4. [Set01]
- {Burucoa et al. 1989} Burucoa C; Mura P; Robert R; Boinot C; Piriou A; et al. 1989. Chlorophacinone Intoxication: Biological and Toxicological Study. *Journal of Toxicology, Clinical Toxicology*. 27(1-2): 79-89. [Set01]
- {Butts and Lewis 1982} Butts KO; Lewis JC. 1982. The Importance of Prairie Dog Towns to Burrowing Owls in Oklahoma. *Proceedings of the Oklahoma Academy of Science*. 62: 46-52. [PrRv]
- {Byers 1976} Byers RE. 1976. New Compound RH-787 1-3 Pyridylmethyl-3-4-Nitrophenyl Urea for Use in Control of Orchard Voles. *Journal of Wildlife Management*. 40 (1): 169-171. [Set01]
- {Byers 1978} Byers RE. 1978. Performance of Rodenticides for the Control of Pine Voles in Orchards. *Journal of the American Society of Horticultural Science*. 103: 65-69. [Set03]
- {Byers and Carbaugh 1987} Byers RE; Carbaugh DH. 1987. Bait Shyness of Pine Voles to Zinc Phosphide and Anticoagulants Stored with Pesticides. *Hortscience*. 22 (2): 239-241. [Set01]
- {Byers and Carbaugh 1989} Byers RE; Carbaugh DH. 1989. Vole Population Shifts Related to Rodenticide Usage. *Hortscience*. 24 (5): 783-785. [Set01]
- {Byers and Carbaugh 1991} Byers RE; Carbaugh DH. 1991. Rodenticides for the Control of Pine and Meadow Voles in Orchards. *Journal of Environmental Horticulture*. 9 (3): 167-172. [Set01]
- {Calabrese 1991} Calabrese, EJ. 1991. Principles of animal extrapolation. Lewis Publishers. Chelsea, MI.[Std]
- {CDC 2013} CDC (Centers for Disease Control). 2013. Plague in the United States, Maps and Statistics. Available at: <http://www.cdc.gov/plague/maps/>. [Set00]
- {CDPR 2013a} CDPR (California Department of Pesticide Regulation). 2013a. Second Generation Anticoagulant Rodenticide Assessment. Memorandum from Deborah Daniels to Ann Prichard dated June 27, 2013. Available at: [http://www.cdpr.ca.gov/docs/registration/reevaluation/chemicals/brodifacoum\\_final\\_assess.pdf](http://www.cdpr.ca.gov/docs/registration/reevaluation/chemicals/brodifacoum_final_assess.pdf). [Set00]
- {CDPR 2013b} CDPR (California Department of Pesticide Regulation). 2013b. Summary of Pesticide Use Report Data 2011, Indexed by Chemical. Report dated June 2013. Available at: <http://www.cdpr.ca.gov/docs/pur/pur11rep/chmrpt11.pdf>. [Std]
- {Chan et al. 2009} Chan J; Vogel SM; Wen J; Alany RG. 2009. Potentiometric Determination of Ionisation Constants for Diphacinone and Chlorophacinone in a Dioxane-Water Cosolvent System. *Journal of Pharmaceutical and Biomedical Analysis*. 50(1):86-9. [Set01]

## Appendix 1: Toxicity to Mammals (*continued*)

{Chataigner et al. 1989} Chataigner D; Garnier R; Elmalem J; Efthymiou ML. 1989. Prolonged hypocoagulability following the ingestion of anticoagulant raticides. *Annales de Médecine Interne (Paris)*. 139: 537–541. (Cited in Papin et al. 2007) [Set02a]

{ChemIDplus 2014} ChemIDplus. 2014. United States National Library of Medicine. Available at: <http://chem.sis.nlm.nih.gov/chemidplus/>. [Std]

{Colvin et al. 1988} Colvin B; Hegdal P; Jackson W. 1988. Review of non-target hazards associated with rodenticide use in the USA. *OEPP/EPPO Bulletin* 18:301-308. [Set02a]

{Coon 2005} Coon MJ. 2005. Cytochrome P450: Nature's Most Versatile Biological Catalyst. *Annual Review of Pharmacology and Toxicology*. 45: 1-25. [Std]

{Del Piero and Poppenga 2006} Del Piero F; Poppenga RH. 2006. Chlorophacinone Exposure Causing An Epizootic of Acute Fatal Hemorrhage in Lambs. *Journal of Veterinary Diagnostic Investigation*. 18(5):483-5. [Set01]

{Doolittle 2010} Doolittle RF. 2010. Coagulation in Vertebrates with a Focus on Evolution and Inflammation. *Journal of Innate Immunity*. DOI: 10.1159/000321005. Published online: October 28, 2010. Available at: <http://doolittle.ucsd.edu/recentpubs/JII2011.review.pdf>. [Std]

{Dunning 1993} Dunning JB. 1993. *CRC Handbook of Avian Body Masses*. CRC Press, Boca Raton FL, 371 pp. [Std]

{Dusein et al. 1984} Dusein P; Manigand G; Taillandier J. 1984. Severe, prolonged hypofibrinemia following poisoning by chlorophacinone. *Presse Medicale [ISSN:0755-4982]*. 13:1845. (Cited in Papin et al. 2007) [Set02a]

{Ecobichon 1998} Ecobichon DJ. 1998. *Occupational Hazards of Pesticide Exposure – Sampling, Monitoring, Measuring*. Taylor & Francis, Philadelphia, PA. 251 pp. [Std]

{ECOTOX 2014} ECOTOX. 2014. Records on Chlorophacinone. U.S. EPA ECOTOX Database, Version 4. Accessed on September 24, 2014. Available at: [http://cfpub.epa.gov/ecotox/quick\\_query.htm](http://cfpub.epa.gov/ecotox/quick_query.htm). [Set00]

{El Bahrawy and Morsy 1990} El Bahrawy AF; Morsy TA. 1990. The Effect of Some Anticoagulants Against Three Commensal Rodents Under Laboratory Conditions. *Journal of the Egyptian Society of Parasitology*. 20 (1): 289-296. [Set01]

{EPI Suite 2011} EPI Suite. 2011. Estimation Program Interface (EPI) Suite, Version 4.1. Copyright 2000-2008 by the U.S. EPA. Available at: <http://www.epa.gov/oppt/exposure/pubs/episuite.htm>. [Std]

{FAO/WHO 2001} FAO/WHO (Food and Agriculture Organization/ World Health Organization). 2001. *Human Vitamin and Mineral Requirements*. Food and Nutrition Division. Available at: <http://www.fao.org/3/a-y2809e.pdf>. [Std]

{Fiedler 1988} Fiedler LA. 1988. Rodent Pest Problems and Management in Eastern Africa. *F.A.O. Plant Protection Bulletin*. 36 (3): 125-134. [Set01]

{Finney 1971} Finney DJ. 1971. *Probit Analysis*. New York: Cambridge University Press. 333 p. [Std]

{Fisher and Timm 1987} Fisher DD; Timm RM. 1987. Laboratory trial of chlorophacinone as a prairie dog toxicant. *Proceedings of the Great Plains Wildlife Damage Control Workshop*. 8:67-69. Available at: <http://digitalcommons.unl.edu/cgi/viewcontent.cgi?article=1064&context=gpwdcwp>. [Set00]

## Appendix 1: Toxicity to Mammals (*continued*)

- {Fisher et al. 2003} Fisher P; O'Connor C; Wright G; Eason CT. 2003. Persistence of four anticoagulant rodenticides in the livers of laboratory rats. Doc Science Internal Series 139. Department of Conservation, Wellington, New Zealand. Available at: <http://www.doc.govt.nz/documents/science-and-technical/dsis139.pdf>. [Set00]
- {Fisher et al. 2007} Fisher P; Spurr EB; Ogilvie SC; Eason CT. 2007. Bait consumption and residual concentrations of diphacinone in the Wellington tree weta (*Hemideina crassidens*) (Orthoptera: Anostostomatidae). New Zealand Journal of Ecology. 31(1), 104-110. [Set03]
- {Fletcher et al. 1994} Fletcher JS; Nellessen JE; Pfleeeger TG. 1994. Literature review and evaluation of the EPA food-chain (Kenega) nomogram, an instrument for estimating pesticide residues on plants. Environ. Toxicol. Chem. 13(9):1383-1391. [Std]
- {Fournier-Chambrillon et al. 2004} Fournier-Chambrillon C; Berny PJ; Coiffier O; Barbedienne P; Dass, B; Delas G; Galineau H; Mazet A; Pouzenc P; Rosoux R; Fournier P. 2004. Evidence of Secondary Poisoning of Free-Ranging Riparian Mustelids by Anticoagulant Rodenticides in France: Implications for Conservation of European Mink (*Mustela lutreola*). Journal of Wildlife Diseases. 40(4):688-95. [Set01]
- {FWS 2012b} FWS (Fish and Wildlife Service). 2012b. Comments on Revised Rozol Label. Letter dated July 20, 2012. Available at: [file:///C:/Users/Owner/Downloads/Fish and Wildlife Services Comment to EPA on Revised Label.pdf](file:///C:/Users/Owner/Downloads/Fish%20and%20Wildlife%20Services%20Comment%20to%20EPA%20on%20Revised%20Label.pdf). [E-Docket02]
- {FWS 2012b} FWS (U.S. Fish and Wildlife Service). 2012a. Final Biological Opinion For Rozol Use on Black-tailed Prairie Dogs Registered Under Section 3 of the Federal Insecticide, Fungicide and Rodenticide Act. Prepared by: U.S. Fish and Wildlife Service, Ecological Services Region 6 and Region 2. Document dated April 9, 2012. Available at: <http://www.fws.gov/southdakotafieldoffice/EC%20web%20page/ROZOL%20BO%20-%20%20FINAL%20-%20%20204-9-12%20%20SENT%20TO%20EPA.pdf>. [Set00]
- {Gabriel et al. 2012} Gabriel MW; Woods LW; Poppenga R; et al. 2012. Anticoagulant Rodenticides on our Public and Community Lands: Spatial Distribution of Exposure and Poisoning of a Rare Forest Carnivore. PLoS ONE. 7(7):e1063. [FS]
- {Gaines. 1969} Gaines TB. 1969. Acute toxicity of pesticides. Tox. Appl. Pharmacol. 14: 515-534.[Std]
- {Garcia-Repetto et al. 1998} Garcia-Repetto R; Soria ML; Gimenez MP; Menendez M; Repetto M. 1998. Deaths from Pesticide Poisoning in Spain from 1991 to 1996. Veterinary and Human Toxicology. 40 (3): 166-168. [Set01]
- {Giban 1974} Giban J. 1974. Use of chlorophacinone in the struggle against the common vole (*Microtus arvalis* Pallas) and against the musk rat (*Ondatra zibethicus*). In: Proceedings of the 6th Vertebrate Pest Conference. Paper 14. Available at: <http://digitalcommons.unl.edu/cgi/viewcontent.cgi?article=1013&context=vpc6>. [Set00]
- {Gill 1990} Gill FB. 1990. Ornithology, Second Edition. W.H. Freeman and Company, New York. 766 pp. [Std]
- {Gill and Redfern 1977} Gill JE; Redfern R. 1977. Some laboratory tests of five rodenticides for the control of *Arvicanthis niloticus*. International Journal of Pest Management. 23(1): 33-37. [Set03]
- {Goldstein et al. 1974} Goldstein A; Aronow L; Kaman SM. 1974. Principles of Drug Action: The Basis of Pharmacology. 2nd ed. John Wiley and Sons, New York, NY. 854 p.[Std]
- {ICRP 1975} ICRP (International Commission on Radiologic Protection). 1975. Report of the Task Group on Reference Man. Recommendations of the International Commission on Radiological Protection (ICRP) Publ. No. 23. Pergamon Press, New York, NY.[Std]
- {Hadler 1990} Hadler MR. 1990. Second Generation Anticoagulant Rodenticides Their Effectiveness and Economics. International Pest Control. 32 (4): 100-102. [Set01]



## Appendix 1: Toxicity to Mammals (*continued*)

{Hardman and Limbird 1996} Hardman JF; Limbird LE. 1996. Goodman and Gilman's CD-ROM, Goodman and Gilman's The Pharmacological Basis of Therapeutics, Ninth Edition. McGraw-Hill, Health Professions Division, N.Y. [Std]

{Hartgrove et al. 1973} Hartgrove R; Hortsfall F; Petrella V; Randolph WC; Webb RE. 1973. Toxicity Studies in Endrin-Susceptible and Resistant Strains of Pine Mice. *Toxicology and Applied Pharmacology*. 25(1): 42-47 [Set01]

{Havelka and Bartova 1992} Havelka J; Bartova P. 1992. Pesticide Toxicity Upon the Aphidophagous Gall-Midge *Aphidoletes aphidimyza* (Diptera, Cecidomyiidae): A Review. *Acta Entomologica Bohemoslovaca*. 89 (6): 395-402. [Set01]

{Hayes 1982} Hayes WJ Jr. 1982. Pesticides studied in man. Baltimore/London: Williams & Wilkins, 672 pp. [Std]

{Hoffbrand and Moss 2011} Hoffbrand AV; Moss PAH. 2011. Essential Haematology. Wiley-Blackwell, 6<sup>th</sup> Edition. Available at: <http://www.wiley.com/WileyCDA/WileyTitle/productCd-EHEP002323.html>. [Std]

{HSDB 2003} HSDB (Hazardous Substances Database). 2003. Chlorophacinone. Last updated October 15, 2003. Available at: <http://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+6432>. [Std]

{HSDB 2011} HSDB (Hazardous Substances Database). 2011. 2,4-Dinitrophenol. Last revision June 15, 2011. Available at: <http://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+529>. [Std]

{Hudson et al. 1984} Hudson RH; Tucker RK; Haegele MA. 1984. Handbook of Toxicity of Pesticides to Wildlife. Resour.Publ.No.153, Fish Wildl. Serv., 2nd Edition, U.S.D.I., Washington, DC :90 p. [Std]

{Hygnstrom and Virchow 1994} Hygnstrom SE; Virchow DR. 1994. Prairie Dogs. The Handbook: Prevention and Control of Wildlife Damage. Paper 20. Available at: <http://digitalcommons.unl.edu/icwdmhandbook>. [Set00]

{Jackson and Ashton 1992} Jackson WB; Ashton AD. 1992. A review of available anticoagulants and their use in the United States. Proceedings of the Fifteenth Vertebrate Pest Conference. 15:156-160. [Set00]

{Katona and Wason 1989} Katona B; Wason S. 1989. Superwarfarin Poisoning. *Journal of Emergency Medicine*. 7(6): 627-632. [Set01]

{Kegley et al. 2014} Kegley SE; Hill BR; Orme S; Choi AH. Chlorophacinone and Flocoumafen Records in PAN Pesticide Database, Pesticide Action Network, North America (Oakland, CA, 2014), <http://www.pesticideinfo.org>. © 2000-2014 Pesticide Action Network, North America. All rights reserved. [Set00]

{Keigwin 1998} Keigwin T. 1998. PHED (Pesticide Handlers Exposure Database) Surrogate Exposure Guide. Dated April 1997 with revisions in August 1998. Copy courtesy of Hank Appleton/USDA/Forest Service. 82 pp. [Std]

{King 1959} King, J. A. 1959. The social behavior of prairie dogs. *Scientific American*. 201:128-40. Also cited in U.S. EPA/OPP/EFED 2010a. [Set02]

{Knisel and Davis 2000} Knisel WG; Davis FM. 2000. GLEAMS (Groundwater Loading Effects of Agricultural Management Systems), Version 3.0, User Manual. U.S. Department of Agriculture, Agricultural Research Service, Southeast Watershed Research Laboratory, Tifton, GA. Pub. No.: SEWRL-WGK/FMD-050199. Report Dated May 1, 1999 and revised August 15, 2000. 194pp. [http://www.tifton.uga.edu/sewrl/Gleams/gleams\\_y2k\\_update.htm](http://www.tifton.uga.edu/sewrl/Gleams/gleams_y2k_update.htm). [Std]

{Lagrange et al. 1999} Lagrange F; Corniot AG; Titier K; Bedry R; Pehourcq F. 1999. Toxicological Management of Chlorophacinone Poisoning. *Acta Clinica Belgica. Supplementum*. 1:13-6. [Set01]

## Appendix 1: Toxicity to Mammals (*continued*)

{Lawley et al. 2006} Lawley WJ; Charlton AJ; Hughson EJ; Grundy HH; Brown PM; Jones A. 2006. Development of a Cell Culture/ELISA Assay to Detect Anticoagulant Rodenticides and its Application to Analysis of Rodenticide Treated Grain. *Journal of Agricultural and Food Chemistry*. 54(5):1588-93. [Set01]

{Lechevin and Vigie 1992} Lechevin JC; Vigie A. 1992. Which useful toxicological information can be drawn from studies on the hepatic fixation of anticoagulant rodenticides. In: Borrecco JF, Marsh RE, editors. *Proc. 15th Vertebrate Pest Conf.*; 1992. p. 204–7. Published at University of Calif., Davis. Available at: <http://digitalcommons.unl.edu/cgi/viewcontent.cgi?article=1044&context=vpc15>. [Set00]

{Lee and Hyngstrom 2007} Lee CD; Hyngstrom SE. 2007. Field efficacy and hazards of Rozol bait for controlling black-tailed prairie dogs. Unpublished report, Liphatech, Inc., Milwaukee, WI, 300 pp. MRID 47333602. From U.S. EPA/OPP/RD 2009a. [ClRev]

{Lee et al. 2005} Lee CD; Gibson P; Wilson J. 2005. In-burrow application of Rozol to manage black-tailed prairie dogs. *Wildlife Damage Management Conferences - Proceedings*. Paper 123. 6 pp. Available at: [http://digitalcommons.unl.edu/cgi/viewcontent.cgi?article=1126&context=icwdm\\_wdmconfproc](http://digitalcommons.unl.edu/cgi/viewcontent.cgi?article=1126&context=icwdm_wdmconfproc). [Set00]

{Lemus et al. 2011} Lemus JA; Bravo C; Garcia-Montijano M; Palacin C; Ponce C; Magaña M; Alonso JC. 2011. Side Effects of Rodent Control on Non-Target Species: Rodenticides Increase Parasite and Pathogen Burden in Great Bustards. *Science of the Total Environment*. 409(22):4729-34. [Set01]

{Lilja 1992} Lilja HS. Acute Dermal Toxicity of Chlorophacinone Powder, Lot CLOMO15. MRID 417028-01. Study summary in U.S. EPA/OPP/RD 1997. [ClRev]

{Liphatech Inc. 2012} Liphatech Inc. 2012. Revised Product Label for Rozol® Prairie Dog Bait. Label dated June 2014. Label version 062012. U.S. EPA file name: EPA-HQ-OPP-2012-0365-0003.pdf. Available at: <file:///C:/Users/Owner/Downloads/EPA-HQ-OPP-2012-0365-0003.pdf>. [E-Docket02]

{Lund 1967} Lund M. 1967. Resistance of rodents to rodenticides. *World Review of Pest Control*. 6: 131-138. [Set02a]

{Lund 1971} Lund M. 1971. The Toxicity of Chlorophacinone and Warfarin to House Mice (*Mus musculus*). *Journal of Hygiene (London)*. 69(1):69-72. [Set01]

{Lynch and Price 2007} Lynch T; Price A. 2007. The effect of cytochrome P450 metabolism on drug response, interactions, and adverse effects. *Am Fam Physician*. 76(3): 391-6. [Std]

{Marsh 1985} Marsh RE. 1985. Are Anticoagulant Rodenticides a Problem for Household Pets. *Pest Control*. 53(8): 20-22, 24. [Set01]

{Marsh et al. 1977} Marsh RE; Howard WE; Cole RE. 1977. The Toxicity of Chlorophacinone and Diphacinone to Deer Mice. *Journal of Wildlife Management*. 41 (2): 298-301. [Set01]

{Mathur and Prakash 1980} Mathur RP; Prakash I. 1980. Laboratory Evaluation of Anticoagulant-Treated Baits for Control of the Northern Palm Squirrel, *Funambulus pennanti* Wroughton. *Journal of Hygiene (London)*. 85(3):421-6. [Set01]

{Mathur and Prakash 1982} Mathur RP; Prakash I. 1982. Laboratory evaluation of chlorophacinone against *Tatera indica* and *Meriones hurrianae*. *Tropical Pest Management*. 28:291-295. [Set02a]

{Mathur and Prakash 1984} Mathur RP; Prakash I. 1984. Reduction in Population of Indian Desert Rodents with Anticoagulant Rodenticides. *Proceedings of the Indian Academy of Sciences (Animal Sciences)*. 93 (6):585-589. [Set01]

## Appendix 1: Toxicity to Mammals (*continued*)

{Mcdonald et al. 1998} Mcdonald RA; Harris S; Turnbull G; Brown P; Fletcher M. 1998. Anticoagulant Rodenticides in Stoats (*Mustela erminea*) and Weasels (*Mustela nivalis*) in England. *Environmental Pollution*. 103 (1): 17-23. [Set01]

{McNamara. 1976} McNamara PP. 1976. Concepts in health evaluation of commercial and industrial chemicals. In: *Advances in Modern Toxicology*, Vol. 1, Part 1. Mehlman MA; Shapiro RE; Blumenthal H Eds. Hemisphere Publishing Co., Washington, DC. [Std]

{Mendenhall and Pank 1980} Mendenhall VM; Pank LF. 1980. Secondary Poisoning of Owls by Anticoagulant Rodenticides. *Wildlife Society Bulletin*. 8(4): 311-315. Also included at [http://www.epa.gov/opp00001/chem\\_search/cleared\\_reviews/csr\\_PC-067707\\_29-Oct-81\\_005.pdf](http://www.epa.gov/opp00001/chem_search/cleared_reviews/csr_PC-067707_29-Oct-81_005.pdf) as EPA Acc# 112701. A 1979 pre-publication copy is included at [http://www.epa.gov/opp00001/chem\\_search/cleared\\_reviews/csr\\_PC-067707\\_2-Aug-02\\_a.pdf/](http://www.epa.gov/opp00001/chem_search/cleared_reviews/csr_PC-067707_2-Aug-02_a.pdf/) [Set01] [CIRev]

{Merson and Byers 1985} Merson MH; Byers RE. 1985. Weathering and the Field Efficacy of Pelletized Rodenticide Baits in Orchards. *Crop Protection*. 4 (4): 511-519. [Set01]

{Mesban et al. 2003} Mesban HA; Tayeb EH; Mourad AK; Younis LK; El Zaher MA; Aly MT. 2003. Toxicology and Histopathology of Some Rodenticides and Palatable Food Items Combinations on the Common Mice (*Mus musculus* Var. albus) in Egypt. *Communications in Agricultural and Applied Biological Sciences*. 68(4 Pt B):771-87. [Set01]

{Mineau et al. 1996} Mineau P; Collins B; Baril A. 1996. On the Use of Scaling Factors to Improve Interspecies Extrapolation of Acute Toxicity in Birds. *Regulatory Toxicology and Pharmacology*. 24: 24-29. [Std]

{Miyazaki 1997} Miyazaki A. 1997. Progress and Prospects of Optically Active Pesticides. *Journal of Pesticide Science*. 22 (2): 136-155. [Set01]

{Mount et al. 1988} Mount ME; Kurth MJ; Jackson DY. 1988. Production of Antibodies and Development of an Immunoassay for the Anticoagulant, Diphacinone. *Journal of Immunoassay*. 9(1):69-81. [Set01]

{Mura et al. 1992} Mura P; Piriou A; Papet Y. 1992. Rapid high performance liquid chromatography assay of chlorphacinone in human serum. *Journal of Analytical Toxicology* 16: 179-81. [Set02a]

{Murdoch 1983} Murdoch DA. 1983. Prolonged Anticoagulation in Chlorphacinone Poisoning. *Lancet*. 1(8320):355-6. [Set01]

{Nehez et al. 1985} Nehez M, Kékes-Szabo A, Mazzag E, Selyes A, & Jarmay K 1985. Histologic and cytogenetic effects of redentin on the spermiogenesis and bone marrow cells of the mouse, an *in vivo* experiment. *Regulatory Toxicology and Pharmacology*. 5: 204-206. [Set02a]

{Ngazizah et al. 1993} Ngazizah A; Idris G; Shamsiah M; Nasir MK; Radzi H. 1993. The Palatability of Three Type Anticoagulant Rodenticides to Rice Field Rats (*Rattus argentiventer*). *Malaysian Agricultural Journal*. 54 (4): 195-199. [Set01]

{Nikodémusz et al. 1981} Nikodémusz E; Nechay G; Imre R. 1981. Histopathological Changes Resulting by Some Pesticides in the Common Vole (*Microtus arvalis* Pallas). *Acta Veterinaria Academiae Scientiarum Hungaricae*. 29(3):317-26. [Set01]

{NPIC 2011} NPIC (National Pesticide Information Center). 2011. Rodenticides: Topic Fact Sheet. Available at: <http://npic.orst.edu/factsheets/rodenticides.pdf>. [Set00]

{Oldemeyer et al. 1993} Oldemeyer JL; Biggins DE; Miller BJ; Crete R. 1993. Proceedings of the Symposium on the Management of Prairie Dog Complexes for the Reintroduction of the Black-footed Ferret. *Fish and Wildlife Service, Biological Report* 13. July 1993. [Set00]

## Appendix 1: Toxicity to Mammals (*continued*)

{Papin et al. 2007} Papin F; Clarot F; Vicomte C; Gaulier JM; Daubin C; Chapon F; Vaz E; Proust B. 2007. Lethal Paradoxical Cerebral Vein Thrombosis Due to Suspicious Anticoagulant Rodenticide Intoxication with Chlorophacinone. *Forensic Science International*. 166(2-3):85-90. [Set01]

{Pauli et al. 2000} Pauli BD; Perrault JA; Money SL. 2000. RATL: A Database of Reptile and Amphibian Toxicology Literature. National Wildlife Research Centre 2000, Canadian Wildlife Service, Environmental Conservation Branch, Technical Report Series Number 357. Available at: <http://dsp-psd.communication.gc.ca/Collection/CW69-5-357E.pdf> [Std]

{PHED Task Force 1995} PHED Task Force. 1995. PHED: The Pesticide Handlers Exposure Database. Version 1.1. Reference Manual. Health Canada, U.S. Environmental Protection Agency, and American Crop Protection Association. [Std]

{Piatkov et al. 2010} Piatkov I; Rochester C; Jones T; Boyages S. 2010. Warfarin Toxicity and Individual Variability-Clinical Case. *Toxins (Basel)*. 2(11):2584-92. [Set01]

{Pinault and Milhaud 1981} Pinault L; Milhaud G. 1981. Method of Toxicological Research of Anticoagulant Rodenticides. *Toxicological European Research*. 3 (1): 51-54. [Set01]

{Posthuma et al. 2002} Posthuma L; Suter GW; Trass TP. 2002. *Species Sensitivity Distributions*. Lewis Publishers, Boca Raton, Florida, 587 pp. [Std]

{Proulx 2011} Proulx G. 2011. Field Evidence of NonTarget and Secondary Poisoning by Strychnine and Chlorophacinone Used to Control Richardson's Ground Squirrels in Southwest Saskatchewan. In Danyluk D, editor. *Proc. Ninth Prairie Conserv. Endang. Species Conf. Winnipeg, MB, Canada*. Pages 128-134. [Set00]

{Quaranta et al. 2009} Quaranta A; Bellantuono V; Cassano G; Lippe C. 2009. Why Amphibians Are More Sensitive than Mammals to Xenobiotics. *PLoS ONE*. 4: (11): 1-4. [Std]

{Quinn et al. 2012} Quinn JH; Girard YA; Gilardi K; Hernandez Y; Poppenga R; Chomel BB; Foley JE; Johnson CK. 2012. Pathogen and Rodenticide Exposure in American Badgers (*Taxidea taxus*) in California. *Journal of Wildlife Diseases*. 48(2): 467-472. [Set02a]

{Radvanyi et al. 1988} Radvanyi A; Weaver P; Massari C; Bird D; Broughton E. 1988. Effects of Chlorophacinone on Captive Kestrels. *Bulletin of Environmental Contamination and Toxicology*. 41(3):441-8. [Set01]

{Raoult et al. 2013} Raoult D; Mouffok N; Bitam I; Piarrous R; Drancourt M. 2013. Plague: History and contemporary analysis. *Journal of Infection*. 66: 18-26. [Set00]

{Ratnapalan et al. 2003} Ratnapalan S; Potylitsina Y; Tan LH; Roifman M; Koren G. 2003. Measuring a toddler's mouthful: toxicologic considerations. *J Pediatr*. 142(6):729-30. [Std]

{Reigart and Roberts 1999} Reigart R; Roberts J. 1999. *Recognition and Management of Pesticide Poisonings*. Fifth Edition. EPA Report Number: EPA #735-R-98-003. Supported by Certification and Worker Protection Branch, Field and External Affairs Division, Office of Pesticide Programs, U.S. Environmental Protection Agency. Available at: <http://www.epa.gov/oppfead1/safety/healthcare/handbook/handbook.htm>. [Std]

{Reid 2006} Reid FA. 2006. *A Field Guide to Mammals of North America North of Mexico*. Fourth Edition. The Peterson Field Guide Series. Houghton Mifflin Company, Boston MA. 570 pp. [Std]

{Riedel et al. 1990} Riedel B; Grun G; Clausing P. The subacute and subchronic toxicity of chlorophacinone in Japanese quail (*Coturnix japonica*). *Archiv für experimentelle Veterinärmedizin*. 44:341-6. [Set03]

{Ruder et al. 2011} Ruder MG; Poppenga RH; Bryan Ja 2nd; Bain M; Pitman J; Keel MK. 2011. Intoxication of Nontarget Wildlife with Rodenticides in Northwestern Kansas. *Journal of Wildlife Diseases*. 47(1):212-6. [Set01]

## Appendix 1: Toxicity to Mammals (*continued*)

- {Sanchez-Barbudo et al. 2012} Sanchez-Barbudo IS; Camarero PR; Mateo R. 2012. Primary and Secondary Poisoning by Anticoagulant Rodenticides of Non-Target Animals in Spain. *Science of the Total Environment*. 420:280-8. [Set01]
- {Sarabia et al. 2008} Sarabia J; Sánchez-Barbudo I; Siqueira W; Mateo R; Rollan E; Pizarrod M. 2008. Lesions Associated with the Plexus Venosus Subcutaneous Collaris of Pigeons with Chlorophacinone Toxicosis. *Avian Diseases*. 52(3):540-3. [Set01]
- {Schafer and Bowles 1985} Schafer EW; Bowles W. 1985. Acute Oral Toxicity and Repellency of 933 Chemicals to House Mice and Deer Mice. *Archives of Environmental Contamination and Toxicology*. 14 (1): 111-129. [Set01]
- {Selypes et al. 1984} Selypes A; Kekes-Szabo A; Nehez M. 1984. Study of the Mutagenic Effect of Redentin on Various Species of Animals. *Acta Veterinaria Hungarica*. 32 (3-4): 213-218. [Set01]
- {SERA 2005} SERA (Syracuse Environmental Research Associates, Inc.). 2005. Strychnine – Human Health and Ecological Risk Assessment - Final Report. SERA TR-052-17-03b. Report dated March 27, 2005. Available at: <http://www.fs.fed.us/foresthealth/pesticide/risk.shtml>. [Std]
- {SERA 2007a} SERA (Syracuse Environmental Research Associates, Inc.). 2007a. Aminopyralid Human Health and Ecological Risk Assessment – FINAL REPORT. SERA TR-052-04-04a. Report dated June 28, 2007. Available at: <http://www.fs.fed.us/foresthealth/pesticide/risk.shtml>. [Std]
- {SERA 2007b} SERA (Syracuse Environmental Research Associates, Inc.). 2007b. Gleams-Driver User Guide (Version 1.8). SERA TR 07-52-05-08a. Report dated December 31, 2007. Available at: [www.sera-inc.com](http://www.sera-inc.com). [Std]
- {SERA 2011a} SERA (Syracuse Environmental Research Associates, Inc.). 2011a. WorksheetMaker Version 6.00, User Guide. SERA TR-052-20-01b. Document dated December 21, 2011. Syracuse Environmental Research Associates, Inc., Fayetteville, NY. Available at [www.sera-inc.com](http://www.sera-inc.com). [Std]
- {SERA 2011b} SERA (Syracuse Environmental Research Associates, Inc.). 2011b. Memorandum on Release of Gleams-Driver 1.9.3. Memo dated November 6, 2011. Available at: [www.sera-inc.com](http://www.sera-inc.com). [Std]
- {SERA 2014a} SERA (Syracuse Environmental Research Associates, Inc.). 2014a. Preparation of Environmental Documentation and Risk Assessments, SERA MD-2014-02b. Document dated November 17, 2014. Syracuse Environmental Research Associates, Inc., Manlius, NY. Available at [www.sera-inc.com](http://www.sera-inc.com). [Std]
- {SERA 2014b} SERA (Syracuse Environmental Research Associates, Inc.). 2014b. Reassessment of Worker Exposure Rates – FINAL REPORT. SERA TR-056-06-02b. Document dated November 17, 2014. Syracuse Environmental Research Associates, Inc., Manlius, NY. Available at: <http://www.fs.fed.us/foresthealth/pesticide/risk.shtml>. [Std]
- {Sharma and McNeill 2009} Sharma V; McNeill JH. 2009. To scale or not to scale: the principles of dose extrapolation. *British Journal of Pharmacology*. 157: 907-921. [Std]
- {Shaver and Tong 1991} Shaver CS; Tong T. 1991. Chemical Hazards to Agricultural Workers. *Occupational Medicine*. 6 (3): 391-414. [Set01]
- {Shefferly 1999} Shefferly, N. 1999. "Cynomys ludovicianus" (On-line), Animal Diversity Web. Accessed June 13, 2015 at [http://animaldiversity.org/accounts/Cynomys\\_ludovicianus/](http://animaldiversity.org/accounts/Cynomys_ludovicianus/). [PrRv]
- {Shlosberg and Egyed 1986} Shlosberg A; Egyed MN. 1986. Stability of Prothrombin Times in Sheep Dosed with Natural and Synthetic Anticoagulants. *Research in Veterinary Science*. 40(2):141-3. [Set01]
- {Sibley 2000} Sibley DA. 2000. *The Sibley Guide to Birds*. National Audubon Society, Chanticleer Press Edition. Alfred A. Knopf Inc., New York. 545 pp. [Std]

## Appendix 1: Toxicity to Mammals (*continued*)

{Smith et al. 2003} Smith FA; Lyons SK; Ernest M; Jones KE; Kauffman DM; Dyan T; Marquet PA; Brown JH; Haskell JP. 2003. Body mass of late Quaternary mammals. *Ecology* 84(12):3403. Full data set available at: <http://www.esapubs.org/archive/ecol/E084/094/> [Std]

{Sparling et al. 2000} Sparling DW; Linder G; Bishop C. 2000. *Ecotoxicology of Amphibians and Reptiles*. SETAC Technical Publications Series. SETAC Press. 1010 N. 12th Avenue, Pensacola, FL. <http://www.setac.org>. [Std]

{St. Romain et al. 2013} St. Romain K; Tripp DW; Salkeld DJ; Antolin MF. 2013. Duration of Plague (*Yersinia pestis*) Outbreaks in Black-Tailed Prairie Dog (*Cynomys ludovicianus*) Colonies of Northern Colorado. *EcoHealth*. 10: 241-245. [Set00]

{Stone et al. 1999} Stone WB; Okoniewski JC; Stedelin JR. 1999. Poisoning of Wildlife with Anticoagulant Rodenticides in New York. *Journal of Wildlife Diseases*. 35(2):187-93. [Set01]

{Stone et al. 2003} Stone WB; Okoniewski JC; Stedelin JR. 2003. Anticoagulant rodenticides and raptors: recent findings from New York, 1998-2001. *Bulletin of Environmental Contamination and Toxicology*. 70:34-40. [Set02a]

{Thompson et al. 2013} Thompson C; Sweitzer R; Gabriel M. 2013. Impacts of rodenticide and insecticide toxicants from marijuana cultivation sites on fisher survival rates in the Sierra National Forest, California. *Conservation Letters*. 7(2): 1-12. [FS]

{Tomlin 2004} Tomlin C. 2004. *The e-Pesticide Manual, Thirteenth Edition*, Crop Protection Publications; British Crop Protection Council. Available at: <http://www.bcpbookshop.co.uk>. [Std]

{Tosh et al. 2011} Tosh DG; Shore RF; Jess S; Withers A; Bearhop S; Montgomery WI; McDonald RA. 2011. User behaviour, best practice and the risks of non-target exposure associated with anticoagulant rodenticide use. *Journal of Environmental Management*. 92(6):1503-8. [Set02a]

{Tucker and Crabtree. 1970} Tucker RK; Crabtree DG. 1970. *Handbook of Toxicity of Pesticides to Wildlife*. Resource Publ. No. 84. Fish and Wildlife Service, U.S. Department of the Interior, Washington, DC. [Std]

{Tuytens and Stuyck 2002} Tuytens FAM; Stuyck JJ. 2002. Effectiveness and efficiency of chlorophacinone poisoning for the control of muskrat (*Ondatra zibethicus*) populations. *New Zealand Journal of Zoology* 29: 33-40. [Set02a]

{U.S. EPA/NCEA 2008} U.S. EPA/NCEA (U.S. Environmental Protection Agency/National Center for Environmental Analysis). 2008. *Child-Specific Exposure Factors Handbook*. EPA/600/R-06/096F. Report dated September 2008. Available at: <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=199243> [Std]

{U.S. EPA/OAQ 1985} U.S. EPA/OAQ (U.S. Environmental Protection Agency/Office of Air Quality). 1985. *Physical-Chemical Properties and Categorization of RCRA Wastes According to Volatility*. Office of Air Quality Planning and Standards, EPA-450/3-85-007. Available at: <http://nepis.epa.gov>. [Std]

{U.S. EPA/OCSPP 2012a} U.S. EPA/OCSPP (U.S. Environmental Protection Agency/Office of Chemical Safety and Pollution Prevention). 2012a. *Ecological Effects Test Guidelines, OCSPP 850.2200: Avian Dietary Toxicity Test*. EPA 712-C-024, January 2012. Available at: <http://www.regulations.gov/#!documentDetail:D=EPA-HQ-OPPT-2009-0154-0011>. [Std]

{U.S. EPA/OCSPP 2012b} U.S. EPA/OCSPP (U.S. Environmental Protection Agency/Office of Chemical Safety and Pollution Prevention). 2012b. *Ecological Effects Test Guidelines, OCSPP 850.3100: Earthworm Subchronic Toxicity Test*. EPA 712-C-016, January 2012. Available at: <http://www.regulations.gov/#!documentDetail:D=EPA-HQ-OPPT-2009-0154-0019>. [Std]

## Appendix 1: Toxicity to Mammals (*continued*)

{U.S. EPA/OCSPP 2013} U.S. EPA/OCSPP (U.S. Environmental Protection Agency/ Office of Chemical Safety and Pollution Prevention). 2013. OCSPP Harmonized Test Guidelines. OPPTS Harmonized Test Guidelines - Master List. Last Updated February, 2013. Available at: [http://www.epa.gov/ocspp/pdfs/OCSPP-TestGuidelines\\_MasterList.pdf](http://www.epa.gov/ocspp/pdfs/OCSPP-TestGuidelines_MasterList.pdf). [Std]

{U.S. EPA/OEI 2009} U.S. EPA/OEI (U.S. Environmental Protection Agency/Office of Environmental Information). 2009. Benchmark Dose Software Version 2.1. Doc No.: 53-BMDS-RPT-0028. Report dated April 30, 2009. Prepared by Lockheed Martin under U.S. EPA Contract No. 68-W-04-005. Available at: <http://www.epa.gov/ncea/bmids/documentation/BMDS%20User's%20Manual%20v2.pdf>. [Std]

{U.S. EPA/OPP 1998a} U.S. EPA/OPP (U.S. Environmental Protection Agency/Office of Pesticide Programs). 1998a. Reregistration Eligibility Decision (RED) Rodenticide Cluster. EPA738-R-98-007. Dated July 1998. Available at: <http://www.epa.gov/oppsrd1/REDs/2100red.pdf>. [Set00]

{U.S. EPA/OPP 1998b} U.S. EPA/OPP (U.S. Environmental Protection Agency/Office of Pesticide Programs). 1998b. R.E.D. FACTS: Rodenticide Cluster. EPA-738-F-98-004. Dated July 1998. Available at: [http://www.epa.gov/opp00001/chem\\_search/reg\\_actions/reregistration/fs\\_G-69\\_1-Jul-98.pdf](http://www.epa.gov/opp00001/chem_search/reg_actions/reregistration/fs_G-69_1-Jul-98.pdf). [Set00]

{U.S. EPA/OPP 2001a} U.S. EPA/OPP (U.S. Environmental Protection Agency/Office of Pesticide Programs). 2001a. GENEEC (Generic Estimated Environmental Concentrations), Version 2.0. August 1, 2001. Environmental Fate and Effects Division, Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington, D.C. Available at: [http://www.epa.gov/oppefed1/models/water/geneec2\\_description.htm](http://www.epa.gov/oppefed1/models/water/geneec2_description.htm). [Std]

{U.S. EPA/OPP 2001b} U.S. EPA/OPP (U.S. Environmental Protection Agency/Office of Pesticide Programs). 2001b. FIRST (FQPA Index Reservoir Screening Tool), Version 1.0 August 1, 2001, Environmental Fate and Effects Division, Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington, D.C. Available at: [http://www.epa.gov/oppefed1/models/water/first\\_description.htm](http://www.epa.gov/oppefed1/models/water/first_description.htm) [Std]

{U.S. EPA/OPP 2008a} U.S. EPA/OPP (U.S. Environmental Protection Agency/Office of Pesticide Programs). 2008a. Rodenticides; Notice of Receipt of Request to Voluntarily Cancel 22 Rodenticide Registrations. Federal Register. 73(248): 79104-79107. Available at: <http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2006-0955-0799>. [E-Docket05]

{U.S. EPA/OPP 2011a} U.S. EPA/OPP (U.S. Environmental Protection Agency/Office of Pesticide Programs). 2011a. Final Cancellation Order for Rozol Prairie Dog Bait Labeled For Use in Montana, New Mexico, North Dakota, and South Dakota. Document dated August 8, 2011. [Set00]

{U.S. EPA/OPP 2012a} U.S. EPA/OPP (U.S. Environmental Protection Agency/Office of Pesticide Programs). 2012a. Approval of Revised Label for Rozol Prairie Dog Bait (EPA Reg. No. 7173-286). Document dated August 8, 2012. Available at: <http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2012-0365-0009>. [E-Docket02]

{U.S. EPA/OPP 2012b} U.S. EPA/OPP (U.S. Environmental Protection Agency/Office of Pesticide Programs). 2012b. Approval of Revised Label for Rozol Prairie Dog Bait (EPA Reg. No. 7173-286). Document dated August 24, 2012. Available at: <http://www.epa.gov/pesticides/ppls/>. [E-Docket02]

{U.S. EPA/OPP 2013a} U.S. EPA/OPP (U.S. Environmental Protection Agency/Office of Pesticide Programs). 2013a. Registration Review: Conventional Cases Schedule: 2012-2015. Document dated Revised July 9, 2013. Available at: [http://www.epa.gov/oppsrd1/registration\\_review/fy12-fy15-conventional-sched.pdf](http://www.epa.gov/oppsrd1/registration_review/fy12-fy15-conventional-sched.pdf). [Set00]

{U.S. EPA/OPP 2013b} U.S. EPA/OPP (U.S. Environmental Protection Agency/Office of Pesticide Programs). 2013b. Rodenticides; Notice of Intent To Cancel Registrations of, and Notice of Denial of Applications for, Certain Rodenticide Bait Products [Warfarin, Brodifacoum, Difethialone]. Federal Register. 78(24): 8123-8128. Available at: <http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2013-0049-0011>. [E-Docket03]

## Appendix 1: Toxicity to Mammals (*continued*)

{U.S. EPA/OPP/EFED 1980a} U.S. EPA/OPP/EFED (U.S. Environmental Protection Agency/Office of Pesticide Programs/Environmental Fate and Effects Division). 1980a. Federally Registered Pesticides for Vertebrate Pest Control. Document dated March 1, 1980. Available at: [http://www.epa.gov/opp00001/chem\\_search/cleared\\_reviews/csr\\_PC-067707\\_1-Mar-80\\_004.pdf](http://www.epa.gov/opp00001/chem_search/cleared_reviews/csr_PC-067707_1-Mar-80_004.pdf). [CIRev]

{U.S. EPA/OPP/EFED 2001} U.S. EPA/OPP/EFED (U.S. Environmental Protection Agency/Office of Pesticide Programs/ Environmental Fate and Effects Division). 2001. Chlorophacinone (067707): secondary hazard studies. Document dated April 18, 2001. Available at: [http://www.epa.gov/opp00001/chem\\_search/cleared\\_reviews/csr\\_PC-067707\\_18-Apr-01\\_a.pdf](http://www.epa.gov/opp00001/chem_search/cleared_reviews/csr_PC-067707_18-Apr-01_a.pdf). [CIRev]

{U.S. EPA/OPP/EFED 2004a} U.S. EPA/OPP/EFED (U.S. Environmental Protection Agency/Office of Pesticide Programs/Environmental Fate and Effects Division). 2005a.

{U.S. EPA/OPP/EFED 2008a} U.S. EPA/OPP/EFED (U.S. Environmental Protection Agency/Office of Pesticide Programs/Environmental Fate and Effects Division). 2008a. Ecological Risk Assessment Evaluating Expanded Uses for Rozol Black Tailed Prairie Dog Bait (Chlorophacinone 0.005%). Document dated Nov. 6, 2008 Available at: [http://www.epa.gov/opp00001/chem\\_search/cleared\\_reviews/csr\\_PC-067707\\_10-Nov-08\\_a.pdf](http://www.epa.gov/opp00001/chem_search/cleared_reviews/csr_PC-067707_10-Nov-08_a.pdf). [CIRev]

{U.S. EPA/OPP/EFED 2010a} U.S. EPA/OPP (U.S. Environmental Protection Agency/Office of Pesticide Programs/Environmental Fate and Effects Division). 2010a. Risks of Chlorophacinone Use on Black Tailed Prairie Dogs to Federally Endangered and Threatened Species. Pesticide Effects Determinations. Document dated September 29, 2010. Available at: <http://www.epa.gov/oppfead1/endanger/litstatus/effects/chlorophacinone/assessment.pdf> [Set00]

{U.S. EPA/OPP/EFED 2011a} U.S. EPA/OPP/EFED (U.S. Environmental Protection Agency/Office of Pesticide Programs/Environmental Fate and Effects Division). 2010a. Risks of Chlorophacinone Use To the Federally Threatened Alameda Whipsnake (*Masticophis lateralis euryxanthus*), California Tiger Salamander (*Ambystoma californiense*), Central California Distinct Population Segment, and the Federally Endangered California Tiger Salamander (*Ambystoma californiense*) Sonoma County Distinct Population Segment and Santa Barbara County Distinct Population Segment, Salt Marsh Harvest Mouse (*Reithrodontomys raviventris*), and San Joaquin Kit Fox (*Vulpes macrotis mutica*) . Document dated June 29, 2011. Available at: <http://www.epa.gov/espp/litstatus/effects/redleg-frog/#chlorophacinone>. [Set00]

{U.S. EPA/OPP/EFED 2011b} U.S. EPA/OPP/EFED (U.S. Environmental Protection Agency/Office of Pesticide Programs/Environmental Fate and Effects Division). 2011b. Ecological Risk Assessment of Rodenticides: Analysis Plan. Presentation by Ed Odenkirchen to SAP, Nov. 29, 2011. EPA files name: EPA-HQ-OPP-2011-0718-0059. [E-Docket03]

{U.S. EPA/OPP/HED 1978} U.S. EPA/OPP/EFED (U.S. Environmental Protection Agency/Office of Pesticide Programs/Health Effects Division). 1978. EPA Reg. No. 7173-113. Review of Chlorophacinone. ROZOL Tracking Powder. Document dated January 23, 1978. Available at: [http://www.epa.gov/opp00001/chem\\_search/cleared\\_reviews/csr\\_PC-067707\\_23-Jan-78\\_001.pdf](http://www.epa.gov/opp00001/chem_search/cleared_reviews/csr_PC-067707_23-Jan-78_001.pdf). [CIRev]

{U.S. EPA/OPP/HED 1979} U.S. EPA/OPP/EFED (U.S. Environmental Protection Agency/Office of Pesticide Programs/Health Effects Division). 1979. EPA Reg. No. 7173-113. Chlorophacinone. Summary of Data Bank Used to Support Labeling of Currently Registered Products. Document dated October 18, 1979. Available at: [http://www.epa.gov/opp00001/chem\\_search/cleared\\_reviews/csr\\_PC-067707\\_18-Oct-79\\_003.pdf](http://www.epa.gov/opp00001/chem_search/cleared_reviews/csr_PC-067707_18-Oct-79_003.pdf). [CIRev]

{U.S. EPA/OPP/HED 1997} U.S. EPA/OPP/EFED (U.S. Environmental Protection Agency/Office of Pesticide Programs/Health Effects Division). 1997. EPA Reg. No. 7173-113. Review of chlorophacinone. Document dated September 13, 1997. Available at: [http://www.epa.gov/opp00001/chem\\_search/cleared\\_reviews/csr\\_PC-067707\\_13-Sep-92\\_006.pdf](http://www.epa.gov/opp00001/chem_search/cleared_reviews/csr_PC-067707_13-Sep-92_006.pdf). [CIRev]



## Appendix 1: Toxicity to Mammals (*continued*)

{U.S. EPA/OPP/HED 2013} U.S. EPA/OPP/EFED (U.S. Environmental Protection Agency/Office of Pesticide Programs/Health Effects Division). 2003. A Retrospective Analysis of Immunotoxicity Studies. Document dated February 2013. Available at: <http://www2.epa.gov/sites/production/files/documents/immunotoxicity-retro-analysis.pdf>. [Std]

{U.S. EPA/OPP/RD 1992a} U.S. EPA/OPP/EFED (U.S. Environmental Protection Agency/Office of Pesticide Programs/Registration Division). 1992a. Chlorophacinone (067707): Liphatech request for waiver of secondary toxicity study; D283438. MRID Nos. 446314-01, 446314-02, and 407514-02. MRID Nos 439222-01 and 439222-02. Document dated August 2, 2002. Available at: [http://www.epa.gov/opp00001/chem\\_search/cleared\\_reviews/csr\\_PC-067707\\_2-Aug-02\\_a.pdf](http://www.epa.gov/opp00001/chem_search/cleared_reviews/csr_PC-067707_2-Aug-02_a.pdf). [CIRev]

{U.S. EPA/OPP/RD 2002a} U.S. EPA/OPP/EFED (U.S. Environmental Protection Agency/Office of Pesticide Programs/Registration Division). 2002a. Chlorophacinone (067707): Liphatech request for waiver of secondary toxicity study; D283438. MRID Nos. 446314-01, 446314-02, and 407514-02. MRID Nos 439222-01 and 439222-02. Document dated August 2, 2002. Available at: [http://www.epa.gov/opp00001/chem\\_search/cleared\\_reviews/csr\\_PC-067707\\_2-Aug-02\\_a.pdf](http://www.epa.gov/opp00001/chem_search/cleared_reviews/csr_PC-067707_2-Aug-02_a.pdf). [CIRev]

{U.S. EPA/OPP/RD 2009a} U.S. EPA/OPP/EFED (U.S. Environmental Protection Agency/Office of Pesticide Programs/Registration Division). 2009a. IRB Efficacy Review. Product Name: Rozol Prairie Dog Bait. Product No.: 7173-EIA. Applicant: Liphatech, Inc. DP Barcode: 350015. PURPOSE: Product registration: New Use under Section 3 of FIFRA. DATA MRID Nos.: 473336-01, 473336-02, and 473336-03. Document dated March 18, 2009. Available at: [http://www.epa.gov/opp00001/chem\\_search/cleared\\_reviews/csr\\_PC-067707\\_18-Mar-09\\_a.pdf](http://www.epa.gov/opp00001/chem_search/cleared_reviews/csr_PC-067707_18-Mar-09_a.pdf). [CIRev]

{U.S. EPA/OPP/RD 2012a} U.S. EPA/OPP/EFED (U.S. Environmental Protection Agency/Office of Pesticide Programs/Registration Division). 2012a. Proposed Approval of Revised Label for Rozol Prairie Dog Bait (EPA Registration No. 7173-286). Document dated June 21, 2012. Available at: <file:///C:/Users/Owner/Downloads/EPA-HQ-OPP-2012-0365-0002.pdf>. [E-Docket02]

{U.S. EPA/OPPTS 1996} U.S. EPA/OPPTS (United States Environmental Protection Agency/Office of Prevention, Pesticides and Toxic Substances). 1996. Ecological Effects Test Guidelines OPPTS 850.2400 Wild mammal acute toxicity. EPA712-C-96-142, April 1996. Available at: [http://www.epa.gov/opptsfrs/publications/OPPTS\\_Harmonized/850\\_Ecological\\_Effects\\_Test\\_Guidelines/Drafts/850-2400.pdf](http://www.epa.gov/opptsfrs/publications/OPPTS_Harmonized/850_Ecological_Effects_Test_Guidelines/Drafts/850-2400.pdf). [Std]

{U.S. EPA/OPPTS 2000} U.S. EPA/OPPTS (U.S. Environmental Protection Agency/Office of Prevention, Pesticides, and Toxic Substances). 2000. Health Effects Test Guidelines, OPPTS 870.3550, Reproduction/Developmental Toxicity Screening Test. EPA712-C-00-367. July 2000. [Std]

{U.S. EPA/ORD 1987} U.S. EPA/ORD (United States Environmental Protection Agency/Office of Research and Development). 1987. IRIS (Integrated Risk Information System) Database. Strychnine, File 0103, Available at: <http://www.epa.gov/IRIS/subst/0103.htm>. [Std]

{U.S. EPA/ORD 1992} U.S. EPA/ORD (U.S. Environmental Protection Agency/Office of Research and Development). 1992. Dermal Exposure Assessment: Principles and Applications. EPA/600/8-91/011B. Interim Report. Exposure Assessment Group, Office of Health and Environmental Assessment, Washington, DC. Available at: <http://cfpub.epa.gov/ncea/cfm/recorddisplay.cfm?deid=12188> [Std]

{U.S. EPA/ORD 1993} U.S. EPA/ORD (U.S. Environmental Protection Agency/Office of Research and Development). 1993. Wildlife Exposure Factors Handbook. Volumes 1 and 2. EPA/600/R-93/187a,b. Pagination not continuous. NTIS PB94-174778 and PB94-174779. Available at: <http://rais.ornl.gov/homepage>. [Std]

{USDA/ARS 2010} USDA/ARS (U.S. Department of Agriculture/Agricultural Research Station). USDA National Nutrient Database for Standard Reference. Available at: <http://www.nal.usda.gov/fnic/foodcomp/search/>. [Std]

## Appendix 1: Toxicity to Mammals (*continued*)

{USDA/FS 2014} USDA/FS (U.S. Department of Agriculture/Forest Service). Black-Tailed Prairie Dog and Black-Footed Ferret. USDA Forest Service Update, March 2013 Available at: [http://www.fs.fed.us/biology/resources/pubs/issuepapers/IssueUpdate\\_PrairieDogFerret\\_March2014.pdf](http://www.fs.fed.us/biology/resources/pubs/issuepapers/IssueUpdate_PrairieDogFerret_March2014.pdf). [Set00]

{USDA/NSERL 2005} USDA/NSERL (United States Department of Agriculture/National Soil Erosion Research Laboratory). 2005. Cligen Weather Generator expanded and improved by USDA Agricultural Research Service and U. S. Forest Service. Available at: <http://horizon.nserl.purdue.edu/Cligen/>. [Std]

{USGS 2007} USGS (U.S. Geological Survey). 2007. The Quality of Our Nation's Waters—Pesticides in the Nation's Streams and Ground Water, 1992–2001: U.S. Geological Survey Circular 1291, Revised February 15, 2007, 172 p. Available at: <http://pubs.usgs.gov/circ/2005/1291/>. [Std]

{USGS 2013} USGS (U.S. Geological Survey). 2013. Preliminary Pesticide Use Maps for 2011. Available at: [http://water.usgs.gov/nawqa/pnsp/usage/maps/compound\\_listing.php](http://water.usgs.gov/nawqa/pnsp/usage/maps/compound_listing.php). Accessed on August 19, 2014. No data on chlorophacinone. [Std]

{Van Den Berg and Nauta 1975} Van Den Berg G; Nauta WT. 1975. Effects of anti-inflammatory 2-aryl-1,3-indandiones on oxidative phosphorylation in rat liver mitochondria. *Biochemical Pharmacology*. 24(7):815-821. (Cited in FWS 2012a). [Set02a]

{van Hemmen 1992} van Hemmen JJ. 1992. Agricultural pesticide exposure data bases for risk assessment. *Rev. Environ. Contam. Toxicol*. 126: 1-85. [Std]

{Vandenbroucke et al. 2008} Vandenbroucke V; Bousquet-Melou A; De Backer P; Croubels S. 2008. Pharmacokinetics of Eight Anticoagulant Rodenticides in Mice After Single Oral Administration. *Journal of Veterinary Pharmacology and Therapeutics*. 31(5):437-45. [Set01]

{Vein et al. 2013} Vein J; Vey D; Fourel I; Berny P. 2013. Bioaccumulation of Chlorophacinone in Strains of Rats Resistant to Anticoagulants. *Pest Management Science*. 69(3):397-402. [Set01]

{Vidal et al. 2009} Vidal D; Alzaga V; Luque-Larena JJ; Mateo R; Arroyo L; Vinuela J. 2009. Possible Interaction Between a Rodenticide Treatment and a Pathogen in Common Vole (*Microtus arvalis*) During a Population Peak. *Science of the Total Environment*. 408(2):267-71. [Set01]

{Vyas and Rattner 2012} Vyas NB; Rattner BA. 2012. Critique on the use of the standardized avian acute oral toxicity test for first generation anticoagulant rodenticides. *Human and Ecological Risk Assessment*. 18: 1069-1077. [Set02a]

{Vyas et al. 2012} Vyas NB; Hulse CS; Rice CP. 2012. Chlorophacinone Residues in Mammalian Prey at a Black-Tailed Prairie Dog Colony. *Environmental Toxicology and Chemistry*. 31(11):2513-6. [Set01]

{Waddell et al. 2013} Waddell LS; Poppenga RH; Drobatz KJ. 2013. Anticoagulant Rodenticide Screening in Dogs: 123 Cases (1996-2003). *Journal of the American Veterinary Medical Association*. 242(4):516-21. [Set01]

{Watt et al. 2005} Watt BE; Proudfoot AT; Bradberry SM; Vale JA. 2005. Anticoagulant Rodenticides. *Toxicological Reviews*. 24(4):259-69. [Set01]

{WHO 1985} WHO (World Health Organization). 1985. Data Sheets on Pesticides No. 62: Chlorophacinone. 7 pp. [Set00]

{WHO 1995} WHO (World Health Organization). 1995. Environmental Health Criteria 175. Anticoagulant Rodenticides. WHO Environmental Health Criteria, 175. Anticoagulant Rodenticides. 121p. Who: Geneva, Switzerland. ISBN 92-4-157175-6. 175 (0): 121p. [Set01]

{Wilson 1977} Wilson EB. 1927. Probable inference, the law of succession, and statistical inference. *Journal of the American Statistical Association*. 22: 209-212. [Std]

## Appendix 1: Toxicity to Mammals (*continued*)

{Witmer and Fagerstone 2003} Witmer GW; Fagerstone KA. 2003. The Use of Toxicants in Black-Tailed Prairie Dog Management: An Overview. Proceedings of the 10<sup>th</sup> Wildlife Damage Management Conference. pp. 359-369. Available at: [http://www.aphis.usda.gov/wildlife\\_damage/nwrc/publications/03pubs/witm034.pdf](http://www.aphis.usda.gov/wildlife_damage/nwrc/publications/03pubs/witm034.pdf). [Set00]

{Wong 2006} Wong RSM. 2006. Superwarfarin (Rodenticide) Poisoning. Poisoning.comm. 1(1):1-8. Available at: <http://www.chp.gov.hk/files/pdf/grp-poison-en-2006102701.pdf>. [Set00]

{Yang 1994} Yang R. 1994. Toxicology of Chemical Mixtures: Case Studies, Mechanisms, and Novel Approaches. Raymond S. Yang, Editor. Academic Press, Chicago, IL. 720pp. [Std]

{Yoder 2008} Yoder CA. 2008. Acute oral toxicity (LD<sub>50</sub>) Chlorophacinone in black-tailed prairie dogs (*Cynomys ludovicianus*). Unpublished report, Project No. QA-H46, National Wildlife Research Center, U.S. Department of Agriculture, Fort Collins, CO, 86 pp. MRID 47333601. From U.S. EPA/OPP/RD 2009a. [CIRev]

Appendix 1: Toxicity to Mammals (*continued*)

**Table 1: Relevant Reviews and Related Documents on Chlorophacinone**

<b>Reference [# pages]<sup>[1]</sup></b>	<b>Comment</b>
CDPR 2013a [53]	Review covering chlorophacinone as well as other first and second generation anticoagulant rodenticides.
<b>FWS 2012a [129]</b>	Biological Opinion for the use of Rozol on Black-tailed Prairie Dogs. Covers much of the open literature.
HDSB 2003 [N/A]	Online summary from TOXNET. Relies extensively on secondary sources.
Kegley et al. 2014 [NA]	Online summary from Pesticide Action Network. Linked to EPA ecotoxicity database.
NPIC 2011 [7]	Brief review of rodenticides including chlorophacinone.
Papin et al. 2007 [6]	Case report with a concise review of open literature focused on human case reports.
<b>U.S. EPA/OPP 1998a</b>	EPA's RED. Key summary of registrant studies relevant to human health
U.S. EPA/OPP/EFED 2008a [68pp.]	EPA ecological risk assessments for the use of Rozol for Black Tailed Prairie Dog
<b>U.S. EPA/OPP/EFED 2010a [122]</b>	Threatened and endangered species assessment for use of Rozol for Black Tailed Prairie Dog
U.S. EPA/OPP/EFED 2011a [111]	EPA ecological risk assessment for several threatened and endangered species. Includes other target species.
U.S. EPA/OPP/HED 1997, 2001 [<1]	Cursory summary of incidents involving dogs
Watt et al. 2005 [11]	Review of human poisonings involving anticoagulant rodenticides.
WHO 1995 [68]	Review of toxicity data on anticoagulant rodenticides covering open and unpublished literature.
WHO/INCHEM 1985 [7]	Cursory data sheet on chlorophacinone. Some reported values do not appear to be credible.

<sup>[1]</sup> Key reviews are indicated by light green shading with the most relevant reviews designated by bold font. Some U.S. EPA/OPP tolerances and other narrowly focused documents – e.g., exposure assessments, registration status, use applications, etc. – are not summarized above but are discussed in the text as appropriate in the text and are listed in Section 5 (References).

See Section 1.1. for discussion.

Appendix 1: Toxicity to Mammals (*continued*)

**Table 2: Summary of Open Literature Most Relevant to Risk Assessment**

<b>Topic</b>	<b>Citations<sup>[1,2]</sup></b>
<b>Human Health</b>	
Mechanism(s)	Andre et al. 2005; Lagrange et al. 1999; Lawley et al. 2006; Papin et al. 2007; Watt et al. 2005
Pharmacokinetics	Burucoa et al. 1989; Papin et al. 2007; LaGrange et al. 1999; Piatkov et al. 2010; Vandenbroucke et al. 2008;
Experimental Mammals	March 1985; Vandenbroucke et al. 2008
Human Poisoning	<b>Binks and Davies 2007 [dermal?]</b> ; Burucoa et al. 1989; Garcia-Repetto et al. 1988; Katona and Wason 1989; LaGrange et al. 1999; Murdoch 1983; <b>Papin et al. 2007</b>
Mutagenicity	Selypes et al. 1984 [marginal]
<b>Terrestrial Species</b>	
<b>Mammals</b>	
Laboratory	Ahmed et al. 1996 <sup>[2]</sup> ; El Bahrawy and Morsy 1990; Giban 1974; Hartgrove et al. 1973; <b>Lee and Hyngstrom 2007<sup>[2]</sup></b> ; Lund 1971; <b>Marsh et al. 1977</b> ; Mathur and Prakash 1980; Mesbah et al. 2003; Ngazizah et al. 1993; Nikodemusz et al. 1981; Yoder 2008
Case Reports	Berny et al. 2006; Del Piero and Poppenga 2006; <b>Ruder et al. 2011</b> ; Sanchez-Barbudo et al. 2012; Stone et al. 1999; Thompson et al. 2013; Waddell et al. 2013
Field Studies	Advani and Prakash 1987; Byers and Carbaugh 1989; Byers and Carbaugh 1991; Fournier-Chambrillon et al. 2004; <b>Proulx 2011</b> ; Vyas et al. 2012
Efficacy	Askham 1985a,b; Baldwin et al. 2014; Fiedler 1988; Giban 1974; Hadler 1990; Mathur and Prakash 1984; <b>Merson and Byers 1985</b> ; Vodál et al. 2009
Resistance	Buckle 2013; Byers 1976; Hartgrove et al. 1973; Vein et al. 2013
Bait Shyness/Aversion	Byers and Carbaugh; <b>Merson and Byers 1985</b> ; Schafer and Bowles 1985; Mesbah et al. 2003; Ngazizah et al. 1993
<b>Birds</b>	
Laboratory	Askham 1988 <sup>[2]</sup> ; Baroch 1997 <sup>[2]</sup> ; Giban 1974; Mendenhall and Pank 1980; Radvanyi et al. 1988
Case Reports/Field Studies	Albert et al. 2010; Askham and Poche 1992; Blus et al. 1985; Braselton et al. 1992; Lemus et a. 2011; Proulx 2011; <b>Ruder et al. 2011</b> ; Sanchez-Barbudo et al. 2012; Sarabia et al. 2008; <b>Vyas et al. 2012</b>
<b>Reptiles/Amphibians</b>	Sanchez-Barbudo et al. 2012 [no useful information]
<b>Terrestrial Invertebrates</b>	Havelka and Bartova 1992 [Czech. marginal]
<b>Aquatic Species</b>	No open literature identified to date
<b>Environmental Fate</b>	Chan et al. 2009 (pKa); Andre et al. 2005 (soil binding)

<sup>[1]</sup> Full bibliographic citations are given in Section 5. More significant studies given in bold print.

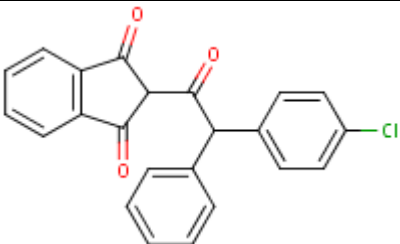
<sup>[2]</sup> Some of the more relevant MRID studies included.

Appendix 1: Toxicity to Mammals (*continued*)

See Section 1.1. for discussion.

Appendix 1: Toxicity to Mammals (*continued*)

**Table 3: Physical and chemical properties of chlorophacinone**

Item	Value	Reference <sup>[1]</sup>								
<b>Identifiers</b>										
Common name:	Chlorophacinone									
CAS Name	2-[(4-chlorophenyl)phenylacetyl]-1H-indene-1,3(2H)-dione	Tomlin 2004								
IUPAC Name	2-[2-(4-chlorophenyl)-2-phenylacetyl]indan-1,3-dione	Tomlin 2004								
CAS No.	3691-35-8	ChemIDplus 2014; Tomlin 2004								
Chemical Group	indandione	U.S. EPA/OPP/EFED 2011a								
Formulations, partial list	Actosin C; Afnor; Baraage; DRAT; Lepit; Microzul; Ratomet; Razol; <b>Rozol</b> <sup>[2]</sup> ; Saviac; Topitox	ChemIDplus 2014								
Development Codes	LM 91 (Lipha)	Tomlin 2004								
Molecular formula	C <sub>23</sub> H <sub>15</sub> ClO <sub>3</sub>	Tomlin 2004								
EPA PC Code	067707	U.S. EPA/OPP/EFED 2011a								
Mode of Action	Anticoagulant; uncouples oxidative phosphorylation	U.S. EPA/OPP/EFED 2011a								
Smiles Code	<chem>C(c1ccc(cc1)Cl)(C(=O)C1C(=O)c2c(C1=O)cccc2)c1ccccc1</chem>	ChemIDplus 2014								
	<chem>c1ccccc1C(c2ccc(Cl)cc2)C(=O)C3C(=O)c4ccccc4C3(=O)</chem>	EpiSuite 2011								
Structure		ChemIDplus 2014								
<b>Chemical Properties<sup>(1)</sup></b>										
Appearance	Pale yellow crystals	Tomlin 2004								
	Yellow microcrystalline powder	U.S. EPA/OPP 1998a, p. 9								
Aqueous photolysis	Half-life: 37 minutes at pH 7	U.S. EPA/OPP 1998a, p. 74								
Henry's Law Constant	5.12 x 10 <sup>-7</sup> atm·m <sup>3</sup> mol <sup>-1</sup> (calculated)	U.S. EPA/OPP/EFED 2011a								
	5.2 x 10 <sup>-8</sup> atm·m <sup>3</sup> mol <sup>-1</sup>	U.S. EPA/OPP 1998a, p. 74								
Hydrolysis (abiotic)	<table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th>pH</th> <th>Hydrolysis Half-life</th> </tr> </thead> <tbody> <tr> <td>5</td> <td>232 days</td> </tr> <tr> <td>7</td> <td>Stable</td> </tr> <tr> <td>9</td> <td>Stable</td> </tr> </tbody> </table>	pH	Hydrolysis Half-life	5	232 days	7	Stable	9	Stable	U.S. EPA/OPP/EFED 2011a, MRID 42205501
pH	Hydrolysis Half-life									
5	232 days									
7	Stable									
9	Stable									
	Stable	U.S. EPA/OPP 1998a, p. 74								

Appendix 1: Toxicity to Mammals (continued)

Item	Value	Reference <sup>[1]</sup>
K <sub>ow</sub>	≈316,000 [Log K <sub>ow</sub> = 5.50] (QSAR estimate)	EPI Suite 2011
	94.5	U.S. EPA/OPP/EFED 2011a, MRID 42237401, Table 2.1
	94	U.S. EPA/OPP 1998a, p. 74
	97	U.S. EPA/OPP/EFED 2011a, MRID 42237401, p. 56.
Melting point	140°C	Tomlin 2004
	141 – 145°C	U.S. EPA/OPP 1998a, p. 9
Molecular weight	374.8	Tomlin 2004
	374.83	EPI Suite 2011
	374.8215	ChemIDplus 2014
pKa	3.4 (25 °C)	Tomlin 2004
	3.67 (25±1 °C)	Chan et al. 2009
Bulk density	0.38 g/cm <sup>3</sup> (20 °C)	Tomlin 2004
	0.56 g/ cm <sup>3</sup>	U.S. EPA/OPP 1998a, p. 9
Vapor pressure	1x10 <sup>-4</sup> mPa (25 °C)	Tomlin 2004
	3.58 x 10 <sup>-6</sup> torr [≈4.8x10 <sup>-1</sup> ]	U.S. EPA/OPP/EFED 2011a, MRID 42237401
Water solubility	100 mg/l (20 °C)	Tomlin 2004
	3.43 mg/L @ 25°C	U.S. EPA/OPP/EFED 2011a, MRID 42237401
	34 mg/L @ 25°C [This appears to be typographical error.]	U.S. EPA/OPP 1998a, p. 74
<b>Environmental Properties</b>		
Aerobic aquatic metabolism half-life	74 days [2 x aerobic soil metabolism used in absence of data]	U.S. EPA/OPP/EFED 2011a, p. 56
Bioconcentration Factor (BCF, L/kg)	BCF = 510.9 L/kg wet-wt [Estimate based on an estimated log Kow of 5.5 (≈316,000)]	EPI Suite 2011
	2.408 Note: Based on EPI Suite algorithm using an experimental Kow of 97.	U.S. EPA/OPP/EFED 2011a, p. 56.
	Not expected to be significant.	U.S. EPA/OPP 1998a, p. 74
K <sub>ads</sub>	341	U.S. EPA/OPP/EFED 2008a, Table 1, p. 9, MRID 42666001
K <sub>oc</sub> (L/kg)	20,299	U.S. EPA/OPP/EFED 2011a, MRID 42666001 and MRID 42205503



Appendix 1: Toxicity to Mammals (*continued*)

Item	Value	Reference <sup>[1]</sup>
	43,411, average of 4 soils.	U.S. EPA/OPP/EFED 2008a, Table 1, p. 9, MRID 42666001
	15,556-135,976	Tomlin 2004
Soil half-life, aerobic	47.2 days (sandy clay loam) 17 days (sandy loam)	U.S. EPA/OPP/EFED 2011a, MRID 43159801
	32.1 days (average of above values)	U.S. EPA/OPP/EFED 2011a, p. 19
	37 days [upper bound of the above values used for GENECC modeling by EPA]	U.S. EPA/OPP/EFED 2011a, p. 56
Photolysis, soil, half-life	4 days	U.S. EPA/OPP 1998a, p. 74
Photolysis, water, half-life	37 minutes	U.S. EPA/OPP 1998a, p. 74
Sediment half-life	36.1 hours (1.5 days)	EPI Suite 2011

<sup>[1]</sup> There are many sources for basic information on chemical identity and physical properties. Multiple citations for these values are avoided. Substantial differences in some reported values are discussed in the text as appropriate.

<sup>[2]</sup> Rozol Prairie Dog Bait (EPA Reg. No. 7173-286) is the only formulation explicitly covered in the current Forest Service risk assessment.

See Section 2.2 for discussion.

Appendix 1: Toxicity to Mammals (continued)

Table 4: Worker Exposure Rates Used in EPA Risk Assessments

Scenario	No clothing <sup>[1]</sup>	Single Layer, No gloves <sup>[1]</sup>	Single layer, Gloves <sup>[1]</sup>	Inhalation <sup>[1]</sup>
1. Dry flowable, open mixing and loading	1.1	0.066	0.066	0.00077
2. Granular, open mixing and loading	0.032	0.0084	0.0069	0.0017
3. All liquids, open mixing and loading	3.1	2.9	0.023	0.0012
4. Wettable powder, open mixing and loading	6.7	3.7	0.17	0.04342
5. Wettable powder, water soluble bags	0.039	0.021	0.0098	0.00024
6. All liquids, closed mixing and loading			0.0086	0.000083
7. Aerial-fixed wing, enclosed cockpit/liquid <sup>[2]</sup>	0.0050	0.0050	0.0022	0.000068
8. Aerial-fixed wing, enclosed cockpit/granular	0.0044	0.0017	0.0017	0.0013
9. Helicopter application, enclosed cockpit		0.0019	0.0019	0.0000018
10. Aerosol application	480	190	81	1.3
11. Airblast application, open cockpit	2.2	0.36	0.24	0.0045
12. Airblast application, enclosed cockpit			0.019	0.00045
13. Groundboom applications, open cab <sup>[2]</sup>	0.046	0.014	0.014	0.00074
14. Groundboom applications, enclosed cab	0.010	0.0050	0.0051	0.000043
15. Solid broadcast spreader, open cab, AG	0.039	0.0099		0.0012
16. Solid broadcast spreader, enclosed cab, AG	0.0021	0.0021	0.0020	0.00022
<b>17. Granular bait dispersed by hand</b>			<b>71</b>	<b>0.47</b>
18. Low pressure handwand	25	12	7.1	0.94
19. High pressure handwand	13	1.8	0.64	0.079
20. Backpack applications	680			0.33
21. Hand gun (lawn) sprayer			0.34	0.0014
22. Paintbrush applications	260	180		0.280
23. Airless sprayer (exterior house stain)	110	38		0.830
24. Right-of-way sprayer	1.9	1.3	0.39	0.0039
25. Flagger/Liquid	0.053	0.011	0.012	0.00035
26. Flagger/Granular	0.0050			0.00015
27. WP or liquid/open pour/airblast/open cab	26			0.021
28. WP or liquid/open pour/airblast/closed cab	0.88	0.37	0.057	0.0013
29. Liquid or DF /open pour/ground boom/closed cab	0.22	0.089	0.029	0.00035
30. Granule/open pour/belly grinder	210	10	9.3	0.062
31. Push type granular spreader		2.9		0.0063
32. Liquid/open pour/low pressure handwand	110	100	0.43	0.030
33. WP/open pour/low pressure handwand			8.6	1.1
34. Liquid/open pour/backpack			2.5	0.03
35. Liquid/open pour/high pressure handwand			2.5	0.12
36. Liquid/open pour/garden hose end sprayer	34			0.0095
37. Liquid/open pour/termiticide injection			0.36	0.0022

<sup>[1]</sup> All rates are in units of mg/lb a.i. handled.

<sup>[2]</sup> The entry bold is discussed in the risk assessment.

Source: Keigwin 1988  
See Section 3.2.2.1 for discussion.

Appendix 1: Toxicity to Mammals (*continued*)

**Table 5: Chemical parameters used in Gleams-Driver modeling**

Parameter	Values	Note/Reference
Halftimes (days)		
Aquatic Sediment	1.5	EPI Suite 2011
Foliar	N/A	1
Soil	32.1 (17-47.2)	2
Water	64 (34-94)	3
Soil $K_{oc}$ , mL/g	20,299	4
Sediment $K_d$ , mL/g	426 (clay); 325 (loam); 142 (sand)	5
Water Solubility, mg/L	3.43	6
Foliar wash-off fraction	N/A	7
Fraction applied to foliage	0.0	8
Depth of Soil Incorporation	10 cm	8
Irrigation after application	none	Section 2
Initial Application Date	<b>Oct. 1</b>	Label

**Notes**

Number	Text
1	Foliar half-life is a required parameter in GLEAMS. A value 1 is used in modelling but this has no impact on the modeling because the fraction applied to foliage is taken as 0.
2	U.S. EPA/OPP/EFED 2011a, MRID 43159801. See Table 3 for details.
3	In the absence of data, used 2x soil half-lives per GENECC guidance (U.S. EPA/OPP/EFED 2011a, p. 56).
4	U.S. EPA/OPP/EFED 2011a, MRID 42666001 and MRID 42205503.
5	Based on organic matter values of 3.7% (clay), 2.9% (loam) and 1.2% (sand) and the relationship $OC = OM \div 1.724$ . $K_d$ calculated as $K_{oc} \times$ proportion of organic carbon – i.e., 0.021 (clay), 0.016 (loam), 0.0070 (sand).
6	U.S. EPA/OPP/EFED 2011a, MRID 42237401.
7	Foliar wash-off fraction is a required parameter in GLEAMS. A value 0.5 is used in modelling but this has no impact on the modeling because the fraction applied to foliage is taken as 0.
8	For subsurface burrow applications, it is reasonable to assume that no bait is applied to vegetation.
9	Use 10 cm (about 4 inches) per U.S. EPA/OPP/EFED 2008a, p. 8 rather than 6 inches assuming ... <i>that some of the bait would be moved up to the surface through bioturbation,</i>

Appendix 1: Toxicity to Mammals (*continued*)

**Table 6: Summary of Modeled Concentrations in Surface Water**

Scenario/Source	Peak Concentrations (ppb or $\mu\text{g/L}$ per lb/acre)	Long-Term Average Concentrations (ppb or $\mu\text{g/L}$ per lb/acre)
<b>Pond, Accidental Spill</b> (Section 3.2.3.4.1)	0.68 (0.045 – 0.91)	N/A
<b>Single Application (Appendix 3)</b>		
Pond, Section 3.2.3.4.4	0.287 (0.05 - 1.27) [Clay] 0.194 (0 - 1.4) [Loam] 0.0003 (0 - 0.23) [Sand]	0.0112 (0.0006 - 0.05) [Clay] 0.0054 (0 - 0.04) [Loam] 3.30E-06 (0 - 0.0029) [Sand]
Stream, Section 3.2.3.4.4	1.66 (0.18 - 14.4) [Clay] 1.24 (0 - 13.7) [Loam] 0.00211 (0 - 2.23) [Sand]	0.05 (0.0017 - 0.28) [Clay] 0.0222 (0 - 0.18) [Loam] 1.33E-05 (0 - 0.01) [Sand]
<b>EPA Tier 1 Models</b>		
GENEEC	1.44	
<b>EPA PRZM Tier 2<sup>[a]</sup></b>	No modeling located	No modeling located

<sup>[a]</sup> From U.S. EPA/OPP/EFED 2008a, p. 8. Peak concentration of 0.0009  $\mu\text{g/L}$  at an application rate of 0.000625 lb a.i./acre. Corresponds to a WRC value of 1.44  $\mu\text{g/L}$  per lb a.i./acre

Appendix 1: Toxicity to Mammals (*continued*)

**Table 7: Concentration rates in surface water used in this risk assessment**

<b>Below Ground Baiting</b>	<b>Peak WCR<sup>[1]</sup></b>	<b>Longer-term WCR<sup>[1]</sup></b>
Central	0.002	0.00005
Lower	0.0002	0.000002
Upper	0.01	0.0003

<sup>[1]</sup> WCR (Water contamination rates) – concentrations in units of mg a.i./L expected at an application rate of 1 lb a.i./acre. Units of mg a.i./L are used in the EXCEL workbook that accompanies this risk assessment. Specific values are based on concentrations in a small stream in an area with predominantly clay soil texture as summarized in Table 6.

See Section 3.2.3.4.6 for discussion

Appendix 1: Toxicity to Mammals (*continued*)

**Table 8: Summary of toxicity values used in human health risk assessment**

**Acute – single exposure**

<b>Element</b>	<b>Derivation of RfD</b>
WHO Document	WHO 1995, p. 39. See also Watt et al. 2005, Table III, p. 265
Study	Unpublished report.
NOAEL Dose	N/A
LOAEL Dose	0.29 mg/kg bw (20 mg dose ÷ 70 kg bw ≈ 0.2857 mg/kg bw)
LOAEL Endpoint(s)	Transient decrease in prothrombin concentrations.
Species, sex	Human volunteers
Uncertainty Factor/MOE	With human data, an UF of 100 would typically be used, 10 for sensitive individuals and 10 for LOAEL-to-NOAEL
Surrogate RfD	0.003 mg/kg bw/day

**Longer-term subchronic exposure**

<b>Element</b>	<b>Derivation of RfD</b>
EPA Document	U.S. EPA/OPP 1998a; U.S. EPA/OPP/EFED 2011a, Appendix E
Study	MRID 92018013, Subchronic Study in Rats (77 days)
NOAEL Dose	0.005 mg/kg bw/day
LOAEL Dose	0.010 mg/kg bw/day
LOAEL Endpoint(s)	Increased coagulation times
Species, sex	Rats, M/F
Uncertainty Factor/MOE	Typically 100 but not specified in EPA documents.
Surrogate RfD	0.00005 mg/kg bw/day

No chronic data are available.

See Section 3.3 for discussion

**Table 9: Terrestrial Ecological Receptors Considered in Assessment**

<b>Receptor</b>	<b>Body Weight (kg)</b>	<b>Comment</b>
<b>Primary Exposure Scenarios (Consumption of Bait)</b>		
Deer	70	Used only in accidental primary exposure scenario.
Grizzly bear	100	Used only for foraging on pocket gopher food caches.
Mallard	1	Representative of relatively small sensitive waterfowl.
Mouse	0.02	Representative of small fossorial mammal.
Pigeon	0.35	Representative of tolerant Columbiformes.
Black-tailed prairie dog	1.0	Used only in accidental exposure scenario to calibrate field intake rates for primary exposures. See Section 4.2.2. for discussion.
Skunk	2.0	Large fossorial which may forage for gopher bait.
Quail	0.2	Representative of tolerant Galliformes.
Raptor	4	Representative of larger predatory bird. Used only in water consumption scenarios as a standard Forest Service receptor.
House sparrow	0.02	Representative of small sensitive passerine.
Squirrel	0.15	Representative of a larger fossorial mammal.
<b>Secondary Exposure Scenarios (Consumption of Prey)</b>		
Coyote	13	Consumption of part of a 1 kg black-tailed prairie dog
Badger	7	Consumption of part of a 1 kg black-tailed prairie dog
Mink	1	Consumption of part of a 1 kg black-tailed prairie dog
Owl (Great horned)	1.5	Consumption of part of a 1 kg black-tailed prairie dog
Rattle snake	0.5	Consumption of all of a 1 kg black-tailed prairie dog
Eagle	N/A	Consumption of fish by a raptor. See Section 4.2.4.
<b>Tertiary Exposure Scenarios (Consumption of Insects)</b>		
Small mammal	0.02	Generic and standard Forest Service receptor.
Small bird	0.01	Generic and standard Forest Service receptor.
Bullfrog, young	0.02	Consumption of contaminated insects
<b>Surface Water Exposure Scenarios</b>		
Canid	5	Generic and standard Forest Service receptor.
Large Mammal	70	Generic and standard Forest Service receptor.
Large Bird	4	Standard Forest Service receptor is a Canada goose. For chlorophacinone, a raptor is used as a more at-risk class of birds.
Small Mammal	0.02	Generic and standard Forest Service receptor.
Small Bird	0.01	Generic and standard Forest Service receptor. Toxicity value for the more sensitive passerines is used in risk characterization.

See Section 4.2.1 for discussion.

Appendix 1: Toxicity to Mammals (*continued*)

**Table 10: Summary of toxicity values used in ecological risk assessment**

Group/Duration	Organism	Endpoint	Toxicity Value (a.i.)	Reference
<b>Terrestrial Animals</b>				
<b>Acute</b>				
	Mammals (including canids)	LOAEL ÷ 10	0.03 mg/kg bw	Section 4.3.2.1.
	Birds	LOAEL ÷ 10	0.6 mg/kg bw	Section 4.3.2.2
<b>Longer-term</b>				
	Mammals	NOAEL (reproduction)	0.005 mg/kg bw/day	Section 4.3.2.1
	Bird	NOAEL (reproduction)	0.07 mg/kg bw/day	Section 4.3.2.2.
<b>Aquatic Animals</b>				
<b>Acute</b>				
Fish	Sensitive	NOAEC, trout	0.12 mg/L	Section 4.3.3.1
	Tolerant	NOAEC, bluegills	0.36 mg/L	
Invertebrates	Sensitive	No data	N/A	Section 4.3.3.3
	Tolerant	<i>Daphnia magna</i> , static	0.28 mg/L	
<b>Longer-term</b>				
Fish	Sensitive	No data	N/A	Section 4.3.3.1
	Tolerant	No data	N/A	
Invertebrates	Sensitive	No data	N/A	Section 4.3.3.3
	Tolerant	No data	N/A	
<b>Aquatic Plants</b>				
Algae	Sensitive	No data	N/A	Section 4.3.3.4
	Tolerant	No data	N/A	Section 4.3.3.4
Macrophytes	Sensitive	No data	N/A	Section 4.3.3.4
	Tolerant	No data	N/A	Section 4.3.3.4

See Section 4.3.3 for discussion.



Appendix 1: Toxicity to Mammals (*continued*)

**Table 11: Assessment of EPA Extrapolation for Mammals**

<b>Species</b>	<b>Body Weight (g)<sup>[1]</sup></b>	<b>Estimated LD50 (mg/kg bw)<sup>[2]</sup></b>	<b>Available Experimental Information</b>
Prairie dog	1,000	0.06	LD <sub>50</sub> of 1.8 mg/kg bw from Yoder (2008).
Meadow voles	23	0.15	LD <sub>50</sub> of 2.5 mg/kg bw from Byers et al. (1978).
Pine voles	46	0.13	LD <sub>50</sub> s of 14-17 mg/kg bw from Byers et al. (1978).
Norway rat	350	0.078	LD <sub>50</sub> of 1.14 mg/kg bw from Teeters (1981).
Sheep	65,500 <sup>[3]</sup>	0.021	A dose of 1 mg/kg bw causes an increase in prothrombin time but no overt signs of toxicity (Teeters 1981).
Humans	70,000 <sup>[4]</sup>	0.021	A dose of 0.29 mg/kg bw causes only a transient decrease in prothrombin concentrations (Watt et al. 2005).

<sup>[1]</sup> Mammalian body weights taken as average of the range of values for the species from Reid (2006) unless otherwise specified.

<sup>[2]</sup> Based on allometric relationship discussed in Section 4.3.2.1 of the current risk assessment and detailed in U.S. EPA/OPP/EFED (2010a, Section 5.1.2, Table 5.2, p. 82).

<sup>[3]</sup> Average body weight of sheep given in Teeters (1981).

<sup>[4]</sup> Standard value from SERA (2014a), adopted from ICRP (1975).

See Section 4.3.2.1 for discussion.

Initial Area of Concern for use of Rozol Prairie Dog Bait



Figure 1: Range of Black-tailed Prairie Dog

Source: U.S. EPA/OPP/EFED 2010a

**Appendix 1: Toxicity to mammals.**

**Note on Appendix 1:** This appendix consists of a series of tables, listed below covering information on the toxicity to mammals.

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**Working Note: Summaries of MRID studies taken from U.S. EPA/OPP 1998a unless otherwise specified. MRID studies specifying authors based on DERs.**

**A1 Table 1: Gavage Acute Oral Toxicity**

<b>Species</b>	<b>Exposure</b>	<b>Response</b>	<b>Reference</b>
Rats, Sprague-Dawley	TGAI 99.36% by gavage in polyethylene glycol 300 at doses of 2, 3.2, 5.2, 8.2, 13.2, and 21 mg/kg bw with a 14-day observation period.	LD <sub>50</sub> : Males: 3.15 (1.48-6.68) mg/kg LD <sub>50</sub> : Females: 10.95(6.46-18.57) mg/kg LD <sub>50</sub> : Combined: 6.26 mg/kg  Symptoms consistent with internal hemorrhage. Death at 4-13 days after dosing.  Working Note: Males more sensitive by a factor of about 3. 95% confidence limits barely overlap.  Toxicity Category I.	MRID 41875301 from U.S. EPA/OPP 1998a  Acceptable  Very highly toxic
Rats (NOS)	Technical material (NOS)	LD <sub>50</sub> : 20.5 mg/kg bw  Working Note: The original source of this LD <sub>50</sub> has not been identified.	WHO 1985, 1995; HSDB 2004; and Vandembroucke et al. 2008 citing secondary sources
Rats, grass ( <i>Arvicanthis niloticus</i> ), 2 per dose	Chlorophacinone, 0.28% concentrate in mineral oil form "commercial source".  3 daily doses of 0.7, 1.4, or 2.8 mg/kg bw.	All rats died. Mean time to death of 4 days (2 lower doses) and 2 days (high dose).	Brooks et al. 1993

Species	Exposure	Response	Reference
Rats, Norway ( <i>Rattus norvegicus</i> ) and Sprague-Dawley 40 Norway and 40 Sprague-Dawley rats. 10 per dose	Technical material (NOS), 5-day repeated gavage dosing in propylene glycol.	Sprague-Dawley Male: 0.18 mg/kg bw/day Female: 0.20 mg/kg bw/day Both sexes: 0.19 mg/kg bw/day Norway (Wild) Male: 0.13 mg/kg bw/day Female: 0.23 mg/kg bw/day Both sexes: 0.16 mg/kg bw/day  Above from Table 4 of paper.	Ashton, et al. 1986
Rats, Norway ( <i>Rattus norvegicus</i> ) and Sprague-Dawley	Technical material (NOS), 5-day repeated gavage dosing.	U.S. EPA/OPP/ EFED 2011a 5-day LD <sub>50</sub> = 0.15 mg a.i./kg bw/day. Cumulative LD <sub>50</sub> : 0.8 mg/kg bw The above appears to be combined values of S-D and Norway rats.	Ashton, et al. 1986 summarized in U.S. EPA/OPP/ EFED 2011a and WHO 1995
Black-tailed prairie dog ( <i>Cynomys ludovicianus</i> ), wild caught, 5 M and 5 F per dose	Chlorophacinone (Rozal 99.4% a.i.) in propylene glycol. Nominal doses of 0, 0.253, 0.6867, 1.127, 1.56 and 2 mg/kg bw. 22 day observation period.	DER LD <sub>50</sub> : 1.8 (1.35-5.29) mg/kg bw  U.S. EPA/OPP/EFED 2012a reports LD <sub>50</sub> of 1.94 mg/kg bw with a slope of 3.45. <b>This LD<sub>50</sub> is used for risk characterization.</b>  Deaths occurred between Day 9 and Day 17 after dosing. <b>No deaths at the three lower doses.</b>  Body weight loss in all groups, including controls. External bleeding and blood in feces noted in some fatally exposed animals and survivors.	Yoder 2008, MRID 47333601  Supplemental  Very Highly Toxic
Rabbit, New Zealand	Technical material (NOS)	Doses of 6-10 mg/kg bw associated with 20-100% mortality. Very few experimental details.	Giban 1974 <sup>[1]</sup>
Rabbit (NOS)	Technical material (NOS)	LD <sub>50</sub> : 50.0 mg/kg bw	WHO 1985; HSDB 2003

Species	Exposure	Response	Reference
Sheep, adult, Texel, n=3m 63-68 kg	Chlorophacinone (NOS), 1 mg/kg bw by gavage in ethanol/dimethyl sulfoxide.  Sheep were also assayed with warfarin and bromadiolone with 2 month recovery times between exposures.	Transient increase in prothrombin time up to a maximum of about 50 seconds (relative to a pretreatment time of about 15 seconds). Prothrombin time peaked at about 140 hours (about 6 days) and returned to near normal values by about 360 hours (15 days).  No signs of frank toxicity but prolonged bleeding at venipuncture sites.	Berny et al. 2006
Mice ( <i>Mus musculus</i> ) 4 doses (NOS), 10/dose	Technical material (NOS), 5-day repeated gavage dosing.	LD <sub>50</sub> values Male: 0.38 (0.16-0.91) mg/kg bw/day Female: 3.48 (1.76-6.87) mg/kg bw/day Both: 1.19 mg (0.52-2.70) a.i./kg bw/day	Ashton et al. 1987  Also summaries in U.S. EPA/OPP/EFED 2011a.
Meadow voles ( <i>Microtus pennsylvanicus</i> )	Single dose (NOS)	LD <sub>50</sub> : 2.5 mg/kg bw	Byers and Carbaugh 1989
Pine voles ( <i>Microtus pinetorum</i> )	Single dose (NOS)	LD <sub>50</sub> : 17.3 mg/kg bw	Byers et al. 1978
Pine voles ( <i>Microtus pinetorum</i> )	Single dose (NOS)	LD <sub>50</sub> : 14.2 mg/kg bw	Byers and Carbaugh 1989

<sup>[1]</sup> Whether this was gavage or feeding is not clear. Very few experimental details.

**A1 Table 2: Dietary Acute Oral Toxicity**

Species	Exposure	Response	Reference
<b>Standard Studies</b>			
Rats, male, 10 per dose in 2 groups of 5 animals. 1 group with and the other without Vitamin K <sub>1</sub> at 24-hours after exposure.	Pelleted EUP, 0.005% chlorophacinone as sole diet for 24, 48, or 72 hours.	Mean doses of 5.28, 4.73 and 5.03 mg chlorophacinone/day. Note: The doses are expressed as mg and not mg/kg. All rats with Vitamin K <sub>1</sub> treatment survived for 24 hours. Mortalities of 3/5 in the 48 hour group and 5/5 in the 72 hours group with Vitamin K <sub>1</sub> treatment. All rats in all groups not receiving Vitamin K <sub>1</sub> treatment died.	MRID 41981101 from U.S. EPA/OPP 1998a  This study is not cited in U.S. EPA/OPP/EFED 2008a, 2010a, 2011a
Rats, Norway, wild-caught, 10 M/10 F	Actosin C (0.006% a.i., 60 mg/kg bait). Bait consumption Males : 20.8 g/kg Females: 24 g/kg Calculated doses: Males: 1.24 mg/kg Females: 1.44 mg/kg	All animals died Time to death: Males: 14 days Females: 10 days.	El Bahrawy and Morsy 1990

Species	Exposure	Response	Reference
Rats, Norway, wild-caught, 10 M/10 F	Actosin L (0.019% a.i., 190 mg/kg bait) for two weeks. Bait consumption Males : 6.26 g/kg Females: 16.7 g/kg	Calculated doses: Males: 1.14 mg/kg Females: 3.173 mg/kg All animals died  Time to death: Males: 5 days Females: 3 days.	El Bahrawy and Morsy 1990
Rats, Norway	Chlorophacinone (NOS), 5 day dietary exposure	LC <sub>50</sub> = 1.14 mg a.i./kg-diet Slope = 7.19	Teeters 1981, unpublished from U.S. EPA/OPP/EFED 2011a, p. 68
Rats, laboratory and wild strains	Chlorophacinone at 50 mg/kg bait for 14 days.	Based on bait consumption (0.06 to 0.08 kg bait/kg bw), the estimated doses were 3 to 4 mg/kg bw. Increase in prothrombin times from Day 4 onward. Some animals euthanized (no details of signs of toxicity provided).	Vein et al. 2013
<b>Wildlife Efficacy</b>			
Black-tailed prairie dog ( <i>Cynomys ludovicianus</i> ), 8 per concentration	TGIA in food at concentrations of 0.0025%, 0.005%, and 0.01% (25 mg/kg, 50 mg/kg, and 100 mg/kg). 25 g food/day for six days. Doses: 0.625 mg, 1.25, 2.5 based on food consumption.. Observed for 21 days.	Assuming an average adult body weight of 0.9 to 1.4 kg [1.15 kg] (Hygnstrom and Virchow 1994), doses correspond to doses of about 0.5, 1.1, and 2.2 mg/kg bw. All animals died.	Fisher and Timm 1987
Black-tailed prairie dog ( <i>Cynomys ludovicianus</i> ), 23	As above but using only 0.0025% bait. Working Note: These animals used in secondary poisoning study of domestic ferrets (see below).	21/23 died after consuming 1.3 to 5.5 mg/kg bw. 2 survivors. One had consumed only 0.4 mg/kg bw. The other consumed an amount in the upper range of fatally exposed animals.	Fisher and Timm 1987
Gerbil ( <i>Tatera indica</i> ), wild caught	0.0075% commercial formulation (NOS) and 0.1% custom formulation in millet grain. Dietary exposure for 1 to 7 days with groups of 10 to 12 animals.	Lethal to all animals with mean time to deaths of 6.6-8.5 days at cumulative doses of 11.3 to 14.8 mg/kg bw. NOAEC (mortality): 4.3 mg/kg bw for one day.	Methur and Prakash 1982
Gerbil ( <i>Meriones hurrianae</i> ), wild caught	0.0075% commercial formulation (NOS) and 0.1% custom formulation in millet grain. Dietary exposure for 1 to 7 days with groups of 10 to 12 animals.	Lethal to all animals with mean time to deaths of 7.5-1.9 day at cumulative doses of 16.9-26.5 mg/kg bw. NOAEC (mortality): Not determined.	Methur and Prakash 1982

Species	Exposure	Response	Reference																																				
Mice, <i>Mus musculus</i> , 10 M and 10 F per group.	Dietary concentration of 0.025% for periods of 1 to 21 days. Individually caged mice with records of bait consumption. Survivors feed uncontaminated bait for 14 days after exposure to chlorophacinone was terminated.	Mortality of 60% (1-day of exposure) to 95% (10 and 21 days of exposure). A general decrease in doses (expressed as mg/kg bw/day) with increasing durations of exposure.  See Supplemental Table below.	Lund 1971																																				
Mice ( <i>Mus musculus</i> var. <i>albus</i> ). Number test not clear.	Chlorophacinone (Caid formulation 0.005% a.i. or 50 mg/kg bait). Mixed with other bait ingredients.	Lethal to mice in 6.8 days (at 44.5 ppm) and 7.2 days (at 25 ppm). Based on Table 5 of paper, estimated doses are 29 mg/kg bw (44.5 ppm) and 20.6 mg/kg bw (25 ppm). Lethal to all mice.	Mesban et al. 2003																																				
Deer mouse ( <i>Peromyscus maniculatus</i> )	Acute dietary (2% a.i.) over 3 days period.  This is a survey study with few details for chlorophacinone.  Note: The concentration used in this study is 400 times more concentrated than Rozol [0.005%].	Approximate lethal dose: 1-3.75 mg/kg bw. 40% decrease in food consumption over 3-day feeding period using 2.0% treated wheat seeds. 4.69% decrease in food consumption over 3-day feeding period using 2.0% treated Douglas fir seeds.	Schafer and Bowles 1985																																				
Deer mouse ( <i>Peromyscus maniculatus</i> ), 5 male and 5 female per group	<b>2 days</b> Chlorophacinone in oat groat baits at concentrations of 0.00125, 0.0025, 0.005, and 0.01, and 0.02% [12.5, 25, 50, 100, and 200 mg/kg] with or without supplemental food.	With supplemental food <table border="1"> <thead> <tr> <th>mg a.i./ kg chow</th> <th>Mortality (%)</th> <th>Average days to death</th> </tr> </thead> <tbody> <tr> <td>12.5</td> <td>30</td> <td>6.3</td> </tr> <tr> <td>25</td> <td>30</td> <td>5.0</td> </tr> <tr> <td>50</td> <td>50</td> <td>5.6</td> </tr> <tr> <td>100</td> <td>60</td> <td>5.0</td> </tr> <tr> <td>200</td> <td>100</td> <td>5.6</td> </tr> </tbody> </table> Without supplemental food <table border="1"> <thead> <tr> <th>mg a.i./ kg chow</th> <th>Mortality (%)</th> <th>Average days to death</th> </tr> </thead> <tbody> <tr> <td>12.5</td> <td>20</td> <td>4.0</td> </tr> <tr> <td>25</td> <td>60</td> <td>5.8</td> </tr> <tr> <td>50</td> <td>60</td> <td>5.3</td> </tr> <tr> <td>100</td> <td>50</td> <td>5.2</td> </tr> <tr> <td>200</td> <td>100</td> <td>6.0</td> </tr> </tbody> </table>	mg a.i./ kg chow	Mortality (%)	Average days to death	12.5	30	6.3	25	30	5.0	50	50	5.6	100	60	5.0	200	100	5.6	mg a.i./ kg chow	Mortality (%)	Average days to death	12.5	20	4.0	25	60	5.8	50	60	5.3	100	50	5.2	200	100	6.0	March et al. 1977
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Deer mouse ( <i>Peromyscus maniculatus</i> ), 5 male and 5 female per group	<b>4 days</b> Chlorophacinone in oat groat baits at concentrations of 0.00125, 0.0025, 0.005, and 0.01, and 0.02% [12.5, 25, 50, 100, and 200 mg/kg] with or without supplemental food.	With supplemental food <table border="1"> <thead> <tr> <th>mg a.i./ kg chow</th> <th>Mortality (%)</th> <th>Average days to death</th> </tr> </thead> <tbody> <tr> <td>12.5</td> <td>70</td> <td>6.1</td> </tr> <tr> <td>25</td> <td>90</td> <td>6.4</td> </tr> <tr> <td>50</td> <td>100</td> <td>5.7</td> </tr> <tr> <td>100</td> <td>100</td> <td>5.9</td> </tr> <tr> <td>200</td> <td>100</td> <td>5.4</td> </tr> </tbody> </table> Without supplemental food <table border="1"> <thead> <tr> <th>mg a.i./ kg chow</th> <th>Mortality (%)</th> <th>Average days to death</th> </tr> </thead> <tbody> <tr> <td>12.5</td> <td>60</td> <td>6.2</td> </tr> <tr> <td>25</td> <td>100</td> <td>6.1</td> </tr> <tr> <td>50</td> <td>90</td> <td>5.7</td> </tr> <tr> <td>100</td> <td>90</td> <td>6.2</td> </tr> <tr> <td>200</td> <td>100</td> <td>5.4</td> </tr> </tbody> </table>	mg a.i./ kg chow	Mortality (%)	Average days to death	12.5	70	6.1	25	90	6.4	50	100	5.7	100	100	5.9	200	100	5.4	mg a.i./ kg chow	Mortality (%)	Average days to death	12.5	60	6.2	25	100	6.1	50	90	5.7	100	90	6.2	200	100	5.4	March et al. 1977
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Natal multimammate mouse ( <i>Mastomys natalensis</i> )	0.005% chlorophacinone in millet and 2% peanut oil. No choice. 2, 3, or 4 days.	<table border="1"> <thead> <tr> <th>Days</th> <th>Mortality</th> <th>Weight (g)</th> </tr> </thead> <tbody> <tr> <td>2</td> <td>3/5</td> <td>44</td> </tr> <tr> <td>3</td> <td>4/4</td> <td>54</td> </tr> <tr> <td>4</td> <td>3/3</td> <td>52</td> </tr> </tbody> </table> Control animals (Day 10) had 0/5 mortality and 54g weight.	Days	Mortality	Weight (g)	2	3/5	44	3	4/4	54	4	3/3	52	Brooks et al. 1993																								
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Muskrats, <i>Ondatra zibethica</i>	Bait 0.005% a.i. (50 mg a.i./kg) in oats Length of test (presumably duration of exposure) given as 1-2 days.	Ingestion of 100 to 300 g (5-15 mg) resulted in nearly complete mortality. Time to death not clear.	Giban 1974																																				
Rats, Rice-field ( <i>Rattus argentiventer</i> ), 5 M and 5 F, individually caged	Chlorophacinone in a 0.01% bait (100 mg/kg bait), 2 days	Survivors: Consumed an average of 0.97 mg/kg bw Non-survivors: Consumed an average of 1.578 mg/kg bw and died from Day 7 to Day 16. (See Table 2 of paper).	Ngazizah et al. 1993																																				
Rat, Nile ( <i>Arvicanthis niloticus</i> ). 5 males and 5 females.	Chlorophacinone, 0.005% in whole meal flour. Apparently fed until end of experiment/death.	Lethal doses: Males: 35 – 79 mg a.i./kg bw Females: 21-43 mg a.i./kg bw Time to death: Males: 7.4 (5-11) days Females: 8.6 (5-15) days	Gill and Redfern 1977																																				
Squirrel, northern palm ( <i>Funambulus pennanti</i> )	Chlorophacinone bait, 0.0075% (75 mg a.i./kg chow) over periods of 1, 3, 5, or 7 days	Lethal doses ranged from 3.06 to 68 mg/kg bw Non-lethal doses ranged from 1 to 35.92 doses. <table border="1"> <thead> <tr> <th>Days</th> <th>Mortality</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>4/10</td> </tr> <tr> <td>3</td> <td>7/12</td> </tr> <tr> <td>5</td> <td>8/12</td> </tr> <tr> <td>7</td> <td>12/12</td> </tr> </tbody> </table> See Table 2 of paper for additional details. No control group.	Days	Mortality	1	4/10	3	7/12	5	8/12	7	12/12	Mathur and Prakash 1980																										
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Species	Exposure	Response	Reference
Vole, <i>Microtus arvalis</i>	0.0075% a.i. in chow. Ad libitum feeding for 1 days 3 days.	Mortality: 1 day: 318/459 (69%) 3 days: 279/289 (97%)	Giban 1974
Vole, <i>Microtus arvalis</i> , 1-4 months old, 5 M and 5 F	Chlorophacinone bait (75 mg/kg bait) for 5 days with a 14 day observation period. Ad libitum feeding.	All animals died. Death in 5-11 days for males and 5-8 days for females. Extensive hemorrhaging and tissue degeneration particularly in lungs, submaxillary (saliva) glands, and thymus. Fatty degeneration of liver. Pathology ( <i>dissolution of cross-striation</i> ) noted in some hearts (NOS) possibly secondary to hypoxia and anemia.	Nikodemusz et al. (1981)
Vole, meadow ( <i>Microtus pennsylvanicus</i> )	Whole oats treated with 0.02 % a.i. chlorophacinone. Ad libitum for 6 days (time to mortality)	Average consumption for voles was 1.14 mg prior to death.  Voles used in study on kestrels, see Appendix 2, Table A2-3.	Radvanyi et al. 1988
Vole, Pine vole ( <i>Microtus pinetorum</i> ), body weights not specified.	Rozol, 0.005% (50 mg a.i./kg bait) for 3 days. Animals observed for several days post dosing.	Mortality in all 10 voles by 5.3±0.8 days after exposure. Cumulative consumption of 11.3 g bait.	Byers 1978
Vole, Pine vole ( <i>Microtus pinetorum</i> ), body weights not specified.	Rozol, 0.005% (50 mg a.i./kg bait). Feeding for 3 days with observation period of 7 days.	Moist Chow: Average consumption of 8.17 g per animal caused mortality in 13/15 animals.  Dry Chow: Average consumption of 5.05 g per vole caused mortality in 14/15 animals.	Merson and Byers 1985
Vole, Pine vole (a.k.a. Pine mouse) ( <i>Microtus pitymys pinetorum</i> ), females	Dietary exposure (not detailed) to chlorophacinone (≥95% purity) Populations of endrin resistant and susceptible animals. Concentrations in chow included 5 and 10 mg/kg.	LD <sub>50</sub> : Susceptible: 3.58 (2.25-4.91) mg/kg bw Tolerant: 1.06 (0.15-1.95) mg/kg bw Time to death decreased with increasing concentrations in chow. Details not reported.	Hartgrove et al. 1973  [Cite in HSDB 2003 as a study in mice referenced to a secondary source.]
<b>Secondary Poisoning</b>			
Domestic ferret ( <i>Mustela putorius furo</i> ), 20	Dead rats poisoned with 0.005% a.i. chlorophacinone for 5 days. Residues in rats ranged from 0.18 to 0.8 mg/kg bw. 21 day post-exposure observation period.	Death in 11/20 ferrets with most deaths from Day 7 to Day 11. One death on Day 5 and one on Day 15.  No additional useful details. EPA reviewer cites limitations of study.	Ahmed et al. 1996; MRID 446314-01

<b>Species</b>	<b>Exposure</b>	<b>Response</b>	<b>Reference</b>
Domestic ferret ( <i>Mustela putorius</i> ), 3/sex with 1/sex as controls	Feed fatally exposed prairie dogs fed 0.0025% bait. One carcass every other day for a total of four carcasses. 30 day observation period.	5/6 ferret died with evidence of anti-coagulant toxicity. Estimates of consumed chlorophacinone not provided.	Fisher and Timm 1987
Mongoose, n=8	Fed rats that had been on a 0.005% a.i. bait diet for 5- days. 1 to 10 rats consumed over 5 day period. 20 day observation period.	7/8 died between 5 and 20 days.  Increased coagulation times.	MRID 2467 from U.S. EPA/ OPP/EFED 2011a, Table 4- 6.
Coyote, n=7	Fed ground squirrels for 5 days. The squirrels had in turn been fed 15 g of 0.01% bait for 6 days 30 day observation period.	3/7 died. Time to death not noted. Internal hemorrhaging.	MRID 42760902 from U.S. EPA/ OPP/EFED 2011a, Table 4- 6.

**Lund: Supplemental Table**

<b>Days</b>	<b>Mortality</b>	<b>Mean Days to Death</b>	<b>Mean Body Weight (g)</b>	<b>Fatal Dose, Lower Bound (mg/kg)</b>	<b>Fatal Dose, Upper Bound (mg/kg)</b>	<b>Fatal Dose, Lower Bound (mg/kg/day)</b>	<b>Fatal Dose, Upper Bound (mg/kg/day)</b>
1	60%	6.8	13.2	23	65	23.0	65.0
2	76%	5.9	19.5	47	101	23.5	50.5
3	70%	7.2	14.8	43	95	14.3	31.7
4	85%	7.8	16.3	109	266	27.3	66.5
5	85%	7.1	15.4	62	340	12.4	68.0
6	90%	6.9	18.4	67	325	11.2	54.2
10	95%	8.4	16.4	58	500	5.8	50.0
21	95%	12.4	12.5	125	1168	6.0	55.6

**A1 Table 3: Human Studies and Case Reports**

<b>Subject/Status/ Country</b>	<b>Exposure</b>	<b>Response</b>	<b>Reference</b>
<b>ORAL</b>			
33 year old male  Survived  France	15 year old female, 625 mg	Decrease in prothrombin time. General weakness and <i>inhalation pneumopathy</i> by hour 80. Chlorophacinone concentration in blood of 43 mg/L at 80 hours with half-life of 7.6 days.	Arditti et al. 1997 <sup>[1]</sup>
General review of poisoning episodes in France from 2004 to 2007.	No details on levels of exposure.	No reported mortalities. Chlorophacinone accounted for 21.4% (n=770x0.214≈165) of cases from 2004 to 2007.	Berny et al. 2010
20 year old female  Survived  France	250 mg chlorophacinone in attempted suicide.	<b>Took 7 days to become symptomatic.</b> Blood in urine. Prothrombin (CF II) deficiency. Survived with vitamin K <sub>1</sub> treatment and supportive therapy for 45 days.	Burucoa et al. 1989
60 year old female  Survived  France	Appears to involve suicide attempt. Dose uncertain.	Blood in urine. Prothrombin (CF II) deficiency and bleeding around mouth. Survived with vitamin K <sub>1</sub> treatment and supportive therapy over a 25 day period.	Burucoa et al. 1989
23 year old male  Survived  France	Apparent voluntary. Amount uncertain. Patient consumed chlorophacinone on two occasions.	Symptoms as above and requiring prolonged vitamin K <sub>1</sub> and supportive treatment for 74 days (after first incident) and 30 days after second incident). Patient survived.	Burucoa et al. 1989
Summary of 9 case reports  No fatalities  France	Doses of 250 to 1200 mg except in 2 patients for which no dose could be estimated.	Other than decreases in clotting times, some patients had no symptoms. Other patients evidenced blood in urine, hematomas, or bleeding in mouth from as early as Day 2 to as late as Day 21.	Chataigner et al. 1989 <sup>[1]</sup>
28 year old male  Survived  France	Amount consumed unknown.	Bleeding in mouth on Day 10.	Dusein et al. 1984 Abstract in French. Summarized in Papin et al. 2007.
1 case report from Spain, no details  <b>Fatal</b>  <b>Spain</b>	No information on exposure	No information on response.  Working Note: Included only because of fatality.	Garci-Repetto et al. 1998

Subject/Status/ Country	Exposure	Response	Reference
33 year old male  Survived  France	Dose of 1875 mg chlorophacinone.	Prothrombin index 96% at 8 hours. No initial decrease in clotting factors. At Day 3, decrease in K-dependent factors(LL, VII, IX and X). Discharged after 17 days with continued home treatment with Vitamin K <sub>1</sub> .	Lagrange et al. 1999
20 patients  France	Assays for chlorophacinone in serum. No details of exposures except for one patient who consumed 500 mg.	In patient consuming 500 mg, bleeding did not occur once serum concentrations were below 1 µg/mL.	Mura et al. 1992
37 year old female, multiple sclerosis patient  Survived  England	250 ml of 'Drat' (containing 0.25% chlorophacinone in paraffin. [2500 mg/L or 2.5 mg/mL] Estimate dose: 625 mg	Prolonged anticoagulant action (i.e., increased prothrombin index) requiring various treatments for up to 45 days. Patient survived.	Murdoch 1983
34-year old female  <b>Fatal</b>  France	Chlorophacinone in urine at 25.9 mg/L on Day 4 before death. After death, levels of 9.4 mg/L in blood, 6.8 mg/L in urine, 4.8 mg/L gastric contents. Total dose uncertain	Initial Symptom: blood in urine. Increased white blood cell count. Day 4: Convulsions and loss of consciousness and <b>death</b> . Low prothrombin time and low levels of clotting factors II, VII, IX, and X. Extensive internal bleeding on autopsy. Observations included ... <i>concentric myocardial hypertrophy</i> .	Papin et al. 2007
<b>Experimental</b>			
3 subjects of experiment. Sex of volunteers not reported.  Survived, no effects	Single oral dose of 20 mg. Body weights not reported. Observation period: 8 days. Based on a standard 70 kg bw, the dose would be 0.29 mg/kg bw.	Lowest prothrombin concentrations were 34-38% of pre-exposure values on Days 2-5 post-dosing. By Day 8, prothrombin concentrations were 80-100% of pre-exposure values with no treatment.	Watt et al. 2005, Table III, p. 265 WHO 1995, p. 39 <sup>[2]</sup>
<b>DERMAL, accidental</b>			
57 year old male  Survived  England	Dermal exposure to 'Drat' (containing 0.25% chlorophacinone in paraffin) [2500 mg/L or 2.5 mg/mL] Spill liquid on torso and arms. Immediately removed clothing and washed.	Symptoms developed after 7 days. Prothrombin time >200 sec. (normal 56 sec). Blood in urine Treated with vitamin K and other supportive care. Not fully recovered for about 2 weeks.	Binks and Davies 2007

<sup>[1]</sup> Summarized and translated from French in Papin et al. (2007).

<sup>[2]</sup> The reported in WHO is cited as an anonymous unpublished report. Watt et al. (2005) notes that the WHO report incorrectly states decreases in prothrombin times but that the decreases were actually in prothrombin concentrations.

While documentation for the correction is not given, the correction is sensible – i.e., an anticoagulant should not decrease prothrombin times but will decrease prothrombin concentrations.

**A1 Table 4: Subchronic and Chronic Toxicity Studies**

<b>Species</b>	<b>Exposure</b>	<b>Response</b>	<b>Reference</b>
<b>Subchronic</b>			
Rats, Sprague-Dawley, 10/sex/dose	Gavage doses of 0, 5, 10, 20 or 40µg/kg/day, 7 days/week. Lowest dose for 77 days and other doses for 113 days. Doses of 80 and 160 µg/kg bw/day for only 3 to 13 days due to mortality.	At 5 µg/kg, no mortality or signs of toxicity. Coagulation times not prolonged. At 10 µg/kg, 1 male and 1 female died due to intubation error. In survivors, an increase in coagulation times in males (28%) and females (6%). At 20 µg/kg, 4/10 males died at 105-111 day. No mortality in females. In survivors, an increase in coagulation times in males (100%) and females (11%). At 40 µg/kg all males died during Days 29-82 and 4/10 females died between Days 69-199. At 113 days, females had a 100% increase in coagulation times. Doses of 80 µg/kg and 160 µg/kg were initiated but all animals died between day 3 and 13.  NOAEL: 5 µg/kg bw.	MRID 92018013
<b>Chronic</b>	<b>No studies available</b>		

**A1 Table 5: Reproductive and Developmental Toxicity Studies**

<b>Species</b>	<b>Exposure</b>	<b>Response</b>	<b>Reference</b>
<b>Developmental</b>			
Rats, Sprague-Dawley, mated females, 8/dose	TGAI: Gavage doses of 0, 1, 5, 25, 50, 100 or 200 µg/kg/day on Days 6-15 of gestation.	No overt toxic effects noted. Increases in prothrombin and activated partial thromboplastin time but not clearly dose-related.	MRID 43349501 <sup>[1]</sup> [Range finding]
Rats, Sprague-Dawley, mated females, 25/dose	TGAI: Gavage doses of 0, 12.5, 25, 50 or 100 µg/kg/day on Days 6-15 of gestation. Corn oil vehicle.	<u>Maternal Effects:</u> 100 µg/kg: Mortality in 18/25 dams on Days 12-16. 50 µg/kg: No overt signs of toxicity.  <u>Developmental Effects:</u> Increases in ureter anomalies at all doses.	MRID 43349501 <sup>[1]</sup> [Full Study]
Rabbits, New Zealand White, mated females, 3/dose.	TGAI: Gavage doses of 0, 1, 2, 5, or 10 µg/kg/day on Days 7-19 of gestation.	Increases in prothrombin and activated partial thromboplastin times at 10 µg/kg bw.  Developmental NOAEL: 10 µg/kg bw Maternal NOAEL: 5 µg/kg bw/day.	MRID 43570801 <sup>[1]</sup> [Range finding]
Rabbits, New Zealand White, mated females, 16/dose.	TGAI: Gavage doses of 0, 5, 10, 25 or 75 µg/kg/day on Days 7-19 of gestation.	<u>Maternal Effects:</u> 75 µg/kg: Mortality in all animals. 25 µg/kg: Mortality in 13/16 animals. Increased incidence of external bleeding and lethargy. 10 µg/kg: Based on observations of increased clotting times in range-finding study. 5 µg/kg: Maternal NOAEL.  <u>Developmental Effects:</u> No indication of fetal effects. NOAEL set at 10 µg/kg due to small litter numbers at higher doses.  <b>U.S. EPA/OPP/EFED 2011a (p. 71) used the developmental NOAEL 10 µg/kg bw/day for chronic risk characterization.</b>	MRID 43570801 <sup>[1]</sup> [Full study]

Species	Exposure	Response			Reference													
Mice ( <i>Mus musculus</i> var. <i>albus</i> ). 5 females/dose, <b>pregnant</b>	Chlorphacinone (Caid formulation 0.005% a.i. mixed with other bait ingredients. Dietary exposure to 0, 10, and 20 mg/kg chow for 20 days.  Working Note: This study was conducted in Egypt but Caid appears to be an English formulation.	<table border="1"> <thead> <tr> <th data-bbox="789 243 938 289">Conc.</th> <th data-bbox="938 243 1084 289">% change BW</th> <th data-bbox="1084 243 1230 289">Mortality</th> </tr> </thead> <tbody> <tr> <td data-bbox="789 289 938 323">0</td> <td data-bbox="938 289 1084 323">+11.64</td> <td data-bbox="1084 289 1230 323">0/5</td> </tr> <tr> <td data-bbox="789 323 938 357">10</td> <td data-bbox="938 323 1084 357">-13.31</td> <td data-bbox="1084 323 1230 357">1/5</td> </tr> <tr> <td data-bbox="789 357 938 390">20</td> <td data-bbox="938 357 1084 390">-16.06</td> <td data-bbox="1084 357 1230 390">2/5</td> </tr> </tbody> </table>			Conc.	% change BW	Mortality	0	+11.64	0/5	10	-13.31	1/5	20	-16.06	2/5	Mesban et al. 2003	
		Conc.	% change BW	Mortality														
		0	+11.64	0/5														
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		20	-16.06	2/5														
		<table border="1"> <thead> <tr> <th data-bbox="789 447 883 493">Conc.</th> <th data-bbox="883 447 1000 493">Number of Fetuses</th> <th data-bbox="1000 447 1094 493">Fetal BW (g)</th> <th data-bbox="1094 447 1230 493">Mortality</th> </tr> </thead> <tbody> <tr> <td data-bbox="789 493 883 527">0</td> <td data-bbox="883 493 1000 527">20</td> <td data-bbox="1000 493 1094 527">1.8</td> <td data-bbox="1094 493 1230 527">0.0%</td> </tr> <tr> <td data-bbox="789 527 883 560">10</td> <td data-bbox="883 527 1000 560">18</td> <td data-bbox="1000 527 1094 560">1.2</td> <td data-bbox="1094 527 1230 560">33.3%</td> </tr> <tr> <td data-bbox="789 560 883 594">20</td> <td data-bbox="883 560 1000 594">12</td> <td data-bbox="1000 560 1094 594">1.2</td> <td data-bbox="1094 560 1230 594">58.3%</td> </tr> </tbody> </table>			Conc.	Number of Fetuses	Fetal BW (g)	Mortality	0	20	1.8	0.0%	10	18	1.2	33.3%		20
Conc.	Number of Fetuses	Fetal BW (g)	Mortality															
0	20	1.8	0.0%															
10	18	1.2	33.3%															
20	12	1.2	58.3%															
Fetal: No malformations but decreases in number and survival.																		
Maternal: Internal hemorrhaging, liver and kidney tubular necrosis.																		
<b>Reproductive</b>	<b>No studies identified</b>																	

<sup>11</sup> Summaries from U.S. EPA/OPP (1998a), pp. 31-33.



**A1 Table 6: Skin and Eye Irritation and Skin Sensitization Studies**

<b>Species</b>	<b>Exposure</b>	<b>Response</b>	<b>Reference</b>
Rabbit, skin irritation	TGAI (NOS)	<i>PIS = 0, but mortalities occurred (same study as dermal LD<sub>50</sub> assay).</i>  Toxicity Category IV	MRID 41702801
Guinea Pigs, Hartley, skin sensitization	TGAI (99.88%). 0.003 g/animal/induction. Mortality at higher induction doses.	No signs of skin sensitization but 2 animals dies, one on Day 8 and the other on Day 13.	MRID 41578601
Rabbits, New Zealand, 6 females.	TGAI (99.88%), 0.1 g into left eye. 72 hours observation period.	<i>No eye irritation at 1, 24, 48, or 72 hours.</i> Toxicity Category IV.	MRID 41874001

**A1 Table 7: Dermal Toxicity, Acute and Subacute**

<b>Species</b>	<b>Exposure</b>	<b>Response</b>	<b>Reference</b>
<b>Acute</b>			
Rabbits, New Zealand White, Males only	TGAI (100%) in acetone spread onto 2x2 cm pads. Doses of 0.25, 0.5 or 0.75 mg/kg for 24 hours with occlusion. 21 day observation period.	LD <sub>50</sub> : 0.329 mg/kg (males)  Deaths occurred at 5 to 19 days after dosing. Symptoms (bloody nasal discharge and hemorrhaging of thoracic cavity) consistent with anticoagulant activity. No signs of skin irritation.  Toxicity Category I.  Working Note: The dermal LD <sub>50</sub> is lower than the oral LD <sub>50</sub> . This is unusual.	MRID 41702801
Rabbit (NOS)	Technical material	LD <sub>50</sub> : 200 mg/kg	WHO 1985
Human case report	See Table A1-3 above.	See Table A1-3 above.	Binks and Davies 2007
<b>Subchronic</b>			
Rabbits, 5/sex/dose	0.2% a.i. (formulated tracking product. Doses of 0.08, 0.4, or 2.0 mg a.i./kg bw for 6 hours/day, 5 days/week, for 3 weeks.	0.08 mg/kg No effects.  0.4 mg/kg No mortality but increased prothrombin times in males (28%) and females (61%).  2 mg/kg Increase in prothrombin times in surviving animals – i.e., an average increase of 50% relative to controls. Moderate to severe liver necrosis in 3/5 males and 1/5 females. Internal hemorrhage and death in 4/5 males from Days 14-18 and death in 1/5 females on Day 21.	MRID 42237402

**A1 Table 8: Inhalation Studies**

<b>Species</b>	<b>Exposure</b>	<b>Response</b>	<b>Reference</b>
Rat, Sprague-Dawley, 7-9/sex/exposure level	4 hours, nose-only, 1.33, 10.3, 11.5 or 14.5 µg/L with 21-day observation period.	LC <sub>50</sub> : Males: 7 µg/L LC <sub>50</sub> : Females: 12 µg/L  NOAEC: 1.33 µg/L Mortality at 3-8 days at higher concentrations.  Note: Some animals died during exposure due to stress-related suffocation.  Toxicity Category I.	MRID 41981102

**A1 Table 9: Efficacy Studies**

<b>Site/Target/ Location</b>	<b>Exposure</b>	<b>Response</b>	<b>Reference</b>
Human dwellings Rodents India	Chlorophacinone 0.0075%, 15 days	Estimate of 96.7% control. No detailed observations of effects on target organisms.	Advani and Prakash 1987
Golf course  Ground squirrel ( <i>Spermophilus columbianus</i> )  Washington State	Rozol pellets, 0.005% a.i. at a rate of 10 lb/acre (0.0005 lb a.i./acre).	65-93% control (see Tables 1 and 2 of paper). No description of effects and no monitoring of residues. Slightly better efficacy for salt treated baits.	Askham 1985a
Orchard  Roof rats ( <i>Rattus rattus</i> )  California	Chlorophacinone 0.005% oat bait.	Completely ineffective. Increase in rat populations in treated sites. In discussion, authors note that it is possible that lack of efficacy was due to mixing error.	Baldwin et al. 2014
Apple orchard  Voles  Virginia	Rozol, 0.005% a.i. at 17 kg Rozol/acre (about 0.00075 lb a.i./acre) by broadcast application.	Greater efficacy in October (77%) relative to December (11%) applications. See Table 1 in paper. No detailed observations of effects on target organisms.	Byers and Carbaugh 1989
Apple orchard  Voles  Virginia	Rozol, 0.005% a.i. at 11.2 kg Rozol/ha (about 0.0005 lb a.i./acre) <i>hand placed</i> in pellets or wheat. The process of hand baiting is not well-described in paper.	69 to 95% reduction in vole populations. See Tables 2 to 5 in paper No detailed observations of effects on target organisms.	Byers and Carbaugh 1989
Apple orchard  Voles  Virginia	Rozol, 0.005% a.i. at 11.2 kg Rozol/ha (about 0.0005 lb a.i./acre), hand placed at 2 to 6 cm below surface ( $\approx 0.8$ to 2.4 inches)	84.7% control. No detailed observations of effects on target organisms.	Byers and Carbaugh 1991
Not specified  Voles  France	Chlorophacinone, 0.0075% in grain, broadcast. 13 to 18 lbs bait/acre (0.000975-0.00135 lb a.i./acre)	80-90% effective depending on pattern of application..	Giban 1974

Site/Target/ Location	Exposure	Response	Reference
Prairie Black-tailed prairie dog Kansas and Nebraska	Rozol Pocket Gopher Bait, 0.005913% a.i. 13 sites, 2.1 to 41.5 acres in area. ¼ cup added per burrow at least 6 inches subsurface.	Data tables not included in DER. Efficacy appears to have been about 75% and characterized as adequate control. <i>...only a small percent (0-6%) of holes had visible bait on the ground surface surrounding them. That 30-72% of holes had no bait visible in or around them a day after treatment seems to mean that some agent(s) consumed, removed, or otherwise concealed the particles.</i> A dead cottontail rabbit found at a site.	Lee and Hyingstrom 2007 MRID 47333602
Prairie Black-tailed prairie dog Kansas	Rozol Pocket Gopher Bait, 0.005% a.i., 54 g per burrow. 15 colonies treated.  21-day observation period.	91.5% control (mean for colonies) with a range of 75%-100%. No description of effects on target species or residues in carcasses.	Lee et al. 2005
Grassland Mixed rodents India	Chlorophacinone 0.0075% in grain bait in bait stations.	62.6%-83.2% based on different measures: active burrows (83.2%), census baitings (62.6%), and live-trapping (73.6%). No data on residues.	Mathur and Prakash 1984
Orchards Voles Virginia	Rozal, 0.005% a.i. pellet baits. 17.5 lbs/acre (0.000875 lb a.i./acre)	86% control. No additional details.	Merson and Byers 1985
Woodlands (≈2 acre areas). Muskrats Belgium	Carrots baited with caid oil containing chlorophacinone at 2.5 g a.i./L.	Apparently satisfactory control but 73% of dead muskrats were found above ground (i.e., possibility of secondary poisoning). Deaths within 5 to 10 days.	Tuytens and Stuyck 2002

Site/Target/ Location	Exposure	Response	Reference
Agricultural land  Voles  Spain	Chlorophacinone 0.0075% at 20 kg/ha [17.84 lb bait/acre; 0.00133 lb a.i./acre] 20,000 ha (≈49,500 acres) treated.	Residues in the liver of voles of 0.082 to 3.8 µg/g with a geometric mean of 0.65 µg/g. Pathology in poisoned voles included hemorrhages. <i>Hemorrhages were present in            voles with (67%) and without CP            residues (75%) (p=0.7).</i> 55.5% of dead voles had detectable levels of chlorophacinone. A pathogen, <i>Francisella tularensis</i> , found in 66.7% of dead voles. Infected voles had lower residues of chlorophacinone. Authors speculate on interaction of pathogen and chlorophacinone.	Vidal et al. 2009
Pasture  Black-tailed prairie dog  Colorado	17.3 ha colony, 4,080 burrows treated with 216 kg Rozol [125 kg Rozol/ha; 11.13 lb Rozol/ac; 0.00056 lb a.i./acre] Observation period up to 29 days after treatment (DAT). Working Note: Focus of study is potential for nontarget effects rather than efficacy.	Several dead or dying black-tailed prairie dog and ground squirrels ( <i>Spermophilus tridecemlineatus</i> ). Excessive bleeding noted but not detailed. Initial chlorophacinone residues in liver of up to 7.56 µg/g decreasing to <0.5 µg/g by 29 DAT. Most carcasses found above ground -- i.e., potential for secondary effects. No damage to nontarget species documented.	Vyas et al. 2012

**A1 Table 10: Case Reports in Domestic and Wildlife Mammals**

Species/Location	Exposure	Response <sup>[1]</sup>	Reference
<p>Survey covering reported poisonings of wildlife from 1991-1994</p> <p>Red fox (<i>Vulpes vulpes</i>), Rabbits (<i>Lepus capensis</i> and <i>Oryctolagus cuniculus</i>), boar (<i>Sus scrofa</i>)</p> <p>France</p>	<p>Analysis of liver samples from wildlife.</p>	<p>Liver concentrations ranging from about 0.2 µg/g to 14.3 µg/g.</p> <p>Author notes that chlorophacinone was not highly regulated and most poisonings could be attributed to misuse/above ground use.</p>	<p>Berny et al. 1997</p>
<p>General review of poisoning episodes in domestic and wild animals from 2004 to 2007.</p> <p>France</p>	<p>No details on levels of exposure.</p>	<p>No reported mortalities. Chlorophacinone accounted for 10.4% of cases of domestic animals and 9.2% of cases involving wildlife from 2004 to 2007.</p>	<p>Berny et al. 2010</p>
<p>Lambs, 11, 1-2 months old.</p> <p>Pennsylvania, USA</p>	<p>Consumption of stored bait containing chlorophacinone at 890 ppm (0.089%). The high concentration in the bait attributed to decomposition of the bait carrier (NOS).</p> <p>Working Note: The duration between the time of ingestion and the onset of symptoms is not clear from the publication. Toxicity may have been delayed but this is not clear.</p>	<p>Sudden onset of nasal hemorrhaging, difficulty in breathing, as well as facial and cervical swelling. Death within 1-2 hours of the development of signs of toxicity.</p> <p>On autopsy, extensive signs of internal bleeding.</p> <p>Chlorophacinone concentrations in the liver of 0.5-0.58 mg/kg (wet weight in 2 livers).</p>	<p>Del Piero and Poppenga 2006</p>

Species/Location	Exposure	Response <sup>[1]</sup>	Reference
<p>European mink (<i>Mustela lutreola</i>)  American mink (<i>Mustela vison</i>)  European otter (<i>Lutra lutra</i>)</p> <p>Total of 122 carcasses.</p> <p>France</p>	<p>Carcasses collected in France from 1990 to 2002.</p> <p>Chlorophacinone used for control of muskrat, rates, mice, and voles.</p>	<p>Chlorophacinone found in 4 American mink and one otter with liver concentrations from 3.4 µg/g to 8.5 µg/g. [Note: Abstract not consistent with body of paper. Liver concentrations above are from the body of the paper.]</p> <p>Animals characterized as being in “good physical condition”.</p> <p>In none of the animals with chlorophacinone residues was death attributed to chlorophacinone.</p> <p>Authors speculate: ... <i>they could have increased vulnerability to other causes of death, such as vehicular collision, predation....This may be related to delayed onset of clinical signs and lesions.</i></p> <p>Working Note: This study does not seem to offer any data indicating adverse effects from chlorophacinone.</p>	<p>Fournier-Chambrillon et al. 2004</p>
<p>Raccoon (<i>Procyon lotor</i>)</p> <p>Kansas</p>	<p>No details on source of chlorophacinone exposure. Study includes consideration of other rodenticides that are available to the general public.</p>	<p>Examination of carcass.</p> <p>Severe hemorrhage throughout GI tract.</p> <p>Chlorophacinone at 1.4 ppm in liver along with 0.5 ppm brodifacoum and 0.37 ppm diphacinone.</p>	<p>Ruder et al. 2011</p>
<p>American badger (<i>Taxidea taxus</i>)</p> <p>Kansas</p>	<p>Chlorophacinone had been used locally for the control of black-tailed prairie dog. Authors suggest that this could be a case of secondary poisoning from preying on black-tailed prairie dog.</p>	<p>Examination of carcass.</p> <p>Severe pulmonary and GI hemorrhage.</p> <p>Chlorophacinone at 4.4 ppm in liver.</p>	<p>Ruder et al. 2011</p>
<p>Variety of domestic and wildlife mammals (n=128): cats, dogs, genet, fox, raccoon, stone marten, otter weasel, hare, and hedgehog.</p> <p>Spain</p>	<p>Exposures appear to be associated with <b>surface applications</b>.</p> <p>7/128 (≈5.5%) positive for chlorophacinone.</p> <p>All 7 detections were found in the Iberian hare (<i>Lepus granatensis</i>).</p> <p><b>No other species had detectable levels of chlorophacinone.</b> See Table 3 of paper.</p>	<p>Examination of wildlife carcasses.</p> <p>Chlorophacinone found in liver most often in primary consumers.</p> <p>Concentrations in the liver of 2.11 (0.58-9.52) µg/g (w.w.)</p>	<p>Sanchez-Barbudo et al. 2012</p>

Species/Location	Exposure	Response <sup>[1]</sup>	Reference
Rodenticide poisoning in mammalian wildlife and birds, cases from 1971 to 1997. New York	General survey of anticoagulant poisoning. No details of exposures.  No chlorophacinone found in chipmunk, raccoon, deer, fox, skunk, or opossum.	One gray squirrel with 0.62 ppm chlorophacinone along with 0.53 ppm brodifacoum in the liver.	Stone et al. 1999
Fisher ( <i>Martes pennanti</i> ), n=58 California	Exposures associated with use of chlorophacinone on illegal marijuana cultivation sites.	Examination of carcasses. Chlorophacinone found only in one fisher. Extensive hemorrhage of abdominal cavity. Concentration in liver < 0.25 µg/g.	Gabriel et al. 2012 Thompson et al. 2013
Reports of poisonings in domestic animals. U.S.A. (NOS)	Most exposures associated with use of 0.005% chlorophacinone bait. No additional details.	15 reports of poisonings. No details.	U.S. EPA/OPP/HED 1997
Range land  Various mammals and birds  Saskatchewan, Canada	2,000 kg of 0.4% chlorophacinone in oats sold in area for control of ground squirrel. <b>Above surface applications</b> in bait stations (see Fig. 1 of paper). Study period: 2008-2009.  Strychnine (not an anticoagulant) also used in area.	1 American Badger ( <i>Taxidea taxus</i> ) and 3 weasels ( <i>Mustela frenata</i> ) found dead one day after a chlorophacinone application. Non-target: Extensive intestinal hemorrhages, gum bleeding, and bleeding from foot pads. Target: Extensive mortality of ground squirrels. No monitoring of residues reported. Working Note: Except for the reports of hemorrhaging, it seems difficult to assess effects of chlorophacinone relative to strychnine.	Proulx 2011
Dogs (n=123) Pennsylvania	Retrospective review of anticoagulant poisoning cases. Exposures not well-characterized.	75 of 123 cases of documented anticoagulant exposures. Only 2/75 associated with chlorophacinone. In the two dogs, concentrations of chlorophacinone of 0.086 and 0.62 ppm in either whole blood or serum (not clear from publication).	Waddell et al. 2013

<sup>[1]</sup> Residues expressed as given in publication. Note that ppm is the same as µg/g.



**Appendix 2: Toxicity to birds**

A2 Table 1: Acute Oral/Gavage Toxicity to Birds ..... 117  
 A2 Table 2: Acute Dietary Toxicity to Birds..... 119  
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**Note: Unless otherwise specified, summaries of MRID studies are taken from U.S. EPA/OPP/EFED 2011a (main body) as well as Appendix D, Summary of Ecotoxicity Data.**

**A2 Table 1: Acute Oral/Gavage Toxicity to Birds**

<b>Species</b>	<b>Exposure</b>	<b>Response</b>	<b>Reference<sup>[1]</sup></b>																
Bobwhite quail ( <i>Colinus virginianus</i> )	100% a.i. 30 day observation period	LD <sub>50</sub> : 258 mg a.i./kg bw Slope=2.88 Mortalities occurred during first 5 days after dosing. [Appendix D of EFED document] Sublethal Effects: <i>lethargy, subcutaneous, intramuscular, and internal hemorrhaging, piloerection, diarrhea, bloody diarrhea, and anorexia.</i>	MRID 41513101  Acceptable  Moderately Toxic																
Bobwhite quail ( <i>Colinus virginianus</i> )	Technical grade 14 day observation period.	LD <sub>50</sub> : 495 mg a.i./kg bw  All mortalities occurred within 10 days of the start of the assay.	MRID 39233  Not reviewed by EPA but summarized in U.S. EPA/OPP/EFED 2011a, Appendix D.																
American kestrels ( <i>Falco sparverius</i> ), Adults n=12 4 (3 M and 1 F) per exposure group.	Doses of 53 mg or 159 mg/day of 2% a.i. suspension – i.e., about 1.06 mg a.i./day or 3.18 mg a.i./day. Dosed on July 4 and observed to July 31, 1980 [27 day observation period.]	Doses below based on initial weight from Table 1 of paper. <table border="1" data-bbox="636 1220 1177 1362"> <thead> <tr> <th>BW (kg)</th> <th>Dose (mg/kg)</th> <th>Ave. BW<sup>[1]</sup></th> <th>Mortality</th> </tr> </thead> <tbody> <tr> <td>0.112</td> <td>0</td> <td>-12</td> <td>0/4</td> </tr> <tr> <td>0.109</td> <td>9.7</td> <td>-22.3</td> <td>4/4</td> </tr> <tr> <td>0.102</td> <td>31.2</td> <td>-10.4</td> <td>1/4</td> </tr> </tbody> </table> <p><sup>[1]</sup> Average change in g. Working Note: The order in Table 1 of paper is control, high dose, low dose. All birds in low and high dose groups exhibited hemorrhaging. Mean time to death 16.5 days. Wing drooping in high dose group at 14 day and n low dose group at 7.5 days. No wing drooping in control birds. Working Note: Wing drooping is possible but tenuous support for fever associated with uncoupling activity.</p>	BW (kg)	Dose (mg/kg)	Ave. BW <sup>[1]</sup>	Mortality	0.112	0	-12	0/4	0.109	9.7	-22.3	4/4	0.102	31.2	-10.4	1/4	Radvanyi et al. 1988  Cited in U.S. EPA/OPP/EFED 2011a, Appendix F but not otherwise discussed.  Cited in U.S. EPA/OPP/EFED 2010a but not discussed
BW (kg)	Dose (mg/kg)	Ave. BW <sup>[1]</sup>	Mortality																
0.112	0	-12	0/4																
0.109	9.7	-22.3	4/4																
0.102	31.2	-10.4	1/4																

**Appendix 2: Toxicity to birds (continued)**

Species	Exposure	Response	Reference <sup>[1]</sup>																
American kestrels ( <i>Falco sparverius</i> ), Juvenile n=12 4 (3 M and 1 F) per exposure group.	Doses of 18 mg or 53 mg/day of 2% a.i. suspension – i.e., about 0.36 mg a.i./day or 1.06 mg a.i./day.  Dosed on Aug. 15 and observed to Sept. 4, 1980 [20 day observation period.]	Doses below based on initial weight from Table 1 of paper. <table border="1" data-bbox="634 289 1179 436"> <thead> <tr> <th data-bbox="634 289 760 346">BW (kg)</th> <th data-bbox="763 289 915 346">Dose (mg/kg)</th> <th data-bbox="919 289 1027 346">Ave. BW<sup>[1]</sup></th> <th data-bbox="1031 289 1179 346">Mortality</th> </tr> </thead> <tbody> <tr> <td data-bbox="634 350 760 378">0.118</td> <td data-bbox="763 350 915 378">0</td> <td data-bbox="919 350 1027 378">-3.2</td> <td data-bbox="1031 350 1179 378">0/4</td> </tr> <tr> <td data-bbox="634 382 760 409">0.119</td> <td data-bbox="763 382 915 409">3.0</td> <td data-bbox="919 382 1027 409">-13.3</td> <td data-bbox="1031 382 1179 409">3/4</td> </tr> <tr> <td data-bbox="634 413 760 441">0.129</td> <td data-bbox="763 413 915 441">8.2</td> <td data-bbox="919 413 1027 441">-23.8</td> <td data-bbox="1031 413 1179 441">4/4</td> </tr> </tbody> </table> <p data-bbox="634 436 1179 802"> <sup>[1]</sup>Average change in g.                      Working Note: The order in Table 1 of paper is control, high dose, low dose. All birds in low and high dose groups exhibited hemorrhaging. Mean time to death 10.3 days (high dose) and 11 days (low dose). The surviving bird in the low dose group appeared to recover completely. Wing drooping in high dose group at 5 days and in low dose group at 6.5 days. No wing drooping in control birds.                      Working Note: Wing drooping is possible but tenuous support for fever associated with uncoupling activity.                 </p>	BW (kg)	Dose (mg/kg)	Ave. BW <sup>[1]</sup>	Mortality	0.118	0	-3.2	0/4	0.119	3.0	-13.3	3/4	0.129	8.2	-23.8	4/4	Radvanyi et al. 1988  Cited in U.S. EPA/OPP/EFED 2011a, Appendix F but not otherwise discussed.  Cited in U.S. EPA/OPP/EFED 2010a but not discussed
BW (kg)	Dose (mg/kg)	Ave. BW <sup>[1]</sup>	Mortality																
0.118	0	-3.2	0/4																
0.119	3.0	-13.3	3/4																
0.129	8.2	-23.8	4/4																

<sup>[1]</sup> MRID entries also include EPA classification of study and toxicity category.

## Appendix 2: Toxicity to birds (continued)

A2 Table 2: Acute Dietary Toxicity to Birds

Species	Exposure	Response	Reference <sup>[1]</sup>															
Bobwhite quail ( <i>Colinus virginianus</i> )	100% a.i., 5-day dietary 30 day observation period.	LC <sub>50</sub> : 56 mg a.i./kg chow Slope=1.49 Mortalities occurred during first 9 days of study. Sublethal Effects: <i>subcutaneous, intramuscular, and internal hemorrhaging, and swollen, bloody feet.</i> Estimated dose <sup>[2]</sup> : 16.8 mg a.i./kg bw/day	MRID 41513102  Acceptable Highly Toxic															
Bobwhite quail ( <i>Colinus virginianus</i> )	Technical grade, 5-day dietary	LC <sub>50</sub> : 242 mg a.i./kg chow  Estimated dose <sup>[2]</sup> : 72.6 mg a.i./kg bw/day	MRID 29144 Not reviewed by EPA															
Japanese quail ( <i>Coturnix japonica</i> )	0.25% oil concentrate	LC <sub>50</sub> : 60 mg a.i./kg chow  Estimated dose <sup>[2]</sup> : 18 mg a.i./kg bw/day	MRID 47323201 Reidel et al, 1990 Supplemental Highly Toxic															
California quail ( <i>Callipepla californica</i> ), n=7	Paraffinized chlorophacinone pellets for up to 12 days.	Severe emaciations and death within 7 to 12 days. 27-60% weight loss. Effects associated with ... <i>selective accumulation of paraffin from the pellets into a compacted mass.</i> No effects on prothrombin time. Effects appear to be associated with physical impaction of GI tract rather than toxicity of chlorophacinone. See case report in Table A2-5 below.	Blus et al. 1985															
Red legged partridge ( <i>Alectoris rufa</i> )	0.0075% (75 ppm) chlorophacinone in grain for 5 or 15 days. See Table 3 of paper  Approximate body weight of about 0.5 kg from Dunning (1993)	<table border="1"> <thead> <tr> <th>Days</th> <th>Daily Dose (mg)</th> <th>Mortality</th> </tr> </thead> <tbody> <tr> <td>5</td> <td>3.00</td> <td>1/10</td> </tr> <tr> <td>10</td> <td>3.00</td> <td>1/10</td> </tr> <tr> <td>12</td> <td>3.00</td> <td>2/10</td> </tr> <tr> <td>15</td> <td>3.00</td> <td>5/10</td> </tr> </tbody> </table> <p>Dose of 3 mg corresponds to a dose of about 6 mg a.i./kg bw.</p>	Days	Daily Dose (mg)	Mortality	5	3.00	1/10	10	3.00	1/10	12	3.00	2/10	15	3.00	5/10	Giban 1974
Days	Daily Dose (mg)	Mortality																
5	3.00	1/10																
10	3.00	1/10																
12	3.00	2/10																
15	3.00	5/10																

**Appendix 2: Toxicity to birds (continued)**

Species	Exposure	Response			Reference <sup>[1]</sup>
Common/grey partridge ( <i>Perdix perdix</i> )	0.0075% (75 ppm) chlorophacinone in grain for 15 or 30 days. See Table 3 of paper. Approximate body weight of about 0.4 kg from Dunning (1993)	<b>Days</b>	<b>Daily Dose (mg)</b>	<b>Mortality</b>	Giban 1974
		15	2.25	0/10	
		30	2.25	4/19	
		15	4.5	3/10	
Working Note: Above doses correspond to about 5.6 and 11.25 mg a.i./kg bw.					
Mallard duck ( <i>Anas platyrhynchos</i> )	100% a.i., 5-day dietary	LC <sub>50</sub> : 172 mg a.i./kg chow Estimated dose <sup>[2]</sup> : 68.8 mg a.i./kg bw/day			MRID 41513103  Acceptable Highly Toxic
Mallard duck ( <i>Anas platyrhynchos</i> )	100% a.i., 5-day dietary	LC <sub>50</sub> : 426 mg a.i./kg chow Estimated dose <sup>[2]</sup> : 170.4 mg a.i./kg bw/day			MRID 29143 Not reviewed by EPA

<sup>[1]</sup> MRID entries also include EPA classification of study and toxicity category. Studies from U.S. EPA/OPP/EFED 2011a (including Appendix D) unless otherwise specified.

<sup>[2]</sup> Food consumption factor of 0.3 kg food/kg bw for quail and 0.4 kg food/kg bw for mallards. See Section 4.1.2.2.2 for discussion.

## Appendix 2: Toxicity to birds (continued)

A2 Table 3: Secondary Toxicity Studies

Species	Exposure	Response	Reference <sup>[1]</sup>
Red-tailed hawks ( <i>Buteo jamaicensis</i> ), n=5 (3F, 2M) Great horned owl ( <i>Bubo virginianus</i> ), n=1 M	2 voles/day for six days, voles previously poisoned with 0.005% chlorophacinone bait. Average dose of 8.05 mg over 6 day feeding period. 37 day observation period.  Approximate body weight of about for 1.1 kg <i>Buteo jamaicensis</i> from Dunning (1993).	One bird (NOS) appeared lethargic on Days 24 and 25. Otherwise, <b>no overt signs of toxicity or abnormal bleeding.</b> EPA notes several limitations in study design, particularly that some of the vole carcasses were “thawed and rotten” on arrival at study site. Working Note: Dose of 8.05 over a 6 day period corresponds to a dose of about 1.2 mg/kg bw/day for the hawks. May be viewed as a marginal NOAEL.	Askham 1988 MRID 40751402  Supplemental in 2001 EPA annotations. Study has originally been classified in 1990 as Invalid. Askham and Poché 1992
Black-billed magpies ( <i>Pica pica</i> ) 20 exposed as 2 replicates of 10, 10 control	Fed rats previously poisoned with 0.005% a.i. chlorophacinone (Rozol Paraffinized Pellets) for 5 consecutive days. Diet supplemented with dry dog food <i>ad libitum</i> . Estimated consumption of carcasses: 1.492 kg/kg bw (Rep. 1) and 1.618 kg/kg bw (Rep. 2) 21-day post-exposure observation.	No overt signs of toxicity. Changes in bw comparable to controls. Necropsy Findings: <i>Possible signs of toxicosis were slight discoloration or yellowing of the liver in 4 treated birds; the spleen of one of these birds was not uniform in color.</i> Working Note: Doses in terms of mg a.i./kg bw cannot be estimated because the residues in the rats are not reported.	Baroch 1997 MRID 44631402  Supplemental
Barn owls ( <i>Tyto alba</i> ), appear to involve one male and one female owl.	Fed rats poisoned with chlorophacinone for 10 days. Coagulation times measured 20 days after initial treatment.  Working Note: The estimated doses may be overestimates (perhaps substantial) in that the doses are based on the amount of chlorophacinone consumed by the rats.	Based on recorded body weights, amount of chlorophacinone in rats, dose to rats (mg a.i.), and weight of rats consumed by owl, doses can be estimated. See Table 2 of paper. Male: 475 g bw, 0.0126 mg a.i./g rat, rats eaten 655 g over 10 days. Cumulative dose: ≈17.4 mg a.i. Daily Dose (NOAEL): 1.74 mg/kg bw/day. Female: 605 g bw, 0.0129 mg a.i./g rat, rats eaten 576 g over 10 days. Cumulative dose: ≈12.3 mg a.i. Daily dose (NOAEL): 1.23 mg/kg bw/day.  <b>No signs of toxicity and effect on coagulation times.</b>	Mendenhall and Pank 1980  Open literature publication assigned as MRID 46750931 in U.S. EPA/OPP/EFED 2011a

**Appendix 2: Toxicity to birds** (*continued*)

<b>Species</b>	<b>Exposure</b>	<b>Response</b>	<b>Reference<sup>[1]</sup></b>
American kestrels <i>(Falco sparverius)</i> 5 M, 5 F/group	Low Dose: 1 poisoned mouse/day every 3 days for 61 days. High Dose: 1 poisoned mouse/day for 21 days. Working Note: Cannot estimate doses.	Wing drooping observed in all groups attributed to external high temperatures during test. No mortality. Hemorrhaging in all birds most of which evidenced effects in multiple organs. Hemorrhaging noted most frequently in heart. (See Table 3 of paper).	Radvanyi et al. 1988 Cited and summarized in U.S. EPA/OPP/EFED 2010a.

## Appendix 2: Toxicity to birds (continued)

A2 Table 4: Case Reports

Species/Location	Exposure	Response	Reference												
<p>Great horned owls (<i>Bubo virginianus</i>) [n=25] GHOW                      Barred owls (<i>Strix varia</i>) [n=25] BDOW                      Barn owls (<i>Tyto alba</i>) [n=78] BNOW                      British Columbia, Canada</p>	<p>Carcasses collected between 1998 and 2003 and assayed for anticoagulants in liver.                      Survey involved several first and second anticoagulant rodenticides.                      Brodifacoum was detected (51%) much more frequently than chlorophacinone.</p>	<table border="1" data-bbox="802 264 1183 485"> <thead> <tr> <th>Species</th> <th>%</th> <th>Average Liver (<math>\mu\text{g/g}</math>)</th> </tr> </thead> <tbody> <tr> <td>GHOW</td> <td>5%</td> <td>0.0029</td> </tr> <tr> <td>BDOW</td> <td>16%</td> <td>0.0043</td> </tr> <tr> <td>BNOW</td> <td>0%</td> <td>N/A</td> </tr> </tbody> </table> <p>Hemorrhaging was generally observed in birds (possibly poisoned with other anticoagulants).                      No indication that chlorophacinone was a cause of death in any cases.</p>	Species	%	Average Liver ( $\mu\text{g/g}$ )	GHOW	5%	0.0029	BDOW	16%	0.0043	BNOW	0%	N/A	<p>Albert et al. 2010</p>
Species	%	Average Liver ( $\mu\text{g/g}$ )													
GHOW	5%	0.0029													
BDOW	16%	0.0043													
BNOW	0%	N/A													
<p>Survey covering reported poisonings of wildlife from 1991-1994                      Buzzard (<i>Buteo buteo</i>), pigeon (<i>Columba livia</i>), eagle (<i>Aquila</i> sp.), barn owl (<i>Tyto alba</i>)                      France</p>	<p>Analysis of liver samples from wildlife.</p>	<p>Liver concentrations ranging from about 0.2 <math>\mu\text{g/g}</math> to 6.2 <math>\mu\text{g/g}</math>.                      Author notes that chlorophacinone was not highly regulated and most poisonings could be attributed to misuse/above ground use.</p>	<p>Berny et al. 1997</p>												
<p>California quail (<i>Callipepla californica</i>), n=1                      Oregon</p>	<p>Crop and gizzard impacted with paraffin pellets containing chlorophacinone. Pellets had been applied (broadcast) for the control of voles.</p>	<p>Emaciated with depleted lipid reserves.                      No increase in prothrombin times from standard values.                      Effects attributable to physical blockage of GI tract with paraffin rather than chlorophacinone.                      See experimental feeding in Table A2-5 above.</p>	<p>Blus et al. 1985</p>												
<p>Several species of birds, cases from 1971 to 1997.                      New York</p>	<p>No details of exposures.</p>	<p>No chlorophacinone found in any birds.                      Most birds had residues of brodifacoum.</p>	<p>Stone et al. 1999</p>												
<p>Great bustard (<i>Otis tarda</i>)                      Spain</p>	<p>Total of 71 carcasses collected from 1991-2010. Chlorophacinone used to control voles by spreading bait on fields (i.e., surface applications).</p>	<p>Chlorophacinone found in 10 birds (14.1%). Liver concentrations of 0.082-3.8 <math>\mu\text{g/g}</math>.                      Primary sign of toxicity, hemorrhaging.                      Causes of death are mixed and not clearly attributed to chlorophacinone.                      Positive association between chlorophacinone concentrations and pathogens/parasites.</p>	<p>Lemus et al. 2011</p>												

**Appendix 2: Toxicity to birds (continued)**

<b>Species/Location</b>	<b>Exposure</b>	<b>Response</b>	<b>Reference</b>
Range land Various birds Saskatchewan, Canada	2,000 kg of 0.4% chlorophacinone in oats sold in area for control of ground squirrel. <b>Above surface applications</b> in bait stations (see Fig. 1 of paper). Study period: 2008-2009.  Strychnine (not an anticoagulant) also used in area.	Possible of poisoning of Swainson's Hawk ( <i>Buteo swainsoni</i> ) and burrowing owl ( <i>Athene cunicularia</i> ). No reports of residues in birds. Working Note: Except for the reports of hemorrhaging, it seems difficult to assess effects of chlorophacinone relative to strychnine.	Proulx 2011
Wild turkeys ( <i>Meleagris gallopavo</i> ), n=2 Kansas	Chlorophacinone had been used locally for the control of black-tailed prairie dog.	Moderate hemorrhage and edema. Chlorophacinone at 0.4 and 0.69 ppm in liver.	Ruder et al. 2011
Wild turkeys ( <i>Meleagris gallopavo</i> ), large groups Kansas	Possible source of chlorophacinone not identified. 6 turkeys examined.	Internal hemorrhaging. Chlorophacinone not detected in liver but was detected in the crop of one turkey. Working Note: Involvement of chlorophacinone in deaths seems unclear.	Ruder et al. 2011
Birds, 42 species (n=271) Spain	Exposures appear to be associated with <b>surface applications</b> .	72/271 (~26.6%) positive for chlorophacinone. Most (n=62) found in rock doves ( <i>Columba livia</i> ) which also had the highest geometric mean liver concentration of 4.15 µg/g. High concentrations in primary consumers associated with surface application. Working Note: Hemorrhages commonly noted but difficult to correlate with exposures	Sanchez-Barbudo et al. 2012
Domestic pigeons ( <i>Columba livia</i> ), n=29 Spain	Chlorophacinone (0.005% in wheat grain) applied to area for control of voles. <b>Appears to be surface application.</b> Pigeons from four different areas.	Hemorrhaging in multiple organs was dominant sign of toxicity. Most severe lesions in lungs. Two pigeons had pericardiac hemorrhages. Concentration in liver of 11.2 (1.48-50.1) µg/g. Four pigeons with no indication of hemorrhages had concentrations of chlorophacinone in the liver of 5.66 to 34.97 µg/g.	Sarabia et al. 2008



**Appendix 2: Toxicity to birds** (*continued*)

**A2 Table 5: Reproductive/ Subchronic Toxicity to Birds**

<b>Species</b>	<b>Exposure</b>	<b>Response</b>	<b>Reference<sup>[1]</sup></b>
Japanese quail, 12 male and 12 females per dose.	13 week dietary (90-day) exposures. 0.25% oil concentrate  Working Note: Based on a food consumption rate of 0.07 kg food/kg bw/day in quail (SERA 2007a), the NOAEC of 1 mg a.i./kg diet corresponds to a daily dose of 0.07 mg a.i./kg bw).	NOAEC: 1 mg a.i./kg diet  LOAEC: 2 mg a.i./kg diet Increased mortality  Frank Effects: 4 and 8 mg/kg diet. Mortality, increased coagulation times, microcytic anemia.  No effect on offspring.	MRID 47323201, supplemental  Published in German literature as Riedel et al. 1990.

**Appendix 3: GLEAMS-Driver Simulations**

**Table 1: Effective Offsite Application Rate (lb/acre)**

<b>Site</b>	<b>Clay</b>	<b>Loam</b>	<b>Sand</b>
Dry and Warm Location	3.60E-06 (0 - 0.00217)	0 (0 - 0.00055)	0 (0 - 0)
Dry and Temperate Location	0.000304 (0 - 0.0041)	0 (0 - 0.00148)	0 (0 - 0)
Dry and Cold Location	0.000094 (0 - 0.00056)	0 (0 - 1.01E-05)	0 (0 - 0)
Average Rainfall and Warm Location	0.0033 (0.00045 - 0.0161)	0.00158 (2.64E-05 - 0.0135)	0 (0 - 2.62E-05)
Average Rainfall and Temperate Location	0.0033 (0.0011 - 0.0123)	0.00096 (0.000108 - 0.0075)	0 (0 - 0)
Average Rainfall and Cool Location	0.0045 (0.002 - 0.0092)	0.00097 (0.000169 - 0.0049)	0 (0 - 0)
Wet and Warm Location	0.0113 (0.0033 - 0.0277)	0.0075 (0.00182 - 0.0218)	2.56E-05 (0 - 0.00246)
Wet and Temperate Location	0.0315 (0.0166 - 0.058)	0.0163 (0.0088 - 0.042)	0 (0 - 0.00257)
Wet and Cool Location	0.035 (0.0215 - 0.057)	0.0115 (0.0057 - 0.0301)	0 (0 - 0.00033)
Average of Central Values:	0.0099	0.0043	2.84E-06
25th Percentile:	3.04E-04	0	0
Maximum:	0.058	0.042	0.00257
Summary:	0.0099 (3.04E-04 - 0.058)	0.0043 (0 - 0.042)	2.84E-06 (0 - 0.00257)

Appendix 3: GLEAMS-Driver Simulations (*continued*)

Table 2: Concentration in Top 12 Inches of Soil (ppm)

<b>Site</b>	<b>Clay</b>	<b>Loam</b>	<b>Sand</b>
Dry and Warm Location	0.262 (0.262 - 0.264)	0.231 (0.231 - 0.232)	0.231 (0.231 - 0.232)
Dry and Temperate Location	0.27 (0.263 - 0.282)	0.238 (0.233 - 0.249)	0.238 (0.232 - 0.249)
Dry and Cold Location	0.41 (0.37 - 0.43)	0.36 (0.315 - 0.38)	0.36 (0.32 - 0.39)
Average Rainfall and Warm Location	0.262 (0.262 - 0.262)	0.231 (0.231 - 0.232)	0.231 (0.231 - 0.232)
Average Rainfall and Temperate Location	0.268 (0.263 - 0.281)	0.237 (0.232 - 0.248)	0.237 (0.232 - 0.244)
Average Rainfall and Cool Location	0.288 (0.269 - 0.314)	0.257 (0.237 - 0.276)	0.254 (0.239 - 0.276)
Wet and Warm Location	0.262 (0.262 - 0.263)	0.231 (0.231 - 0.232)	0.231 (0.231 - 0.232)
Wet and Temperate Location	0.277 (0.265 - 0.295)	0.244 (0.234 - 0.26)	0.245 (0.234 - 0.261)
Wet and Cool Location	0.34 (0.301 - 0.36)	0.295 (0.257 - 0.32)	0.297 (0.264 - 0.32)
Average of Central Values:	0.293	0.258	0.258
25th Percentile:	0.262	0.231	0.231
Maximum:	0.43	0.38	0.39
Summary:	0.293 (0.262 - 0.43)	0.258 (0.231 - 0.38)	0.258 (0.231 - 0.39)

Appendix 3: GLEAMS-Driver Simulations (*continued*)

Table 3: Concentration in Top 36 Inches of Soil (ppm)

<b>Site</b>	<b>Clay</b>	<b>Loam</b>	<b>Sand</b>
Dry and Warm Location	0.087 (0.087 - 0.088)	0.077 (0.077 - 0.077)	0.077 (0.077 - 0.077)
Dry and Temperate Location	0.09 (0.088 - 0.094)	0.079 (0.078 - 0.083)	0.079 (0.077 - 0.083)
Dry and Cold Location	0.137 (0.125 - 0.145)	0.119 (0.105 - 0.127)	0.12 (0.106 - 0.128)
Average Rainfall and Warm Location	0.087 (0.087 - 0.087)	0.077 (0.077 - 0.077)	0.077 (0.077 - 0.077)
Average Rainfall and Temperate Location	0.089 (0.088 - 0.094)	0.079 (0.077 - 0.083)	0.079 (0.077 - 0.081)
Average Rainfall and Cool Location	0.096 (0.09 - 0.105)	0.086 (0.079 - 0.092)	0.085 (0.08 - 0.092)
Wet and Warm Location	0.087 (0.087 - 0.088)	0.077 (0.077 - 0.077)	0.077 (0.077 - 0.077)
Wet and Temperate Location	0.092 (0.088 - 0.098)	0.081 (0.078 - 0.087)	0.082 (0.078 - 0.087)
Wet and Cool Location	0.112 (0.1 - 0.121)	0.098 (0.086 - 0.106)	0.099 (0.088 - 0.108)
Average of Central Values:	0.097	0.086	0.086
25th Percentile:	0.087	0.077	0.077
Maximum:	0.145	0.127	0.128
Summary:	0.097 (0.087 - 0.145)	0.086 (0.077 - 0.127)	0.086 (0.077 - 0.128)

Appendix 3: GLEAMS-Driver Simulations (*continued*)

Table 4: Maximum Penetration into Soil Column (inches)

<b>Site</b>	<b>Clay</b>	<b>Loam</b>	<b>Sand</b>
Dry and Warm Location	4 (4 - 8)	4 (4 - 8)	8 (4 - 8)
Dry and Temperate Location	8 (4 - 8)	8 (4 - 8)	8 (8 - 8)
Dry and Cold Location	8 (4 - 8)	8 (4 - 8)	8 (8 - 8)
Average Rainfall and Warm Location	8 (8 - 8)	8 (8 - 8)	8 (8 - 12)
Average Rainfall and Temperate Location	8 (8 - 8)	8 (8 - 8)	8 (8 - 12)
Average Rainfall and Cool Location	8 (8 - 8)	8 (8 - 8)	12 (8 - 12)
Wet and Warm Location	8 (8 - 8)	8 (8 - 8)	12 (8 - 12)
Wet and Temperate Location	8 (8 - 8)	8 (8 - 12)	12 (12 - 12)
Wet and Cool Location	8 (8 - 8)	8 (8 - 12)	12 (12 - 12)
Average of Central Values:	7.56	7.56	9.78
25th Percentile:	8	8	8
Maximum:	8	12	12
Summary:	7.56 (8 - 8)	7.56 (8 - 12)	9.78 (8 - 12)

Appendix 3: GLEAMS-Driver Simulations (*continued*)

Table 5: Stream, Maximum Peak Concentration in Surface Water (ug/L or ppb)

<b>Site</b>	<b>Clay</b>	<b>Loam</b>	<b>Sand</b>
Dry and Warm Location	0.003 (0 - 1.36)	0 (0 - 0.5)	0 (0 - 0)
Dry and Temperate Location	0.18 (0 - 1.93)	0 (0 - 1)	0 (0 - 0)
Dry and Cold Location	0.06 (0 - 0.32)	0 (0 - 0.008)	0 (0 - 0)
Average Rainfall and Warm Location	1.5 (0.25 - 8.8)	1.08 (0.017 - 8)	0 (0 - 0.023)
Average Rainfall and Temperate Location	1.03 (0.3 - 4.6)	0.5 (0.05 - 3.5)	0 (0 - 0)
Average Rainfall and Cool Location	0.9 (0.4 - 2.74)	0.4 (0.07 - 1.77)	0 (0 - 0)
Wet and Warm Location	4 (1 - 12)	3.5 (0.7 - 12.3)	0.019 (0 - 2.23)
Wet and Temperate Location	4.5 (2.07 - 14.4)	3.9 (1.55 - 13.7)	0 (0 - 1.57)
Wet and Cool Location	2.73 (1.06 - 8.2)	1.74 (0.5 - 6.8)	0 (0 - 0.27)
Average of Central Values:	1.66	1.24	0.00211
25th Percentile:	0.18	0	0
Maximum:	14.4	13.7	2.23
Summary:	1.66 (0.18 - 14.4)	1.24 (0 - 13.7)	0.00211 (0 - 2.23)

Appendix 3: GLEAMS-Driver Simulations (*continued*)

Table 6: Stream, Annual Average Concentration in Surface Water (ug/L or ppb)

<b>Site</b>	<b>Clay</b>	<b>Loam</b>	<b>Sand</b>
Dry and Warm Location	0.00022 (0 - 0.011)	0 (0 - 0.003)	0 (0 - 0)
Dry and Temperate Location	0.0017 (0 - 0.021)	0 (0 - 0.007)	0 (0 - 0)
Dry and Cold Location	0.0005 (0 - 0.0025)	0 (0 - 0.00006)	0 (0 - 0)
Average Rainfall and Warm Location	0.02 (0.003 - 0.09)	0.009 (0.00014 - 0.07)	0 (0 - 0.00011)
Average Rainfall and Temperate Location	0.026 (0.01 - 0.07)	0.006 (0.0007 - 0.031)	0 (0 - 0)
Average Rainfall and Cool Location	0.025 (0.012 - 0.05)	0.005 (0.001 - 0.023)	0 (0 - 0)
Wet and Warm Location	0.08 (0.021 - 0.16)	0.05 (0.016 - 0.11)	0.00012 (0 - 0.01)
Wet and Temperate Location	0.17 (0.11 - 0.28)	0.09 (0.04 - 0.18)	0 (0 - 0.009)
Wet and Cool Location	0.13 (0.08 - 0.2)	0.04 (0.019 - 0.1)	0 (0 - 0.0015)
Average of Central Values:	0.05	0.0222	1.33E-05
25th Percentile:	0.0017	0	0
Maximum:	0.28	0.18	0.01
Summary:	0.05 (0.0017 - 0.28)	0.0222 (0 - 0.18)	1.33E-05 (0 - 0.01)

Appendix 3: GLEAMS-Driver Simulations (*continued*)

Table 7: Pond, Maximum Peak Concentration in Surface Water (ug/L or ppb)

<b>Site</b>	<b>Clay</b>	<b>Loam</b>	<b>Sand</b>
Dry and Warm Location	0.0008 (0 - 0.4)	0 (0 - 0.14)	0 (0 - 0)
Dry and Temperate Location	0.05 (0 - 0.5)	0 (0 - 0.3)	0 (0 - 0)
Dry and Cold Location	0.016 (0 - 0.1)	0 (0 - 0.0026)	0 (0 - 0)
Average Rainfall and Warm Location	0.4 (0.06 - 1.07)	0.25 (0.005 - 1)	0 (0 - 0.004)
Average Rainfall and Temperate Location	0.28 (0.09 - 1.04)	0.13 (0.015 - 0.8)	0 (0 - 0)
Average Rainfall and Cool Location	0.24 (0.1 - 0.5)	0.09 (0.026 - 0.3)	0 (0 - 0)
Wet and Warm Location	0.6 (0.19 - 1.27)	0.5 (0.12 - 1.27)	0.0027 (0 - 0.23)
Wet and Temperate Location	0.6 (0.3 - 1.26)	0.5 (0.23 - 1.4)	0 (0 - 0.21)
Wet and Cool Location	0.4 (0.2 - 0.8)	0.28 (0.1 - 1.1)	0 (0 - 0.031)
Average of Central Values:	0.287	0.194	0.0003
25th Percentile:	0.05	0	0
Maximum:	1.27	1.4	0.23
Summary:	0.287 (0.05 - 1.27)	0.194 (0 - 1.4)	0.0003 (0 - 0.23)



Appendix 3: GLEAMS-Driver Simulations (*continued*)

Table 8: Pond, Annual Average Concentration in Surface Water (ug/L or ppb)

<b>Site</b>	<b>Clay</b>	<b>Loam</b>	<b>Sand</b>
Dry and Warm Location	0.000007 (0 - 0.004)	0 (0 - 0.0015)	0 (0 - 0)
Dry and Temperate Location	0.0006 (0 - 0.007)	0 (0 - 0.003)	0 (0 - 0)
Dry and Cold Location	0.00018 (0 - 0.001)	0 (0 - 0.000025)	0 (0 - 0)
Average Rainfall and Warm Location	0.006 (0.0012 - 0.019)	0.004 (0.00006 - 0.013)	0 (0 - 0.00005)
Average Rainfall and Temperate Location	0.01 (0.004 - 0.022)	0.0028 (0.0003 - 0.012)	0 (0 - 0)
Average Rainfall and Cool Location	0.009 (0.004 - 0.016)	0.002 (0.0005 - 0.008)	0 (0 - 0)
Wet and Warm Location	0.016 (0.006 - 0.032)	0.011 (0.004 - 0.023)	0.00003 (0 - 0.0029)
Wet and Temperate Location	0.03 (0.021 - 0.05)	0.018 (0.009 - 0.04)	0 (0 - 0.0023)
Wet and Cool Location	0.029 (0.018 - 0.04)	0.011 (0.005 - 0.024)	0 (0 - 0.0004)
Average of Central Values:	0.0112	0.0054	3.30E-06
25th Percentile:	0.0006	0	0
Maximum:	0.05	0.04	0.0029
Summary:	0.0112 (0.0006 - 0.05)	0.0054 (0 - 0.04)	3.30E-06 (0 - 0.0029)