SELECTED COMMERCIAL FORMULATIONS OF HEXAZINONE - Human Health and Ecological Risk Assessment Final Draft

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ACRONYMS, ABBREVIATIONS, AND SYMBOLS

2,4-D	dichlorophenoxyacetic acid
a.i.	active ingredient
AEL	adverse-effect level
ACGIH	American Conference of Governmental Industrial Hygienists
AChE	acetylcholinesterase
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
bw	body weight
CBI	confidential business information
cm	centimeter
CNS	central nervous system
DAA	days after application
DF	dry flowable
d.f.	degrees of freedom
EC_{25}	concentration causing 25% inhibition of a process
EC_{50}	concentration causing 50% inhibition of a process
F	female
F_1	first filial generation
g	gram
HQ	hazard quotient
k_a	absorption coefficient
k_e	elimination coefficient
kg	kilogram
$K_{o/c}$	organic carbon partition coefficient
$K_{o/w}$	octanol-water partition coefficient
Kp	skin permeability coefficient
L	liter
lb	pound
LC_{50}	lethal concentration, 50% kill
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
m	meter
M	male
MCS	multiple chemical sensitivity
mg	milligram
mg/kg/day	milligrams of agent per kilogram of body weight per day
mL	milliliter
mM	millimole
MW	molecular weight
MOS	margin of safety
MSDS	material safety data sheet
NCI	National Cancer Institute

ACRONYMS, ABBREVIATIONS, AND SYMBOLS (*continued*)

NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NRC	National Research Council
OPPTS	Office of Pesticide Planning and Toxic Substances
ppm	parts per million
PSP	phenolsulfonphthalein
RBC	red blood cells
RfD	reference dose
UF	uncertainty factor
ULW	ultra low weight
U.S.	United States
U.S. EPA	U.S. Environmental Protection Agency
>	greater than
≥	greater than or equal to
<	less than
≤	less than or equal to
=	equal to
≃	approximately equal to
~	approximately

COMMON UNIT CONVERSIONS AND ABBREVIATIONS

To convert ...	Into ...	Multiply by ...
acres	hectares (ha)	0.4047
acres	square meters (m^2)	4,047
atmospheres	millimeters of mercury	760
centigrade	Fahrenheit	1.8C°+32
centimeters	inches	0.3937
cubic meters (m^3)	liters (L)	1,000
Fahrenheit	centigrade	0.556F°-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 (hg/ha)	pounds per acre (lb/acre)	0.892
kilometers (km)	miles (mi)	0.6214
liters (L)	cubic centimeters (cm^3)	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^3)	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 gallon (lb/gal)	grams per liter (g/L)	119.8
square centimeters (cm^2)	square inches (in^2)	0.155
square centimeters (cm^2)	square meters (m^2)	0.0001
square meters (m^2)	square centimeters (cm^2)	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

BACKGROUND

Hexazinone is a s-triazine herbicide that inhibits photosynthesis and is used by the Forest Service in vegetation management programs. At ambient temperatures, hexazinone is a white crystalline solid that is chemically stable, highly soluble in water, and relatively insoluble in various organic solvents. All currently marketed commercial formulations of hexazinone are granular. Most of these are applied as dry granules (Pronone 10G, Pronone MG, Velpar ULW, and Velpar ULW DF). One granular formulation, Velpar DF, is applied as an aqueous suspension. A liquid formulation of hexazinone, Velpar L, is no longer marketed; however, existing stock may still be used.

Both liquid and granular formulations of hexazinone may be used in aerial or ground applications. Virtually all of the hexazinone used by the Forest Service in 1995 involved either site preparation or conifer release. Relatively small amounts have been used for noxious weed control and hardwood thinning. The average application rates used by the Forest Service in site preparation (2.5 lbs a.i./acre) and conifer release (1.4 lbs a.i./acre) are at the lower end of the recommended labeled rate. Usually, application rates used by the Forest Service will not exceed 4 lbs a.i./acre, although applications of up to 6 lbs a.i./acre may be used in some cases. Preliminary figures for 1996 indicate that hexazinone use has increased from previous years to about 16,000 lbs a.i. applied to about 10,000 acres.

HUMAN HEALTH RISK ASSESSMENT

The toxicity of hexazinone is relatively well characterized in experimental mammals. The acute toxicity of hexazinone is low, with oral LD_{50} values in experimental mammals ranging from approximately 500 to 3500 mg/kg. There are no remarkable or systematic differences in sensitivity among various species.

The effects observed in mammals after subchronic or chronic exposure to hexazinone are generally limited to decreases in body weight, increases in liver weight, and changes in blood enzyme levels associated with liver toxicity. Although the mechanism of action is unclear, the signs of acute toxicity are generally consistent with cholinesterase inhibiting pesticides. No studies that assay the affect of hexazinone on cholinesterase activity were encountered in the literature. At doses that are substantially greater than the threshold for systemic toxic effects, hexazinone may cause reproductive effects, including kidney abnormalities and/or delayed ossification as well as decreases in the survival rate of offspring in experimental mammals.

There are limited data suggesting that hexazinone may be a carcinogen. These data are limited to a 2-year bioassay in mice in which females but not males had a slight increase in the total number of malignant tumors. The U.S. EPA judged that this dose-response pattern is equivocal evidence for carcinogenicity and designated hexazinone as Class D, not classifiable as to human carcinogenicity. U.S. EPA does not recommend a quantitative risk assessment of hexazinone

based on carcinogenicity. An independent review of this study was conducted as part of this risk assessment. This independent review supports the position of the U.S. EPA.

Both powdered and liquid formulations of hexazinone as well as technical grade hexazinone are shown to be moderate to severe eye irritants. The available human data suggest that dust associated with the application of some batches of granular formulations may be sufficiently dense to cause eye irritation and respiratory tract irritation in workers.

As discussed in the exposure assessment, dermal exposure is the primary route of concern for workers. The available data indicate that the dermal toxicity of hexazinone is relatively low and that hexazinone is not well absorbed after dermal exposure. Nonetheless, an occupational study of workers applying a granular formulation of hexazinone indicates that dermal absorption will occur.

Two studies are available on worker exposure, one involving biomonitoring of hexazinone levels in the urine and the other involving estimates of dermal deposition and inhalation. In general, worker exposure to hexazinone is likely to compare with exposure to 2,4-D, given appropriate corrections for differences in dermal absorption rates. Workers involved in the ground or aerial application of liquid formulations will receive similar levels of exposure, with central estimates of about 0.01-0.03 mg/kg/day per lb a.i. applied per acre.

The use of an over the shoulder broadcast applicator (*belly grinder*) in the ground application of a granular formulation of hexazinone may lead to levels of exposure that are about an order of magnitude higher, about 0.2 mg/kg/day per lb a.i. applied per acre. The difference in anticipated exposure levels appears to be due to the nature of the application device. This piece of equipment is a spreader that is strapped to the torso, and the granules are dispensed from the base of a hopper by turning a side-mounted handle.

It is not clear that all applications of granular formulations of hexazinone will result in similarly high levels of exposure. The available data on 2,4-D suggest that in some applications, workers applying liquid and granular formulations will receive comparable levels of exposure.

Except for accidental exposure scenarios, the general public should be exposed to hexazinone at levels far less than those for workers. Most routine exposure scenarios lead to estimated daily doses in the range of 0.001-0.006 mg/kg/day. Nonetheless, hexazinone is relatively persistent in the environment and is transported to groundwater and surface water. Consequently, subchronic exposure to hexazinone is plausible.

The U.S. EPA derived two RfDs for hexazinone. The RfD currently listed on IRIS is 0.033 mg/kg/day. In the re-registration process, the U.S. EPA Office of Pesticides derived an RfD of 0.05 mg/kg/day, based on more recent data that addresses some of the concerns with the original RfD. Relative to the wide range of exposures derived in the exposure assessment, there is functionally no difference between the RfDs of 0.033 mg/kg/day and 0.05 mg/kg/day. The more

recent RfD of 0.05 mg/kg/day is used in this risk assessment as the basis for characterizing risk. The available animal toxicity data are used qualitatively to characterize plausible effects associated with exposure above the RfD.

The major hazard associated with the use of hexazinone will involve accidental or incidental ocular or respiratory tract exposure. Hexazinone is a severe eye irritant. In addition, respiratory tract irritation was noted in workers applying granular formulations of hexazinone that contained high levels of dust or fine particulates.

For workers, the uncertainties in the characterization of risk is dominated by the very wide range of projected exposures. Over the range of plausible application rates, all worker groups may be exposed to hexazinone at levels that exceed the RfD. Although workers using a *belly grinder* may be exposed to much higher levels of hexazinone, compared with other worker groups, the basic characterizations of risks are similar for all worker groups. The effects that are most likely to be observed after exposure to hexazinone are irritation to the eyes, respiratory tract, and skin. In general, irritant effects on the eyes and respiratory tract are likely to be more severe than effects on the skin. Even under the most extreme exposure scenarios, frank systemic effects are not likely to be observed. Nonetheless, using the available animal data to characterize dose-severity relationships, the upper estimates of exposure levels could be associated with subclinical effects and possibly reproductive effects.

In some accidental and extreme exposure scenarios, members of the general public may be exposed to levels of hexazinone above the RfD but still far below the levels projected for workers. While any exposure above the RfD is considered unacceptable by definition, the exposure estimates for the general public are in a range where the occurrence and nature of potential toxic effects cannot be well characterized. For the general public, as for workers, no signs of frank systemic effects are anticipated after accidental exposure to hexazinone.

ECOLOGICAL RISK ASSESSMENT

The toxicity of hexazinone to terrestrial wildlife, particularly invertebrates, is not well characterized. Consequently, the assessment of effects on terrestrial species is based primarily on the available data on experimental mammals. Although the limited data available regarding the toxicity of hexazinone to wildlife and the observations from the available field studies do not suggest cause for substantial concern, field studies usually are not designed to detect effects on nontarget species. One field study that was designed to detect effects on nontarget terrestrial species suggests that hexazinone may have an effect on the behavior of soil mites. It is not clear, however, that the observed effect—changes in the position of mites in the soil column—is related to toxicity, avoidance, or some other unidentified factor.

The toxicity of hexazinone to terrestrial plants is well characterized, as is true for most herbicides. In addition to the inhibition of photosynthesis, hexazinone also inhibits the synthesis of RNA, proteins, and lipids. Hexazinone is absorbed readily by plant roots, and, once absorbed, is

translocated readily in most species. Although some foliar absorption may occur, the major route of exposure involves hexazinone washing from the soil surface to the root system of plants, where it is readily absorbed. The differential toxicity of hexazinone to plants is based on variations in the ability of different plants to absorb, degrade, and eliminate the herbicide.

Effects on plants may lead to secondary ecological effects due to changes in habitat, food supply, lighting, and other conditions. For example, the use of a herbicide or a mechanical treatment to remove or suppress hardwood species and encourage the growth of conifer species will lead to secondary effects on terrestrial animals. Such changes are associated with changes in plant cover or composition and are not specific to hexazinone or even to herbicide use in general. Consequently, such changes are not addressed specifically in this risk assessment.

The toxicity of hexazinone to aquatic species is well-characterized. Comparable studies on aquatic algae and aquatic animals clearly indicate that most algal species are much more sensitive to hexazinone (EC_{50} values for growth inhibition of 0.003-10 mg/L), compared with fish and aquatic invertebrates (LC_{50} values generally greater than 100 mg/L). By analogy to the toxicity of hexazinone to terrestrial plants, it seems likely that aquatic macrophytes also may be very sensitive to the toxic effects of hexazinone. Other than lethality, the most common effect noted on aquatic animals is growth inhibition, which is also the most sensitive effect in experimental mammals. Only one study on amphibians is available in the literature, and it suggests that amphibians are less sensitive to hexazinone than fish or aquatic invertebrates.

Based on the available toxicity data and the estimated levels of exposure, there is very little indication that hexazinone is likely to cause adverse effects in terrestrial animal species. The consumption of contaminated water or vegetation yields hazard indices that are far below a level of concern at any plausible application rate either immediately after hexazinone applications or over prolonged periods after applications.

One potential exception involves an exposure scenario in which birds consume hexazinone granules immediately after application. In this instance, reproductive effects and possibly overt signs of toxicity are possible. The plausibility of this risk for birds, however, is questionable. There are no data indicating that birds will consume any of the granular formulations that contain hexazinone. Thus, a lower limit on the exposure assessment is zero. If birds were to consume these granules preferentially, exposure levels could be much higher. In such a case, toxic effects including mortality could occur. Without additional information with which to improve the exposure assessment, this risk cannot be characterized further.

Nontarget terrestrial plants may be affected during the application of hexazinone. Direct deposition, from unintentional direct spraying or from spray drift is a plausible hazard for most herbicides, including those containing hexazinone. If plants are sprayed accidentally at the application rates used by the Forest Service, the plants, particularly hardwoods or sensitive pines, are likely to be damaged. During aerial applications at a rate of 1 lb a.i./acre and at distances less than 30 m from the application site, some damage to nontarget vegetation is plausible due to drift

of liquid formulations. Ground applications of granular formulations or spot treatments with liquid applications of hexazinone should be associated with little significant drift. Soil contamination and transport of hexazinone to offsite nontarget vegetation, however, may occur. The magnitude of any observed effects will be determined predominantly by local conditions, particularly soil type and rainfall. In porous and/or sandy soils with low levels of organic matter and under conditions of high rainfall, adverse effects on offsite vegetation are most plausible.

Under any plausible conditions of exposure, including accidental direct applications to a stream, effects on fish or aquatic invertebrates are unlikely. Conversely, effects on algal species are virtually certain but are likely to be transient because of the transport and dilution of hexazinone in aquatic systems. Based on stream ecosystem studies, it is unclear that changes in the population of aquatic algae will lead to detectable secondary ecological effects on aquatic animals.

1. INTRODUCTION

Hexazinone is a herbicide used by the Forest Service in vegetation management programs. One liquid formulation (Velpar L) and four granular formulations (Velpar ULW DF, Velpar DF, Pronone 10G, and Pronone MG) may be used, primarily for site preparation and conifer release. The production of Velpar L was discontinued recently; however, the product is included in this risk assessment because existing stock may still be used. In 1989, the Southern Region of the Forest Service prepared a series of environmental impact statements with accompanying risk assessments that concern the use of these products (USDA 1989a,b,c). The present document provides updated risk assessments for both human health and ecological effects to support a reassessment of the environmental consequences of using these products in future Forest Service programs.

This document has four chapters, including the introduction, program description, risk assessment for human health effects, and risk assessment for ecological effects or effects on wildlife species. Each of the two risk assessment chapters has four major sections, including an identification of the hazards associated with the commercial formulations of hexazinone, an assessment of potential exposure to these products, an assessment of the dose-response relationships, and a characterization of the risks associated with plausible levels of exposure. These are the basic steps recommended by the National Research Council of the National Academy of Sciences (NRC 1983) for conducting and organizing risk assessments.

Although this is a technical support document and addresses some specialized technical areas, an effort has been 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 and terms common to all parts of the risk assessment are described in as plain a language as possible in a separate document: *The Preparation of Environmental Documentation and Risk Assessments for the Forest Service* (SERA 1995a). In addition, these terms are defined in the glossary to this risk assessment. Moreover, some of the more complicated terms and concepts are defined, as necessary, in the text.

The risk assessments presented in this document are not, and are not intended to be, comprehensive summaries of all of the available information. Much of the early literature is summarized in the previous chemical background statement on hexazinone (Sassaman et al. 1984), previous risk assessments and environmental impact statements covering this compound (USDA 1989a,b,c), as well as unpublished reviews prepared for the U.S. EPA (Ghassemi et al. 1981) and the Department of Natural Resources of the State of Washington (Shipp et al. 1986).

As part of the pesticide registration process, manufacturers are required to conduct various studies regarding the toxicity and environmental fate of pesticides. These studies are classified as confidential business information (CBI) and, although these studies are submitted to the U.S. EPA, they are not generally released for public review. Summaries of the studies used in the original registration process are contained in the various reviews cited above. The U.S. EPA has

reviewed additional studies on hexazinone and hexazinone formulations, including more recent CBI studies, as part of the reregistration process. Summaries of these studies have been published by U.S. EPA (1994a). As necessary, copies of the original studies have been obtained from the U.S. EPA as part of this risk assessment.

Because the existing reviews provide adequate summaries of most of the available information on hexazinone and in the interest of economy, an updated chemical background statement has not been prepared with the current risk assessment. Much of the information that would be included in such an update is presented in the above cited reviews. In addition, the information most relevant to this risk assessment, taken from previous reviews as well as more recent publications, is summarized in the appendices that accompany this document.

2. PROGRAM DESCRIPTION

2.1. OVERVIEW

Hexazinone is a s-triazine herbicide that inhibits photosynthesis. At ambient temperatures, hexazinone is a white crystalline solid that is chemically stable, highly soluble in water, and relatively insoluble in various organic solvents. All currently marketed commercial formulations of hexazinone are granular. Most of these are applied as dry granules (Pronone 10G, Pronone MG, Velpar ULW, and Velpar ULW DF). One granular formulation, Velpar DF, is applied as an aqueous suspension. A liquid formulation of hexazinone, Velpar L, is no longer marketed; however, existing stock may still be used.

Both liquid and granular formulations of hexazinone may be used in ground or aerial applications. Virtually all (99.9%) of the hexazinone used by the Forest Service in 1995 involved either site preparation (~60%) or conifer release (~39.9%). Relatively small amounts (6.3 of 6377.3 lbs) were used for noxious weed control and hardwood thinning. The average application rates used by the Forest Service in site preparation (2.5 lbs a.i./acre) and conifer release (1.4 lbs a.i./acre) are at the lower end of the recommended labeled rate. Usually, application rates used by the Forest Service will not exceed 4 lbs a.i./acre, although applications of up to 6 lbs a.i./acre may be used in some cases. Preliminary figures for 1996 indicate that hexazinone use has increased from previous years to about 16,000 lbs a.i. applied to about 10,000 acres.

2.2. CHEMICAL DESCRIPTION AND COMMERCIAL FORMULATIONS

Hexazinone is the common name for 3-cyclohexyl-6-dimethylamino-1-methyl-1,3,5-triazine-2,4(1*H*,3*H*)-dione:

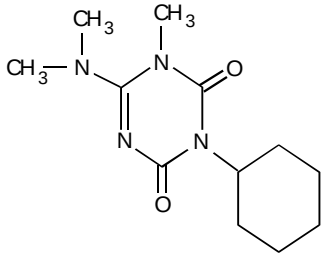

Table 2-1. Nomenclature and properties of hexazinone

Element	Description (Source)
CAS Name	3-cyclohexyl-6-dimethylamino-1-methyl-1,3,5-triazine-2,4(1*H*,3*H*)-dione
CAS Number	51235-04-2 (Budavari et al. 1989, Tomlin 1994)
Physical form	white odorless crystals at ambient temperature (Tomlin 1994, WSSA 1989)
Molecular weight	252.3 (Tomlin 1994, WSSA 1989)
Melting point	115-117°C (Tomlin 1994, WSSA 1989) 97-100.5°C (Budavari et al. 1989)
Density	1.25 (Tomlin 1994, WSSA 1989)
Vapor pressure	0.03 mPa at 25°C (Tomlin 1994) 85 mPa at 86°C (Tomlin 1994) $6.4 \bullet 10^{-5}$ mm Hg at 86°C (WSSA 1989)
Water solubility	33 g/kg at 25°C (Tomlin 1994, WSSA 1989)
K_{ow}	11.3 at pH 7 (Tomlin 1994)
Chemical stability	Stable in aqueous media between pH 5 and pH 9 and below 37°C. Stable to light (Tomlin 1994). Photodegradation is enhanced in aqueous solutions by the presence of inorganic salts (WSSA 1989).

K_{ow} = Octanol/water partition coefficient

A general description of the chemical and physical properties of hexazinone is presented in Table 2-1. At ambient temperatures, hexazinone is a white crystalline solid that is chemically stable, highly soluble in water, and relatively insoluble in various organic solvents (i.e., has a low K_{ow}). The binding of hexazinone to soil is highly dependent on soil type; hence, K_{oc} values are not summarized in Table 2-1. Soil binding and transport are discussed in detail in section 4.2.2.2.

The primary mechanism of phytotoxicity for hexazinone involves the inhibition of photosynthesis (Sung et al. 1985, Wood et al. 1992). Hexazinone is absorbed rapidly by plant roots and readily translocated in most species (Wood et al. 1993, Yanase and Andoh 1992). Although some foliar absorption may occur, most application methods involve soil treatment with subsequent washing into the soil column and absorption by the roots into the plant (Glover et al. 1991).

Table 2-2. Summary of commercial formulations containing hexazinone covered by this risk assessment

Formulation (Producer)	Ingredient	Concentration of Ingredient	Type of Formulation
Velpar L (Du Pont) [a]	hexazinone (25% w/w) ethanol (40-45% w/w) other inerts (30-35% w/w)	2 lbs/gal	Sprayable liquid, specific gravity of 0.9776.
Velpar ULW (Du Pont) [b]	hexazinone (75% w/w) inerts (25%)	0.75 lb/lb	granules, specific gravity of 1.25.
Velpar ULW DF (Du Pont) [c]	hexazinone (75% w/w) inerts (25%)	0.75 lb/lb	granules, density 0.73 g/ml
Velpar DF (Du Pont) [d]	hexazinone (75% w/w) inerts (25%)	0.75 lb/lb	water-dispersible granules, density 0.58 g/ml
Pronone 10G [e] (Pro-Serve, Inc.)	hexazinone (10% w/w) inerts (90% w/w)	0.1 lb/lb	granules, 1/8-1/4" [3.8-7.6 cm] density 35-40 lb/cu. ft. [0.56-0.64 g/cm^3]
Pronone MG [f] (Pro-Serve, Inc.)	hexazinone (10% w/w) inerts (90%)	0.1 lb/lb	granules, 1/16-1/8" [1.9-3.8 cm] density 35-40 lb/cu. ft. [0.56-0.64 g/cm^3]

[a] Du Pont 1993a and 1993b.
[b] Du Pont 1992 and 1994.
[c] Du Pont 1996a and 1997a.
[d] Du Pont 1996b,c, 1997b.
[e] Pro-Serve, Inc. 1991 and 1993a
[f] Pro-Serve, Inc. 1993b

The commercial formulations of hexazinone covered by this risk assessment are summarized in Table 2-2. Only one liquid formulation, Velpar L, is used by the Forest Service. The production of Velpar L was discontinued recently; however, existing stock may still be used. Consequently, Velpar L is included in this risk assessment. As indicated in Table 2-2, Velpar L contains 25% hexazinone and 40-45% (w/w) ethanol. The other hexazinone products are formulated as granules. An early formulation, referred to as Velpar Gridballs, contained an average of 0.35 g of hexazinone per pellet (Miller and Bace 1980).

According to Feng et al. (1989a), Pronone 10G consists of 2-5 mm particles with an average weight of 20 mg per particle. This particle size is in the range of that reported by Pro-Serve (1993a,b) for Pronone 10G and Pronone MG. The particles consist of an insoluble clay-based material that is surface coated with hexazinone. The granules have an outer coating of a hexazinone-free material that is designed to minimize the formation of dust (Feng et al. 1989a).

Details regarding the precise differences between Velpar ULW, Velpar ULW DF, and Velpar DF are not available in the open literature. All three formulations are granular and all three contain hexazinone at a concentration of 75% w/w. The only apparent difference among these formulations is density. Velpar ULW has a specific gravity of 1.25 at 77°F (Du Pont 1992). Velpar ULW DF has a density of 0.73 g/mL (Du Pont 1997a) and the corresponding value for Velpar DF is 0.58 g/mL (Du Pont 1997b). As indicated in Table 2-2, these properties are similar to the reported values for the Pronone formulations. As discussed in section 2.3, all of these granular formulations of hexazinone except Velpar DF are applied dry as dry granules. Velpar DF is a water dispersable granule and is mixed with water prior to application (Du Pont 1997c,d).

A recent court decision has directed the U.S. EPA to release the identity of the inert ingredients in Velpar and several other herbicides (PENNA 1996). This decision was implemented and is likely to be appealed. This document does not specifically identify the proprietary inerts used in any of the hexazinone formulations.

2.3. APPLICATION METHODS

Detailed descriptions of the uses of herbicides in silviculture and the various methods of herbicide application are available in the general literature (e.g., Cantrell and Hyland 1985) and earlier risk assessments conducted by the Forest Service (USDA 1989a,b,c). The following summary focuses on those aspects of application that are most germane to the exposure assessments (sections 3.2 and 4.2).

Both liquid and granular formulations of hexazinone may be applied by aircraft. In aerial applications of either liquid or granular formulations, approximately 40–100 acres may be treated per hour. Liquid formulations are applied using specially designed spray nozzles and booms. The nozzles are designed to minimize turbulence and maintain a large droplet size, both of which contribute to a reduction in spray drift. Aerial applications may only be made under meteorological conditions that minimize the potential for spray drift.

Special equipment is required to apply granular formulations in order to ensure an even application of the granules (Du Pont 1994, 1996a,b,c, Pro-Serve 1993a,b). Velpar ULW DF granules may be applied only by helicopter using the Du Pont ULW Applicator (Du Pont 1996a). Unlike the other granular hexazinone formulations, however, Velpar DF is applied after mixing 2 2/3 pounds of Velpar DF with sufficient water to make one gallon of suspension. Like Velpar ULW DF, Velpar DF requires that helicopters be used in aerial applications (Du Pont 1996b,c).

Both liquid and granular formulations may be applied from the ground. While the specific equipment varies between the liquid and granular formulations, both types of formulations are applied such that the herbicide sprayer (liquid or suspended granules) or container (granules) is carried by backpack or some other appropriate container. Usually, hexazinone is applied directly to the soil rather than sprayed on the vegetation; however, sometimes, directed foliar applications are used. In soil applications, the hexazinone is applied in spots using a defined pattern. Because this treatment method is associated with little if any direct application to the vegetation, worker exposure to the herbicide from contact with contaminated vegetation is minimal. In directed foliar applications, however, crews may treat up to shoulder high brush; consequently, chemical contact—either to the liquid formulation or dust from the granules—with the arms, hands, or face is plausible. To reduce the likelihood of significant exposure, application crews are directed not to walk through treated vegetation. In directed foliar applications, a worker will treat approximately 0.5 acres/hour with a plausible range of 0.25-1.0 acres/hour. In soil spot treatments, workers may typically treat about 1 acre/hour with a plausible range of 0.5-1.5 acres/hour.

Boom spray or roadside hydraulic broadcast spraying is used primarily in rights-of-way management. Spray or spreader equipment is mounted on tractors or trucks and is used to apply the herbicide along the side of the roadway. Boom spray may also be used for maintenance or rehabilitation of wildlife openings, with spray equipment mounted on or towed behind tractors. For liquid formulations, about 8 acres will be treated in a 45-minute period (approximately 11 acres/hour) with approximately 200 gallons of the herbicide mixture (270 gallons/hour). Some special truck mounted spray systems may be used to treat up to 12 acres in a 35-minute period with approximately 300 gallons of herbicide mixture (about 21 acres/hour and 510 gallons/hour). For granular applications, about 6-15 acres can be treated in 35-45 minutes (about 8-26 acres/hour) (USDA 1989b; pp. 2-9 to 2-10).

As discussed by Haywood (1994), brown (with hexazinone) and burn treatment accelerates pine release relative to standard prescribed burns without the use of a herbicide. Thus, hexazinone treated areas may be subsequently burned. For hexazinone, post-treatment burns in brown-and-burn operations are generally not conducted until the compound has washed into the soil and been absorbed by the plants through root uptake. The amount of time required for this to occur will vary with the amount of rainfall and soil type (section 4). Generally, burns are not conducted until 45–180 days after treatment.

2.4. USES AND APPLICATION RATES

The uses of hexazinone by the Forest Service are summarized in Table 2-3. As indicated in this table, virtually all (99.9%) of the hexazinone used by the Forest Service in 1995 involved either site preparation (~60%) or conifer release (~39.9%). Relatively small amounts (6.3 of 6377.3 lbs) were used for noxious weed control and hardwood thinning. More than 90% of hexazinone use by the Forest Service occurs in Region 8: the southeastern United States, including Alabama, Arkansas, Florida, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and part of West Virginia (USDA/FS 1995).

Table 2-3. Nationwide use of hexazinone by the Forest Service in Government Fiscal Year 1995*

Management Objective	Acres Treated	Pounds a.i. Used	Average Application Rate (a.i. lbs/acre)
Site Preparation	1517.4	3813	2.5
Conifer Release	1775	2558	1.4
Noxious Weed Control	8	4	0.5
Hardwood Thinning	7	2.3	0.3
TOTALS	3307.3	6377.3	

*Source: USDA/FS 1996

All formulations of hexazinone are labeled for site preparation, conifer release, and weed control. The liquid formulation, Velpar L, is also labeled for selective brush control, and various non-crop agricultural uses. Recommended application rates vary substantially with soil type.

Velpar L is not recommended at any application rate in sandy soil (>85% sand), loamy sand or sandy loam with less than 2% organic matter, or any soil with less than 1% organic matter. For site preparation, application rates of 1-3 gallons/acre (2-6 lbs a.i./acre) are recommended. For conifer release, recommended application rates range from about 1-3 lbs a.i./acre. The lower end of these ranges apply to soils containing relatively high levels of sand, and the upper end of the ranges apply to soils containing high levels of clay. Because hexazinone acts primarily through root absorption, at least 1-2 inches of rain are needed to ensure sufficient absorption (Du Pont 1993a).

Recommended application rates for Velpar ULW used for site preparation range from 2½ to 8 lbs/acre. These rates are almost the same as the recommended application rates for Velpar L expressed in units of pounds of hexazinone per acre (i.e., ~1.9-6 lbs a.i./acre). Also as with Velpar L, the recommended application rates for conifer release are about half of the recommended rates for site preparation.

For both Pronone formulations, the recommended application rates for site preparation range from 10-40 lbs of product/acre or 1-4 lbs a.i./acre. These rates are somewhat less than recommended rates for the Velpar formulations. As with the Velpar formulations, the lower end of these ranges apply to soils containing relatively high levels of sand and the upper end of the ranges to soils containing high levels of clay. As discussed in section 4, the relationships of application rate to soil types is a function of the transport and adsorption of hexazinone in different types of soils.

As illustrated in Table 2-3, the average application rates used by the Forest Service in site preparation (2.5 lbs a.i./acre) and conifer release (1.4 lbs a.i./acre) are at the lower end of the recommended

labeled rate. Usually, application rates used by the Forest Service will not exceed 4 lbs a.i./acre, although applications of up to 6 lbs a.i./acre (the maximum labeled rate) may be used in some cases.

In previously conducted Forest Service vegetation management programs (USDA 1989a,b,c), hexazinone was applied to relatively large areas. For example, in Forest Service Region 8, there are approximately 12,000,000 acres of National Forests and Grassland, of which up to 600,000 acres are treated with various herbicides each year. In the late 1980s, hexazinone was applied to 48,700 acres, 0.4% of the total area and 8.1% of the treated area (USDA 1989b, p.2-4). As of 1995, the Forest Service use of herbicides in Region 8 was reduced to treatment of fewer than 100,000 acres/year (USDA/FS 1996). As summarized in Table 2-3, only 3307.3 acres were treated with hexazinone in 1995 (i.e., about 6.8% of the area treated in the 1980s). The use of 6377.3 lbs. a.i. of hexazinone by the Forest Service nationwide is about 2% of the total use of hexazinone in the United States for 1992 (434,000 lbs. a.i.), the most recent year for which total use data for the United States are available (Gianessi and Puffer 1992).

The final report for herbicide use by the Forest Service in 1996 is not yet available. Preliminary figures indicate that hexazinone use has increased to about 16,000 lbs a.i. applied to 9155 acres. Most of this use-15,860 lbs a.i. on about 7000 acres (an average of about 2.3 lbs a.i./acre)—involved the application of hexazinone alone. The remaining amount-144 lbs a.i. on 2150 acres—involved the application of hexazinone in combination with sulfometuron.

3. HUMAN HEALTH RISK ASSESSMENT

3.1. HAZARD IDENTIFICATION

3.1.1. Overview. The toxicity of hexazinone is relatively well characterized in experimental mammals. The acute toxicity of hexazinone is low, with oral LD_{50} values in experimental mammals ranging from approximately 500 to 3500 mg/kg. There are no remarkable or systematic differences in sensitivity among various species. The effects observed in mammals after subchronic or chronic exposure to hexazinone are generally limited to decreases in body weight, increases in liver weight, and changes in blood enzyme levels associated with liver toxicity. Although the mechanism of action is unclear, the signs of acute toxicity are generally consistent with cholinesterase inhibiting pesticides. Studies that assay the effect of hexazinone on cholinesterase activity were not found in the literature. At doses that are substantially greater than the threshold for systemic toxic effects, hexazinone may cause reproductive effects, including kidney abnormalities and/or delayed ossification as well as decreases in the survival rate of offspring in experimental mammals.

There are limited data suggesting that hexazinone may be a carcinogen. These data are limited to a 2-year bioassay in mice in which females but not males had a slight increase in the total number of malignant tumors. The U.S. EPA judged that this dose-response pattern is equivocal evidence for carcinogenicity and designated hexazinone as Class D, not classifiable as to human carcinogenicity. U.S. EPA does not recommend a quantitative risk assessment of hexazinone based on carcinogenicity. An independent review of this study has been conducted as part of this risk assessment. This independent review supports the EPA's position.

Both powdered and liquid formulations of hexazinone as well as technical grade hexazinone are shown to be moderate to severe eye irritants. The available human data suggest that dust associated with the application of some batches of granular formulations may be sufficiently dense to cause symptoms of eye and respiratory irritation in workers.

As discussed in the exposure assessment, dermal exposure is the primary route of concern for workers. The available data indicate that the dermal toxicity of hexazinone is relatively low and that hexazinone is not well absorbed after dermal exposure. Nonetheless, an occupational study of workers applying a granular formulation of hexazinone (Samuel et al. 1991, 1992) indicates that dermal absorption will occur. Thus, for this risk assessment, estimates of dermal absorption rates are used to estimate the amounts of hexazinone that might be absorbed by workers. These estimates are then used with the available dose-response data to characterize risk.

3.1.2. Acute Toxicity and Mechanisms of Action. The acute toxic potency of hexazinone is relatively well characterized in several mammalian species. For the most part, these studies were conducted as part of the registration process for hexazinone and are summarized by Kennedy (1984), Schneider and Kaplan (1983), and various reviews cited in appendix 1.

The reported acute oral LD_{50} values for technical grade hexazinone (i.e., ~95-99% pure; appendix 1) range from 530 mg/kg (Crl-CD rat) (Kennedy 1984) to greater than 3400 mg/kg (beagle dog)

(Kennedy 1984). As discussed in section 4, the acute toxicity data in mammals and other species do not suggest any systematic allometric relationship. In other words, with respect to body weight, there does not appear to be remarkable or systematic differences in sensitivity among various species. No reports of human poisoning by hexazinone were found in the literature.

Although several bioassays were conducted on the acute toxicity of hexazinone, relatively little is known about its mechanism(s) of toxicity in mammals. Generally, the signs of toxicity in various mammalian species are similar, including lacrimation, salivation, vomiting, tremors/ataxia/weakness, diarrhea, and increased rates of respiration and/or labored breathing (appendix 1). These signs are generally consistent with cholinesterase inhibiting pesticides (e.g., description given by ATSDR 1993). Nevertheless, assays of hexazinone for AChE inhibition were not found in the literature.

There is relatively little information available on organ or tissue specific effects. Tissue pathology in animals with signs of acute poisoning are generally non-specific or unremarkable [i.e., enlarged liver or lungs (Schneider and Kaplan 1983)]. These effects indicate general tissue congestion, which is an effect commonly observed in organisms after fatal exposure to any one of a wide variety of toxic agents.

3.1.3. Subchronic or Chronic Systemic Toxic Effects. Several standard subchronic and chronic bioassays were conducted on hexazinone (appendix 1), and none of the studies suggest a specific mode of toxic action. Most of the reported effects are limited to decreases in body weight, increases in liver weight, and changes in blood enzyme levels associated with liver toxicity.

Decreased body weight is the most commonly reported effect of subchronic or chronic exposure to hexazinone. This effect is reported in studies involving relatively short-term dietary exposure [i.e., 10 days in rats (Kennedy 1984)], subchronic exposure [i.e., 90 days in dogs (Kennedy and Kaplan 1984) and rats (Schneider and Kaplan 1983)], and chronic exposure [i.e., 2 years in mice (Kennedy and Kaplan 1984) and rats (Schneider and Kaplan 1983)]. Although decreases in body weight are non-specific, this endpoint is used by the U.S. EPA as the critical effect for hexazinone (i.e., the toxic effect that occurs at the lowest dose level). As discussed in section 3.3, decreased body weight noted in the study by Schneider and Kaplan (1983) is the basis of the original RfD derived by the U.S. EPA for this compound. As discussed in section 4.3.3., decreases in growth appear to be the most sensitive endpoint in fish, also.

The interpretation of the toxicological significance of decreased body weight depends on the pathogenesis of the condition. In feeding studies, decreased body weight may be associated with a decrease in food consumption, which, in turn, may be associated with a lack of palatability of the food or with some underlying toxicity (i.e., sick or intoxicated animals will often lose their appetites). In most studies that report both changes in body weight and food consumption rates, the decreases in body weight are associated with decreased food consumption (quail, Kennedy 1984; dogs, U.S. EPA 1982, Newton and Dost 1981). Schneider and Kaplan (1983) report a decrease in food conversion efficiency in rats exposed to hexazinone in the diet at 5000 ppm for 90 days or 1000 and 5000 ppm for 2 years. In mice, however, there is no statistically significant difference in food conversion

efficiency between controls and animals exposed to up to 10,000 ppm hexazinone in the diet. Nonetheless, the reported decrease in food conversion efficiency in rats suggests that the decrease in body weight cannot always be attributed to decreased food consumption. This notion supports U.S. EPA's position that decreased body weight is an appropriate endpoint to use in deriving an RfD for hexazinone.

The other common effect of hexazinone in subchronic or chronic feeding studies is increased liver weight (mice, Kennedy and Kaplan 1984, Newton and Dost 1981; dogs, U.S. EPA 1982). No dose-related changes in liver weight were observed in rats even at dose levels associated with decreased body weight (Kennedy and Kaplan 1984). At least in mice, increased liver weight was associated with an increase in the size of the liver cells (Kennedy and Kaplan 1984). The combination of increased liver weight and increased size of liver cells is often associated with enzyme induction, specifically the induction of mixed-function oxidases, an enzyme system associated with the metabolism of many xenobiotics. Although somewhat speculative, these data suggest that the changes in liver weight, when observed in mice, reflect enzyme induction rather than liver toxicity. In dogs, however, Kennedy and Kaplan (1984) observed increases in blood enzyme levels that are suggestive of liver damage. On histopathological examination of the liver, however, no evidence of liver damage was noted. Thus, in balance, there is no clear indication that hexazinone is a specific liver toxin.

3.1.4. Reproductive and Teratogenic Effects. The results of four bioassays on the potential reproductive and teratogenic effects of hexazinone are included in the publication by Kennedy and Kaplan (1984), which summarizes unpublished studies conducted as part of the registration process for this compound. Additional studies are also summarized in the U.S. EPA Reregistration Eligibility Document for hexazinone (U.S. EPA 1994a). Experimental details for all of these studies are summarized in appendix 2.

U.S. EPA (1994a) classifies 900 mg/kg/day as the LOAEL for rats (MRID 40397501, Mullin 1987), based on an increase in fetuses with kidney abnormalities and/or delayed ossification. No such effects were seen at 400 mg/kg/day, the dose classified as a NOAEL. Similarly, in rabbits, increased resorptions were noted at 125 mg/kg/day but not at lower doses (20 or 50 mg/kg/day) (MRID 00028863, Serota et al. 1980). In multi-generation feeding studies at dietary levels up to 5000 ppm, no effects were noted on reproductive capacity (Kennedy and Kaplan 1984). However, in a more recent multi-generation feeding study in rats, decreased pup survival was noted in the $F2_b$ generation at 5000 ppm (250 mg/kg bw/day) but not at 200 ppm (10 mg/kg/day) or 2000 ppm (100 mg/kg/day). At 2000 ppm, however, decreases in pup weight as well as maternal body weight were observed (MRID 42066501, Mebus 1991). This effect level for decreased pup weight is only a factor of 2 greater than the effect level for changes in adult body weight in the study on which the RfD is based. The NOEL of 5 mg/kg/day on which the RfD is based is, nonetheless, below any of the effect levels for reproductive toxicity.

3.1.5. Carcinogenicity and Mutagenicity. Published studies regarding the carcinogenicity of hexazinone are not available. U.S. EPA (1994a) conducted a review of two unpublished studies on the potential carcinogenicity of hexazinone. In a study using rats, no carcinogenic effects were apparent over a 2-year exposure to dietary levels up to 2500 ppm (MRID 00108638, Kaplan et al. 1977). This study appears to be identical to the 2-year feeding study of Crl-CD rats summarized by Kennedy and Kaplan (1984) (see appendix 1 for details).

Table 3-1. Summary of tumor incidence (all sites combined) in a 2-year feeding study in mice exposed to hexazinone*

MALES				
Endpoint	0 (ppm)	200 (ppm)	2500 (ppm)	10,000 (ppm)
Number of animals	80	79	80	79
Number of malignant tumors	3	3	3	4
FEMALES				
Endpoint	0 (ppm)	200 (ppm)	2500 (ppm)	10,000 (ppm)
Number of animals	80	80	80	80
Number of malignant tumors	0	0	4	3

*Source: Du Pont 1992b, MRID No. NR425093-01

There is a mouse study in the unpublished literature (MRID 00079203, Goldenthal and Trumball 1981), however, that is more difficult to interpret. The tumor incidence from this study, based on a re-evaluation of the pathology slides conducted by Du Pont (1992b, MRID NR425093-01) is summarized in Table 3-1. In this study, CD-1 mice were exposed to hexazinone at dietary levels of 200, 2500, or 10,000 ppm. In males, there is no indication of carcinogenic activity. In females, the incidence of malignant tumors is increased but these increases are not statistically significant at dietary levels of 2500 ppm (p=0.06) and 10,000 ppm (p=0.12). The U.S. EPA judged that this dose-response pattern is equivocal evidence for carcinogenicity and designated hexazinone Class D, not classifiable as to human carcinogenicity.

The decision of U.S. EPA to decline to conduct a quantitative risk assessment for the carcinogenicity of hexazinone is supported by the lack of mutagenic activity of hexazinone in several *in vivo* and *in vitro* bioassays, although one bioassay for chromosomal damage was positive. As discussed in U.S.

EPA (1994a), hexazinone yielded negative results in the Ames assay, the Chinese hamster ovary cell HGPRT assay, a chromosome aberration assay using bone marrow cells from rats, and an assay for unscheduled DNA synthesis in rat hepatocytes. In a chromosome aberration assay using Chinese hamster ovary cells, however, there was a significant increase in the number of structural chromosomal aberrations per cell at concentrations of 15.85 mM and above, with and without metabolic activation.

Although cancer remains an endpoint of concern, as articulated by the U.S. EPA in the *Reregistration Eligibility Document*, the position not to conduct a quantitative risk assessment for carcinogenicity seems reasonable. This decision is supported by an independent review of the CBI files relating to this assessment and additional consideration by USDA personnel as well as external peer-review.

3.1.6. Irritation and Sensitization. Hexazinone is a severe irritant to the eyes but has a much lesser effect on the skin. Details of studies regarding the irritant effects of hexazinone on the eyes and skin are summarized in appendices 3 and 4, respectively.

Both powdered and liquid formulations of hexazinone as well as technical grade hexazinone are shown to be moderate to severe eye irritants. Hexazinone is classified as a severe eye irritant by U.S. EPA (1994a), and this classification is amply supported by the available data (appendix 3). Eye damage may include corneal injury with opacity as well as conjunctivitis.

The recently published material safety data sheet for Velpar ULW indicates that the product caused irreversible eye damage in a primary eye irritation study in rabbits (Du Pont 1997a). This warning is not included on the recent material safety data sheet for Velpar DF (Du Pont 1997b). It is unclear whether the study in question refers to Velpar ULW or the active ingredient, hexazinone. The ocular toxicity of hexazinone is extremely well documented (appendix 3). The precautionary statement by Du Pont (1997a) may reference the report in Kennedy (1984). If so, it is not clear why this statement is not also in the material safety data sheet for Velpar DF. In Kennedy (1984), corneal damage in rabbits persisted up to 28 days after exposure, at which time the study was terminated. The corneal damage, however, seems to be restricted to unwashed eyes. Most of the studies detailed in appendix 3 indicate that longer-term and potentially irreversible ocular effects are observed only in unwashed eyes after the instillation of hexazinone.

Based on human experience with a granular formulation of hexazinone, Spencer et al. (1996) report that dust associated with the application of some batches of granular formulations may be sufficiently dense to cause eye and respiratory irritation in workers. These effects are transient and do not persist after exposure is terminated.

Both technical grade and wettable powder formulations of hexazinone are much less irritating to the skin. The threshold for systemic toxicity (i.e., elevations in blood SGPT indicative of liver damage) after dermal exposure seems to be comparable to the threshold for skin irritation. In other words, levels of hexazinone that are sufficient to elicit systemic toxic effects are associated with only mild

reddening (erythema) of the skin (Schneider and Kaplan 1983) (appendix 4). Furthermore, skin sensitization studies on hexazinone are negative (Schneider and Kaplan 1983).

3.1.7. Systemic Toxic Effects from Dermal Exposure. Based on a comparison of acute oral and dermal LD_{50} values, it appears that the dermal absorption rate is much less than the rate of absorption after oral exposure. As summarized in section 3.1.2. and discussed in appendix 1, oral LD_{50} values for hexazinone generally range from about 500 to 3500 mg/kg. Conversely, dermal exposure to as much as 7500 mg/kg (Schneider and Kaplan 1983) (appendix 4) is not associated with mortality. Based on a comparison of the acute oral and dermal toxicity of hexazinone, the U.S. EPA waived the registration requirement for a dermal penetration study for this compound (U.S. EPA 1994a). Moreover, because of the apparent low dermal absorption of hexazinone, the U.S. EPA determined that: *For occupational/residential exposure, there are no toxicological end-points of concern for hexazinone* (U.S. EPA 1994a, p. 19).

Oral absorption is probably extensive and relatively rapid, as it is with many relatively low molecular weight organic compounds. Two papers relating to oral absorption were published by Du Pont personnel (Rhodes and Jewell 1980, Reiser et al. 1983). These studies seem to summarize different aspects of the same experiment in which rats were placed on a diet containing 2500 ppm unlabelled hexazinone and then given a gavage dose of ^{14}C-labelled hexazinone. After 24 hours, about 80% of ^{14}C-labelled hexazinone was recovered in the urine (57.2%%) and feces (23.2%). By 3 days after administration, 93% of ^{14}C-labelled hexazinone was recovered in the urine (61%) or feces (32%). Thus, as a lower limit, the oral absorption rate coefficient of hexazinone for rats appears to be 0.5 day^{-1} (i.e., assuming that fecal residues represent unabsorbed hexazinone). In the urine, all residues were metabolites of hexazinone, as discussed further in section 3.1.9.1.

In two human subjects, only about 20% of orally administered hexazinone was recovered in the urine (Samuel et al. 1991). The investigators indicate that the low level of urinary excretion may suggest incomplete absorption of hexazinone from the gastrointestinal track. This finding, however, may also indicate biliary excretion of hexazinone metabolites.

Studies regarding the dermal absorption kinetics of hexazinone were not found in the literature. Based on an analysis of human dermal absorption of 47 diverse organic compounds, Durkin et al. (1995) proposed the following relationship between the average daily absorption rate (AR in % applied dose per day) and molecular weight (MW):

$$\log AR_{Ave} = -0.004\ MW + 1.5.$$

For hexazinone (MW=252.3), the estimated rate coefficient is 3.1% or 0.031 day^{-1}. As further discussed in Durkin et al. (1995), however, the above equation is useful for relatively lipophilic compounds, specifically those with a log K_{ow} greater than 1.85. For less lipophilic compounds, the above equation may substantially overestimate absorption. As summarized in Table 2-1, the K_{ow} for hexazinone at a neutral pH is 11.3 (log 11.3 = 1.05). Thus, the dermal absorption rate of 0.031 day^{-1} for hexazinone may be an overestimate.

Another index of dermal absorption, which is used in some of the exposure assessments in section 3.2, is the dermal permeability coefficient, K_p, expressed in cm/hour. An experimentally determined K_p for hexazinone was not found in the available literature. Based on structure-activity relationships (U.S. EPA 1992a), a K_p of 0.00032 cm/hour for an aqueous solution of hexazinone can be calculated from the following equation:

$$\log K_p = -2.7 + 0.71 \log K_{o/w} - 0.0061\, MW$$

where $\mathbf{K_{ow}}$ is the octanol water partition coefficient and **MW** is the molecular weight. For hexazinone, the molecular weight is 252.3 and the log K_{ow} at neutral pH is 1.05 (Tomlin 1994). Thus, based on the above equation, the K_p for hexazinone is estimated to be 0.00032 cm/hr [Log K_p = -2.7 + 0.71·1.05 - 0.0061·252.3 = -3.49; $K_p = 10^{-3.49}$ = 0.00032 cm/hr].

The above estimates of the dermal absorption rate and the dermal permeability coefficient are low but not insignificant. For example, 2,4-D is a widely used herbicide whose dermal absorption characteristics are relatively well characterized. In humans, approximately 5.8% of a dermal dose of 2,4-D was eliminated in the urine over a 5-day observation period (Feldman and Maibach 1974) yielding an estimated average daily absorption rate of about 0.012 day^{-1}. Similarly, the dermal permeability of an aqueous solution of 2,4-D at neutral pH is estimated at 0.000025 cm/hour, based on the above equation and a log K_{ow} of -0.75 at pH 7 (SERA 1996) and a molecular weight of 221 g/mole. Thus, based on estimates of dermal permeability, the dermal absorption of hexazinone is about 13 times greater than that of 2,4-D. This is at least qualitatively consistent with the higher rate of dermal absorption for hexazinone relative to 2,4-D based on the method of Durkin et al. (1995).

As discussed further in section 3.2, there is ample evidence that significant amounts of 2,4-D are absorbed by workers during typical applications of this herbicide. The data on hexazinone is far more limited. In one study conducted in Quebec (Samuel et al. 1992), applications of liquid formulations of hexazinone resulted in urinary levels of hexazinone metabolites of up to 33,600 µg/L. For granular formulations, urinary levels were much lower, with a maximum of only 90 µg/L. Although the amount of hexazinone handled by these workers was not recorded, these levels clearly suggest that occupational exposure should not be ignored. Similarly, a worker exposure study recently completed in California (Spencer et al. 1996) estimates that workers applying granular formulations of hexazinone may be exposed to hexazinone at levels that are substantially above the RfD. Thus, unlike the position taken by U.S. EPA, this document will consider several specific dermal exposure scenarios, as discussed further in section 3.2.

3.1.8. Inhalation Exposure [including Brown-and-Burn Operations]. Although inhalation of hexazinone is not a typical route of exposure, it may occur during brown-and-burn operations. As discussed in section 2.3 on application methods, the post-treatment burns in brown-and-burn operations are conducted 45–180 days after treatment with the herbicide. As discussed by Bush et al. (1987), the combustion of several herbicides does not result in exposure to toxic air concentrations of herbicides. These investigators, however, did not look specifically at hexazinone and did not take toxic combustion products into consideration.

As summarized in appendix 5, the lowest reported inhalation LC_{50} for hexazinone is about 4 mg/L or 4 g/m^3 [10,000 L/m^3] (Shapiro 1990) and no adverse effects were observed after repeated exposure to 2 mg/L (Schneider and Kaplan 1983). These air concentrations are far below any plausible exposure during brown-and-burn operations. Nonetheless, no information is available regarding the combustion products of hexazinone. Given the implausibility of significant residues of hexazinone on treated vegetation (as also discussed in section 3.4), this adds relatively little to uncertainties associated with this risk assessment. On the other hand, as discussed in section 3.1.6, hexazinone is a respiratory irritant. As documented in the study by Spencer et al. (1996), workers applying hexazinone may be exposed to sufficient levels of the compound in air to cause respiratory irritation.

3.1.9. Metabolites, Impurities, and Adjuvants.

3.1.9.1. Metabolites -- Hexazinone is metabolized extensively in plants and animals, with little parent product recovered in tissue. An overview of the metabolic pathways for hexazinone is presented in Figure 3-1. The letter designations given in Figure 3-1 are identical to those used in Reiser et al. (1983) and Rhodes and Jewell (1980). In rats (Rhodes and Jewell 1980) and humans (Samuel et al. 1991, 1992), the levels of urinary metabolites are A > C > D. Thus, the primary metabolic pathway in rats and humans appears to be hydroxylation, with lesser amounts of hexazinone undergoing deamination and demethylation. There is relatively little information available regarding the toxicity of the metabolites. Reiser et al. (1983) report that the approximate lethal dose for metabolites A through E is about 5000 mg/kg, which is somewhat greater than the LD_{50} for hexazinone.

The relative paucity of information about the toxicity of these metabolites does not have a significant impact on this risk assessment. The toxicity studies on which the hazard identification and subsequent dose-response assessment are based involve *in vivo* exposure to hexazinone, and, presumably, the subsequent formation of hexazinone metabolites. Therefore, the toxicological effects, if any, of the metabolites are likely to be captured by animal toxicology studies involving whole-body exposure to hexazinone. This approach to examining the potential importance of the metabolites of a chemical agent is common in the risk assessment of xenobiotics, which generally involve the formation of one or more metabolites, some of which may differ in toxicity from the parent compound. Usually, the parent compound is selected as the agent of concern because the toxicology studies and monitoring studies provide information about the agent. Thus, the dose metameter for the risk assessment is most clearly expressed as the parent compound. In cases where a toxic metabolite is known to be handled differently by humans, this simple approach may be modified. The available data, however, suggest that hexazinone is handled similarly by rats and humans as well as plant species. Thus, no modification to this approach seems to be warranted.

3.1.9.2. Impurities -- There is no information available on the identity or toxicity of any impurities in hexazinone. Most toxicity studies (appendix 1) use what is referred to as technical grade hexazinone containing about 98% hexazinone. Thus, the presence of impurities may be inferred. Although the lack of information on impurities adds some uncertainty to this risk assessment, the use

of technical grade hexazinone in the toxicity studies on which the dose-response assessment is based (section 3.3) is likely to encompass any potential toxic effect of the impurities.

3.1.9.3. Adjuvants -- As noted in section 2, Velpar L contains 40-45% ethanol. The toxicity of ethanol is extremely well characterized in humans, and the hazards of exposure include intoxication from acute exposure as well as liver cirrhosis and fetal alcohol syndrome (WHO 1988). For chronic exposure, the alcohol (30-35% w/w) contained in Velpar L is not likely to be of toxicological significance because of the rapid breakdown of alcohol in the environment and the relatively high levels of alcohol associated with chronic alcohol poisoning. For acute dermal exposure, ethanol will volatilize rapidly from the surface of the skin and toxicologically significant effects are not anticipated. Acute oral exposure is implausible, except in cases of accidental or suicidal ingestion. In such cases, the amount of ethanol could be significant. For example, approximately 15 mL of alcohol is contained in 1 oz of an alcoholic beverage containing 50% alcohol (100 proof) [0.5 · 1 oz · 29.6 mL/oz ≃ 14.8 mL]. This alcohol level may cause mild intoxication in sensitive individuals. Each mL of Velpar L contains about 0.4 mL of ethanol. Therefore, approximately 37 mL [14.8 mL/0.4], of Velpar L must be consumed to equal the amount of alcohol contained in 1 oz of an alcoholic beverage. This amount of Velpar L contains 8700 mg of hexazinone [37 mL · 0.25 · 0.9776 g/mL

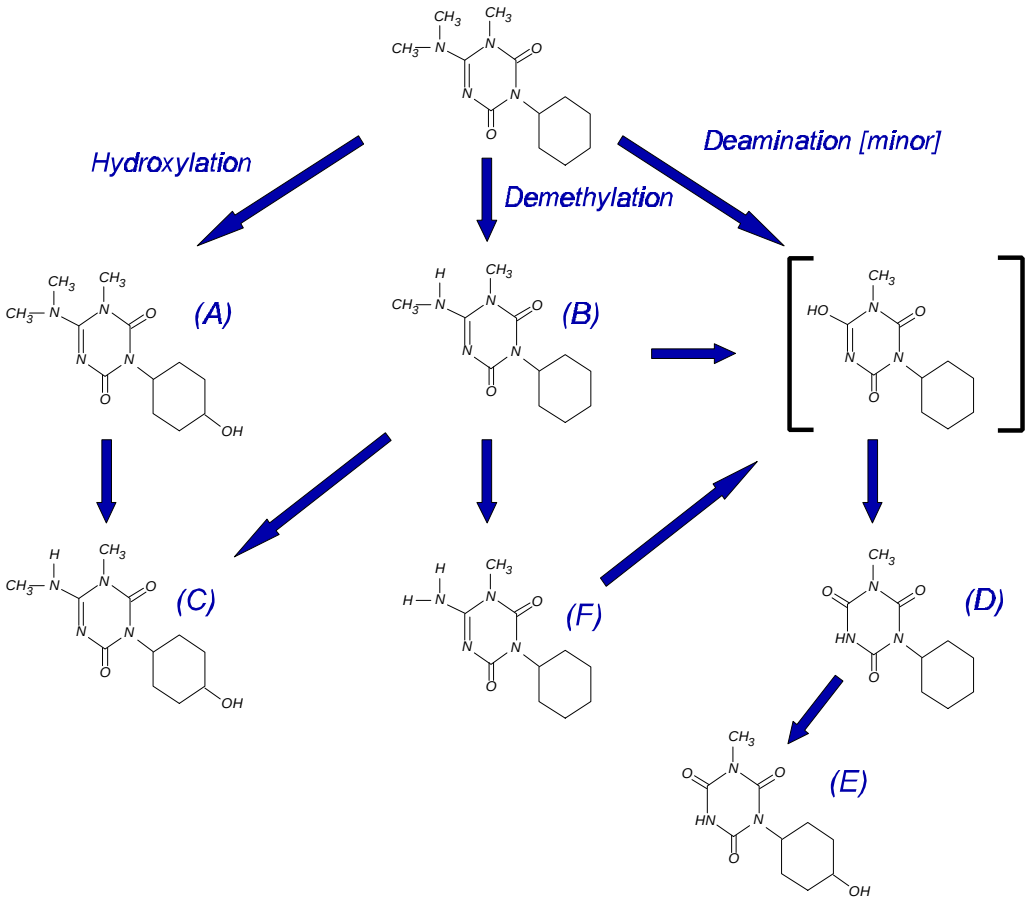

Figure 3-1: Metabolic pathways for hexazinone (redrawn from Reiser et al. 1983).

≃ 9.0 g or 9,000 mg]. For a 70 kg man, this dose would equal approximately 130 mg hexazinone/kg. Based on the acute toxicity of hexazinone, no adverse effects are anticipated. Thus, in the case of acute oral exposure to Velpar L, ethanol is the toxic agent of primary concern. This scenario is not of substantial concern to this risk assessment because, as noted above, this type of exposure will be associated only with massive oral doses of Velpar L, which are plausible only with suicide attempts or other extreme exposure scenarios.

Ethanol is a strong eye irritant, and the presence of ethanol may contribute to the irritant effects of Velpar L (see section 3.1.6). As discussed in appendix 4, hexazinone itself is an eye irritant and the available data are inadequate to characterize potential interactions between ethanol and hexazinone. Nonetheless, as discussed in section 3.1.6, eye irritation is an endpoint of concern in handling commercial formulations of hexazinone.

The identity of the carrier or carriers in the granular formulations of hexazinone is considered proprietary. Based on references from the published literature, the major component of granular formulations of hexazinone appears to be clay. Based on the acute toxicity of these formulations relative to technical grade hexazinone, there is no indication that the carriers contribute to the toxicity of the granular formulations of hexazinone. For example, as summarized in appendix 1, the acute LD_{50} values for a 20% gridball formulation range from about 6300 to 12,000 mg/kg (Schneider and Kaplan 1983) or 1260 to 2400 mg/kg of hexazinone. As noted in section 3.1.2, the acute LD_{50} of technical grade hexazinone (98% pure) to the rat ranges from about 530 to 1700 mg/kg (Kennedy 1984). Thus, if anything, the granular formulations of hexazinone appear to be slightly less toxic than hexazinone itself. This is also evident in the aquatic toxicity studies using formulations relative to hexazinone itself (section 4.3.3.1).

3.2. EXPOSURE ASSESSMENT

3.2.1. Overview. Two general exposure assessments are presented in this section, job-specific assessments and incident assessments. Job-specific assessments estimate absorption associated with relatively complex job activities, such as mixing, loading, or applying hexazinone, in which multiple routes of exposure are likely. All of these assessments are given as a range based on the projected application rates, empirical observations of variability in exposure rates, and projected variations in herbicide usage (i.e., number of acres treated/hour). Incident assessments are relatively easy to make. They estimate absorption from spilling a solution onto the skin or wearing contaminated clothing. All of these scenarios are extreme or accidental in nature, as discussed in sections 3.2.2 and 3.2.3.

Two studies are available on worker exposure, one involving biomonitoring of hexazinone levels in the urine (Samuel et al. 1991, 1992) and the other involving estimates of dermal deposition and inhalation (Spencer et al. 1996). In general, worker exposure to hexazinone is likely to compare with exposure to 2,4-D, given appropriate corrections for differences in dermal absorption rates. Workers involved in the ground or aerial application of liquid formulations will receive similar levels of exposure, with central estimates of about 0.01-0.03 mg/kg/day per lb a.i. applied per acre.

The use of an over the shoulder broadcast applicator (*belly grinder*) in the ground application of a granular formulation of hexazinone may lead to levels of exposure that are about an order of magnitude higher, about 0.2 mg/kg/day per lb a.i. applied per acre. This difference appears to be due to the nature of the application device. This piece of equipment is a spreader that is strapped to the torso, and the granules are dispensed from the base of a hopper by turning a side-mounted handle.

It is not clear that all applications of granular formulations of hexazinone will result in similarly high levels of exposure. The available data on 2,4-D suggest that in some applications workers applying liquid and granular formulations will receive comparable levels of exposure.

Except for accidental exposure scenarios, the general public should be exposed to hexazinone at levels far less than those for workers. Most routine exposure scenarios lead to estimated daily doses in the range of 0.001-0.006 mg/kg/day. Nonetheless, hexazinone is relatively persistent in the environment and is transported to groundwater and surface water. Consequently, subchronic exposure to hexazinone is plausible.

3.2.2. Workers.

3.2.2.1. ***Job Categories*** **--** As outlined in the program description (see section 2), this risk assessment is concerned with both aerial and ground broadcast applications of liquid and granular formulations of hexazinone. As discussed in SERA (1995a), occupational exposure generally involves inhalation and dermal exposure, with the dermal route generally contributing far more to exposure than the inhalation route. For job category specific exposure assessments, exposure rates are usually expressed as mg of agent per kg of body weight per pound of agent handled by the worker. In this and other Forest Service risk assessments, these rates are also expressed in abbreviated units of mg agent/kg bw · lb a.i handled.

As a general practice, any available compound specific data are used as the basis for the occupational exposure assessment. In addition, the compound specific data are usually compared with the available data on 2,4-D. This approach is taken because much of the literature regarding occupational exposure rates involves exposure to 2,4-D and the pharmacokinetics of this compound are well characterized (SERA 1993, 1995b).

Two exposure studies are available for ground applications of hexazinone, one conducted in Quebec (Samuel et al. 1991, 1992) and the other conducted and recently completed in California (Spencer et al., 1996). There are no available studies regarding workers involved in the aerial application of hexazinone. Both of the hexazinone studies are more clearly interpreted by comparison to the available data on 2,4-D. Thus, the available data on 2,4-D are discussed prior to a detailed description of the worker data on hexazinone.

For ground applications of 2,4-D, plausible estimates and ranges of exposure rates are 9.6×10^{-5} (4.9×10^{-6} to 1.9×10^{-3}) mg/kg/lb a.i. for roadside hydraulic spraying and 1.4×10^{-3} (4.4×10^{-5} to 4.2×10^{-2}) mg/kg/lb a.i. for cut surface, streamline, and directed foliar applications (see Table 3-2 in SERA 1995b). Some ground applications of 2,4-D can lead to much higher exposure rates. For example,

as discussed in SERA (1993, Table 3, p. 22), exposure rates of about 0.03 (0.01-0.1) mg/kg/lb a.i. handled were determined in backpack applications of 2,4-D in which workers received heavy dermal exposure from contact with treated vegetation (Lavy et al. 1987). Such exposure conditions are considered atypical of Forest Service sponsored applications, and this exposure rate is not routinely used in worker exposure assessments.

Exposure rates for workers involved in aerial applications are generally much less than those for ground workers (SERA 1993). For 2,4-D, exposure rates ranging from $2x10^{-5}$ to $4x10^{-5}$ mg/kg/lb a.i. are typical for pilots as well as mixer/loaders. As with ground workers, exposure rates for workers involved in aerial applications vary widely, with the upper and lower limits of exposure spanning about an order of magnitude (SERA 1993, see Table 11). Thus, for workers involved in the aerial application of 2,4-D, a typical rate with plausible ranges for exposure is $3x10^{-5}$ ($3x10^{-6}$ to $3x10^{-4}$) mg/kg/lb a.i. handled. All of these exposure rates are based on studies in which exposure was measured by assays for 2,4-D in the urine. Thus, these rates express absorbed doses rather than exposure doses.

The confidence intervals for the exposure rate estimates provided above are extremely broad, ranging from more than a factor of 100 for aerial workers to almost a factor of 1000 for workers involved in cut surface, streamline, and directed foliar applications, with an intermediate variability—a factor of about 400—for workers involved in hydraulic spraying. This degree of variability is common in the assessment of individual worker data and may relate to both differences among individual workers in work habits and/or pharmacokinetics (SERA 1993).

As noted above, there are two exposure studies regarding ground applications of hexazinone, one conducted in Quebec (Samuel et al. 1991, 1992) and the other conducted and recently completed in California (Spencer et al., 1996). In the Quebec study, hexazinone and hexazinone metabolites were measured in the urine of workers after the application of Velpar L or Pronone (Samuel et al. 1991, 1992). The specific Pronone formulation is not given but the material is referred to as granules and is presumably Pronone 10G. The liquid formulation was applied using a spot gun (backpack), a laterally mounted spray rig (referred to as a ramp), or boom jet sprayer. The method of applying the granular formulation is not specified in detail. Because this study does not report the amounts of hexazinone applied by each worker, exposure rates in units of mg/kg/lb a.i. handled, comparable to those for 2,4-D presented above, cannot be derived.

The pharmacokinetics of hexazinone are characterized in two volunteers, as part of the Samuel et al. (1991) study. Daily oral doses of 0.5 and 1.0 mg hexazinone were associated with hexazinone concentrations in the urine of 4741 and 5864 µg/L, respectively. The half-times for elimination of hexazinone metabolites ranged from about 24 to 48 hours, and approximately 20% of the administered dose was recovered in the urine. Urine concentrations in workers applying the granular formulation tended to be lower by factors of about 10-30, compared with those of workers applying the liquid formulation (Samuel et al. 1992, Table 3, p. 15). As noted above, however, this publication does not discuss the method used to apply the granular formulation. Like other worker studies, however, this study involves substantial inter-individual variability. For example, urine levels in

individual workers involved in spot gun treatments varied by a factor of 280 (Samuel et al. 1991, Table 3), comparable to the variability in exposure rate estimates for 2,4-D (i.e., factors of 100-1000) discussed above.

In the California study (Spencer et al. 1996), workers applied Pronone 10G using a *belly grinder*. Absorbed dose was estimated from monitoring air levels of hexazinone and the deposition of hexazinone on hands and clothing. For inhalation exposure, 100% absorption was assumed. For dermal exposure, 10% absorption was assumed. Based on these assumptions, the estimated average absorbed dose was 0.52 mg/kg/day at an average application rate of 2.4 lbs a.i./acre. Normalized for application rate, this corresponds to about 0.22 mg/kg/day · lb a.i./acre. The estimated exposure rates on different days of application [based on Table IX, p. 17, in Spencer et al. (1996)] ranged from a low of 0.012 mg/kg/day · lb a.i. applied to a high of 1.3 mg/kg/day · lb a.i. applied. This range, spanning a factor of about 100, is typical of ranges seen with 2,4-D, as discussed above. About 97% of the estimated absorbed dose was attributed to dermal absorption (Spencer et al. 1996, Table VI, p. 15).

The use of a 10% dermal absorption factor for hexazinone is not documented by Spencer et al. (1996) but appears to be based on a default assumption. This assumption has a substantial impact on the exposure assessment because, as indicated above, the great majority of the estimated absorbed dose was associated with dermal exposure. As discussed in section 3.1.7, the estimated absorption rate for hexazinone is 0.031 day^{-1} or 0.0013 hr^{-1}. Assuming that workers are exposed for 8 hours/day, the daily absorption fraction would be about 0.01 rather than 0.1. Thus, the estimated exposure rates would be lower by a factor of 10. Making this adjustment, the exposure rate estimate from the California study would be about 0.02 (0.001-0.13) mg/kg/day · lb a.i./acre. This exposure rate is comparable to the rate for backpack applications of liquid 2,4-D formulations in which workers were heavily exposed to runoff from treated vegetation [i.e., 0.03 (0.01-0.1) mg/kg/lb a.i. handled as discussed above]. These data suggest that, like the Lavy et al. (1987) study, the California study involved exposure levels that are much higher than what is typical for most ground applications of herbicides. This finding is consistent with the description of worker exposure given by Spencer et al. (1996):

> *On the highest exposure day, hexazinone dust was present in unusual amounts ... There was visible dustiness in the air and workers, USFS staff and study staff all noted ill effects from the presence of excessive dust... Intermittent excessive dustiness was noted on five other days...* (Spencer et al. 1996, pp. 13-14).

This description of worker exposure is similar to the description of extreme exposure conditions offered in the Lavy et al. (1987) study regarding backpack applications of 2,4-D:

> *...backpack applicators sprayed the area and then walked through herbicide-soaked vegetation 2 to 7 m high.... Field observations indicated that the clothing of the backpack crew members was commonly soaked with dew, perspiration and/or spray by the end of the day* (Lavy et al. 1987, pp. 219 and 220).

The comparable exposure rates for a liquid formulation of 2,4-D and a granular formulation of hexazinone—both under extreme conditions— is consistent with a study concerning the application of liquid and granular formulations of 2,4-D (Harris et al. 1992). In this study, average levels of 2,4-D in the urine of applicators applying a liquid formulation were about 200 µg/person with an average amount handled of 300 g (Table IV in Harris et al. 1992), including workers with undetectable levels of 2,4-D in the urine. In workers applying an average of 550 g of a granular formulation, the average urine level was about 20 µg/person. As discussed in this publication, the detectable levels of 2,4-D in the urine of workers applying liquid formulations were all associated with accidental spills. Only one of nine workers applying the granular formulation had detectable levels of 2,4-D in the urine (169 µg/person per 1200 g or 141 µg/person·kg a.i. handled). Ignoring non-detectable or trace quantities in workers handling the liquid formulations (Table IV in Harris et al. 1992), the average exposure rate was about 250 µg/kg a.i. handled for workers using a liquid formulation. Thus, while the use of a granular formulation of 2,4-D lead to lesser average exposures when all workers were considered, the exposure levels were comparable between the formulations for individuals in which 2,4-D could be detected.

For this risk assessment, the exposure rate for workers involved in the application of granular formulations of hexazinone using a *belly grinder* will be 0.02 (0.001-0.13) mg/kg/day · lb a.i./acre. As discussed above, this exposure rate is based on the data from the California study but uses a dermal absorption rate of 0.031 day^{-1} rather than an assumed rate of 10%. Even with this lower and more plausible dermal absorption rate, the use of the California study may be extremely conservative. As discussed above, the exposure conditions in the California study appear to be extreme and it is not clear that these conditions will reflect typical applications. Nonetheless, in the absence of additional studies on hexazinone demonstrating lower exposure levels for this type of application, the use of exposure data from the California study seems justified.

Other exposure rates will be based on 2,4-D, adjusting for differences in dermal absorption between 2,4-D and hexazinone. As summarized in section 3.1.7, the primary determinants of dermal absorption are lipophilicity (expressed as the K_{ow}) and molecular weight. Since hexazinone and 2,4-D are both water soluble (i.e., non-lipophilic compounds) and have similar molecular weights (252.3 vs 221 g/mole), the estimates of dermal absorption rates and dermal permeability coefficients are similar but consistently indicate that hexazinone may be absorbed more rapidly than 2,4-D by a factor of about 2.5 based on absorption rate [0.031 day^{-1} ÷ 0.012 day^{-1}] and a factor of about 13 [0.00032 cm/hour ÷ 0.000025 cm/hour] based on dermal permeability. For this risk assessment, the exposure rates for 2,4-D, summarized above, will be adjusted upward by a factor of 2.5 to reflect differences in dermal absorption rate. This approach is taken because, as discussed in Durkin et al. (1995), dermal permeability is most appropriate for estimating dermal absorption for immersion scenarios and dermal absorption rates are more appropriate for estimating dermal absorption following the deposition of a compound on the skin. For occupational exposure, deposition will be more common than immersion.

Thus, for typical ground applications of liquid hexazinone, plausible estimates and ranges of exposure rates are $2.4x10^{-4}$ ($1.2x10^{-5}$ to $4.8x10^{-3}$) mg/kg/lb a.i. handled [$2.5 \cdot 9.6x10^{-5}$ ($4.9x10^{-6}$ to $1.9x10^{-3}$)

mg/kg/lb a.i. handled] for roadside hydraulic spraying and $3.5x10^{-3}$ ($1.1x10^{-4}$ to $1.1x10^{-1}$) mg/kg/lb a.i. handled [$2.5 \cdot 1.4x10^{-3}$ ($4.4x10^{-5}$ to $4.2x10^{-2}$) mg/kg/lb a.i. handled] for cut surface, and directed foliar applications (see Table 3-2 in SERA 1995b). For pilots and mixer/loaders in aerial applications, exposure rates are estimated at $7.5x10^{-5}$ ($7.5x10^{-6}$ to $7.5x10^{-4}$) mg/kg/lb a.i. handled [$2.5 \cdot 3x10^{-5}$ ($3x10^{-6}$ to $3x10^{-4}$) mg/kg/lb a.i. handled].

All of the above application rates are summarized in Table 3-2. In this table, plausible levels of exposure for ground and aerial applications are estimated as the product of an application rate of 1 lb a.i./acre, the area treated per hour (acres treated/hour by a worker), and the exposure rate (mg/kg bw/lb a.i.). All calculations assume that the worker applies the product for 8 hours/day. This is a reasonably conservative estimate for workers on an extended 10-hour day but an overestimate for workers on a standard 8-hour day. This potential overestimate is a relatively minor factor, given the variability in exposure rates among individuals. With the exception of the applications involving the use of a *belly grinder*, the exposure rates apply to both granular and liquid formulations of hexazinone.

Table 3-2. Quantitative summary of occupational exposure to hexazinone, excluding accidental or incidental exposures

Treatment method	Treatment rate (acres/hour)	Exposure rate (mg/kg/lb a.i.)	Daily dose (mg/kg bw)[a]
Boom spraying	15 11-21	$2.4 \cdot 10^{-4}$ $1.2 \cdot 10^{-5}$ - $4.8 \cdot 10^{-3}$	0.029 (0.0011-0.81)
Backpack	0.5 0.25-1	$3.5 \cdot 10^{-3}$ $1.1 \cdot 10^{-4}$ - $1.1 \cdot 10^{-1}$	0.014 (0.0002-0.88)
Belly grinder, granular only	1.0 (0.5-1.5)	$2.0 \cdot 10^{-2}$ $1 \cdot 10^{-3}$ - $1.3 \cdot 10^{-1}$	0.16 (0.004-1.6)
Aerial applications (pilots and mixer/loaders)	60 40-100	$7.5 \cdot 10^{-5}$ $7.5 \cdot 10^{-6}$ - $7.5 \cdot 10^{-4}$	0.036 (0.0024-0.6)

[a] Assuming an application rate of 1 lb/acre and an 8-hour work day.

Estimated daily doses are presented as a central value and a range. The central value is based on the approximate geometric mean of the anticipated range of treatment rates and mean exposure rate. The lower range of the daily dose is based on the lower range of the treatment rates and the lower range of the exposure rate. The upper range of the daily dose is based on the upper range of treatment rates and the upper range of the exposure rate.

This exposure assessment methodology assumes a linear relationship between exposure and the application rate. As discussed in section 2.4, the Forest Service typically uses an application rate of about 2.5 lbs a.i./acre and may apply up to 6 lbs/acre. The consequences of these differing rates of application are discussed in the risk characterization (section 3.4).

3.2.2.2. ***Immersion or Contaminated Clothing*** **--** Incidental occupational exposure may occur from improper handling or use of the herbicide, or from accidental contamination of the skin or clothing by a spill. All of these scenarios can be modelled using Fick's first law. As discussed in Durkin et al. (1995), scenarios that use Fick's first law require an estimate of the permeability coefficient, K_p, expressed in cm/hour. As summarized in section 3.1.7., the estimated K_p for an aqueous solution of hexazinone is 0.00032 cm/hour.

During the handling process, an individual may immerse a part of the body into the formulation for a short time, either through mischance or imprudent handling. An extreme scenario could involve a worker who places both hands in the concentrated formulation of Velpar L (2 lbs a.i./gal or about 240 g/L). For this risk assessment, the surface area of the hands will be estimated as 0.084 m^2 (U.S. EPA 1992a). Concentrations of 240 g/L are equivalent to 240 mg/mL, which, in turn, is equivalent to 240 mg/cm^3.

For this scenario, the estimated absorbed dose, using Fick's first law, is approximately 0.015 mg/kg

$$0.00032 \text{ cm/hour} \cdot 240 \text{ mg/cm}^3 \cdot 1/60 \text{ hour} \cdot 840 \text{ cm}^2 \div 70 \text{ kg}.$$

Estimated doses for other immersed areas and durations can be calculated in a similar way. If, however, the scenario involves contaminated clothing (e.g., the chemical spilled inside of gloves), which might be worn for a long time, absorbed doses could be much higher. For example, contaminated gloves worn for 1 hour would lead to an exposure 60 times greater than that described for the immersion scenario (i.e., 0.92 mg/kg).

Granular formulations could lead to comparable levels of exposure if dust from the granules comes into contact with skin and the hexazinone dissolves from the granules into perspiration. As a worst case scenario, this could result functionally in dermal exposure to a saturated aqueous solution of hexazinone (i.e., 330 g/L or 330 mg/cm^3) (see Table 2-1). For example, if a 20 cm by 20 cm area of the skin is contaminated with a carrier containing hexazinone and if the hexazinone dissolves into perspiration, this would be equivalent to an exposure of 400 cm^2 of skin surface to a 330 mg/mL or 330 mg/cm^3 aqueous solution of hexazinone. For a worker involved in such an application for 4 hours, the total absorbed dose would be 2.4 mg/kg,

$$0.00032 \text{ cm/hour} \cdot 330 \text{ mg/cm}^3 \cdot 4 \text{ hour} \cdot 400 \text{ cm}^2 \div 70 \text{ kg}.$$

Using an elimination half time of about 24 hours (Samuel et al. 1991, Table 7), a urinary output of about 2 L/day, and assuming that excretion in the urine accounts for approximately half of the hexazinone eliminated from the body, average levels in the urine would be about 600 µg/L during the

first 24 hours after exposure [2.4 mg/kg · 0.5 ÷ 2 L]. This is only somewhat above the highest monitored level of hexazinone metabolites, 290 µg/L, in the urine of workers applying granular formulations of hexazinone (Samuel et al. 1991, Table 2). Given that the product of the surface area and duration of exposure in an actual field application could easily vary by a factor of 10, the relatively close agreement between the 600 µg/L estimate and the monitored concentration of 290 µg/L suggests that the estimated exposure of up to 2.4 mg/kg is plausible.

3.2.2.3. ***Accidental Spills*** **--** In accidental spill scenarios, it is important to estimate the amount of liquid adhering to the surface of the skin. In one study, as much as 4 mg liquid/cm^2 of skin surface was retained on hands removed immediately from beakers containing water or ethanol (Mason and Johnson 1987). When beakers containing light paraffin oil were used, approximately twice this amount was retained. In most instances, using these values should result in a plausible upper estimate of retention because chemical loss from the skin surface due to moving or washing are not considered. Thus, the amount of chemical transferred to the skin after a spill may be calculated as:

$$D_{Skin} = RF \cdot P \cdot A$$

where:

D_{Skin} = *dose remaining on surface of skin* (µg)

RF = *retention factor* (µg/cm^2) (*for example,* 4000–8000µg/cm^2)

P = *proportion of agent in the liquid*

A = *skin area exposed* (cm^2)

Any person handling a concentrated formulation or located near the area where the handling takes place may be subject to an accidental spill. This is different from immersion in that most of the liquid will run off the surface of the skin immediately after the spill unless the material is kept in contact with the skin by saturated clothing. If the clothing is saturated, the scenario outlined above applies.

Consider the effects of spilling hexazinone over the lower legs. The surface area of the lower legs is taken as 2070 cm^2 (U.S. EPA 1992a). The upper limit of the amount of liquid adhering to the surface of the skin is taken as 8 mg/cm^2 of skin (Mason and Johnson 1987). Since Velpar L has a specific gravity of 0.9776 (Table 2-2), this is equivalent to about 0.0078 mL/cm^2. Hence, the volume of liquid adhering to the skin is 16.15 mL [2070 cm^2 · 0.0078 mL/cm^2]. For a concentration of 330 mg/mL, the amount of hexazinone adhering to the skin can be estimated as approximately 5330 mg [16.15 mL · 330 mg hexazinone/mL].

To estimate the absorbed dose, some estimate of absorption rate as percent of applied dose/hour is necessary. As discussed in Section 3.1.7., an absorption rate of 0.031 day^{-1} or about 0.0013 hr^{-1} will be used.

Assuming that the skin is washed thoroughly after 1 hour, the absorbed dose can be estimated as 0.1 mg/kg

$$5330 \text{ mg} \cdot 0.0013 \text{ hr}^{-1} \div 70 \text{ kg}.$$

These exposures assume a contaminated skin surface of 2070 cm^2. The exposure estimate using Fick's first law in section 3.2.2.2 involves a surface area of 840 cm^2 and yields estimated absorbed doses of 0.92 mg/kg for a 1-hour exposure. Using the above absorption rate of 0.0013 hr^{-1} and a surface area of 840 cm^2, the estimated absorbed dose would be about 0.04 mg/kg. Thus, for comparable exposure conditions, the method based on simple absorption rate yields an estimate that is approximately 23 times less than estimates based on Fick's first law. This adds a substantial uncertainty to the risk assessment and the interpretation of dermal exposure scenarios.

3.2.3. General Public.

3.2.3.1. ***Scenarios and Assumptions*** **--** Under normal conditions, members of the general public should not be exposed to substantial levels of hexazinone. During application, the general public is excluded from treatment areas. In cases of accidental spills, exclusion zones are established and the general public is not permitted to enter the area.

Nonetheless, any number of exposure scenarios could be constructed for the general public, based on varying assumptions concerning application rates, dispersion, canopy interception, and human activity. For this risk assessment, several very conservative scenarios are developed. As discussed below, most of these scenarios should be regarded as extreme, some to the point of limited plausibility.

Many of the exposure scenarios for the general public involve a child. This is because the relationships of surface area and consumption rates to body weight result in estimated doses (mg agent/kg body weight) for young children that are higher than those for adults (U.S. EPA 1989a). Consumption-specific values are taken from U.S. EPA (1989a,b). The chemical-specific assumptions for hexazinone are the same as those used for workers.

Dermal exposure scenarios that involve children use the same set of assumptions: the child is 2- to 3-years old, weighs 10–11 kg, and has a total body surface area of 0.6 m^2 or 6000 cm^2 for a body weight of 11 kg (U.S. EPA 1992c). For most scenarios, the child is assumed to be naked, maximizing the surface area of the body in contact with the chemical. In all cases, there are linear relationships among the exposed surface area of the body, the estimated absorbed dose, and the subsequent risk.

3.2.3.2. ***Direct Spray*** **--** For this exposure scenario, it will be assumed that during a ground application of hexazinone, a naked child is sprayed directly with hexazinone from a hydraulic sprayer. The scenario also assumes that the child is completely covered (that is, 100% of the surface area of the body is exposed). The highest spray concentration recommended for Velpar L is 1 gallon of herbicide formulation in 5 gallons of water (Du Pont 1993a), or 16.7%, which corresponds to about 40 g a.i./L or 40 mg a.i./mL [240 g/L·0.167]. Thus, the dose deposited on the child will be 1920 mg

$$0.008\ mL/cm^2 \cdot 40\ mg/mL \cdot 6000\ cm^2$$

Taking the absorption rate of 0.0013 hr^{-1} and assuming that the child is washed completely 1 hour after being sprayed, the absorbed dose is estimated as approximately 0.23 mg/kg,

$$1920 \text{ mg} \cdot 0.0013 \text{ hr}^{-1} \div 11 \text{ kg}.$$

For a young woman, it will be assumed that the feet and legs (2915 cm^2) are sprayed directly with a 40 mg/L solution of hexazinone. The dose deposited on the woman will be approximately 933 mg,

$$0.008 \text{ mL/cm}^2 \cdot 40 \text{ mg/mL} \cdot 2915 \text{ cm}^2.$$

Assuming a 1-hour exposure period, the absorbed dose is estimated as approximately 0.019 mg/kg,

$$933 \text{ mg} \cdot 0.0013 \text{ hr}^{-1} \div 64 \text{ kg}.$$

3.2.3.3. ***Dermal Exposure from Contaminated Vegetation*** **--** In this exposure scenario, it is assumed that the herbicide is sprayed at a given application rate and that an individual comes in contact with treated vegetation or other contaminated surfaces at some period after the spray operation. As discussed in Durkin et al. (1995), some estimate of dislodgeable residue of the herbicide must be available. This information is not available for hexazinone. Moreover, empirical estimation methods for relating dislodgeable residue to application rates and chemical/physical properties have not been published.

Immediately after the spray application, levels of exposure may approximate those involving contact with direct spray, as estimated above. Generally, after the liquid carrier dries, exposure levels decrease. For example, in a study by Harris and Solomon (1992), 2,4-D was applied to turf at a nominal rate of 11 $\mu g/cm^2$. Immediately after the liquid carrier dried, the dislodgeable residue of 2,4-D was 0.92 $\mu g/cm^2$, about 10 times less than the nominal rate.

As discussed above, the typical application rate for hexazinone is about 2.5 lbs a.i./acre or approximately 0.028 mg a.i./cm^2 (28 μg a.i./cm^2). If the dislodgeable residue for hexazinone follows a pattern similar to that of 2,4-D, the dislodgeable residue immediately after the liquid carrier dries will be approximately 0.0028 mg/cm^2 or approximately 2.8 $\mu g/cm^2$. Following the methods provided by Durkin et al. (1995, equation 4, p. 68), the transfer rate would be about 3.4 $\mu g/(cm^2 \cdot \text{hour})$ [$10^{0.537}$]

$$[(1.09 \cdot \log(2.8 \ \mu g/cm^2)] + 0.05 = 0.537.$$

The exposure dose for an individual, wearing shorts and a short-sleeved shirt, in contact with the contaminated vegetation for 1 hour will be 18,000 μg or approximately 18 mg

$$3.4 \ \mu g/(cm^2 \cdot \text{hour}) \cdot 5300 \text{ cm}^2 \cdot 1 \text{ hour}.$$

Taking the dermal absorption rate of 0.0013 h^{-1} or 0.031 day^{-1}, and assuming a 64 kg body weight for a young woman, the absorbed dose will be 0.0087 mg/kg

$$18 \text{ mg} \cdot 0.031 \text{ day}^{-1} \cdot 1 \text{ day} \div 64 \text{ kg}.$$

3.2.3.4. ***Contaminated Water*** **--** Water can be contaminated from runoff, leaching from contaminated soil, from a direct spill, or unintentional contamination from aerial or ground applications. Hexazinone is relatively stable in aqueous solutions. A half-time of several years was reported for hexazinone incubated in natural water at 30°C (Bouchard et al. 1985). Nonetheless, hexazinone levels in ambient water decrease rapidly after initial application. The dissipation half-time in lake water is about 3.8 days ($k=0.18$ days^{-1}) (Solomon et al. 1988). While decreases in environmental levels may be associated partially with photodegradation (WSSA 1989) and/or biodegradation (Rhodes 1980a, Felding 1992), hexazinone has a low affinity for soils and sediments (e.g., Rhodes 1980b, Solomon et al. 1988); consequently, much of the decrease in aqueous levels may be attributable to simple dilution.

Several field monitoring studies were conducted on ambient water contamination associated with both ground and aerial applications of liquid and granular formulations of hexazinone. Details of these studies are provided in appendix 6, and the most relevant of these studies are summarized briefly in Table 3-3. Generally, these studies are relatively consistent and indicate ambient water concentrations of approximately 1-40 µg/L·lb a.i. applied. There seems to be no systematic differences associated with the formulation (liquid or granular) or specific water types (i.e., streams or lakes). These rates in terms of the amount of hexazinone applied are similar to levels of hexazinone based on *worst case* conditions in studies using lysimeters (Stone et al. 1993) in which an application rate of 2.24 kg/ha (2 lb/ac) was associated with hexazinone levels in soil leachates of about 10-80 µg/L or 5-40 µg/L·lb a.i. applied. In the study by Stone et al. (1993) as well as in several of the field studies (e.g., Lavy et al. 1989, Felding 1992), peak levels of hexazinone in water may be delayed and levels over time may be highly variable depending on levels of precipitation.

The studies reported by Miller and Bace (1980) and Neary et al. (1983) report atypically high water levels of hexazinone for the application rates used (see Table 3-3). In the study by Neary et al. (1983), all samples were collected after storm events. Relatively high levels of hexazinone, about 100-400 µg/L, as well as much lower levels of two hexazinone metabolites, were detected in runoff water during the first month after application. Over a period of 13 months after application, hexazinone levels in the water were more typical of the other values reported in Table 3-3: about 10-30 µg/L. The very high level of 2400 µg/L reported by Miller and Bace (1980) is attributed to a direct application of hexazinone pellets over a stream. Such applications would not normally occur in Forest Service applications of this herbicide. Any direct application of hexazinone to a stream or other body of open water would only occur as a result of accidental application or misapplication.

For this risk assessment, accidental exposure will be based on the data of Miller and Bace (1980). The application rate of 0.8 kg/ha used in this study corresponds to 80 mg/m^2 [800,000 mg/10,000 m^2]. At a mixing depth of 1 m, this would result in a water concentration of 80 mg/m^3 [0.08 mg/L or 80 µg/L]. Thus, the observed concentration of 2400 µg/L would correspond to a very shallow functional mixing depth of about 0.033 m or 1.2 inches [80 mg/m^2÷0.033 m ~ 2424 mg/1000 L or 2424 µg/L], assuming instantaneous mixing. In streams, the dynamics would be more complex and this peak level would rapidly diminish. For example, in the Miller and Bace (1980) study, the hexazinone concentration in the water dropped from the peak of about 2400 to about 500 µg/L in

Table 3-3. Summary of field studies assessing water contamination after the application of hexazinone

Application	Maximum Water Levels	Concentration Rate	Reference
2.0 kg a.i./ha, Velpar L, using spot-gun sprayers.	14 μg/L in stream water	7.8 μg/L •lb/ac	Bouchard et al. 1985
2 kg a.i./ha on sandy loam.	2.09 μg/L in soil water.	1.2 μg/L •lb/ac	Felding 1992
	42.66 μg/L in soil water	24 μg/L •lb/ac	Felding 1992
1.36 kg a.i./ha, Velpar L, spot gun, 15 m buffer.	16 µg/L in stream water.	13 μg/L •lb/ac	Lavy et al. 1989
2 kg/ha, Velpar L, aerial application, clay loam, 30 m buffer.	4μg/L in stream water during a 9-week monitoring period	2.2 μg/L •lb/ac	Leitch and Flinn 1983
1.6-2.9 kg a.i./ha, Velpar L, spot applications	6-37 µg/L in surface water	1.1 - 14 μg/L •lb/ac	Michael and Neary 1993
1.7 kg a.i./ha, Velpar L, boom spray	1.3 µg/L in surface water	0.85 μg/L •lb/ac	
1.7 kg a.i./ha, clay pellets, aerial application	N.D. [< 1µg/L]	<0.65 μg/L •lb/ac	Neary 1983
0.8 kg a.i./ha, Velpar Gridball, aerial over stream	2,400 µg/L	3,363 µg/L •lb/ac	Miller and Bace 1980
1.02 kg/ha, Velpar (NOS), clay loam soil.	38 μg/L in ground water after irrigation	38 µg/L •lb/ac	Miller et al. 1995
1.68 kg a.i./ha, pellets, spot applications	442 µg/L in storm runoff water	295 µg/L •lb/ac	Neary et al. 1983
2.24 kg a.i./ha to surface soils, ^{14}C-labelled Hexazinone	60.6 μg/L in soil water	30 µg/L •lb/ac	Stone et al. 1993
2.76-3.0 kg a.i./ha, Velpar L, spotgun	85 μg/L in surface water	31 µg/L •lb/ac	Williamson 1988

less than 2 hours and the time-weighted concentration over the 24-hour period after application—estimated graphically from Figure 2 in Miller and Bace (1980)—appears to be about 300

µg/L. Adjusting for differences in application rates, this is approximately the level noted by Neary et al. (1983) for concentrations in storm runoff (see Table 3-3). Thus, for accidental exposure, a concentration of 300 µg/L·lb a.i. per acre applied will be used. Assuming that a 10 kg child consumes 1 L of the contaminated water, the dose of hexazinone would be 0.03 mg/kg/day:

$$0.3 \text{ mg/L} \cdot 1 \text{ L} \div 10 \text{ kg}.$$

This dose would increase linearly with the application rate, as discussed further in the risk characterization (section 3.4).

As indicated in Table 3-3, more typical levels of hexazinone in water associated with ground or aerial applications of liquid or granular formulations of hexazinone range from about 1 to 40 µg/L in groundwater or surface water. The leaching of any herbicide into the aquifer depends strongly on rainfall and groundwater depth. This is particularly so for hexazinone because it does not bind tightly to soils, as discussed further in section 4. Thus, the variability in water concentrations after hexazinone applications may be attributable to different meteorological and local geological conditions. In this respect, local variations of the nature described seem to be more significant than the application rate. As discussed by Felding (1992), differences in soil microflora also may be an important factor in the long-term levels of hexazinone in surface or groundwater.

Another complication in estimating levels of hexazinone for 'typical' longer-term scenarios is the time course of water contamination. Although hexazinone may show a rapid initial dispersion with concomitant decrease in water concentrations (e.g., Miller and Bace 1980, Solomon et al. 1988), several studies report relatively irregular fluctuations over periods of 1 year or longer after application (Bouchard et al. 1985, Lavy et al. 1989, Williamson 1988) with peak levels occurring up to several months after application (Miller et al. 1995, Neary et al. 1983). Hence, soil microflora may degrade hexazinone substantially in some soils; however, hexazinone may be highly persistent in others. Although this apparent persistence is inconsistent with the rapid mobility of hexazinone in soil, hexazinone may bind extremely tightly to lignin (Privman et al. 1994). It is possible that soils that are high in lignin may act as sinks or reservoirs for hexazinone. This speculation is consistent with the observation by Lavy et al. (1989) that the litter layer may serve as a reservoir for hexazinone.

The apparent variability in the relationship of water levels to hexazinone applications over relatively long periods of time cannot be resolved. For this risk assessment, long-term exposure will be based on the full range of 1-40 µg/L·lb a.i. applied per acre. Assuming that a 10 kg child consumes 1 L of water/day, the estimated dose for prolonged exposure is 0.1–4 μg/kg/day or 0.0001–0.004 mg/kg/day

$$1\text{-}40 \ \mu\text{g/L} \cdot 1 \text{ L/day} \div 10 \text{ kg}.$$

For a 70 kg adult consuming 2 L of water per day, the corresponding estimates are 0.03–1 μg/kg/day or 0.00003–0.001 mg/kg/day

$$1\text{-}40 \ \mu\text{g/L} \cdot 2 \text{ L/day} \div 70 \text{ kg}.$$

As with the short term exposure assessment, these levels assume an application rate of 1 lb a.i./acre. The consequences of higher application rates are discussed in the risk characterization (section 3.4).

3.2.3.5. ***Oral Exposure from Contaminated Fish*** **--** Many chemicals may be concentrated or partitioned from water into the tissues of animals or plants in the water. This process is referred to as bioconcentration (see glossary). Generally, bioconcentration is measured as the ratio of the concentration in the organism divided by the concentration in the water. For example, if the concentration in the organism is 5 mg/kg and the concentration in the water is 1 mg/L, the bioconcentration factor (BCF) is 5 L/kg [5 mg/kg ÷ 1 mg/L]. As with most absorption processes, bioconcentration is initially dependent on the duration of exposure but eventually reaches steady state. Details regarding the relationship of bioconcentration factor to standard pharmacokinetic principles are provided in Calabrese and Baldwin (1993).

Hexazinone has a relatively low potential for bioconcentration. In a bioconcentration study using ^{14}C-hexazinone, bioconcentration in bluegill sunfish exposed to levels in water of 10–1000 μg/L ranged from about 1-4 after 1 day of exposure to about 2-5 after 14-21 days of exposure. Most of the recovered radioactivity was in the form of unchanged hexazinone (91%). The remainder was recovered as metabolite A in Figure 2-1, which is also a common metabolite in mammals and plants (Rhodes 1980a).

As discussed above, peak levels of hexazinone in ambient water are not likely to exceed 300 µg/L·lb a.i. applied per acre. Longer-term levels in water may vary from 1 to 40 µg/L·lb a.i. applied per acre.

For estimating hexazinone residues in fish shortly after application, a 1-day bioconcentration factor of 4 will be used as a conservative upper limit. Thus, residues in fish of 1.2 mg/kg fish·lb a.i. applied would be expected [300 µg/L·lb a.i. applied · 4 L/kg = 1200 µg/kg·lb a.i. applied or 1.2 mg/kg·lb a.i. applied]. Assuming that a 70 kg man consumes a maximum of 158 g of fish per day (Ruffle et al. 1994, Table II, p. 397), the resulting dose associated with an application rate of 1 lb/acre would be 0.003 mg/kg,

$$1.2 \text{ mg/kg fish} \cdot 0.158 \text{ kg} \div 70 \text{ kg}.$$

For estimating hexazinone residues in fish for prolonged periods after application, a 14-21 day BCF of 5 will be used. Typical levels in ambient water may be in the range of 1-40 μg/L·lb applied. Thus, residues in fish would be estimated as greater than a rate of 5-200 μg/kg·lb applied. Using the same maximum value for fish consumption as above, the resulting dose associated with the typical application rate of 1 lb/acre would be 0.00001-0.0005 mg/kg

$$0.005\text{-}0.2 \text{ mg/kg fish} \cdot 0.158 \text{ kg} \div 70 \text{ kg}.$$

As with other exposure scenarios in this section, the consequences of higher application rates are discussed in the risk characterization (section 3.4).

3.2.3.6. ***Oral Exposure from Contaminated Vegetation*** **--** After ground or aerial applications, hexazinone will be deposited on vegetation. Although the general public is excluded from the area while treatments are being conducted, it is conceivable that contaminated vegetation could be consumed by individuals shortly after treatment.

No information is available regarding hexazinone levels on vegetation that might be consumed by humans. After a spot gun application of liquid hexazinone to the forest floor at a rate of 1.36 kg/ha (1.2 lb/acre), residues on leaves ranged from about 0.49 to 0.96 mg/kg over a 2-month period after application. This corresponds to a residue rate of about 0.4-0.8 mg/kg·lb a.i./acre (Lavy et al. 1989). Based on a monitoring study of several different tree species 273-707 days after the application of hexazinone granules at a rate of 4 kg/ha (3.6 lb/ac), Sidhu and Feng (1993) estimated maximum total hexazinone residues at 28.75 mg/kg. These residues consisted of unchanged hexazinone as well as metabolites A and B in Figure 3-1 [see Table 3 in Sidhu and Feng (1993)]. This is equivalent to about 8 mg/kg·lb/acre, a factor of 10-20 times the rate derived from Lavy et al. (1989). Taking only the hexazinone data from Sidhu and Feng (1993), which is more comparable to the data presented by Lavy et al. (1989), the residue rate is about 2 mg/kg·lb/acre, comparable to the rate reported in the Lavy study.

Although these estimates may be adequate for soil applications, they could underestimate exposure from consuming vegetation immediately after a direct spray with liquid hexazinone. For example, it is possible to construct an exposure scenario involving the consumption of fruit, such as berries, consumed shortly after a spray. The amount of herbicide on the surface of the fruit will depend on the application rate. An application rate of 1 lb a.i./acre corresponds to 0.0112 mg/cm^2. Because of the relationship of surface area to volume, smaller size fruits will tend to be more contaminated than larger size fruits. For example, a berry with a 1 cm diameter (d) or a radius (r) of 0.5 cm has a volume (V) of 0.52 cm^3 ($V=1/6\cdot\pi d^3$) and a planar surface area of 0.78 cm^2 ($SA=\pi r^2$). Taking the application rate of 0.0112 mg/cm^2 and assuming a density of 1 g/cm^3 for the berry, the nominal residue would be 16.8 mg/kg

$$0.0112 \text{ mg/cm}^2 \cdot 0.78 \text{ cm}^2 \div 0.00052 \text{ kg}.$$

Using the same set of calculations for a fruit with a diameter of 5 cm (about 2 inches), the corresponding residue would be 3.4 mg/kg [SA = 16.6 cm^2, V = 65 cm^3].

For comparison, empirical relationships based on initial residues for a large number of pesticides shortly after various application methods suggest typical residue rates of 125 mg/kg·lb a.i./acre on leaves and leafy crops and extreme residue rates of 240 mg/kg·lb a.i./acre on range grass. For fruits, grains, and seed pods, the corresponding estimates are 1.5-12 mg/kg (Hoerger and Kenaga 1972).

For this exposure assessment, the residues immediately after application will be estimated at about 2-20 mg/kg·lb a.i. applied. This range is based on the calculations for different sized fruits, adjusted slightly to accommodate the empirical ranges for different types of edible vegetation presented by

Hoerger and Kenaga (1972). Assuming that a 64 kg woman (U.S. EPA 1989a) consumes 1 pound (0.454 kg) of contaminated vegetation, the dose is estimated as 0.01-0.1 mg/kg

$$2\text{-}20 \text{ mg/kg} \cdot 0.454 \text{ kg} \div 64 \text{ kg}.$$

For chronic exposure, direct deposition on vegetation will be less important than deposition to and transport in soil with subsequent uptake by the roots, as discussed in section 4. Also, based on the data reported by Sidhu and Feng (1993), there is little reason to assume a systematic decrease in hexazinone residues over time. Thus, for chronic exposure, residue rates of 0.4-2 mg hexazinone/kg·lb/acre will be used, encompassing the data presented by Lavy et al. (1989) and Sidhu and Feng (1993). Because the chronic toxicity of hexazinone metabolites was not thoroughly investigated (see section 3.1.9.1), this residue rate will be adjusted upwards by a factor of 4, consistent with the data of Sidhu and Feng (1993) on the relative amounts of metabolites A and B in leaf samples. Thus, the residue rate will be taken at 1.6-8 mg hexazinone/kg·lb/acre for this exposure assessment.

Using the same consumption estimate as for acute exposure (i.e., l lb of contaminated vegetation per day), the estimated dose is 0.01-0.06 mg/kg

$$1.6\text{-}8.0 \text{ mg/kg} \cdot 0.454 \text{ kg} \div 64 \text{ kg}.$$

This should be regarded as an extreme upper range because, in general, individuals will not consume 1 lb of vegetation per day. A more reasonable estimate would be 0.051 kg, the central estimate of the daily consumption of vegetables by adults (U.S. EPA 1989b). Using this consumption rate, the estimated dose is 0.0013-0.0064 mg/kg

$$1.6\text{-}8.0 \text{ mg/kg} \cdot 0.051 \text{ kg} \div 64 \text{ kg}.$$

These estimates apply to an application rate of 1 lb/acre and would increase in a linear fashion as the application rate increases. The consequences of increased application rates are discussed in the risk characterization (section 3.4).

3.3. DOSE-RESPONSE ASSESSMENT

3.3.1. Overview. The U.S. EPA derived two RfDs for hexazinone. The RfD currently listed on IRIS is 0.033 mg/kg/day. In the re-registration process, the U.S. EPA Office of Pesticides derived an RfD of 0.05 mg/kg/day, based on more recent data that addresses some of the concerns with the original RfD. Relative to the wide range of exposures derived in the exposure assessment, there is functionally no difference between the RfDs of 0.033 mg/kg/day and 0.05 mg/kg/day. The more recent RfD of 0.05 mg/kg/day is used in this risk assessment as the basis for characterizing risk. The available animal toxicity data are used qualitatively to characterize plausible effects associated with exposure above the RfD.

3.3.2. Existing Guidelines. The U.S. EPA RfD for hexazinone listed on IRIS is 0.033 mg/kg/day (U.S. EPA 1993a). This is based on the 2-year rat feeding study of Schneider and Kaplan (1983), summarized in appendix 1, in which a dietary level of 200 ppm was associated with no observable effects and 2500 ppm was associated with decreased body weight gain and food efficiency in male rats and female rats. In this RfD, the U.S. EPA assumes that rats consume food at a rate equivalent to 5% of their body weight per day. Thus, the NOAEL for this study is 10 mg/kg bw/day (200 mg/kg food · 0.05 mg food/kg bw) and the LOAEL is 125 mg/kg/day (2500 mg/kg food · 0.05 mg food/kg bw). This RfD was derived using an uncertainty factor of 300 to account for species-to-species extrapolation (10), sensitive subgroups (10), and the lack of a chronic study on dogs (3).

This last uncertainty factor of 3 was applied because the U.S. EPA considered dogs more sensitive than rats to hexazinone in a 90-day feeding study. This decision appears to be based on the 90-day feeding studies in rats and dogs reported by Kennedy and Kaplan (1984). In both studies, decreased body weight gain was noted at dietary levels of 5000 ppm and no effects were seen at 1000 ppm. Because small animals consume greater amounts of food per unit body weight per day, compared with large animals, the dose levels [mg agent/kg body weight] for dogs (NOEL=25 mg/kg/day, LEL=125 mg/kg/day assuming that dogs consume an amount of food that is equal to 2.5% of their body weight per day) are lower than those for rats (NOEL=50 mg/kg/day, LEL=250 mg/kg/day assuming that rats consume an amount of food that is equal to 5% of their body weight per day). These food consumption estimates appear to be taken from the 1986 U.S. EPA report, *Reference Values for Risk Assessment* (U.S. EPA 1986).

In the process of reregistration, a 2-year feeding study in dogs was submitted to the U.S. EPA Office of Pesticides (U.S. EPA 1994a). In this study, doses of 41.24 and 37.57 mg/kg/day in males and females, respectively, were associated with changes in clinical chemistry and histopathology. The NOEL for these effects was 5 mg/kg/day. Based on this NOEL and using an uncertainty factor of 100 for species-to-species extrapolation (10) and sensitive subgroups (10), the Office of Pesticides derived an RfD of 0.05 mg/kg/day (U.S. EPA 1994a, 1995).

In terms of the uncertainties associated with this risk assessment, there is functionally no difference between the RfDs of 0.033 mg/kg/day and 0.05 mg/kg/day. The more recent RfD of 0.05 mg/kg/day will be used as the basis for characterizing risk. As discussed in the following section, the most important aspects of interpreting higher levels of exposure involve the assessment of dose-severity relationships.

3.3.3. Dose-Response and Dose-Severity Relationships. As discussed in section 3.2, many of the projected exposures for workers and members of the general public exceed the RfDs of 0.033 and 0.05 mg/kg/day.

Based on studies in experimental mammals, a dose of 125 mg/kg/day is clearly unacceptable. As discussed in section 3.2.4. (Reproductive and Teratogenic Effects), a dose of 125 mg/kg/day was associated with increased resorptions in rabbits (MRID 00028863, Serota et al. 1980). No effects were seen at lower doses (20 or 50 mg/kg/day). In addition, the multi-generation feeding study in

rats (MRID 42066501, Mebus 1991) reported decreased pup survival at 250 mg/kg bw/day but no effects at 10 or 100 mg/kg/day. While weight loss might not be interpreted as a severe toxic effect, fetal resorptions clearly are severe toxic effects.

The lowest dose associated with any adverse effect is the dose of 40 mg/kg/day from the 1-year dog feeding study in which pathological effects as well as changes in clinical chemistry were observed. At this level of exposure, overt signs of toxicity would probably not be apparent.

The major uncertainty in applying these dose-severity relationships to the risk assessment involves species to species extrapolation. As discussed in the previous section, the dog may be more sensitive than the rat to the chronic toxic effects of hexazinone. This is consistent with the general assumption in the use of the species-to-species uncertainty factor (i.e., large animals are more sensitive than smaller animals). For many chemicals, such differences in species sensitivity are apparent and indicate that small animals are less sensitive (i.e., have higher LD_{50} values) than large animals. This general pattern is the basis for the uncertainty factor of 10 used for animal-to-human extrapolation in the derivation of the RfD (Dourson and Stara 1983).

For hexazinone, however, this pattern does not appear to hold for acute toxicity. As summarized in Appendix 1, acute LD_{50} values for guinea pigs, rats, and quail—all of which have body weights in the range of 0.2-0.4 kg—range from about 530 to more than 2000 mg/kg. The reported LD_{50} for dogs, however, is >3400 mg/kg. Thus, the acute toxicity data are inconsistent with the assumption that dogs are more sensitive than rats. In terms of acute lethal potency or signs of gross toxic effects, doses of about 500 mg/kg are clearly hazardous.

For this risk assessment, a dose of 125 mg/kg/day will be treated as a frank effect level in experimental mammals because of the resorptions noted in the rabbit teratology study. Although 100 mg/kg/day could be used as a NOAEL based on the rat multi-generation reproduction study, this dose level is extremely close to the frank effects level. Consequently, the NOAEL will be taken as 50 mg/kg/day from the rabbit teratology study. This is supported by a lower dose, 20 mg/kg/day, that was also a NOAEL in rabbits. For characterizing potential human risks, an uncertainty factor of 10 for sensitive individuals is appropriate. Thus, a dose of 12.5 mg/kg/day will be regarded as clearly hazardous. While no frank toxic effects would be anticipated, reproductive effects could be evident. The potential risks of lower doses (i.e., doses above the RfD of 0.05 mg/kg/day but below the clearly hazardous dose of 12.5 mg/kg/day) cannot be well characterized. Using the additional uncertainty factor of 10 for species extrapolation as done by U.S. EPA, a dose as low as 1.25 mg/kg/day could be viewed as hazardous in terms of reproductive effects.

Based on the 40 mg/kg/day AEL in dogs, subclinical signs of toxicity would be anticipated at a dose of 4.0 mg/kg, using an uncertainty factor of 10 for sensitive subgroups. Applying an additional uncertainty factor of 10 for species extrapolation, the dose level of concern would be 0.4 mg/kg. In this range of exposure, overt signs or symptoms of toxicity would be unlikely.

Table 3-4. Dose-severity relationships used for risk characterization.

Dose (mg/kg/day)	HQ	Plausible Effect
500	10,000	probably lethal
100	2000	potentially lethal dose, overt signs or symptoms of toxicity after acute exposures
10 to 100	200 to 2,000	probable effects on reproduction; signs of toxicity are plausible
1.25 to 12.5	25 to 250	potential reproductive effects
0.4 to 4	8 to 80	potential subclinical toxic effects
>0.05 to 0.4	>1 to 8	nature and severity of toxic effects for longer term exposures are uncertain.
≤0.05	≤ 1	no effects anticipated over lifetime exposures.

Based on the above discussion, the dose-severity estimates used for characterizing human risk are summarized in Table 3-4. As indicated in this table, several of the severity levels are associated with overlapping ranges of exposure. This is due to the uncertainties and variability in the available data, as discussed above.

3.4. RISK CHARACTERIZATION

3.4.1. Overview. The major hazard associated with the use of hexazinone will involve accidental or incidental ocular or respiratory exposure. As discussed in the hazard identification (see section 3.1.6), hexazinone is a severe eye irritant. In addition, the California worker study (Spencer et al. 1996) suggests that respiratory irritation is plausible or even likely in the use of granular formulations of hexazinone that contain high levels of dust or fine particulates.

Based on the exposure assessments discussed in section 3.2 and the dose-response assessments discussed in section 3.3, the quantitative risk assessments for workers and the general public are summarized in Tables 3-5, 3-6, and 3-7. In these tables, risk is characterized as the hazard quotient, the ratio of the anticipated level of the exposure to some index of acceptable exposure or exposure associated with a defined risk. Thus, if the hazard quotient is less than unity, concern for the exposure is minimal. As the hazard quotient increases above unity, concern also increases.

For workers, the uncertainties in the characterization of risk is dominated by the very wide range of projected exposures. Over the range of plausible application rates, all worker groups may be exposed to hexazinone at levels that exceed the RfD. Although workers using a *belly grinder* may be exposed to much higher levels of hexazinone, compared with other worker groups, the basic characterizations

Table 3-5. Summary of risk characterization for occupational exposures to hexazinone by job category, excluding accidental or incidental exposure

Treatment Method	Daily Dose (mg/kg bw)[a]	Hazard Quotient for Specific Application Rate[b]	
		1 lb/acre	6 lbs/acre
Boom spraying	0.029 0.0011-0.81	0.6 0.02-16	3 0.1-97
Directed foliar and spot treatments	0.014 0.0002-0.88	0.3 0.004-18	2 0.02-100
Belly grinder, granular only	0.16 0.004-1.6	3 0.08-32	19 0.5-200
Aerial applications (pilots and mixer/loaders)	0.036 0.0024-0.6	0.7 0.05-12	4 0.3-70

[a] Assuming an application rate of 1 lb a.i./acre. [See Table 3-2 for details of exposure estimate.]

[b] Based on the RfD of 0.05 mg/kg/day (see section 3.3.2).

of risks are similar for all worker groups. The effects that are most likely to be observed after exposure to hexazinone are irritation to the eyes, respiratory tract, and skin. In general, irritant effects on the eyes and respiratory tract are likely to be more severe than effects on the skin. Even under the most extreme exposure scenarios, frank toxic effects are not likely to be observed. Nonetheless, using the available animal data to characterize dose-severity relationships, the upper estimates of exposure levels could be associated with subclinical effects and possibly reproductive effects.

In some accidental and extreme exposure scenarios, members of the general public may be exposed to levels of hexazinone above the RfD but still far below the levels projected for workers. While any exposure above the RfD is considered unacceptable by definition, the exposure estimates for the general public are in a range where the occurrence and nature of potential toxic effects cannot be well characterized. As with workers, no signs of frank toxic effects are anticipated.

3.4.2. Workers. A quantitative summary of the risk characterization for each of the job categories covered in this risk assessment is presented in Table 3-5. For each worker group, the second column of this table gives the estimated daily doses and ranges on the doses taken from Table 3-2. The next two columns give the hazard quotients based on the reference application rate of 1 lb a.i./acre and the maximum application rate of 6 lbs/acre. These hazard quotients are based on the RfD of 0.05 mg/kg/day derived by the U.S. EPA (see section 3.3.2). These hazard quotients, combined with the

Table 3-6. Quantitative summary of risks for workers after accidental or incidental exposure to hexazinone[a]

Activity	Scenario	Dose (mg/kg/day)	HQ[b]
Immersion of hands	1 minute	0.015	0.3
Wearing contaminated gloves	1 hour	0.92	18
Dermal exposure to dust	4 hours	2.4	48
Accidental spill on lower legs	effective washing after 1 hour	0.1	2

[a] See sections 3.2.2.2. and 3.2.2.3. for details regarding the exposure assessment.

[b] Based on the RfD of 0.05 mg/kg/day (see section 3.3.2).

dose severity estimates given in Table 3-2, are used to characterize qualitatively the potential hazards of systemic toxic effects. The irritant effects of hexazinone are considered separately at the end of this section.

For systemic toxic effects, risks to workers involved in boom spraying, spot treatments, directed foliar applications, or aerial applications are comparable because the levels of exposure are similar, with central estimates of exposure encompassing a relatively narrow range: 0.014-0.036 mg/kg/day per lb a.i. applied per acre. The central estimate of exposure for workers applying the granular formulation using a *belly grinder* is higher by a factor of about 10.

At the lower limit of projected exposures, the hazard quotient is not exceeded for any worker group at even the highest application rate. The simple interpretation of this is that hexazinone can be applied safely so long as measures are taken to minimize exposure.

At the central estimates of projected exposures, the hazard quotient is exceeded for all worker groups at the maximum application rate of 6 lbs a.i./acre. As summarized in Table 3-5, the hazard quotients of 2-4 for workers involved in boom spraying, spot treatments or directed foliar applications, or aerial applications are in a region where the nature and severity of toxic effects cannot be well defined. For workers using *belly grinder* apparatus, the central estimate of the hazard quotient (19) is associated with subclinical effects. Based on observations in experimental animals, these effects might include an increase in liver weight associated with enzyme induction.

At the upper limit of projected exposures, hazard quotients exceed unity for all worker groups: hazard quotients of 12-32 at an application rate of 1 lb a.i./acre and 70-200 at an application rate of 6 lbs a.i./acre (Table 3-5). As summarized in Table 3-4, this range of exposures may be associated with subclinical effects and possibly adverse effects on reproduction. Even under the most extreme exposure conditions, frank signs of systemic toxicity would not be anticipated. Nonetheless, these exposure levels are substantially greater than levels that generally are considered acceptable or prudent.

Except for workers applying hexazinone using a *belly grinder* at the highest application rate, the carcinogenic risks are below $1 \cdot 10^{-5}$. As discussed above, the risk estimates depend strongly on assumptions regarding exposure duration, and the assumptions used in the risk characterization may be considered highly conservative. More importantly, the qualitative determination that hexazinone poses any risk to workers is also highly conservative (see section 3.1.5). The quantitative risk characterization presented in Table 3-5 is presented primarily in an effort to illustrate what the upper limits of risk could be for workers applying hexazinone over prolonged periods of time.

The longer-term accidental scenarios—wearing contaminated gloves and dermal contact with dust—yield hazard quotients that should be regarded with a high level of concern. Again, while frank toxic effects are unlikely, the dose estimates range from 1 to 2.5 mg/kg/day. The potential for adverse reproductive effects in female workers is plausible.

As summarized in section 3.1.6, hexazinone is a severe eye irritant. Quantitative risk assessments for irritation are not usually derived, and, for hexazinone specifically, the available data do not support any reasonable quantitative dose-response modeling. Nonetheless, human experience with this compound (Spencer et al. 1996) indicates that such effects are clearly plausible for granular formulations. Splashing liquid formulations into the eye would probably also cause severe eye irritation, based on the animal studies summarized in Appendix 3. While skin irritation could also occur, it would probably be less severe than effects on the eyes.

3.4.3. General Public. The quantitative hazard characterization for the general public for systemic toxic effects is summarized in Table 3-7. For short-term exposure scenarios, only the direct spray of the naked child yields estimated levels of exposure that are substantially above the RfD. The maximum anticipated application rate of 6 lbs/acre would be associated with a dose of about 1.4 mg/kg [6 lbs a.i./acre · 0.23 mg/kg·lb a.i./acre]. This is in the range of subclinical toxic effects but should not be associated with any overt signs of systemic toxicity (see Table 3-4).

The greatest practical consequence of a direct spray probably would be eye irritation, which could be severe. While the studies cited by U.S. EPA (1996a) suggest that this effect would probably be reversible if properly and promptly treated, the report of irreversible eye damage in the Velpar ULW DF material safety data sheet (Du Pont 1997a) increases concern for this scenario.

Table 3-7. Quantitative summary of risks for the general public from exposure to hexazinone[a]

Activity	Scenario	Dose (mg/kg/day)	Hazard Quotient[b]
Direct spray	naked child, entire body surface, wash after 1 hour.	0.23	5
	young woman, feet and legs, wash after 1 hour	0.019	0.4
Walking through treated area	dermal Absorption, contaminated vegetation	0.0087	0.2
Contaminated water	10 kg child consuming 1 L immediately after spraying.	0.03	0.6
	1.0-40 μg/L in ambient water.	0.0001 to 0.004	0.002-0.08
Consumption of contaminated fish	shortly after spraying.	0.003	0.06
	over prolonged periods	0.00001 to 0.0005	0.0002 to 0.01
Consumption of contaminated vegetation	berries shortly after spraying.	0.01 to 0.1	0.2 to 2
	0.05 kg of vegetation per day for up to 1 year after application	0.0013 to 0.0064	0.03 to 0.1

[a] Application rate of 1 lb a.i./acre. See section 3.2.3. for details regarding the exposure assessment.

[b] Based on RfD of 0.05 mg/kg/day (section 3.3.2).

Of the longer-term scenarios, only the consumption of unwashed berries immediately after application yields hazard quotients that are substantially greater than unity. At the highest labelled application rate of 6 lbs/acre, the estimated dose would be about 0.06-0.6 mg/kg/day. The upper end of this range slightly exceeds the dose at which subclinical toxic effects might be seen (0.4-4 mg/kg/day, Table 3-4). In addition, this scenario may be extremely conservative in that it does not consider the effects of washing contaminated vegetation.

The longer-term consumption of contaminated vegetation does not yield estimates of exposure that exceed the RfD, even at the maximum anticipated application rate. In most instances, it will not be reasonable to assume that contaminated vegetation is consumed each day or that hexazinone is applied each year in an area from which an individual consumes contaminated food. For example, as discussed in Spencer et al. (1996), herbicides usually are applied only 3 times during a forest stand rotation of 50-150 years, once for site preparation and up to 2 times for release.

3.4.4. Sensitive Subgroups. Because hexazinone was demonstrated to induce fetal resorptions, pregnant women are an obvious group at increased risk. As discussed above, this group is given explicit consideration and is central to the risk characterization. There are no other reports in the literature suggesting subgroups that may be sensitive to hexazinone exposure. There is no indication that hexazinone causes sensitization or allergic responses. Nonetheless, this does not negate the possibility that some individuals with multiple chemical sensitivity may be sensitive to hexazinone as well as many other chemicals.

3.4.5. Connected Actions. There is very little information available on the interaction of hexazinone with other compounds. As summarized in section 3.1, the available data suggest that hexazinone may be metabolized by and may induce cytochrome P-450. This is a very important enzyme in the metabolism of many endogenous as well as xenobiotic compounds (e.g., Mumtaz et al. 1994). Thus, it is plausible that the toxicity of hexazinone may be affected by and could affect the toxicity of many other agents. The nature of the potential effect (i.e., synergistic or antagonistic) would depend on the specific compound and perhaps the sequence of exposure.

4. ECOLOGICAL RISK ASSESSMENT

4.1. HAZARD IDENTIFICATION

4.1.1. Overview. The toxicity of hexazinone to terrestrial wildlife species, particularly invertebrates, is not well characterized. Consequently, the assessment of effects on terrestrial species is based primarily on the available data on experimental mammals. Although the limited data available on the toxicity of hexazinone to wildlife species and the observations from the available field studies do not suggest a cause for substantial concern, field studies are not usually designed to detect effects on nontarget species. One field study that was designed to detect effects on nontarget terrestrial species suggests that hexazinone may have an effect on the behavior of soil mites. It is not clear, however, that the observed effect—changes in the position of mites in the soil column—is related to toxicity, avoidance, or some other unidentified factor.

The toxicity of hexazinone to terrestrial plants is well characterized, as is true for most herbicides. Hexazinone and other s-triazine herbicides act by inhibiting photosynthesis. In addition, hexazinone also inhibits the synthesis of RNA, proteins, and lipids. Hexazinone is absorbed readily by plant roots, and, once absorbed, is translocated readily in most species. Although some foliar absorption may occur, the major route of exposure involves the washing of hexazinone from the soil surface to the root system of plants, where hexazinone is absorbed readily. The differential toxicity of hexazinone to various plant species is based on variations in the ability of different plants to absorb, degrade, and eliminate the herbicide.

Effects on plants may lead to secondary ecological effects due to changes in habitat, food supply, lighting, and other conditions. For example, the use of a herbicide or a mechanical treatment to remove or suppress hardwood species and encourage the growth of conifer species will lead to secondary effects on terrestrial animals (Freemark and Boutin 1995, Hurlbert 1975). Such changes, however, are associated with changes in plant cover or composition and are not specific to hexazinone or even to herbicide use in general. Consequently, such changes are not addressed specifically in this risk assessment.

The toxicity of hexazinone to aquatic species is well-characterized. Comparable studies on aquatic algae and aquatic animals clearly indicate that most algal species are much more sensitive to hexazinone (EC_{50} values for growth inhibition of 0.003-10 mg/L), compared with fish and aquatic invertebrates (LC_{50} values generally greater than 100 mg/L). By analogy to the toxicity of hexazinone to terrestrial plants, it seems likely that aquatic macrophytes also may be very sensitive to the toxic effects of hexazinone. Other than lethality, the most common effect noted on aquatic animals is growth inhibition, which is also the most sensitive effect in experimental mammals. Only one study regarding amphibians was located, and it suggests that amphibians are less sensitive than fish or aquatic invertebrates to hexazinone.

4.1.2. Toxicity to Terrestrial Animals. As summarized in the human health risk assessment (see section 3), exposure to hexazinone is associated with decreased weight gain and reproductive effects in several standard test species, including rats, dogs, and rabbits. These data can be used directly in

the ecological risk assessment to estimate effects on nontarget mammalian species. The limited data on other vertebrate wildlife species (appendix 1) are quantitatively considered in the dose-response assessment for wildlife species (section 4.3.1.)

There is some evidence suggesting that soil microarthropods may be sensitive to hexazinone treatments. A study of soil mites conducted in Nigeria suggests that mites in soil treated with hexazinone at a rate of 1 kg a.i./ha (formulation not specified) tend to migrate deeper into the soil column than mites from untreated plots (Badejo and Akinyemiju 1993, Badejo and Adejuyigbe 1994). It is not clear that this is a toxic response or a response that is secondary to other changes in the soil. Mayack et al. (1982) demonstrated that soil macroarthropods may contain body burdens of hexazinone ranging from 0.13 to 0.35 ppm over periods when hexazinone residues in forest floor material range from 0.01 to 0.18 ppm. For both forest floor material and residues in macroarthropods, some sampling periods yielded levels that were below the limits of detection. Although no effect on community microarthopod composition could be demonstrated in the study by Mayack et al. (1982), the detection of hexazinone in the soil macroarthropods together with the observations in the studies by Badejo and coworkers (Badejo and Akinyemiju 1993, Badejo and Adejuyigbe 1994) suggests that hexazinone treatments may affect soil microarthropods. Although this effect cannot be quantified further, it is addressed qualitatively in the risk characterization (section 4.4).

There is relatively little additional data on terrestrial invertebrates. At dietary concentrations of about 5000 mg/kg, hexazinone did not increase mortality in terrestrial snails (Schuytema et al. 1994). The only other invertebrate study is the required contact LD_{50} study in honey bees (U.S. EPA 1994b) where the LD_{50} is reported as >100 µg/bee. Assuming an average body weight for a bee of 0.093 g (USDA 1993), this is equivalent to an LD_{50} of >1075 mg/kg, comparable to the values reported in experimental mammals (appendix 1 and section 3.1).

4.1.3. Toxicity to Terrestrial Plants. Hexazinone and other s-triazine herbicides act by inhibiting photosynthesis (Sung et al. 1985, Wood et al. 1992). The effect on photosynthesis may be bi-phasic in some cases. For example, Sung et al. (1985) note that concentrations of hexazinone at $1 \cdot 10^{-8}$ to $1 \cdot 10^{-7}$ moles/L increased photosynthesis in loblolly pine seedling, whereas photosynthesis was inhibited at concentrations of $1 \cdot 10^{-6}$ moles/L or greater. At higher levels of exposure, hexazinone also inhibits the synthesis of RNA, proteins, and lipids (Hatzios and Howe 1982).

Although aerial applications or directed sprays of liquid formulations of hexazinone may result in some foliar absorption, applications of granular formulations or spot applications of liquid formulations involve soil treatments with subsequent absorption by the roots and into the plant (Glover et al. 1991). Hexazinone is readily absorbed by plant roots (Wood et al. 1993) and, once absorbed, is readily translocated in most species (Yanase and Andoh 1992).

The metabolites of hexazinone (see Figure 3-1) appear to be much less potent than the parent compound, based on bioassays of loblolly pine seedlings in which metabolite B (see Figure 3-1) was about 100-fold less potent than hexazinone itself, and other tested metabolites (i.e., A, C, D, and E)

were inactive (Sung et al. 1985). The relatively low phytotoxicity of hexazinone metabolites may account at least partially for differences in toxicity among plant species. The differential toxicity of hexazinone to various plant species is based on variations in the ability of different plants to degrade the herbicide (Jensen and Kimball 1987, McNeil et al. 1984, Wood et al. 1992). In some cases, differential toxicity may also be partially attributable to differences in absorption rates, as in the case of the differences in sensitivity of red pine and jack pine (Wood et al. 1992) or the restriction of translocation as in the relative resistance of blueberries to hexazinone (Baron and Monaco 1986).

As discussed in the dose-response assessment (section 4.3), hexazinone, like most herbicides, generally is much more toxic to plants than to animals. This is particularly evident in comparisons of LC_{50} and EC_{50} values of aquatic plants and animals in which exposure conditions are comparable.

During application, nontarget terrestrial plants may be exposed to hexazinone from inadvertent direct deposition or drift. After application, the hexazinone will move through the soil column and nontarget plants may be exposed through the absorption of hexazinone from the soil by the roots (e.g., Allender 1991). These exposure pathways require separate exposure and dose-response assessments, as discussed in sections 4.2 and 4.3.

The available data on the effects of hexazinone on soil microorganisms are extremely limited. Chakravarty and Chatarpaul (1990) report that hexazinone can inhibit the growth of some soil fungi. These data are considered further in both the dose-response and exposure assessment, paralleling the assessment of the effects on higher plants.

4.1.4. Toxicity to Aquatic Species. The acute toxicity of hexazinone to aquatic animals as well as several algal species is well characterized. As noted above and discussed in section 4.3.3., comparable studies on aquatic algae and aquatic animals clearly indicate that most algal species are much more sensitive to hexazinone (EC_{50} values for growth inhibition of 0.003-10 mg/L), compared with fish and aquatic invertebrates (LC_{50} values generally greater than 100 mg/L). By analogy to the toxicity of hexazinone to terrestrial plants, it seems likely that aquatic macrophytes also may be very sensitive to the toxic effects of hexazinone. Studies regarding the toxicity of hexazinone to aquatic macrophytes were not available in the published literature. A single study on *Lemna gibba*, a simple aquatic herb, summarized in U.S. EPA (1994a) reports an EC_{50} of 37.4 µg/L suggesting that larger plant species may show effects at exposure levels comparable to those of unicellular plants.

Acute toxicity studies on aquatic species also provide some information on the likely contribution of the inerts in hexazinone formulations. As discussed in the dose-response assessment for aquatic species (section 4.3.4), the available data suggest that the carriers/inerts in formulations of Velpar L as well as Pronone 10G appear to antagonize the toxicity of hexazinone to fish (Wan et al. 1988). For Velpar L, no such antagonistic effect is apparent for algal species (Schneider et al. 1995, Thompson et al. 1993, Williamson 1988).

The limited subchronic and chronic toxicity studies in aquatic animals, also discussed in section 4.2.4., suggest that thresholds of toxicity are about a factor of 10 less than acute LC_{50} values and still above comparable effect levels for growth inhibition in algae.

4.2. EXPOSURE ASSESSMENT

4.2.1. Terrestrial Animals. Terrestrial animals may be exposed to any applied herbicide from direct spray; the ingestion of contaminated media (vegetation, prey species, or water); grooming activities; indirect contact with contaminated vegetation; or inhalation. There are no data regarding hexazinone residues in terrestrial animals as a result of field applications. Consequently, exposure levels must be modelled based on plausible estimates of residue in various environmental media. Estimates of oral exposure are expressed in the same units as the available toxicity data (i.e., oral LD_{50} values, no effect levels, adverse effect levels, and so forth). As in the human health risk assessment, these units are usually expressed as milligram of agent per kilogram of body weight and abbreviated as mg/kg body weight. For dermal exposure, the units of measure usually are expressed in milligrams of agent per square centimeter of surface area of the organism and abbreviated as mg/cm^2. In estimating dose, however, a distinction is made between exposure dose and absorbed dose. *Exposure dose* is the amount of material on the organism (i.e., the product of the residue level in mg/cm^2 and the amount of surface area exposed), which can be expressed either as mg/organism or mg/kg body weight. *Absorbed dose* is the proportion of the exposure dose that is actually absorbed by the animal.

For the exposure assessments discussed below, general allometric relationships are used to model exposure. In the biological sciences, allometry is the study of the relationship of body size or mass to various anatomical, physiological, or pharmacological parameters (e.g., Boxenbaum and D'Souza 1990). Allometric relationships take the general form:

$$y = aW^x \qquad \textbf{(3)}$$

where W is the weight of the animal, y is the variable to be estimated, and the model parameters are **a** and **x**.

For most allometric relationships used in this exposure assessment, such as the relationship of body weight to surface area and the consumption of food and water, **x** ranges from approximately 0.65 to 0.75. These relationships dictate that, for a fixed level of exposure (e.g., levels of a chemical in food or water), small animals will receive a higher dose, in terms of mg/kg body weight, than large animals will receive. Examples of this relationship are cited in the following sections.

Conversely, allometric relationships for interspecies sensitivity to toxicants (section 4.3) often indicate that for exposure levels expressed as mg toxicant per kilogram body weight (mg/kg body weight), large animals, compared with small animals, are more sensitive. This, however, is not the case for hexazinone. Consequently, for the exposure estimates discussed in the following sections, generic estimates of exposure are given for a small mammal. A body weight of 20 g is used for a small animal, which approximates the body weight of small mammals such as mice, voles, shrews, and small

bats. All body weight values cited in this section are taken from U.S. EPA (1989a). As necessary, other body weights are used for exposure estimates of specific species or groups of animals.

4.2.1.1. ***Direct Spray*** **--** During the application of liquid formulations of hexazinone such as Velpar L, wildlife species may be sprayed directly. This is similar to the accidental exposure scenarios for the general public discussed in section 3.2.2. Unlike the human health risk assessment, however, there are no validated methods for estimating absorbed dose in nontarget species. Thus, the use of oral toxicity data for interpreting exposures involving direct spray is highly uncertain. Moreover, as discussed in the following dose-response assessment, there is no information regarding the contact toxicity of hexazinone or any of its salts to nontarget species except the honey bee.

Because of these data deficiencies, exposure estimates for direct spray scenarios are based on information extrapolated from animal studies. In a scenario involving exposure to direct spray, the extent of dermal contact depends on the surface area of the organism. For mammals, surface area (*SA*) can be calculated as a function of body weight (Boxenbaum and D'Souza 1990):

$$SA\ (cm^2) = 1110 \cdot BW(kg)^{0.65}$$

where:

SA = *surface area* (cm^2)
BW = *body weight* (kg)

There are species specific variations of this relationship [e.g., Davidson et al. (1986)]; however, the above equation is adequate for the general purposes of this risk assessment. A discussion of the general usefulness of the surface area relationship in toxicology is provided by Mantel and Schneiderman (1975).

The application rate of a herbicide is another major factor in estimating exposure dose. As discussed in section 2, the maximum anticipated application rate is 6 lbs. a.i./acre or approximately 0.067 mg a.i./cm^2. This is about a factor of 2 higher than the average application rate of 2.5 lbs/acre used in site preparation. For conifer release and minor uses, typical application rates are closer to 1 lb a.i./acre or less (see Table 2-3). To accommodate this range of application rates, all exposures will be modelled for an application rate of 1 lb a.i./acre, as is done in the human health risk assessment. The impact of using greater or lesser application rates is discussed in the risk characterization.

According to the relationship of surface area to body weight, small animals have a greater amount of surface area/unit body weight than do large animals. For example, the calculated surface area of a 20 g mouse is approximately 87 cm^2 [$1110 \cdot 0.020^{0.65}$] or 4.4 cm^2/g body weight; for a large mammal, such as a 500 kg cow, the estimated surface area is 63,045 cm^2 [$1110 \cdot 500^{0.65}$] or 0.13 cm^2/g body weight, which is a factor of 35 less than the corresponding value for a mouse. Consequently, in terms of exposure levels measured in mg agent/kg body weight, small animals, compared with large animals, will be subject to higher doses. At an application rate of 1 lb/acre (0.0112 mg a.i./cm^2), the mouse would be exposed to approximately 25 mg/kg

$$0.5 \cdot 87\ cm^2 \cdot 0.0112\ mg\ a.i./cm^2 \div 0.020\ kg.$$

Here, surface area is divided by 0.5, assuming that only 50% of the body surface is exposed to the direct spray.

As summarized in section 3.1.7, the estimated dermal absorption rate for hexazinone is 0.031 day^{-1} or 0.0013 $hour^{-1}$. Although using this rate may overestimate the dermal absorption of hexazinone, (see section 3.1.7), it is used in this risk assessment as a conservative estimate of dermal absorption in wildlife. Thus, using this dermal absorption rate of 0.031/day, the estimated absorbed dose for the small mammal is approximately 0.775 mg/kg [25 mg/kg · 0.031].

While this estimate of daily absorbed dose, 0.775 mg/kg, may bracket plausible levels of exposure for many vertebrates, some animals, particularly birds, groom frequently, and grooming may contribute to the total absorbed dose by the direct ingestion of hexazinone on the fur or feathers (Hartung 1962). Furthermore, other vertebrates, particularly amphibians, may have skin that is far more permeable than the skin of most mammals (Moore 1964). Quantitative methods for considering the effects of grooming or increased dermal permeability were not found in the available literature. As discussed in section 4.4, even if instantaneous and complete dermal absorption is assumed, the estimated exposure dose—25 mg/kg/day—is of minimal concern. Consequently, this exposure assessment uses the assumption of complete and instantaneous absorption as an upper limit of exposure to account for the effects of grooming or atypically high dermal permeability.

4.2.1.2. ***Indirect Contact*** **--** As in the human health risk assessment (see section 3.2.3.3), the only approach for estimating the potential significance of indirect dermal contact is to assume a relationship between the application rate and dislodgeable foliar residue. The study by Harris and Solomon (1992), discussed in section 3.2.3.3, is used to estimate that the dislodgeable residue will be lower than the nominal application rate by a factor of about 100. Thus, at an application rate of 1 lb a.i./acre or approximately 0.0112 mg/cm^2, the estimated dislodgeable residue will be 0.0001 mg/cm^2.

Unlike the human health risk assessment, however, no transfer rates are available for wildlife species. As discussed in Durkin et al. (1995), the transfer rates for humans are based on brief (e.g., 0.5–1 hour) exposures that measure the transfer from contaminated soil to uncontaminated skin. Wildlife, compared with humans, may spend much longer periods of time in contact with contaminated vegetation. It is reasonable to assume that for prolonged exposures an equilibrium may be reached between levels on the skin and levels on contaminated vegetation, although there are no available data regarding the kinetics of such a process. The available bioconcentration data on hexazinone discussed in section 3.2.3.5 suggests that hexazinone is not likely to partition strongly from the surface of contaminated vegetation to the surface of skin, feathers, or fur. Plausible partition coefficients range from about 1 to 5 (i.e., the residue on the animal will be equal to or as much as 5 times greater than the dislodgeable residue on the vegetation). Using this approach and taking the dislodgeable residue estimate of 0.0001 mg/cm^2 for vegetation, the estimated residues on animals in contact with contaminated vegetation range from 0.0001 to 0.0005 mg/cm^2.

The exposure dose may be estimated in a manner similar to that for direct dermal exposure (section 4.2.2.1). For a 20 g mammal with a surface area of 87 cm^2, the exposure dose is 0.435–2.175 mg/kg

$$87\ cm^2 \cdot 0.0001–0.0005\ mg/cm^2 \div 0.020\ kg.$$

Note that, unlike the calculation for direct dermal exposure, this calculation assumes that 100%, rather than 50%, of the body surface is exposed to the contamination.

As with the direct contact scenario, these estimates of exposure dose are the upper limits of absorbed dose and may apply to animals that groom extensively or animals that have highly permeable skin. For other species, the absorbed doses would be estimated using a dermal absorption rate of 0.031 day^{-1}. Thus, the absorbed dose for the small animal would be 0.013–0.067 mg/kg.

4.2.1.3. ***Ingestion of Granules, Contaminated Vegetation or Prey --*** As in the human health risk assessment, the consumption of contaminated vegetation is a plausible route of exposure. As discussed in section 3.2.3.6, residue rates of 2-20 mg/kg·lb a.i. applied are plausible immediately after exposure, and, as in the human health risk assessment, these rates will be used to estimate doses in wildlife. Also, as in the human health risk assessment, residue rates of 0.4-2 mg hexazinone/kg·lb/acre will be used to estimate intakes of hexazinone for longer-term exposure.

Allometric relationships and species specific data on laboratory mammals (U.S. EPA 1989a) suggest that the amount of food consumed per day by a small mammal (i.e., approximately 20 g) is equal to about 15% of the mammal's total body weight. Somewhat higher estimates of food consumption for a 20 g mammal (i.e., about 25% of body weight) can be made from allometric relationships based on field studies summarized in the U.S. EPA's *Wildlife Exposure Factors Handbook* (U.S. EPA 1993a,b). Nevertheless, as discussed in the following section, the corresponding estimates of water consumption from the same document are substantially less than those made based on laboratory studies summarized in U.S. EPA (1989a). Given that the exposure rate estimates for hexazinone residues, 2–20 mg/kg·lb a.i. applied, varies over a factor of 10 and given that the estimates of food and water consumption from the two U.S. EPA sources are essentially offsetting, the 15% estimate will be used for food consumption.

Using the 15% estimate, the range of 2–20 mg/kg·lb a.i. for residues immediately after application yields a dose estimate of 0.3–3 mg/kg

$$0.15 \cdot 2–20\ mg/kg·lb\ a.i.$$

Using the residue rate of 0.4-2 mg hexazinone/kg·lb/acre for longer-term exposures, the dose estimates are 0.06–0.33 mg/kg

$$0.15 \cdot 0.4–2\ mg/kg·lb\ a.i.$$

All of these estimates are based on the assumption that 100% of the diet is contaminated. Under the assumption that only 10% of the diet is contaminated, the dose estimates decrease by a factor of 10.

Although other species specific exposure scenarios could be constructed, the above dose estimates are far below any level of plausible concern, as discussed in section 4.4. Thus, even if the above exposure estimates underestimate exposure by factors of 10-100, no adverse effects would be anticipated.

It is possible that in addition to consuming contaminated vegetation, certain wildlife species may directly consume granules that contain hexazinone, particularly those granules that are applied dry. For example, birds may consume pellets or granules based on size, color, or texture of the particles (e.g., Balcomb et al. 1984). Although there are no reports in the literature suggesting that birds will consume any of the granular formulations of hexazinone, there is no information suggesting that birds will avoid these granules. Because of this uncertainty, the potential consequences of direct consumption will be estimated using conservative but plausible assumptions.

Based on the publication by Nagy (1987), the U.S. EPA (1993a,b) recommends the following allometric relationship for food intake (as dry matter) in birds:

$$I_{(g/day)} = 0.648\ W_{(kg)}^{0.0651}$$

As with the allometric relationship for mammals, smaller birds will consume greater amounts of food per day per unit body weight, compared with larger birds (i.e., the exponential term in the above equation is less than unity). All of the birds included in the U.S. EPA *Wildlife Exposure Factors Handbook* (1993a,b) are relatively large and/or do not consume seeds as a major part of their diet. For this exposure assessment, a 27 g house sparrow (USDA 1993) will be used. USDA (1993) indicates that this bird will consume 6.5 g of food per day, 3 g of which are seeds. The above allometric equation estimates that a 27 g bird would consume 5.5 g of dry food per day. Using the slightly more conservative USDA values, the exposure estimate will be based on a 27 g bird consuming 6.5 g of dry matter per day.

A plausible but conservative scenario would involve the bird randomly consuming applied pellets along with normal food items on the surface of the soil. As indicated in Table 2-2, the average diameter of the Pronone formulations is about 1/8 inches or 3.8 cm. Assuming a spherical shape, the volume of such a sphere would be 3.6 cm^3 ($V=1/6 \cdot \pi d^3$). Using the mean density of Pronone (0.6 g/cm^3), the 1/8 inch granule weighs about 2.15 g [3.6 cm^3 • 0.6 g/cm^3] and contains 0.215 g of hexazinone. This particle would cover a planar surface area of 11.3 cm^2 ($SA=\pi r^2$). Thus, the rate of application on the spot where the granule lands would be 0.019 g/cm^2 [0.215 g/11.3 cm^2] or 19 mg/cm^2. At the highest application rate, 6 lbs/acre, hexazinone is applied at a rate of about 0.067 mg/cm^2. Thus, the proportion of the ground covered would be approximately 0.0035 [0.067 mg/cm^2 ÷ 19 mg/cm^2]. Assuming that the bird randomly consumes 6.5 g of particles from the ground on the day of application, the bird would consume 0.022 g of Pronone 0.0228 g [6.5 g • 0.0035] or 0.00228 g of hexazinone. Thus, the estimated dose would be 81.4 mg/kg [2.2 mg ÷ 0.027 kg].

4.2.1.4. ***Ingestion of Contaminated Water*** **--** As in the human health risk assessment, a contamination rate of 300 µg/L·lb a.i. applied will be used to estimate the effects of acute exposures

immediately after the application of liquid or granular hexazinone. For longer-term exposures, contamination rates of 1-40 µg/L·lb i.a. applied will be used. Data supporting these estimates are summarized in Table 3-1 and discussed in section 3.2.3.4 of the human health risk assessment.

There are well established relationships between body weight and water consumption across a wide range of mammalian species [e.g., U.S. EPA (1989a)]. In general, small mammals consume more water per unit body weight than is consumed by larger mammals. For example, mice, weighing about 0.02 kg, consume approximately 0.005 L of water/day (i.e., 0.25 L/kg body weight/day). On the other hand, the typical water consumption for a 500 kg mammal is approximately 18 L/day (i.e., approximately 0.04 L/kg body weight/day). [All of these estimates are taken from Table 2-3 in U.S. EPA 1986.] Thus, the use of a small mammal to estimate potential effects will be conservative yet plausible.

As noted above, studies summarized in the U.S. EPA's *Wildlife Exposure Factors Handbook* (U.S. EPA 1993a,b) yield substantially lower estimates of water consumption (i.e., about 2.9 mL for a 20 g mammal) and somewhat higher estimates of food consumption than those derived from U.S. EPA (1989a). The values from U.S. EPA (1989a) are used in this risk assessment for both food and water consumption. When combined food and water exposures as well as the likely variability in ambient levels of hexazinone in both food and water (section 4.4) are taken into consideration, the use of either set of values has no substantial effect on the characterization of risk.

For the acute exposure scenario, the estimated dose for a small mammal is 0.075 mg/kg,

$$0.3 \text{ mg/L} \cdot 0.005 \text{ L} \div 0.02 \text{ kg}.$$

The corresponding estimate for a chronic or longer-term dose is approximately 0.00025 to 0.01 mg/kg

$$0.001 \text{ to } 0.04 \text{ mg/L} \cdot 0.005 \text{ L} \div 0.02 \text{ kg}.$$

As with estimates of dose levels from the ingestion of contaminated food (section 4.2.2.3), the dose estimates provided here for the small mammal are far below levels of plausible concern, and a more detailed elaboration of these exposure scenarios does not appear to be warranted.

4.2.2. Terrestrial Plants. The primary routes of concern for nontarget terrestrial plants are unintended direct deposition and soil transport. Direct deposition may be modelled in a manner similar to the direct spray of terrestrial animals. There are substantial data regarding the movement of hexazinone in soil and its subsequent effects on nontarget plants. In addition, soil transport may be estimated using vadose zone models. While volatilization may be an import route of transport for some herbicides, the vapor pressure of hexazinone is extremely low (see Table 2-1). Consequently, vapor transport and volatilization are not considered quantitatively in this risk assessment.

4.2.2.1. ***Spray Drift*** **--** Unintentional direct deposition poses a risk to nontarget plants. Although the potential drift of the liquid formulation of hexazinone, Velpar L, can be estimated

relatively well by analogy to other herbicides, there are substantial uncertainties associated with the potential drift of granular formulations.

Applications of Velpar L, like applications of liquid formulations of other herbicides, involve droplet sizes of 100 µ (or larger) sprayed from 3 feet above the ground or 400 µ (raindrop nozzles) sprayed from up to 6 feet above the ground. Using Stokes' law and ignoring the initial downward velocity of the droplet, a 100 µ droplet would remain in the air for approximately 3 seconds. Under recommended conditions of application, the wind velocity should be no more than 5 miles/hour (Mistretta 1995), which is equivalent to approximately 7.5 feet/second (1 mile/hour = 1.467 feet/second). Assuming a wind direction perpendicular to the line of application, 100 µ particles could drift as far as 23 feet (3 seconds · 7.5 feet/second). At wind speeds of 15 miles/hour, applying the herbicide would constitute clear misuse. Taking this as an extreme scenario, the herbicide could drift as far as 68 feet (3 seconds · 15 · 1.5 feet/second).

These estimates are only order of magnitude approximations and do not take into consideration the effects of nozzle velocity, turbulence, terrain, and foliar interception. No field studies regarding drift after ground or aerial applications of hexazinone were located in the literature. As discussed in SERA (1996), the off-site drift of liquid formulations of glyphosate is relatively well characterized. Because off-site drift is more or less a physical process that depends on droplet size and meteorological conditions—rather than the specific properties of the herbicide—the data on glyphosate will be used as a surrogate of hexazinone.

The extent of drift will depend on conditions during application, such as wind speed, wind direction, topography, the distance from the ground at which the herbicide is applied, and the droplet size of the herbicide spray. Aerial applications are likely to generate greater drift than will be generated by ground applications, as illustrated by Yates et al. (1978). Nonetheless, even for aerial applications conducted under relatively unfavorable conditions, off-site deposition at 30–50 m is likely to be less than 0.1 of the nominal application rate. At 200 m downwind, the levels are likely to be only 0.002-0.005 of the nominal application rate.

No quantitative data are available on drift or offsite deposition of the granular formulation of hexazinone, and models for such drift were not found in the published literature. This is a relatively serious limitation. Although the granular formulations of hexazinone nominally involve relatively large granules that, in themselves, probably have a low potential for drift, some dust formation would seem inevitable in the processes of transport, loading, and application. In addition, based on the recently completed California study (Spencer et al. 1996), dust formation may be a problem with granular formulations of hexazinone. Small particles of dust with a relatively low density could drift substantially during aerial application. Although this occurrence cannot be modelled, the uncertainties associated with such drift are discussed in the risk characterization.

4.2.2.2. ***Soil Exposure*** **--** The environmental fate of hexazinone in soil was studied extensively in both laboratory and field studies (appendix 6). Two general processes are important in estimating soil exposure: degradation and transport. Degradation encompasses any of the processes that remove

hexazinone from the soil column. As summarized in section 2, hexazinone is chemically stable under ambient conditions and the primary mechanism of degradation appears to be metabolism/mineralization by microorganisms. Transport involves any of the diffusive or advective processes by which hexazinone may migrate in soil. Hexazinone is poorly absorbed by most types of soils (Rhodes 1980a, Bouchard et al. 1985). Since hexazinone is a very weak base, the limited soil adsorption that does occur is probably the result of non-polar mechanisms (Bouchard and Lavy 1985). In addition, hexazinone is highly soluble in water. Because of its low adsorption to most types of soils and high water solubility, the primary mechanism of dispersion in soil involves movement in soil water.

The degradation of hexazinone in soil is temperature dependent. Bouchard et al. (1985) examined the degradation of hexazinone in two soil types: sandy loam (Mountainburg) and silt loam (Taloka) soil. In soil cultures incubated at 30°C, apparent first order degradation rates (k_e) were virtually identical: 0.00897 day^{-1} (Taloka) and 0.00907 day^{-1} (Mountainburg), corresponding to half times of 77 and 76 days, respectively ($t_{½}=ln(2)/k_e$). At 10°C, the respective half-times were 502 and 426 days. In greenhouse studies, half-times for the disappearance of radiolabelled hexazinone were 90-120 days for a variety of soil types. Half-times for the disappearance of total radioactivity (i.e., presumably the complete mineralization of hexazinone and its metabolites) ranged from 90 days to 1-year (Rhodes 1980a). The temperature at which these tests were conducted was not specified.

In field studies, initial dissipation (i.e., degradation and transport) rates generally are much more rapid than degradation rates in laboratory soil preparations. This finding is consistent with relatively high mobility of hexazinone in soil. For example, in the study by Feng (1987), soil concentrations of hexazinone in a clay loam soil were about 7 µg/g 9 days after the application of Velpar L at 4.2 kg a.i./ha and decreased to 2.9 µg/g after 28 days, and 2.09 µg/g after 104 days. Most hexazinone and hexazinone metabolites remained in the 5-10 cm thick surface duff and humus. No hexazinone or hexazinone metabolites (A or B) were detected in soil below 15 cm. During the 104-day study period, 12 rain events occurred (amounts not specified) (Feng 1987). The 7 µg/g concentration of hexazinone 9 days after application is about what would be expected from simple dispersion into a 5-10 cm thick layer. The application rate of 4.2 kg a.i./ha corresponds to about 42 $µg/cm^2$. Thus, with uniform dispersion in a 5-10 cm thick soil layer, the expected concentrations would be 4.2-8.4 $µg/cm^3$.

Under conditions of greater rainfall or snow melt, hexazinone was shown to reach up to 80 cm into the soil column (Feng et al. 1989b). In lysimeter studies under conditions simulating very heavy rainfall, approximately 1-2% of applied hexazinone reached a depth of 150 cm (Stone et al. 1993).

Table 4-1. Relationship of hexazinone concentrations in soil leachates to time after application and volume of leachate after the application of Pronone 10G (adapted from Feng et al. 1989b)

Application Rate (kg a.i./ha)	Soil Depth (cm)	Equation
2	30	W = 163 + 0.0466V - 65.8 log D
	55	W = 55.3 + 0.0252V - 22 log D
	80	W = 111 + 0.0260V - 42.8 log D
4	30	W = 1392 + 0.0378V - 536 log D
	55	W = 1070 + 0.0505V - 414 log D
	80	W = 411 + 0.0566V - 163 log D

W = µg hexazinone/L soil water
D = days after treatment
V = volume of leachate collected at time D.

The relationship of hexazinone concentrations in soil leachates to the time after application of Pronone 10G at two applications rates is summarized in Table 4-1 (Feng et al. 1989b). The deeper penetration of hexazinone into the soil horizon may have been facilitated by the formation of channels made by decayed tree roots (Feng et al. 1992).

Roy et al. (1989) studied the differences in dissipation of hexazinone in clay and sand forest soils in Canada. At an application of 4 kg a.i./ha or 40 µg/cm^2 Velpar L, the time required for 50% dissipation from peak concentrations was 43 days in both soil types. The major difference between the two soil types was that peak levels in the upper level of clay soil (1491.8 µg) did not occur until about 14 days post spray, while peak levels in sandy soil (1559.4 µg) occurred 2 days post spray. These levels reported by Roy et al. (1989, Tables VI and VII, p 446) appear to be in total amounts of hexazinone or hexazinone metabolites (µg) per soil sample rather than in soil concentrations (µg/g). As indicated in the methods section of this paper (Sampling, p. 445), the soil samples were taken as cores with a 10 cm diameter. Thus, the maximum values of about 1500 µg in the upper 5-10 cm organic layer of the soil column corresponds to concentrations of about 1.9 to 3.8 µg/cm^3

$$1500\ \mu g \div (\pi \cdot 5\ cm^2 \cdot (5 \text{ to } 10\ cm)).$$

This is about a factor of 2 less than would be expected from uniform distribution in a 5-10 cm soil column at an application rate of 40 µg/cm^2: 4-8 µg/cm^3.

The extent to which hexazinone migrates laterally depends on rainfall and soil slope (Harrington et al. 1982). Allender (1991) reported an incident in which the lateral movement of hexazinone as well

as bromacil is associated with damage to trees. Based on soil samples, no lateral movement of hexazinone was detected down a 7-8° slope during an observation period of up to 792 days from either sand or clay sites (Roy et al. 1989). Similarly, no lateral movement was detected 20 and 40 m outside of or down slope of a white spruce plot treated with Velpar L at 4.3 kg a.i./ha (Feng 1987). Some lateral movement to groundwater, however, can be inferred based on the apparent transport of hexazinone from soil to groundwater, although lateral movement appears to be much less significant than downward migration [e.g., Williamson (1988)] (see section 3.2.3.4).

After an initial rapid dissipation, hexazinone levels in soil may stabilize in some soils, as noted by Bouchard et al. (1985). In this study, hexazinone soil levels dropped to 10% of their initial values; however, over a 1-year period after initial dissipation, levels remained relatively constant (ca. 0.2-0.5 ppm after an application of 2.0 kg a.i./ha or about 0.1-3 ppm/lb a.i. applied).

Not all field studies report a pattern of initial rapid decline followed by a slower rate of decline. For example, if hexazinone is applied late in the season (early fall in northern climates), relatively little dissipation will occur in the winter months initially after application and the apparent rate of dissipation will increase in the spring (Feng and Navratil 1990). This is probably attributable to both the slower rate of degradation at lower temperatures, as noted by Bouchard et al. (1985), and the slower rate of water movement through the soil during the winter months.

Hexazinone tends to remain in the upper soil layer for clay or loam soils but move more rapidly through sandy soils (Helbert 1990, Jensen and Kimball 1987, Roy et al. 1989). In litter covered soil, hexazinone may remain in the litter at 10- to 20-fold higher concentrations than found in any of the soil layers (Lavy et al. 1989). Similarly, in lysimeter studies, litter-humus layers significantly impeded the leaching rates of hexazinone (Stone et al. 1993). This effect may be at least partially attributable to the adsorption of hexazinone to lignin, to which as much as 40% of applied hexazinone may be bound essentially irreversibly (Privman et al. 1994), which also may explain why hexazinone appears to be less effective in the control of broadleaf weeds when applied to peat, compared with sandy loam soils (May 1978).

Field half-times for Velpar L were observed at 186 days in northern climates in sandy loams soils (Helbert et al. 1990). In southern climates, soil half-times may range from 11 to 180 days at application rates of 1.6-2.9 kg/ha (Michael and Neary 1993).

Although the liquid and granular formulations of hexazinone require precipitation for transport into the soil column, rain is required to wash the hexazinone from the granular formulations before any significant levels of hexazinone will appear in the upper soil layer. Thus, Velpar L is applied almost instantaneously to the soil surface, whereas the granular formulations involve a time-release application. Under laboratory conditions, about 50 mm of rain is required to release 90% of the hexazinone in Pronone 10G (Feng et al. 1988). In field trails, the release of hexazinone from Pronone 10G granules fit a double log relationship with respect to rainfall and time after application:

$$\log(y) = 1.83 - 0.966\ D - 0.62\ R$$

where y is the percent active ingredient remaining in the granule, R is the cumulative rainfall in mm and D is the number of days after application (Feng et al. 1989a). Although the horizontal distribution of hexazinone after granular applications is more heterogeneous than that of liquid formulations immediately after application, this difference is much less apparent by one year after treatment (Feng et al. 1992).

4.2.3. Aquatic Organisms. In the aquatic environment, exposure levels can be characterized simply as concentrations of hexazinone in water. Moreover, as discussed in the exposure assessment for human health (see section 3.2), there is a relatively rich body of data relating hexazinone levels in water to the use of hexazinone in vegetation control. The analysis is further simplified because the available toxicity data on aquatic organisms are expressed in units of water concentration (e.g., LC_{50} and EC_{50} values).

For this risk assessment, the concentration derived in section 4.2.2.3, 300 µg/L·lb a.i./acre, is used to characterize the effects of acute exposure to hexazinone after accidental spills. Also consistent with the exposure assessment for human health effects, a concentration range of 1-40 μg/L·lb a.i./acre is used to assess the consequences of hexazinone levels that are likely to be present in ambient water after the application of hexazinone for vegetation management.

4.3. DOSE-RESPONSE ASSESSMENT

4.3.1. Terrestrial Animals. As summarized in the human health risk assessment (see section 3.3), hexazinone has a low order of acute toxicity to mammals. As noted in the hazard identification for ecological effects (see section 4.1.2), there is relatively little information regarding the toxicity of hexazinone to other terrestrial animals. The information on birds (Kennedy 1984 as discussed in appendix 1) suggests that the acute and subchronic lethal potency of hexazinone to birds and mammals is similar. The LD_{50} for quail, 2258 (1628-3130) mg/kg (Kennedy 1984), is in the range of and in most cases somewhat higher than corresponding values in dogs, rats, and guinea pigs (appendix 1). The signs of toxicity in quail (i.e., body weight loss, lack of coordination, and convulsions) are similar to those seen in experimental mammals.

For nontarget terrestrial species, the approach will be similar to that taken in the human health risk assessment, except that uncertainty factors will not be used because data are available on nontarget species. Thus, for assessing the effects of acute exposure, a NOAEL of 100 mg/kg will be used. This value is below any short-term effect level reported for mammals and birds (appendix 1). Because none of the acute exposure scenarios described in section 4.2 approach this level, it is not necessary to elaborate on the dose-severity relationships for acute exposure.

To assess the potential for longer-term toxic effects, the NOAEL of 5 mg/kg/day will be used, consistent with the derivation of the RfD for the protection of human health (see section 3.3.2). Subclinical toxic effects (i.e., histopathological changes) might be expected at the corresponding LOAEL, 40 mg/kg/day. As discussed in the previous section, no subchronic exposure assessments exceed the NOAEL. Thus, a further elaboration of dose-severity relationships for subchronic exposure is not necessary.

4.3.2. Terrestrial Plants. As discussed in the exposure assessment for terrestrial plants (see section 4.2.2), there are two types of exposure to be considered: direct contact (i.e., either direct spray or drift) and soil contamination. As discussed in section 4.4.2, a different dose-response assessment is required to determine the consequences of both types of exposure.

4.3.2.1. ***Direct Spray*** **--** For direct spray or drift, the relevant exposure metameter is the application rate or functional rate of deposition expressed in units of toxicant weight per unit area (e.g., lb a.i./acre). In some respects, the product labels for hexazinone (Du Pont 1993a, 1994, Pro-Serve 1993a,b) provide useful information on effective levels of application and suggest differences in species or life-stage sensitivity. Because of the differences in the movement of hexazinone in different types of soil (see section 4.2.2.2.), recommended application rates depend on the soil type. In sand or sandy loam soils, the recommended rates for Pronone MG or 10G range from 0.5 to 1.0 lbs a.i./acre for herbaceous weed control to 1-3 lbs a.i./acre for site preparation. In clay or silt clay soils, higher application rates are recommended: from 1.0-1.25 lbs a.i./acre for herbaceous weed control to 3-4 lbs a.i./acre for site preparation. For loam to clay loam soils, intermediate application rates are recommended. For a given soil type, recommended rates for brush control are intermediate between those used for herbaceous weed control and site preparation. Similar rates of application are recommended for Du Pont's granular formulation of hexazinone, Velpar ULW: 1.875 lbs a.i./ acre for site preparation and 0.75-1.5 lbs a.i./ acre for conifer release in sand or sandy loam soils. In soils with relatively high amounts of clay, 2- to 3-fold higher application rates are recommended (Du Pont 1994). The recommended application rate for site preparation using Velpar L is 1-3 gallons/acre or 2-6 lbs a.i./acre (Du Pont 1993a). The recommended rates for site preparation and conifer release—the major uses of hexazinone by the Forest Service—are consistent with the average rates used by the Forest Service: 2.5 lbs a.i./acre for site preparation and 1.4 lbs a.i./acre for conifer release (see Table 2-3).

The reregistration eligibility document for hexazinone includes a tabular summary of the effects of hexazinone on nontarget vegetation (U.S. EPA, 1994a, Table 2, p. 29). Based on measures of total plant weight or shoot weight, the most sensitive plants appear to be the rape, tomato, pea, and sugar beet, all of which have EC_{25} values ranging from 0.011 to 0.013 lbs a.i./acre. Other nontarget plants, including onion, corn, wheat, sorghum, and soybeans have EC_{25} values ranging from 0.020 (wheat) to 0.071 (corn) lbs a.i./acre. EC_{25} values based on bioassays for seedling emergence were comparable: 0.010 lbs a.i./acre for the most sensitive species (sugar beet) to 0.055 lbs a.i./acre for the least sensitive species (soy bean).

A more elaborate dose-response assessment for direct spray or drift can be developed based on field studies with hexazinone (appendix 6). As with most herbicides, hardwoods and shrubs are generally more sensitive to hexazinone than pines (e.g., Haywood 1995, Long and Flinchum 1992, McDonald et al. 1994, Pehl and Shelnutt 1990), although the degree of sensitivity may vary depending on site-specific conditions (Wilkins et al. 1993). This differential toxicity is the basis of the use of hexazinone in site preparation and pine release. A detailed efficacy study of broadcast applications of granular and liquid formulations of hexazinone at various locations in the southern United States is reported by Glover et al. (1991) and Minogue et al. (1988). At recommended application rates (about 1-2 lbs

a.i./acre, depending on soil type), both types of formulations generally provided adequate control of hardwood species with little mortality to pine. Pine mortality did occur at twice the recommended rate of application. At two locations with loamy sand soil, granular formulations were associated with higher rates of pine mortality than liquid formulations. In the control of upland willows, spot-gun applications of liquid hexazinone or the broadcast applications of hexazinone granules may be more effective than the broadcast application of liquid hexazinone, at comparable application rates (Pollack et al. 1990). Although not discussed specifically by Pollack et al. (1980), it appears that the broadcast application of diluted hexazinone formulations may be less effective than spot applications of concentrated solutions or pellets so long as rainfall is adequate to wash the concentrated hexazinone applied to the soil surface into the soil column. This difference in effectiveness is suggested also by the comparable results in aerial applications of Velpar L and Velpar ULV for the control of raspberry competition with black spruce seedlings (Reynolds and Roden 1995).

Coffman et al. (1993) report substantial differences in sensitivity among species of commercial crops to hexazinone. In this study, hexazinone (a commercial formulation of 240 g hexazinone/L, consistent with Velpar L) was applied to silt loam soil at rates of 2.2, 4.5, and 6.7 kg/ha by ground sprayer. Different kinds of vegetation were planted at various times after application and observed for damage. No soil residues were determined. The least sensitive species appeared to be the potato, which could be grown on treated plots at 47 days after treatment. Corn could not be grown on any of the hexazinone treated plots until 436 days after treatment and then only on the 4.5 kg/ha treated plot. Wheat, kidney beans, squash, and okra could not be grown on any of the treated plots over the 436 day post treatment planting period. After 2 years, all sites were covered by indigenous species with no apparent differences between treated and untreated sites.

Hexazinone applications at a rate of 0.5-1.0 kg/ha appeared to have no effect on alfalfa or nectar sugar production by alfalfa (Curry et al. 1995).

4.3.2.2. ***Soil Exposure*** **--** As discussed in section 4.2.2.2, there are extensive studies regarding the environmental fate of hexazinone in soil. The most relevant exposure metameter for this type of exposure is soil concentration, either in terms of total soil weight or free hexazinone in soil water. The latter could be a more relevant exposure metameter for soils high in lignin because hexazinone may bind tightly to lignin (Privman et al. 1994) (see section 4.2.2.2.).

There are relatively few bioassays, however, in which soil concentrations were used as a measure of exposure. In the report of Allender (1991), damage to trees—presumably from the lateral movement of hexazinone through the soil—occurred at soil concentrations of 0.24-1.15 mg/kg. In bioassays of plant cell preparations isolated from soybean leaves, exposure to a 0.1 µM solution of hexazinone (25.23 µg/L) for 2 hours inhibited photosynthesis—assayed as a decrease in $^{14}CO_2$ fixation—by 60%. A 10-fold higher concentration inhibited photosynthesis by 90% (Hatzios and Howe 1982). In an *in vitro* assay of photosynthetic inhibition using loblolly pine needles, complete inhibition (i.e., no needles floated in test media) was noted over a 9-hour exposure period at a concentration of $1 \cdot 10^{-5}$ M or 2.5 µg/L. At a concentration of 0.25 µg/L, the percentage of needles floating was about 60% of control values. Lower concentrations lead to an apparent enhancement or stimulation of

photosynthesis (Sung et al. 1985). This assay was also tested on metabolites A-E (see Figure 2-1). Only metabolite B elicited any response. Based on this assay, this metabolite is about 10-fold less potent than hexazinone.

4.3.3. Aquatic Organisms.

4.3.3.1. Fish -- Information regarding the toxicity of hexazinone and its commercial formulations is presented in appendix 7. All 24-hour LC_{50} values for hexazinone are greater than 100 mg/L. Most studies (i.e., Kennedy 1984, Wan et al. 1988) also report 48- and 96-hour values, and, in all cases, the decrease in the longer-term LC_{50} is less than 25%, indicating a relatively weak duration-response relationship. The bioassays conducted by Wan et al. (1988) on hexazinone itself, as well as the Pronone 10G and Velpar L formulations, indicate that the commercial formulations are substantially less toxic than hexazinone even when exposures are normalized for hexazinone levels. Thus, the carriers appear to antagonize the acute toxicity of hexazinone. Wan et al. (1988) also tested the carriers used in Pronone 10G and Velpar L (not described in appendix 7). These materials were much less toxic than hexazinone to rainbow trout. The published values are consistent with those summarized in the reregistration eligibility document for hexazinone (U.S. EPA 1994a).

The only subchronic toxicity data available on hexazinone is the early life stage study on fathead minnow. In this study, the NOEL was 17 mg/L and the LEL, based on a reduction in fish length, was 35.5 mg/L (Pierson 1990a, MRID 41406001). It is interesting that the endpoint, essentially a reduction in growth, is similar to one of the most common endpoints observed in mammalian toxicity studies (see section 3.3).

No field studies regarding the effects of hexazinone on fish or fish populations were found in the literature.

4.3.3.2. Aquatic Invertebrates -- Information regarding the toxicity to aquatic invertebrates of hexazinone and the commercial formulations of hexazinone are presented in appendix 7 along with data on fish. The available LC_{50} values suggest that some aquatic invertebrates such as daphnids and glass shrimp may be somewhat although not remarkably more sensitive to hexazinone than fish with 48 hour LC_{50} values ranging from about 100 to 150 mg/L for daphnids and glass shrimp. For daphnids, 8% mortality was observed at 50 mg/L and no mortality was observed at 1 mg/L. Larger salt water invertebrates are less sensitive, with LC_{50} values of >300 mg/L (appendix 7). In a life cycle study using Daphnia magna, the NOEL for survival was 29 mg/L with a LOAEL of 81 mg/L (U.S. EPA 1994, Pierson 1990b, MRID 41406002).

No effects were noted on invertebrate drift in five stream channels over a 14 day period of observation after 12 hour exposures to hexazinone at concentrations that ranged from 3.1 to 4.1 mg/L. Five untreated stream channels served as controls. At the end of the 14-day observation period, no significant pairwise differences between treated and control channels were noted for 14 taxa of macroinvertebrates. Overall, however, there was a significant increase in abundance in treated versus control channels (Kreutzweiser et al. 1995). In a similarly designed study, no effects on stream

invertebrates were observed after the application of Velpar L at a level that resulted in hexazinone levels of 0.145-0.432 mg/L over a 24-hour exposure period (Schneider et al. 1995).

Mayack et al. (1982) reported no effects on stream macroinvertebrates at water concentrations of 8-44 µg/L. These concentrations were the result of the application of hexazinone pellets (formulation not specified but consistent with Pronone 10G) at a rate of 16.8 kg/ha in four small watersheds located in mixed hardwood-pine stands. One additional watershed served as an untreated control.

4.3.3.3. Aquatic Plants -- Bioassays regarding the toxicity of hexazinone to algae are summarized in appendix 8. EC_{50} values in these species range as low as 0.003 mg/L (*Chrysophyta* species) (Thompson et al. 1993). This is a factor of about 10,000 below the NOEL of 29 mg/L for reproductive effects in daphnia, as described in the previous section. In the stream channel study by Schneider et al. (1995), described in the previous section, the EC_{50} for chlorophyll-*a*-specific productivity in stream periphyton was 0.0036 mg/L, very similar to the most sensitive algal species based on laboratory bioassays by Thompson et al. (1993). In the stream channel study by Kreutzweiser et al. (1995), substantial inhibition of photosynthesis was observed but algal biomass was unaffected at 2.7 mg/L. This, however, is inconsistent with the results of Abou-Waly et al. (1991) in which both ^{14}C-uptake and biomass were reduced during 5-day exposure to hexazinone at levels of 0.03-0.1 mg/L. As reported by Kreutzweiser et al (1995), the effects on photosynthesis were rapidly reversible after the hexazinone concentrations cleared. A rapid reversibility in the inhibition of photosynthesis was also observed in the stream channel study by Schneider et al. (1995). The other studies summarized in appendix 8, all of which are standard flask bioassays, did not continue the bioassays through a recovery period.

4.4. RISK CHARACTERIZATION

4.4.1. Overview. Based on the available toxicity data and the estimated levels of exposure, there is little indication that hexazinone is likely to cause adverse effects in terrestrial animal species. The consumption of contaminated water or vegetation yields hazard indices that are well below a level of concern at any plausible application rate either immediately after hexazinone applications or over prolonged periods after applications.

A potential exception to this exposure assessment involves a scenario in which birds consume hexazinone granules immediately after application; in which case, reproductive effects and possibly overt signs of toxicity might occur. The plausibility of this risk for birds, however, is questionable. There are no data indicating that birds will consume any of the granular formulations that contain hexazinone. Thus, a lower limit on the exposure assessment is zero. If birds were to consume these granules preferentially, exposure levels could be much higher. In that case, toxic effects including mortality could occur. Without additional information with which to improve the exposure assessment, this risk cannot be characterized further.

As discussed in the hazard identification, there is some evidence that the application of hexazinone at a rate of 1 kg a.i./ha or 0.89 lbs a.i./acre affects soil microarthropods. It is not clear, however, if

the noted effects—a deeper migration of soil mites into the soil layer—can be attributed to toxicity, avoidance, or other changes in soil characteristics.

Nontarget terrestrial plants may be affected during the application of hexazinone. Direct deposition, from unintentional direct spraying or from spray drift is a plausible hazard for most herbicides, including those containing hexazinone. If plants are sprayed accidentally at the application rates used by the Forest Service, the plants, particularly hardwoods or sensitive pines, are likely to be damaged. During aerial applications at a rate of 1 lb a.i./acre and at distances less than 30 m from the application site, some damage to nontarget vegetation is plausible due to drift of liquid formulations. Ground applications of granular formulations or spot treatments with liquid applications of hexazinone should be associated with little significant drift. Soil contamination and transport of hexazinone to offsite nontarget vegetation, however, may occur. The magnitude of any observed effects will be highly dependent on local conditions, particularly soil type and rainfall. In porous and/or sandy soils with low levels of organic matter and under conditions of high rainfall, adverse effects on offsite vegetation are most plausible.

Under any plausible conditions of exposure, including accidental direct applications to a stream, effects on fish or aquatic invertebrates are unlikely. Conversely, effects on algal species are virtually certain but are likely to be transient because of the transport and dilution of hexazinone in aquatic systems. Based on stream ecosystem studies, it is unclear that changes in the population of aquatic algae will lead to detectable secondary effects on aquatic animals.

4.4.2. Terrestrial Animals. The risk characterization for terrestrial animals is summarized in Table 4-2, which expresses each of the quantitative exposure assessments made in section 4.2.1. for the small (20 g) mammal. For each of the exposure assessments, the last column in the table gives the HQ associated with the exposure assessment. For acute exposure scenarios (i.e., scenarios based on peak exposure immediately after application) the hazard quotient is based on the acute NOEL of 100 mg/kg. For longer-term exposure, the hazard quotient is based on the chronic NOEL which also serves as the basis for RfD in the human health risk assessment. Because the individual components of the exposure assessments are pathway specific, this section ends with a discussion of concern for multi-pathway exposures. All exposures are based on an application rate of 1 lb a.i./acre. The highest labelled application rated is 6 lbs a.i./acre. Thus, for the highest application rate, any hazard quotients above 0.17 in Table 4-2 would exceed unity and be a cause for potential concern.

There are two risk characterizations for dermal exposure. One involves direct spray, and the other involves dermal contact with contaminated vegetation. For both of these scenarios, a dermal absorption rate of 0.031 day^{-1} is used as a plausible estimate of the dermal absorption rate and complete absorption (i.e., dermal contact is completely absorbed each day) is used as an upper limit. Using the estimated absorption rate of 0.031 day^{-1}, neither the direct spray nor the indirect contact scenarios result in hazard quotients that approach a level of concern even at the maximum application rate of 6 lbs a.i./acre. Based on the very conservative assumption of complete absorption, the direct

Table 4-2. Summary risk characterization for a 20 g terrestrial mammal after exposure to hexazinone at an application rate of 1 lb a.i./acre

Media/Scenario	Exposure Estimates (mg/kg) Small Mammal (20 g)	HQ
Direct spray, dermal		
Absorption rate of 0.031 day^{-1}	0.775	0.008[a]
Complete absorption	25	0.25
Indirect dermal contact		
Absorption rate of 0.031 day^{-1}	0.013-0.067	0.003-0.01[b]
Complete absorption	0.44-2.1	0.09-0.4
Consumption of vegetation		
Acute exposure		
10% of diet contaminated	0.03-0.3	0.0003-0.003[a]
100% of diet contaminated	0.3-3	0.003-0.03[a]
Longer-term exposure		
10% of diet contaminated	0.006-0.033	0.001-0.007[b]
100% of diet contaminated	0.06-0.33	0.01-0.07[b]
Consumption of water		
Immediately after application	0.075	0.0008[a]
Prolonged exposures	0.00025-0.01	0.00005-0.002[b]

[a] HQ based on nonlethal acute dose of 100 mg/kg.

[b] HQ based on long-term NOEL of 5 mg/kg.

spray scenario slightly exceeds a hazard quotient of unity at an application rate of 6 lbs. a.i./acre. The indirect dermal contact scenario leads to lower estimates of daily absorbed dose (i.e., 0.44-2.1 mg/kg/day) than the direct spray scenario but the hazard quotients are higher because the chronic rather than acute NOEL is used. While application rates of 1-2 lbs a.i./acre would result in hazard quotients less than unity, rates of 3-6 lbs a.i./acre would yield hazard quotients in the range of 1.2-2.4 corresponding to daily doses of up to about 13 mg/kg. This is about a factor of 3 below the chronic LOAEL of 40 mg/kg/day associated with histopathological changes (see section 4.3.1) and about a factor of 3 above the chronic NOEL of 5 mg/kg/day. NOAELs of up to 20 mg/kg/day are reported in subchronic exposure studies (Serota et al. 1980) (see section 3.3.3). Thus, while these exposure estimates trigger concern, the consequences, if any, of these exposures are not likely to be substantial.

The consumption of contaminated water or vegetation yields hazard quotients that are far below a level of concern at any plausible application rate either immediately after hexazinone applications or over prolonged periods after applications.

An exposure assessment for birds consuming granular formulations of hexazinone is presented in section 4.2.1.3. This exposure assessment assumes that granules are randomly consumed along with normal food items from the soil surface. Based on this assumption, the estimated dose is approximately 80 mg/kg at an application rate of 6 lbs a.i./acre. As indicated in Table 3-4, dose-severity relationships suggest that a dose of 80 mg/kg could be associated with reproductive effects and possibly with overt signs of toxicity. The plausibility of this risk for birds, however, is questionable. There are no data indicating that birds will consume any of the granular formulations that contain hexazinone. Thus, a lower limit on the exposure assessment is zero. If birds were to consume these granules preferentially, exposure levels could be much higher. In that case, toxic effects including mortality would be plausible. Without additional information with which to improve the exposure assessment, this risk cannot be characterized further.

As discussed in section 4.1.2., there is some evidence that the application of hexazinone at a rate of 1 kg a.i./ha or 0.89 lbs a.i./acre affects soil microarthropods (Badejo and Akinyemiju 1993). It is not clear from these reports, however, if the noted effects—a deeper migration of soil mites into the soil layer—can be attributed to toxicity, avoidance, or other changes in soil characteristics. The only other information available on soil arthropods is the report by Mayack et al. (1982) indicating that soil macroarthropods may accumulate hexazinone to a greater degree than other organisms. No effects, however, were noted on community structure. This information is not used quantitatively in this risk assessments because the nature of the endpoint from the Nigerian study is unclear. While the Mayack et al. (1982) study suggests the potential for greater concentration of hexazinone than might be expected by analogy to other organisms, no toxic effects or other changes in macroarthropod populations were noted. Nonetheless, the report from Nigeria suggests an area of uncertainty that may merit additional investigation.

4.4.3. Terrestrial Plants. Direct deposition, from unintentional direct spraying or from spray drift is a plausible hazard for most herbicides, including those containing hexazinone. If plants are sprayed accidentally at the application rates used by the Forest Service, the plants, particularly hardwoods or sensitive pines, are likely to be damaged. This exposure scenario may be regarded as accidental and is relatively easy to control with proper management and application. The extent and duration of the resulting damage will depend on the time of application and the plant species, as discussed in section 4.3.

Hexazinone EC_{25} values as low as 0.01 lbs a.i./acre are reported for commercial crops (see section 4.3.2.1). Thus, at an application rate of 1 lb a.i./acre and distances less than 30 m from the application site, some damage to nontarget vegetation is plausible due to drift of liquid formulations. At distances up to 800 m downwind, exposures could reach 0.00025 or about 0.0015 lbs a.i./acre with a nominal application rate of 6 lbs a.i./acre. This is about a factor of 10 below the lowest EC_{25} and, little if any, damage to nontarget vegetation would be anticipated.

The potential for drift after aerial applications of granular formulations is uncertain. These formulations are designed to minimize drift. Under proper conditions, the application of such products might be expected to have a lower rate of offsite drift than liquid applications. Studies supporting this speculation, however, are not available in the literature. In addition, the California worker study (Spencer et al. 1996) suggests that some formulations may contain high levels of dust that could have a substantial potential for offsite drift.

Ground applications of granular formulations or spot treatments with liquid applications of hexazinone should be associated with little significant drift. Soil contamination and transport of hexazinone to offsite nontarget vegetation, however, may occur. Although there is a wealth of information about the movement of hexazinone in soil, there is relatively little information on the potential effects of low levels of hexazinone in soil on nontarget vegetation. Aqueous solutions of hexazinone ranging from 0.0002 to 0.02 mg/L are shown to have phytotoxic effects on plant cell preparations (see section 4.3.2.2). This is in the range of or somewhat lower than concentrations that adversely affect aquatic algae (see section 4.3.3.3). In addition, there is one report of hexazinone levels of 0.24-1.15 mg/kg soil, presumably due to soil transport from treated sites, associated with damage to nontarget trees. As discussed in section 4.2.2.2, initial levels of hexazinone in the upper soil layer (5-10 cm) are often near or somewhat below levels that might be expected based on uniform distribution (e.g., 2-4 $\mu g/cm^3$ or about 2-4 ppm at an application rate of 4 kg/ha or approximately 4 lbs a.i./acre). Thus, as a conservative approximation, soil levels of 1 ppm (mg/kg soil) are plausible for each lb a.i./acre applied. In addition, as summarized in section 3.2.3.4., water levels of 0.001-0.04 mg/L·lb a.i. applied were observed not only in potable water but also in soil water and runoff water (see Table 3-2).

Based on the limited dose-response data available in plants, these levels of exposure are likely to be toxic to nontarget as well as target vegetation. The magnitude of any observed effects will depend on local conditions, particularly soil type and rainfall. In porous and/or sandy soils with low levels of organic matter and under conditions of high rainfall, adverse effects on offsite vegetation are most plausible.

4.4.4. Aquatic Organisms. Plausible levels of acute exposure in standing water and streams range from about 0.3 mg/L at an application rate of 1 lb a.i./acre to about 1.2 mg/L at an application rate of 4 lbs a.i./acre. Longer-term exposure may range from 0.001-0.04 mg/L at an application rate of 1 lb a.i./acre to about 0.004-0.16 mg/L at an application rate of 4 lbs a.i./acre.

Over these broad ranges of exposure, no effects on fish or the most sensitive aquatic invertebrates are anticipated. In standard laboratory bioassays, the lowest reported effect level for any aquatic animal is 81 mg/L (*Daphnia magna* chronic assay) (see section 4.3.3.2.). This is a factor of over 60-fold higher than the maximum anticipated water concentration at the highest anticipated application rate and a factor of about 30-fold higher than any monitored level of hexazinone in water. Although accidental exposures could be devised that would lead to projected fish or invertebrate kills, such exposures could be devised for literally any substance. Under any plausible conditions of exposure,

including accidental direct applications to a stream, effects on fish or aquatic invertebrates are unlikely.

Effects on algal species, on the other hand, are virtually certain. The lower limit - i.e. least conservative estimate—of longer-term levels of hexazinone in water associated with an application of 1 lb a.i./acre is 0.001 mg/L). This is only a factor of about 3 below the level associated with the inhibition of photosynthesis in stream channels (i.e., model chambers intended to simulate a stream environment). The upper limits of projected longer-term exposures, 0.16 mg/L, are substantially greater than reported EC_{50} values in algal species, except for *Selenastrum* (appendix 8).

The long-term effects that such contamination may have are more difficult to assess. Mayack et al. (1982) noted no detectable change in aquatic macroinvertebrate community structure (Shannon-Weaver Index, Fig. 3, p. 214) in streams with hexazinone levels of 0.006-0.044 mg/L over an observation period of about 7 months. Since these levels are in the range of EC_{50} values for most species of freshwater aquatic algae, some secondary effects on aquatic invertebrates could be expected. The lack of an apparent effect on stream invertebrates at levels shown to produce effects in algae are also apparent in the model stream studies (Kreutzweiser et al. 1995, Schneider et al. 1995). Thus, while effects on aquatic plants seem not only plausible but also highly likely, it is less clear that such effects will result in secondary effects on aquatic animals, either fish or invertebrates.

There is little data regarding the toxicity of hexazinone to amphibians. The one available study (Berrill et al. 1994, appendix 7), however, does not suggest that amphibians are more sensitive than fish or aquatic invertebrate species. A hexazinone concentration of 100 mg/L over an 8-day exposure period was associated only with a reduced avoidance response in newly hatched tadpoles. These exposure levels, however, had no effect on hatching success (Berrill et al. 1994). Comparable concentrations of hexazinone over shorter periods of exposure have been associated with marked mortality in fish and aquatic invertebrates (Kennedy 1984). Thus, based on the limited available data, amphibians do appear to be less sensitive than fish or aquatic invertebrates to hexazinone.

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6. GLOSSARY

Absorption -- The process by which the agent is able to pass through the body membranes and enter the bloodstream. The main routes by which toxic agents are absorbed are the gastrointestinal tract, lungs, and skin.

Acetylcholine -- A naturally occurring chemical responsible for the transmission of impulses between nerve cells or between nerve cells and an effector cell (such as a muscle cell). Broken down to inactive compounds by acetylcholinesterase.

Acetylcholinesterase -- An enzyme responsible for the degradation of acetylcholine to acetic acid and choline. The inhibition of this enzyme leads to an excess of acetylcholine in nerve tissue. This can lead to a broad spectrum of clinical effects (Table 7-2).

Acute exposure -- A single exposure or multiple exposure occurring within a short time (24 hours or less).

Additive Effect -- A situation in which the combined effects of two chemicals is equal to the sum of the effect of each chemical given alone. The effect most commonly observed when two chemicals are given together is an additive effect.

Adenosine Diphosphate (ADP) -- A molecule used as a substrate in metabolism of nutrients in which the chemical energy in the nutrient is converted to ATP.

Adenosine Triphosphate (ATP) -- A molecule used as an energy source in many biochemical reactions in living things. During the energy transfer process, the ATP is converted to ADP and inorganic phosphorous.

Adjuvant(s) -- Formulation factors used to enhance the pharmacological or toxic agent effect of the active ingredient.

Adrenergic -- A type of nerve which uses an adrenaline like substance as a neurotransmitter.

Adsorption -- The tendency of one chemical to adhere to another material.

Adverse-Effect Level (AEL) -- Signs of toxicity that must be detected by invasive methods, external monitoring devices, or prolonged systematic observations. Symptoms that are not accompanied by grossly observable signs of toxicity. In contrast to Frank-effect level.

Aerobes -- Organisms that require oxygen.

Allometric -- pertaining to allometry, the study and measure of growth. In toxicology, the study of the relationship of body size to various physiological, pharmacological, pharmacokinetic, or toxicodynamic processes among species.

Anaerobes -- Organisms that do not require oxygen.

Ascites -- The accumulation of fluid in the peritoneal cavity. Tis condition may be caused by increased venous pressure or decreased plasma albumin and is often associated with cardiac failure, cirrhosis of the liver, or renal deficiency.

Assay -- A kind of test (noun); to test (verb).

Bioconcentration Factor -- The concentration of a compound in an aquatic orgainism divided by the concentration in the ambient water of the organism.

Biologically Sensitive -- A term used to identify a group of individuals who, because of their developmental stage or some other biological condition, are more susceptible than the general population to a chemical or biological agent in the environment.

Broadleaf weed -- A nonwoody dicotyledonous plant with wide bladed leaves designated as a pest species in gardens, farms, or forests.

Cancer Potency Parameter -- A model-dependent measure of cancer potency $(mg/kg/day)^{-1}$ over lifetime exposure. [Often expressed as a q_1^* which is the upper 95% confidence limit of the first dose coefficient (q_1) from the multistage model.]

Carcinogen -- A chemical capable of inducing cancer.

Carcinoma -- A malignant tumor.

Carrier -- In commercial formulations of insecticides or control agents, a substance added to the formulation to make it easier to handle or apply.

Cholinergic -- Refers to nerve cells that release acetylcholine.

Chronic Exposure -- Long-term exposure studies often used to determine the carcinogenic potential of chemicals. These studies are usually performed in rats, mice, or dogs and extend over the average lifetime of the species (for a rat, exposure is 2 years).

Confounders -- A term used in discussions of studies regarding human populations (epidemiology studies) to refer to additional risk factors that if unaccounted for in a study, may lead to erroneous conclusions.

Conifer -- An order of the Gymnospermae, comprising a wide range of trees, mostly evergreens that bear cones and have needle-shaped or scalelike leaves; timber commercially identified as softwood.

Connected Actions -- Exposure to other chemical and biological agents in addition to exposure to the control agent during program activities to control vegetation.

Contaminants -- For chemicals, impurities present in a commercial grade chemical. For biological agents, other agents that may be present in a commercial product.

Controls -- In toxicology or epidemiology studies, a population that is not exposed to the potentially toxic agent under study.

Cumulative Exposures -- Exposures that may last for several days to several months or exposures resulting from program activities that are repeated more than once during a year or for several consecutive years.

Cytosolic -- Found in the cytoplasm of a cell.

Dams -- Females.

Degraded -- Broken down or destroyed.

Dermal -- Pertaining to the skin.

Dislodgeable Residues -- The residue of a chemical or biological agent on foliage as a result of aerial or ground spray applications, which can be removed readily from the foliage by washing, rubbing or having some other form of direct contact with the treated vegetation.

Dose-response Assessment -- A description of the relationship between the dose of a chemical and the incidence of occurrence or intensity of an effect. In general, this relationship is plotted by statistical methods. Separate plots are made for experimental data obtained on different species or strains within a species.

Drift -- That portion of a sprayed chemical that is moved by wind off a target site.

EC_{50} -- A concentration that causes 50% inhibition or reduction. As used in this document, this values refers to a 50% inhibition of growth.

EC_{100} -- A concentration that causes complete inhibition or reduction. As used in this document, this values refers to a complete inhibition of growth.

Empirical -- Refers to an observed, but not necessarily fully understood, relationship in contrast to a hypothesized or theoretical relationship.

Enzymes -- A biological catalyst; a protein, produced by an organism itself, that enables the splitting (as in digestion) or fusion of other chemicals.

Epidemiology Study -- A study of a human population or human populations. In toxicology, a study which examines the relationship of exposures to one or more potentially toxic agent to adverse health effects in human populations.

Exposure Assessment -- The process of estimating the extent to which a population will come into contact with a chemical or biological agent.

Extrapolation -- The use of a model to make estimates outside of the observable range.

Fibroma -- A benign tumor composed mainly of fibrous or fully developed connective tissue.

Formulation -- A commercial preparation of a chemical including any inerts or contaminants.

Frank effects -- Obvious signs of toxicity.

Frank-effect Level (FEL) -- The dose or concentration of a chemical or biological agent that causes gross and immediately observable signs of toxicity.

Gavage -- The placement of a toxic agent directly into the stomach of an animal, using a gastric tube.

Genotoxic -- Causing direct damage to genetic material. Associated with carcinogenicity.

Geometric Mean -- The measure of an average value often applied to numbers for which a log normal distribution is assumed.

Gestation -- The period between conception and birth; in humans, the period known as pregnancy.

Half-time or Half-life -- For compounds that are eliminated by first-order kinetics, the time required for the concentration of the chemical to decrease by one-half.

Hazard Quotient (HQ) -- The ratio of the estimated level of exposure to the RfD or some other index of acceptable exposure.

Hazard identification -- The process of identifying the array of potential effects that an agent may induce in an exposed human population.

Hematological -- Pertaining to the blood.

Hematology -- One or more measurements regarding the state or quality of the blood.

Henry's law constant -- An index of the tendency of a compound to volatilize from aqueous solutions.

Herbaceous -- A plant that does not develop persistent woody tissue above the ground (annual, biennial, or perennial, but whose aerial portion naturally dies back to the ground at the end of a growing season. They include such categories as grasses and grass-like vegetation.

Herbicide -- A chemical used to control, suppress, or kill plants, or to severely interrupt their normal growth processes.

Histopathology -- Signs of tissue damage that can be observed only by microscopic examination.

Hydrolysis -- Decomposition or alteration of a chemical substance by water.

Hydroxylation -- The addition of a hydrogen-oxygen or hydroxy (-OH) group to one of the rings. Hydroxylation increases the water solubility of aromatic compounds. Particularly when followed by conjugation with other water soluble compounds in the body, such as sugars or amino acids, hydroxylation greatly facilitates the elimination of the compound in the urine or bile.

Hyperemia -- An increase in the amount of blood in an organ or region of the body with distention of the blood vessels. This may be caused either by an increase in dilation of the blood vessels (active hyperemia) or a hindance of blood drainage from the site (passive hyperemia).

Hypoactivity -- Less active than normal.

Hypovolemia -- Low or decreased blood volume. If this condition is sufficiently severe, the individual may go into shock and die.

In vivo -- Occurring in the living organism.

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

Inerts -- Adjuvants or additives in commercial formulations of glyphosate that are not readily active with the other components of the mixture.

Interpolation -- The use of mathematical models within the range of observations

Intraperitoneal -- Injection into the abdominal cavity.

Invertebrate -- An animal that does not have a spine (backbone).

Irritant Effect -- A reversible effect, compared with a corrosive effect.

Larva (pl. larvae) -- An insect in the earliest stage after hatching.

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

Lethal Dose$_{50}$ (LD$_{50}$) -- The dose of a chemical calculated to cause death in 50% of a defined experimental animal population over a specified observation period. The observation period is typically 14 days.

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

Malignant -- Cancerous.

Margin of safety (MOS) -- The ratio between an effect or no effect level in an animal and the estimated human dose.

Metabolite -- A compound formed as a result of the metabolism or biochemical change of another compound.

Metameter -- Literally, the unit of measure. Used in dose-response or exposure assessments to describe the most relevant way of expressing dose or exposure.

Microorganisms -- A generic term for all organisms consisting only of a single cell, such as bacteria, viruses, and fungi.

Microsomal -- Pertaining to portions of cell preparations commonly associated with the oxidative metabolism of chemicals.

Minimal Risk Level (MRL) -- A route-specific (oral or inhalation) and duration- specific estimate of an exposure level that is not likely to be associated with adverse effects in the general population, including sensitive subgroups.

Mitochondria -- Subcellular organelles involved in the conversion of food to stored chemical energy.

Most Sensitive Effect -- The adverse effect observed at the lowest dose level, given the available data. This is an important concept in risk assessment because, by definition, if the most sensitive effect is prevented, no other effects will develop. Thus, RfDs and other similar values are normally based on doses at which the most sensitive effect is not likely to develop.

Multiple Chemical Sensitivity -- A syndrome that affects individuals who are extremely sensitive to chemicals at extremely low levels of exposure.

Mutagenicity -- The ability to cause genetic damage (that is damage to DNA or RNA). A mutagen is substance that causes mutations. A mutation is change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Myeloma -- primary tumor of the bone marrow.

Myotonic -- pertaining to muscle spasms.

Neuropathy -- Damage to the peripheral nervous system.

Neurotransmitter -- A substance used by a nerve cell in the transmission of impulses between nerve cells or between nerve cells and an effector cell.

Non-target -- Any plant or animal that a treatment inadvertently or unavoidably harms.

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

No-Observed-Effect Level (NOEL) -- The dose of a chemical at no treatment-related effects were observed.

Normal Distribution -- One of several standard patterns used in statistics to describe the way in which variability occurs in a populations.

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

Ocular -- Pertaining to the eye.

Oxidative phosphorylation -- An metabolic process in which the metabolism of molecules in or derived from nutrients is linked to the conversion (phosphorylation) of ADP to ATP, a major molecule for storing energy in all living things.

Parenteral -- Any form of injection.

Partition -- In chemistry, the process by which a compound or mixture moves between two or more media.

Pasquill-Gifford vertical dispersion parameter -- A term which mathematically describes the upward dispersion of a gas as it travels downwind.

Pasquill stability category -- A method of classifying air stability based on a set of general descriptions such as wind speed and cloud cover.

Pathway -- In metabolism, a sequence of metabolic reactions.

Perennial -- A plant species having a lifespan of more than 2 years.

pH -- The negative log of the hydrogen ion concentration. A high pH (>7) is alkaline or basic and a low pH (<7) is acidic.

pK_a -- The negative log of the hydrogen ion concentration or pH at which 50% of a weak acid is dissociated.

pK_b -- The negative log of the hydrogen ion concentration or pH at which 50% of a weak base is dissociated.

Pharmacokinetics -- The quantitative study of metabolism (i.e., the processes of absorption, distribution, biotransformation, elimination).

Plasma Cholinesterase -- Another term for **Pseudocholinesterase**. The normal physiological role of this cholinesterase is not known. Inhibition of this enzyme is considered an index of exposure to many organophosphate insecticides.

Plasma -- The fluid portion of the blood in which particulates are suspended.

Precommercial thinning -- Cutting in immature stands to improve the quality and growth of the remaining stand.

Prospective -- looking ahead. In epidemiology, referring to a study in which the populations for study are identified prior to exposure to a presumptive toxic agent, in contrast to a retrospective study.

Pseudocholinesterase -- A term for cholinesterase found in the plasma. The normal physiological role of this cholinesterase is not known. Inhibition of this enzyme is considered an index of exposure to many organophosphate insecticides.

Release -- A work done to free desirable trees from competition with overstory trees, less desirable trees or grasses, and other forms of vegetative growth.

Reference Dose -- Oral dose (mg/kg/day) not likely to be associated with adverse effects over lifetime exposure, in the general population, including sensitive subgroups.

Reproductive Effects -- Adverse effects on the reproductive system that may result from exposure to a chemical or biological agent. The toxicity of the agents may be directed to the reproductive organs or the related endocrine system. The manifestations of these effects may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions dependent on the integrity of this system.

Resorption -- Removal by absorption. Often used in describing the unsuccessful development and subsequent removal of post-implantation embryos.

Retrospective -- looking behind. In epidemiology, referring to a study in which the populations for study are identified after exposure to a presumptive toxic agent, in contrast to a prospective study.

RfD -- A daily dose which is not anticipated to cause any adverse effects in a human population over a lifetime of exposure. These values are derived by the U.S. EPA.

Right-of-way -- a corridor of low growing shrubs or grasses that facilitate the maintenance and protection of utility power lines and provide transport pathways for humans or wildlife.

Route of Exposure -- The way in which a chemical or biological agent enters the body. Most typical routes include oral (eating or drinking), dermal (contact of the agent with the skin), and inhalation.

Scientific Notation -- The method of expressing quantities as the product of number between 1 and 10 multiplied by 10 raised to some power. For example, in scientific notation, 1 kg = 1,000 g would be expressed as 1 kg = 1 x 10^3 g and 1 mg = 0.001 would be expressed as 1 mg = 1 x 10^{-3}.

Sensitive subgroup -- Subpopulations that are much more sensitive than the general public to certain agents in the environment.

Site preparation -- The removal of competition and conditioning of the soil to enhance the survival and growth of seedlings or to enhance the seed germination.

Species-to-Species Extrapolation -- A method involving the use of exposure data on one species (usually an experimental mammal) to estimate the effects of exposure in another species (usually humans).

Subchronic Exposure -- An exposure duration that can last for different periods of time, but 90 days is the most common test duration. The subchronic study is usually performed in two species (rat and dog) by the route of intended use or exposure.

Substrate -- With reference to enzymes, the chemical that the enzyme acts upon.

Synapse -- The space between two nerve cells or a nerve cell and an effector cell such as muscle.

Synergistic Effect -- A situation is which the combined effects of two chemicals is much greater than the sum of the effect of each agent given alone.

Systemic Toxicity -- Effects that require absorption and distribution of a toxic agent to a site distant from its entry point at which point effects are produced. Systemic effects are the obverse of local effects.

Teratogenic -- Causing structural defects that affect the development of an organism; causing birth defects.

Teratology -- The study of malformations induced during development from conception to birth.

Threshold -- The maximum dose or concentration level of a chemical or biological agent that will not cause an effect in the organism.

Toxicity -- The inherent ability of an agent to affect living organisms adversely.

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

Urinalysis -- Testing of urine samples to determine whether toxic or other physical effects have occurred in an organism.

Vehicle -- A substance (usually a liquid) used as a medium for suspending or dissolving the active ingredient. Commonly used vehicles include water, acetone, and corn oil.

Vertical dispersion parameter -- A term which mathematically describes the upward dispersion of a gas as it travels downwind.

Vertebrate -- An animal that has a spinal column (backbone).

Volatile -- Referring to compounds or substances that have a tendency to vaporize. A material that will evaporate quickly.

Xenobiotic -- A chemical that does not naturally occur in an organism.

7. SUBJECT INDEX

Appendix 1. Oral toxicity of hexazinone to mammals and birds [sorted by duration / species / formulation / author]

Citation	Formulation	Species/ Strain/Sex	Dose	Exposure	Effects	Comments
Kennedy 1984	95.8% active	dog/beagle/male	1000 mg/kg	1 day, single dose, gelatin capsule	vomiting, tremors, salivation, and rapid respiration 10-20 minutes post dosing; all signs of toxicitiy, except diarrhea, disappeared the day after treatment, and the dog survived with no further signs of toxicity	1) dog was young adult 2) one dog was treated
Kennedy 1984	95.8% active	dog/beagle/male	2250 or 3400 mg/kg	1 day, single dose, gelatin capsule	prominent clinical signs of toxicity that included lacarimation for up to 1 day after treatment; dogs survived and showed no signs of toxicity 15 days after treatment	1) dogs were young adults 2) one dog/ t reatment group
Kennedy 1984	95.8% active	dog/beagle/male	>3400 mg/kg	1 day, single dose, gelatin capsule	LD50	1) dogs were young adults 2) two dogs were treated
Kennedy 1984	98+% pure technical grade	guinea pig/NS/male	860 (±420-1260) mg/kg	1 day, single dose, gavage	LD50	1) vehicle not specified 2) 10 guinea pigs were treated 3) guinea pigs were adults 4) guinea pigs weighed approximately 500 g
Kennedy 1984	98+% pure technical grade	guinea pig/NS/male	700, 850, 900, 1000 mg/kg	1 day, single dose, gavage	principal signs of toxicity similar to those observed in rats (see above); mortality rates were 3/10 animals at 700 mg/kg, 3/10 animals at 850 mg/kg, 7/10 animals at 900 mg/kg, and 7/10 animals at 1000 mg/kg.	1) vehicle not specified 2) 10 guinea pigs/group were treated 3) guinea pigs were adults 4) guinea pigs weighed approximately 500 g
Newton and Dost 1981, WSSA 1983	unformulated	guinea pig/ Albino/male	860 (450-1260) mg/kg bw	1 day, single dose, gavage	LD50; lethargy, ataxia, convulsions, weight loss, prostration, salivation, lacrimation, and ruffled fur	1) vehicle = suspension in 15:85 acetone: corn oil 2) 10 animals per group 3) animals observed for 14 days

Appendix 1. Oral toxicity of hexazinone to mammals and birds [sorted by duration / species / formulation / author]

Citation	Formulation	Species/ Strain/Sex	Dose	Exposure	Effects	Comments
Kennedy 1984	98+% pure technical grade	quail/bobwhite/male	398, 631, 1000, 1590, or 2510 mg/kg body weight	1 day, single dose/gavage	quail exposed to ≤1000 mg/kg body weight survived to 14 days after treatment; at 1590 mg/kg body weight , 2/10 quail died, and at 2510 mg/kg body weight, 6/10 quail died; the LD50 (calculated using probit analysis) was equal to 2258 (±1628-3310) mg/kg body weight. Quail exposed to 398 mg/kg body weight showed no signs of toxicity; at 631 mg/kg body weight, 1/10 quail showed signs of toxicity similar to those observed in the high dose group and 1/10 quail showed signs of head pecking on day 9 after treatment; at 1000 and 1590 mg/kg body weight, the quail had effects similar to those observed at the highest dose, except that the birds in the lower dose groups recovered on days 2 and 3, respectively. Immediately after exposure to 2510 mg/kg body weight, 3/10 quail depressed and had a decreased response to sound and movement; within 4 hours, all surviving birds exposed to 2510 mg/kg body weight were depressed and had wing droop, loss of coordination, lower limb weakness, prostration, loss of righting reflex, and clonic convulsions. In surviving quail, lethargy continued for 3 days after treatment, by which time the quail show no signs of toxicity. Food consumption at the three highest dose levels appeared to be dose related during the first week after treatment.	1) quail were 20 weeks old 2) quail were fasted 15 hours before exposure 3) vehicle = corn oil 4) there was a 14-day post treatment observation period
U.S. EPA 1982	technical	quail/bobwhite/male, female	2258 (1628-3130) mg/kg	1 day, single dose, gavage	LD50	1) animals were fasted 2) animals were 20 weeks old 3) animals were observed for 14 days [2 weeks] for toxic effects and mortality
Schneider and Kaplan 1983	20% gridball	rat, ChR:CD, F	6352 (5243-10,371) mg/kg bw	1 day, single dose, gavage	LD50; prostration, half-closed eyes, stained perinea, weakness salivation, weight loss, convulsions at lethal doses, and gross pathological changes inlungs, liver stomach, thymus, and occasionally in salivary lymph nodes, spleen and brain	1) vehicle = corn oil 2) 10 animals per sex per dose (not specified) 3) all animals weighed and observed for 14 days, then sacrificed and examined for changes in gross pathology
Schneider and Kaplan 1983	20% gridball	rat/ChR:CD/male	11,798 (10,721-13,155) mg/kg bw	1 day, single dose, gavage	LD50; prostration, half-closed eyes, stained perinea, weakness salivation, weight loss, convulsions at lethal doses, and gross pathological changes inlungs, liver stomach, thymus, and occasionally in salivary lymph nodes, spleen and brain	1) vehicle = corn oil 2) 10 animals per sex per dose (not specified) 3) all animals weighed and observed for 14 day, then sacrificed and examined for changes in gross pathology

Appendix 1. Oral toxicity of hexazinone to mammals and birds [sorted by duration / species / formulation / author]

Citation	Formulation	Species/ Strain/Sex	Dose	Exposure	Effects	Comments
Schneider and Kaplan 1983	25% liquid	rat/ ChR:CD/male	6887 mg/kg bw	1 day, single dose, gavage	LD50; slight to moderate weight losses, weakness, half closed eyes, wet and stained perinea, stained face, laboared breathing, ataxia, and convulsions; at gross examination discolored and heavy lungs at all doses	1) 10 animals per dose (6000-9000 ppm) 2) survivors weighed and observed for 14 days, then sacrificed for examination of gross pathology
Schneider and Kaplan 1983	25% liquid	rat/ ChR:CD/male	7080 (6666-8753) mg/kg bw	1 day, single dose, gavage	LD50; nondose-related prostration; wet and stained perinea and nasal areas, lethargy, congestion, irregular respiration, and convulsions; gross examination revealed no compound-related pathological changes	1) 10 animals per dose (not specified) 2) animals were observed for 14 days 3) three animals from highest doses and two animals from other doses examined for changes in gross pathology
Schneider and Kaplan 1983	25% liquid	rat/ChR:CD/male	9000 mg/kg bw	1 day, single dose, gavage	AEL; slight to moderate weight losses, weakness, half closed eyes, wet and stained perinea, stained face, laboared breathing, ataxia, and convulsions; at gross examination slightly heavy liver in one rat	1) 10 animals per dose (6000-9000 ppm) 2) survivors weighed and observed for 14 days, then sacrificed for examination of gross pathology
Schneider and Kaplan 1983	66% wettable powder	rat/ChR:CD/male	4495 (3808-5263) mg/kg bw	1 day, single dose, gavage	LD50; prostration, salivation, piloerection, wet and stained perinea, stained mouth and nose, half-closed eyes, labored breathing, tremors, and convulsions; no treatment-related change in gross pathology	1) 10 animals per dose (3200, 5000, 6000 ppm) 2) vehicle = corn oil 3) observed for 14 days, two animals from each dose group examined for gross pathology
U.S. EPA 1982	66% wettable powder suspension	rat/ ChR:CD/male	4495 (3808-5263) mg/kg bw	1 day, single dose, gavage	LD50	formulation = 66% wettable powder suspension in corn oil
Schneider and Kaplan 1983	89.3% a.i.	rat/ ChR:CD/male	5000 mg/kg bw	1 day, single dose, gavage	ALD; congestion, stained nose and mouth and transient weight loss at sublethal doses; rapid and labored respiration, pallor, prostration, lethargy, half-closed eyes, and convulsions at lethal dose	1) table species "ALD" as effect 2) vehicle = corn oil 3) one animal per dose (not specified) 4) animals were observed for 14 days
Kennedy 1984	98+% technical grade	rat/Crl-CD/male	500, 550, or 600 mg/kg	1 day, single dose, intraperitoneal injection	clinical signs of toxicity were similar to those observed after oral administration of high doses of hexazinone to rats (see below)	1) three groups of 10 rats 2) hexazinone was administered in a 7-10% saline sususpension 3) clinical signs were monitored for 14 days

Appendix 1. Oral toxicity of hexazinone to mammals and birds [sorted by duration / species / formulation / author]

Citation	Formulation	Species/ Strain/Sex	Dose	Exposure	Effects	Comments
Kennedy 1984	98+% pure technical grade	rat/Crl-CD albino/male	1200, 1400, 1600, or 2000 mg/kg	1 day, single dose, gavage	all rats showed lethargy, ataxia, salivation, prostration, chewing motions, and ruffled fur immediately after treatment and up to 48 hours after dosing. Mortality rates were 1/10 animals at 1200 mg/kg, 0/10 animals at 1400 mg/kg, 4/10 animals at 1600 mg/kg, and 9/10 animals at 2000. Rats that died generally had clonic convulsions. Mortality occurred within 2 days of treatment.	1) vehicle = 10-15% suspension in 15:85 acetone:corn oil 2) 10 rats were treated 3) rats weighed 227-272 g
Kennedy 1984	98+% pure technical grade	rat/Crl-CD albino/male	1690 (±1560-1880) mg/kg	1 day, single dose, gavage	LD50	1) vehicle = 10-15% suspension in 15:85 acetone:corn oil 2) 10 rats were treated 3) rats weighed 227-272 g
Kennedy 1984	98+% technical grade	rat/Crl-CD/male	530 (±300-570) mg/kg	1 day, single dose, intraperitoneal injection	LD50	1) three groups of 10 rats 2) hexazinone was administered in a 7-10% saline sususpension
Schneider and Kaplan 1983	unformulated	rat/ ChR:CD/male	2012 mg/kg bw	1 day, single dose, gavage	LD50; tremors and convulsions on day of dosing; weakness and wet perinea on day after dosing; weight loss for 1-2 days after dosing	1) vehicle = corn oil 2) 10 animals per dose (not specified) 3) animals were observed for 14 days
Schneider and Kaplan 1983	unformulated	rat/ ChR:CD/male	1500 mg/kg bw	1 day, single dose, gavage	ALD; prostration, irregular respiration and half-closed eyes on day of dosing; apprehension, incoordination, and convulsions at lethal doses	1) table species "ALD" as effect 2) vehicle = corn oil 3) one animal per dose (not specified) 4) animals were observed for 14 days
Schneider and Kaplan 1983	unformulated	rat/ ChR:CD/male	1690 (1560-1880) mg/kg bw	1 day, single dose, gavage	LD50; lethargy, ataxia, convulsions, weight loss, prostration, salivation, lacrimation, and ruffled fur	1) vehicle = suspension in 15:85 acetone: corn oil 2) 10 animals per group 3) animals observed for 14 days
Kennedy 1984	98+% pure technical grade	quail/bobwhite/male	0, 625, 1250, 2500, 5000, or 10,000 ppm	5 days/diet	mortality rates were 2/10 in one of the five control groups and 1/10 in two of the five control groups, 3/10 at 625 ppm, 2/10 at 1250 ppm, 5/10 at 2500 ppm, 1/10 at 5000 ppm, and 2/10 at 10,000 ppm; no clinical signs of toxicity, and body weights were lower than controls; food consumption was lower in quail that lost weight. LD50 was considered to be >10,000 ppm	1) quail were 14 days [2 weeks] old 2) five separate groups of control were studied 3) 10 quail/treatment group 4) treated diets provided for 5 days with basal diets given to all groups for last 3 days 5) no LD50 was calculated due to variable occurrence of mortality

Appendix 1. Oral toxicity of hexazinone to mammals and birds [sorted by duration / species / formulation / author]

Citation	Formulation	Species/ Strain/Sex	Dose	Exposure	Effects	Comments
Kennedy 1984	98+% pure technical grade	quail/bobwhite/male	0, 625, 1250, 2500, 5000, or 10,000 ppm	5 days/diet	mortality rates were 1/10 in two of the five control groups, 5/10 at 625 ppm, 1/10 at 1250 ppm, 8/10 at 2500 ppm, 2/10 at 5000 ppm, and 1/10 at 10,000 ppm; no clinical signs of toxicity, and body weights were greater than controls. LD50 was considered to be >10,000 ppm.	1) quail were 14 days [2 weeks] old 2) five separate groups of control were studied 3) 10 quail/treatment group 4) treated diets provided for 5 days with basal diets given to all groups for last 3 days 5) no LD50 was calculated due to variable occurrence of mortality 6) study was replicated (see entry below)
Kennedy 1984	98+% pure technical grade	quail/bobwhite/male	>5000 ppm	5 days/diet	LD50	1) 10-15 day old quail 2) 5 groups of 10 quail 3) quail exposed to graded levels of hexazinone ranging from 312.5 to 5000 ppm (levels not otherwise specied) 4) 3-day observation period after exposure
Kennedy 1984	98+% pure technical grade	quail/bobwhite/male	156, 312, 625, 1250, 2500, or 5000 ppm	5 days/diet	mortality rates were 0/10 at 156 ppm, 0/10 at 312 ppm, 0/10 at 625 ppm, 1/10 at 1250 ppm, 0/10 at 2500 ppm, and 3/10 at 5000 ppm; general body weight loss observed in treated quail, compared with controls, but there was no apparent no dose-response relationship; food consumption was comparable to that of controls, and there were no treatment related effects determined at necropsy. LD50 considered to be >5000 ppm.	70 quail were assigned randomly to treatment groups
Kennedy 1984	89.3% a.i.	rat/Crl-CD/male	300 mg/kg	010 days, single dose/gavage	no reduction in body weight gain; no outward signs of toxicity; no gross or histopathological changes in rats necropsied after 4 hours or 14 days of the last dose	1) six rats/group 2) rats weighed approximately 230 3) vehicle = corn oil 4) daily treatment for 5 consecutive days, followed by 2 rest days and treatment for an additional 5 consecutive days (10 doses total) 5) six rats intubated with corn oil served as controls 6) clinical evaluation included microscopic examination of lungs, trachea, bronchi, liver, kidney, spleen, heart, testis, epididymis, thymus, thyroid, adrenal, esophagus, stomach, intestine, pancreas, brain, eye, and bone marrow.

Appendix 1. Oral toxicity of hexazinone to mammals and birds [sorted by duration / species / formulation / author]

Citation	Formulation	Species/ Strain/Sex	Dose	Exposure	Effects	Comments
Kennedy 1984	98+% pure technical grade	rat/Crl-CD/male	300 mg/kg	010 days, single dose/gavage	slight reduction in body weight gain; no outward signs of toxicity; no gross or histopathological changes in rats necropsied after 4 hours or 14 days of the last dose	1) six rats/group 2) rats weighed approximately 230 3) vehicle = corn oil 4) daily treatment for 5 consecutive days, followed by 2 rest days and treatment for an additional 5 consecutive days (10 doses total) 5) six rats intubated with corn oil served as controls 6) clinical evaluation included microscopic examination of lungs, trachea, bronchi, liver, kidney, spleen, heart, testis, epididymis, thymus, thyroid, adrenal, esophagus, stomach, intestine, pancreas, brain, eye, and bone marrow.
Schneider and Kaplan 1983	89.3% a.i.	rat/ChR:CD/male	300 mg/kg/day	14 days [2 weeks], 5 times/week, gavage	AEL; all rats survived; slight weight loss; no treatment-related changes in microscopic pathology	1) vehicle =5 % corn oil suspension 2) six animals were treated 3) three treated and three control rats sacrificed at 4 hours and 14 days after last dose and examined for changes in microscopic pathology
Schneider and Kaplan 1983	89%.3 a.i.	rat/ChR:CD/male	1000 mg/kg/day	14 days [2 weeks], 5 times/week, gavage	AEL; all rats survived; slight weight loss, wet and stained perinea, congestion, salivation, and chromodacryorrhea that were treatment related; increased liver weight and slightly to moderately enlarged hepatocytes noted at end of treatment period and were treatment related	1) vehicle = 6% corn oil suspension 2) 10 animals per group 3) five treated rats and five control rats were sacrificed at 4 hours and 14 days afater the last dose and examined for changes in microscopic pathology
Schneider and Kaplan 1983	unformulated	rat/ChR:CD/male	1000 mg/kg/day	14 days [2 weeks], 5 days/week, gavage	AEL; no deaths; compound related increased liver weight and larger hepatocytes; wet and stained perinea, congestion, slight weight loss, and salivation	
Schneider and Kaplan 1983	unformulated	rat/ChR:CD/male	300 mg/kg/day	14 days [2 weeks], 5 times/week, gavage	NOEL; all rats survived; no clinical signs of toxicity; no treatment-related changes in microscopic pathology	1) vehicle =5 % corn oil suspension 2) six animals were treated 3) three treated and three control rats sacrificed at 4 hours and 14 days after last dose and examined for changes in microscopic pathology

Appendix 1. Oral toxicity of hexazinone to mammals and birds [sorted by duration / species / formulation / author]

Citation	Formulation	Species/ Strain/Sex	Dose	Exposure	Effects	Comments
WSSA 1983, Newton and Dost 1981	unformulated	rat/ChR:CD/male	300 mg/kg/day	14 days [2 weeks], 5 days/week, gavage	NOEL; no deaths; no evidence of cumulative toxicity	no clinical or histopathological changes
Richmond 1979	Gridball pellets	deer/White-tailed/NS	2-100 pellets	21-35 days [3-5 weeks], continuous, diet	NOEL; no mortality or unusual behavior	pellets were placed in feeding territories in natural habitat
Richmond 1979	Gridball pellets	opossum/NS/NS	2-100 pellets	21-35 days [3-5 weeks], continuous, diet	NOEL; no mortality or unusual behavior; nibbling and urine marking by prairie voles caused no adverse effects	pellets were placed in feeding area of live-trapped animals
Richmond 1979	Gridball pellets	rabbit/Cottontail/ NS	2-100 pellets	21-35 days [3-5 weeks], continuous, diet	NOEL; no mortality or unusual behavior	pellets were placed in feeding territories in natural habitat
Richmond 1979	Gridball pellets	racoon/NS/NS	2-100 pellets	21-35 days [3-5 weeks], continuous, diet	NOEL; no mortality or unusual behavior; nibbling and urine marking by prairie voles caused no adverse effects	pellets were placed in feeding area of live-trapped animals
Richmond 1979	Gridball pellets	rat/Norway/NS	2-100 pellets	21-35 days [3-5 weeks], continuous, diet	NOEL; no mortality or unusual behavior	pellets were placed in feeding territories in natural habitat
Richmond 1979	Gridball pellets	skunk/NS/NS	2-100 pellets	21-35 days [3-5 weeks], continuous, diet	NOEL; no mortality or unusual behavior; nibbling and urine marking by prairie voles caused no adverse effects	pellets were placed in feeding area of live-trapped animals
Richmond 1979	Gridball pellets	squirrel/Grey/NS	2-100 pellets	21-35 days [3-5 weeks], continuous, diet	NOEL; no mortality or unusual behavior	pellets were placed in feeding territories in natural habitat
Richmond 1979	Gridball pellets	vole/prairie/NS	2-100 pellets	21-35 days [3-5 weeks], continuous, diet	NOEL; no mortality or unusual behavior; nibbling and urine marking by prairie voles caused no adverse effects	pellets were placed in feeding area of live-trapped animals
Richmond 1979	Gridball pellets	vole/Prairie/NS	2-100 pellets	21-35 days [3-5 weeks], continuous, diet	NOEL; no mortality or unusual behavior	pellets were placed in feeding territories in natural habitat

Appendix 1. Oral toxicity of hexazinone to mammals and birds [sorted by duration / species / formulation / author]

Citation	Formulation	Species/ Strain/Sex	Dose	Exposure	Effects	Comments
Ghassemi et al. 1981, Newton and Dost 1981	unformulated	hamster/Engle/male, female	0-10,000 ppm	56 days [8 weeks], continuous, diet	NOEL; no mortality or clinical signs of toxicity	animals were weanlings
Kennedy and Kaplan 1984	95% pure	mouse/CD-1/male, female	0, 250, 500, 1250, 2500, or 10,000 ppm	56 days [8 weeks], continous, diet	no effects on appearance, general behavior, mortality, body weight, food consumption, or calculated food efficiency at ≤10,000 ppm; increased absolute and relative liver weight observed at 10,000 ppm; necropsy revealed no gross pathological lesions	1) range-finding study 2) two control groups used concurrently 3) groups of 10 mice/sex 4) age of animals not specified
Ghassemi et al. 1981, Newton and Dost 1981	unformulated	mouse/ChR:CD/male, female	250 ppm	56 days [8 weeks], continuous, diet	NOEL; no effects	1) 10 animals per group 2) animals were weanlings 3) table indicatest that NOEL = 5000 ppm
Ghassemi et al. 1981, Newton and Dost 1981	unformulated	mouse/ChR:CD/male, female	1250 ppm	56 days [8 weeks], continuous, diet	NOEL; no effects	1) 10 animals per group 2) animals were weanlings 3) table indicatest that NOEL = 5000 ppm
Ghassemi et al. 1981, Newton and Dost 1981	unformulated	mouse/ChR:CD/male, female	10,000 ppm	56 days [8 weeks], continuous, diet	LOAEL; increased liver weight in both sexes; no other clinical, behavioral, nutritional, or pathological signs of toxicity	1) 10 animals per group 2) animals were weanlings 3) table indicatest that NOEL = 5000 ppm
Ghassemi et al. 1981, Newton and Dost 1981	unformulated	mouse/ChR:CD/male, female	500 ppm	56 days [8 weeks], continuous, diet	NOEL; no effects	1) 10 animals per group 2) animals were weanlings 3) table indicatest that NOEL = 5000 ppm
Ghassemi et al. 1981, Newton and Dost 1981	unformulated	mouse/ChR:CD/male, female	5000 ppm	56 days [8 weeks], continuous, diet	NOEL; no effects	1) 10 animals per group 2) animals were weanlings 3) table indicatest that NOEL = 5000 ppm
Ghassemi et al. 1981, Newton and Dost 1981	unformulated	mouse/ChR:CD/male, female	2500 ppm	56 days [8 weeks], continuous, diet	NOEL; no effects	1) 10 animals per group 2) animals were weanlings 3) table indicatest that NOEL = 5000 ppm

Appendix 1. Oral toxicity of hexazinone to mammals and birds [sorted by duration / species / formulation / author]

Citation	Formulation	Species/ Strain/Sex	Dose	Exposure	Effects	Comments
Kennedy and Kaplan 1984	>98% pure white crystalline soild	dog/beagle/male,female	0, 200, 1000, or 5000 ppm	90 days, continuous, diet	decreased body weight gain and clinical enzyme changes suggestive of liver damage (although microscopic examination revealed no alterations) at 5000 ppm; no effects observed at 200 or 1000 ppm, compared with controls; NOEL = 1000 ppm	1) groups of four/sex 2) dogs were 10-18 months old 3) during 1st week 5000 ppm group at less feed and lost body weight, so the diet for this group was adjusted to 2500 ppm for 4 days during 2nd week, 3750 ppm for 3 days, and then to 5000 ppm thereafter
U.S. EPA 1982, Newton and Dost 1981	unformulated	dog/beagle/male, female	1000 ppm	90 days, continuous, diet	NOEL; no effects	1) animals were young adults 2) table indicates that NOEL = 1000 ppm 3) clinical pathological examinations were conducted at 30, 60, and 90 days
U.S. EPA 1982, Newton and Dost 1981	unformulated	dog/beagle/male, female	5000 ppm	90 days, continuous, diet	LOAEL; reduced body weight gain, decreased food consumption, elevated alkaline phosphatase, lover albumin:globulin ratios, increased liver weight; no histopathological behavioral, clinical, or other nutritional, biochemical, or gross pathological evidence of toxicity	1) animals were young adults 2) table indicates that NOEL = 1000 ppm 3) clinical pathological examinations were conducted at 30, 60, and 90 days
U.S. EPA 1982, Newton and Dost 1981	unformulated	dog/beagle/male, female	200 ppm	90 days, continuous, diet	NOEL; no effects	1) animals were young adults 2) table indicates that NOEL = 1000 ppm 3) clinical pathological examinations were conducted at 30, 60, and 90 days
Schneider and Kaplan 1983	unformulated	rat/ChR:CD/male, female	200 ppm	90 days, continuous, diet	NOEL; no effects	table indicates NOEL = 1000 ppm
Schneider and Kaplan 1983	unformulated	rat/ChR:CD/male, female	1000 ppm	90 days, continuous, diet	NOEL; no effects	1) table indicates NOEL = 1000 ppm 2) animals were weanlings 3) clinical pathological observations were conducted at 30, 60, and 90 days
Schneider and Kaplan 1983	unformulated	rat/ChR:CD/male, female	5000 ppm	90 days, continuous, diet	LOAEL; decreased body weight and food efficiency in both sexes; no other behavioral nutritional, clinical, biochemical, or pathological evidence of toxicity observed	1) table indicates NOEL = 1000 ppm 2) animals were weanlings 3) clinical pathological observations were conducted at 30, 60, and 90 days

Appendix 1. Oral toxicity of hexazinone to mammals and birds [sorted by duration / species / formulation / author]

Citation	Formulation	Species/ Strain/Sex	Dose	Exposure	Effects	Comments
Kennedy and Kaplan 1984	white crystalline solid (>98% pure)	rat/Crl-CD/male, female	0, 200, 1000, or 5000 ppm	90 days, continuous, diet	no treatment related toxicological or pharmacological effects; rats fed 5000 ppm grew slightly less than lower dose or control group rats; hematology tests and urinalysis in 10 male and 10 female rats from the 0, 1000, or 5000 ppm groups at 1, 2, or 3 months of exposure were unremarkable; furthermore, complete pathological examination (gross necropsy, organ weight data, and light microscopy of tissues) revealed no indication of toxic damage to the rats after dietary exposure	1) diet contained 1% corn oil 2) rats were of weanling age 3) 4 groups of 16 males and 16 females each in feeding study 4) 10 males and 10 females in hematology study
Newton and Dost 1981	unformulated	hamster/NS/male, female	5000 ppm	336 days [48 weeks], continuous, diet	NOEL; no adverse effects	infectious disease interrupted study at 336 days [48 weeks]
Newton and Dost 1981	unformulated	hamster/NS/male, female	5000 ppm	336 days [48 weeks], continuous, diet	NOEL;	
Kennedy and Kaplan 1984	95% pure (1st 18 months)/99% pure (last 6 months)	mouse/CD-1/male, female	0, 200, 2500, or 10,000 ppm	730 days [2 years], continuous, diet	corneal opacity and sloughing and discoloration of distal tip of the tail observed at week 4 in control and treated mice; incidence of tail sloughing and discoloration greater in 2500 or 10,000 ppm treatment groups; no treatment related effects on mortality; survival rates for males were 43/80 at 0 ppm, 41/80 at 200 ppm, 44/80 at 2500 ppm, and 55/80 at 10,000 ppm; survival rates for females were 38/80 at 0 ppm, 54/80 at 200 ppm, 40/80 at 2500 ppm, and 41/80 at 10,000 ppm; general decrease in body weights observed at all treatment levels, but statistically significant at 2500 and 10,000 ppm; at 200 ppm body weights were occasionally significantly less than controls; slight increase in food consumption at 10,000 ppm, but no significant difference in food efficiency ratios between treated mice and controls; no treatment-related hematological effects; liver weights increased significantly at 10,000 ppm; liver changes included hypertrophy of centrilobular parenchymal cells (69/80 males, 22/80 females) at 10,000 ppm and 24/80 males, 0/80 females at 2500 ppm, increased incidence of hyperplastic liver nodules in males (12/80, 10/80, 13/80, and 22/80 at 0, 200, 2500, and 10,000 ppm, respectively), increased incidence and severity of liver cell necrosis (7/80, 7/80, 2/80, and 24/80 at 0, 200, 2500, and 10,000 ppm, respectively); no histopathological effects were observed in males or females at 200 ppm or in females at 2500 ppm; no rare or unusual neoplasms and no evidence of tumorigenic response	1) animals were 4 weeks old 2) males weighed 23-33 g; females weighed 18-26 g 3) 10 mice/sex/group

Appendix 1. Oral toxicity of hexazinone to mammals and birds [sorted by duration / species / formulation / author]

Citation	Formulation	Species/ Strain/Sex	Dose	Exposure	Effects	Comments
Schneider and Kaplan 1983	unformulated	mouse/ChR:CD/male, female	200 ppm	730 days [24 months], continuous, diet	NOEL; no effects	1) animals were weanlings 2) hematology conducted at 1, 3, 6, 12, 18, and 730 days [24 months]
Schneider and Kaplan 1983	unformulated	mouse/ChR:CD/male, female	5000 ppm	730 days [24 months], continuous, diet	AEL;	
Schneider and Kaplan 1983	unformulated	mouse/ChR:CD/male, female	5000 ppm	730 days [24 months], continuous, diet	AEL; nonneoplastic hepatocellular effects in males and females; no behavior, clinical, or nutritional signs of toxicity	1) animals were weanlings 2) hematology conducted at 1, 3, 6, 12, 18, and 730 days [24 months]
Schneider and Kaplan 1983	unformulated	mouse/ChR:CD/male, female	2500 ppm	730 days [24 months], continuous, diet	LOAEL; nonneoplastic hepatocellular effects in males	1) animals were weanlings 2) hematology conducted at 1, 3, 6, 12, 18, and 730 days [24 months]
Schneider and Kaplan 1983	90% wettable powder	rat/ChR:CD/male,F	2500 ppm	730 days [2 years], continuous, diet	AEL; decreased body weight gain and food efficiency in both sexes, decreased food consumption in males, leukocytosis and eosinophilia in males, incrased urine alkalinity in both sexes; no behavioral clinical, pathological or other nutritional and biochemical evidence of toxicity	1) 36 animals per sex per group 2) animals were weanlings 3) clinical pathology evaluated at 1,2,3,6,9, 12, 18, and 730 days [24 months] 4) interim sacrifice at 12 months
Schneider and Kaplan 1983	90% wettable powder	rat/ChR:CD/male,F	200 ppm	730 days [2 years], continuous, diet	NOEL; no effects	1) 36 animals per sex per group 2) animals were weanlings 3) clinical pathology evaluated at 1,2,3,6,9, 12, 18, and 730 days [24 months] 4) table indicates NOEL = 200 ppm
Schneider and Kaplan 1983	90% wettable powder	rat/ChR:CD/male,F	1000 ppm	730 days [2 years], continuous, diet	LOAEL; body weight gain and food efficiency decreased in females	1) 36 animals per sex per group 2) animals were weanlings 3) clinical pathology evaluated at 1,2,3,6,9, 12, 18, and 730 days [24 months] 4) interim sacrifice at 12 months

Appendix 1. Oral toxicity of hexazinone to mammals and birds [sorted by duration / species / formulation / author]

Citation	Formulation	Species/ Strain/Sex	Dose	Exposure	Effects	Comments
Kennedy and Kaplan 1984	94.0% active ingredient (first 14 months)/ 95.8% active ingredient (remainder of study)	rat/Crl-CD/male, female	0, 200, 1000, or 2500 ppm	730 days [2 years], continous, diet	decreased body weights in females at 1000 ppm and in males and females at 2500 ppm, compared with controls; food consumption slightly less among males 2500 ppm during final 3 months of treatment; no signs of toxicity attributed to dietary exposure; no effects on survival; at 2500 ppm, males had slightly elevated leukocyte counts; urine of males and females fed 2500 ppm was more alkaline, compared with controls or other treatment groups; biochemical results were unremarkable except for a decrease in alkaline phosphatase activity in males at 1000 or 2500 ppm no significant differences between treated rats and controls observed at the 1-year sacrifice; at the 2-year sacrifice statistically significant differences between treated rats and controls included increased relative lung weights in males at 1000 ppm, decreased kidney, relative liver and heart weights in males at 2500 ppm, increased liver and spleen weights in females at 200 ppm, and increased stomach and relative brain weights in females at 2500 ppm; at necropsy, pathological findings in treated rats were unremarkable	1) rats were of weanling age 2) two separate control groups were used concurrently 3) rats observed daily for signs of toxicosis

Appendix 2: Reproductive toxicity of hexazinone

Organism	Chemical	Effects	Reference
Mated Sprague-Dawley rats	daily exposure to 0, 40, 100, 400, or 900 mg/kg/day hexazinone on days 7-16 of gestation	effects observed only in dams exposed to 400 or 900 mg/kg/day included alopecia, stained chin and nose, decreased body weight gain, decreased food consumption; and increased relative liver weight. In most cases, the maternal effects observed in the 900 mg/kg/day group were statistically significant ($p \leq 0.05$), compared with controls. In the 400 mg/kg/day group, the maternal effects were minimal and only occasionally statistically significant. developmental effects observed only in the 400 or 900 mg/kg/day groups included decreased fetal weight and an increased number of fetuses with no kidney papilla and with ossified sternebrae. In most cases, the developmental effects observed in the 900 mg/kg/day group were statistically significant ($p \leq 0.05$), compared with the controls. In the 400 mg/kg/day group, the maternal effects were minimal and only occasionally statistically significant. NOELs for maternal and developmental effects = 100 mg/kg/day; LOAELs for maternal and developmental effects = 400 mg/kg/day.	Mullin 1987

Appendix 2: Reproductive toxicity of hexazinone

Organism	Chemical	Effects	Reference
Pregnant New Zealand white rabbits	daily exposure to 0, 20, 50, or 125 mg/kg/day hexazinone on days 6-19 of gestation	maternal effects observed only at 125 mg/kg/day included increased incidence of depression, increased discharge from the eyes; decreased body weight gain, and increased resorptions. developmental effects observed only at 125 mg/kg/day included decreased fetal body weight gain and delayed ossification of the extremeties. NOELs for maternal and developmental effects = 50 mg/kg/day; LOELs for maternal and developmental effects = 125 mg/kg/day.	Serota et al. 1980
male and female Sprague-Dawley rats	dietary exposure to 0, 200, 2000, or 5000 ppm hexazinone for two generations	no effects observed at 200 ppm; effects observed at 2000 or 5000 ppm included decreased body weight gain in P_1 and F_1 females during growth and gestation; decreased food consumption in F_1 females during gestation; decreased pup weight in F_1, F_2, and F_{2b} litters, and decreased pup survival in F_{2b} litters exposed to 5000 ppm. NOELs for systemic effects and reproductive toxicity = 200 ppm (10 mg/kg/day); LOELs for systemic effects and reproductive toxicity were = 2000 ppm (100 mg/kg/day).	Mebus 1991

Appendix 2: Reproductive toxicity of hexazinone

Organism	Chemical	Effects	Reference
4 groups of 6 male and 6 female weanling Crl-CD rats	dietary exposure to 0, 200, 1000, or 5000 ppm hexazinone (white crystalline solid >98% pure) for 94-96 days	no effects observed on fertility, the numbers of young delivered and surviving through lactation period; body weights of progeny at 21 days were lower in 5000 ppm group, compared with other test groups or controls	Kennedy and Kaplan 1984
20 male and 20 female Crl-CD rats	dietary exposure to 0, 200, 1000, or 2500 ppm hexazinone (94.0% a.i.) for three generations	no effects observed on fertility, number of pregnancies, numbers of young delivered and surviving through lactation period; in second and third generations, pups at 2500 ppm had decreased growth rate, compared with controls	Kennedy and Kaplan 1984
25 femaleCrl-CD rats	dietary exposure to 0, 200, 1000, or 5000 ppm hexazinone (97.5% pure) on days 6-15 of gestation	no signs of teratogenicity; lower body weights observed at 1000 and 5000 ppm; food consumption slightly lower at 1000 and 5000 ppm, compared with controls; no significant difference in number of implantation sites, live fetuses, or resorptions; no effects on fetal weight or length; no major fetal abnormalities; and no major skeletal or internal abnormalities in fetuses from dams at 5000 ppm.	Kennedy and Kaplan 1984

Appendix 2: Reproductive toxicity of hexazinone

Organism	Chemical	Effects	Reference
17 female New Zealand white rabbits (weighing 3.0-5.5g)	daily gavage exposure to 0, 20, 50, or 125 mg/kg hexazinone (in 0.5% aqueous methyl cellulose) on days 6-19 of gestation	no signs of teratogenicity; no effects on survival; no signs of maternal toxicity; no effects on pregnancy rates; no significant difference in corpor lutea or implantations/group or in fetal viability or size; the number of resorptions in the 20 and 50 mg/kg groups were lower than those in the control or high dose groups; no treatment related increases in external malformations.	Kennedy and Kaplan 1984

Appendix 3: Eye irritation studies on hexazinone

Organism	Chemical	Effects	Reference
2 rabbits	10 mg powder (unformulated) applied to right eye; eye of one rabbit washed, eye of one rabbit not washed; eyes examined after 1 and 4 hours and 1, 2, 3, 7, and 9 hours	eye irritant: moderate corneal injury and moderate conjunctivitis with no iritic effect in unwashed and slightly less in washed eyes; corneal damage reverted in 9 days in unwashed eye and in 7 days in washed eye	Newton and Dost 1981, Ghassemi et al. 1981, Schneider and Kaplan 1983
6 rabbits	0.1 mL powder (90% soluble) applied to right eyes; eyes examined 24, 48, and 72 hours after treatment	eye irritant: corneal and conjunctival damage in six of six animals through 72 hours	Ghassemi et al. 1981, Schneider and Kaplan 1983
5 rabbits	1 mg powder (90% soluble) applied to right eyes on day 1; days 2-5 one rabbit removed from treatment group; eyes not washed, but examined at 4 hours and on days 1, 2, 3, 4, 5, 7, and 14	three of five eyes had localized corneal opacity, minimal conjunctivitis, and no iritic effect; all effects reversible within 3-14 days; no cumulative effects	Ghassemi et al. 1981, Schneider and Kaplan 1983
2 albino rabbits	48 mg powder applied to right conjunctival sac; after 20 seconds of exposure, treated eye of one rabbit washed with tap water for 1 minute (treated eye of other rabbit not washed); observation of cornea, iris, and conjunctiva with slit lamp at 1 and 4 hours and at days 1, 2, 3, 7, and 14.	eye irritant; in unwashed eye, exposure caused moderate but deep corneal injury 1 day after treatment and mild, superficial vacularizaiton in 14 days; minimal congestion of the iris was observed 4 hours after exposure along with moderate iritis for 2 days after exposure, but not on day 3; pronounced redness, swelling and copious conjunctival dishcarge occurred from 1 hour to 2 days after exposure, with minimal redness present at 7 days, but absent at 14 days. Eye washed within 20 seconds of exposure showed moderate corneal injury, mild conjunctivitis, and no significant iritic effects; eye was normal within 7 days.	Kennedy 1984

Appendix 3: Eye irritation studies on hexazinone

Organism	Chemical	Effects	Reference
9 rabbits	42 mg powder applied to one eye; treated eyes of six rabbits washed; treated eyes of other three rabbits not washed; 28-day post treatment observation period..	In unwashed eyes, mild to moderate corneal cloudiness and severe conjunctivitis were observed; five of the six treated eyes had moderate iritis; four of the six treated eyes had mild to moderate conreal cloudiness with vascularization in the lower portion of the cornea, which persisited until at least day 28; the eyes of the other two rabbits appeared to be normal within 14 days. Washed eyes had slight ot mild corneal cloudiness, moderate iritis, and mild to severe conjunctivitis, with recovery taking place within 21 to 28 days.	Kennedy 1984
6 rabbits	0.1 mL (23.3 mg) powder (66% wettable) applied to right eyes; eyes examined on days 1, 2, 3, 7, and 14	eye irritant: corneal opacity observed in three of six animals on day 7 and in two of six animals on day 14	U.S. EPA 1982
9 rabbits (New Zealand white)	0.1 mL 0.5% liquid hexazinone applied to left eyes; eyes of six rabbits washed, eyes of three rabbits not washed; eyes examined at 24, 48, and 72 hours and on days 4 and 7	no corneal opacity, iritis or conjunctive irritation	U.S. EPA 1982
9 rabbits (New Zealand white)	0.1 mL (42 mg) unform-ulated hexazinone applied to right eyes; eyes of three rabbits washed, eyes of six rabbits not washed; eyes examined and on days 1, 2, 3, 4, 7, 14, 21, and 28 and scored according to Draize	mild to moderate corneal cloudiness and severe conjunctivitis in six of six unwashed eyes; moderate iritis in five of six eyes that reversed to normal in two of six eyes within 14 days; corneal injury persisted through 28 days in four of six unwashed eyes; slight to mild corneal cloudiness, moderate iritis, and mild to severe conjunctivitis in washed eyes; all washed eyes normal in 21 days	Schneider and Kaplan 1983
2 rabbits	10 mg 89.3% a.i. hexazinone to right conjunctival sac; eye of one rabbit washed, eye of one rabbit not washed; eyes examined after 1 and 4 hours and on days 1, 2, 7 and 14	mild corneal opacity persisted 14 days in both treated eyes; transient mild to moderate conjunctivitis observed in both treated eyes	Schneider and Kaplan 1983

Appendix 3: Eye irritation studies on hexazinone

Organism	Chemical	Effects	Reference
2 rabbits	0.1 mL powder (90% wettable diluted in water to 4% a.i.) to right conjunctival sac; eye of one rabbit washed, eye of one rabbit not washed; eyes examined after 1 and 4 hours and on days 1, 2, and 3	moderate to mild conjunctival irritation in unwashed eye was normal within 3 days; minimal conjunctivitis in washed eye was normal in 1 day	Schneider and Kaplan 1983
6 rabbits	0.1 mL (25% liquid) hexazinone applied to right eyes; eyes examined at 24, 48, and 72 hours	eye irritant: corneal iritic and conjunctival injury in all animals through 72 hours	Schneider and Kaplan 1983
2 rabbits	0.1 mL (25% liquid) hexazinone applied to right conjunctival sac; eye of one rabbit washed, eye of one rabbit not washed; eyes examined after 1 and 4 hours and on days 1, 2, and 3, 7, and 14	moderate corneal damage; moderate iritis with flare, and severe to moderate conjunctival irritation in unwashed eyes with slightly less severe effects in washed eyes; all effects reverted to normal in 14 days in unwashed eyes and in 7 days in washed eyes	Schneider and Kaplan 1983
9 rabbits	0.1 mL (25% liquid) hexazinone applied to right eyes; eyes of three rabbits washed, eyes of six rabbits not washed; eyes examined and on days 1, 2, 3, 4, 7, 14, and 21 and scored according to Draize	mild to severe corneal irritation, slight to moderate iritis, and severe conjunctivitis in unwashed eyes with corneal effects and conjunctivitis lingering at 21 days; mild to moderate corneal irritation, moderate to severe conjunctivitis and slight iritis in washed eyes; all cleared except corneal opacity in one eye at 21 days	Schneider and Kaplan 1983
6 rabbits	0.1 mL (25% liquid) hexazinone applied to right conjunctival sac; eyes of three rabbits washed with tap water, eyes of three rabbits not washed; eyes examined after 1 and 6 hours and on days 1, 2, 3, 4, 7, 14, 21, 29, and 35 by ophthalmoscope and biomicroscope (U.K. Procedure)	severe to moderate corneal cloudiness with moderate iritis and conjunctivitis in unwashed eyes; corneal effects persisted 35 days; iritic and conjunctival effects reverted in 21 days; mild to moderate corneal moderate cloudiness	
2 rabbits	0.1 mL (25% liquid diluted in water to 4% a.i.) hexazinone applied to right conjunctival sac; eye of one rabbit washed, eye of one rabbit not washed; eyes examined after 1 and 4 hours and on days 1, 2, and 3	mild to minimal conjunctival irritation and no corneal or iritic involvement in unwashed and washed eyes; washed eye normal in 3 days and washed eye normal in 1 day	Schneider and Kaplan 1983

Appendix 3: Eye irritation studies on hexazinone

Organism	Chemical	Effects	Reference
9 rabbits	0.1 mL (5% liquid) hexazinone applied to right eyes; eyes of three rabbits washed, eyes of six rabbits not washed; eyes examined and on days 1, 2, 3, 4, 11, and 14 and scored according to Draize	mild corneal cloudiness moderate iritis and moderate conjunctivitis observed in all unwashed eyes; all effects reversed within 14 days; slight corneal cloudiness in one washed eye and moderate conjunctivitis in three washed eyes; all effected reverted in 4 days	Schneider and Kaplan 1983
9 rabbits (New Zealand white)	0.1 mL (1.25% liquid) hexosane applied to left eyes; eyes of three rabbits washed, eyes of six rabbits not washed; eyes examined at 24, 48, and 72 hours and scored according toDraizee	no ocularr irritation	Schneider and Kaplan 1983

Appendix 4: Dermal toxicity and irritation studies with hexazinone

Organism	Chemical	Effects	Reference
3 male rabbits	single dose of 60 mL 90% soluble powder (24% aqueous suspension) applied to intact skin on shaved trunk area and covered with gauze and occlusive wrappings for 24 hours	Approximate lethal dose of 5278 mg/kg bw; mild erythema in one animal; all animals had normal appearance and behavior by 24 hours after treatment	Ghassemi et al. 1981, Schneider and Kaplan 1983
6 male rabbits	0, 68, or 680 mg a.i./kg bw 90% soluble powder applied to intact skin and covered with gauze and occlusive wrappings; 6 hours/day for 10 days; clinical and pathological examination conducted on all animals at sacrifice	transient elevation in glutamicpyruvic transaminase activity at 680 mg a.i./kg bw; no evidence of liver or other tissue injury	Ghassemi et al. 1981, Schneider and Kaplan 1983
6 male rabbits	0, 35, 150, or 770 mg a.i./kg bw 90% soluble powder applied to intact skin and covered with gauze and occlusive wrappings; 6 hours/day for 10 days; blood analyzed on days 14, 28, and 53 after treatment	transient elevation in glutamicpyruvic transaminase activity at 770 mg a.i./kg bw; no evidence of liver or other tissue injury	Ghassemi et al. 1981, Schneider and Kaplan 1983
3 male rabbits (weighing between 2.5 and 2.9 kg)	5278 mg/kg bw hexazinone (93% active technical formulation) applied as 24% aqueous suspension to shaved trunk (approximately 10% total body surface area) using gauze pads that surrounded trunk and were wrapped with Saran wrap Kling bandages and Elastoplast adhesive; 24 hours after treatment, rabbits were unwrapped and and the treated area was washed with tap water; application site was observed daily for 14 days .	rabbits showed transient signs of of skin irritation; one of three treated rabbits had mild erythema immediately after 24-hour exposure but recovered within 24 hours after application site was unwrapped and rinsed with tap water; all three treated rabbits appeared normal during the 14-day observation period.	Kennedy 1984
6 male rabbits (weighing between 2 and 2.5 kg)	0, 70, 06 680 mg/kg/day hexazinone (aqueous suspension) on gauze pads applied and wrapped onto shaved trunks for contact of 6 hours/day for 10 consecutive days; application sites were rinsed with warm water and patted dry.	no skin irritation or toxic signs observed at any dose level; no cellular damage to liver, despite trend toward increased SAP and SGPT levels. ***NOTE: this study was repeated (see entry below)***	Kennedy 1984

Appendix 4: Dermal toxicity and irritation studies with hexazinone

Organism	Chemical	Effects	Reference
6 male rabbits (weighing between 2 and 2.5 kg)	0, 35, 150, 770 mg/kg/day hexazinone (aqueous suspension) on gauze pads applied and wrapped onto shaved trunks for contact of 6 hours/day for 10 consecutive days; application sites were rinsed with warm water and patted dry.	SAP and SGPT levels elevated at 770 mg/kg/day, but not at 150 mg/kg/day; enzyme activities normal in all treated rabbits after 53 days of recovery.	Kennedy 1984
male albino rabbit (number not specified)	0.5 g 60% dry flowable hexazinone applied to intact and abraded skin under gauze	not a primary irritant	U.S. EPA 1982
5 male and 5 female New Zealand white rabbits	2 g/kg 0.5% liquid hexazinone applied to abraded skin and covered with occlusive wrappings for 24 hours; observations made at 1, 3, 7, 10, and 14 days	LD_{50} >2 g/kg	U.S. EPA 1982
10 male guinea pigs	0.05 mL unformulated hexazinone (25 and 50% suspension in distilled water) applied to shaved intact shoulder skin followed by examination after 24 and 48 hours	no skin irritation	U.S. EPA 1982
10 male guinea pigs	sensitization induced by 4 weekly intradermal injections of 0.1 mL of 1% test material in dimethyl-phthalate; 13 days after last injection, the animals were topically challenged with 0.05 mL unformulated hexazinone (25 and 50% aqueous suspension) and examined after 24 and 48 hours	no skin sensitization	U.S. EPA 1982
1 male rabbit	single dose of 2250, 3400, 5000, or 7500 mg/kg bw applied to intact skin and covered with gauze and occlusive wrappings for 24 hours; observed for 14 days after treatment	LD_{50} >7500 mg/kg bw; no mortalities or adverse clinical effects	Schneider and Kaplan 1983
5 male rabbits	single dose of 7500 mg/kg bw applied to intact skin and covered with gauze and occlusive wrappings for 24 hours; observed for 14 days after treatment	LD_{50} >7500 mg/kg bw; no mortalities or adverse clinical effects	Schneider and Kaplan 1983

Appendix 4: Dermal toxicity and irritation studies with hexazinone

Organism	Chemical	Effects	Reference
5 male and 5 female New Zealand white rabbits	single dose of 2000 mg/kg bw applied to abraded skin and covered with gauze and occlusive wrappings for 24 hours; observed for 14 days after treatment then sacrificed; two animals per sex given gross and microscopic examination of treated skin	LD_{50} >2000 mg/kg bw; moderate skin irritation at 24 hours, normal by 14 days; no gross or microscopic pathological abnormalities	Schneider and Kaplan 1983
6 male rabbits	9100 mg/kg bw 66% wettable powder (63% aqueous paste) applied to intact skin covered with gauze and occlusive wrappings for 24 hours; observed for 14 days	LD_{50} >9100 mg/kg bw (600 mg/kg a.i.); moderate irritation at 24 hours, normal at 7 days	Schneider and Kaplan 1983
6 male New Zealand white rabbits	applied 0.5 g unformulated solid test material (moistened with saline) to two intact and two abraded areas of skin on each animal and covered treated areas for 24 hours; treated areas washed and scored according to Draize after 48, 72, and 96 hours	not a primary skin irritant; Draize scores from 0.5-1.5	Schneider and Kaplan 1983
6 male New Zealand white rabbits	applied 0.5 g 25% liquid hexazinone (moistened with saline) to two intact and two abraded areas of skin on each animal and covered treated areas for 24 hours; treated areas washed and scored according to Draize after 24 and 72 hours	not a primary skin irritant; Draize scores from 0.0-0.75	Schneider and Kaplan 1983
6 male New Zealand white rabbits	applied 0.5 g 66% wettable powder (moistened with saline) to two intact and two abraded areas of skin on each animal and covered treated areas for 24 hours; treated areas scored according to Draize after 24 and 72 hours	not a primary skin irritant; Draize scores = 0	Schneider and Kaplan 1983
5 male and 5 female New Zealand white rabbits	50 mg/kg/day technical grade hexazinone applied to intact skin; animals were exposed 6 hours/day for 21 days	no effects	Malek 1989

Appendix 4: Dermal toxicity and irritation studies with hexazinone

Organism	Chemical	Effects	Reference
5 male and 5 female New Zealand white rabbits	400 mg/kg/day technical grade hexazinone applied to intact skin; animals were exposed 6 hours/day for 21 days	no effects	Malek 1989
5 male and 5 female New Zealand white rabbits	1000 mg/kg/day technical grade hexazinone applied to intact skin; animals were exposed 6 hours/day for 21 days	no effects	Malek 1989
10 guinea pigs (sex not specified)	1 drop (approximately 0.05 mL) 25 or 50% distilled water suspension applied to separate areas of shaved intact shoulder skin; primary irritation scored at 24 and 48 hours after treatment; to test for sensitization, guinea pigs received intradermal injections of 0.1 mL hexazinone (1% solution in dimethyl phthalate) in dorsal sacral region once/week for 4 weeks; 2-week rest period followed by topical application of 0.5 mL of 25 of 50% aqueous suspension to shaved shoulder; control group consisted of 10 previously untreated guinea pigs given a similar challenge.	no skin irritation or evidence of dermal sensitization in any of the treated guinea pigs	Kennedy 1984
male guinea pig (number not specified)	0.05 mL 100% test material (25% liquid hexazinone) and 10% solution of test material in distilled water applied to shaved intact shoulder skin followed by examination after 24 and 48 hours	mild transient irritation at 100%	Schneider and Kaplan 1983
10 male guinea pigs	sensitization induced by 4 weekly intradermal injections of 0.1 mL of 1% test material in saline; 13 days after last injection, the animals were topically challenged with 0.05 mL 100% test material and 10% test material in distilled water and examined at 24 and 48 hours	no sensitization	Schneider and Kaplan 1983

Appendix 5: Inhalation studies with hexazinone

Organism	Chemical	Effects	Reference
Rats	Hexazinone, Batch #GG1-15	LC_{50} of 3.94 mg/L	Shapiro 1990,[MRID 41756701]
10 male ChR:CD rats	single 1-hour exposure to 2.94, 5.14, or 7.48 mg/L unformulated hexazinone (median diameter 3.5 μm and at least 46.3% of particles <3.2 μm)	ALD>7.48 mg/L; 100% survival; irregular respiration and salivation; no deaths.	Ghassemi et al. 1981, Schneider and Kaplan 1983
male ChR:CD rats (number not specified)	head only exposure to 2.0 mg/L 90% wettable powder 6 hours/day for 15 days with 2 days rest after 5th and 10th exposure; mass median diameter 7.85 μm with 28.7% of particles <3.2 μm	all animals survived; no clinical or histopatho-logical findings	Ghassemi et al. 1981, Schneider and Kaplan 1983
10 male rats (200-300 g)	1-hour exposure to 2.94 (±0.07) mg/L hexazinone particles suspended in 20 L glass cylinder	0/10 died	Kennedy 1984
10 male rats (200-300 g)	1-hour exposure to 5.14 (±2.51) mg/L hexazinone particles suspended in 20 L glass cylinder	0/10 died	Kennedy 1984
10 male rats (200-300 g)	1-hour exposure to 7.48 (±0.95) mg/L hexazinone particles suspended in 20 L glass cylinder	0/10 died; LC50 >7.48 mg/L	Kennedy 1984
5 male and 5 female Sprague-Dawley rats (261-338 g)	4-hour exposure to 5.0-5.5 ppm 0.5% liquid hexazinone	normal behavior	U.S. EPA 1982
6 male ChR:CD rats (weighed and observed for 14 days)	single 1-hour exposure to 0, 4.1, 6.1, 7.3 mg/L 90% wettable powder (mass median diameters 10.5 and 6.0μm in mid and high concentrations, 28.3 and 18.7% particles <3.2 μm in mid and high concentrations, respectively)	ALD>7.3 mg/L; no deaths	Schneider and Kaplan 1983

Appendix 5: Inhalation studies with hexazinone

Organism	Chemical	Effects	Reference
10 male ChR:CD rats (observed for 14 days after exposure; at sacrifice 5 test and 5 control rats examined for changes in gross and microscopic pathology)	repetitive head only exposure to 0 or 2.0 mg/L 90% wettable powder 6 hours/day 5 days/week for 3 weeks (mass median diameter of particles was 7.85 μm with 28.7% <3.2 μm)	no deaths; no treatment related clinical or pathological abnormalities	Schneider and Kaplan 1983

Appenxix 6: Summary of field or field simulation studies on hexazinone formulations

Application	Observations	Reference
Hexazinone residues of 0.24-1.15 mg/kg in soil samples taken from seven sites in New South Wales, Australia in 1988. The area had been sprayed previously (date not specified) with bromacil (Hyvar x'®).	Possible association between damage to trees and shrubs and the unexpected detection of hexazinone ('Velpar'®) at four of the examined sites (bromacil was detected at five of the sites). Patterns of dead native flora suggest that hexazinone may have moved through soil layers away from its target area and affected or destroyed the xerophytic native species. The movement of hexazinone may have been aided by the event of unusually heavy rainfall (327.8 mm/annum) in 1987, compared with the average rainfall of 226 mm/annum).	Allender 1991
1.0 kg a.i./ha hexazinone (formulation not specified)	The vertical distribution of dominant mite groups in the treated plots was different from control plots [i.e., in hexazinone treated plots, mite density was significantly less in the upper layers (0-7.5 and 7.5-15.0 cm) of soil, and unusually high (especially for *Annectacarus* sp.) in the deeper layers (15.0-22.5 cm). The downward migration of the mites is more likely due to rain than to toxicity. Furthermore, the effect on mites is secondary to the effect on vegetation.	Badejo and Akinyemiju 1993, 1994
Broadcast application of hexazinone (Pronone 5G®) granules at 1 lb a.i./acre to vegetation on 0.25 acre (65 x 168 ft) plots of loblolly pine (*Pinus taeda*). The study area consisted of a 40-acre tract in Oktibbeha County, Mississippi. The soil in the study area consisted of Falkner silt loam with slopes of 0-5%. Granular hexazinone was applied by helicopter with an Isolair spreader bucket.	Total plant biomass was significantly greater ($P<0.10$) on control plots, compared with plots treated by broadcast application of Pronone 5G, during the first growing season; however differences were not apparent by the end of the second growing season The amount of foraging by white-tailed deer (Odocoileus virginianus) was significantly less ($P<0.10$) on plots treated by broadcast application of Pronone 5G, compared with control plots, after the first year's growth, but there were no differences during the second growing season.	Blake et al. 1987

Appenxix 6: Summary of field or field simulation studies on hexazinone formulations

Application	Observations	Reference
Banded application of liquid hexazinone (Velpar L®) at 1 lb a.i./acre to vegetation on 0.25 acre (65 x 168 ft) plots of loblolly pine (*Pinus taeda*). The study area consisted of a 40-acre tract in Oktibbeha County, Mississippi. The soil in the study area consisted of Falkner silt loam with slopes of 0-5%. Liquid hexazinone was applied with pressurized, hand-pump, backpack sprayers.	Total plant biomass was significantly greater ($P<0.10$) on control plots, compared with plots treated by banded application of Velpar L, during the first growing season; however differences were not apparent by the end of the second growing season The amount of foraging by white-tailed deer (Odocoileus virginianus) was significantly less ($P<0.10$) on plots treated by banded application of Velpar L, compared with control plots, after the first year's growth, but there were no differences during the second growing season.	Blake et al. 1987
Broadcast application of hexazinone (Pronone 5G®) granules at 3 lbs a.i./acre to a 390-acre tract of loamy sands in Georgia on May 25, 1990. A prescribed burn took place in October 1990. The hexazinone was broadcast with an Omni spreader	1 year after treatment, the areas treated with hexazinone produced more food plants for bobwhite quail (*Colinus virginianus*) and white-tailed deer (*Odocoileus virginianus*), than did the areas treated with picloram, triclopyr, or imazapyr. In addition, the diversity of herbaceous plant species and woody plant species was lowest in the areas treated with hexazinone than in the areas treated with the other herbicides.	Brooks et al. 1993
Liquid hexazinone (Velpar L®) applied at 2.0 kg a.i./ha to Fleming Creek experi-mental watershed in Arkansas. The terrain was characterized by fine sandy loam surface horizons and stony clay loam subsoils, with average slopes of 30%. The liquid formulation of hexazinone was applied using spot-gun sprayers.	4 days after application, following a light rainfall of 0.6 cm, the concentration of hexazinone in stream discharge was 1μg/L; the highest hexazinone concentration in stream water was 14μg/L in a 1-hour period during high stream discharge after a heavy rainfall of 5.6cm; hexazinone was stable in incubated stream water, with 50% disappearance of the compound over several years. In soil, hexazione degradation followed first-order kinetics and had a half-life of 77 days, with no differences noted in degradation rates between the two soils. The amount of applied hexazinone returned to the forest floor as leaf deposition was <0.10%, as indicated by analyses of collected oak leaf and leaf litter on the forest floor.	Bouchard et al. 1985

Appenxix 6: Summary of field or field simulation studies on hexazinone formulations

Application	Observations	Reference
Broadcast applications of 0.7, 1.1, or 2.5 kg a.i./ha liquid hexazinone (Velpar L®) or 1.0 or 1.7 kg a.i./ha granular hexazinone (Pronone 10G®) were made to randomly selected 0.6-0.8 ha plots of loblolly pine (*Pinus taeda* L.) in central Georgia. The liquid formulation was applied using a spray system mounted on a crawler-tractor; the granules were applied using a similarly-mounted spreader system..	There were no observed effects on species richness or diversity 7 years after treatment; however, hexazinone treatments significantly decreased the number of water oaks (*Quercus nigra* L.), compared with the controls.	Boyd et al. 1995
Hand applications of hexazinone granules (Pronone 5G®) at 1, 2, or 8 kg a.i./ha were made to 4 m^2 blocks of sandy loam soil in Ontario, Canada.	Hexazinone treatments had no effect on fungal and bacterial populations 2 and 6 months after application; carbon dioxide evolution was not affected by any of the three application rates.	Chakravarty and Chatarpaul 1990
Ground spray application of 2.2, 4.5, or 6.7 kg/ha hexazinone (commercial formulation of 240 g a.i./L) to 3 x 4 m plots of Elkton silt loam soil having a 0-2% slope. The plots, which were in Prince Geroge's County, MD, were plowed, disced, and harrowed and treated in May 1988. Field investigations were conducted from 1988 through 1991. Different kinds of vegetation including, wheat *Triticum aestivum* L.), kidney bean (*Phaseolus vulgaris* L.), field corn (*Zea mays* L.), summer squash (*Cucurbita pepo* L.), okra [*Abelmoschus esculentus* (L.)], potato (*Solanum tuberosum* L.), and dwarf banana (*Musa acuminata* Colla) were planted at various times after application.	Only potato tolerated residual hexazinone through the last planting (436 days after application). Corn did not tolerate hexazione through the 1988 growing season (82 days after application); however, by the middle of the 1989 growing season sufficient degradation of the herbicide resulted in corn tolerance at application rates of 2.2 and 4.5 kg/ha. None of the other crops tolerated hexazinone for the duration of the investigation. Indigenous plant species were not established in 50% of the hexazinone treated plots by August 1989, but completely covered the plots by midsummer 1990.	Coffman et al. 1993
Hexazinone (NOS) was applied at a rate of 0.5 or 1.0 kg/ha to alfalfa stands in Melfort, Saskatchewan each spring from 1978 to 1981. The treated plots were 2.5 x 6.0 m of silty-clay loam soil. The compound was applied using 8001 flat fan spray nozzles mounted on a small tractor.	Hexazinone did not injure the alfalfa or significantly affect nectar sugar production.	Curry et al. 1995

Appenxix 6: Summary of field or field simulation studies on hexazinone formulations

Application	Observations	Reference
Hexazinone (NOS) was applied at a rate of 0.5 or 1.0 kg/ha to alfalfa at two sites (Shellbrook and Zenon Park) in 1985. The herbicide was applied to one half of each 6.0 x 7.0 plot in late October 1986 and to the other half in late April 1987. Repeat applications were made in late October 1987 and late April 1988.	Spring and fall applications of hexazinone caused temporary stunting of the alfalfa at both sites in 1988. Applications of 1.0 kg/ha hexazinone, compared with the lower application rate, increased nectar sugar production significantly ($P<0.03$) at the Shellbrook site. At the same site, hexazinone applications made in the late fall also significantly ($P<0.01$) increased nectar sugar production, compared with early spring applications. At Zenon Park, there was no significant effect on nectar sugar producation in early August.	Curry et al. 1995
Hexazinone (NOS) was sprayed annually at a rate of 2 kg/ha on approximately 0.6 ha at Bremervold, Denmark from the spring of 1987 onwards (NOS). The plough layer of soil consisted of sandy loam.	Water samples collected by means of stainless steel tubes inserted into the soil indicated that hexazinone concentrations ranged from 0.07 to 2.09 μg/L.	Felding 1992
Hexazinone (NOS) was sprayed annually at a rate of 2 kg/ha on approximately 8 ha at Koege, Denmark from the spring of 1985 onwards (NOS). The plough layer of soil consisted of sandy loam.	Water samples collected by means of stainless steel tubes inserted into the soil indicated that hexazinone concentrations ranged from 3.47 to 42.66 μg/L, and a single metabolite [3-cyclohexyl-6-methylamino-1-methyl-1,3,5-triazine-2,4(1*H*,3*H*)-dione] was detected in the sample with the highest concentration of hexazinone.	Felding 1992

Appenxix 6: Summary of field or field simulation studies on hexazinone formulations

Application	Observations	Reference
Velpar L (4.3 kg a.i./ha) was applied May 5, 1984 by a Bell-47 helicopter with MICROFOIL boom to 12 x 12 m plots of white spruce in Peace River area, British Columbia. The average slope of the plots was 5-10%. A 4-day rainfall amounting to 3.64 mm of rain occurred on May 6, 1984.	Soil samples from three depths including, a surface organic layer, and mineral layers at 0-15 and 15-30 cm were collected during prespray and at days 9, 23, 55, and 104 after treatment (see Table 1 of this reference for data). Degradation and dissipation accounted for 66% of the hexazinone at the end of the 104-day monitoring period. 3-(4-hydroxycyclohexyl)-6-(dimethylamino)-1-methyl-1,3,5-triazine-2,4(1H,3H)-dione, a hydroxylation product of hexazinone (metabolite A) was detected 9 days after treatment and persisted throughout the sampling periods and represented 30-50% of the hexazinone concentration per sample. 3-cyclohexyl-6-(methylamino)-1-methyl-1,3,5-triazine-2,4(1H,3H)-dione, a demethylation product of hexazinone (metabolite B) represented 0-10% of the hexazinone concentration per sample. Leaching from the surface organic layer of the forest floor to the mineral layer of soil at 15 cm was detected only in the sample taken on day 55. The mineral contained approximately 14% hexazinone and 20% metabolite A of that found in the organic layer. Metabolite B was not detected in the 55-day sample, and there were no detectable residues beyond the 15-cm mineral layer. No quantifiable residues of hexazinone or its metabolites were detected 20 and 40 m outside and downslope of the treated plot during the 104-day monitoring period.	Feng 1987

Appenxix 6: Summary of field or field simulation studies on hexazinone formulations

Application	Observations	Reference
Velpar L (liquid formulation of hexazinone) was applied by backpack sprayer to 42.5 x 50 m plots of silty loam to sand clay (covered by 8-cm layer of organic soil) in Edmonton, Alberta Canada. The hexazinone was applied at an estimated rate of 3 kg/ha on September 18, 1986.	Hexazinone residues in soil samples collected immediately after spraying were 3.8 kg/ha (using the glass jar method of recovery) and 0.8 kg/ha (using the corer method of recovery). In the postwinter samples collected using the corer method of recovery, hexazinone residues in the 0-15 cm soil layers were equivalent to 1.5 kg/ha 210 days after application and 0.25 360 days after application. In the 15-30 cm soil layers, hexazinone residues were equivalent to 0.5 kg/ha 210 days after application and 0.1 kg/ha 360 days after application. The authors conjecture that the unusually long dissipation time (206 days) for 50% of hexazinone in the 0-30 cm layer of soil was probably due to the late application in fall and the frozen ground in winter.	Feng and Navratil 1990
Pronone 10G® applied as a surface coat to determine the release of hexazinone residue from a granular formulation under forest conditions. The study site was located northwest of Edmonton, Alberta Canada.	The amount of hexazinone released from the granules depended on the length of the exposure period and the cumulative amount of rainfall, as determined by multiple regression analysis.	Feng et al. 1989
Pronone 10G® (a granular formulation containing 10% (w/w) surface-coated hexazinone) was applied at rates of 0, 2, or 4 kg a.i./ha on August 28, 1986 to three 1.6 ha plots (2% slope) that were part of a 3-year-old clear-cut forest of predominantly 1 m high Apen in Grande Prairie, Alberta Canada. The soil at the study sitel was silty clay to clay in texture. The hexazinone was applied by a helicopter equipped with an Isolair Series 2600-45 Applicator-Spreader.	The transport of hexazinone through soil as deep as 80 cm can result when heavy precipitation or snow melt causes active soil water percolation. In this study, however, hexazinone concentrations in soil were extremely low (0.5 ppm) at the end of the 448-day monitoring period (see text of paper for details).	Feng et al. 1989

Appenxix 6: Summary of field or field simulation studies on hexazinone formulations

Application	Observations	Reference
Pronone 10G® (granualar formulation of hexazinone) was aerially applied to 80 x 200 m plots in a logged stand of 80% 50-65 year old aspen (*Populus tremuloides*) and 20% white spruce (*Picea glauca*) and lodgepole pine (*Pinus contorta*) in Alberta Canada on August 28, 1986. The hexazinone was applied by a Bell-206 helicopter equipped with an Isolair Series 2600-45 Applicator-Spreader at a an average rate of 2.3 or 4.1 kg a.i./ha. In May 1987, the study site was planted with "plug +1" white spruce and "container grown" lodgepole pine. The vegetation in the study site was comprised of grasses, shrubs and aspen regrowth. The soil was gleyed solonetzic grey soil.	The average residues levels of hexazinone in the 0-10 cm surface layer of soil 1 year after application were 0.25 (±0.09) kg/ha in the plot treated with 2.3 kg a.i./ha and 0.40 (±0.02) kg/ha in the plot treated with 4.1 kg a.i./ha. The ratio of vertical distribution of hexazinone residues at soil depths of 0-10, 10-20, and 20-30 cm was 10:11:2 in the plot treated with 2.3 kg a.i./ha and 10:5:2 in the plot treated with 4.1 kg a.i./ha. The two metabolites of hexazinone, 3-(4-hydroxycyclohexyl)-6-(dimethyl-amino)-1-methyl-1,3,5-triazine-2,4(1*H*,3*H*) dione and 3-cyclohexyl-6-methylamino-1-methyl-1,3,5-triazine-2,4(1*H*,3*H*)-dione, accounted for 15% and 30% of hexazinone residues, respectively. Hexazinone was detectable at a depth of 40 cm in both the 2.3 and 4.1 kg a.i./ha treated plots 2 years after application. In the plot treated with 2.3 kg a.i./ha, trace amounts of the compound were detectable at 130 cm.	Feng et al. 1992
Broadcast applications of two formulations of hexazinone Velpar Brush Killer ® (0.5 cc pellets, 10% a.i., applied by hand) and Velpar L® (2 lb a.i./gal liquid, applied as foliar spray) were made at 0.6x, 1.0x, 1.4x and 2.0x the normal use rate. The applications took place in the spring of 1986. The 30 x 150 ft treatment plots having various soil characteristics were located in seven areas across the South.	There was a positive correlation between pine mortality and hexazinone treatment at four of the study sites. At two of the sites, mortality was significantly greater as a result of the pellet formulation, compared with the liquid formulation of hexazinone.	Glover et al. 1991
Broadcast application of hexazinone (NOS) in September 1984 and 1985 to gently sloping (1%-3%) plots of loblolly pine seedlings planted in 1981.	Pines were large enough in the third growing season to tolerate treatment with hexazinone. The produciton of competing vegetation was significantly reduced by the herbicide treatment.	Haywood 1994
Velpar®L was applied at a rate of 3.0 kg a.i./ha (89% of manufacturer's recommended rate of 3.36 kg a.i./ha) in April 1986 to a forest stand comprised of a loblolly pine-hardwood mixture. The soil in the Louisiana study area is composed of Beauregard silt loam. Two low intensity backfire burns were executed in December 1985 and March 1989.	Hexazinone treatment significantly reduced the rate of hardwoods in the study site; however, treatment (burn or chemical) had no effect on the rate of herbaceous plant development.	Haywood 1995

Appenxix 6: Summary of field or field simulation studies on hexazinone formulations

Application	Observations	Reference
Velpar L was applied by a backpack mist blower at a rate of 19.5 kg a.i./ha (11 times higher than recommended, by error). The study site was located in Gambo Pond, Newfoundland and was dominated by black-spruce stand (*Picea mariana*). The soil was described (under the Canadian System of Soil Classification) as Orthic Humo Ferric Podzol, was well-drained, and had a sandy loam texture.	90% of applied hexazinone disappeared in less than 486 days; the t_{50} = 186 days. (See text of paper for details; note kinetics in Figure 2 on page 135.)	Helbert 1990
Treatment 1: Hexazinone (Velpar 90% SP) was applied to native blueberry fields on the Pugwash and Tormentine sandy loam sites at rates of 2 and 4 kg/ha in either November 1980 or May 1981 and soil samples were collected on May 2 (for fall treatments), July 6, Dec 3, 1981 and April 28, 1982. Treatment 2: Hexazinone was applied to newly burned commercial blueberry fields at 2.0 kg/ha in May 1984, and soil samples were collected on the day of application, and July 19, and Nov 20.	Although hexazinone dissipates rapidly from soil in blueberry fields, the rate of dissipation was greater in the newly burned, commercial blueberry fields than in the sandy loam native blueberry fields.	Jensen and Kimball 1987
60 L of Velpar L (liquid formulation of hexazinone) was surface-applied to a 10-ha steep forested watershed (average slope of 40%) area of silt loam soil. The hexazinone formulation was applied using a spot-gun applicator at an application rate of 1.36 kg/ha.	Hexazinone concentrations in stream water, soil, leaves, and sediment were monitored for 43 months after application. The maximum concentration in the stream was 16 mg/m^3, the maximium runoff concentration was ~4 mg/m^3, and the maximum residues on leaves was ~<1.0 mg/kg.	Lavy et al. 1989
Aerial application of hexazinone as Dupont Velpar L Weed Killer Water Miscible Liquid at a rate of 2 kg/ha (spray volume 60 L/ha) to a 46.4-ha area of open forest in Victoria Australia. The soil in the treated area was composed of gravelly clay loams. The hexazinone formulation, which included a carrier of water and petroleum oil (33% v/v Ulvapron), was applied from a ell Jetranger 206B helicopter fitted with a 10.9 m boom spray on December 16, 1981.	Of the 69 streamwater samples taken every 0.25-2.0 hours during the 9-week study period, only six samples contained concentrations of 4μg/L of hexazinone; the remaining samples contained levels less than the lowest detectable concentration of 2 μg/L. The low residues levels of hexazinone in streamwater following aerial application were attributed partly to the presence of a 30 m wide vegetation reserve on either side of the stream.	Leitch and Flinn 1983
Hexazinone pellets (Velpar® Gridballs®) were applied by hand at a rate of 0.3, 0.6 or 0.9 lbs/acre to 28 0.2-acre plots characterzied by loamy siliceous, hyperthermic Arenic Hapludulf soil in Florida.	Hexazinone at all three application rates significantly reduced the the number of oaks in the treatment area.	Long and Flinchum 1992

Appenxix 6: Summary of field or field simulation studies on hexazinone formulations

Application	Observations	Reference
Hexazinone (90% w/w/ w.s.p.) was applied at rates of 0.2, 0.6, or 1.8 kg a.i./ha to glasshouse pots of *Stellaria media* L, *Polygonum lapathifolium* L., *Poa annua* L., and turnip.	Hexazinone treatments (incorporated or surface applied) resulted in significantly lower weights of all four species. At the lower application rates, hexazione had a greater effect on the organic fine sandy loam than on the peat. Furthermore, incorporation was more effective than surface application.	May 1978
Hexazinone pellets (10% a.i.; pellet size-2 cm^3) were applied by hand at a rate of 16.8 kg/ha to four of five 1-ha watersheds in April 1979; one watershed area served as a control. The soil in the treated area was mostly Cecil sandy loam and the areas were made up of mostly hardwood-pine stands. The study area was located int he Chattahoochee National Forest in Georgia.	During the 8-month monitoring period, residue levels in terrestrial invertebrates were 1-2 times greater than residues in forest floor material (i.e., litter and decomposed humus material above the mineral soil); aquatic organisms were exposed to intermittent concentrations of 6-44 ppb; residues were generally not detected in aquatic invertebrates or macrophytes; treatment did not appear to influence species composition or diversity.	Mayack et al. 1982
Hexazinone (as Velpar L) was applied at a rate of 2, 4, or 8 kg a.i./ha to a surface organic layer of forest soil (L-H horizons).	During the 150-day laboratory incubation, treatment had no effect on CO_2 evolution, amonnification, nitrification, or net sulfur mineralization. The investigators concluded that at the recommend application rates of 2 or 4 kg a.i./ha, hexazinone would not have a significant impact on the nutrient-cycling process int he L-H horizons of mixed wood cutovers.	Maynard 1993
Hexazinone as Velpar L was applied at a rate of 3 lbs a.i./acre to a dense brushfield containing a few ponderosa pine (*Pinus ponderosa* var. *ponderosa*) in California. The application was made in the fall of 1986 using a carbon-dioxide pressurized boom that simulated helicopter application. Kraft paper sacks were used to cover the pine seedlings in order to minimize spray damage.	After six growing seasons, the mean diameter of the ponderosa pines treated with Velpar L was 2.03 inches, compared with 1.28 inches among the controls, and the cover of combined shrubs was about 3% with Velpar, compared with 51% for the control plot.	McDonald et al. 1994

Appenxix 6: Summary of field or field simulation studies on hexazinone formulations

Application	Observations	Reference
Hexazinone liquid formulation (containing 0.24 kg a.i./L) or pellets (formulated with 10% a.i.) was applied on a clay substrate in the southern United States. The liquid formulation was applied either by soil spot application in a grid network at 1.6-2.9 kg a.i./ha or by hand or ground equipment at 1.7 kg a.i./ha. The pellets were applied either by aerial broadcast at 0.8-1.7 kg a.i./kg, or by spot application at 1.7 kg a.i./ha.	The maximum observed residues in surface water after spot application of liquid hexazinone ranged from 6 to 37 μg/L, and after ground or hand application of the liquid formulation, the maximum residue in surface water was 1.3 μg/L. For the granular formulation, the maximum residue levels of hexazinone in surface water after aerial broadcast ranged from not detected (at application rate of 1.7 kg a.i./ha) to 2400 μg/L (at application rate of 0.8 kg a.i./ha), while the maxium residue level after the spot application was 442 μg/L, which resulted from placing the pellets directly in ephemeral drainage channels. In groundwater hexazinone residues (not otherwise specified) were detected in 6 of 23 6-m samplings wells; the maximum residue level was 69 μg/L The half-life of hexazinone applied at 1.6-2.9 kg a.i./ha ranged from 11 to 180 days in soil and from 4 to 15 days in plants.	Michael and Neary 1993
Hexazinone formulated as Velpar® Gridball® was applied by a helicopter fitted with a Simplex Airblown Seeder at a rate of 1.8 kg a.i./ha to a 66 x 122 m plot. ***Investigators note that one swath was applied directly over the flood plain and that pellets were seen falling into the stream.***	The highest concentrations of hexazinone in streamwater (2.4 ppm) occurred 30 minutes after application, and decreased to 1.1 ppm at 1 hour after application. At 2 hours, the concentration had decreased to 0.49 ppm.	Miller and Bace 1980
Hexazinone formulated as Velpar was applied at a rate of 1020 g a.i./ha in the fall of 1990 in Alberta, Canada. The soil in the treated areas was a clay loam soil. The hexazinone was applied in irrigation water.	Hexazinone residues were detected in 27% of the groudwater samples. In May, prior to irrigation, the groundwater concentrations were <0.20 μg/L; in groundwater was 2.7 μg/L after the first irrigation and 38 μg/L after the second irrigation.	Miller et al. 1995

Appenxix 6: Summary of field or field simulation studies on hexazinone formulations

Application	Observations	Reference
Hexazinone formulated as pellets or foliar sprays was applied at four rates to each of eight separate locations to investigate hardwood control and safety to loblolly pine (*Pinus taeda* L.). Each of the eight treated locations had different soil characteristics.	In areas treated with the granular formulation of hexazinone there was a negative correlation between hardwood density reduction and the percent silt, clay, soil organic matter, and cation exchange capacity; however, there was a positive correlation with percent sand. Furthermore, pine mortality was positively correlated to percent sand. In areas treated with the foliar sprays, there was a positive correlation between hardwood density reduction and the application rate and a negative correlation with soil pH. Pine mortality was negatively correlated to soil pH.	Minogue et al. 1988
Hexazinone formulated as pellets was applied by helicopter to parts of two forested watersheds in Tennessee at an application rate of 15 lbs/acre (1.5 lbs a.i./acre or 16.8 kg a.i./ha) in April 1980 (Lost Creek) and April 1981 (Coleman Hollow). Most of the water movement in the treated watershed ares was subsurface. The soil in the treated area was predominantly cherty loam. In the Lost Creek study site, the closest hexazinone-treated area was 1000 feet from the monitoring site; the Coleman Hollow application boundary ran long the edge of hte main ephermal drainage channel for 3000 feet.	There were no detectable residues of hexazinone or its two primary metabolites in samples taken from a watershed located 66 feet from where hexazinone was applied in 1981. In addition, springflow residues from the watershed trated in 1980 were free of residues.	Neary 1983
Hexazinone formulated as pellets (10% a.i.) was applied at a rate of 1.68 kg a.i./ha to four forest watersheds inthe Chattahoochee National Forest in Georgia on April 23, 1979. Residue levels of hexazinone in water, soil, and litter samples were monitored during 26 storms beginning at the end of April 1979 until May 1980.	During the first storm, 3 days after application, residue levels in storm runoff peaked at a mean concentration of 442 ±53 ppbw for the four treated watersheds and decreased with subsequent storms. Residues in mineral soil showed a regular decrease over time, with a half-life of 10-30 days.	Neary et al. 1983.

Appenxix 6: Summary of field or field simulation studies on hexazinone formulations

Application	Observations	Reference
Hexazinone (formulation not specified) was applied on May 1, 1984 by backpack boom sprayer to 20 0.02-ha plots in Georgia composed of acid clay soils. Hexazinone was applied at a rate of 0.0, 0.4, 0.9, or 1.3 kg a.i./ha.	Hexazinone treatment increased control of competing vegetation resulting in significantly greater heights and diameters of loblolly pine (*Pinus taeda*) during the first three growing seasons. There was, however, no evidence that hexazinone stimulated the rate of growth or affected the foliar nutrient levels or soil nitrogen availability, or influenced nitrogen mineralization. Although the survival rate for loblolly pine apparently was unaffected significantly during the first growing season, second- and third-year survival in two of three hexazinone treated plots were lower, compared with survival in control and glyphosate treated plots. The investigators suggest that the adverse effect on survival may have been due to tip-moth predation, noting that according to the product label, insect damage following application of hexazinone may result in damage to conifers..	Pehl and Shelnutt 1990
In study 1, hexazinone as Velpar L™ (liquid formulation) was applied with spot guns to 20 m^2 plots in an upland willow *Salix* spp.at a rate of 1.68, 3.36, or 5.04 kg a.i./ha; in study 2, hexazinone as Pronone 10G™ (10% granular formulation) was applied to 20 m^2 plots in an upland willow *Salix* spp.at a rate of 2.0, 3.0, or 4.0 kg a.i./ha; in study 3, liquid hexazinone was broadcast with CO_2 powered backpack sprayers and flood nozzles to 300 m^2 plots in an upland willow *Salix* spp at a rate of 4.3 kg a.i./ha. The study area was in British Columbia.	Spotgun application of hexazinone in study 1 was effective in controlling the upland willow, and similar results were achieved with application of the granular formulation in study 2. Furthermore, in both studies 1 and 2 there was a linear relationship between the rate of application, the efficacy of the herbicide, and the total height of the willows. Broadcast application of liquid hexazinone (study 3) was not effective in controlling the upland willow, resulting in little mortality of the saplings. After broadcast application, the hexazinone was evenly distributed over the soil surface and adsorbed by the thin layer of organic material. Hence, damage in study 3 consisted of infrequent leaf necrosis and occasional leader dieback.	Pollack et al. 1990
Liquid hexazinone as Velpar L was applied on the evening of June 25, 1987 from a Bell 206B helicopter equipped with a Simplex conventional boom and nozzles, while dry-flowable hexazinone as Velpar ULW was applied on the evening of June 23 using the same aircraft slung with a modified Simplex seeder. Both herbicides were applied at a rate of 2 kg a.i/ha to a northern New Brunswick clearcut to reduce raspberry (*Rubus idaeus* L var. *strigosus)* competition.	The formulation of hexazinone did not affect raspberry control, seedling survival, or growth. After 5 growing seasons, treated plots generally had less raspberry cover, compared with control plots.	Reynolds and Roden 1995

Appenxix 6: Summary of field or field simulation studies on hexazinone formulations

Application	Observations	Reference
Hexazinone as Velplar L (24% a.i.) was applied by backpack sprayer to plots containing sand or clay soil in Ontario, Canada. The herbicide was applied at a rate of 4 kg a.i./ha.	In both clay and sand soils, it took 43 days before hexazinone residues remained consistently below 50% of the highest recovered concentration. In the mobility study, there was no lateral movement of the herbicide in runoff water or through subsurface flow.	Roy et al. 1989
Hexazinone as Velpar L ® was applied to plots of mature mixed pine hardwood stands composed of sandy clay loam soils in Putnam County, Georgia. The rate of application was of 3.5 lbs a.i./acre	Velpar was significantly better than Tordon, Garlon, or Roundup at controlling water/willow oaks	Shiver et al. 1990
Hexazinone as Pronone 10G™ was applied on August 28, 1986 at a rate of 0, 2, or 4 kg a.i./ha. The 80 x 150 m plots were located in a 3-year old mixed wood cutover in a boreal forest in Alberta, Canada	Concentrations of Ca, Mg, K, P, S, and N in the foliage of trembling aspen increased during the first and second growing seasons after hexazinone treatment at the 4 kg a.i./ha rate.	Sidhu 1994
Hexazinone as Pronone 10G™ was applied on August 28, 1986 at a rate of 0, 2, or 4 kg a.i./ha. The 80 x 180 m plots were located in a mixed wood section of a boreal forest in Alberta, Canada	Hexazinone concentrations in stems of trembling aspen, Saskatoon boery and willow ranged from 0.02 to 0.05 μg/dry weight 64 days after treatment. The investigators estimate that based on the highest residue concentrations in several plant species, wildlife would ingest a maximum of 16, 28, or 24 mg hexazinone, metabolite A, or metabolite B, respectively, for every kg of dry matter consumed.	Sidhu and Feng 1993
Liquid hexazinone formulated as Velpar L (25% a.i.) was applied to enclosures located in a typical bog lake in a sandy soil area in northeastern Ontario, Canada. The herbicide was applied at at rates of 0.4 or 4.0 kg/ha, which yielded nominal concentrations of 16.75 or 167.5 μg/L, respectively.	Hexazinone concentrations in water decreased rapidly after either application and were not detectable 21 and days after the low application rate or 42 days after the high application rate. Furthermore, hexazinone did not adsorb to sediments. There was a significantly dose-dependent reduction in oxygen concentrations in the hexazinone corrals for approximately 2 weeks after treatment. The estimated dissipation rates for the two application rates are: DT_{50} (0.4 kg/ha) = 3.7 DT_{50} (4.0 kg/ha) = 3.8 DT_{95} (0.4 kg/ha) = 11.4 DT_{95} (4.0 kg/ha) = 13.4	Solomon et al. 1988

Appenxix 6: Summary of field or field simulation studies on hexazinone formulations

Application	Observations	Reference
Hexazinone spiked with ^{14}C-labelled material was applied at 2.24 kg a.i./ha to surface soils of 36 15 x150 cm lysimeters with intact soil columns collected from six national forest sites in Minnesota, Wisconsin, and Michigan. Soil water samples were collected once from the 10, 20, and 40 cm layers and 10 times from the 150 cm layer during the 130-day post treatment period.	Hexazinone concentrations at the 150 cm level ranged from 10.4 to 60.6 μg/L on days 52-130. Leaching of hexazinone was affected significantly by litter-humus treatment; the lack of humus cover increased the amount of of hexazinone at 150 cm by almost 3-fold.	Stone et al. 1993
Hexazinone pellets formulated as Gridball™ were applied by hand to 10 x10 m plots of shrubby mixed wood stands in Ontario, Canada. In the center of each plot, 16 white spruce were underplanted either closely together or widely apart. Hexazinone was applied at 4.2 kg a.i./ha to the closely planted spruce and at 1.4 kg a.i./ha to the widely spaced spruce.	There was no detectable effect on the species composition of vegetation in the hexazinone treated plots 10 years after herbicide application.	Sutton 1993
Liquid hexazinone formulated as Velpar L© was applied at a rate of 2.14 kg a.i./ha by spot gun in August 1985 (Oates site) and by backpack pressure sprayer in the spring of 1986. The purpose of the study was to determine the relative effectiveness of various silvicultural treatments for establishing white spruce plantations in boreal Ontario mixed wood stands.	The criteria for measuring the effectiveness of hexazinone treatment yield disparate results in this study due to the circumstances under which the study was performed.	Sutton and Weldon 1995
Velpar (10% hexazinone gridballs) were broadcast manually at an application rate of 5.53 kg a.i./ha during April 1983. The study area in northeastern Oklahoma was a refuge for white-tailed deer. The soil in the area was predominantly acid and dominated by a well developed oak/hickory forest.	The greatest overstory defoliation efficacy was observed on Velpar treated ridgetops. The cost of treatment with Velpar gridbass was $129.63/ha plus 10 days labor amounting to a total expense of 153.00/ha.	Thompson et al. 1991
Hexazinone formulated as Velpar L (24% a.i.) was applied (rate not specified) by backpack sprayer to triplicate *in situ* enclosures made of impervious polyethylene sidewalls deployed in a mixed wood boreal forest lake in Ontario, Canada.	The dissipation rates of hexazinone were unexpectedly slow and differed depending on the initial concentrations (10^4 and 10^3); however, the investigators note that the differences were of little practical significance. The investigators also note that the slow rate of dissipation may have been influenced by the environmental conditions in Canadian forest watersheds, including low light intensity and short day length, which affect photolysis, the primary degradation pathway.	Thompson et al. 1992

Appenxix 6: Summary of field or field simulation studies on hexazinone formulations

Application	Observations	Reference
Hexazinone formulated as Velpar L (240 g/L) was applied by backpack sprayer at nominal concentrations of 0.0, 0.01, 0.1, 1, or 10 mg/L (in an attempt to span the expected environmental concentration) to the surface of *in situ* enclosures to determine the impact of hexazinone treatment on the plytoplankton community of a typical forest lake.	Hexazinone treatment had a substantial, statistically significant and persistent impact on the natural phytoplankton communities chronically exposed to concentrations >0.1 mg/L.	Thompson et al. 1993
Hexazinone was applied to three 1-year-old clearcuts in north central Florida: the **xeric sandhill** composed of well-drained, deep, acid sands; the **mesic flatwoods** (previously occupied by an 18- to 25-year-old slash pine plantation) composed of loamy, siliceous soil (somewhat poorly drained); and the **hydric hammock**, a distinctive type of forested, freshwater wetland dominated by by evergreen, with poorly drained, shallow loamy-textured marine sediment soil. Hexazinone was applied at rates of 0.0, 1.7, 3.4 or 6.8 kg a.i./ha in the spring of 1990 as Pronone 10G™ by a modified handheld fertilizer spreader (xeric sandhill and mesic flatwoods sites) or as Velpar ULW™ from a modified Solo™ power blower (hydric hammock site).	*Woody plant compositions on xeric sandhill and mexic flatwoods sites shifted largely as a result of different response models among dominant species (i.e., hexazinone acted in a selective manner on these sites). This contrasts with the responses measured for dominant woody species onthehydric hammock site, where all tended to decrease with increasing hexazinone rates.*	Wilkins et al. 1993
Liquid hexazinone formulated as Velpar L was applied by spotgun to a 20.8 ha plot of coarse sand (drainage = imperfect to excessive) at a rate of 2760 g a.i./ha on July 13, 16, 17, and 20, 1984 and to a 13.7 ha plot of coarse sand (drainage = imperfect) at a rate of 3000 g a.i./ha on July 25 and 26 1985. The purpose of the study was to monitor the movement of hexazinone in surface water and groundwater.	Lateral movement of hexazinone was limited (<10 μg/L detected in groundwater samples within 5 m of the application site); residues of the herbicide were detected in test wells for approximately 1000 days after application.	Williamson 1988

Appendix 7: Toxicity of hexazinone to aquatic animal species

Organism	Chemical	Effects	Reference
Tadpoles (newly hatched) of leopard frogs	continuous exposure to 100 ppm hexazinone for 9 days	no mortality; no indication of diminished avoidance response when prodded; bullfrog tadpoles initially unresponsive to prodding but underwent gradual recovery over the duration of exposure	Berrill et al. 1994
Bluegill	static exposure to hexazinone for 96 hours; pH 7.1	24-hour LC50 = 425 (±366-493) mg/L 48-hour LC50 = 370-420 mg/L 96-hour LC50 = 370-420 mg/L 96-hour NOEL =370 mg/L treated fish had a generally darker color than controls, were lethargic and lost equilibrium prior to death; no adverse response was observed in untreated controls or controls treated with acetone	Kennedy 1984
Rainbow trout	static exposure to hexazinone for 96 hours; pH 7.1	24-hour LC50 = 401 (±326-492) mg/L 48-hour LC50 = 388 (±307-490) mg/L 96-hour LC50 = 320-420 mg/L 96-hour NOEL = 240 mg/L treated fish had a generally darker color than controls, were lethargic and lost equilibrium prior to death; no adverse response was observed in untreated controls or controls treated with acetone	Kennedy 1984
Fathead minnow	static exposure to hexazinone for 96 hours; pH 7.1	24-hour LC50 = 453 (±369-556) mg/L 48-hour LC50 = 370-490 mg/L 96-hour LC50 = 274 (±207-361) mg/L 96-hour NOEL = 160 mg/L treated fish had a generally darker color than controls, were lethargic and lost equilibrium prior to death; no adverse response was observed in untreated controls or controls treated with acetone	Kennedy 1984

Appendix 7: Toxicity of hexazinone to aquatic animal species

Organism	Chemical	Effects	Reference
Daphnia magna	exposure to hexazinone concentrations ranging from 1 to 300 ppm under static unaerated conditions; pH 7.4	48-hour LC50 = 152 (±125-173) ppm; 100% mortality at concentrations ≥250 ppm; no mortality at concentrations ≤50 ppm.	Kennedy 1984
Daphnia magna	exposure to hexazinone concentrations ranging from 1 to 300 ppm under static unaerated conditions; pH 7.4	48-hour LC50 = 152 (±125-173) ppm; 100% mortality at concentrations ≥250 ppm; 8% mortality observed at concentrations of 50 ppm and 1 ppm; no mortality observed at concentrations of 10 ppm	Kennedy 1984
Eastern oysters (embryos)	48-hour exposure in natural sea water containing 100 to 1000 ppm hexazinone; pH 8 (±0.05); salinity 21%	48-hour EC50 >320 but<560 ppm; no normally developed animals were observed after exposure to 560 or 1000 ppm; at concentrations ≤320 ppm, there was no decrease observed in the number of normallly developed embryos, compared with controls.	Kennedy 1984
Grass shrimp	96-hour exposure in natural sea water containing 56 to 560 ppm hexazinone; pH 8 (±0.05); salinity 22%; temperature 19 (±1)°C	24-hour LC50 = 241 (±95-607) ppm; 48-hour LC50 = 94 (±50-176) ppm; 96-hour LC50 = >56 but <100 ppm; after 96 hours of exposure, mortality was 0% at 56 ppm and 100% at ≥100ppm	Kennedy 1984
Fiddler crabs	96-hour exposure in natural sea water containing 10 to 1000 ppm hexazinone; pH 8 (±0.05); salinity 26%; temperature 19 (±1)°C	96-hour LC50 = >1000 ppm; no effects observed at concentrations ≤1000 ppm	Kennedy 1984

Appendix 7: Toxicity of hexazinone to aquatic animal species

Organism	Chemical	Effects	Reference
Coho salmon	96-hour exposure to hexazinone (95% Hex)	24-hour LC50 = 290 mg/L 48-hour LC50 = 282 mg/L 72-hour LC50 = 265 mg/L 96-hour LC50 = 246 mg/L LC50 change (24-96 hours) = 15%	Wan et al. 1988
Chum salmon	96-hour exposure to hexazinone (95% Hex)	24-hour LC50 = 321 mg/L 48-hour LC50 = 288 mg/L 72-hour LC50 = 288 mg/L 96-hour LC50 = 285 mg/L LC50 change (24-96 hours) = 11%	Wan et al. 1988
Chinook salmon	96-hour exposure to hexazinone (95% Hex)	24-hour LC50 = 394 mg/L 48-hour LC50 = 323 mg/L 72-hour LC50 = 318 mg/L 96-hour LC50 = 317 mg/L LC50 change (24-96 hours) = 20%	Wan et al. 1988
Pink salmon	96-hour exposure to hexazinone (95% Hex)	24-hour LC50 = 309 mg/L 48-hour LC50 = 280 mg/L 72-hour LC50 = 280 mg/L 96-hour LC50 = 236 mg/L LC50 change (24-96 hours) = 24%	Wan et al. 1988
Rainbow trout	96-hour exposure to hexazinone (95% Hex)	24-hour LC50 = 320 mg/L 48-hour LC50 = 286 mg/L 72-hour LC50 = 271 mg/L 96-hour LC50 = 257 mg/L LC50 change (24-96 hours) = 20%	Wan et al. 1988
Sockeye salmon	96-hour exposure to hexazinone (95% Hex)	24-hour LC50 = 363 mg/L 48-hour LC50 = 332 mg/L 72-hour LC50 = 318 mg/L 96-hour LC50 = 317 mg/L LC50 change (24-96 hours) = 13%	Wan et al. 1988

Appendix 7: Toxicity of hexazinone to aquatic animal species

Organism	Chemical	Effects	Reference
Pink salmon	96-hour exposure to Pronone 10G (10% Hex/kg granular product)	24-hour LC50 = 1760 mg/L 48-hour LC50 = 1621 mg/L 72-hour LC50 = 1559 mg/L 96-hour LC50 = 1408 mg/L LC50 change (24-96 hours) = 20%	Wan et al. 1988
Rainbow trout	96-hour exposure to Pronone 10G (10% Hex/kg granular product)	24-hour LC50 = 2513 mg/L 48-hour LC50 = 2084 mg/L 72-hour LC50 = 2043 mg/L 96-hour LC50 = 1964 mg/L LC50 change (24-96 hours) = 22%	Wan et al. 1988
Coho salmon	96-hour exposure to Velpar® L (25% Hex/L liquid product)	24-hour LC50 = 1192 mg/L 48-hour LC50 = 1131 mg/L 72-hour LC50 = 1041 mg/L 96-hour LC50 = 923 mg/L LC50 change (24-96 hours) = 23%	Wan et al. 1988
Chum salmon	96-hour exposure to Velpar® L (25% Hex/L liquid product)	24-hour LC50 = 934 mg/L 48-hour LC50 = 934 mg/L 72-hour LC50 = 934 mg/L 96-hour LC50 = 934 mg/L LC50 change (24-96 hours) = 0%	Wan et al. 1988
Chinook salmon	96-hour exposure to Velpar® L (25% Hex/L liquid product)	24-hour LC50 = 1096 mg/L 48-hour LC50 = 1096 mg/L 72-hour LC50 = 1096 mg/L 96-hour LC50 = 1096 mg/L LC50 change (24-96 hours) = 0%	Wan et al. 1988
Pink salmon	96-hour exposure to Velpar® L (25% Hex/L liquid product)	24-hour LC50 = 978 mg/L 48-hour LC50 = 839 mg/L 72-hour LC50 = 728 mg/L 96-hour LC50 = 676 mg/L LC50 change (24-96 hours) = 31%	Wan et al. 1988

Appendix 7: Toxicity of hexazinone to aquatic animal species

Organism	Chemical	Effects	Reference
Rainbow trout	96-hour exposure to Velpar® L (25% Hex/L liquid product)	24-hour LC50 = 962 mg/L 48-hour LC50 = 889 mg/L 72-hour LC50 = 875 mg/L 96-hour LC50 = 872 mg/L LC50 change (24-96 hours) = 10%	Wan et al. 1988
Sockeye salmon	96-hour exposure to Velpar® L (25% Hex/L liquid product)	24-hour LC50 = 1167 mg/L 48-hour LC50 = 974 mg/L 72-hour LC50 = 927 mg/L 96-hour LC50 = 925 mg/L LC50 change (24-96 hours) = 20%	Wan et al. 1988
Rainbow trout	96-hour exposure to Carrier P (Pronone 10G carrier-100% solid carrier-identity is proprietary information)	24-hour LC50 = >2000 mg/L 48-hour LC50 = >2000 mg/L 72-hour LC50 = >2000 mg/L 96-hour LC50 = >2000 mg/L LC50 change (24-96 hours) = 0%	Wan et al. 1988
Rainbow trout	96-hour exposure to Carrier V (Velpar L carrier-100% liquid carrier-identity is proprietary information)	24-hour LC50 = 4330 mg/L 48-hour LC50 = 4330 mg/L 72-hour LC50 = 4330 mg/L 96-hour LC50 = 4330 mg/L LC50 change (24-96 hours) = 0%	Wan et al. 1988

Appendix 8: Toxicity of hexazinone to algae

Organism	Chemical	Effects	Reference
Anabaena flos-aquae (Lyng) (glue-green alga)	0.70, 0.90, 1.20, 1.50, or 2.00 mg/L hexazinone (98% pure) was added to unicultural algal cultures and biomass was measured using ^{14}C uptake over 1, 3, 5,and 7 days. Three samples were kept in the dark and three samples were incubated under fluorescent light for 4 hours/replicate.	^{14}C uptake was zero for all dark treated samples; in the light treated samples, biomass and ^{14}C uptake were inhibited on day 1, but began recovering on day 3 at all concentration ranges. On days 1-3, ^{14}C uptake was about 50, compared with controls.	Abou-Waly et al. 1991
Selenastrum capricornutum (Printz) (green alga)	0.03, 0.04, 0.055, 0.075, or 0.1 mg/L hexazinone (98% pure) was added to unicultural algal cultures and biomass was measured using ^{14}C uptake over 1, 3, 5,and 7 days. Three samples were kept in the dark and three samples were incubated under fluorescent light for 4 hours/replicate.	^{14}C uptake was zero for all dark treated samples; in the light treated samples, biomass and ^{14}C uptake were significantly reduced over 7 days at all concentrations. Effects were considered dose related..	Abou-Waly et al. 1991
Anabaena flos-aquae (Lyng) (glue-green alga)	0.056 mg/L for 3 days	EC_{50}	Abou-Waly et al. 1991
Anabaena flos-aquae (Lyng) (glue-green alga)	0.085 mg/L for 5 days	EC_{50}	Abou-Waly et al. 1991
Anabaena flos-aquae (Lyng) (glue-green alga)	0.126 mg/L for 7 days	EC_{50}	Abou-Waly et al. 1991
Selenastrum capricornutum (Printz) (green alga)	2.014 mg/L for 3 days	EC_{50}	Abou-Waly et al. 1991
Selenastrum capricornutum (Printz) (green alga)	2.375 mg/L for 5 days	EC_{50}	Abou-Waly et al. 1991
Selenastrum capricornutum (Printz) (green alga)	2.752 mg/L for 7 days	EC_{50}	Abou-Waly et al. 1991

Appendix 8: Toxicity of hexazinone to algae

Organism	Chemical	Effects	Reference
Selenastrum capricornutum	24.5 (±14.5-33.1) μg/L for 96 hours	EC_{50}	St-Laurent et al. 1992
Cyanophyta	0.01 (±0.01-0.02) mg/L for 10 days	EC_{50}	Thompson et al. 1993
Chlorophyta	0.05 (±0.02-0.69) mg/L for 21 days	EC_{50}	Thompson et al. 1993
Chrysophyta	0.003 (±0.003-0.005) mg/L for 21 days	EC_{50}	Thompson et al. 1993
Chrysophyta	0.004 mg/L for 56 days	EC_{50}	Thompson et al. 1993
Cryptophyta	0.04 (±0.002-0.07) mg/L for 10 days	EC_{50}	Thompson et al. 1993
Cryptophyta	0.05 mg/L for 21 days	EC_{50}	Thompson et al. 1993
Cryptophyta	0.03 mg/L for 35 days	EC_{50}	Thompson et al. 1993
Bacilliarophyceae	0.03 (±0.02-0.03) mg/L for 10 days	EC_{50}	Thompson et al. 1993
Total phytoplankton	0.03 mg/L for 10 days	EC_{50}	Thompson et al. 1993
Periphyton	24-hour exposure to 200 μg/L hexazinone as Velpar L® added to outdoor experimental stream channels	mean concentrations of hexazinone varied over time from 145-432 μg/L. Periphyton chlorophyll-a-specific productivity decreased by 80% during the addition of hexazione , but returned to normal within 24 hours. The 4-hour EC50 value for chlorophyll-a-specific productivity was 3.6 μg/L, which is lower than published bioassay results for single species.	Schneider et al. 1995
Selenastrum capricornutum	22.5 (±15.91-31.50) μg/L Velpar L for 18 days	EC_{50}	Williamson 1988

Appendix 8: Toxicity of hexazinone to algae

Organism	Chemical	Effects	Reference
Selenastrum capricornutum	24.5 (SD = 3) μg/L Velpar L for 4 days; mode of action was apparently through blockage of photosynthetic processes	EC_{50}	Williamson 1988