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Hexazinone -
Human Health and Ecological Risk Assessment – Final Report

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ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
a.e.	acid equivalents
AEL	adverse-effect level
a.i.	active ingredient
ALS	acetolactate synthase
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
bw	body weight
CBI	confidential business information
CI	confidence interval
cm	centimeter
CNS	central nervous system
DAA	days after application
DAT	days after treatment
d.f.	degrees of freedom
EC_x	concentration causing X% inhibition of a process
EC_{25}	concentration causing 25% inhibition of a process
EC_{50}	concentration causing 50% inhibition of a process
ExToxNet	Extension Toxicology Network
F	female
FH	Forest Health
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FQPA	Food Quality Protection Act
g	gram
ha	hectare
HQ	hazard quotient
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
k_a	absorption coefficient
k_e	elimination coefficient
kg	kilogram
$K_{o/c}$	organic carbon partition coefficient
$K_{o/w}$	octanol-water partition coefficient
K_p	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

mg	milligram
mg/kg/day	milligrams of agent per kilogram of body weight per day
mL	milliliter
mM	millimole
MOS	margin of safety
MRID	Master Record Identification Number
MSDS	material safety data sheet
MW	molecular weight
NCI	National Cancer Institute
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level
NOS	not otherwise specified
NRC	National Research Council
NTP	National Toxicology Program
OM	organic matter
OPP	Office of Pesticide Programs
OPPTS	Office of Pesticide Planning and Toxic Substances
OSHA	Occupational Safety and Health Administration
ppm	parts per million
RBC	red blood cells
RED	re-registration eligibility decision
RfD	reference dose
SERA	Syracuse Environmental Research Associates
TEP	typical end-use product
t.g.i.a.	Technical grade active ingredient
TRED	Tolerance Reassessment Eligibility Decision
UF	uncertainty factor
U.S.	United States
USDA	U.S. Department of Agriculture
U.S. EPA	U.S. Environmental Protection Agency
USGS	U.S. Geological Survey
WHO	World Health Organization

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	1.8 °C+32
centimeters	inches	0.3937
cubic meters (m^3)	liters (L)	1,000
Fahrenheit	centigrade	0.556 °F-17.8
feet per second (ft/sec)	miles/hour (mi/hr)	0.6818
gallons (gal)	liters (L)	3.785
gallons per acre (gal/acre)	liters per hectare (L/ha)	9.34
grams (g)	ounces, (oz)	0.03527
grams (g)	pounds, (oz)	0.002205
hectares (ha)	acres	2.471
inches (in)	centimeters (cm)	2.540
kilograms (kg)	ounces, (oz)	35.274
kilograms (kg)	pounds, (lb)	2.2046
kilograms per hectare (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 acre (lb/acre)	mg/square meter (mg/m^2)	112.1
pounds per acre (lb/acre)	µg/square centimeter ($\mu g/cm^2$)	11.21
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

OVERVIEW

Hexazinone is a herbicide used in Forest Service programs almost exclusively in conifer release and site preparation in the southeastern United States. The toxicity of hexazinone is relatively well-characterized the areas of concern can be identified based on potential effects on humans as well as nontarget species.

For both workers and members of the general public, pregnant women and their developing offspring are the group that may be at greatest risk due to excessive exposure to hexazinone. For workers, exposures to hexazinone during application are likely to exceed exposures that would generally be regarded as acceptable unless workers follow prudent handling practices that will minimize exposure. For members of the general public, none of the acute exposure scenarios result in hazard quotients that exceed a level of concern with the exception of the accidental spill of a liquid or granular formulation into a small pond. The only non-accidental scenarios that result in hazard quotients which substantially exceed the level of concern are those associated with longer-term exposure to contaminated vegetation after the application of Velpar L, the only liquid formulation of hexazinone considered in this risk assessment. In areas in which members of the general public might consume contaminated vegetation, particularly broadleaf vegetation or other plant products that might contain comparable residues, the use of granular formulations of hexazinone should be given preference to the use of liquid formulations.

Because hexazinone is an effective herbicide, unintended effects on nontarget vegetation are plausible. The effective use of hexazinone is achieved by applying the compound to target vegetation at a time and in a manner which will minimize effects on nontarget plant species. If this is done properly and with care, effects on nontarget vegetation should be minor and perhaps negligible. Nonetheless, in the normal course of applications of granular or liquid formulations at rates that are effective in weed control, adverse effects on terrestrial plants are plausible due to either drift or runoff. Depending on local conditions and the proximity of streams or ponds to hexazinone applications, damage to aquatic vegetation is also plausible and could be substantial.

The potential for adverse effects in animals is far less clear and is somewhat dependent on the type of formulation that is applied. Granular formulations of hexazinone appear to pose a very low risk to any terrestrial or aquatic animal. adverse effects are plausible in mammals consuming contaminated vegetation after the application of liquid formulations and adverse reproductive effects in some mammalian species could occur. There is no indication that substantial numbers of mammals would be subject to lethal exposure to hexazinone. Consequently, adverse effects such as weight loss and reproductive impairment could occur but might not be readily apparent or easy to detect. Birds appear to be much more tolerant to hexazinone than mammals and adverse effects on birds do not seem plausible. Similarly, there is no indication that direct toxic effects are likely in aquatic animals.

PROGRAM DESCRIPTION

Hexazinone is a triazine herbicide that is used in Forest Service programs almost exclusively in conifer release and site preparation in the southeastern United States. In general, liquid formulations may be preferred in clay or loam soils but granular formulation may be preferable in sandy soil due to the slow release of hexazinone which reduces loss from the soil due to percolation. Most formulations of hexazinone are granular and only one liquid formulation, Velpar L, is used by the Forest Service. Both liquid and granular formulations of hexazinone may be applied by aircraft and this application method is covered in the current risk assessment. The highest labeled application rate for hexazinone is about 8 lbs a.i./acre for the control of woody vegetation. For conifer release, the labeled application rates are about 2 lbs a.i./acre to 5 lbs ai./acre. Lower application rates may be used for conifer release, in the range of about 0.75 lbs a.i./acre to 3 lbs a.i./acre depending on soil type. For this risk assessment, the typical application rate for hexazinone is taken as 2 lbs/acre and the range of application rates is taken as 0.5 lbs/acre to 4 lbs/acre. Hexazinone is also used on a number of crops, primarily alfalfa. The average use of hexazinone by the Forest Service appears to be less than 10% of the amount used in agriculture.

HUMAN HEALTH RISK ASSESSMENT

Hazard Identification **–** The toxicity of hexazinone has been relatively well-characterized in a number of standard bioassays that are required by U.S. EPA for the registration on pesticides. Acute oral toxicity studies indicate the the oral LD_{50} for hexazinone in mammals is in the range of 1000 mg/kg. No adverse effects are anticipated at ten-fold lower doses – i.e., 100 mg/kg/day – based on the results of short-term repeated dosing. Standard chronic toxicity studies indicate that long-term exposures to hexazinone at doses of about 5 mg/kg/day will not be associated with any identifiable adverse effect.

At very high doses – i.e., those in the range of the LD_{50} – lacrimation, salivation, vomiting, tremors/ataxia/weakness, diarrhea, and increased rates of respiration and/or labored breathing are often noted. While these types of effects can be caused by neurotoxins, they are not specific indicators of neurotoxicity and these effects may be secondary to other mechanisms of toxicity. There is no basis for assuming that hexazinone is a direct neurotoxin. In less severely poisoned animals, the most commonly noted effect induced by hexazinone is weight loss. In mice and dogs, this effect is usually associated with and attributable to a decrease in food consumption. In rats, particularly female rates, weight loss has been associated with a decrease in food conversion efficiency. The underlying mechanism for the decreased food conversion efficiency is unclear.

Hexazinone appears to be rapidly absorbed after oral exposure and it is rapidly metabolized and excreted. While hexazinone seems to be absorbed much more slowly during dermal exposures compared to oral exposures, the available acute and longer-term dermal studies indicate that hexazinone may be absorbed by the skin in sufficient amounts to cause at least sensitive signs of toxicity, particularly weight loss. While hexazinone is only mildly irritating to the skin, it is severely irritating to the eyes.

Certain types of effects are of particular concern and are assessed with a specific subset of toxicity tests. Such effects include those on the nervous system, immune system, endocrine function, development or reproduction, and carcinogenicity or mutagenicity. Hexazinone does not appear to be a direct neurotoxin and hexazinone does not appear to cause effects on the immune system. While somewhat speculative, the effects on food conversion efficiency could be related to effects on the endocrine system. This, however, has not been clearly demonstrated. Except at doses that cause frank signs of toxicity in females, hexazinone does not appear to cause birth defects or other adverse effects on the young. Two standard carcinogenicity studies are available on hexazinone, one in mice and the other in rats. The results of the assay in mice indicated no carcinogenic potential but the results in rats were equivocal. Consequently, the U.S. EPA determined that hexazinone is *not classifiable as to human carcinogenicity* and declined to quantify cancer risk.

Exposure Assessment – Exposure assessments are made for both granular and liquid formulations. The major difference between these two types of formulations involves hexazinone residues on contaminated vegetation. A field study is available that clearly indicates that granular formulations will not tend to adhere to the surface of vegetation after application to the extent seen with liquid formulations. Other differences between the exposures estimated for granular and liquid formulations are less substantial and significant. Specifically, there is no basis for asserting that worker exposure rates are likely to differ substantially between applications of granular and liquid formulations. This conclusion is based on an analysis of the deposition of hexazinone on workers during the application of a granular formulation. While somewhat counter intuitive, there is also no basis for asserting that contamination of surface or ground water is likely to be substantially different between comparable applications of granular and liquid formulations. This conclusion is based on both monitoring data as well as environmental modeling.

For workers applying hexazinone, three types of application methods are modeled: directed ground spray, broadcast ground spray, and aerial spray. Based on the limited available data on worker exposures to hexazinone, worker exposure rates typically used in Forest Service risk assessments appear to be applicable to both granular and liquid formulations of hexazinone. Central estimates of exposure for workers are approximately 0.03 mg/kg/day for aerial and backpack workers and about 0.045 mg/kg/day for broadcast ground spray workers. Upper ranges of exposures are approximately 0.3 mg/kg/day for broadcast ground spray workers and 0.16 mg/kg/day for backpack and aerial workers.

For the accidental exposure scenarios, exposure estimates for granular and liquid formulations differ. All of the accidental exposure scenarios for workers involve dermal exposures and most of these accidental exposures lead to estimates of dose that are substantially below the general exposure estimates for workers. The one exception involves wearing contaminated gloves for one-hour. The upper range of exposure for this scenario is about 0.33 mg/kg bw for liquid formulations and 0.23 mg/kg bw for granular formulations. This relatively minor difference is due to the fact that the upper range of exposure to liquid formulation exceeds the solubility of hexazinone in water, a limiting factor in exposures for the granular formulation. The high exposure to the liquid formulation appears to be associated with the presence of adjuvants in the

liquid formulation (probably ethanol) that functionally increases the solubility of hexazinone in the field solution.

For the general public, the range for acute exposures is about 0.0002 mg/kg bw to about 4 mg/kg bw for granular formulations. The corresponding values for the liquid formulation is about 0.04 mg/kg bw to 4 mg/kg bw. The lower bound of exposures for the granular formulation relative to the liquid formulation is due to the lower deposition of the granular formulation on contaminated vegetation. For both formulations, the upper bound of exposure, 4 mg/kg bw, is associated with an accidental spill into a small pond. This is a highly arbitrary exposure scenario for both types of formulations.

For chronic or longer term exposures, the modeled exposures are much lower than for acute exposures. Exposures to hexazinone associated with the consumption of contaminated water or fish are identical for both granular and liquid formulations and range from about 0.000000003 mg/kg/day to 0.002 mg/kg/day. The upper bound of this range is associated with the longer-term consumption of contaminated water. For granular formulations, the longer-term consumption of contaminated vegetation leads to a similar estimated dose, about 0.006 mg/kg/day. For the liquid formulation, however, the estimated dose is much greater, about 0.16 mg/kg/day. Again, this substantial difference relates to the well-documented differences between liquid and granular formulations in the deposition of hexazinone on the vegetation.

Dose-Response Assessment – The U.S. EPA has derived acute and chronic RfDs for hexazinone. Following standard practices for Forest Service risk assessments, the RfD values derived by U.S. EPA are adopted directly. U.S. EPA has derived a chronic RfD for hexazinone of 0.05 mg/kg/day. This chronic RfD is well-documented and is used directly for all longer term exposures to hexazinone. This value is based on a NOAEL of 5 mg/kg/day in dogs and an uncertainty factor of 100 – two factors of 10 for interspecies and intraspecies variability. The acute RfD derived by U.S. EPA is 4 mg/kg. The RfD is based on an experimental dose of 400 mg/kg/day that did not cause any adverse effects in offspring but did cause adverse effects in dams. Again, the RfD is based on an uncertainty factor of 100. The acute RfD is applied to all incidental or accidental exposures that involve an exposure period of 1 day.

Risk Characterization – For both workers and members of the general public, pregnant women and their developing offspring are the group that may be at greatest risk due to excessive exposure to hexazinone.

Risks to workers are the dominant element in the risk characterization for potential effects in humans. Unless measures are taken to ensure that workers take measures to minimize exposure to hexazinone during applications, workers are likely to be exposed to hexazinone at levels that are greater than the chronic RfD. All of the upper bounds of the hazard quotients for the different groups of workers exceed the level of concern (HQ=1) for both the typical application rate of 2 lbs/acre (HQs ranging from 3 to 6) and the highest anticipated application rate (HQs ranging from 6 to 12). Even at the lowest anticipated application rate, 0.5 lb/acre, the upper range of the hazard quotient for workers involved in broadcast ground applications modestly exceeds the level of concern with an HQ of 1.5. Conversely, the lower bounds of the hazard

quotients do not exceed a level of concern even at the highest application rate. The simple interpretation of these hazard quotients is that worker exposures to hexazinone during application are likely to exceed exposures that would generally be regarded as acceptable unless workers follow prudent handling practices that will minimize exposure.

For members of the general public, none of the acute exposure scenarios result in hazard quotients that exceed a level of concern with the exception of the accidental spill of a liquid or granular formulation into a small pond.

The only non-accidental scenarios that result in hazard quotients which substantially exceed the level of concern are those associated with longer-term exposure to contaminated vegetation after the application of Velpar L, the only liquid formulation of hexazinone considered in this risk assessment. At the highest application rate (4 lbs/acre), the consumption of contaminated broadleaf vegetation exceeds the level of concern even at the lower limit of plausible exposures: hazard quotients with a central estimate of 5 and a range of 1.1 to 45. In areas in which members of the general public might consume contaminated vegetation, particularly broadleaf vegetation or other plant products that might contain comparable residues, the use of granular formulations of hexazinone should be given preference to the use of liquid formulations.

For both workers and members of the general public, the risk characterization for acute exposure is highly dependant on the confidence in the acute RfD. As discussed in the dose-response assessment, the acute RfD derived by the U.S. EPA for hexazinone is 4 mg/kg.

ECOLOGICAL RISK ASSESSMENT

Hazard Identification – Hexazinone is an effective herbicide. Hexazinone inhibits photosynthesis and, at higher levels of exposure, inhibits the synthesis of RNA, proteins, and lipids in plants. The toxicity of hexazinone is very well characterized in terrestrial plants and the difference in sensitivity among different types of terrestrial plants is related to differences in absorption as well as metabolism. At least in terrestrial plants, the metabolites of hexazinone are much less toxic then hexazinone itself. While the toxicity of hexazinone to aquatic plants has not been characterized as completely as in terrestrial plants, hexazinone is much more toxic to aquatic plants than to aquatic animals. This is true for most herbicides. The effects of hexazinone on plants can cause secondary effects in animals – e.g., changes in food availability or habitat. This has been demonstrated for mammals and birds. These secondary effects are not necessarily adverse. For both birds and mammals, short-term reductions in preferred vegetation may be followed by an increase in preferred vegetation.

Based on classification schemes developed by the U.S. EPA, hexazinone is *practically nontoxic* to birds, fish, and aquatic invertebrates. The acute toxicity to mammals is also low, with rat oral gavage LD_{50} values in the range of about 600 to 1800 mg/kg. No clear patterns in sensitivity among different species of mammals are apparent. Based on an acute gavage LD_{50} in quail of 2258 (1628-3130) mg/kg, birds appear to be somewhat less sensitive than mammals to hexazinone. Relatively little information is available on the toxicity of hexazinone to insects. Based on an acute topical application to honey bees, the LD_{50} value is greater than 1075 mg/kg bw. This is consistent with dermal studies in mammals indicating dermal LD_{50} values of greater

than 5000 mg/kg. Terrestrial microorganisms can be adversely affected by hexazinone in standard laboratory culture bioassays. Nonetheless, field studies are available that demonstrate no adverse effects on terrestrial microorganisms after applications at rates that are substantially above those used in Forest Service programs. At high concentrations of hexazinone in water, fish and aquatic invertebrates may be adversely affected. The acute LC_{50} values for these organisms are in the range of about 100 mg/L to over 1000 mg/L. The carriers and/or inerts in formulations of Velpar L as well as Pronone 10G appear to antagonize the toxicity of hexazinone to fish. At least for Velpar L, no such antagonistic effect is apparent for aquatic plants.

Exposure Assessment – The exposure assessments generated for the ecological risk assessment parallel the exposure scenarios used in the human health risk assessment and the scenarios fall into two general groups: exposures that may be anticipated in the normal use of hexazinone and atypical exposures that could occur as a result of mischance or misapplication. In some cases, the atypical exposures have somewhat different interpretations. The direct spray of a human is regarded as accidental and unlikely to occur. While the direct spray of a small mammal or insect during any broadcast application would also be accidental (unintended), such exposures for some individual animals are both plausible and likely. Nonetheless, it is highly unlikely that a substantial proportion of small mammals or insects would be directly sprayed. Exposures would likely be reduced both by animal behavior as well as foliar interception.

For terrestrial animals, exposure assessments are developed for direct spray, the ingestion of contaminated media (vegetation, prey species, or water), grooming activities, or indirect contact with contaminated vegetation. Not all exposure scenarios are developed for all groups of animals because toxicity data are not available in all groups to support the use of such exposure assessments in the risk characterization. For terrestrial plants, exposure assessments are developed for direct spray, spray drift, and off-site movement of the compound by percolation, runoff, wind erosion of soil. For aquatic species, the concentrations in water are identical to those used in the human health risk assessment.

Also as in the human health risk assessment, differences in exposures after granular and liquid formulations are considered. The major difference will be in residues on contaminated vegetation, where applications of liquid formulations lead to much higher residues than applications of granular formulations.

Dose-Response Assessment – The available toxicity data support separate dose-response assessments in eight classes of organisms: mammals, birds, terrestrial invertebrates, terrestrial plants, fish, aquatic invertebrates, aquatic algae, and aquatic macrophytes. Different units of exposure are used for different groups of organisms depending on how exposures are likely to occur and how the available toxicity data are expressed.

Based on dietary toxicity values, mammals appear to be more sensitive to hexazinone than birds. For mammals, the dose-response assessment is based on the studies used to derive RfDs in the human health risk assessment – i.e., an acute NOAEL of 400 mg/kg and a chronic NOAEL of 5 mg/kg/day. A comparison of gavage studies between mammals and birds suggest that birds may be less sensitive to hexazinone than mammals. Based on a comparison of short-term dietary

NOAELs, the sensitivity of birds is somewhat less that seen in mammals. The acute dietary NOAEL for birds is 550 mg/kg/day, a factor of about 1.4 above the acute NOEL of 400 mg/kg/day that is used for mammals. Since most of the exposure assessments developed in this risk assessment involve gradual intake during the day rather than gavage like exposures, the acute dietary NOEL of 550 mg/kg/day is used for the risk characterization in birds. No lifetime toxicity studies in birds have been encountered. Based on the reproduction study, the chronic NOAEL for birds is set at 150 mg/kg/day. This is about a factor of 30 above the NOAEL of 5 mg/kg/day used for mammals. Relatively little information is available on terrestrial insects. A contact toxicity value of 1075 mg/kg bw is taken as a marginal LOEC. This is consistent with corresponding dermal toxicity data in mammals.

The toxicity of hexazinone to terrestrial plants can be characterized relatively well and with little ambiguity. Hexazinone is relatively ineffective in inhibiting seed germination but is toxic after either direct spray or soil application. Based on toxicity studies in which exposure can be characterized as an application rate, hexazinone is more toxic in pre-emergent soil applications than direct spray. In pre-emergent soil applications, the NOEC values for the most sensitive and tolerant species are 0.000348 lb/acre and 0.0234 lb/acre, respectively. The corresponding values for direct spray (post-emergent bioassays) are 0.00391 lb/acre and 0.0626 lb/acre.

Hexazinone is not very toxic to aquatic animals. The acute NOEC values for sensitive and tolerant species of fish cover a very narrow range, 160 mg/L to 370 mg/L. For longer term exposures, the data are not sufficient to identify tolerant and sensitive species and a single NOEC value of 17 mg/L is used. Somewhat greater variability is apparent in aquatic invertebrates, with acute NOEC values ranging from 20.5 mg/L to 320 mg/L. This may, however, be an artifact of comparisons between freshwater and saltwater species. An NOEC of 10 mg/L from a reproduction study in daphnids is used to assess the effects of longer-term exposures in sensitive aquatic invertebrates. No longer-term NOEC is available for tolerant invertebrates and the relative potency from acute studies is used to estimate a longer-term NOEC for tolerant species at 160 mg/L.

Aquatic plants are much more sensitive to hexazinone and the variability in this group appears to be much greater than that for fish and aquatic invertebrates. For sensitive aquatic algae, risk is characterized using the lowest NOEC from a standard 5-day bioassay, 0.004 mg/L. The most tolerant species of algae has a corresponding NOEC of 0.15 mg/L. Aquatic macrophytes appear to fall within the range of algae and a single NOEC of 0.012 mg/L is used for this group.

Risk Characterization – As with most ecological risk assessments, the characterization of risk for hexazinone is limited by the comparison of the available data to the number of species that might be exposed and the interactions that could occur among these species. Hexazinone has been tested in only a limited number of species and under conditions that may not well-represent natural populations of nontarget organisms. This leads to uncertainties that may result in underestimates or overestimates of risk. The methods and assumptions used in both the exposure and dose-response assessments are intended to consider these uncertainties by using protective assumptions in developing both the exposure and dose-response assessments which form the basis of the risk characterization.

Because hexazinone is an effective herbicide, unintended effects on nontarget vegetation are plausible. The effective use of hexazinone is achieved by applying the compound to target vegetation at a time and in a manner which will minimize effects on nontarget plant species. If this is done properly and with care, effects on nontarget vegetation should be minor and perhaps negligible. Nonetheless, in the normal course of applications of granular or liquid formulations at rates that are effective in weed control, adverse effects on terrestrial plants are plausible due to either drift or runoff. Depending on local conditions and the proximity of streams or ponds to hexazinone applications, damage to aquatic vegetation is also plausible and could be substantial.

The potential for adverse effects in animals is far less clear and is somewhat dependent on the type of formulation that is applied. Granular formulations of hexazinone appear to pose a very low risk to any terrestrial or aquatic animal. The application of liquid formulations will result in much higher concentrations of hexazinone in terrestrial vegetation than will comparable applications of granular formulations. This has a major impact on the potential for adverse effects in mammals. Over the range of application rates used in Forest Service programs, adverse effects could be anticipated in mammals who consume contaminated vegetation over prolonged periods of time. It is unclear whether or not frank effects such as severe weight loss might occur or be evident. Adverse reproductive effects do not appear to be plausible. There is no indication that substantial numbers of mammals would be subject to lethal exposure to hexazinone. Consequently, adverse effects such as weight loss could occur but might not be readily apparent or easy to detect. Birds appear to be much more tolerant to hexazinone than mammals and adverse effects on birds do not seem plausible. Similarly, there is no indication that direct toxic effects are likely in aquatic animals.

The most likely consequences to both terrestrial and aquatic animals of hexazinone applications appear to be effects that are secondary to direct toxic effects on vegetation. These effects would likely be variable over time and among different species of animals. Some effects could be detrimental for some species – i.e., a reduction in the supply of preferred food or a degradation of habitat – but beneficial to other species – i.e., an increase in food or prey availability or an enhancement of habitat.

1. INTRODUCTION

The USDA Forest Service uses hexazinone in its vegetation management programs. This document is an update to a risk assessment prepared in 1997 (SERA 1997) and provides risk assessments for human-health effects and ecological effects to support an assessment of the environmental consequences of these uses.

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 hexazinone and its commercial formulation, an assessment of potential exposure to the product, 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 was made to ensure that the document can be understood by individuals who do not have specialized training in the chemical and biological sciences. Certain technical concepts, methods, and terms common to all parts of the risk assessment are described in plain language in a separate document (SERA 2001). Technical terms that are common to this and many other risk assessments conducted for the Forest Service is available on the internet at www.sera-inc.com.

The human health and ecological risk assessments presented in this document are not, and are not intended to be, comprehensive summaries of all of the available information. Much of the early literature on hexazinone is summarized in the previous chemical background statement on hexazinone (Sassaman et al. 1984), previous USDA risk assessments and environmental impact statements covering this compound (Durkin and Diamond 2002; SERA 1997; USDA 1989a,b,c), as well as unpublished reviews prepared for the U.S. EPA (Ghassemi et al. 1981). In addition, the U.S. EPA has reviewed much of the unpublished data on hexazinone that was submitted in support of the registration of this compound (U.S. EPA 1990, 1994a,b,c,d) and has recently reevaluated the toxicity of hexazinone under the requirements of the Food Quality Protection Act (FQPA) (U.S. EPA 2002a,b,c,d,e,f,g,h). All of these reviews were consulted in the preparation of this risk assessment and the most relevant studies are summarized in the appendices included with this risk assessment. Nonetheless, the discussions in Section 3 (Human Health Risk Assessment) and Section 4 (Ecological Risk Assessment) focuses on those studies that have a direct impact on the risk characterization for hexazinone.

In addition, a complete search of the U.S. EPA FIFRA/CBI files was conducted. Full text copies of relevant studies were kindly provided by the U.S. EPA Office of Pesticide Programs (n=178). These studies were reviewed, are discussed in Sections 3 and 4 as necessary, and synopses of the most relevant studies are provided in the appendices to this document.

The Forest Service will update this and other similar risk assessments on a periodic basis and welcomes input from the general public on the selection of studies included in the risk assessment. This input is helpful, however, only if recommendations for including additional studies specify why and/or how the new or not previously included information would be likely to alter the conclusions reached in the risk assessments.

Almost no risk estimates presented in this document are given as single numbers. Usually, risk is expressed as a central estimate and a range, which is sometimes very large. Because of the need to encompass many different types of exposure as well as the need to express the uncertainties in the assessment, this risk assessment involves numerous calculations. Most of the calculations are relatively simple, and the very simple calculations are included in the body of the document.

Some of the calculations, however, are cumbersome. For those calculations, worksheets are included as attachments to the risk assessment. For hexazinone, two sets of worksheets are given in two different EXCEL workbooks – i.e., collections of worksheets. One workbook covers Velpar L, the only liquid formulation considered in this risk assessment. The other workbook covers the remaining formulations, all of which are granular. The specific formulations are discussed in Section 2 and the need for separating Velpar L from the granular formulations is discussed in the appropriate subsections of the exposure assessment for human health (Section 3.2) and the exposure assessment for ecological effects (Section 4.2).

The worksheets provide the detail for the estimates cited in the body of this document. The worksheets are divided into the following sections: general data and assumptions, chemical specific data and assumptions, exposure assessments for workers, exposure assessments for the general public, and exposure assessments for effects on nontarget organisms. SERA (2004a) contains documentation for the use of the EXCEL workbooks.

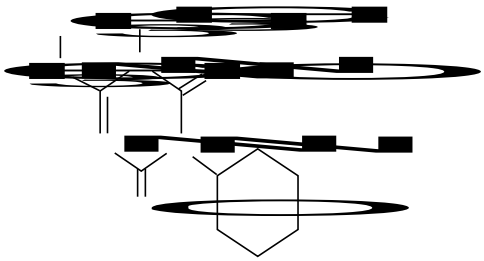
2. PROGRAM DESCRIPTION

2.1. OVERVIEW

Hexazinone is a triazine herbicide that is used in Forest Service programs almost exclusively in conifer release and site preparation in the southeastern United States. In general, liquid formulations may be preferred in clay or loam soils but granular formulation may be preferable in sandy soil due to the slow release of hexazinone which reduces loss from the soil due to percolation. Most formulations of hexazinone are granular and only one liquid formulation, Velpar L, is used by the Forest Service. Both liquid and granular formulations of hexazinone may be applied by aircraft and this application method is covered in the current risk assessment. The highest labeled application rate for hexazinone is about 8 lbs a.i./acre for the control of woody vegetation. For conifer release, the labeled application rates are about 2 lbs a.i./acre to 5 lbs ai./acre. Lower application rates may be used for conifer release, in the range of about 0.75 lbs a.i./acre to 3 lbs a.i./acre depending on soil type. For this risk assessment, the typical application rate for hexazinone is taken as 2 lbs/acre and the range of application rates is taken as 0.5 lbs/acre to 4 lbs/acre. Hexazinone is also used on a number of crops, primarily alfalfa. The average use of hexazinone by the Forest Service appears to be less than 10% of the amount used in agriculture.

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:



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. Soil binding and transport are discussed in detail in Section 3.2.3.4 under the discussion of modeling concentrations of hexazinone in water using GLEAMS.

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. 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). As noted in Table 2-2, all granular formulations of hexazinone require wetting-in. This is necessary because hexazinone is absorbed primarily and 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. In general, liquid formulations may be preferred in clay or loam soils but granular formulation may be preferable in sandy soil due to the slow release of hexazinone which reduces loss from the soil due to percolation (Glover et al. 1991).

The identity of all inerts for each formulation has been disclosed to the U.S. EPA as part of the registration process and this information has been reviewed in the preparation of this risk assessment (Section 3.1.15). The specific studies are specified in Table 2-2. This information is classified as CBI (confidential business information) under Section 7(d) and Section (10) of FIFRA. Some information, however, is available in the open literature. 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).

2.3. APPLICATION METHODS

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 (C&P Press 2004, Pro-Serve 2004). Velpar ULW DF granules may be applied only by helicopter using the Du Pont ULW Applicator. 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.

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).

Brown (with hexazinone) and burn treatment accelerates pine release relative to standard prescribed burns without the use of a herbicide (Bush et al. 1986; Haywood 1994, 1995). 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. Generally, burns are not conducted until 45–180 days after treatment.

2.4. MIXING AND APPLICATION RATES

The specific application rates used in a ground application vary according to local conditions and the nature of the target vegetation. As detailed in Table 2-2, the application rates for hexazinone vary substantially with the purpose of the application (e.g., site preparation, conifer release, and control of undesirable woody vegetation), type of soil, and region of the country. The highest labeled application rate for any application is about 8 lbs a.i./acre – the upper range of the application rate of 10.66 lbs Velpar ULW/acre for the control of woody vegetation. Lower application rates – i.e., in the range of about 2 lbs a.i./acre to 5 lbs ai./acre – are used for site preparation. For conifer release, labeled application rates range from about 0.75 lbs a.i./acre to 3 lbs a.i./acre depending on soil type.

The uses of hexazinone in Forest Service Programs for the years 2000 through 2003 are summarized in Table 2-3 in terms of vegetation management objective. In terms of acres treated, the uses of hexazinone are about equally divided between site preparation and conifer release. As noted above, the application rates for site preparation are higher than those for conifer release and thus the use in terms of total pounds is substantially greater for site preparation (85% of total) than for conifer release (about 15% of total). All other uses for hexazinone are insubstantial – a total of about 64 lbs or about 0.4% of total use by weight. Based on the total amount used and number of acres treated, the average application rate for hexazinone is approximately 1.8 lbs/acre. The maximum application used in any Forest Service program was 4 lbs/acre. As noted in Table 2-3, this excludes a reported application of 17.25 lbs/acre, which is far above any labeled use rate and is probably a reporting error.

For this risk assessment, the typical application rate for hexazinone will be taken as 2 lbs/acre, which is the approximate average application rate for all applications conducted by the Forest Service from 2000 to 2003 rounded to one significant digit. The range of application rates will be taken as 0.5 lbs/acre to 4 lbs/acre. The lower end of this range is based on the average application used in Forest Service programs for conifer release. The upper end of this range is based on the maximum reported application rate in any Forest Service program. As noted in Table 2-3, this occurred in Forest 7 in Region 8 in 2000 and 2001.

In site-preparation and conifer release, mixing volumes of about 5 gallons per acre are recommended for aerial applications and 25 gallons per acre are recommended for ground applications of Velpar L. The other granular formulations are typically applied without mixing with water although liquid applications may be made for some minor uses. For this risk assessment, the extent to which these formulations are diluted prior to application primarily influences dermal and direct spray scenarios, both of which are dependent on the 'field dilution' (i.e., the concentration of hexazinone in the applied spray). The higher the concentration of hexazinone , the greater the risk. For this risk assessment, the lowest dilution will be taken at 5 gallons/acre, the minimum recommended for aerial applications. The highest dilution (i.e., that which results in the lowest risk) will be based on 25 gallons of water per acre, the application volume recommended for ground broadcast applications. The central estimate will be taken as 10 gallons per acre, the approximate geometric mean of the range. The exposures for applications of granular formulations are addressed as a special case as detailed in Section 3.2.2.

2.5. USE STATISTICS

The USDA Forest Service (USDA/FS 2002) tracks and reports its use of pesticides by geographical areas referred to as "*Regions*". As illustrated in Figure 2-1, the Forest Service classification divides the U.S. into nine regions designated from Region 1 (Northern) to Region 10 (Alaska). [Note: There is no *Region 7* in the Forest Service system.] As illustrated in Figure 2-1 and detailed further by region in Table 2-4, the use of hexazinone by the Forest Service between 2000 and 2004 occurred predominantly in the southern region (96.4% of total by weight) with much lesser amounts used in the Pacific Northwest Region (3%) and Pacific Southwest Region (1%). The use of hexazinone in other regions has been insubstantial. The total amount of hexazinone used in all regions over the four year period was about 14,680 lbs (Table 2-2) for an average of about 3,700 lbs/year.

Hexazinone is used on a number of crops and a summary of the agricultural uses of hexazinone is presented in Figure 2-2 (USGS 1998a). These use statistics are for 1992, the most recent year for which data are available. As indicated in this figure, about 46,150 lbs of hexazinone were applied to crops, primarily to alfalfa hay (95% of total). Other minor uses include blueberries, field and grass seed, and sugar cane. The geographic distribution of the agricultural uses of hexazinone is broader than the uses by the Forest Service, which cover all Forest Regions except Regions 1 and 2 (Northern and Rocky Mountain Regions). Most of the agricultural applications of hexazinone occur in Regions 5, 6, and 9. The average use of hexazinone by the Forest Service from 2000 to 2004 (3,700 lbs/year) is about 8% of the amount used in agriculture in 1992.

More recent data are available on the total amounts of pesticides applied in California in 2001 (California Department of Pesticide Regulation 2002). During 2001, about 99,302 lbs of hexazinone were applied in California (California Department of Pesticide Regulation 2002, p. 185). Between 2000 and 2004, the average amount used by the Forest Service in California was about 46 lbs/year – i.e., about 0.05% of the total. The total average use by all regions – i.e., 3,700 lbs/year – is only about 3.7% of the total applied in California during 2001. Thus, based both on the national data from 1992 (USGS 1998a) as well as the more recent data from California (California Department of Pesticide Regulation 2002), it appears that the use of hexazinone in Forest Service programs is minor relative to the total amount of hexazinone used in agriculture and in other non-Forest Service applications.

3. HUMAN HEALTH RISK ASSESSMENT

3.1. HAZARD IDENTIFICATION

3.1.1. Overview

The toxicity of hexazinone has been relatively well-characterized in a number of standard bioassays that are required by U.S. EPA for the registration on pesticides. Acute oral toxicity studies indicate the the oral LD_{50} for hexazinone in mammals is in the range of 1000 mg/kg. No adverse effects are anticipated at ten-fold lower doses – i.e., 100 mg/kg/day – based on the results of short-term repeated dosing. Standard chronic toxicity studies indicate that long-term exposures to hexazinone at doses of about 5 mg/kg/day will not be associated with any identifiable adverse effect.

At very high doses – i.e., those in the range of the LD_{50} – lacrimation, salivation, vomiting, tremors/ataxia/weakness, diarrhea, and increased rates of respiration and/or labored breathing are often noted. While these types of effects can be caused by neurotoxins, they are not specific indicators of neurotoxicity and these effects may be secondary to other mechanisms of toxicity. There is no basis for assuming that hexazinone is a direct neurotoxin. In less severely poisoned animals, the most commonly noted effect induced by hexazinone is weight loss. In mice and dogs, this effect is usually associated with and attributable to a decrease in food consumption. In rats, particularly female rates, weight loss has been associated with a decrease in food conversion efficiency. The underlying mechanism for the decreased food conversion efficiency is unclear.

Hexazinone appears to be rapidly absorbed after oral exposure and it is rapidly metabolized and excreted. While hexazinone seems to be absorbed much more slowly during dermal exposures compared to oral exposures, the available acute and longer-term dermal studies indicate that hexazinone may be absorbed by the skin in sufficient amounts to cause at least sensitive signs of toxicity, particularly weight loss. While hexazinone is only mildly irritating to the skin, it is severely irritating to the eyes.

Certain types of effects are of particular concern and are assessed with a specific subset of toxicity tests. Such effects include those on the nervous system, immune system, endocrine function, development or reproduction, and carcinogenicity or mutagenicity. Hexazinone does not appear to be a direct neurotoxin and hexazinone does not appear to cause effects on the immune system. While somewhat speculative, the effects on food conversion efficiency could be related to effects on the endocrine system. This, however, has not been clearly demonstrated. Except at doses that cause frank signs of toxicity in females, hexazinone does not appear to cause birth defects or other adverse effects on the young. Two standard carcinogenicity studies are available on hexazinone, one in mice and the other in rats. The results of the assay in mice indicated no carcinogenic potential but the results in rats were equivocal. Consequently, the U.S. EPA determined that hexazinone is *not classifiable as to human carcinogenicity* and declined to quantify cancer risk.

3.1.2. Mechanism of Action

While the mechanism of action of hexazinone in plants is well understood (Section 4.1.2.4), relatively little information is available on the specific mechanism(s) of toxicity of hexazinone in humans or other species of mammals. While hexazinone is classified as a triazine herbicide, hexazinone is structurally different from and *is not likely to be toxicologically related to other triazine pesticides* (U.S. EPA 2002h, pp. 14-15).

As discussed in the following subsections and detailed in Appendix 1 (acute toxicity) and Appendix 2 (subchronic and chronic toxicity), the toxicity of hexazinone has been examined in a relatively complete set of standard toxicity studies. Some signs of toxicity commonly associated with high dose exposures to hexazinone are suggestive of neurologic effects – i.e., lacrimation, salivation, vomiting, tremors/ataxia/weakness, diarrhea, and increased rates of respiration and/or labored breathing (Appendices 1 and 2). These signs of toxicity are common to effects seen after exposure to cholinesterase inhibiting pesticides (ATSDR 1993). As discussed in Section 3.1.6, specific assays on the potential neurotoxicity of hexazinone have not been conducted. In addition, the U.S. EPA (2002h) has reviewed a large number of studies on the toxicity of hexazinone and found no basis for requiring specific tests for the neurotoxicity of hexazinone.

Another commonly noted effect in toxicity studies on hexazinone involves a loss of body weight or decreased weight gain. This type of effect can be secondary to other toxic effects but it has also been associated with some agents that alter endocrine function (Section 3.1.8). Weight loss or reduced body weight gain have been noted in several acute toxicity studies after oral exposure (Culik et al. 1974; Gluck 1983a; Mullin 1987; Redgate and Sarver 1986; Sarver 1989; Filliben 1994b,c), dermal exposure (Finlay 1994d,g; Gargus et al. 1983a; Vick and Sarver 1986a), and inhalation exposure (Bamberger 1994a; Bamberger 1994b; Finlay 1995). These effects (loss of body weight or decrease weight gain) have also been reported in several subchronic or chronic oral toxicity studies (Kennedy 1984; Goldenthal and Trumball 1981) and reproduction studies (Kennedy and Kaplan 1984; Mebus 1991; Mullin 1987; Munley 2002; Serota et al. 1980). In most instances, the loss of body weight is slight (i.e., in the range of 5% or less) although some more substantial decreases in body weight have been observed (e.g., 12% in rats in the study by Finlay 1995 and up to about 20% in dogs in the study by Dalgard 1991).

The reduced body weight in experimental mammals has often been associated with and appears to be secondary to decreased food consumption (Kennedy and Kaplan 1984 ; Mebus 1991; Serota et al. 1980). For example, in a two year feeding study in mice, decreased body weight was associated with a decrease in food consumption (Goldenthal and Trumball 1981). While decreased body weights in mice were noted at all dietary concentrations, these effects appeared to be related solely to a decrease in food consumption and were not associated with a change in food efficiency ratios. A similar pattern is seen in dietary exposures in dogs (Dalgard 1991). In this study, statistically significant decreases in body weight were associated with statistically significant decreases in food consumption and the magnitudes of the decreases were similar – i.e., a 16.7% decrease in the body weight of female dogs which was accompanied by a 22.2% decrease in food consumption.

The only notable exception appears to be in female rats. In a two year feeding study in rats (Kaplan et al. 1987), decreased body weight gain was attributed to decreased food consumption in males. In female rats, however, this effect was attributed to a decrease in food conversion efficiency rather than a decrease in food consumption (U.S. EPA/OPP 1994a). Similarly, in a dietary developmental study in rats, decreased body weight was noted and this effect was attributed to a decrease in food conversion efficiency (from the study by Culik et al. 1974 as reviewed by U.S. EPA/OPP 2002g,h). In a multi-generation reproduction study (Mebus 1991), a decrease in food conversion efficiency was noted in male rats at high doses (5000 ppm in the diet) but this effect was more pronounced and noted at lower doses in female rats. As noted above, diarrhea has been noted in some studies in both rats (Munley 2002) and dogs (Kennedy 1984). Diarrhea does not appear to be sufficiently prevalent or pronounced to fully account for the apparent decrease in food conversion efficiency.

There is relatively little information available on organ or tissue effects to suggest any specific mode of action. Tissue pathology in animals with signs of acute poisoning is generally non-specific or unremarkable (Appendix 1 and Appendix 2). Many of the observed effects on various organs indicate general tissue congestion or other signs of damage that are commonly observed in organisms after fatal exposure to any one of a wide variety of agents.

3.1.3. Pharmacokinetics and Metabolism

3.1.3.1. Metabolism – The known metabolites and presumed metabolic pathways for hexazinone are summarized in Figure 3-1. This figure is based on a number of studies in mammals including humans (Samuel et al. 1991, 1992), rats (Rapisarda 1980), goats (Hawkins et al. 1992a,c; Holt et al. 1979; Rapisarda 1978), and cattle (Mulcahey et al. 1995), studies in birds (Hawkins et al. 1990a; Hawkins et al. 1992b; Hawkins et al. 1993c,d) as well as studies in vegetation (Bollin 1991; DuPont De Nemours 1979; Rapisarda 1979) and soil (Priester and Sheftic 1990). Several of the studies conducted in the late 1970's have been reviewed by Fisher (1980) and the more recent studies have been reviewed by the U.S. EPA in the preparation of the RED for hexazinone (U.S. EPA 1994a,c) as well as the reassessment of hexazinone conducted in response to the requirements of the Food Quality Protection Act (U.S. EPA 2002g,h).

Hexazinone is extensively metabolized in mammals and in the environment (i.e., vegetation and soil) and the metabolic pathways appear to be similar. While Figure 3-1 may appear complex, the metabolic transformations are limited to hydroxylation (addition of a -OH group), demethylation (removal of a $-CH_3$ group), and oxidation (replacement of the dimethylamino group, $-N(CH_3)_2$ with a double bond oxygen, =O). These are relatively simple and common processes in the metabolism of many pesticides as well as other compounds that occur naturally in the body. All of these steps tend to make the metabolites more water soluble and increase the rate of excretion by the kidney (i.e., urinary as opposed to fecal excretion). While detailed studies on the kinetics of excretion have not been encountered (Section 3.1.3.3), only metabolites of hexazinone and no hexazinone itself are recovered in the urine and feces. In addition, both urinary and fecal excretion are rapid – i.e., urinary excretion is virtually complete within 48 hours and fecal excretion virtually complete within 72 hours. Thus, the metabolism of hexazinone by mammals appears to be both essentially complete and very rapid.

In terms of the hazard identification, the extensive and rapid metabolism of hexazinone in mammals (*in vivo* metabolism) and in the environment add relatively little complexity to this risk assessment. The standard *in vivo* bioassays on hexazinone involve exposures to both hexazinone itself as well as the metabolites of hexazinone. Consistent with the approach taken by U.S. EPA (e.g., U.S. EPA 2002 g,h), this risk assessment will assume that the metabolites of hexazinone are equally toxic to hexazinone itself. This recognizes the simple reality that humans, other mammals, and other species considered in this document are exposed to mixtures of hexazinone and its metabolites both in toxicity bioassays as well as in instances of environmental contamination.

3.1.3.2. Absorption – Very little direct information is available on the kinetics of the absorption of hexazinone by oral, dermal, or inhalation routes. As summarized in Section 3.1.3.2, studies on the metabolism of orally administered hexazinone indicate that this compound is virtually completely metabolized in mammals (i.e., no parent compound is excreted) and that most of the excretion of metabolites occurs in the urine over a period of only two days. This implies relatively complete and rapid absorption after oral administration.

Based on a comparison of acute oral and dermal LD_{50} values (Table 3-1), it appears that the dermal absorption rate is much less than the rate of absorption after oral exposure. As illustrated in Table 3-1, the acute oral LD_{50} values for hexazinone in mammals (rats and guinea pigs) are in the range of 860 to 1200 mg/kg. Dermal LD_{50} values of hexazinone have not been determined because the dermal toxicity of hexazinone appears to be very low. Instead, limit tests have been conducted on the dermal toxicity of hexazinone. Limits tests are required by the U.S. EPA for registration (U.S. EPA/OPPTS 2005, OPPTS 870.1100) and are conducted at a single high dose of a compound, typically 2000 or 5000 mg/kg. If the compound does not cause mortality at this high dose, no additional testing is required. The limit test for the dermal toxicity using technical grade hexazinone used a dose of 5000 mg/kg bw and no mortality was noted (Filliben 1994b). Thus, additional dermal testing was not required by the U.S. EPA for the registration of hexazinone (U.S. EPA/OPP 1994a).

For the current risk assessment, dermal exposures are considered quantitatively in a number of different exposure scenarios (Section 3.2.2.2). Two types of dermal exposure scenarios are considered: those involving direct contact with a solution of the herbicide (e.g., immersion) and those associated with accidental spills of the herbicide onto the surface of the skin. As detailed in SERA (2001), dermal exposure scenarios involving immersion or prolonged contact with chemical solutions use Fick's first law and require an estimate of the permeability coefficient, K_p, expressed in cm/hour. Using the method recommended by U.S. EPA (1992), the estimated dermal permeability coefficient for hexazinone is 0.00037 cm/hour with a 95% confidence interval of 0.00024 to 0.00058 cm/hour (Worksheet B05). These estimates are used in all exposure assessments that are based on Fick's first law. For exposure scenarios like direct sprays or accidental spills, which involve deposition of the compound on the skin's surface, dermal absorption rates (proportion of the deposited dose per unit time) rather than dermal permeability rates are used in the exposure assessment. The estimated first-order dermal absorption coefficient is 0.0023 $hour^{-1}$ with 95% confidence intervals of 0.0011 to 0.0048 $hour^{-1}$. The calculations for these estimates are presented in Worksheet B06.

It should be noted that the U.S. EPA/OPP (2002g) uses a *dermal absorption factor* of 12.5%. This is based on the ratio of a 21-day dermal NOAEL value of 1000 mg/kg from the study by Malek 1989 to an oral LOAEL of 125 mg/kg/day from the 21-day reproduction study by (Munley 2002). Both of these studies are summarized in Appendix 2. This is a standard approach used by U.S. EPA. This approach is not used in Forest Service risk assessments because it does not lead to a kinetic rate constant that can be reasonably used in exposure assessments that are developed in Forest Service risk assessments. Nonetheless, it should be noted that the *factor* of 12.5% would correspond to an absorption rate 0.0056 $hour^{-1}$ if applied to a period of 24 hours [k=ln(1-0.125)/24 hours = 0.00556 $hour^{-1}$]. This is only somewhat greater than the upper range used in the current risk assessment and this could be attributed to the comparison of a dermal NOAEL to an oral LOAEL. If the EPA factor of 12.5% were applied to a 21-day period (504 hours), the duration of the studies used by the U.S. EPA, the estimated dermal absorption rate would be 0.00026 $hour^{-1}$ [k=ln(1-0.125)/504 hours = 0.0002649 $hour^{-1}$], a much lower (less protective) dermal absorption rate than that used in the current risk assessment.

3.1.3.3.Excretion – As with absorption, very little quantitative information is available on the kinetics of the excretion of hexazinone. As noted in Section 3.1.3.1 (Metabolism), hexazinone itself is so rapidly metabolized that hexazinone itself is not actually excreted. Instead, it is metabolized and the metabolites are excreted, primarily in the urine. Most metabolism studies, however, do not provide sufficient time-course information to quantify the rate of excretion. In a metabolism study on goats dosed with ^{14}C-hexazinone, 84.2% of the of the radioactivity (i.e., parent compound and metabolites) was excreted over a 5 day period. Assuming first-order excretion, this information can be used to calculate a whole-body halftime using the following relationship:

$$(1-f) = e^{-ke\,T} \qquad \text{(Eq. 3-1)}$$

where ***f*** is the proportion of the dose excreted at time, ***T***, and ***ke*** is the excretion rate. Using this relationship, ke can be estimated at 0.36 day^{-1} [ke = -ln(1-f)/t] which corresponds to a halftime of about 2.9 days [$t_{1/2}$ = ln(2)/ke]. The only other quantitative information on excretion comes from a kinetic study on the urinary excretion of hexazinone metabolites by two human volunteers (Samuel et al. 1991). Daily oral doses of 0.5 and 1.0 mg hexazinone were associated with hexazinone concentrations in the urine of 4741 and 5864 g/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.

3.1.4. Acute Oral Toxicity

Information regarding the acute oral toxicity of hexazinone is summarized in Table 3-1 and detailed further in Appendix 1. Most of the available studies are standard bioassays conducted as part of the registration process for hexazinone and hexazinone formulations. Some additional information on the acute oral toxicity of hexazinone is taken from the review by Kennedy (1984). The review by Kennedy (1984) summarizes a number of additional standard toxicity studies conducted by Du Pont, the registrant for hexazinone, but not all of these studies appear to have been submitted to the U.S. EPA in support of the registration of hexazinone. This may be because some of the studies that are summarized in the Kennedy (1984) review – e.g., the

intraperitoneal study in rats and the sublethal acute toxicity study in dogs – are not required by the U.S. EPA in the registration of pesticides.

Hexazinone has a very low order of acute toxicity to mammals and is classified by the U.S. EPA/OPP (1994a) as Category III for acute oral toxicity. As summarized by U.S. EPA/OPP (2003), this is the second lowest oral toxicity category and this category is used for pesticides with acute oral toxicity values between 500 mg/kg to 5000 mg/kg. This classification is based on the results of a standard single-dose gavage study in female rats in which the reported LD_{50} value is 1200 mg/kg with a 95% confidence interval of 1000 to 2000 mg/kg (Sarver 1989).

As summarized in Table 3-1, acute oral toxicity data on species other than rats are limited to an LD_{50} in guinea pigs of 860 (420 to 1260) mg/kg and reported non-lethal doses in dogs of 1000 and 3400 mg/kg. The dog study is not comparable to the studies in rats and guinea pigs because the dog study involved capsules rather than gavage administration. The apparently higher tolerance in dogs could be due to slow absorption from the capsule administration relative to that occurring after gavage administration. Thus, the available data on hexazinone do not permit an assessment of systematic differences in sensitivity among various species. This limitation is discussed further in Section 4 (Ecological Risk Assessment).

3.1.5. Subchronic or Chronic Systemic Toxic Effects

Systemic toxicity encompasses virtually any effects that a chemical has after the chemical has been absorbed. Certain types of effects are of particular concern and are assessed with a specific subset of toxicity tests. Such effects are considered in following subsections and include effects on the nervous system (Section 3.1.6), immune system (Section 3.1.7), endocrine function (Section 3.1.8), development or reproduction (Section 3.1.9), and carcinogenicity or mutagenicity (Section 3.1.10). This section summarizes the available information on other systemic effects and non-specific toxicity.

As summarized in Appendix 2, several subchronic and chronic studies have been conducted on hexazinone. While a summary of some of these studies has been published in the open literature (Kennedy and Kaplan 1984), all studies appear to have been conducted and/or sponsored by Du Pont and submitted to the U.S. EPA in the registration of hexazinone. These studies have been independently reviewed by the U.S. EPA for data quality and have been classified as acceptable (e.g., U.S. EPA 1994a; U.S. EPA 2002 h).

Several standard subchronic and chronic bioassays were conducted on hexazinone (Appendix 2) and none of the studies suggest a specific mode of toxic action. Most of the reported effects from longer-term exposures are limited to decreases in body weight, increases in liver weight, and changes in blood enzyme levels associated with liver toxicity. As discussed in Section 3.1.2, body weight decreases are typically slight and appear to be related primarily with decreases in food consumption rather than changes in food conversion efficiency. Although decreases in body weight appear to be non-specific rather than secondary to an identifiable mode of toxic action, this endpoint is used by the U.S. EPA (e.g. U.S. EPA/OPP 1994a, 2002h) as the critical effect for hexazinone (i.e., the toxic effect that occurs at the lowest dose level).

The study selected by the U.S. EPA for the chronic RfD is the 1-year feeding study in dogs. As detailed in Appendix 2, this study (Dalgard 1991) involved feeding male and female beagles (5 per sex per dose) diets with concentrations of hexazinone of 0, 200, 1500, and 6000 ppm (mg hexazinone per kg diet). Decreases in body weight were noted in the mid- and high-dose groups and the U.S. EPA/OPP (2002h) has characterized the effect as a ... *severe body weight decrement* (U.S. EPA/OPP 2002h, p. 39). As noted in Appendix 2, however, the decreases in body weight gain were statistically significant only in the female dogs at the highest dose level. In this group, the body weights were 16.7% less than the body weights in the corresponding control group – i.e., female dogs not exposed to hexazinone. Based on measured total food consumption over the length of the study, the food consumption in the high dose female dogs was about 22.2% less than that in the corresponding control animals. Thus, consistent with the results of the two year feeding study in mice (Goldenthal and Trumball 1981), the effect on body weight appears to be associated with decreased food consumption.

The interpretation of the toxicological significance of decreased body weight depends on the pathogenesis of the condition. In feeding studies such as those available on hexazinone, decreased body weight gain is 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.

Kaplan et al. (1977) noted a decrease in body weight gains of males and female rats exposed to hexazinone in the diet at 5000 ppm for two years. In males, the decrease in body weight was associated with a decrease in food consumption. In females, the decrease in body weight was associated with a decrease in apparent food conversion efficiency – i.e., the decrease in weight gain in female rats could not be attributed to a decrease in food consumption. At 1000 ppm hexazinone in the diet, female rats evidenced about a 5% decrease in body weight gain compared to controls. Again, this effect could not be attributed to decreased food consumption. As discussed in Section 3.1.2, no statistically significant difference in food conversion efficiency in mice was noted between controls and animals exposed to up to 10,000 ppm hexazinone in the diet (Goldenthal and Trumball 1981). 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. As discussed further in Section 3.3, this supports the use of decreased body weight in the dog feeding study (Dalgard 1991) as an appropriate endpoint to use in deriving a chronic RfD for hexazinone (U.S. EPA/OPP 1994a,2002h).

3.1.6. Effects on Nervous System

As discussed in Durkin and Diamond (2002), a neurotoxicant is a chemical that disrupts the function of nerves, either by interacting with nerves directly or by interacting with supporting cells in the nervous system. This definition of neurotoxicant distinguishes agents that act directly on the nervous system (direct neurotoxicants) from those agents that might produce neurologic effects that are secondary to other forms of toxicity (indirect neurotoxicants). Virtually any chemical will cause signs of neurotoxicity in severely poisoned animals and, thus, can be classified as an indirect neurotoxicant.

Based on a review of studies submitted for registration, the U.S. EPA has concluded that: *there is no evidence of neurotoxicity* (referring to direct effects on the nervous system) in the available studies on hexazinone (U.S. EPA/OPP 2002h, p. 15). Based on this determination, the U.S. EPA has waived the requirements for acute, subchronic, and developmental neurotoxicity studies on hexazinone (U.S. EPA/OPP 2002h, p. 15). No other studies specifically relating to the neurotoxicity of hexazinone have been encountered in the open literature.

Nonetheless, acute toxicity studies conducted in various mammalian species as well as in birds have noted lethargy, impaired coordination, weakness, labored respiration, and tremors in animals exposed to lethal or near-lethal dose levels of hexazinone (Appendices 1, 2, and 3). While these signs can be considered neurologic, there is no indication that the effects are attributable to direct action on the nervous system.

3.1.7. Effects on Immune System

As discussed by Durkin and Diamond (2002), a variety of tests have been developed to assess the effects of chemical exposures on various types of immune responses, including assays of antibody-antigen reactions, changes in the activity of specific types of lymphoid cells, and assessments of changes in the susceptibility of exposed animals to resist infection from pathogens or proliferation of tumor cells. No such studies have been conducted on hexazinone. As discussed in Section 3.1.11, skin sensitization studies involving hexazinone have been conducted. These studies provide information about the potential for hexazinone to act as a skin sensitizer but they provide no information useful for directly assessing the immunosuppressive potential of hexazinone.

As discussed in this hazard identification and detailed further in the appendices, the toxicity of hexazinone has been examined in numerous acute, subchronic, and chronic bioassays. Although these studies are not designed to specifically detect changes in immune function, substantial effects on immune function would likely be evidenced by observable changes in lymphoid tissue as well as changes in differential blood cell counts. No such effects have been noted. The most commonly noted changes in blood are those indicative of damage to liver cells (e.g., Dalgard 1991; Kennedy and Kaplan 1984).

3.1.8. Effects on Endocrine System

Assessment of the direct effects of chemicals on endocrine function are most often based on mechanistic studies on estrogen, androgen, or thyroid hormone systems (i.e., assessments on hormone availability, hormone receptor binding or postreceptor processing). The U.S. EPA has not yet adopted standardized screen tests for endocrine disruptors (e.g., U.S. EPA/OPP 2002h).

Hexazinone has been tested in the E-SCREEN assay (Sonnenschein and Soto 1998). This test system uses a human breast cell line (MCF-7) and measures estrogen-induced proliferation in the number of these cells and the inhibition or enhancement of this proliferation by the test agent (Soto et al. 1995). Hexazinone as well as a number of other herbicides were found to influence the activity of estrogen in this assay system (Sonnenschein and Soto 1998).

Additional inferences concerning the potential effect of hexazinone on endocrine function must be based on results from standard toxicity studies. The U.S. EPA has concluded that:

> *In the available toxicity studies on hexazinone, there was no evidence of endocrine disruptor effects* (U.S. EPA/OPP 2002h, p. 19).

While this statement is substantially correct, some studies have suggested that hexazinone exposures may be associated with reductions in food conversion efficiency – i.e., reduced body weights that cannot be directly attributed to decreases in food consumption. This effect has been demonstrated clearly in female rats in three studies (Culik et al. 1974; Kaplan et al. 1987; Mebus 1991) and in male rats in one study (Mebus 1991). Kaplan et al. (1987) did note a decrease in food conversion efficiency in male rats but this effect was not dose-related – i.e., it was noted in the 1000 ppm exposure group but not the 2500 ppm exposure group.

In addition, Kaplan et al. (1987) reported a statistically significant dose-related increase in thyroid C-cell adenomas in male rats. The differences were not statistically significant, however, based on comparisons of incidence of these adenomas in any exposed group relative to the incidence in the matched control group. The occurrence of thyroid tumors is noteworthy because thyroid adenomas can secrete thyroxine (also known as thyroid hormone or T_4), which causes weight loss through an increase of the basal metabolic rate, thereby leading to a hyperthyroid state (Hansen 1998). While hexazinone may not directly disrupt the endocrine system, thyroid adenomas may secondarily cause of weight loss through alteration of thyroid function. The development of adenomas seen in this study, however, cannot be clearly related to the more commonly seen decrease in food conversion efficiency noted in other studies.

As noted by U.S. EPA/OPP (2002h), the EPA may elect to have hexazinone screened for effects on endocrine function once standardized screening assays have been developed. Such tests would help to clarify any possible endocrine involvement associated with exposure to hexazinone.

3.1.9. Reproductive and Developmental Effects

3.1.9. 1. Developmental Studies – Developmental studies are used to assess whether the compound has the potential to cause birth defects or other adverse effects on the embryo or fetus. These studies typically entail gavage administration to pregnant rats or rabbits on specific days of gestation. Teratology assays as well as studies on reproductive function (Section 3.1.9.2) are typically required for the registration of pesticides. Protocols for developmental studies have been established by U.S. EPA/OPPTS (2005).

Hexazinone has been subject to a relatively complete set of studies for teratogenicity including a gavage study in rats (Mullin 1987), a dietary study in rats (Culik 1974), and two gavage studies in rabbits (Munley 2002; Serota et al. 1980). The results of these bioassays are summarized in Appendix 2. At doses that cause signs of maternal toxicity – i.e., the 900 mg/kg/day dose group in rats from the study by Mullin 1987 – kidney malformations and delayed bone development were observed in offspring. At lower but still maternally toxic doses, only delayed bone

development was observed – i.e., the 125 mg/kg/day dose group in rabbits from the study by Serota et al. 1980. As discussed in Section 3.1.2 and Section 3.1.8, decreased body weights were commonly observed in both dams and offspring in these studies on rats and rabbits.

3.1.9.2. Multigeneration Reproduction Studies – Reproduction studies involve exposing one or more generations of the test animal to the compound. Relatively standardized protocols for reproduction studies have been established by U.S. EPA/OPPTS (2005) – i.e., OPPTS 870-3800. The general experimental method involves dosing the parental (P) generation (i.e., the male and female animals used at the start of the study) to the test substance prior to, during mating, after mating, and through weaning of the offspring (F1). In a two-generation reproduction study, this procedure is repeated with male and female offspring from the F1 generation to produce another set of offspring (F2). During these types of studies, standard observations for gross signs of toxicity are made. Additional observations often include the length of the estrous cycle, assays on sperm and other reproductive tissue, and number, viability, and growth of offspring.

A single two-generation reproduction study (Mebus 1991) has been submitted to and reviewed by the U.S. EPA (U.S. EPA/OPP 1994a, 2002g,h). As summarized in Appendix 2, this study involved male and female rats fed diets containing hexazinone at concentrations of 0, 200, 2000, and 5000 ppm (mg/kg diet). At 200 ppm, no effects were noted on offspring or adults. The only frank reproductive effect involved decreased pup survival at 5000 ppm. At 2000 ppm, the only effect on offspring was decreased body weight. At this concentration, decreased body weight and decreased food consumption were also noted in the parental generation.

As noted in Section 3.1.2, decreased body weight is commonly seen in experimental mammals after exposure to hexazinone but it not always associated with a decrease in food conversion efficiency. In the Mebus (1991) study, statistically significant changes in food consumption were seen in F_1 males at 5000 ppm (90% of controls) and this was accompanied by a significant decrease in food conversion efficiency (93% of controls). In the pre-mating period for P_1 and F_1 females, food consumption was not significantly reduced. Statistically significant decreases in food conversion efficiency, however, were seen in P_1 females at 2000 ppm (80% of controls) and 5000 ppm (64% of controls) and in F_1 females at 5000 ppm (90%) of controls. During gestation, decreased food conversion efficiency was also seen in P1 female rats in the 5000 ppm dose group (81% of controls). This effect was not noted in the F1 female rats.

Two additional reproduction studies have also been conducted on Crl-CD rats. These studies have been summarized in the open literature review by Kennedy and Kaplan (1984) but are not addressed in risk assessments by the U.S. EPA (e.g., U.S. EPA/OPP 1994a, 2002g,h) and were not noted in a search of the FIFRA submissions conducted for the current Forest Service risk assessment. The studies (summarized in Appendix 2) are consistent with Mebus (1991) indicating decreased weight gain at high dietary concentrations – i.e., 2500 ppm and 5000 ppm. Consistent with the study by Mebus (1991) no adverse reproductive effects were noted at any concentration.

3.1.9. 3. Target Organ Toxicity – As part of most standard acute and chronic toxicity studies, observations are often made on reproductive tissue – e.g., ovaries and testes. No specific signs

of toxicity in these tissues have been noted in the studies on hexazinone. Very little hexazinone, either as parent or metabolite, is found in the ovaries or testes (Rapisarda 1980; U.S. EPA 1994a, p. 14). A decrease in absolute testes weight as well as the absolute weight of many other organs was noted in male dogs in the chronic feeding study in dogs (Dalgard 1991) as well as in rats in the multigeneration study by Mebus (1991). This effects, however, appeared to be secondary to a general decrease in body weight and do not appear to indicate any organ specific toxicity. This is noted by U.S. EPA/OPP (2002g) in the review of the Mebus (1991) study: *The testes weight changes in males would appear to be incidental* (U.S. EPA/OPP 2002g, p. 13).

3.1.10. Carcinogenicity and Mutagenicity

Three kinds of data are commonly used to assess potential carcinogenic hazard. These data include epidemiology studies, bioassays on mammals, and tests for genetic toxicity, including mutagenicity. No epidemiology studies have been encountered on the literature that would permit an assessment of the association of exposure to hexazinone with the development of cancer in humans.

Two standard chronic toxicity/carcinogenicity studies are available, one in mice (Goldenthal and Trumball 1981) and the other in rats (Kaplan et al. 1977). These studies are summarized in Appendix 2 and the signs of systemic toxicity observed in these studies are discussed in Section 3.1.5. Both of these studies have been reviewed by U.S. EPA and classified as acceptable (U.S. EPA/OPP 1994a, 2002g,h). In the bioassay using rats (Kaplan et al. 1977), no statistically significant increases in tumor incidences were observed except for a dose-related trend in C-cell thyroid tumors. Interpretation of the study by the U.S. EPA is as follows: *Under the conditions of this study, carcinogenic potential of hexazinone is considered negative* (U.S. EPA/OPP 2002g, p. 18). Similar results were noted in the study using mice (Goldenthal and Trumball 1981). Although no statistically significant increase in the incidence of malignant tumors was observed in terms of pair-wise comparisons (i.e., control group vs a treated group), a number of liver endpoints did evidence a statistically significant dose-response relationship. These effects included abnormal cellular foci in males as well as all hepatocellular neoplasms combined and hepatocellular adenomas in females. This study was classified by the U.S. EPA as follows: *evidence of carcinogenic potential was equivocal: a positive trend test for neoplasia was observed in female mice, but no significant difference was determined by pair-wise comparison* (U.S. EPA/OPP 2002g, pp. 16-17).

As discussed in U.S. EPA (1994a, 2002g,h), 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 (about 4,000 mg/L) and above, with and without metabolic activation.

The World Health Organization (i.e., International Programme on Chemical Safety or the International Agency for Research on Cancer) have not evaluated the carcinogenicity of hexazinone. Based on the weight of evidence, the U.S. EPA's ...*Health Effects Division*

Carcinogenicity Peer Review Committee (CPRC) concluded that hexazinone should be classified as a Group D (not classifiable as to human carcinogenicity) (7/27/94) (U.S. EPA/OPP 2002g, p. 16). Consequently, the U.S. EPA did not conduct a quantitative risk assessment for carcinogenicity associated with exposures to hexazinone. This risk assessment will defer to the position taken by the U.S. EPA and no quantitative risk assessment for carcinogenicity will be proposed.

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

Studies on effects of pesticides and pesticide formulations are relatively standardized and include assays for acute eye irritation (OPPTS 870.2400), acute dermal irritation (OPPTS 870.2500), and skin sensitization (OPPTS 870.2600). The acute irritation studies typically involve rabbits. The test material is applied either to one eye of the animal or to an area of the skin (intact or abraded). In the eye irritation studies, the untreated eye of the animal typically serves as the control. In the dermal studies, an untreated area of the skin typically serves as a control. Both eye and skin irritations studies are used to classify pesticides (corrosive to non-irritant) and these classifications reflect how the pesticide or pesticide formulations must be labeled.

Based on the available studies in rabbits, hexazinone and hexazinone formulations appear to cause only minimal irritation to the skin but may cause substantial and persistent damage to the eyes. Severe eye irritation has been noted for both technical grade hexazinone (Dashiell and Henry 1982a). These investigators as well as U.S. EPA/OPP (2002g, p. 5) have classified technical grade hexazinone as a severe eye irritant. Severe eye irritation has also been noted for several hexazinone formulations, as detailed in Appendix 1. Very limited incident data on humans suggests the potential for severe effects on the skin. As noted by the U.S. EPA/OPP (2002f), however, the incidents associated with hexazinone involve relatively few cases and no clear conclusions can be drawn from these incidents alone.

3.1.11.1. Effects on the Skin – Information on the irritant effects of hexazinone and hexazinone formulations is summarized in Appendix 1. Hexazinone itself is a mild skin irritant that the U.S. EPA classifies as Category 4, the least toxic category used by U.S. EPA for skin irritation. This classification is based on the the Dashiell and Henry (1982b) study in which minor irritation was seen in rabbits on Days 1 to 3 of the study but irritation was seen by Day 4 – i.e., three days after the compound was removed.

As detailed in Appendix 1, some formulations of hexazinone appear to cause little if any irritant effects. These include Velpar L (Finlay 1994h), Pronone 25G (Fitzgerald 1991d), and Pronone 10G (Gluck 1983c). No formulations appear to cause substantial or severe skin irritation. Nonetheless, a few formulations appear to cause somewhat greater skin irritation than hexazinone itself. These formulations include an unspecified Velpar formulation (Filliben 1994d), a 75% hexazinone formulation that appears to be Velpar DF (Finlay 1994f), Velpar 75 DF (Sarver 1995b; Vick and Sarver 1986b). *[Note for Reviewers and Readers: Some studies on formulations that are submitted to EPA identify the formulation only by an internal company specific code. While these codes can sometimes be linked to a specific formulation, this is not*

possible in all cases. This is a common problem in the the review of studies on pesticide formulations.]

While there is minor variability in the results of studies on dermal irritation, studies on hexazinone and hexazinone formulations indicate consistently that these materials do not cause dermal sensitization.

The U.S. EPA/OPP (2002f) has identified incident reports involving the effects of dermal exposure in humans. One worker reported a relatively severe effect – i.e., skin peeling on the hands and feet – and another worker reported burning and red welts on the legs. Both of these incident appear to have involved backpack applications of liquid formulations. It should be noted that essentially all of these reports come from the OPP Incident Data System (IDS). These are characterized by EPA (2002f) as generally representing anecdotal reports or allegations.

3.1.11.2. Effects on the Eyes – Unlike effects on the skin, there is ample evidence that hexazinone can cause severe eye irritation. Based on the study by Dashiell and Henry (1982a), the U.S. EPA/OPP (2002g, p. 3) has classified hexazinone as a severe eye irritant – i.e., Category I, the classification given to the most hazardous compounds. As detailed in Appendix 1, the study by Dashiell and Henry (1982a) noted mild to moderate corneal opacity and moderate iritis in the unwashed eyes of rabbits after the application of technical grade hexazinone.

Severe eye irritation has also been noted in tests on several formulations of hexazinone including an unspecified Velpar formulation (Filliben 1994c), a 75% hexazinone formulation that appears to be Velpar DF (Finlay 1994e), and Velpar 75DF (Grandizio and Henry 1986; Henry 1995). The Pronone formulations, however, appear to be less irritating than hexazinone or the other hexazinone formulations. In rabbits, Pronone 25G failed to cause any irritation (Fitzgerald 1991e) and Pronone 10G caused only transient irritation, with complete recovery by Day 7 of the study (Gargus et al. 1983b). It is unclear why Pronone 25G would be less irritating than Pronone 10G.

The U.S. EPA/OPP (2002f) has also identified incident reports involving the effects of effects on the eyes of individuals after exposure to hexazinone. Temporary eye irritation was reported in workers who were exposed to hexazinone in a mixture with other pesticides (not identified) for a period of about 1.5 hours in an enclosed area. An incident of eye irritation was also summarized by U.S. EPA/OPP (2002f) based on a survey of Poison Control Center Data. One individual reported eye irritation that was sufficient to cause the individual to seek medical care. Other details are not provided.

3.1.12. Systemic Toxic Effects from Dermal Exposure

3.1.12.1. Acute Dermal Toxicity – Most studies on the dermal toxicity of pesticides involve acute (single application) exposures and follow relatively standard protocols – e.g. acute dermal irritation assay given in OPPTS 870.2500. As summarized in Table 3-1, standard acute dermal toxicity studies are available on hexazinone and several hexazinone formulations. It is important to note that all of these studies are "limit tests". In limits tests, the compound or formulation is applied at a single *high* dose. As defined by the U.S. EPA/OPP (2005), the limit for dermal

toxicity studies is at least 2000 mg/kg. In all of the acute dermal toxicity studies summarized in Table 3-1, no mortality was noted. Consequently, no further testing was required by the U.S. EPA. All of the products were tested at 5000 mg a.i. or formulation per kilogram body weight except Pronone 10G which was tested at 2000 mg/kg. This difference is probably due simply to the fact that the U.S. EPA/OPP (2005) requires precautionary label statements unless the limit test demonstrates that the dermal LD_{50} is above 5000 mg/kg. The very low dermal toxicity of hexazinone and hexazinone formulations (EPA Category IV) is probably due to the low dermal absorption of hexazinone relative to oral absorption (Section 3.1.3.2).

Notwithstanding the low dermal toxicity ranking, it should be noted that these dermal toxicity values are not necessarily NOAELs. In some of the dermal studies on hexazinone itself as well as liquid hexazinone formulations, weight loss was noted (Filliben 1994b; Filliben 1994c; Finlay 1994d; Finlay 1994g).

Weight loss was not seen, however, with any of the Pronone formulations (Fitzgerald 1990b; Fitzgerald 1991a; Gargus et al. 1983a; Gargus et al. 1983d; Groves 1983a). This is similar to the lesser irritant effects of the Pronone formulations on the skin and eyes (Section 3.1.11). While somewhat speculative, this suggests that the matrix in the Pronone formulations (primarily clay) will effectively bind the hexazinone and reduce the irritant effects and toxicity of hexazinone.

3.1.12.2. Subchronic Dermal Toxicity – Occasionally, longer term subchronic studies such as the 21/28-day study given in OPPTS 870.2500 or the 90-day study given in OPPTS 870.3250 may be available. For hexazinone, a 21-day repeated dermal toxicity study was conducted in rabbits and submitted to U.S. EPA (Malek 1989). In addition, the publication by Kennedy (1984) summarizes two 10-day toxicity studies that were conducted by DuPont. These studies are not discussed in any of the U.S. EPA reviews (e.g., U.S. EPA/OPP 1994a, 2002g,h) and it is not clear if these studies were submitted to U.S. EPA.

In any event, as detailed in Appendix 2, no frank signs of toxicity were noted in any of these dermal studies at daily doses of up to 1000 mg/kg/day. It is noteworthy, however, that the 10-day studies both report biochemical markers of liver toxicity (e.g., an increase in a plasma enzyme, SGPT) at doses of 680 or 770 mg/kg/day (Kennedy 1984).

Referring to his study, Malek (1989) notes that there is *... no evidence in the present study that supports these earlier findings, the liver is not considered a target organ of toxicity*. Given the well-documented effects on the liver from oral toxicity studies (Appendix 2) and in the absence of any reason to discount the results of the earlier dermal studies summarized by Kennedy (1984), the basis for this conclusion is unclear.

The earlier studies summarized by Kennedy (1984) and discussed by Malek (1989) clearly suggest that longer-term dermal exposures may lead to toxicity. This is consistent with the effects noted in the acute dermal exposure studies (Section 3.1.12.1). This is an important point to the current risk assessment because, as detailed further in Section 3.3. (Exposure Assessment) many of the exposure scenarios developed in this risk assessment involve dermal exposure.

3.1.13. Inhalation Exposure

For most pesticides, particularly the herbicides covered in Forest Service risk assessments, inhalation is not a significant or substantial route of exposure (e.g., Ecobichon 1998; van Hemmen 1992). Nonetheless, as noted in Section 3.1.11.2, the U.S. EPA/OPP (2002f) reported one incident in which workers were exposed to hexazinone in an enclosed area for at least a short period of time. In addition, Spencer et al. (1996) has noted that workers applying a granular formulation of hexazinone (an unidentified Pronone formulation) have exhibited upper respiratory tract irritation (reported burning sensations in mouth, nose and throat, coughing, spitting) at the highest operational levels of exposure. Spenser et al. (1996) did not attempt to determine if the potential effects were attributable to hexazinone or the clay matrix used in Pronone formulation.

All of the available inhalation studies in experimental mammals are very short-term, involving exposures to very high concentrations of hexazinone or hexazinone formulations for a period of about 1 hour to 4 hours (Appendix 1). No mortality has been reported after exposures to hexazinone at concentrations of up to 7.48 mg/L (Bamberger 1994b; Kennedy 1984; Shapiro 1990). Consistent with the oral and dermal studies, however, several studies on both hexazinone and hexazinone formulations report decreases in body weight (Bamberger 1994a,b,c). It seems plausible to assert that this weight loss is attributable to hexazinone. The study by Shapiro 1990, reports shallow respiration and decreased movement. These types of effects are commonly observed in inhalation exposures to many compounds at high concentrations and it is unclear if this is attributable to hexazinone toxicity or simply a response to stress.

The Velpar L may be more toxic than hexazinone itself in inhalation exposures. As reported by Finlay (1995), a 4-hour exposure to Velpar L at 7.5 mg/L (corresponding to 1.8 mg a.i./L) resulted in mortality in 1/5 male and 1/5 female rats. These mortality rates, however, do not even approach statistical significance(p=0.5 using the Fisher Exact test). Nonetheless, the signs of toxicity noted by Finlay (1995) – i.e., weakness in 4/5 female rats and gasping in 1/5 female rats – seem more severe than the other inhalation studies on hexazinone and other hexazinone formulations. While the sample size is small, a response of 4/5 relative to 0/5 is statistically significant using the Fisher Exact test [p=0.02381]. As noted in Section 2, Velpar L contains ethanol at a concentration of 40-45 % of the formulation. It is plausible that these effects could be due to the narcotic action of ethanol.

3.1.14. Inerts and Adjuvants

With the exception of ethanol in Velpar L, there is very little basis for asserting that inerts play a significant role in the potential toxicity of hexazinone formulations to humans. 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 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. Based on the acute toxicity of hexazinone and Velpar L (Table 3-1), Velpar L appears to be only slightly more toxic than hexazinone in terms of hexazinone equivalents – i.e., 1030 mg a.i./kg for Velpar L and 1690 (1560-1880) mg a.i./kg for the t.g.a.i.

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. This scenario, however, 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 (Section3.1.11.2.). As noted in this section, hexazinone itself is an eye irritant and the available data are inadequate to characterize potential interactions between ethanol and hexazinone. Nonetheless, 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, however, the major component of granular formulations of hexazinone is 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 Table 3-1, the non-lethal dose of Pronone 10G is 5000 mg/kg, corresponding to 500 mg a.i./kg, in rats. This is only somewhat less than the lower range of the LD_{50} of hexazinone in male rats. As noted in previous Sections, Pronone formulations appear to less toxic than hexazinone in dermal and ocular exposures and this may be due to the sequestering of the hexazinone in the clay formulation. This is also consistent with the aquatic toxicity studies using Pronone relative to hexazinone itself (Section 4.1.3.1).

3.1.15. Impurities and Metabolites

As detailed in Section 3.1.3.1, hexazinone is virtually completely metabolized in mammals. 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. Nonlethal doses in rats for metabolites A through E have been reported in the range of 4686 mg/kg to >7,500 mg/kg (Schneider and Kaplan 1983). All of these values are substantially greater than the LD_{50} for hexazinone in rats – i.e., about 1100 mg/kg to 1690 mg/kg. Thus, as with metabolism by plants (Section 4.1.2.4), the metabolism of hexazinone by mammals appears to be a detoxication step, at least in terms of acute lethality. The U.S. EPA has made the more conservative assumption that: *the metabolites and parent hexazinone are assumed to have equal toxicity based upon similarity in chemical structure* (U.S. EPA/OPP 2002h, p. 21-22). This assumption is discussed further in the exposure assessment.

Any uncertainty with the estimates of the toxicity of the metabolites of hexazinone 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 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 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.

There is no information available in the open literature on the identity or toxicity of any impurities in hexazinone. The identity of impurities in hexazinone has been disclosed to the U.S. EPA but has not been made available for the current risk assessment. The U.S. EPA, however, has reviewed the information on the impurities and determined that:

> *There are no reported impurities of toxicological concern in hexazinone* (U.S. EPA/OPP, 2002h).

In addition, most toxicity studies covered in this risk assessment use technical grade hexazinone – i.e., a material that contains about 98% hexazinone with the remaining amount consisting of impurities. Although the lack of information in the open literature on impurities may be disconcerting to some individuals, the use of technical grade hexazinone in the toxicity studies that form the basis of the dose-response assessment for both human health and ecological effects is likely to encompass any potential toxic effect of the impurities.

3.1.16. Toxicologic Interactions

There is no direct information available on the interaction of hexazinone with other compounds. Hexazinone may be metabolized by cytochrome P-450, an enzyme system that is commonly involved in the oxidation of many xenobiotics. 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.

3.2. EXPOSURE ASSESSMENT

3.2.1. Overview

The exposure assessments for hexazinone are summarized in Worksheet E01 for workers and Worksheet E02 for the general public in two EXCEL workbooks that accompany this risk assessment. One workbook is provided for Velpar L, the only liquid formulation covered in this risk assessment. The other workbook covers the granular formulations that may be used in Forest Service program activities. The major difference between these two types of formulations involves hexazinone residues on contaminated vegetation. A field study is available that clearly indicates that granular formulations will not tend to adhere to the surface of vegetation after application to the extent seen with liquid formulations. Other differences between the exposures estimated for granular and liquid formulations are less substantial and significant. Specifically, there is no basis for asserting that worker exposure rates are likely to differ substantially between applications of granular and liquid formulations. This conclusion is based on an analysis of the deposition of hexazinone on workers during the application of a granular formulation. While somewhat counter intuitive, there is also no basis for asserting that contamination of surface or ground water is likely to be substantially different between comparable applications of granular and liquid formulations. This conclusion is based on both monitoring data as well as environmental modeling. Both workbooks contain relatively standard sets of exposure scenarios for workers and members of the general public. All exposure assessments are conducted at the typical application rate for hexazinone of 2 lbs a.i./acre. The consequences of using lower or higher application rates are discussed in the risk characterization (Section 3.4).

For workers applying hexazinone, three types of application methods are modeled: directed ground spray, broadcast ground spray, and aerial spray. Based on the limited available data on worker exposures to hexazinone, worker exposure rates typically used in Forest Service risk assessments appear to be applicable to both granular and liquid formulations of hexazinone. Central estimates of exposure for workers are approximately 0.03 mg/kg/day for aerial and backpack workers and about 0.045 mg/kg/day for broadcast ground spray workers. Upper ranges of exposures are approximately 0.3 mg/kg/day for broadcast ground spray workers and 0.16 mg/kg/day for backpack and aerial workers.

For the accidental exposure scenarios, exposure estimates for granular and liquid formulations differ. All of the accidental exposure scenarios for workers involve dermal exposures and most of these accidental exposures lead to estimates of dose that are substantially below the general exposure estimates for workers. The one exception involves wearing contaminated gloves for one-hour. The upper range of exposure for this scenario is about 0.33 mg/kg bw for liquid formulations and 0.23 mg/kg bw for granular formulations. This relatively minor difference is due to the fact that the upper range of exposure to liquid formulation exceeds the solubility of hexazinone in water, a limiting factor in exposures for the granular formulation. The high exposure to the liquid formulation appears to be associated with the presence of adjuvants in the liquid formulation (probably ethanol) that functionally increases the solubility of hexazinone in the field solution.

For the general public, the range for acute exposures is about 0.0002 mg/kg bw to about 4 mg/kg bw for granular formulations. The corresponding values for the liquid formulation is about 0.04

mg/kg bw to 4 mg/kg bw. The lower bound of exposures for the granular formulation relative to the liquid formulation is due to the lower deposition of the granular formulation on contaminated vegetation. For both formulations, the upper bound of exposure, 4 mg/kg bw, is associated with an accidental spill into a small pond. This is a highly arbitrary exposure scenario for both types of formulations.

For chronic or longer term exposures, the modeled exposures are much lower than for acute exposures. Exposures to hexazinone associated with the consumption of contaminated water or fish are identical for both granular and liquid formulations and range from about 0.000000003 mg/kg/day to 0.002 mg/kg/day. The upper bound of this range is associated with the longer-term consumption of contaminated water. For granular formulations, the longer-term consumption of contaminated vegetation leads to a similar estimated dose, about 0.006 mg/kg/day. For the liquid formulation, however, the estimated dose is much greater, about 0.16 mg/kg/day. Again, this substantial difference relates to the well-documented differences between liquid and granular formulations in the deposition of hexazinone on the vegetation.

3.2.2. Workers

The Forest Service uses a standard set of exposure assessments in all risk assessment documents. While these exposure assessments vary depending on the characteristics as well as the relevant data on the specific chemical, the organization and assumptions used in the exposure assessments are standard and consistent. All of the exposure assessments for workers as well as members of the general public are detailed in the worksheets on hexazinone that accompany this risk assessment [SERA EXWS 43-20-02a]. Detailed documentation for these worksheets is presented in SERA (SERA 2004a). This section on workers and the following section on the general public provide a plain verbal description of the worksheets and discuss hexazinone specific data that are used in the worksheets.

A summary of the exposure assessments for workers is presented in Worksheet E01 of the worksheets. Two types of exposure assessments are considered: general and accidental/incidental. The term *general* exposure assessment is used to designate those exposures that involve estimates of absorbed dose based on the handling of a specified amount of a chemical during specific types of applications. The accidental/incidental exposure scenarios involve specific types of events that could occur during any type of application. The exposure assessments developed in this section as well as other similar assessments for the general public (Section 3.2.3) are based on the typical application rate of 2 lbs a.i./acre (Section 2). The consequences of using different application rates in the range considered by the Forest Service are discussed further in the risk characterization (Section 3.4) and these risks are detailed in Worksheets E02a (central application rate), E02b (lower bound of application rate), and E02c (upper bound of application rate).

3.2.2.1. General Exposures – As described in SERA (2001), worker exposure rates are expressed in units of mg of absorbed dose per kilogram of body weight per pound of chemical handled. These estimates are derived from biomonitoring studies – i.e., studies in which the estimates of absorbed dose are based on measurements of the amount of pesticides excreted by workers. Based on analyses of several different pesticides using a variety of application

methods, default exposure rates are estimated for three different types of applications of liquid formulations: directed foliar (backpack), boom spray (hydraulic ground spray), and aerial. The general exposure rates used for each group of workers are:

directed foliar	0.003	(0.0003 - 0.01)	mg/kg per lb a.i. handled/day
boom spray	0.0002	(0.00001 - 0.0009)	mg/kg per lb a.i. handled/day
aerial	0.00003	(0.000001 - 0.0001)	mg/kg per lb a.i. handled/day.

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.

In the Quebec study (Samuel et al. 1991, 1992), 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 specified. Velpar L, 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 in Forest Service risk assessments, cannot be derived.

In the California study (Spencer et al. 1996), workers applied Pronone 10G using a *belly grinder*. Unlike the biomonitoring studies used to estimate worker exposure rates in Forest Service risk assessments (SERA 2001), the study by Spencer et al. (1996) involved measurements of exposure based on the deposition of hexazinone on hands and clothing and measurements of hexazinone concentrations in the breathing zone of the workers. 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 per lb a.i. applied to a high of 1.3 mg/kg/day per lb a.i. applied. This range, spanning a factor of about 100, is typical of ranges seen in other occupational exposure studies and this type of variability is reflected in the standard values used in Forest Service risk assessments (SERA 2001). About 97% of the estimated absorbed dose was attributed to dermal absorption (Spencer et al. 1996, Table VI, p. 15). Again, this is a common pattern in work exposures during the application of pesticides (Ecobichon 1998).

Spencer et al. (1996) provide estimates of exposure and absorbed dose rates normalized for application rate. These are not comparable to the exposure estimates used in Forest Service risk assessments (see above) which are normalized for the amount handled per day. It should be noted that Spencer et al. (1996) used an assumed dermal absorption rate of 10% per day. 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. In any event, the rate used by Spencer et al. (1996) is similar to the assumption 12.5% used by U.S. EPA/OPP (2002g). As discussed in Section 3.1.3.2, the current risk assessment uses estimated first-order dermal absorption rates of 0.0023 (0.0011 to 0.0048) $hour^{-1}$ and these estimates reasonably consistent with those of U.S. EPA/OPP (2002g).

Based on data provided by Spencer et al. (1996) and using the first-order absorption rates discussed in Section 3.1.3.2, estimates of absorbed dose-rates in units mg/kg bw per day per lb a.i. handled are given in Table 3-2. The data are for 4 groups of workers applying Pronone 10G on a total of 11 different occasions. In Table 3-2, the number of workers in each group (column 2) and the total amount of hexazinone handled by each group (column 3) is used to calculate the average amount handled per worker (column 4). This value as well as an assumed body weight of 70 kg per worker are divided into the average dermal deposition in each group of workers (column 5) to calculate the deposition rate (*DP*) in units of mg a.i./kg body weight per pound handled. The central, lower limit, and upper limit of the absorbed dose rates (*DR*) are then calculated using the first-order dermal absorption rates (*k*) of 0.0023 (0.0011 to 0.0048) $hour^{-1}$ using an 8-hour period of exposure (*t*) and the standard approach for first-order absorption (SERA 2001): $DR = DP \times (1 - e^{-kt})$.

Based on this analysis of the Spencer et al. (1996) data, the central estimate of absorbed dose rate averaged over all groups is 0.0033 mg/kg bw per lb a.i. handled. This is virtually identical to the exposure rate of 0.003 mg/kg bw per lb a.i. handled used in standard Forest Service risk assessments for the directed foliar spray of liquid pesticide solutions. In addition, the confidence intervals used in standard Forest Service risk assessments for backpack spray, 0.0003 to 0.01 mg/kg bw per lb a.i. handled/day, encompass the corresponding values of 0.0016 to 0.0068 mg/kg bw per lb a.i. handled/day based on Spencer et al. (1996) data. At the upper limit of absorbed dose rates, only one value from the Spencer et al. (1996) data – i.e., the third application at Site I – exceeds the upper range of 0.01 mg/kg bw per lb a.i. handled/day used in standard Forest Service risk assessments. Because of this reasonable correspondence between the standard assumptions for absorbed dose rate and the corresponding estimates from Spencer et al. (1996) data, no adjustments are made to the approach that is used generally in Forest Service risk assessments. The absorbed dose rate for workers involved in ground applications of granular hexazinone formulations is taken as 0.003 (0.0003 to 0.01) mg/kg bw per lb a.i. handled and this same value is used for backpack workers applying liquid formulations (Worksheet C01a).

No studies are available for workers involved in ground broadcast or aerial applications of hexazinone. For these groups, the standard absorbed dose rate estimates noted above are used to calculate the absorbed doses for workers in ground broadcast applications (Worksheet C01b) and aerial applications (Worksheet C01c).

3.2.2.2. Accidental Exposures – Typical occupational exposures may involve multiple routes of exposure (i.e., oral, dermal, and inhalation); nonetheless, dermal exposure is generally the predominant route for herbicide applicators (Ecobichon 1998; van Hemmen 1992). Typical multi-route exposures are encompassed by the methods used in Section 3.2.2.1 on general exposures. Accidental exposures, on the other hand, are most likely to involve splashing a solution of herbicides into the eyes or to involve various dermal exposure scenarios.

As summarized in Section 3.1.11, hexazinone may cause substantial and persistent damage to the eyes. The available literature does not include quantitative methods for characterizing exposure or responses associated with splashing a solution of a chemical into the eyes or the

effects of dust from hexazinone granules getting into the eyes. Consequently, accidental exposure scenarios of this type are considered only qualitatively in the risk characterization (Section 3.4).

There are various methods for estimating absorbed doses associated with accidental dermal exposure (U.S. EPA/ORD 1992; SERA 2001). Two general types of exposure are modeled: those involving direct contact with a solution of the herbicide and those associated with accidental spills of the herbicide onto the surface of the skin. Any number of specific exposure scenarios could be developed for direct contact or accidental spills by varying the amount or concentration of the chemical on or in contact with the surface of the skin and by varying the surface area of the skin that is contaminated.

For the liquid formulation covered in this risk assessment, Velpar L, two exposure scenarios are developed for each of the two types of dermal exposure, and the estimated absorbed dose for each scenario is expressed in units of mg chemical/kg body weight. Both sets of exposure scenarios are summarized in Worksheet E01, which references other worksheets in which the specific calculations are detailed. For the granular formulations, *spills* on to the hands or legs are not a meaningful scenario. Hands, legs, or other parts of the body may become contaminated with hexazinone in the normal course of use. This is discussed in the previous subsection. For accidental exposures, dust from granular formulations of hexazinone may be deposited on the skin. These exposures are estimated based on zero-order absorption, as discussed further in this section.

Exposure scenarios involving direct contact with solutions of the chemical are characterized by immersion of the hands for 1 minute or wearing contaminated gloves for 1 hour. Generally, it is not reasonable to assume or postulate that the hands or any other part of a worker will be immersed in a solution of a herbicide for any period of time. On the other hand, contamination of gloves or other clothing is quite plausible. For these exposure scenarios, the key element is the assumption that wearing gloves grossly contaminated with a chemical solution is equivalent to immersing the hands in a solution. In either case, the concentration of the chemical in solution that is in contact with the surface of the skin and the resulting dermal absorption rate are essentially constant.

Exposure scenarios involving chemical spills onto the skin are characterized by a spill onto the lower legs as well as a spill onto the hands. In these scenarios, it is assumed that a solution of the chemical is spilled onto a given surface area of skin and that a certain amount of the chemical adheres to the skin. The absorbed dose is then calculated as the product of the amount of the chemical on the surface of the skin (i.e., the amount of liquid per unit surface area multiplied by the surface area of the skin over which the spill occurs and the concentration of the chemical in the liquid), the first-order absorption rate, and the duration of exposure.

The methods used in developing these accidental dermal dose estimates are typically applied only to liquid formulations. For granular formulations, no standard methods for estimating exposure are available. Nonetheless, granular hexazinone on the surface of the skin might be regarded as analogous to exposure to a neat (undiluted) solution. For such exposures, the U.S.

EPA/ORD (1992) recommends using the solubility of the compound in water as an approximation of the concentration of the chemical on the surface of the skin. The apparent rationale for this approach is that the amount of the chemical on the surface of the skin will saturate the pore water of the skin and the limiting factor on the concentration in pore water will be solubility of the chemical in water. As indicated in Table 2-1, the water solubility of hexazinone is 33,000 mg/L (Tomlin 2005), which is equivalent to 33 mg/mL. As noted in the Worksheets for zero-order absorption for granular formulations (C02a and C02b), the concentrations of hexazinone used in these exposure assessments is set at the water solubility of hexazinone. For the Velpar L formulation, the maximum modeled concentration is 48 mg/mL. While this concentration exceeds the water solubility of hexazinone, it is used under the assumption that the adjuvants in the Velpar L formulation permit this concentration of hexazinone in the water-ethanol solution. As discussed in Section 3.4 (Risk Characterization), these exposures are substantially below a level of concern and this possibly conservative assumption has no impact on the risk characterization.

3.2.3. General Public

3.2.3.1. General Considerations – Under normal conditions, members of the general public should not be exposed to substantial levels of hexazinone. Nonetheless, any number of exposure scenarios can be constructed for the general public, depending on various assumptions regarding application rates, dispersion, canopy interception, and human activity. Several standard and highly conservative scenarios are developed for this risk assessment.

Both acute and longer-term or chronic exposure scenarios are developed. All of the acute exposure scenarios are primarily accidental. They assume that an individual is exposed to the compound either during or shortly after its application. Specific scenarios are developed for direct spray, dermal contact with contaminated vegetation, as well as the consumption of contaminated fruit, water, and fish. Most of these scenarios should be regarded as extreme, some to the point of limited plausibility. The longer-term or chronic exposure scenarios parallel the acute exposure scenarios for the consumption of contaminated fruit, water, and fish but are based on estimated levels of exposure for longer periods after application.

For some exposure scenarios, distinctions are made between the liquid formulation of hexazinone, Velpar L, and the granular formulations. As discussed in Section 3.2.2.2 for dermal exposures, accidental spills on to the surface of the skin are not relevant to granular formulations. Thus, the accidental spill Worksheets, D01a and D01b, are included in the worksheets for liquid formulations but omitted in the worksheets for granular formulations.

The most significant quantitative distinction between the granular and liquid formulations involves exposure scenarios involving contaminated vegetation. As detailed in Table 3-3 and discussed further below, residues of hexazinone on vegetation will be substantially greater with liquid formulations than with granular formulations. This pattern is not seen in exposure scenarios involving contaminated water. Based on both modeling and monitoring, peak and average concentrations of hexazinone in surface waters are likely to be similar after the application of either liquid or granular formulations. Differences may and probably will occur in

time to peak concentrations after applications of granular and liquid formulations but these differences do not have a quantitative impact on the risk assessment.

All of the exposure scenarios developed for the general public are summarized in Worksheet E02 of the workbooks for liquid and granular formulations. As with the worker exposure scenarios, details of the assumptions and calculations involved in these exposure assessments are given in the worksheets that accompany this risk assessment (Worksheets D01a–D10b). The remainder of this section focuses on a qualitative description of the rationale for and quality of the data supporting each of the assessments.

3.2.3.2. Direct Spray – Direct sprays involving ground applications are modeled in a manner similar to accidental spills for workers (Section 3.2.2.2). In other words, it is assumed that the individual is sprayed with a solution containing the compound and that an amount of the compound remains on the skin and is absorbed by first-order kinetics. For these exposure scenarios, it is assumed that during a ground application, a naked child is sprayed directly with hexazinone. These scenarios also assume that the child is completely covered (that is, 100% of the surface area of the body is exposed) (Worksheet D01a). These are extremely conservative exposure scenarios and are likely to represent upper limits of plausible exposure. An additional set of scenarios is included involving a young woman who is accidentally sprayed over the feet and legs (Worksheet D01b). For each of these scenarios, specific assumptions are made regarding the surface area of the skin and body weight as detailed in Worksheets D01a and D01b along with the sources used for making the assumptions. These exposures all involve a liquid spray and thus are not included in the workbook for granular formulations.

3.2.3.3. Dermal Exposure from Contaminated Vegetation – In this exposure scenario, it is assumed that the herbicide is applied at a given rate and that an individual comes in contact with sprayed vegetation or other contaminated surfaces at some period after the spray operation. For these exposure scenarios, some estimates of dislodgeable residue and the rate of transfer from the contaminated vegetation to the surface of the skin must be available. No such data are available on dermal transfer rates for hexazinone and the estimation methods of Durkin et al. (1995) are used as defined in Worksheet D02 of the workbooks for liquid and granular formulations. The exposure scenario assumes a contact period of one hour and assumes that the chemical is not effectively removed by washing until 24 hours after exposure. Other estimates used in this exposure scenario involve estimates of body weight, skin surface area, and first-order dermal absorption rates, as discussed in the previous section.

Although data on dislodgeable residues for hexazinone are not available, data are available indicating that total residues on plants are much greater after applications of liquid formulations than after applications of granular formulations. This is discussed further in Section 3.2.3.6 based on the data of Michael (1992) as summarized in Table 3-3 of the current risk assessment. Consequently, for the granular formulation, a downward adjustment (a factor of 25) is made to the estimate of dislodgeable residue for granular formulations. This has no impact on the risk characterization. As indicated in the workbook for liquid formulations (i.e., the higher risk), the hazard quotient for this scenario is very low (i.e., 0.01) even at the highest application rate.

3.2.3.4. Contaminated Water – Water can be contaminated from runoff, as a result of leaching from contaminated soil, from a direct spill, or from unintentional contamination from drift during an application. For this risk assessment, three exposure scenarios are considered for the acute consumption of contaminated water: an accidental spill into a small pond (0.25 acres in surface area and 1 meter deep), accidental direct spray of or incidental drift into a pond and stream, and the contamination of a small stream and pond by runoff, sediment loss, or percolation. In addition, longer-term estimates of concentrations in water are based on a combination of modeling and monitoring data. Each of these scenarios is considered in the following subsections.

3.2.3.4.1. Accidental Spill – The accidental spill scenario assumes that a young child consumes contaminated water shortly after an accidental spill into a small pond. The specifics of this scenarios are given in Worksheet D05 of the workbooks for liquid and granular formulations. Because this scenario is based on the assumption that exposure occurs shortly after the spill, no dissipation or degradation of the pesticide is considered. This scenario is dominated by arbitrary variability and the specific assumptions used will generally overestimate exposure. The actual concentrations in the water would depend heavily on the amount of compound spilled, the size of the water body into which it is spilled, the time at which water consumption occurs relative to the time of the spill, and the amount of contaminated water that is consumed.

For liquid formulations, Forest Service risk assessments use a standard scenario – the spill of 200 gallons of a *field solution* – i.e., the pesticide diluted with water to the concentration that is anticipated in Forest Service programs (Section 2). Based on the spill scenario for a liquid formulation at an application rate of 2 lbs/acre, the concentration of hexazinone in a small pond is estimated to range from about 9 mg/L to 36 mg/L with a central estimate of about 18 mg/L (Worksheet D05). These concentrations are linearly related to application rate as illustrated in the accidental spill concentrations for Worksheets G03a-c.

Applications of granular formulations are less often encountered in Forest Service programs and no standard exposure scenario has been developed for the accidental spill of a granular formulation into a small pond. As noted in Section 2.4, the central estimate of the application volume for liquid formulations of hexazinone is 10 gallons/acre with a range of 5 gallons/acre to 25 gallons/acre. Thus, a spill of 200 gallons is equivalent to an amount that would be applied to 20 acres with a range of 8 acres to 40 acres. Based on the standard application rate of 2 lbs/acre, the spill of the liquid formulation would correspond to 40 lbs with a range of 16 lbs to 80 lbs. These values are used in all of the worksheets involving spills of granular formulations into a small pond. Apart from very small rounding errors, the corresponding concentrations in water for the spill of a granular formulation are identical to those of the corresponding spill of a liquid formulation.

3.2.3.4.2. Accidental Direct Spray/drift for a Pond or Stream – These scenarios are less severe but more plausible than the accidental spill scenario described above. The U.S. EPA typically uses a two meter deep pond to develop exposure assessments (SERA 2004b). If such a pond is directly sprayed with hexazinone at the nominal application rate of 2 lbs/acre, the peak

concentration in the pond would be about 0.11 mg/L, equivalent to 110 µg/L or 110 ppb (Worksheet D10a). This concentration is a factor of about 327 below the upper bound of the peak concentration of 36 mg/L after the accidental spill of a liquid formulation and a factor of about 25 below the upper bound of the peak concentration of 2.7 mg/L after the accidental spill of a liquid formulation (Worksheets D05 in the workbooks for liquid and granular formulations). The D05 worksheets also model concentrations at distances of 100 to 500 feet down wind based on standard values adapted from AgDrift (SERA 2004a).

Similar calculations can be made for the direct spray of or drift into a stream. For this scenario, the resulting water concentrations will be dependant on the surface area of the stream that is sprayed and the rate of water flow in the stream. The stream modeled using GLEAMS (see below) is about 6 feet wide (1.82 meters) and it is assumed that the pesticide is applied along a 1038 foot (316.38 meters) length of the stream with a flow rate of 710,000 L/day. Using these values, the concentration in stream water after a direct spray is estimated at about 0.2 mg/L. Much lower concentrations, about 0.0002 mg/L to 0.03 mg/L, are estimated based on drift at distances of 25 to 900 feet (Worksheet 10b).

It should be noted that no distinction is made between the application of liquid and granular formulations. Drift estimates used in Forest Service risk assessments are based on AgDrift, a model developed as a joint effort by the EPA Office of Research and Development and the Spray Drift Task Force, a coalition of pesticide registrants (Teske et al. 2001). AgDrift does not explicitly incorporate options for the application of granular products and no field data have been encountered on drift of hexazinone after the application of granular formulations. The extent to which the general drift estimates used for liquid formulations are appropriate for granular applications is unclear. This uncertainty has little direct impact on this exposure scenario, however, because only the direct spray scenario is used quantitatively.

3.2.3.4.3. Gleams Modeling – For compounds such as hexazinone, which may be applied over a large proportion of a watershed, drift and even direct spray are not the only and may not be the greatest source of contamination of surface water. Water contamination may also occur from soil runoff, sediment, or percolation. Depending on local conditions, these losses can lead to substantial contamination of ponds or streams. Estimates of concentrations of hexazinone in surface waters can be based both on modeling and monitoring data. This section describes the relatively standardized modeling approach used in Forest Service risk assessments. This is followed by subsections on both other modeling efforts and the available monitoring data.

Modeling of concentrations in stream water conducted for this risk assessment are based on GLEAMS (Groundwater Loading Effects of Agricultural Management Systems) modeling. GLEAMS is a root zone model that can be used to examine the fate of chemicals in various types of soils under different meteorological and hydrogeological conditions (Knisel and Davis 2000). As with many environmental fate and transport models, the input and output files for GLEAMS can be complex. The general application of the GLEAMS model and the use of the output from this model to estimate concentrations in ambient water are detailed in SERA (2004b).

For the current risk assessment, the application site was assumed to consist of a 10 hectare square area that drained directly into a small pond or stream. The chemical specific values as well as the details of the pond and stream scenarios used in the GLEAMS modeling are summarized in Table 3-4.

GLEAMS is not designed to assess the application of granular formulations. Nonetheless, some attempt was made to qualitatively assess plausible differences between the application of liquid formulations and granular formulations. As discussed further in Section 3.2.3.6, one of the major differences between granular formulations and liquid formulations will be the amount that is retained on treated vegetation. As indicated in Table 3-4, the fraction applied to foliage is taken as 0.5 of the amount of liquid formulation applied. Based on the study by Michael (1992), a much lower value, 0.01, was used in a set of GLEAMS runs for granular formulations. In an attempt to mimic the slow release of hexazinone from granular formulations (e.g., Feng et al. 1989a), the proportion of clay, organic matter, and silt in upper 1 cm of soil for model runs in loam and sand was set to the values typically used for modeling clay (SERA 2004b). Other characteristics such as soil porosity and saturated conductivity were not changed because the number of granules applied in normal applications are not likely to alter these characteristics. The results of this analysis are summarized in Appendix 12.

A third set of GLEAMS runs were made assuming only negligible degradation. The results of this modeling are summarized in Appendix 13. As noted in Section 3.1.3.1, hexazinone is extensively metabolized *in vivo* by mammals and is also metabolized rapidly in the environment. As discussed in the following subsection (Section 3.2.3.4.4), the U.S. EPA/OPP (2002g,h) has attempted to model both hexazinone as well as hexazinone equivalents. This risk assessment takes a somewhat different approach. Because insufficient data are available to model all metabolites using GLEAMS, GLEAMS was rerun using the parameters for the application of the liquid formulation except that all halftimes were set to 9999 days. Using this approach, degradation over a one year period would be only about 2.5% [$\ln(2)/9999 = 0.000069$ day^{-1}, $1- e^{-0.000069 \times 365 \text{ days}} = 0.02498$]. Thus, the concentrations modeled in this run primarily reflect dispersion rather than degradation and may be used to assess exposures to hexazinone and hexazinone degradation products.

Using the adjustments for granular applications, no substantial differences were noted in the modeled values for granular applications compared to liquid applications. In general, however, the peak concentrations of hexazinone in water were modeled to be somewhat higher with granular than with liquid formulations. This can be seen by an comparison of the results in Appendix 12 with the corresponding tables cited in the body of this risk assessment. For example, the peak concentration modeled in a stream for loam was 14.4 ppb per lb a.i./acre based on the modeling approach for the liquid formulation (Table 3-5 of this risk assessment) and 24 ppb per lb a.i./acre using the modeling approach for the granular formulations (Table 3-6 in Appendix 6). Note that the same pattern is seen for clay soils, with a peak of 399 ppb using the standard approach and 435 ppb using the approach for granular formulations. For clay soils, the difference (a factor of about 9% higher for granular formulations) can be attributed only to the difference in deposition on vegetation, 0.5 for the standard approach and 0.01 for the granular formulation. The relative difference in loam soil is much greater, a factor of about 67%

[24 ppb / 14.4]. This appears to reflect the adjustment of the proportion of clay, organic matter, and silt in top soil layer for loam, as specified above. While perhaps fortuitous, a monitoring study after applications of both liquid and granular formulations also noted higher peak concentrations in streams after the application of granular compared to liquid formulations (Michael 1992). This is discussed further in Section 3.2.3.4.5 (Monitoring Studies). Only very minor differences, however, are apparent in average concentrations of hexazinone in streams or ponds. The remainder of this sections focuses on a discussion of the standard run using a liquid formulation. The differences in peak concentrations are considered further in the selection of water contamination rates used in the risk assessment (Section 3.2.3.4.6).

The GLEAMS modeling yielded estimates of runoff, sediment and percolation that were used to calculate concentrations in the stream adjacent to a treated plot, as detailed in Section 6.4 of SERA (2004b). The results of the GLEAMS modeling for the small stream are summarized in Table 3-5 and the corresponding values for the small pond are summarized in Table 3-6. These estimates are expressed as both average and maximum concentrations in water. The top section of each table gives the water contamination rates (WCR) – i.e., the concentration of the compound in water in units of ppb (µg/L) normalized for an application rate of 1 lb/acre. The bottom section of each table gives the estimated maximum and average concentrations at a rate of 2 lbs/acre (Section 2.3).

No surface water contamination is estimated in very arid regions – i.e., annual rainfall of 10 inches or less. At higher rainfall rates and the normalized application rate of 1 lb/acre, the modeled peak concentrations in streams range from about 1.5 ppb (sand at an annual rainfall rate of 15 inches) to about 400 ppb (clay soil at an annual rainfall rate of 100 inches per year) (Table 3-5).

Modeled peak concentrations in a small pond (Table 3-6) are only somewhat lower than those modeled in the stream. As with the stream modeling, no surface water contamination is expected in very arid regions. For regions with annual rainfall rates of 15 inches or more, the modeled peak concentrations in ponds at an application rate of 1 lb a.i./acre range from less than 0.00002 ppb (loam at an annual rainfall rate of 20 inches) to about 315 ppb (clay at an annual rainfall rates of 150 inches per year).

The GLEAMS scenarios do not specifically consider the effects of accidental direct spray. As discussed in Section 3.2.3.4.2, direct spray of a standard pond could result in peak concentrations of about 110 ppb, about a factor of 2 less than the 240 ppb peak concentration modeled in ponds as a result of contamination associated with severe rainfall events – i.e., 4.17 inches of rainfall. Thus, while accidental direct sprays may be worst-case scenarios in areas in which extreme rainfall events are unlikely, accidental direct sprays may not be worst-case in areas with extreme rainfall.

3.2.3.4.4. Other Modeling Efforts – A summary of the GLEAMS modeling discussed above as well as modeling of hexazinone conducted by the U.S. EPA/OPP (2002g,h) is given in Table 3-7. U.S. EPA/OPP (2002g,h) used two water contamination models: GENEEC (U.S. EPA/OPP 2001a) and SCI-GROW (U.S. EPA/OPP 2001b). These are Tier 1 screening models

developed by the U.S. EPA that are intended to provide very conservative upper range estimates of concentrations of a compound in surface water (FIRST) and groundwater (Sci-Grow) based on a given application rate, number of applications, the interval between applications, and standard environmental fate parameters for a specific compound (i.e., a subset of those summarized in Table 3-4).

The estimate of the peak concentration from FIRST is 130 ppb at an application rate of 1.5 lbs/acre. Adjusted to an application rate of 2 lbs/acre, comparable to the GLEAMS estimates given in Table 3-7, this corresponds to a concentration of about 175 ppb. This concentration is about a factor of two below the peak pond concentration modeled using GLEAMS – i.e., about 360 ppb for clay at an annual rainfall rate of 200 inches per year. The longer-term average concentration estimated using FIRST is 47.1 ppb at 1.5 lbs/acre which would correspond to a concentration of about 60 ppb at an application rate of 2 lbs/acre. This is very close to the highest average concentration modeled using GLEAMS – i.e., 61.6 ppb for sand at an annual rainfall of 25 inches per year.

One important difference between the GLEAMS modeling and the modeling presented by U.S. EPA/OPP (2002g,h) is that the GLEAMS modeling is based on concentrations of hexazinone alone while EPA/OPP (2002g,h) states that the FIRST and SCI-GROW models express results as hexazinone equivalents – i.e., hexazinone plus hexazinone metabolites. Precisely how U.S. EPA/OPP (2002g,h) determined the concentrations of hexazinone plus hexazinone metabolites is not clear. FIRST and SCI-GROW are screening models that do not explicitly incorporate the output of metabolite concentrations. As noted in Figure 3-1, there are a large number of hexazinone metabolites and the metabolic pathway is somewhat complex. In addition, information on the fate properties of the metabolites of hexazinone is not sufficient to permit explicit modeling.

As noted in Section 3.2.3.4.3, the current risk assessment considers exposure to hexazinone and hexazinone metabolites with an alternate GLEAMS run in which the degradation of hexazinone was considered negligible. For peak exposures occurring over short periods of time in which little degradation would occur, this consideration makes little difference. As noted in Table 3-6 of Appendix 13, the peak concentration rate modeled for a small pond with clay soil is 185 ppb per lb/acre, corresponding to 370 ppb at an application rate of 2 lb/acre. This is only modestly higher than the 360 ppb concentration modeled in the GLEAMS run based on normal rates of degradation (Table 3-6 of this risk assessment). Minimizing the degradation, the highest yearly average concentration in a pond with clay soil modeled by GLEAMS is about 30.3 ppb per lb/acre (Appendix 13, Table 3-6) or about 60.6 ppb at an application rate of 2 lb/acre. Again, this is only modestly different from the average value estimated by U.S. EPA/OPP (2002g,h), 63 ppb at an application rate of 2 lb/acre (Table 3-7).

The GLEAMS runs minimizing degradation (Appendix 13) do not lead to radically different peak concentrations because the maximum concentrations occur very shortly after application and are due to runoff and sediment loss. Much greater differences are seen for loam and sand, in which delayed runoff or sediment loss and percolation are more substantial factors in both peak and average values.

3.2.3.4.5. Monitoring Data – Relevant monitoring studies on hexazinone in surface and ground water are summarized in Table 3-8 and additional details of these studies are provided in Appendix 7. Two types of studies are available, general measures of background concentrations of hexazinone in water and systematic measurements of concentrations of hexazinone in water after applications of hexazinone to specific sites. A common source of general monitoring data on pesticides is the NAWQA Pesticide National Synthesis Project (USGS 2003). No data, however, are provided on hexazinone in USGS (2003). The only general study summarized in Table 3-8 is from monitoring in Maine summarized by U.S. EPA/OPP (2002h) which reported low concentrations (<4 ppb) of hexazinone in both ground and surface water.

All of the other studies summarized in Table 3-8 are studies that are associated with specific applications of hexazinone. As indicated in the first column of Table 3-8, most of these studies were conducted using Velpar L. Those studies involving granular applications are identified by a shaded background in Table 3-8.

Virtually all of the water contamination rates presented in the third column of Table 3-8 are within the range of the modeled concentrations based on GLEAMS for the pond and stream (Table 3-7). The only exception is the report by Miller and Bace (1980) of a water concentration of 2,400 ppm in a stream after a direct spray of the stream as well as applications to either side of the stream using a granular formulation at an application rate of 1.02 kg a.i./ha or about 0.9 lb a.i./acre. As indicated in Table 3-8, this resulted in an estimated water contamination rate of 3,363 ppb per lb/acre. This is about a factor of about 8 higher than any of the peak concentrations modeled using GLEAMS (i.e., 400 ppb). In terms of Forest Service programs, the direct spray of a stream would be an unintentional event. This type of event is modeled in the current risk assessment with the accidental spill scenarios (Worksheet D05 in the workbooks for liquid and granular formulations). The equivalent water contamination rate for this accidental exposure scenario is about 18,000 ppb per lb/acre, a factor of over five higher than the incident documented by Miller and Bace (1980).

The study by Bouchard et al. (1985) is among the most directly useful studies in terms of assessing the utility of the estimated concentrations of hexazinone in water based on the GLEAMS modeling. Bouchard et al. (1985) describe both the soil characteristics and the rainfall events that were associated with peak concentrations in a stream. As summarized in Appendix 7, the study by Bouchard et al. (1985) involved an application rate of 2.0 kg a.i./ha (about 1.8 lb a.i./acre) as Velpar L in an area with sandy loam/clay loam soil. The highest hexazinone concentration in stream water was 14 ppb or about 7.8 ppb per lb/acre. This concentration was monitored after a rainfall of 5.6 cm or about 2.2 inches. As summarized in Table 3-5, the estimated peak concentration rates in a stream based on loam soil texture after rainfall events of 1.39 inches and 2.78 inches are 6.38 ppb per lb/acre and 14.4 ppb per lb/acre. Interpolating to a rainfall of 2.2 inches, the estimated peak contamination rate is about 11 ppb per lb/acre, somewhat higher – i.e., a more protective estimate – than the rate of 7.8 ppb per lb/acre from Bouchard et al. (1985).

As discussed in Section 3.2.3.4.3, an attempt was made to mimic the slow release of hexazinone from granular formulations by setting the proportion of clay, organic matter, and silt in upper 1

cm soil layer for model runs in loam and sand to the values that are typically used for modeling clay. The results of this attempt (Appendix 12) were not substantially different than the standard modeling using a liquid formulation (as summarized in Table 3-5 for streams and Table 3-6 for ponds). The major difference involved somewhat higher peak concentrations in ambient water after the application of granular as compared to liquid formulations.

The lack of substantial and consistent differences between concentrations in surface water after the application of granular and liquid formulations is also reflected in the available monitoring studies (Table 3-8). The most relevant study for this comparison appears to be the study by Michael (1992). In this study, two very similar sites in adjacent stream watersheds were treated. One site was treated with Velpar ULV (a granular formulation) on one day (April 23, 1990) and the other site was treated with Velpar L (a liquid formulation) on the next day (April 24, 1990). Thus, both sites were subject to similar weather conditions. As noted in Table 3-8, the peak stream concentrations for both formulation were generally similar, ranging from 35-65 ppb for Velpar L and 40-65 ppb for Velpar ULV. The major exception was a stream concentration of 125 ppb in area treated with Velpar ULV. This was measured one day after application and after a very light rainfall (about 4mm). While somewhat speculative, it is possible that this peak associated with Velpar ULV could have been due to wind transport of the granules rather than any runoff event.

3.2.3.4.6. Concentrations in Water Used for Risk Assessment – A summary of the concentrations of hexazinone in water that are used for the current risk assessment is given in Table 3-9. The upper part of this table gives the concentrations expected at the typical application rate of 2 lbs a.i./acre in units of micrograms per liter or ppb. The lower part of this table gives the water contamination rates, the normalized concentrations in water converted to units of ppm or mg/L per lb a.i./acre. The conversion from ppb to ppm is made because hese latter units – i.e., ppm or mg/L – are used in the worksheets in the various exposure scenarios involving contaminated water in both the human health and ecological risk assessments.

The upper range of the expected peak concentration of hexazinone in surface water is taken as 800 ppb/L at the typical application rate of 2 lbs/acre. This corresponds to a water contamination rate of 400 ppb/L or 0.2 mg/L per lb/acre. This is based on the upper range of concentrations estimated in streams from the GLEAMS modeling. This concentration also encompasses accidental direct sprays of both a small stream and small pond (Table 3-7). In most instances, concentrations in surface water are likely to be much lower. At the lower extreme, an argument may be made that concentrations of hexazinone are likely to be essentially zero – i.e., applications at sites that are distant from open bodies of water and in areas in which runoff or percolation are not likely to occur. For this risk assessment, the lower range of the peak water contamination rate will be set at 0.5 ppb or 0.0005 mg/L per lb/acre. This is in the lower range of non-zero concentrations modeled in streams and ponds in relatively arid regions. The central estimate of peak water contamination rate will be taken as 100 ppb or 0.1 mg/L per lb/acre. This is based on the central estimate of the peak concentration of 200 ppb modeled in streams at an application rate of 2 lbs/acre (Table 3-7).

Longer term concentrations of hexazinone in surface water will be much lower than peak concentrations. At an application rate of 1 lb/acre, the highest longer term concentration will be taken as 70 ppb or 0.07 mg/L. This is the maximum longer term concentration modeled using GLEAMS (Table 3-6, sand, 50 inches of rain per year) and is near the maximum longer term concentration (63 ppb) given by U.S. EPA/OPP (2002h) after adjusting for differences in application rate (Table 3-7). As with lower range of peak concentrations, the lower range of longer term concentrations will approach zero. For this risk assessment, the lower range of longer term concentrations is taken as 0.00001 mg/L per lb/acre. This is based on the concentration of 0.01 ppb, the lowest non-zero value modeled for hexazinone in steams at the application rate of 2 lb/acre – i.e., 0.02 ppb divided by 2 lbs/acre = 0.01 ppb per lb/acre. This lower range is arbitrary but has no impact on the risk assessment. The central value for longer term concentrations of hexazinone in water will be taken as 20 ppb or 0.02 mg/L per lb/acre. This is based on the central estimate of the longer term concentrations in ponds modeled using GLEAMS – i.e., 40 ppb at an application rate of 2 lbs/acre. This longer term central estimate in ponds is substantially higher than the central estimate of 1 ppb for the longer term concentration in streams (Table 3-7).

As noted in Table 3-7, these water contamination rates are likely to encompass non-accidental exposures – i.e., concentrations in water that could be associated with the normal application of hexazinone. Much higher concentrations could occur by accident. These are discussed above in Section 3.2.4.1 and detailed in the D05 worksheets in the workbooks for granular and liquid formulations.

Note that only a single set of water contamination rates is used and that these are applied to both granular and liquid formulations. As discussed in 3.2.3.4.5, the available monitoring data as well as the modeling efforts do not support a quantitative distinction between the granular and liquid formulations in terms of concentrations of hexazinone in ambient water.

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. Generally, bioconcentration is measured as the ratio of the concentration in the organism to the concentration in the water and is expressed in units of kg/L.

Only one study, Rhodes (1974), has been encountered on the bioconcentration of hexazinone. As summarized in Appendix 9, bluegill sunfish were exposed to concentrations of 0.1 and 1.0 mg/L of ^{14}C-hexazinone for 4 weeks. For the edible portion, referred to as the carcass in Rhodes (1974), the first measurement of bioconcentration is reported on Day 3 of the study with a value of 1 kg/L. The maximum concentration in the edible portion is reported as 2.1 L/kg on Day 14. For all human exposures involving the consumption of contaminated fish, a BCF value of 1 L/kg will be used for acute exposures and a BCF value of 2.1 L/kg will be used for longer-term exposures.

Rhodes (1974) also provides data on concentrations of hexazinone in the liver and viscera. On Day 3, the BCF values were 1.3 L/kg for liver, and 2 L/kg for viscera. On Day 14, the BCF

values were 5 L/kg for liver and 5.5 L/kg for viscera. The higher values for viscera are used in the ecological risk assessment for all exposures involving contaminated fish.

For the acute and longer-term exposure scenarios involving the consumption of contaminated fish, the water concentrations of hexazinone used are identical to the concentrations used in the contaminated water scenarios (Section 3.2.3.4.6). The acute exposure scenario is based on the assumption that an adult angler consumes fish taken from contaminated water shortly after an accidental spill into a pond.

Because of the available and well-documented information and substantial differences in the amount of caught fish consumed by the general public and native American subsistence populations, separate exposure estimates are made for these two groups, as illustrated in Worksheet D08a and D08b. The chronic exposure scenario is constructed in a similar way, as detailed in Worksheets D09a and D09b.

3.2.3.6. Oral Exposure from Contaminated Vegetation – Although none of the Forest Service applications of hexazinone will involve the treatment of crops, Forest Service risk assessments typically include standard exposure scenarios for the acute and longer-term consumption of contaminated vegetation. Two sets of exposure scenarios are provide: one for the consumption of contaminated fruit and the other for the consumption of contaminated vegetation. These scenarios are detailed in Worksheets D03a and D03b for acute exposure and Worksheets D04a and D04b for chronic exposure.

In most Forest Service risk assessments, the concentration of the pesticide on contaminated fruit and vegetation is estimated using the empirical relationships between application rate and concentration on different types of vegetation (Fletcher et al. 1994). This is identical to the approach used by U.S. EPA/OPP (1994a) for liquid formulations.

This approach, however, is not applicable to granular formulations such as the Pronone formulations of hexazinone or Velpar ULV. This is illustrated in the study by Michael (1992) and relevant details from this study are summarized in Table 3-3. As discussed in Section 3.2.3.4.5, this study involved similar aerial applications of Velpar L and Velpar ULV. As indicated in Table 3-3, the initial residues normalized for application rate are in the range of those recommended by Fletcher et al. (1994) for Velpar L. For Velpar ULV, however, the residues are lower by factors ranging from about 26 (grass) to over 400 (blueberries). This is to be expected because granular formulation will not tend to adhere to the surface of vegetation.

For the current risk assessment, the standard residue rates from Fletcher et al. (1994) are used for Velpar L. For all granular formulations, the residue rates from Fletcher et al. (1994) are divided by a factor of 25 based on the minimum difference in residues on vegetation noted in the study by Michael (1992) after applications of granular and liquid formulations. This adjustment substantially reduces estimates of exposure to humans as well as other species for all exposure scenarios that involve the consumption of contaminated vegetation after application of granular formulations. As discussed in Section 3.4 (Risk Characterization for Human Health), this adjustment has a substantial impact on the conclusions of risk assessment.

For chronic exposures, both initial concentrations and a halftime on vegetation is required to estimate the time-weighted average exposure (Worksheet D04). Based on estimates made in the Michael (1992) study, summarized in Appendix 7, there is relatively little difference in halftimes between the liquid and granular formulations – i.e., a range of 26-59 days for the granular formulation and a range of 19-36 days for liquid formulation. For this risk assessment, the halftime of 30 days is taken from the recommended value in Knisel and Davis (2000). This has very little impact on the risk characterization for either type of formulation.

3.3. DOSE-RESPONSE ASSESSMENT

3.3.1. Overview

The U.S. EPA has derived acute and chronic RfDs for hexazinone. Following standard practices for Forest Service risk assessments, the RfD values derived by U.S. EPA are adopted directly. U.S. EPA has derived a chronic RfD for hexazinone of 0.05 mg/kg/day. This chronic RfD is well-documented and is used directly for all longer term exposures to hexazinone. This value is based on a NOAEL of 5 mg/kg/day in dogs and an uncertainty factor of 100 – two factors of 10 for interspecies and intraspecies variability. The acute RfD derived by U.S. EPA is 4 mg/kg. The RfD is based on an experimental dose of 400 mg/kg/day that did not cause any adverse effects in offspring but did cause adverse effects in dams. Again, the RfD is based on an uncertainty factor of 100. The acute RfD is applied to all incidental or accidental exposures that involve an exposure period of 1 day.

3.3.2. Chronic RfD

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 Kaplan et al. (1977), summarized in Appendix 2. In this study, 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 deriving the RfD, the U.S. EPA assumed that rats consume food at a rate equivalent to 5% of their body weight per day. Thus, the NOAEL for this study was set at 10 mg/kg bw/day (200 mg/kg food x 0.05 mg food/kg bw) and the LOAEL is 125 mg/kg/day (2500 mg/kg food x 0.05 mg food/kg bw). As noted in Appendix 2, Kaplan et al. (1977) report food consumption for the rats and the actual values for the NOAEL were 10.2 mg/kg/day for males and 12.5 mg/kg/day for females.

The RfD of 0.033 mg/kg/day 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 smaller animals consume greater amounts of food per unit body weight per day compared with larger 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 1-year feeding study in dogs (Dalgard 1991) was submitted to the U.S. EPA Office of Pesticides (U.S. EPA/OPP 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 in the Dalgard (1991) study 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/OPP 1994a).

The chronic RfD of 0.05 mg/kg/day is maintained in the more recent assessment of hexazinone (U.S. EPA 2002h,g). In the more recent assessment, the U.S. EPA did consider an additional uncertainty factor of 10 for the protection of infants and children. For hexazinone, the U.S. EPA/OPP (2002h,g) determined that the additional uncertainty factor is not required because of the information indicating that hexazinone does not have developmental or reproductive effects (loss of body weight) at doses below those associated with the same effect in dams (U.S. EPA/OPP 2002h,g, p. 15). Hence, the RfD should protect against effects in both dams and offspring.

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.

3.3.3. Acute RfD

Based on developmental studies in rats and rabbits, the U.S. EPA/OPP (2002h, pp. 15-17) identified acute dietary exposures to women of child bearing age as a potential concern and derived an acute RfD of 4 mg/kg. For the general population, no acute RfD was proposed because ... *no appropriate endpoint attributable to a single-dose* [was] *identified in the database* (U.S. EPA/OPP 2002h, pp. 15). The RfD of 4 mg/kg is based on the developmental NOAEL of 400 mg/kg/day from the study by Mullin (1987) and an uncertainty factor of 100. As detailed in Appendix 2, the dose of 400 mg/kg/day did not cause any adverse effects in offspring but did cause adverse effects in dams – i.e., weight loss and decreased food consumption – and was classified as a maternal LOAEL.

In the derivation of the acute RfD, the U.S. EPA/OPP (2002h) notes that developmental studies are also available in rabbits but does not explicitly discuss these studies in the derivation of the acute RfD. As summarized in Appendix 2, a recent developmental study in rabbits (Munley 2002) has been classified as acceptable by U.S. EPA/OPP (2002h) and this study reports a maternal and developmental NOAEL of 50 mg/kg/day and a maternal and developmental LOAEL of 125 mg/kg/day. In the preparation of this current Forest Service risk assessment, this study was considered during the peer review process as the basis for a lower alternate acute RfD of 0.5 mg/kg and the U.S. EPA's Office of Pesticide Programs was queried for a more explicit rationale for using the developmental NOAEL of 400 mg/kg/day in rats from the study by Mullin (1987) which is above the developmental LOAEL of 125 mg/kg/day in rabbits (Munley 2002). The following response to this query was provided by the Health Effects Division of OPP (Anderson 2005):

> *...the rabbit developmental toxicity study [MRID# 45677801, Munley, 2002] was not chosen because the abortions occurred later in gestation (GD 18-27) and maternal death at 175 mg/kg/day occurred late in gestation and thus could not be ascribed to a single dose. The interpretation of the survival of litters at 175 mg/kg/day where only one dam survived is meaningless. The malformations that*

> *occurred in controls and dosed groups in this rabbit study were considered random. The only fetal developmental effect at 125 mg/kg/day was based on fetal weight decrement, which the HIARC* (Hazard Identification Review Committee) *does not consider to be a single dose effect.* (Anderson 2005).

Thus, the U.S. EPA/OPP did consider the study by Munley (2002) but judged that the adverse effects seen at 125 mg/kg/day and 175 mg/kg/day were the result of exposures that occurred over the entire gestation period rather than effects that could be plausibly associated with an exposure occurring in single day. Consequently, the U.S. EPA/OPP judged that the Munley (2002) was not an appropriate study for deriving an acute RfD – i.e., the effects on fetal weight gain would be considered in longer-term exposures and would be assessed using the the chronic rather than acute RfD.

For the current risk assessment, the acute RfD of 4 mg/kg derived by U.S. EPA/OPP (2002h) is accepted and used for the characterization of risks associated with acute exposures. The rationale for the acute RfD is clear from the documentation provided by Anderson (2005) and the judgements articulated by Anderson (2005) are reasonable.

3.4. RISK CHARACTERIZATION

3.4.1. Overview

For both workers and members of the general public, pregnant women and their developing offspring are the group that may be at greatest risk due to excessive exposure to hexazinone.

Risks to workers are the dominant element in the risk characterization for potential effects in humans. Unless measures are taken to ensure that workers take measures to minimize exposure to hexazinone during applications, workers are likely to be exposed to hexazinone at levels that are greater than the chronic RfD. All of the upper bounds of the hazard quotients for the different groups of workers exceed the level of concern (HQ=1) for both the typical application rate of 2 lbs/acre (HQs ranging from 3 to 6) and the highest anticipated application rate (HQs ranging from 6 to 12). Even at the lowest anticipated application rate, 0.5 lb/acre, the upper range of the hazard quotient for workers involved in broadcast ground applications modestly exceeds the level of concern with an HQ of 1.5. Conversely, the lower bounds of the hazard quotients do not exceed a level of concern even at the highest application rate. The simple interpretation of these hazard quotients is that worker exposures to hexazinone during application are likely to exceed exposures that would generally be regarded as acceptable unless workers follow prudent handling practices that will minimize exposure.

For members of the general public, none of the acute exposure scenarios result in hazard quotients that exceed a level of concern with the exception of the accidental spill of a liquid or granular formulation into a small pond.

The only non-accidental scenarios that result in hazard quotients which substantially exceed the level of concern are those associated with longer-term exposure to contaminated vegetation after the application of Velpar L, the only liquid formulation of hexazinone considered in this risk assessment. At the highest application rate (4 lbs/acre), the consumption of contaminated broadleaf vegetation exceeds the level of concern even at the lower limit of plausible exposures: hazard quotients with a central estimate of 5 and a range of 1.1 to 45. In areas in which members of the general public might consume contaminated vegetation, particularly broadleaf vegetation or other plant products that might contain comparable residues, the use of granular formulations of hexazinone should be given preference to the use of liquid formulations.

3.4.2. Workers

A quantitative summary of the risk characterization for workers is presented in Worksheet E02a (typical application rate), Worksheet E02b (lowest anticipated application rate), and Worksheet E02c (highest anticipated application rate) of the workbooks for liquid and granular formulations. The quantitative risk characterization is expressed as the hazard quotient, which is the ratio of the estimated exposure from Worksheet E01 to the RfD. For acute accidental/incidental exposures, the acute RfD of 4 mg/kg is used (Section 3.3.3). For longer term general exposures – i.e., exposures that could occur over the course of several days, weeks, or months during an application season – the chronic RfD of 0.05 mg/kg/day is used (Section 3.3.2). As discussed in Section 3.2.2.1, no quantitative distinction is made in the general exposures for workers applying granular and liquid formulations – i.e., the longer-term exposure scenarios. Thus, the longer-term hazard quotients for granular and liquid formulations are

identical. There are relatively minor differences in the acute accidental exposure scenarios (Section 3.2.2.2).

At the maximum application of 4 lbs/acre, the lower bound of the hazard quotients associated with general exposures of different groups of workers range from 0.02 to 0.05, indicating that no risks are plausible. The simple interpretation of these hazard quotients is that hexazinone can be applied safely so long as measures are taken to minimize exposure.

Conversely, all of the upper bounds of the hazard quotients for the different groups of workers exceed the level of concern (HQ=1) for both the typical application rate of 2 lbs/acre (HQs ranging from 3 to 6) and the highest anticipated application rate (HQs ranging from 6 to 12). Even at the lowest anticipated application rate, 0.5 lb/acre, the upper range of the hazard quotient for workers involved in broadcast ground applications modestly exceeds the level of concern with an HQ of 1.5. The simple interpretation of these hazard quotients is that worker exposures to hexazinone are likely to exceed exposures that would generally be regarded as acceptable if workers do not follow prudent handling practices that will minimize exposure. Based on central estimates of exposure, the level of concern for workers is exceeded only at the highest anticipated application rate but the hazard quotient for ground broadcast workers approaches a level of concern at the typical application rate (HQ=0.9).

Based on the acute RfD of 4 mg/kg (Section 3.3.3), none of the accidental exposure scenarios exceed a level of concern. The highest hazard quotient for any accidental exposure scenario is 0.08 (the upper bound of the hazard quotient for wearing gloves contaminated with a liquid formulation for one hour).

In addition to hazards associated with systemic toxicity, hexazinone can cause eye irritation (section 3.1.11). Quantitative risk assessments for irritation are not derived; however, from a practical perspective, eye irritation is probably the overt effect this is most likely to be observed as a consequence of mishandling hexazinone. This effect can be minimized or avoided by prudent industrial hygiene practices during the handling of the compound.

3.4.3. General Public

A quantitative summary of the risk characterization for members of the general public is presented in Worksheet E04a (typical application rate), Worksheet E04b (lowest anticipated application rate), and Worksheet E04c (highest anticipated application rate) of the workbooks for liquid and granular formulations of hexazinone. As with the risk characterization for workers, hazard quotients, the ratio of the estimated exposure from Worksheet E02 to the RfD, are used to quantitatively characterize risk. For acute accidental/incidental exposures, the acute RfD of 4 mg/kg is used (Section 3.3.3). For longer term general exposures – i.e., exposures that could occur over the course of several weeks or months during an application season – the chronic RfD of 0.05 mg/kg/day is used (Section 3.3.2).

As discussed in Section 3.2.3, distinctions are made between Velpar L (a liquid formulation) and the granular formulations of hexazinone and the most substantial difference involves exposure scenarios for contaminated vegetation. For these scenarios, levels of exposure to hexazinone

after applications of Velpar L are estimated to be much higher than those associated with applications of granular formulations. In terms of the risk characterization, this distinction is important only for longer-term exposures to contaminated vegetation. For granular formulations, the upper range of the hazard quotient for this scenario is 0.3 for fruit and 1.8 for broadleaf vegetation at the maximum application rate.

For liquid formulations, however, much higher residue rates are modeled on both fruit and broadleaf vegetation (Table 3-3). Even at the lowest application rate (0.5 lb/acre), the level of concern is exceeded at the upper range of exposure (HQ=6) for broadleaf vegetation. At the highest application rate (4 lbs/acre), the consumption of contaminated broadleaf vegetation exceeds the level of concern even at the lower limit of plausible exposures: hazard quotients with a central estimate of 5 and a range of 1.1 to 45.

A discussed in Section 3.3.2, the chronic RfD is based on a NOAEL of 5 mg/kg/day. The corresponding LOAEL was about 40 mg/kg/day based on minor body weight changes and changes in blood chemistry indicated of liver toxicity. This LOAEL is a factor of 8 (40 mg/kg/day ÷ 5 mg/kg/day) above the NOAEL. At the highest dose tested, about 160 mg/kg/day and a factor of 32 above the NOAEL, effects included decreased body weight gain (over 15% less than controls), more pronounced changes in blood chemistry indicative of liver damage, and some histopathological changes in the liver. The relationship of the experimental NOAEL to the LOAEL or higher doses cannot be used as a direct measure of plausible effects in humans at doses above the chronic RfD. Nonetheless, the hazard quotient of 6 at the lowest application rate (0.5 lb a.i./acre) is a concern. The hazard quotient of 23 at the application rate of 2 lbs a.i./acre and the hazard quotient of 45 at an application rate of 4 lbs a.i./acre are clearly a serious concern. In areas in which members of the general public might consume contaminated vegetation, particularly broadleaf vegetation or other plant products that might contain comparable residues, the use of granular formulations of hexazinone should be given preference to the use of liquid formulations.

The only other hazard quotient that exceeds 1 is that associated with the upper range of exposure to water contaminated with hexazinone for a young child after a spill of Velpar L. At the highest anticipated application rate, the hazard quotient is 2. As discussed in Section 3.2.3.4.1, this is a highly arbitrary exposure scenario in which 200 gallons of a field solution are accidently spilled into a small pond. Higher or lower hazard quotients could be generated under different assumptions. This is a standard exposure scenario used in all Forest Service risk assessments to provide a crude indication of steps that might need to be taken in the event of an accident involving the contamination of body of water that might be used as a source of drinking water.

All other exposure scenarios are below a level of concern. For chronic exposures other than the consumption of contaminated vegetation, the highest hazard quotient is 0.2, the upper range for the consumption of contaminated water at the maximum application rate. This is below the level of concern by a factor of 5 [1 / 0.2].

3.4.4. Sensitive Subgroups

Because hexazinone can induce fetal resorptions and other adverse developmental effects (Section 3.1.9.1), pregnant women and developing offspring are an obvious group at increased risk. As discussed above, the potential developmental effects of hexazinone are explicitly considered in the dose-response assessment and this endpoint 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.

3.4.5. Connected Actions

Connected actions typically refers to activities other than those associated with the agent of concern (hexazinone in this risk assessment) that might impact an individual's response to the agent of concern. Potentially significant connected actions associated with a chemical risk assessment would include exposures to other agents that might alter an individual's response to the agent of concern.

There is very little information available on the interaction of hexazinone with other compounds. As noted in Section 3.1.14, there is no indication that the inerts and adjuvants in hexazinone formulations will enhance the toxicity of hexazinone in humans or mammals.

As summarized in section 3.1, the available data suggest that hexazinone is metabolized via oxidation and demethylation. This type of metabolism is often mediated by mixed-function oxidases often referred to as the cytochrome P-450 system. In addition, hexazinone can cause increased liver weight (Section 3.1.5) and this effect is often seen in chemicals that induce cytochrome P-450. Cytochrome P-450 is a very important enzyme in the metabolism of many endogenous as well as xenobiotic compounds. While speculative, it is possible 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.

3.4.6. Cumulative Effects

The consideration of cumulative effects typically refers to the consequences of repeated exposure to the agent of concern (i.e., hexazinone) as well as exposures to other agents that an individual might be exposed to that have the same mode of action as the agent of concern.

It is beyond the scope of the current risk assessment to identify and consider all agents that might have the same mode of action as hexazinone. To do so quantitatively would require a complete set of risk assessments on each of the other agents that would be considered. The U.S. EPA similarly declined to consider cumulative risk associated with other chemicals having the same mode of action as part of the recent risk assessment of hexazinone (U.S. EPA/OPP 2002h). The rationale presented by U.S. EPA is as follows:

> *HED* [Health Effects Division] *did not perform a cumulative risk assessment as part of the TRED for hexazinone because HED has not yet initiated a comprehensive review to determine if there are any other chemical substances that have a mechanism of toxicity common with that of hexazinone. For purposes of this TRED, the Agency has assumed that hexazinone does not have a common mechanism of toxicity with other substances.* – U.S. EPA/OPP 2002h, p. 41

Nonetheless, the current Forest Service risk assessment does specifically consider the effect of repeated exposures to hexazinone for both workers and members of the general public. The chronic RfD is used as an index of acceptable longer-term exposures. Consequently, the risk characterizations presented in this risk assessment specifically addresses and encompasses the potential impact of long-term exposure and the effects that could be caused by such exposures.

4. ECOLOGICAL RISK ASSESSMENT

4.1. HAZARD IDENTIFICATION

4.1.1. Overview

Hexazinone is an effective herbicide. Hexazinone inhibits photosynthesis and, at higher levels of exposure, inhibits the synthesis of RNA, proteins, and lipids in plants. The toxicity of hexazinone is very well characterized in terrestrial plants and the difference in sensitivity among different types of terrestrial plants is related to differences in absorption as well as metabolism. At least in terrestrial plants, the metabolites of hexazinone are much less toxic then hexazinone itself. While the toxicity of hexazinone to aquatic plants has not been characterized as completely as in terrestrial plants, hexazinone is much more toxic to aquatic plants than to aquatic animals. This is true for most herbicides. The effects of hexazinone on plants can cause secondary effects in animals – e.g., changes in food availability or habitat. This has been demonstrated for mammals and birds. These secondary effects are not necessarily adverse. For both birds and mammals, short-term reductions in preferred vegetation may be followed by an increase in preferred vegetation.

Based on classification schemes developed by the U.S. EPA, hexazinone is *practically nontoxic* to birds, fish, and aquatic invertebrates. The acute toxicity to mammals is also low, with rat oral gavage LD_{50} values in the range of about 600 to 1800 mg/kg. No clear patterns in sensitivity among different species of mammals are apparent. Based on an acute gavage LD_{50} in quail of 2258 (1628-3130) mg/kg, birds appear to be somewhat less sensitive than mammals to hexazinone. Relatively little information is available on the toxicity of hexazinone to insects. Based on an acute topical application to honey bees, the LD_{50} value is greater than 1075 mg/kg bw. This is consistent with dermal studies in mammals indicating dermal LD_{50} values of greater than 5000 mg/kg. Terrestrial microorganisms can be adversely affected by hexazinone in standard laboratory culture bioassays. Nonetheless, field studies are available that demonstrate no adverse effects on terrestrial microorganisms after applications at rates that are substantially above those used in Forest Service programs. At high concentrations of hexazinone in water, fish and aquatic invertebrates may be adversely affected. The acute LC_{50} values for these organisms are in the range of about 100 mg/L to over 1000 mg/L. The carriers and/or inerts in formulations of Velpar L as well as Pronone 10G appear to antagonize the toxicity of hexazinone to fish. At least for Velpar L, no such antagonistic effect is apparent for aquatic plants.

4.1.2. Toxicity to Terrestrial Organisms

4.1.2.1. Mammals – Most of the information on the toxicity of hexazinone to mammals as well as other species comes from unpublished bioassays submitted to the U.S. EPA for the registration of hexazinone. These studies as well as other studies submitted for registration are conducted using methods specified by the U.S. EPA (e.g., U.S. EPA/OPP 2005). While some studies may be conducted directly by the registrant, most toxicity studies are performed by commercial testing laboratories. All studies submitted for registration are independently reviewed by U.S. EPA and all toxicity studies on mammals and other species that are cited in this Forest Service risk assessment were obtained and reviewed in the preparation of this risk assessment.

As summarized in the human health risk assessment (Section 3.1) and detailed in Appendices 1 and 2, the toxicity of hexazinone to mammals is relatively well-characterized in a large number of standard acute, subchronic, and chronic toxicity studies on mice, rats, rabbits, and dogs, an acute toxicity study in guinea pigs and a number of standard skin sensitization studies in guinea pigs.

Although the mode of action of hexazinone in plants is well understood, the mode of action in mammals is unclear. The most consistent effect of hexazinone in mammals is weight loss, an effect that has been seen in acute and longer-term toxicity studies by multiple routes of exposure. While this effect often appears to be attributable to decreased food consumption, decreased food conversion efficiency has been noted in some instances (Section 3.1.2).

As noted in Section 3.1.2, the acute oral toxicity of hexazinone in mammals is classified by U.S. EPA/OPP (1994a, 2002g,h) as Category III, the second lowest oral toxicity category. This classification is based on a gavage LD_{50} value in female rats of 1200 (1000 to 2000) mg/kg (Sarver 1989). There are no clear patterns in sensitivity among different species of mammals. Based on acute oral toxicity studies, guinea pigs may be somewhat more sensitive than rats but the differences are neither substantial nor statistically significant (Table 3-1). Acute sublethal effects in dogs have been reported at doses of 1000 to 3400 mg/kg. These are above reported LD_{50} values in rats and guinea pigs (Table 3-1) but this difference could be due to the fact that dogs were dosed with capsules and the other species were dosed by gavage.

In terms of assays for chronic toxicity, the most sensitive mammalian species is the dog – i.e., a chronic NOAEL of about 5 mg/kg/day with a LOAEL of about 40 mg/kg/day (Dalgard 1991, Appendix 2). These toxicity values for dogs are somewhat less than the corresponding values for rats (NOAEL of about 10 mg/kg/day for males with a corresponding LOAEL of about 50 mg/kg/day in Kaplan et al. 1977, Appendix 2) and mice (NOAEL of about 30 mg/kg/day for males with a corresponding LOAEL of about 366 mg/kg/day in Goldenthal and Trumball 1981, Appendix 2). It is difficult to determine if these differences are associated with true differences in the sensitivity of the different species of mammals or an artifact of differences in experimental design such as the selection of the experimental doses.

Secondary effects on mammals may occur due to changes in habitat associated with the effect of hexazinone on vegetation. This has been noted in decreased foraging by white-tailed deer on plots treated with hexazinone (Blake et al. 1987, summarized in Appendix 6). Decreased foraging was noted only in the first year after application. This is consistent with the observation by Brooks et al. (1993) that the plants on sites treated with hexazinone have more abundant food for deer one year after hexazinone application.

4.1.2.2. Birds – The toxicity studies on birds are summarized in Appendix 3 and these studies have been reviewed by the U.S. EPA (i.e., U.S. EPA/OPP 1994a,d). The available toxicity studies in birds include acute gavage studies (Fink et al. 1978; Kennedy 1984), avian acute oral dietary studies (Fletcher 1973a,b; Kennedy 1984; Dudeck and Bristol 1980;); and two avian reproductive toxicity studies (Beavers et al. 1991a,b,c). While several field studies are available

on the effects of hexazinone on plants, none of the field studies have addressed direct toxic effects in birds.

Based on a single acute gavage LD_{50} value, birds may be somewhat less sensitive to hexazinone than mammals. The acute gavage LD_{50} in quail is 2258 (1628-3130) mg/kg (Fink et al. 1978). As noted in Table 3-1, the corresponding values in mammals are somewhat lower: 860 (420-1260) mg/kg for guinea pigs and 1690 (1560-1880) mg/kg for rats. The signs of toxicity in birds after lethal or nearly lethal gavage doses are similar to those seen in mammals and include many effects that might be associated with neurologic damage – e.g., incoordination, weakness, loss of righting reflex, and lower limb rigidity. As discussed in Section 3.1.6, however, these types of effects are commonly seen in severely poisoned animals and do not necessarily indicate a specific effect on the nervous system.

Acute dietary studies have been conducted in both Mallard ducks (Fletcher 1973a) and bobwhite quail (Fletcher 1973b; Kennedy 1984; Dudeck and Bristol 1980). Mortality was sporadic among the various studies and dose groups. No consistent concentration-response relationships are apparent. The U.S. EPA (1994a,d) classified the hexazinone as practically non-toxic to birds with dietary LC_{50} values of >5000 ppm or >10,000 ppm (U.S. EPA 1994d, p. 12). The difference in the >5,000 ppm and >10,000 ppm values reflect the different maximum concentrations used in the studies rather than any apparent difference in toxicity.

In the mallard study by Fletcher (1973a), it should be noted that the 5000 ppm concentration is essentially a NOEC – i.e., no effects were noted on mortality, food consumption, body weight or gross signs of toxicity. A NOEC is somewhat more difficult to identify in the quail studies because of sporadic mortality. Nonetheless, 5000 ppm is clearly below the LC_{50} value. The studies by Fletcher (1973b) and Dudeck and Bristol (1980) reported body weight and food consumption. The birds in these studies consumed food at a rate equivalent to about 22% of their body weight per day. Thus, the 5000 ppm dietary concentration would correspond to a daily dose of about 1100 mg/kg/day. This is about a factor of 2 below the gavage LD_{50}. Assuming that the quail in the studies summarized by Kennedy (1984) also consumed about 22% of their body weight per day as food, the 10,000 ppm dietary concentrations would correspond to about 2,200 mg/kg/day, very near to the gavage LD_{50} value of 2258 mg/kg bw in quail reported by Fink et al. (1978).

Standard avian reproductive toxicity studies have been conducted on bobwhite quail (Beavers et al. 1991a) and mallard ducks (Beavers et al. 1991b,c). The mallard study noted no effects at dietary concentrations of up to 1000 ppm, the maximum concentration tested. This exposure was classified as an NOEC by the U.S. EPA (1994d). Based on food consumption data provided in the study, this concentration corresponded to a dose of about 180 mg/kg/day. The interpretation of the study in quail (Beavers et al. 1991a) is somewhat more complicated. As detailed in Appendix 3, the dietary exposures were identical to those used in the study on mallards: 0, 100, 300, and 1000 ppm. As in the study using mallards, no mortality or other signs of frank toxicity were observed. In the 1000 ppm group, increased food consumption with a corresponding increase in body weight gain was noted. In the 100 ppm group, however, a body weight decrease of about 10% was seen in 14-day hatchlings relative to the control hatchlings.

Beavers et al. (1991a) determined that this decrease was not statistically significant. The control body weights in 14-day hatchlings are reported as 21±3 g and the corresponding value in the 100 ppm group was 19±3 g (Table 5A. p. 39 of Beavers et al. 1991a).

The U.S. EPA/OPP (1991) re-analyzed the data of Beavers et al. (1991a) using a SAS program called *BirdAll* that was developed by U.S. EPA. This program is no longer in use and a copy of the SAS code is not available. Based on the re-analysis using the *BirdAll* program, U.S. EPA/OPP (1991) determined that the decrease in the body weight of the 14-day hatchlings was statistically significant ($p<0.05$). A decrease in hatchling weight was not seen at higher concentrations: average 14-day survivor body weights at 300 ppm and 1000 ppm were 20 ± 3 and 22 ±3 grams.

As with mammals, effects on vegetation may lead to secondary effects on birds. The only such effect noted in the literature is the report by Brooks et al. (1993) that areas treated with hexazinone produce more food plants for bobwhite quail. Such an effect is likely to be time-dependant and it seems plausible that transient decreases in food plants could occur for some species of birds.

4.1.2.3. Terrestrial Invertebrates – As is the case with most herbicides, relatively little information is available on the toxicity of hexazinone to terrestrial invertebrates. Under the assumption that herbicides are not generally directly toxic to insects, the U.S. EPA (U.S. EPA/OPP 1994a,d) required only one direct contact bioassay using the honey bee (Hoxter et al. 1989). An additional study was submitted to the U.S. EPA – i.e., Meade (1978) – but this study is not cited in the assessments by U.S. EPA/OPP (1994a,d).

As noted by the U.S. EPA/OPP (1994d, p. 14), the Hoxter et al. (1989) study indicated that the LD_{50} for hexazinone in the honey bee is greater than 0.100 mg/bee in an assay at doses ranging from 0.013 to 0.1 mg/bee. As noted in Appendix 4, the highest observed mortality (4/50) was only marginally significant with respect to the control response and no dose-response relationship is apparent. Hoxter et al. (1989) does not report the body weight of the bees. Using a body weight of 0.093 g for the honey bee (USDA/APHIS 1993), the dose of 0.1 mg/bee is equivalent to about 1075 mg/kg bw [0.1 mg/0.000093 kg]. This is consistent with the dermal limit assays in mammals (Table 3-1) indicating that the dermal LD_{50} for hexazinone is greater than 1000 mg/kg bw. Meade (1978) also noted no clear dose-response relationship in a contact bioassay on bees at dosed from 0.02 to 0.06 mg/bee (Appendix 4). The Meade (1978) report is actually a very brief letter with some tabulated data and appears to be on a Velpar (NOS) formulation rather than the active ingredient. This may account for the Meade (1978) report not being cited by U.S. EPA/OPP (1994a,d).

In a field study conducted in northern California, hexazinone was applied to pine plantations at a rate of 2.7 lb a.i./acre (Busse et al. 2001). No significant differences were found between treated and control plots in the numbers of mites, spiders, beetles, or springtails (Appendix 6). In two field studies conducted in Nigeria (Badejo and Adejuyigbe 1994; Badejo and Akinyemiju 1993), changes in the vertical distribution of mites and other microarthropods have been reported in soils treated with hexazinone compared to untreated sites. As noted in Appendix 6, it is unclear

if the differences reported by Badejo and Adejuyigbe (1994) were statistically significant. Badejo and Akinyemiju (1993) do report statistical analyses that indicate significant reductions in some species of mites, particularly in the top 7.5 cm soil layer. Badejo and Akinyemiju (1993) suggest that the changes in the density of mite populations in soil could be due to a downward migration of the mites in the soil column.

4.1.2.4. Terrestrial Plants (Macrophytes) – The mechanism of action of hexazinone in plants is well-characterized. 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 seedlings, 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). Hexazinone is readily absorbed by plant roots (Allender 1991; Wood et al. 1993) and, once absorbed, is readily translocated in most species (Yanase and Andoh 1992).

As with mammals, hexazinone is metabolized by plants and differences in sensitivity among species appear to be related to differences in the rates at which the plants metabolize hexazinone. For terrestrial plants, the available information clearly indicates that this metabolism is a detoxification – i.e., the metabolites of hexazinone appear to be much less phytotoxic than hexazinone itself. Based on bioassays of loblolly pine seedlings, metabolite B 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) (see Figure 3-1). 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 (Wood et al. 1992) or the restriction of translocation (Baron and Monaco 1986).

The U.S. EPA typically relies on standardized bioassays for seed germination, seedling emergence (pre-emergence applications), and vegetative vigor (post-emergence applications) to assess the potential effects of herbicides on nontarget plants (U.S. EPA/OPP 2005). As summarized in Appendix 5 these standardized studies are available on hexazinone.

Hexazinone has relatively little effect on seed germination with an NOEC of 12 lbs/acre in standard seed germination studies (McKelvey and Heldreth 1994; McKelvey 1995). This relatively low toxic potency for seed germination is confirmed by published bioassays indicating substantial effects on seed germination for Velpar L only at hexazinone concentrations of 5000 ppm. Pronone 10G, however, appears to be somewhat more toxic with some inhibition occurring at soil concentrations of 10 to 1000 ppm and a complete inhibition of seed germination at 5000 ppm (Morash and Freedman 1989). The greater activity of Pronone 10G may be due to the slow release of hexazinone from the clay matrix over the 29 day duration of the study.

Although aerial applications or directed sprays of liquid formulations of hexazinone may result in some foliar absorption (post-emergence), applications of granular formulations or spot

applications of liquid formulations involve soil treatments (pre-emergence) with subsequent absorption by the roots (Glover et al. 1991).

Based on standard pre-emergence and post-emergence bioassays in sensitive species (Leavitt 1988; McKelvey and Heldreth 1994), soil treatments (pre-emergence assay) are more toxic than direct spray (post-emergence assay). In the study by McKelvey and Heldreth (1994) this difference is pronounced, with the most sensitive post-emergence species (cucumber) having an NOEC for all endpoints of 0.00391 lb/acre. For pre-emergence applications, however, the NOEC was about a factor of 10 lower – i.e., an NOEC for height of tomatoes of 0.000348 lb a.i./acre. For less sensitive species, the differences are less remarkable. For example, the NOEC for corn was 0.0625 lb a.i./acre in post-emergence applications and 0.0234 lb a.i./acre in pre-emergence applications. As summarized in Appendix 5, greenhouse bioassays indicate that pines may be adversely effected by hexazinone but only at application rates that are in the range of about 1 kg/ha or more – i.e., about 0.89 lb/acre (Chakravarty and Chatarpaul 1988; Chakravarty and Sidhu 1987; Johnson and Stelzer 1991; Sidhu and Chakravarty 1990).

In addition to the relatively standard bioassays for phytotoxicity, a large number of field studies focusing on terrestrial vegetation are available. These studies are detailed in Appendix 6 and an overview of these studies is presented in Table 4-1. The laboratory studies on toxicity, summarized above, typically involve very low application rates and assay for relatively subtle signs of toxicity. The field studies, on the other hand, are typically conducted at or above the recommended application rates and tend to focus on efficacy rather than unintended adverse effects. As indicated in Table 4-1, hexazinone is effective in forestry management of pine stands. While hexazinone may result in some pine mortality immediately after application (e.g., Glover et al. 1991; Pehl and Shelnutt 1990), adverse effects on hardwoods and shrubs tend to be greater than those on pine. As a consequence, competition from hardwoods and shrubs is reduced and the net productivity of the pine is increased.

4.1.2.5. Terrestrial Microorganisms **–** As detailed in Appendix 4, three types of studies are available on the effects of hexazinone on soil microorganisms: laboratory studies in artificial growth media, laboratory studies of microbial populations in soil samples, and field studies on microbial populations on treated plots.

Laboratory studies in artificial growth media are the most closely controlled type of study and these studies are used for qualitative assessments of antimicrobial activity and assessments of quantitative differences in sensitivity among different microorganisms. Five such studies are available on hexazinone (Chakravarty and Chatarpaul 1990; Estok et al. 1989; Litten et al. 1985; Krause 1975; Laatinkainen and Heinonen-Tanski 2002) and two of these studies (Chakravarty and Chatarpaul 1990; Krause 1975) include both assays in artificial media as well as laboratory soil assays or field studies. In culture media, hexazinone can inhibit microbial growth at relatively high concentrations – e.g., 5000 ppm (mg/L) as demonstrated in the study by Estok et al. 1989. The lowest concentration reported to inhibit growth is from the study by Chakravarty and Chatarpaul (1990) in which growth inhibition (assayed as mycelial dry weight) was noted in some species of ectomycorrhizal fungi at 0.0125 ppm (mg/L) and in all species at concentrations of 0.05 ppm (mg/L).

While artificial media studies can be useful in identifying relative sensitivities among species, the most directly relevant studies that those that have microbial populations after field applications. Field studies conducted by Chakravarty and Chatarpaul (1990) noted no effects on mixed fungal and bacterial populations after application rates of up to 8 kg/ha (about 7 lbs/acre).

Fungicides and some other pesticides may decrease the degradation of hexazinone in soil, presumably due to toxicity to microorganisms (Torstensson and Stenstrom 1990).

4.1.3. Aquatic Organisms

4.1.3.1. Fish – Standard toxicity bioassays to assess the effects of hexazinone on fish are summarized in Appendix 9. The data available on hexazinone include several standard acute toxicity studies submitted to the U.S. EPA for pesticide registration (DuPont De Nemours 1976; Hutton 1989a,b; Okolimna 1980a,b; Schneider 1976a; Sleight 1973), a standard egg and fry study in fathead minnows (Pierson 1990a) and a standard study in bluegill sunfish to determine the bioconcentration of hexazinone (Rhodes 1974). Some of the standard acute toxicity studies submitted to the U.S. EPA are summarized in the open literature (Kennedy 1984). Nonetheless, copies of all of these studies were obtained and reviewed for the current Forest Service risk assessment. In addition to these studies, Wan et al. (1988) conducted a series of acute toxicity studies on hexazinone, hexazinone formulations, and inerts used in hexazinone formulations.

The U.S. EPA/OPP (1994a, p. 25) has classified technical grade hexazinone as practically nontoxic to fish. As indicated in U.S. EPA/EFED (2001) this is the least toxic category for toxicity to fish and is reserved for compounds with 96-hour LC_{50} values greater than 100 mg/L for the most sensitive fish species. The classification given in U.S. EPA/OPP (1994a) is based specifically on the acute LC_{50} values reported by Sleight (1973) for rainbow trout (>320 mg/L), fathead minnow (274 mg/L) and bluegill sunfish (>370 mg/L) as well as the LC_{50} value for bluegill sunfish of 505 mg/L. It should be noted that U.S. EPA/OPP (1994a) attributes the 505 mg/L value to Schneider 1976a (i.e., MRID 00076959). As detailed in Appendix 9, Schneider (1976a) assayed a hexazinone formulation that appears to be Velpar L. The 505 mg/L LC_{50} value for technical grade hexazinone in bluegill is presented in the submission by DuPont De Nemours (1976, MRID 00047178).

The U.S. EPA/OPP (1994a, p. 26) also classifies an unspecified TEP (typical end-use product) as practically nontoxic to fish. While the U.S. EPA does not specify the formulation of hexazinone, the studies used to support this classification – i.e., LC_{50} values of >1000 mg/L in bluegills and >585.6 mg/L in trout – refer to the studies by Hutton (1989a,b) on Velpar L and the concentrations cited by U.S. EPA appear to be in units of mg formulation/L.

U.S. EPA/OPP (1994a,d) does not discuss studies on Pronone. Based on the data reported by Wan et al. (1988), Pronone 10G appears to be less toxic than Velpar L and both Velpar L and Pronone 10G are less toxic than hexazinone itself (see Appendix 9). This is true even when comparisons are made on a mg a.i./L basis. Thus, the inerts in both Velpar L and Pronone 10G appear to antagonize the toxicity of hexazinone to fish. For Pronone 10G, an antagonism of toxicity might be expected based on the presumably slower release of hexazinone from the clay matrix of the carrier pellets (Section 2). For Velpar L, the basis for the antagonism is not clear.

The Wan et al. (1988) study also indicated that the both the Pronone 10G carrier and the Velpar L carrier are essentially nontoxic with LC_{50} values in rainbow trout of >2000 mg/L and 4330 mg/L, respectively. As noted in Section 2, a major component of the Velpar L carrier is ethanol. The rainbow trout LC_{50} value of 4330 mg carrier/L for the Velpar L carrier reported by Wan et al. (1988) is close to the rainbow trout LC_{50} value of 11,200 mg/L for ethanol reported by Majewski et al. (1978).

The only longer term toxicity study of hexazinone in fish is the egg-and-fry study by Pierson (1990a). As discussed further in Section 4.3, this study defines a clear NOEC of 17 mg/L and an LOEC of 35.5 mg/L. In the four week assay for bioconcentration in bluegill sunfish (Rhodes 1974), no signs of toxicity were noted at concentrations of 0.1 or 1 mg/L. This is consistent with the 17 mg/L NOEC from the egg-and-fry study.

4.1.3.2. Amphibians – Very little information is available on the toxicity of hexazinone to amphibians. A hexazinone concentration of 100 mg/L over an 8-day exposure period was associated with transient reduced avoidance behavior in newly hatched tadpoles. These exposure levels, however, had no effect on hatching success (Berrill et al. 1994).

4.1.3.3. Aquatic Invertebrates – The available information on the toxicity of hexazinone to aquatic invertebrates is limited to studies submitted to the U.S. EPA for pesticide registration. All of these studies are summarized in Appendix 10. As with fish and for the same reasons, the U.S. EPA/OPP has classified hexazinone as *practically nontoxic* to freshwater invertebrates (U.S. EPA, 1994a, p. 26). This is based on the acute toxicity study in *Daphnia magna* using technical grade hexazinone in which the 48-hour LC_{50} value was 151.6 (125.2-172.8) mg/L. Based on an acute toxicity bioassay of Velpar L in *Daphnia magna* (Hutton 1989c), the typical end use formation (TEP) is also classified as *practically nontoxic* by U.S. EPA. As noted in Appendix 10, the LC_{50} value for Velpar L expressed as hexazinone equivalents is 110 (83-130) mg a.i./L (Hutton 1989c). This LC_{50} value is somewhat less than (although not significantly different from) the LC_{50} value for hexazinone itself. Thus, unlike the case in fish, there is no indication that the inerts in Velpar L antagonize the toxicity of hexazinone to daphnids.

Grass shrimp, small salt water crustaceans, appear to be about equally sensitive as daphnids to hexazinone with a 48-hour LC_{50} value of 94 (50-176) mg/L (Heitmuller 1976). Because the central estimate of the LC_{50} value is below 100 mg/L, the U.S. EPA/OPP (1994a, p. 27) classifies hexazinone as moderately toxic to saltwater crustaceans. A much larger crustacean, the fiddler crab, is much less sensitive with a NOEC for mortality of over 1000 mg/L (Heitmuller 1976). Data are available on only a single mollusk, embryos of the eastern oyster. In this assay, the NOEC for the mollusk was 320 mg/L, substantially above the LC_{50} values for small crustaceans.

As summarized in Appendix 10, two reproduction studies in *Daphnia magna* are available: Schneider (1977) and Pierson (1990b). Because of reporting deficiencies, both of these studies are classified as *Supplemental* rather than *Core* by the U.S. EPA/OPP (1994a,d). Taken together, the U.S. EPA/OPP (1994a,d) did consider that these studies satisfy the requirements for an aquatic invertebrate reproduction assay. The only NOEC discussed by U.S. EPA/OPP

(1994a,d) is the 29 mg/L NOEC reported in the study by Pierson (1990b). As indicated in Appendix 10, the concentration of 29 mg/L is very close to the 21-day LC_{50} value of 33.1 (28.1-36.9) mg/L reported by Schneider (1977). As discussed further in Section 4.3, the NOEC (based on numbers of offspring produced) of 10 mg/L from Schneider (1977) may be a more appropriate NOEC for the current risk assessment.

Additional information on the effects of hexazinone on aquatic invertebrates is also available in field or field simulation assays (Appendix 10). In one such study, 13 species of stream macroinvertebrates were exposed to very high concentrations of hexazinone, 70 mg/L to 80 mg/L, for one hour in an artificial stream followed by a 48-hour observation period. The most sensitive species were two species of Ephemeroptera, an *Isonychia* sp and *Epeorus vitrea*, both of which exhibited 14% mortality. Mortality in all other species ranged from 0% to 4% (Kreutzweiser et al. 1992). In a subsequent study (Kreutzweiser et al. 1995), 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. At the end of the 14-day observation period, no significant pair-wise differences between treated and control channels were noted for 14 taxa of macroinvertebrates. Overall, however, there was a significant increase in abundance of invertebrate taxa 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). In addition, Mayack et al. (1982) reported no effects on stream macroinvertebrates at water concentrations of 0.008 mg/L to 0.044 mg/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.

4.1.3.4. Aquatic Plants – Studies on the effects of hexazinone on aquatic plants are summarized in Appendix 11. Hexazinone is an effective herbicide and the mechanism of action of hexazinone, the inhibition of photosynthesis (Section 4.1.2.4), affects aquatic plants as well as terrestrial plants. This is true of most herbicides. Consequently, the U.S. EPA requires a relatively standard group of studies on both unicellular aquatic algae as well as aquatic macrophytes. These studies are typically conducted over a 5-day period under controlled laboratory conditions.

Based on the standard bioassays submitted to U.S. EPA for registration, relatively substantial differences in sensitivity to hexazinone are apparent among species of algae. The differences span a factor of approximately 24 based on the EC_{25} values and 38 based on the NOEC values. The most sensitive species appears to be *Selenastrum capricornutum* (a freshwater green alga) with a 5 day-EC_{50}: 0.0068 (0.0063-0.0072) mg/L and a corresponding NOEC of 0.004 mg/L (Forbis 1989). The least sensitive species appears to be *Anabaena flos-aquae* (a freshwater blue-green alga) with a 5-Day EC_{25} of 0.16 (0.02-0.24) mg/L and a corresponding NOEC 0.15 mg/L (Thompson 1994). The proximity of the NOEC to the calculated EC_{25} appears to be an artifact of the method used to calculate the EC_{25}. Details of the calculation of the EC_x values are described by Thompson (1994) only briefly: *"linear interpolation of the initial measured test*

concentrations against measured parameter". Based on an examination of the concentration-response data, the NOEC is virtually identical to the EC_{25} because the dose-response is flat at the lowest concentration (0.29 mg/L at which the cell density is essentially identical to that of the controls) but very steep at the next higher concentration (0.66 mg/L at which the cell density is much less than the controls).

The relative sensitivity of *Selenastrum capricornutum* and tolerance of *Anabaena flos-aquae* to hexazinone is also confirmed in the published study by Abou-Waly et al. (1991). As detailed in Appendix 11, *Selenastrum capricornutum* is more sensitive than *Anabaena flos-aquae* by a factor of about 24 based on the 5-day EC_{50} values reported by Abou-Waly et al. (1991) for these two species. The specific values reported by Abou-Waly et al. (1991) are much higher than those reported in the studies submitted to EPA – i.e., Thompson (1994) or Forbis (1989). For example,
Abou-Waly et al. (1991) reports a 5-Day EC_{50} for *Selenastrum capricornutum* of 0.085 mg/L and Forbis (1989) reports a 5-Day EC_{50} of 0.0068 – a factor of 12.5 lower. This may be due to simple variability or differences in experimental methods – i.e., the studies submitted to U.S. EPA are based on cell counts using a hemocytometer whereas the study by Abou-Waly et al. (1991) is based on chlorophyll-*a* measured using a spectrophotometer.

Relatively little information is available on the toxicity of hexazinone to macrophytes. As summarized in Appendix 11, three studies are available on duckweed (i.e., *Lemna* sp.). In the standard bioassay on *Lemna gibba* submitted to U.S. EPA (Kannuck and Sloman 1994), an NOEC was not defined. Adverse effects (a reduction in frond count and reduced biomass) were noted at the lowest concentration tested, 0.026 mg/L with exposures over a 14-day period. The EC_{25} for the most sensitive endpoint (frond count) was estimated by Kannuck and Sloman (1994) at 0.027 mg/L. Of the two published studies (Peterson et al. 1994, 1997), the earlier study involved a very high concentration, about 3 mg/L, and complete inhibition of growth was observed in *Lemna minor*. The later study calculated a 7-day EC_{50} value of 0.07 mg/L but does not report an NOEC. Based on graphical data presented in the publication (Peterson et al. 1997, Figure 3a, p. 128), the lowest concentration tested, 0.012 mg/L, appears to be an NOEC.

As discussed in Section 4.1.3.1, 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 aquatic plants (Schneider et al. 1995, Thompson et al. 1993, Williamson 1988).

In addition to standard bioassays, a relatively large number of papers on the effects of hexazinone on aquatic algae have been published in the open literature. These are less standardized and some (e.g., Thompson et al. 1993) are conducted over longer periods of time and under conditions that may be less well controlled but may more closely mimic natural conditions. For hexazinone, the differences in the results of these two types of studies are substantial.

The lowest EC_{50} value from a field simulation study is 0.003 mg/L for *Chrysophyta* species (Thompson et al. 1993). In a 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 EC_{50} of 0.003 mg/L reported 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.

4.2. EXPOSURE ASSESSMENT

4.2.1. Overview

A number of different exposure scenarios are developed mammals, birds, terrestrial invertebrates, terrestrial plants and aquatic species. The specific levels of exposure for each group of organisms are summarized in the G-Series worksheets in EXCEL workbooks for liquid and granular formulations.

In many respects, these exposures parallel the exposure scenarios used in the human health risk assessment and the scenarios fall into two general groups: exposures that may be anticipated in the normal use of hexazinone and atypical exposures that could occur as a result of mischance or misapplication. In some cases, the atypical exposures have somewhat different interpretations. The direct spray of a human is regarded as accidental and unlikely to occur. While the direct spray of a small mammal or insect during any broadcast application would also be accidental (unintended), such exposures for some individual animals are both plausible and likely. Nonetheless, it is highly unlikely that a substantial proportion of small mammals or insects would be directly sprayed. Exposures would likely be reduced both by animal behavior as well as foliar interception.

For terrestrial animals, exposure assessments are developed for direct spray, the ingestion of contaminated media (vegetation, prey species, or water), grooming activities, or indirect contact with contaminated vegetation. Not all exposure scenarios are developed for all groups of animals because toxicity data are not available in all groups to support the use of such exposure assessments in the risk characterization. For terrestrial plants, exposure assessments are developed for direct spray, spray drift, and off-site movement of the compound by percolation, runoff, wind erosion of soil. For aquatic species, the concentrations in water are identical to those used in the human health risk assessment.

Also as in the human health risk assessment, differences in exposures after granular and liquid formulations are considered. The major difference will be in residues on contaminated vegetation, where applications of liquid formulations lead to much higher residues than applications of granular formulations.

4.2.2. Terrestrial Animals

Terrestrial animals might be exposed to any applied pesticide from direct spray, the ingestion of contaminated media (vegetation, prey species, or water), grooming activities, or indirect contact with contaminated vegetation.

In the exposure assessments for the ecological risk assessment, estimates of oral exposure are expressed in the same units as the available toxicity data. As in the human health risk assessment, these units are usually expressed as mg of agent per kg of body weight and abbreviated as mg/kg for terrestrial animals. For dermal exposures to terrestrial animals, the units of measure are expressed in mg of agent per cm^2 of surface area of the organism and abbreviated as mg/cm^2. In estimating dose, however, a distinction is made between the exposure dose and the absorbed dose. The *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. The *absorbed dose* is the proportion of the exposure dose that is actually taken in or absorbed by the animal.

As with the human health exposure assessment, two sets of exposure scenarios are provided in two separated EXCEL workbooks. One workbook covers Velpar L, the only liquid formulation considered in this risk assessment, and the other workbook covers the granular formulations. These exposure assessments are generally similar in nature but some of the computational details differ in ways that are mandated by differences between granular and liquid formulations. In addition, there is a substantial quantitative difference in residue rates on contaminated vegetation, with much higher residues expected after the application of Velpar L compared to those expected after applications of granular formulations.

In each workbook, the exposure assessments for terrestrial animals are summarized in Worksheet G01. The computational details for each exposure assessment presented in this section are provided as scenario specific worksheets (Worksheets F01 through F16b). Given the large number of species that could be exposed to pesticides and the varied diets for each of these species, a very large number of different exposure scenarios could be generated. For this generic risk assessment, an attempt is made to limit the number of exposure scenarios.

Because of the relationship of body weight to surface area as well as to the consumption of food and water, small animals will generally receive a higher dose, in terms of mg/kg body weight, than large animals will receive for a given type of exposure. Consequently, most general exposure scenarios for mammals and birds are based on a small mammal or bird. For mammals, the body weight is taken as 20 grams, typical of mice, and exposure assessments are conducted for direct spray (F01 and F02a), consumption of contaminated fruit (F03, F04a, F04b), and contaminated water (F05, F06, F07). Grasses will generally have higher concentrations of herbicides than fruits and other types of vegetation (Fletcher et al. 1994). Because small mammals do not generally consume large amounts of grass, the scenario for the assessment of contaminated grass is based on a large mammal (Worksheets F10, F11a, and F11b). Other exposure scenarios for a mammals involve the consumption of contaminated insects by a small mammal (Worksheet F14a) and the consumption of small mammals contaminated by direct spray by a large mammalian carnivore (Worksheet F16a). Exposure scenarios for birds involve the consumption of contaminated insects by a small bird (Worksheet F14b), the consumption of contaminated fish by a predatory bird (Worksheets F08 and F09), the consumption by a predatory bird of small mammals contaminated by direct spray and the consumption by a large bird of contaminated grasses (F12, F13a, and F13b).

While a very large number of other exposure scenarios could be generated, the specific exposure scenarios developed in this section are designed as conservative screening scenarios that may serve as guides for more detailed site-specific assessments by identifying the groups of organisms and routes of exposure that are of greatest concern.

4.2.2.1. Direct Spray – In the broadcast application of any insecticide, wildlife species may be sprayed directly. This scenario is similar to the accidental exposure scenarios for the general public discussed in Section 3.2.3.2. In a scenario involving exposure to direct spray, the amount

absorbed depends on the application rate, the surface area of the organism, and the rate of absorption.

For this risk assessment, three groups of direct spray or broadcast exposure assessments are conducted (Worksheets F01, F02a, and F02b). For the granular formulations, a spray is not a meaningful concept. By analogy to residues on contaminated vegetation (Section 3.2.3.6), it is also likely that the clay pellets from granular formulations of hexazinone will not stick to the mammal or other ecological receptors considered in this risk assessment. Unlike vegetation, however, data for adjusting estimates of pellet deposition are not available. Consequently, exposures to granular formulations, like liquid formulations, are taken at the nominal application rate. As discussed further in Section 4.4, all risks are far below a level of concern and any over-estimate of exposure has no impact on the conclusions reached in the current risk assessment.

The first spray scenario, which is defined in Worksheet F01, involves a 20 g mammal that is sprayed directly over one half of the body surface as the chemical is being applied. This scenario assumes first-order dermal absorption. The second exposure scenario, detailed in Worksheet F02a, is developed in which complete absorption over day 1 of exposure is assumed. This very conservative assumption is likely to overestimate exposure and is included to encompass any increase in exposure due to grooming. The third exposure assessment is developed using a body weight of a honey bee, again assuming complete absorption of the compound. Direct spray scenarios are not given for large mammals. Allometric relationships dictate that large mammals will be exposed to lesser amounts of a compound in any direct spray scenario than smaller mammals.

4.2.2.2. 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. Unlike the human health risk assessment in which transfer rates for humans are available, there are no transfer rates available for wildlife species. Wildlife, compared with humans, are likely to spend 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, rates of absorption, and levels on contaminated vegetation. No data regarding the kinetics of such a process, however, are available. In the absence of such data, no quantitative assessments are made for this scenario in the ecological risk assessment.

4.2.2.3. Ingestion of Contaminated Vegetation or Prey – Since hexazinone will be applied to vegetation, the consumption of contaminated vegetation is an obvious concern and separate exposure scenarios are developed for acute and chronic exposure scenarios for a small mammal (Worksheets F04a and F04b) and large mammal (Worksheets F10, F11a, and F11b) as well as large birds (Worksheets F12, F13a, and F13b). Similarly, the consumption of contaminated insects is modeled for a small bird (Worksheet 14a) and a small mammal (Worksheet 14b). No monitoring data have been encountered on the concentrations of hexazinone in insects after applications of hexazinone. The empirical relationships recommended by Fletcher et al. (1994) are used as surrogates as detailed in Worksheets F14a and F14b. A similar set of scenarios is provided for the consumption of small mammals by either a predatory mammal (Worksheet 16a)

or a predatory bird (Worksheet 16a). In addition to the consumption of contaminated vegetation, insects, and other terrestrial prey, hexazinone may reach ambient water and fish. Thus, a separate exposure scenario is developed for the consumption of contaminated fish by a predatory bird in both acute (Worksheet F08) and chronic (Worksheet F09) exposures. Details of each scenario are given in the cited worksheets.

Multi-route exposures (e.g., the consumption of contaminated vegetation and contaminated water) are likely. Any number of combinations involving multiple routes of exposure could be developed. Such scenarios are not developed in the current risk assessment because the predominant route of plausible exposure is contaminated vegetation. Explicit considerations of multiple routes of exposure would have no impact on the characterization of risk.

As discussed in Section 3.2.3.6 (oral exposure from contaminated vegetation by humans), the study by Michael (1992) clearly indicates that residues on vegetation are likely to be much greater after applications of Velpar L compared to applications of the granular formulations. As in the human health risk assessment, the standard residue rates from Fletcher et al. (1994) are used directly in the worksheets for Velpar L but are divided by a factor of 25 for applications of granular formulations based on the minimum differences in residues on vegetation noted in the study by Michael (1992) after applications of both granular and liquid formulations.

4.2.2.4. Ingestion of Contaminated Water – Estimated concentrations of hexazinone in water are identical to those used in the human health risk assessment (Worksheet B04). The only major differences involve the weight of the animal and the amount of water consumed. These differences are detailed and documented in the worksheets that involve the consumption of contaminated water (F05, F06, F07).

Unlike the human health risk assessment, estimates of the variability of water consumption are not available. Thus, for the acute scenario, the only factors affecting the estimate of the ingested dose include the field dilution rates (i.e., the concentration of the chemical in the solution that is spilled) and the amount of solution that is spilled. As in the acute exposure scenario for the human health risk assessment, the amount of the spilled solution is taken as 200 gallons for liquid formulations. For granular formulations, the amount spilled (in lbs) is calculated based on the number of acres that would be treated with the corresponding liquid formulation(s) and the range of application rates covered by this risk assessment.

In the exposure scenario involving contaminated ponds or streams due to contamination by runoff or percolation, the factors that affect the variability are the water contamination rate, (see Section 3.2.3.4.2) and the application rate.

4.2.3. Terrestrial Plants

In general, the primary hazard to nontarget terrestrial plants associated with the application of most herbicides is unintended direct deposition or spray drift. In addition, herbicides may be transported off-site by percolation or runoff or by wind erosion of soil.

4.2.3.1. Direct Spray – Unintended direct spray will result in an exposure level equivalent to the application rate. For many types of herbicide applications, it is plausible that some nontarget plants immediately adjacent to the application site could be sprayed directly. This type of scenario is modeled in the worksheets that assess off-site drift (see below).

4.2.3.2. Off-Site Drift – 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, estimates of off-site drift can be modeled using AgDrift (Teske et al. 2001). AgDrift is a model developed as a joint effort by the U.S. EPA, the Forest Service, and the Spray Drift Task Force, a coalition of pesticide registrants.

For aerial applications, AgDrift permits very detailed modeling of drift based on the chemical and physical properties of the applied product, the configuration of the aircraft, as well as wind speed and temperature. For ground applications, AgDrift provides estimates of drift based solely on distance downwind as well as the types of ground application: low boom spray, high boom spray, and orchard airblast. Representative estimates based on AgDrift (Version 1.16) are given in Worksheets G05a-c for low boom applications and Worksheets G06a-c for aerial applications. For the current risk assessment, the AgDrift estimates are used for consistency with comparable exposure assessments conducted by the U.S. EPA. In addition, AgDrift represents a detailed evaluation of a very large number of field studies and is likely to provide more reliable estimates of drift (Teske et al. 2001).

While drift of droplets during backpack applications is likely to be less and probably much less than any form of broadcast application, comparable methods of quantifying drift after backpack applications are not available.

4.2.3.3. Runoff – Hexazinone or any other herbicide may be transported to off-site soil by runoff, sediment loss, or percolation. All of these processes are considered in estimating contamination of ambient water. For assessing off-site soil contamination, however, only runoff and sediment losses are considered. This approach is reasonable because off-site runoff and sediment loss could contaminate the off-site soil surface and could impact nontarget plants. Percolation, on the other hand, represents the amount of the herbicide that is transported below the root zone and thus may impact water quality but should not impact off-site terrestrial vegetation.

Based on the results of the GLEAMS modeling (Section 3.2.3.4.2), the proportion of the applied hexazinone lost by runoff and sediment loss is estimated for clay, loam, and sand at rainfall rates ranging from 5 inches to 250 inches per year. Note that the GLEAMS modeling is based on the assumption that rainfall occurs uniformly every tenth day (SERA 2004b). Thus, the annual rainfall rates correspond to rainfall events ranging from 0.14 inches to 6.94 inches. These values are summarized in Table 4-4. These values are used in Worksheets G04a-c to estimate functional off-site exposure rates to nontarget plants that are associated with runoff and sediment losses.

The pesticide that is not washed off in runoff or sediment will penetrate into the soil column and the depth of penetration will depend on the properties of the chemical, the properties of the soil, and the amount of rainfall. GLEAMS outputs concentrations in soil layers of varying depths. These concentrations are output by GLEAMS in mg pesticide/kg soil (ppm). The minimum non-zero value that GLEAMS will output is 0.000001 mg/kg, equivalent to 1 nanogram/kg soil or 1 part per trillion (ppt). The deepest penetration of hexazinone in clay, loam, and sand modeled using GLEAM is summarized in Table 4-5. Based on the GLEAMS modeling, hexazinone may penetrate to about 36 inches in clay. In loam or sand, detectable residues are modeled to occur at 60 inches. Because the GLEAMS modeling used a 60 inch root zone, the actual penetration in loam or sand could be greater than 60 inches. These estimates are consistent with the field monitoring studies reporting soil penetration, summarized in Appendix 7 (Bollin 1992a,b; Miles et al. 1990).

4.2.3.4. Contaminated Irrigation Water – Unintended direct exposures of nontarget plant species may occur through the use of contaminated ambient water for irrigation. Effects on nontarget vegetation have been observed with irrigation water contaminated by other herbicides (e.g., Bhandary et al. 1997; Gomez de Barreda et al. 1993).

The levels of exposure associated with this scenario will depend on the concentration of hexazinone in the ambient water used for irrigation and the amount of irrigation water that is applied. As detailed in Section 3.2.3.4, hexazinone is relatively mobile and peak concentrations of hexazinone in ambient water can be quantified.

The amount of irrigation water that may be applied will be highly dependent on the climate, soil type, topography, and plant species under cultivation. Thus, the selection of an irrigation rate is somewhat arbitrary. Typically, plants require 0.1 to 0.3 inch of water per day (Delaware Cooperative Extension Service 1999). In the absence of any general approach of determining and expressing the variability of irrigation rates, the application of one inch of irrigation water will be used in this risk assessment. This is somewhat higher than the maximum daily irrigation rate for sandy soil (0.75 inches/day) and substantially higher than the maximum daily irrigation rate for clay (0.15 inches/day) (Delaware Cooperative Extension Service 1999).

Based on the estimated concentrations of hexazinone in ambient water and an irrigation rate of 1 inch per day, the estimated functional application rate of hexazinone to the irrigated area is about 2×10^{-3} (3×10^{-6} to 2×10^{-2}) lb/acre (Worksheet F15). This level of exposure is comparable to contamination associated with offsite drift after low boom ground applications [Worksheets G05a-c]. Thus, specific worksheets characterizing risk for this exposure scenario are not developed.

4.2.3.5. Wind Erosion – Wind erosion is a major transport mechanism for soil (e.g., Winegardner 1996). Although no specific incidents of nontarget damage from wind erosion have been encountered in the literature for hexazinone, this mechanism has been associated with the environmental transport of other herbicides (Buser 1990).

Wind erosion leading to off-site contamination of pesticides will be highly site specific. The amount of hexazinone that might be transported by wind erosion depends on several factors, including the application, the depth of incorporation into the soil, the persistence in the soil, the wind speed, and the topographical and surface conditions of the soil. Under desirable conditions, like relatively deep (10 cm) soil incorporation, low wind speed, and surface conditions that inhibit wind erosion, it is likely that wind transport of hexazinone would be neither substantial nor significant.

For this risk assessment, the potential effects of wind erosion are estimated in Worksheets G07a-c. In these worksheets, it is assumed that hexazinone is incorporated into the top 1 cm of soil. This is identical to the depth of incorporation used in GLEAMS modeling. Average soil losses are estimated at from 1 to 10 tons/ha·year with a typical value of 5 tons/ha·year. These estimates are based on field studies conducted on agricultural sites that found that wind erosion may account for annual soil losses ranging from 2 to 6.5 metric tons/ha (Allen and Fryrear 1977; USDA 1998).

Wind erosion may be of particular concern for applications of granular formulations of hexazinone. While somewhat speculative, it seems plausible that granular formulations would be more susceptible to wind erosion than applications of liquid formulations. No data have been located, however, that would permit a quantitative adjustment in estimates of off-site transport by wind. Thus, the worksheets for the granular and liquid formulations are identical.

4.2.4. Soil Organisms

Limited data are available on the toxicity of hexazinone to soil invertebrates as well as soil microorganisms. The data on soil invertebrates are only semi-quantitative and the reported effects are not associated with concentrations of hexazinone in soil (Section 4.1.2.3). For soil microorganism, the toxicity data are expressed in units of soil concentration – i.e., mg hexazinone/kg soil which is equivalent to parts per million (ppm) concentrations in soil (Section 4.1.2.5).

The GLEAMS modeling discussed in Section 3.2.3.4 provides estimates of concentration in soil as well as estimates of off-site movement (runoff, sediment, and percolation). Based on the GLEAMS modeling, concentrations in clay, loam, and sand over a wide range of rainfall rates are summarized in Table 4-2 for the top 60 inches of soil and Table 4-3 for the top one foot of soil. Peak soil concentrations in the top one foot of soil in the range of about 0.2 to 0.3 ppm in arid regions at an application rate of 1 lb/acre. As rainfall rate increases, maximum soil concentrations are substantially reduced in sand and, to a lesser extent, in loam because of losses from soil through percolation. The potential consequences of such exposures for soil microorganisms are discussed in Section 4.4 (Risk Characterization).

4.2.5. Aquatic Organisms

The plausibility of effects on aquatic species is based on estimated concentrations of hexazinone in water that are identical to those used in the human health risk assessment. These values are summarized in Table 3-9 and are discussed in Section 3.2.3.4.6.

4.3. DOSE-RESPONSE ASSESSMENT

4.3.1. Overview

The specific toxicity values used in this risk assessment are summarized in Table 4-6 and the derivation of each of these values is discussed in the various subsections of this dose-response assessment. The first column in Table 4-6 specifies the organism to which the toxicity value applies. The available toxicity data support separate dose-response assessments in eight classes of organisms: terrestrial mammals, birds, terrestrial invertebrates, terrestrial plants, fish, aquatic invertebrates, aquatic algae, and aquatic macrophytes. Different units of exposure are used for different groups of organisms depending on how exposures are likely to occur and how the available toxicity data are expressed.

Based on dietary toxicity values, mammals appear to be more sensitive to hexazinone than birds. For mammals, the dose-response assessment is based on the studies used to derive RfDs in the human health risk assessment – i.e., an acute NOAEL of 400 mg/kg and a chronic NOAEL of 5 mg/kg/day. A comparison of gavage studies between mammals and birds suggest that birds may be less sensitive to hexazinone than mammals. Based on a comparison of short-term dietary NOAELs, the sensitivity of birds is somewhat less that seen in mammals. The acute dietary NOAEL for birds is 550 mg/kg/day, a factor of about 1.4 above the acute NOEL of 400 mg/kg/day that is used for mammals. Since most of the exposure assessments developed in this risk assessment involve gradual intake during the day rather than gavage like exposures, the acute dietary NOEL of 550 mg/kg/day is used for the risk characterization in birds. No lifetime toxicity studies in birds have been encountered. Based on the reproduction study, the chronic NOAEL for birds is set at 150 mg/kg/day. This is about a factor of 30 above the NOAEL of 5 mg/kg/day used for mammals. Relatively little information is available on terrestrial insects. A contact toxicity value of 1075 mg/kg bw is taken as a marginal LOEC. This is consistent with corresponding dermal toxicity data in mammals.

The toxicity of hexazinone to terrestrial plants can be characterized relatively well and with little ambiguity. Hexazinone is relatively ineffective in inhibiting seed germination but is toxic after either direct spray or soil application. Based on toxicity studies in which exposure can be characterized as an application rate, hexazinone is more toxic in pre-emergent soil applications than direct spray. In pre-emergent soil applications, the NOEC values for the most sensitive and tolerant species are 0.000348 lb/acre and 0.0234 lb/acre, respectively. The corresponding values for direct spray (post-emergent bioassays) are 0.00391 lb/acre and 0.0626 lb/acre.

Hexazinone is not very toxic to aquatic animals. The acute NOEC values for sensitive and tolerant species of fish cover a very narrow range, 160 mg/L to 370 mg/L. For longer term exposures, the data are not sufficient to identify tolerant and sensitive species and a single NOEC value of 17 mg/L is used. Somewhat greater variability is apparent in aquatic invertebrates, with acute NOEC values ranging from 20.5 mg/L to 320 mg/L. This may, however, be an artifact of comparisons between freshwater and saltwater species. An NOEC of 10 mg/L from a reproduction study in daphnids is used to assess the effects of longer-term exposures in sensitive aquatic invertebrates. No longer-term NOEC is available for tolerant invertebrates and the relative potency from acute studies is used to estimate a longer-term NOEC for tolerant species at 160 mg/L.

Aquatic plants are much more sensitive to hexazinone and the variability in this group appears to be much greater than that for fish and aquatic invertebrates. For sensitive aquatic algae, risk is characterized using the lowest NOEC from a standard 5-day bioassay, 0.004 mg/L. The most tolerant species of algae has a corresponding NOEC of 0.15 mg/L. Aquatic macrophytes appear to fall within the range of algae and a single NOEC of 0.012 mg/L is used for this group.

4.3.2. Toxicity to Terrestrial Organisms

4.3.2.1. Mammals – As summarized in the dose-response assessment for the human health risk assessment (Section 3.3), the Office of Pesticide Programs of the U.S. EPA has derived an acute RfD of 4 mg/kg/day and a chronic RfD of 0.05 mg/kg/day for hexazinone. The acute RfD is based on a dose of 400 mg/kg/day that did not cause any adverse effects in offspring but did cause weight loss and decreased food consumption in dams (Section 3.3.3 and the study by Mullin 1987 in Appendix 2). Following the rationale articulated by U.S. EPA/OPP (Anderson 2005) and as discussed in Section 3.3.3, the acute NOAEL of 400 mg/kg/day for developmental effects will be used to characterize risks associated with acute exposures.

The chronic RfD is based on a 1-year dietary NOAEL in dogs of 5 mg/kg/day from the study by Dalgard (1991). This study is summarized in Appendix 2 and discussed in Section 3.3.2. The chronic NOAEL of 5 mg/kg/day does appear to be protective of the most sensitive mammalian species and this NOAEL is used in the current risk assessment to characterize the risks associated with longer-term exposures of mammals to hexazinone. The corresponding LOAEL of about 40 mg/kg/day was associated with decreased body weight and subtle signs of liver toxicity. The highest dose, about 160 mg/kg/day, was associated with substantial decreases in body weight and clear signs of liver toxicity. These dose-severity relationships are used to characterize risks associated with hazard quotients that exceed one.

4.3.2.2. Birds – As noted in Section 4.1.2.2, comparable single dose gavage studies suggest that birds may be somewhat less sensitive to hexazinone than mammals, although the differences are slight and do not appear to be statistically significant. Based on dietary exposures, however, birds appear to be substantially more tolerant to hexazinone than mammals.

Based on short-term dietary exposures, the concentration of 156 ppm in bobwhite quail from the study by Dudeck and Bristol (1980) is clearly a NOEC for mortality, changes in body weight, and signs of toxicity. Based on measured food consumption and body weights, the birds in this study consumed food at a rate of about 0.22 of their body weight per day. Thus, the 156 ppm dietary exposure corresponds to a dose of about 34 mg/kg/day. As noted in Appendix 3, however, the study by Dudeck and Bristol (1980) did not yield any consistent dose-response relationship, and deaths or signs of toxicity were absent at a concentration a concentration of 2500 ppm. For short-term dietary exposures, the U.S. EPA/OPP (1994a, p. 32) uses a dietary LC_{50} value of 10,000 ppm. As discussed by U.S. EPA, the LC_{50} value is actually greater than 10,000 ppm because no acute studies in birds noted 50% mortality or any dose-related increase in mortality. For the current risk assessment, 2500 ppm (equivalent to 550 mg/kg) will be used as an NOEC based on the study by Dudeck and Bristol (1980). This is below the concentration of 5000 ppm which was associated with the highest observed mortality (3/10). It should be

noted that the response of 3/10 is not significantly different from the control response of 1/10 [p=0.105 using the Fisher Exact test].

Reproduction studies are generally used to assess the consequences of longer-term exposures for birds. As summarized in Appendix 3 and discussed in Section 4.1.2.2, most of the reproduction studies in birds suggest that dietary concentrations of 1000 ppm will not cause any adverse effects. In the study by Beavers et al. (1991a), a weight loss of about 10% was noted in 14-day hatchlings at the lowest concentration tested – i.e., 100 ppm which corresponds to a dose of 15 mg/kg/day. This effect was not seen at higher doses. Beavers et al. (1991a) did not regard the response in the 100 ppm group as statistically or biologically significant. U.S. EPA/OPP (1991), however, re-analyzed the data of Beavers et al. (1991a) and classified the response in 100 ppm group as a LOEC – i.e., an adverse effect. This classification is reflected in the RED for hexazinone (U.S. EPA/OPP 1994a, p. 25). Notwithstanding this classification, the U.S. EPA/OPP 1994a, p. 32-33) recognized the lack of any dose-response relationship and elected to use 1000 ppm as the NOEC for the risk characterization. Given the relatively minor response observed at 100 ppm in the study by Beavers et al. (1991a) and the lack of any dose-response relationship, this approach is clearly sensible and will be adopted in the current risk assessment. Thus, for longer-term exposures, the NOEL will be taken as 150 mg/kg/day – i.e., the birds consumed food at a rate equivalent to about 15% of their body weight per day.

4.3.2.3. Terrestrial Invertebrates – There is very little information on the toxicity of hexazinone to terrestrial insects. This is the case with most herbicides, which are generally presumed to be relatively nontoxic to insects and other invertebrates. Based on the study by Hoxter et al. (1989), the acute contact LD_{50} for hexazinone is reported as greater than 0.100 mg/bee, a dose which corresponds to about 1075 mg/kg bw. This is consistent with the dermal toxicity data in mammals. As discussed in Section 4.1.2.3, the highest mortality observed at any dose (4/40) is only marginally statistically significantly higher than the control response (1/100) and no dose-response relationship is apparent in the Hoxter et al. (1989) study. The value of 1075 mg/kg bw is used to characterize risk for honey bees and is taken as a marginal LOEC (Table 4-6).

4.3.2.4. Terrestrial Plants (Macrophytes) – As discussed in Section 4.1.2.4, hexazinone is relatively ineffective in inhibiting seed germination. While direct spray of target vegetation (post-emergence assays) can be effective, soil treatment (pre-emergence assays) with subsequent absorption through the plant root system appears to be the most effective mode of application and this is the application method used for all granular formulations.

For assessing the potential consequences of exposures to nontarget plants via runoff or direct soil treatment, the pre-emergence bioassays by McKelvey and Heldreth (1994) are used (Appendix 5). In this bioassay, the most sensitive species was tomato with an NOEC for all effects of 0.000348 lb/acre. The most tolerant species was corn, with an NOEC for all effects of 0.0234 lb/acre. These values are used in all worksheets assessing the consequences of soil treatment (Worksheets G04a-c in the workbooks for granular and liquid formulations).

For assessing the impact of drift, the post-emergent (vegetative vigor) bioassays by McKelvey and Heldreth (1994) are used. In this series of bioassays, the most sensitive species was

cucumber, with an NOEC of 0.00391 lb/acre for all endpoints. As noted in Appendix 6, U.S. EPA/OPP rejected the cucumber data because another pesticide (thiram) was used as a seed treatment prior to the start of the study (U.S. EPA/OPP 1994a, p. 29). McKelvey (1995) states that interaction with thiram is implausible. The NOEC for cucumbers is the lowest NOEC and this value is used in this Forest Service risk assessment for characterizing risk to sensitive plant species after direct spray or drift. As with the pre-emergence assays, the least sensitive species was corn, with an NOEC of 0.0626 lb/acre. These values are used to characterize risks to nontarget terrestrial vegetation in all worksheets assessing the consequences of accidental direct spray or drift (Worksheets G05a-c, G06a-c, and G07a-c).

4.3.2.5. Terrestrial Microorganisms – There is a relatively robust literature on the toxicity of hexazinone to soil bacteria and fungi (Section 4.1.2.5 and Appendix 4). Much of the available information, however, involves laboratory cultures in artificial growth media. While such studies may be used in the absence of other types of information, field studies have been conducted on hexazinone at application rates of up to about 7 lbs/acre and no adverse effects have been noted on soil bacteria or fungi (Chakravarty and Chatarpaul 1990). This information is used directly in the risk characterization for terrestrial microorganisms.

4.3.3. Aquatic Organisms

4.3.3.1. Fish – The toxicity of hexazinone and hexazinone formulations to fish has been well characterized in standard bioassays. Technical grade hexazinone as practically nontoxic to fish (U.S. EPA/OPP 1994a, p. 25) and both granular and liquid formulations of hexazinone appear to be less toxic to fish than technical grade hexazinone (Section 4.1.3.1). Based on 96-hour NOEC values, there is relatively little difference in sensitivity among species. The lowest and highest acute NOEC values come from the study by Sleight (1973): 160 mg/L for fathead minnows and 370 mg/L for trout. These values are used to characterize risks to sensitive and tolerant fish species from all acute exposure scenarios (Worksheet G03a-c).

Less information is available on chronic effects in fish. A single egg-and-fry study in fathead minnows (Pierson 1990a) defines a NOEC of 17 mg/L. Because of the relatively narrow range in the acute NOEC values as well as acute LC_{50} values and because fathead minnows appear to be the most sensitive species based on the available acute toxicity values, the chronic NOEC of 17 mg/L is used to characterize risks for both tolerant and sensitive fish species (Worksheet G03a-c).

4.3.3.2. Amphibians – Only a single study (Berrill et al. 1994) is available on the toxicity of hexazinone to amphibians (Section 4.1.3.2). The 8-day NOEC for hatching of 100 mg/L, which was accompanied by transient reduced avoidance in newly hatched tadpoles, is somewhat lower than the acute NOEC for sensitive fish. This 8-day NOEC, however, is free standing – i.e., no information is available on where effects on hatching might be seen. This study does not seem adequate to propose an independent toxicity value for amphibians.

4.3.3.3. Aquatic Invertebrates – A much greater range of sensitivities is apparent in aquatic invertebrates than in fish. Based on standard acute (48 hour) bioassays, the most sensitive species is *Daphnia magna* with an NOEC of 20.5 mg/L (Table 4-6). Other species of aquatic

invertebrates are much less sensitive. As noted in Section 4.1.3.3, the fiddler crab, a much larger crustacean, is much less sensitive with a NOEC for mortality of over 1000 mg/L (Heitmuller 1976). For this risk assessment, however, the NOEC of 320 mg/L for oyster embryos is used as a representative tolerant species. It is noted that both oyster embryos and fiddler crabs are saltwater species. Nonetheless, in this risk assessment as well as other Forest Service risk assessments, variability in aquatic invertebrates is characterized using both freshwater and saltwater species unless there are data indicating that comparable freshwater and saltwater differ substantially in sensitivity. For hexazinone, this is not the case.

The only species of aquatic invertebrate on which chronic toxicity data are available is *Daphnia magna*. Two standard daphnid reproduction studies in *Daphnia magna* are available (Pierson 1990b; Schneider 1977). The U.S. EPA/OPP (1994a,d) elected to use the NOEC of 29 mg/L from the more recent study by Pierson (1990b). As discussed in Section 4.1.3.3, however, this is very close to the 21-day LC_{50} value of 33.1 (28.1-36.9) mg/L reported by Schneider (1977). While the Forest Service will generally adopt the same values as those used by U.S. EPA, the proximity of the 29 mg/L NOEC to the LC_{50} value suggests that the lower NOEC of 10 mg/L reported by Schneider (1977) should be used. The U.S. EPA/OPP (1994a,d) does not discuss the rationale for using the higher NOEC and classifies both the Pierson (1990b) and Schneider (1977) studies as equally acceptable. Thus, for chronic effects in sensitive invertebrates, the NOEC of 10 mg/L is used in this Forest Service risk assessment (Table 4-6).

Because of the substantial difference in the sensitivity of aquatic invertebrates based on acute toxicity, the relative acute potency – i.e., the NOEC in tolerant species divided by the NOEC in *Daphnia* [320 mg/L divided by 20.5 mg/L or about 16] – is used to estimate a chronic NOEC in tolerant species of 160 mg/L [10 mg/L x 16].

4.3.3.4. Aquatic Plants – The relevant data on the toxicity of hexazinone to aquatic plants are discussed in Section 4.1.3.4 and summarized in Appendix 5. As is common with herbicides, the toxicity values for aquatic plants are much lower than those for aquatic animals. Based on standard bioassays for growth inhibition, the most sensitive aquatic plant species appears to be *Selenastrum capricornutum*, a common species of green algae, with a 5-day NOEC for growth inhibition of 0.004 mg/L (Forbis 1989). The sensitivity of green algae to hexazinone has also been noted by Peterson et al. (1997) who reported a greater than 10% inhibition of photosynthesis at a somewhat lower concentration, 0.0014 mg/L.

The most tolerant aquatic plant species on which data are available is *Anabaena flos-aquae*, a common species of blue-green algae, with a 5-day NOEC for growth inhibition of 0.15 mg/L (Forbis 1989). This difference in sensitivity (a factor of about 38) is much greater than that seen in acute bioassays of fish (a factor of about 2) and substantially greater than that seen in aquatic invertebrates (a factor of about 16).

Less data are available on aquatic macrophytes (Section 4.1.3.4). The lowest estimated NOEC is 0.012 mg/L (Peterson et al. 1997), very close to the geometric mean of the NOEC values for tolerant algae (0.004 mg/L) and sensitive algae (0.15 mg/L). For the current risk assessment, the

range of the algal NOEC values is used for tolerant and sensitive algae but only a single NOEC of 0.012 mg/L is used for macrophytes.

4.4. RISK CHARACTERIZATION

4.4.1. Overview

As with most ecological risk assessments, the characterization of risk for hexazinone is limited by the comparison of the available data to the number of species that might be exposed and the interactions that could occur among these species. Hexazinone has been tested in only a limited number of species and under conditions that may not well-represent natural populations of nontarget organisms. This leads to uncertainties that may result in underestimates or overestimates of risk. The methods and assumptions used in both the exposure and dose-response assessments are intended to consider these uncertainties by using protective assumptions in developing both the exposure and dose-response assessments which form the basis of the risk characterization.

Because hexazinone is an effective herbicide, unintended effects on nontarget vegetation are plausible. The effective use of hexazinone is achieved by applying the compound to target vegetation at a time and in a manner which will minimize effects on nontarget plant species. If this is done properly and with care, effects on nontarget vegetation should be minor and perhaps negligible. Nonetheless, in the normal course of applications of granular or liquid formulations at rates that are effective in weed control, adverse effects on terrestrial plants are plausible due to either drift or runoff. Depending on local conditions and the proximity of streams or ponds to hexazinone applications, damage to aquatic vegetation is also plausible and could be substantial.

The potential for adverse effects in animals is far less clear and is somewhat dependent on the type of formulation that is applied. Granular formulations of hexazinone appear to pose a very low risk to any terrestrial or aquatic animal. The application of liquid formulations will result in much higher concentrations of hexazinone in terrestrial vegetation than will comparable applications of granular formulations. This has a major impact on the potential for adverse effects in mammals.

Over the range of application rates used in Forest Service programs, adverse effects are plausible in mammals consuming contaminated vegetation after the application of liquid formulations and adverse reproductive effects in some mammalian species could occur. There is no indication that substantial numbers of mammals would be subject to lethal exposure to hexazinone. Consequently, adverse effects such as weight loss and reproductive impairment could occur but might not be readily apparent or easy to detect. Birds appear to be much more tolerant to hexazinone than mammals and adverse effects on birds do not seem plausible. Similarly, there is no indication that direct toxic effects are likely in aquatic animals.

The most likely consequences to both terrestrial and aquatic animals of hexazinone applications appear to be effects that are secondary to direct toxic effects on vegetation. These effects would likely be variable over time and among different species of animals. Some effects could be detrimental for some species – i.e., a reduction in the supply of preferred food or a degradation of habitat – but beneficial to other species – i.e., an increase in food or prey availability or an enhancement of habitat.

4.4.2. Terrestrial Organisms

4.4.2.1. Mammals – The quantitative risk characterization for mammals and other terrestrial animals is summarized in Worksheets G02a-c of the EXCEL workbooks for liquid and granular formulations. These worksheets summarize the hazard quotients for the range of application rates specifically considered in this risk assessment: a typical rate of 2 lbs/acre (Worksheet G02a), the lowest anticipated application rate of 0.5 lb/acre (Worksheet G02b), and the highest anticipated application rate of 4 lbs/acre (Worksheet G02c). In this and all other similar worksheets, risk is characterized as the hazard quotient, the estimated dose (taken from Worksheet G01) divided by toxicity value. The toxicity values used for each group of animals – mammals, birds, and insects – are summarized in Table 4-6 and the specific toxicity values used for mammals are discussed in Section 4.3.2.1. These toxicity values are repeated in the last column of the worksheets. A hazard quotient of one or less indicates that the estimated exposure is less than the toxicity value. When this is the case, there is no basis for asserting that adverse effects are plausible.

As in the human health risk assessment (Section 3.4), large differences are apparent in the hazard quotients for liquid and granular formulations for all exposure scenarios based on contaminated vegetation. These differences are due solely to the much higher estimates of hexazinone on contaminated vegetation after the application of liquid formulations relative to granular formulations (Section 3.2.3.6 and Table 3-3).

For granular formulations, none of the hazard quotients for mammals exceed a level of concern even at the highest application rate of 4 lbs/acre. At the highest application rate, the direct spray of a mammal reaches a level of concern (HQ=1) only under the assumption of 100% absorption. This is not a reasonable assumption for dermal absorption but is included in order to consider other factors such a grooming that may increase exposures for some mammals (Section 4.2.2.1).

For liquid formulations of hexazinone, hazard quotients exceed the level of concern at all application rates and all of the scenarios involving residue rates for contaminated vegetation or insects from Fletcher et al. (1994). At the lowest application rate, the hazard quotients only modestly exceed the level of concern (i.e., HQs of up to 2). At the highest application rate, the highest acute hazard quotient is 3 (the consumption of contaminated insects by a small mammal) and the highest chronic hazard quotient is 16 (the on-site consumption of contaminated vegetation by a large mammal).

As discussed in Section 4.3.2.1, the study that was used to define the NOAEL of 5 mg/kg/day (Dalgard 1991) had a LOEL of 40 mg/kg/day (a modest decrease in body weight and subtle signs of liver toxicity) and a frank effect level of 160 mg/kg/day (associated with substantial decreases in body weight and clear signs of liver toxicity). The LOAEL corresponds to a hazard quotient of 8 [40 mg/kg/day ÷ 5 mg/kg/day] and the frank effect level corresponds to a hazard quotient of 32 [160 mg/kg/day ÷ 5 mg/kg/day]. Thus, at the upper ranges of exposure to hexazinone, the LOAEL is reached or exceeded at both the typical application rate of 2 lbs/acre and the highest anticipated application rate of 4 lbs/acre. For those hazard quotients that exceed 8, adverse effects would be expected. None of the hazard quotients exceed 32 – i.e., the dose associated

with frank signs of toxicity. Nonetheless, toxic effects such as substantial weight loss and liver damage cannot be ruled out.

The highest acute dose is estimated at about 280 mg/kg bw (the consumption of contaminated grass by a large mammal at an application rate of 4 lbs/acre) and the highest long-term dose is estimated at about 80 mg/kg/day (the on-site consumption of contaminated grass by a large mammal at an application rate of 4 lbs/acre). This is below the acute NOAEL of 400 mg/kg/day.

The verbal interpretation of the quantitative risk characterization is relatively simple after the application of granular formulations: no adverse effects are anticipated at any application rate. For liquid formulations, however, the interpretation is somewhat less clear. Over the range of application rates used in Forest Service programs, adverse effects could be anticipated in mammals who consume contaminated vegetation over prolonged periods of time. It is unclear whether or not frank effects such as severe weight loss might occur or be evident. Adverse reproductive effects do not appear to be plausible.

This risk characterization for terrestrial mammals is consistent with the risk assessments by the U.S. EPA/OPP (1994a) in which hazard quotients exceed the level of concern for both endangered and non-endangered small mammals (U.S. EPA/OPP 1994a, p. 47). The risk quotients cited by U.S. EPA/OPP (1994a) are not quantitatively comparable to those cited in the current Forest Service risk assessment because the U.S. EPA/OPP (1994a) bases the hazard quotients on LD_{50} values rather than NOEC values (U.S. EPA/OPP 2001a).

As noted in Section 4.1.2.1, the effect of hexazinone on vegetation may alter habitat and these alterations may increase or decrease food availability. These secondary effects are likely to be variable over time and among different species of mammals.

4.4.2.2. Birds – Worksheets G02a-c of the EXCEL workbooks for liquid and granular formulations also summarize the risk characterization for birds. As noted in Section 4.3.2.2 and summarized in Table 4-6, birds appear to be substantially more tolerant of hexazinone than do mammals in terms of both the acute NOAEL (a factor of 5.5 higher in birds) and the longer-term NOAEL (a factor of 30 higher in birds). These differences have a substantial impact on the risk characterization for birds.

At the highest anticipated application rate and the at the upper limit of exposure, none of the hazard quotients exceed a level of concern (HQ=1). Thus, there is no basis for asserting that any adverse effects are plausible in birds with the application of liquid or granular formulations of hexazinone. This unambiguous risk characterization is consistent with the risk characterization for birds given by the U.S. EPA/OPP (1994a) in the registration document for hexazinone.

As with mammals, secondary effects on some species of birds may occur through changes in vegetation that may impact food availability and habitat (Section 4.1.2.2). These effects may be beneficial or detrimental and are likely to vary over time. There is no basis for asserting, however, that negative impacts on populations of birds will be substantial or severe.

4.4.2.3. Terrestrial Invertebrates – Except for two bioassays in the honey bee, no information is available on the toxicity of hexazinone to terrestrial invertebrates. Given the large number of terrestrial invertebrate species, this severely limits the risk characterization.

Based on the limited available information, there is no basis for asserting that terrestrial insects or other terrestrial invertebrates will be directly affected by the use of hexazinone in Forest Service programs. Notwithstanding this assertion, hexazinone may have effects on nontarget vegetation that result in secondary effects on terrestrial invertebrates. The extent with which such effects would be regarded as beneficial or detrimental is speculative. Some field studies suggest that changes in the distribution of soil invertebrates could occur. It is not clear if these effects are due to the toxicity of hexazinone to the soil invertebrates or secondary to other changes in the soil associated with effects on plants.

4.4.2.4. Terrestrial Plants – A quantitative summary of the risk characterization for terrestrial plants is presented in Worksheets G04a-c for runoff, Worksheets G05a-c for drift after low boom ground applications, G06a-c for drift after aerial applications, and Worksheets G07a-c for off-site contamination due to wind erosion. As with the worksheets for terrestrial animals, the a-c designations represent groups of three worksheets for the typical application rate (*a*), the lowest anticipated application rate (*b*), and the highest anticipated application rate (*c*). Also analogous to the approach taken for terrestrial animals, risk in these worksheets is characterized as a ratio of the estimated exposure to a benchmark exposure (i.e., exposure associated with a defined response). For both worksheets, the benchmark exposure is a NOEC, as derived in Section 4.3.2.4, for both sensitive and tolerant species.

There are few quantitative differences in the risk characterizations associated with the application of granular and liquid formulations of hexazinone. As discussed in Section 3.2.3.4.3, GLEAMS modeling suggests that runoff could be somewhat greater with granular applications. These differences, however, are rather small and are not incorporated into the worksheets. A somewhat more important difference may involve the potential for drift. As discussed in 4.2.3.2, AgDrift is used to estimate drift after low boom ground application and aerial applications. These estimates are based on liquid rather than granular applications. It seems likely that the application of granular formulations could result in much different patterns of drift than those found with liquid formulations. Again, the available information does not permit a quantitative consideration of these differences and the significance of this information gap cannot be well characterized.

Hexazinone is an effective herbicide and adverse effects on some nontarget plant species due to direct application or drift are likely. Direct spray or direct application is likely to damage both tolerant and sensitive plant species. For low boom ground applications (Worksheets G05a-c), damage to off-site vegetation may occur at distances of up to about 300 feet at the highest application rate and up to about 25 feet at the lowest application rate. Aerial sprays are likely to result in somewhat greater drift and damage could be apparent at distances of up to 500 feet at the highest application rate and up to about 100 feet at the lowest application rate (Worksheets G06a-c).

Whether or not damage due to drift would actually be observed after the application of hexazinone would depend on several site-specific conditions, including wind speed and foliar interception by the target vegetation. In other words, in applications conducted at low wind speeds and under conditions in which vegetation at or immediately adjacent to the application site would limit off-site drift, damage due to drift should be inconsequential or limited to the area immediately adjacent to the application site.

Thus, all of these risk characterizations for drift should be viewed as only a crude approximation of the potential for damage during any actual application. AgDrift is a highly parameterized model and the output of the model is sensitive to a number of site-specific and application specific variables – e.g., wind speed, type of aircraft, and elevation at which the pesticide is released. It is not feasible and would not be particularly useful to elaborate a large number of different drift scenarios based on the many variables that could be modified. The generic drift modeling presented in Worksheets G05a-c and Worksheets G06a-c suggests that efforts should be made to minimize drift. If threatened or endangered species are in the area to be treated, the site-specific application of AgDrift or some other appropriate drift model should be considered.

In contrast to drift that could occur during application, relatively conservative estimates of pesticide transport by wind erosion of soil (Worksheets G07a-c) suggest that this process is not likely to result in exposures that would be of concern. At the highest application rate (Worksheet G07c), the upper bound of the hazard quotient for the most sensitive species is only 0.1.

As summarized in Worksheet G04a-c, the off-site transport of hexazinone by runoff and sediment losses could cause substantial damage under conditions that favor runoff and sediment loss – i.e., high rainfall rates and clay soil. Based on the generic GLEAMS modeling for off-site pesticide losses (Table 4-4), adverse effects in sensitive and tolerant species could be expected across the range of application rates in clay soils. In loam, much less offsite transport is modeled. In predominantly sandy soils, the major transport mechanism is percolation into the soil with very little risk of off-site loss due to runoff or sediment loss. As with AgDrift, GLEAMS is a highly parameterized model that is designed for site-specific assessments (Knisel and Davis 2000; SERA 2004b). The use of the generic modeling in the current risk assessment is simply to illustrate factors that may need to be considered in assessing the potential for significant off-site movement. For hexazinone, the potential appears to be high, particularly for predominantly clay soils.

This risk characterization is reasonably consistent with the risk characterization given by U.S. EPA/OPP (1994a). Although based on different modeling, different exposure scenarios, and different toxicologic endpoints (i.e., EC_{25} values rather than NOEC values), the risk quotients for terrestrial plants given by U.S. EPA/OPP (1994a, p. 39) range from about 8 to over 2,000. The risk quotients given the worksheets for the current Forest Service risk assessment range from less than 1 to over 7,000.

The simple verbal interpretation for the quantitative risk characterization is that sensitive and tolerant plant species could be adversely affected by the runoff, sediment loss, or off-site drift of

hexazinone under a variety of different scenarios depending on local site-specific conditions that cannot be generically modeled. If hexazinone is applied in the proximity of sensitive crops or other desirable sensitive plant species, site-specific conditions and anticipated weather patterns will need to considered if unintended damage is to be avoided.

4.4.2.5. Soil Microorganisms – As detailed in Appendix 4 and discussed in Section 4.1.2.5, several studies have been conducted on the toxicity of hexazinone to soil bacteria and fungi. Most of these studies, however, were conducted under laboratory conditions and are not directly useful for risk characterization. The most useful study is that of Chakravarty and Chatarpaul (1990) in which no effects were noted on mixed fungal and bacterial populations after field application at rates of up to 7 lbs/acre. This is substantially higher than the maximum application rate of 4 lbs/acre that will be used in Forest Service programs.

4.4.3. Aquatic Organisms

4.4.3.1. Fish – The risk characterization for fish is based on a reasonably complete set of standard toxicity studies and is relatively simple and unambiguous. Under foreseeable (non-accidental) conditions, there is no indication that hexazinone will cause direct toxic effects in fish even at the highest anticipated application rate of 4 lbs/acre. At this rate, the highest hazard quotient for peak exposure is 0.01 and the highest hazard quotient for longer-term exposure is 0.02. Under standard exposure scenarios involving the accidental spill of hexazinone into a small body of water, the highest hazard quotient is 0.5.

As with other groups that do not appear to be directly at risk from the toxic effects of hexazinone, secondary effects on fish could be associated with damage to aquatic vegetation (Section 4.4.3.4). The nature of these effects could be beneficial or detrimental and could be variable over time and probably among different species of fish.

4.4.3.2. Amphibians –The risk characterization for amphibians is severely limited by the lack of data on the toxicity of hexazinone to amphibians (Section 4.1.3.2). A concentration of 100 mg/L has been reported to cause transient reduced avoidance in newly hatched tadpoles (Berrill et al. 1994). This is essentially the only relevant information that is available on the toxicity of hexazinone to amphibians.

The highest estimated peak concentration of hexazinone is 0.4 mg/L per pound of hexazinone applied per acre (Table 3-9), corresponding to a concentration of 1.6 mg/L at the maximum application rate of 4 lbs/acre. The highest estimated concentration in water after an accidental spill is about 36 mg/L (Worksheet G03c for liquid formulations). This might have a short-term effect on avoidance behavior. Whether or not this would result in any substantial impact on amphibian populations is unclear.

As with fish and other animals, effects on amphibians that are secondary to the effects of hexazinone on terrestrial or aquatic vegetation could occur. Again, however, the nature of these effects could be either beneficial or detrimental.

4.4.3.3. Aquatic Invertebrates – The risk characterization for aquatic invertebrates is virtually identical to that for fish. Based on a conservative analysis of a reasonably complete set of standard toxicity studies, there is little basis for asserting that direct toxic effects on aquatic invertebrates are plausible. None of the hazard quotients for non-accidental exposures exceed a level of concern based on either peak or longer-term concentrations of hexazinone in water at the maximum application rate of 4 lbs/acre. In the event of an accidental spill at the maximum application rate, the maximum hazard quotient is above the level of concern by a factor of 4. In this instance, direct toxic effects could occur.

Many ecologically important aquatic invertebrates are primary consumers of aquatic vegetation. It is virtually certain that effects on aquatic vegetation (Section 4.4.3.4) would have a far more important effect on aquatic invertebrates than any direct toxic effect on the invertebrates from hexazinone.

4.4.3.4. Aquatic Plants – Although there is very little basis for suggesting that direct adverse effects on aquatic animals are plausible, adverse effects on aquatic vegetation are virtually certain unless effective measures at taken to ensure that bodies of open water are not contaminated.

Based on the estimated concentrations in water used in other parts of this risk assessment for non-accidental exposures, hazard quotients for aquatic vegetation substantially exceed the level of concern across all ranges of application rates except at the lower limit of estimated concentrations – i.e., those applications in which efforts to limit water contamination are effective. Even at the lowest application rate, the hazard quotients for sensitive species range from 13 to 50 over the central to upper ranges of plausible peak concentrations. At the highest application rate, the corresponding hazard quotients range from 100 to 400 for peak exposures. Accidental exposures result in hazard quotients in the range of 15 to over 18,000. This risk characterization is consistent with that of U.S. EPA/OPP (1994a, p. 40) in which hazard quotients of up to about 5,000 were estimated.

This risk characterization is tempered only modestly by a field study that reported no adverse effects at a very high application rate – i.e., 16.8 kg/ha or about 15 lb/acre (Mayack et al. 1982). As noted in Appendix 6, substantial effects on species composition and diversity were not seen in either aquatic invertebrates or macrophytes. While this is acknowledged, concern is not substantially reduced because Mayack et al. (1982) monitored concentrations in the water that only intermittently reached concentrations of 6 ppb to 44 ppb. Over this concentration range, which would correspond to hazard quotients of 0.5 to about 3.5 for macrophytes, substantial effects on macrophytes would not be expected. Thus, the Mayack et al. (1982) study may simply be an example of the application of hexazinone in a manner that effectively limited contamination of surface water.

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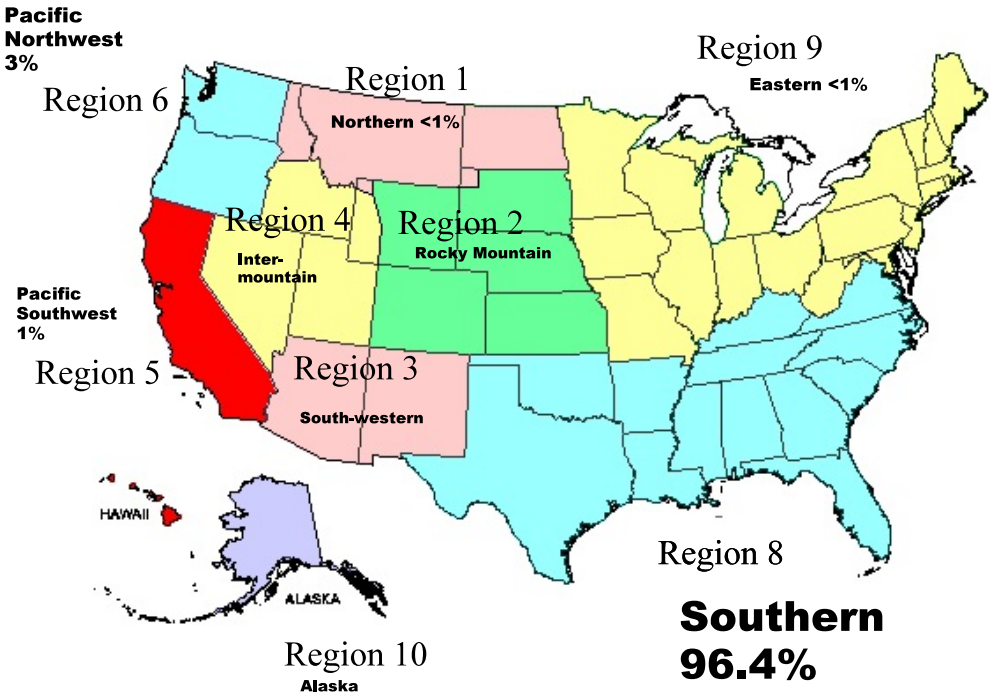

Figure 2-1: Use of hexazinone by the Forest Service between 2000 and 2003 by region of the country as a percentage of the total pounds of hexazinone used in all Forest Service programs (see Table 2-4 for data).

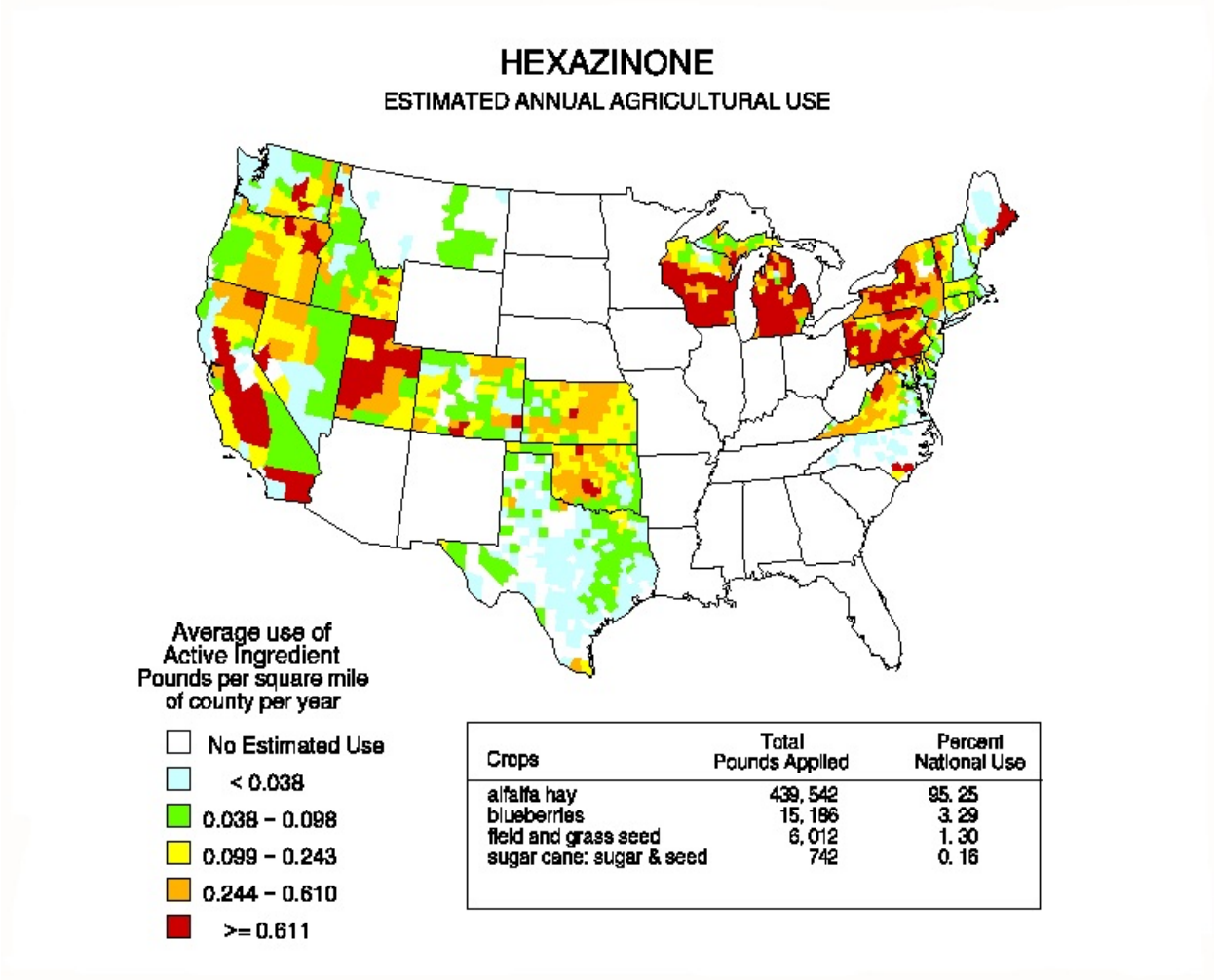

Figure 2-2: Agricultural uses of hexazinone in the United States (USGS 1998).

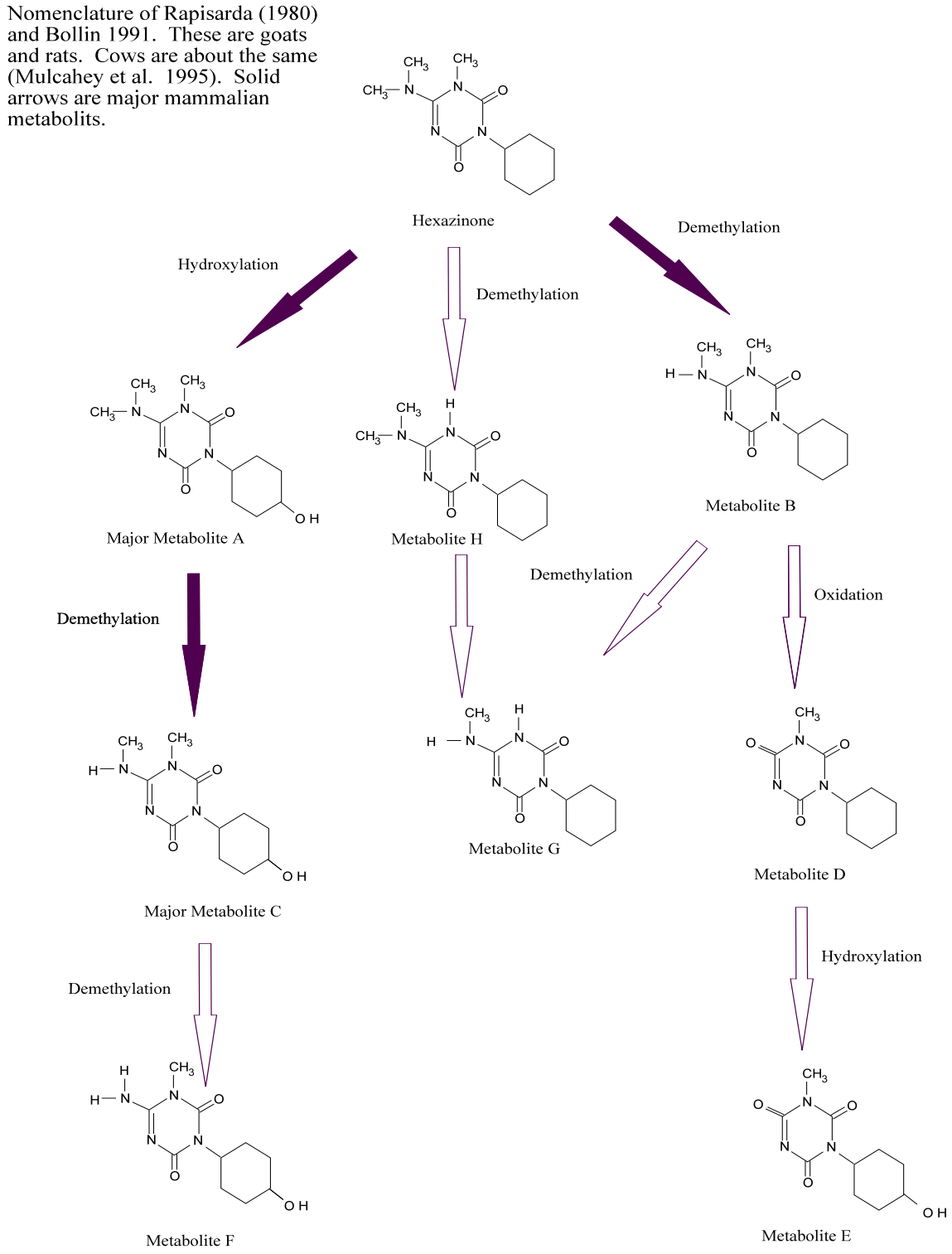

Figure 3-1: Major metabolites of hexazinone in mammals (solid arrows) and in the environment (see Section 3.1.3 for discussion).

Table 2-1. Selected physical and chemical properties of hexazinone.

Appearance, ambient	Colorless, odorless crystals (Tomlin 2005)
CAS number	51235-04-2 (Budavari et al. 1989, Tomlin 2005, USDA/ARS 1995)
Chemical Name	3-cyclohexyl-6-dimethylamino-1-methyl-1,3,5-triazine-2,4(1*H*,3*H*)-dione (ACS, IUPAC) (Tomlin 2005)
Density	1.25 (Tomlin 2005)
Field half-time for dissipation (days)	79 (30-180) (USDA/ARS 1995) 75 (Silt loam, DE, pH 6.4, 2.7% OM)(USDA/ARS 1995) 75 (Silt loam, IL, pH 5.0, 4.0% OM)(USDA/ARS 1995) 154 (Silt loam, MS, pH 7.0, 0.7% OM)(USDA/ARS 1995) 123 (Loam, DE, pH 6.3, 1.5% OM)(USDA/ARS 1995) 140 (Sandy loam, CA, pH 8.1, 1.1% OM)(USDA/ARS 1995; Bollin 1992b) 55-77 days (field study, two sites)(Michael 1992) 275 days (field study, soil under litter)(Michael 1992)
Foliar half-time (days)	30 (recommended value) (Knisel and Davis 2000) 26-59 days for granular formulation in field study (Michael 1992) 19-36 days for liquid (Velpar L) formulation in field study (Michael 1992)
Foliar wash-off fraction	0.9 (recommended value) (Knisel and Davis 2000)
Hydrolysis	Stable between pH 5 and pH 9 (Tomlin 2005) Stable (USDA/ARS 1995)
$K_{o/c}$	54 (recommended value) (Knisel and Davis 2000) 53.7 [Estimated Log $K_{o/w}$=1.73] (Liu and Qian 1995) 30 (forest nursery soils) (Torstensson and Stenstrom 1990) see Appendix 8 for additional values.
$K_{o/w}$	15.8 at pH 7 [Log $K_{o/w}$=1.2] (Tomlin 2005) 14.8 (14.5 - 15.4) [Log $K_{o/w}$=1.17 (1.16 - 1.19)](USDA/ARS 1995) 22.9 [Log $K_{o/w}$=1.36] (Liu and Qian 1995)
Melting point	115-117°C (Tomlin 1994, WSSA 1989) 97-100.5°C (Budavari et al. 1989)
Molecular formula	$C_{12}H_{20}N_4O_2$
Molecular weight	252.3 (Tomlin 2005)
Photolysis half-time(days)	Stable (aqueous) (Tomlin 2005) 81.5 days (0.0085 day^{-1} soil) (USDA/ARS 1995) > 301 days (0.0023 day^{-1} aqueous) (USDA/ARS 1995)
pKa	2.2 (Tomlin 2005; USDA/ARS 1995)
Soil half-time (days)	Highly variable, about 5 to over 200. See Appendix 8 for details.
Soil sorption, K_d/K_{oc}	Highly variable, about 0.2 to 10. See Appendix 8 for details.
SMILES Notation	CN(C)c1nc(=O)n(C2CCCCC2)c(=O)n1C (Tomlin 2005)
Synonyms	Hexazinone t.g.i.a., DPX A3674(Tomlin 2005; Palmer et al. 1996), DPX-A3674-207 (Sarver 1989). Velpar DF, DPX-GH427 (Patton 1999) Velpar DF, DPX-A3674-268. (Mathison 1996) Velpar L, DPX-A3674-208 (Hutton 1989c)

Table 2-1. Selected physical and chemical properties of hexazinone.

Vapor pressure	0.03 mPa (extrapolated) (25 ˚C); 8.5 mPa (86 ˚C) (Tomilin 2005)
Water solubility	33 g/kg at 25°C (Tomlin 2005) 33,000 mg/L (Knisel and Davis 2000) 29800 mg/L (USDA/ARS 1995) 330 g/L at 25°C (Budavari 1989) [This appears to be typo in Budavari (1989).]

Table 2-2: Hexazinone Formulations with Forestry Applications [1]

Brand Name Company/Composition	Application Rate (Specified by Label) [2]	Inerts (Specified)
Pronone 10G **PRO-SERVE, INC** **10% hexazinone**: combination of technical grade hexazinone (98.7% purity) [CAS No. 51235-04-2] and Velpar L(25.33% purity) CAS No. 51235-04-2 **90% inert ingredients**: including Pluronic L61 CAS No. 9003-11-6 (according to MSDS) ***Spherical granules with a particle size of 1/8" to 1/4"*** ***Aerial and ground application***	**GENERAL WEED-CONTROL** 60-120 lbs/acre for season-long control of many annual, biennial, and perennial weeds 30- 60 lbs/acre for short-term (up to 3 months) control of many annual, biennial, and perennial weeds **Brush Control**: 40-50 lbs/acre to soil between winter and early summer **Individual Stem Treatment**: ½ to ¾ oz for each 1" steam diameter at breast height ****For small areas, 1 lb PRONONE-10G per 500 sq ft is approximately 85 lbs/acre***	MSDS specifies Pluronic L61, which is supplied by BASF. This is a ethylene oxide/propylene oxide block copolymer surfactant [CAS No. 9003-11-6] (BASF 2002). Additional information on inerts has been disclosed to the U.S. EPA (Cochran 1995c)[3].
Pronone MG **PRO-SERVE, INC** **10% hexazinone**: combination of technical grade hexazinone (98.7% purity) [CAS No. 51235-04-2] and Velpar L(25.33% purity) CAS No. 51235-04-2 **90% inert ingredients**: including Pluronic L61 CAS No. 9003-11-6 (according to MSDS) ***According to Pro-Serve website, Pronone MG is an 8/20 mesh granule containing 10% hexazinone and used mainly for herbaceous weed control on forestry or wild blueberries*** No reference to surfactant(s) on label ***Aerial and ground application***	**GENERAL WEED-CONTROL** 60-120 lbs/acre for season-long control of many annual, biennial, and perennial weeds 30- 60 lbs/acre for short-term (up to 3 months) control of many annual, biennial, and perennial weeds **Brush Control**: 40-50 lbs/acre to soil between winter and early summer **Individual Stem Treatment**: ½ to ¾ oz for each 1" steam diameter at breast height ****For small areas, 1 lb PRONONE-10G per 500 sq ft is approximately 85 lbs/acre***	MSDS specifies Pluronic L61, which is supplied by BASF. See note above. No additional references to the inerts in this formulation has been encountered in a search of the U.S. EPA FIFRA submissions.

Table 2-2: Hexazinone Formulations with Forestry Applications [1]

Brand Name Company/Composition	Application Rate (Specified by Label) [2]	Inerts (Specified)
Pronone 25G **PRO-SERVE, INC**	**SITE PREPARATION & CONIFER RELEASE**	None specified on label or MSDS.
25% hexazinone **75% inert ingredients**	6-18 lbs/acre for site preparation, depending on soil texture (coarse to fine)	Product chemistry discussed in Cochran 1995b.[3]
According to Pro-Serve website, Pronone 25G is an 8/20 mesh granule containing 25% hexazinone	3-12 lbs/acre for conifer release, depending on soil texture (coarse to fine)	
No reference to surfactant(s) on label ***Aerial and ground application***	**HERBACEOUS WEED & WOODY PLANT CONTROL** 4-8 lbs/acre for herbaceous weed control, depending on soil texture (coarse or fine) 6-12 lbs/acre for wood plant (brush) control, depending on soil texture (coarse or fine)	

Table 2-2: Hexazinone Formulations with Forestry Applications [1]

Brand Name Company/Composition	Application Rate (Specified by Label) [2]	Inerts (Specified)
Velpar DF **DuPont** 75% hexazinone 25% inert ingredients Dispersible granules **label recommends use of surfactant for specific applications** ***Aerial and ground application***	**GENERAL WEED CONTROL** 2⅔ - 10⅔ lbs/acre, depending on soil texture (coarse to fine) **FORESTRY SITE PREPARATION** 2¾-6⅔ lbs/acre for weed and brush control in eastern US and lake states, depending on soil texture (coarse to fine) 1⅓-4 lbs/acre for weed and brush control in western US, depending on soil texture (coarse to fine) **SITE PREPARATION—GRID and SINGLE STEM APPLICATIONS** (Velpar DF Suspension) 3-6 quarts/acre (coarse soil) and 8-10 quarts/acre (medium/fine soil) **RELEASE—HARDWOOD SUPPRESSION** 1⅓-5⅓ lbs/acre in eastern US, depending on soil and crop species 1⅓- 4 lbs/acre in western US, depending on soil and crop species	None specified on label or MSDS. Product formulation, including inerts, discussed in Kern (1994b).[3]

Table 2-2: Hexazinone Formulations with Forestry Applications [1]

Brand Name Company/Composition	Application Rate (Specified by Label) [2]	Inerts (Specified)
Velpar L **DuPont** 25% hexazinone 75% inert ingredients Water Dispersible Liquid 2 lbs a.i./gallon Labeled for both forestry and agricultural uses ***Aerial and ground application***	**SITE PREPARATION – Broadcast** 2 to 10 quarts/acre depending on soil type and region (lesser rates in sandy soil and in western U.S.). May be combined with burning after treatment. 25 gallons of water/acre in ground applications. At least 5 gallons of water/acre in aerial applications. Pine Trees: weed control. Broadcast applications in spring prior to pine bud break. 4 to 8 pints/acre depending on soil type and age of pines. 5 gallons of water per gallon of Velpar L. **SITE PREPARATION – Undiluted grid applications:** Soil application with handgun. 3 to 10 quarts/acre. Also labeled for stem applications and injection as well as brush suppression.	Ethanol [CAS No. 64-17-5] is identified on the MSDS as an inert that comprises 40-45 % of the formulation. Additional information on inerts has been disclosed to the U.S. EPA (Bloemer 1995e; Puig 1995c; Roche 1995a).[3]
Velpar ULW **DuPont** 75% hexazinone 25% inert ingredients Soluble granules Forestry and non-crop uses only. Broadcast application of dry product to soil surface ***Aerial and ground application***	**SITE PREPARATION**: 2.5 to 6.33 lb/acre (lesser amounts in sandy soil, greater amounts in clay soil). **CONIFER RELEASE**: 1 to 4 lb/acre (lesser amounts in sandy soil, greater amounts in clay soil). **WOODY PLANTS**: 5 $^{1}/_{3}$ to 10 $^{2}/_{3}$ lb/acre.	No inerts are specified on the MSDS. Additional information on inerts have been disclosed to the U.S. EPA (Bloemer 1994a; Bloemer 1995c; DuPont De Nemours 1986; Kern 1994b; Kern 1995b; Puig 1995a; Puig 1995d; Roche 1995c; Roche 1995d).[3]

Table 2-2: Hexazinone Formulations with Forestry Applications [1]

Brand Name Company/Composition	Application Rate (Specified by Label) [2]	Inerts (Specified)

[1] Unless otherwise noted, information is taken from the product labels and material safety data sheets (C&P Press 2004; Pro-Serve Inc. 2004).
[2] All application specified in this column are in units of formulation (oz, gallons, or pounds) per acre. Application rates used in Forest Service programs are discussed in Section 2.4.
[3] The information submitted to U.S. EPA has been reviewed in the conduct of this risk assessment. This information, however, is classified as CBI (confidential business information) under Section 7(d) and Section (10) of FIFRA and cannot be disclosed in this document. See Section 3.1.14 for a discussion of the potential significance of inerts and adjuvants and Section 3.1.15 for a discussion of the potential significance of impurities.

Table 2-3: Uses of hexazinone by the Forest Service between 2000 and 2004 by management objective*.

Management Objective	Pounds	Acres	Pounds/Acre	Proportion	
				lbs	acres
Site Preparation	12464.22	4064.20	3.07	0.85	0.50
Conifer Release	2150.50	3985.00	0.54	0.15	0.49
Insect Eradication	0.02	0.01	2.77	<0.01	<0.01
Noxious Weed Control	5.27	12.00	0.44	<0.01	<0.01
Right-of-Way Management	43.00	37.00	1.16	<0.01	<0.01
Seed Orchard Protection	10.60	27.00	0.39	<0.01	<0.01
Understory / Midstory treatment	5.00	6.00	0.83	<0.01	<0.01
Total	14678.61	8131.21	1.81		

Source: http://www.fs.fed.us/foresthealth/pesticide/reports.shtml

* The maximum application rate at a single site was 4 lbs/acre (Forest 7 in Region 8 in 2000 and 2001). This excludes a reported application of 2.76 lbs on 0.16 acres [17.25 lbs/acre] which appears to be a reporting error from Forest 8, Region 5 in 2000.

Table 2-4: Uses of hexazinone by the Forest Service between 2000 and 2004 by Forest Service Region between 2000 and 2004.

Region	Pounds	Acres	lb/acre	Proportion	
				Lbs	Acres
1: Northern	27.22	81.50	0.33	<0.01	0.01
5: Pacific Southwest	185.22	70.51	2.63	0.01	0.01
6: Pacific Northwest	368.47	468.20	0.79	0.03	0.06
8: Southern	14078.70	7501.00	1.88	0.96	0.92
9: Eastern	19.00	10.00	1.90	<0.01	<0.01
Grand	14678.61	8131.21	1.81	1.00	1.00

Source: http://www.fs.fed.us/foresthealth/pesticide/reports.shtml

Table 3-1: Summary of acute intraperitoneal and oral LD_{50} values and non-lethal acute dermal doses of hexazinone and hexazinone formulations [1].

Material/Species	Toxicity of formulation (mg formulation/kg bw)	Toxicity as Active Ingredient (mg a.i./kg bw)	Reference(s)
INTRAPERITONEAL LD_{50}			
Hexazinone (t.g.a.i.)			
Rat	N/A	530 (300-570)	Kennedy 1984
ORAL LD_{50} (all doses as gavage unless otherwise specified)			
Hexazinone (t.g.a.i.)			
Dog, **sublethal dose**	N/A	1000 to 3400 (capsules)	Kennedy 1984
Guinea pig	N/A	860 (420-1260)	Kennedy 1984
Rat	N/A	1690 (1560-1880)	Kennedy 1984
Rat, male	N/A	1100 (810-1800)	Sarver 1989
Rat, female	N/A	1200 (1000-2000)	Sarver 1989
Pronone 10G			
Rats, **sublethal dose**	5000	500	Gargus et al. 1983c
Velpar L (25% a.i.)			
Rats	4120	1030	Finlay 1994b
Velpar 75 DF			
Rats, males	1300 (1110-1350)	975 (833-1010)	Redgate and Sarver 1986
Rats, females	1100 (900-1400)	825 (675-1050)	Redgate and Sarver 1986
Rats, males and females	1310 (560-1800)	982 (420-1350)	Finlay 1994c
90% formulation (NOS)			
Rats	1100 (500-5000)	990 (450-4500)	Filliben 1994a
DERMAL LIMIT ASSAYS (Doses in rabbits that did not cause mortality)			
Hexazinone (a.i.)	N/A	5000	Filliben 1994b
Velpar DF (75% a.i)	5000	3750	Finlay 1994d

Velpar ULW (75% a.i.)	5000	3750	Filliben 1994c
Velpar L (25% a.i.)	5000	1250	Finlay 1994g
Pronone 25G (25% a.i.)	5000	1250	Fitzgerald 1990a,b
Pronone 10G (10% a.i.)	2000	200	Gargus et al. 1983a, Groves 1983b

[1] See Appendix 1 for details of the cited studies.

Table 3-2: Estimate of absorbed dose rates for workers applying Pronone 10G using *belly grinder* applicators (data from Spencer et al. 1996).

Site[1]	Number of workers[1]	Total Amount Handled[2] (lbs a.i.)	Amount Handled per Worker (lbs a.i.)	Dermal Deposition[3] (mg a.i.)	Deposition Rate (mg a.i./kg bw per lb handled)[4]	Absorbed dose rate (mg/kg per lb handled)[5]		
						Central	Lower	Upper
I	10	147.5	14.75	60.3	0.058	0.0011	0.0005	0.0022
I	10	193	19.30	296.69	0.220	0.0040	0.0019	0.0083
I	10	266	26.60	1668.85	0.896	0.0163	0.0079	0.0338
II	11	193	17.55	227.22	0.185	0.0034	0.0016	0.0070
II	11	209	19.00	149.78	0.113	0.0021	0.0010	0.0042
II	11	184	16.73	358.72	0.306	0.0056	0.0027	0.0115
III	12	195	16.25	20	0.018	0.0003	0.0002	0.0007
III	12	330	27.50	50.78	0.026	0.0005	0.0002	0.0010
III	12	235	19.58	116.89	0.085	0.0016	0.0007	0.0032
IV	6	82.5	13.75	26.79	0.028	0.0005	0.0002	0.0010
IV	6	107.5	17.92	72.69	0.058	0.0011	0.0005	0.0022
					Average	0.0033	0.0016	0.0068

[1] Table I, p. 6 of Spencer et al. 1996
[2] Table III, p. 11 of Spencer et al. 1996
[3] Table IV, p. 12 of Spencer et al. 1996, total dermal deposition for all workers (last column in table).
[4] Dermal deposition divided by 70 kg and the amount handled per worker.
[5] Based on and 8 hour exposure and the first-order absorption rate of 0.0023 (0.0011 to 0.0048) $hour^{-1}$. See Section 3.1.3.2 of this risk assessment and Worksheet B06.

Table 3-3: Maximum residues (hexazinone at 0 to 3 DAT) on plants after applications of 6 lb a.i./acre (data from Michael 1992) [1] compared to generic residue rates given by Fletcher et al. (1994).

Plant (DAT) [2]		Velpar ULV (granular)	Velpar L (liquid)	
Averages		Residues after application in ppm		
Dogwood	(2 DAT/DAT 0)	5.53	702.41	
Ferns	(0 DAT)	1.05	383.98	
Grass [3]	(3 DAT/1 DAT)	24.07	626.23	
Blueberries [4]	(2 DAT/1 DAT)	1.24	525.63	
Litter	(0 DAT/1 DAT)	146.37	164.98	
Normalized Rates		Residues after application in ppm/lb per acre		Ratio of Liquid to Granular
Dogwood	(2 DAT/DAT 0)	0.92	117.07	127.02
Ferns	(0 DAT)	0.18	64.00	365.70
Grass [3]	(3 DAT/1 DAT)	4.01	104.37	26.02
Blueberries [4]	(2 DAT/1 DAT)	0.21	87.61	423.90
Litter	(0 DAT/1 DAT)	24.40	27.50	1.13
Values from Fletcher et al. (1994)		Standard values for residues after application in ppm/lb per acre		
		Central	Upper	
Short grass		85.00	240.00	
Tall grass		36.00	110.00	
Broadleaf/forage plants and small insects		45.00	135.00	
Fruits, pods, seeds, and large insects		7.00	15.00	
Adjusted values used for residues of granular formulations of hexazinone		Adjusted values for residues after application in ppm/lb per acre		
		Central	Upper	
Short grass		3.40	9.60	
Tall grass		1.44	4.40	
Broadleaf/forage plants and small insects		1.80	5.40	

Fruits, pods, seeds, and large insects	0.28	0.60

[1] Data from tables 19 to 28 of Michael (1992).
[2] When DAT values differ, the first is for Velpar ULV and the second is for Velpar L.
[3] DAT 0 residues in grass for Velpar ULV were 0.24 ppm.
[4] DAT 0 residues in blueberries for Velpar ULV were 0.25 ppm.

Table 3-4: Chemical and site parameters used in GLEAMS modeling for hexazinone.

Chemical Specific Parameters

Parameter	Clay	Loam	Sand	Comment/ Reference
Halftimes (days)				
Aquatic Sediment		230		Hawkins et al. 1990c
Foliar		30		Note 1
Soil		120		Note 2
Water		730		Note 3
Ko/c, mL/g		54		Note 4
K_d, mL/g	2.7	0.59	0.18	Note 5
Water Solubility, mg/L		33000		Knisel and Davis 2000 and Tomlin 2005
Foliar wash-off fraction		0.9		Knisel and Davis 2000
Fraction applied to foliage		0.5 / 0.01		Note 6

Note 1	Value recommended by Knisel and Davis (2000). Consistent with values reported in the field study by Michael (1992) for both granular and liquid formulations. See Table 2-1.
Note 2	The approximate geometric mean of the range used by U.S. EPA/OPP 2002h. This is close to the value of 90 days recommended by Knisel and Davis (2000). Reported halftimes are be highly variable, ranging from about 5 days to over 200 day. See Appendix 8
Note 3	Hexazinone is stable in water both in terms of hydrolysis and photolysis. See Appendix 8. The value of 730 days has a negligible impact on degradation in the GLEAM modeling.
Note 4	Value recommended by Knisel and Davis (2000). This is very close to the average of values reported in USDA/ARS 1995 (see Appendix 8) as well as the value estimated by Liu and Qian (1995)
Note 5	Values for Sand and Loam adapted from USDA/ARS (1995) summarized in Appendix 8. Sand taken as value for sandy loam soil with 0.9% OM or about 0.5% OC. Loam based on CA loam with 1.9% OM. Value for clay is based on the Ko/c of 54 assuming a 5% OM: 54 x 0.05 = 2.7.

Note 6	A foliar fraction of 0.5 is used or liquid formulation and 0.01 is used for granular applications. See text for discussion.

Site Parameters (see SERA 2004b for details)	
Pond	1 hectare pond, 2 meters deep, with a 0.01 sediment fraction. 10 hectare (24.71 acre) square field (1037' by 1037') with a root zone of 60 inches.
Stream	Base flow rate of 710,000 L/day with a flow velocity of 0.08 m/second or 6912 meters/day. Stream width of 2 meters (about 6.6 feet'). 10 hectare square field (1037' by 1037') with a root zone of 60 inches.

Table 3-5: Summary of modeled concentrations of hexazinone in streams (all units are µg/L or ppb) based on GLEAMS.

Annual Rainfall (inches)	Rainfall per Event (inches)[1]	Clay		Loam		Sand	
		Average	Maximum	Average	Maximum	Average	Maximum
		Concentration per lb/acre applied (from GLEAMS)					
5	0.14	0	0	0	0	0	0
10	0.28	0	0	0	0	0	0
15	0.42	0.301	28.8	0	0	0.0339	1.5
20	0.56	0.516	62.2	2.92E-07	3.54E-05	0.425	8.75
25	0.69	0.696	97.9	0.0112	0.52	0.935	13.1
50	1.39	1.16	245	0.419	6.38	2.08	44
100	2.78	1.28	399	0.854	14.4	2.13	69.6
150	4.17	1.17	382	0.851	14	1.76	78
200	5.56	1.05	342	0.783	14.2	1.47	78.5
250	6.94	0.935	306	0.712	13.8	1.26	78.4
Application rate:		**2**	lbs/acre				
		Concentration at above application rate					
5	0.14	0	0	0	0	0	0
10	0.28	0	0	0	0	0	0
15	0.42	0.602	57.6	0	0	0.0678	3
20	0.56	1.032	124.4	0	0	0.85	17.5
25	0.69	1.392	195.8	0.0224	1.04	1.87	26.2
50	1.39	2.32	490	0.838	12.76	4.16	88
100	2.78	2.56	798	1.708	28.8	4.26	139.2
150	4.17	2.34	764	1.702	28	3.52	156
200	5.56	2.1	684	1.566	28.4	2.94	157
250	6.94	1.87	612	1.424	27.6	2.52	156.8

[1] Rain is assumed to occur at the same rate every 10th day – i.e., 36 rainfall events per year.

Table 3-6: Summary of modeled concentrations of hexazinone in ponds (all units are µg/L or ppb) based on GLEAMS.

Annual Rainfall (inches)	Rainfall per Event (inches)[1]	Clay		Loam		Sand	
		Average	Maximum	Average	Maximum	Average	Maximum
		Concentration per lb/acre applied (from GLEAMS)					
5	0.14	0	0	0	0	0	0
10	0.28	0	0	0	0	0	0
15	0.42	24.3	37.8	0	0	0.931	3.6
20	0.56	25.2	62.4	3.71E-06	1.71E-05	11.1	19.2
25	0.69	25.9	84.7	0.0734	0.49	21.1	29.7
50	1.39	25.6	167	4.15	6.78	33.8	51.6
100	2.78	22.2	301	7.95	10.3	27.5	67.6
150	4.17	18.8	315	7.62	10.1	22	71
200	5.56	16.2	297	6.8	9.96	18.2	71.4
250	6.94	14.2	276	6.03	9.44	15.6	70.8
Application rate:		**2**	lbs/acre				
		Concentration at above application rate					
5	0.14	0	0	0	0	0	0
10	0.28	0	0	0	0	0	0
15	0.42	48.6	75.6	0	0	1.862	7.2
20	0.56	50.4	124.8	0	0	22.2	38.4
25	0.69	51.8	169.4	0.1468	0.98	42.2	59.4
50	1.39	51.2	334	8.3	13.56	67.6	103.2
100	2.78	44.4	602	15.9	20.6	55	135.2
150	4.17	37.6	630	15.24	20.2	44	142
200	5.56	32.4	594	13.6	19.92	36.4	142.8
250	6.94	28.4	552	12.06	18.88	31.2	141.6

[1] Rain is assumed to occur at the same rate every 10th day – i.e., 36 rainfall events per year.

Table 3-7: Estimated environmental concentrations (µg/L or ppb) of hexazinone in surface and groundwater based on modeling.

Scenario	Peak	Long-Term Average
GLEAMS MODELING FOR THIS RISK ASSESSMENT (2 lb/acre)		
Direct Spray of Pond (Worksheet D10a)	112	N/A
Pond, drift at 100 feet (Worksheet D10a)	2.2	N/A
Direct Spray of Stream (Worksheet D10b)	183	N/A
Stream, drift at 100 feet (Worksheet D10b)	3.6	N/A
GLEAMS Pond, Table 3-6	120 (1 - 630)	40 (0.1 - 70)
GLEAMS, Stream, Table 3-4	200 (1 - 800)	2 (0.02 - 4.3)
OTHER MODELING AS HEXAZINONE EQUIVALENTS (U.S. EPA/OPP 2002h adjusted to 2 lb/acre)		
FIRST Version 1, Pond	173	63
Sci-Grow 2.3, groundwater	20.2	N/A

Table 3-8: Summary of field studies assessing water contamination after the application of hexazinone (see Appendix 7 for details; granular applications shaded for convenience).

Application	Maximum Concentration	Water Contamination Rate	Reference
2.0 kg a.i./ha, Velpar L, using spot-gun sprayers	14 ppb in stream water	7.8 ppb per lb/acre	Bouchard et al. 1985
0.75 lb/acre to alfalfa, Velpar L	9.2 ppb hexazinone 41.8 ppb hexazinone equivalents	12.2 ppb hexazinone per lb/acre 55.7 ppb hexazinone equivalents per lb/acre	Hanson et al. 2000 (see also U.S. EPA/OPP 2002h, pp. 35-38)
1.36 kg a.i./ha, Velpar L, spot gun, 15 m buffer.	16 ppb in stream water.	13 ppb per lb/acre	Lavy et al. 1989
2 kg/ha, Velpar L, aerial application, clay loam, 30 m buffer.	maximum concentration of 4 ppb in stream water during a 9-week monitoring period	2.2 ppb per lb/acre	Leitch and Flinn 1983
6.72 kg/ha, Velpar L, aerial application, loam	Daily average peak concentrations of 35-65 ppb.	5.8 - 11 ppb per lb/acre	Michael 1992
6.72 kg/ha, Velpar ULV, aerial application, loam	Daily average peak concentrations of 40-65 ppb.	6.7 - 11 ppb per lb/acre	Michael 1992
6.72 kg/ha, Velpar ULV, aerial application, loam	Peak of 125 ppb. No substantial rainfall (4 mm or 0.16 inches).	21 ppb per lb/acre	Michael 1992
1.6-2.9 kg a.i./ha, Velpar L, spot applications, 7 sites	6-37 ppb in surface water, 7 sites	3.8 - 14.3 ppb per lb/acre	Michael and Neary 1993
1.7 kg a.i./ha, Velpar L, broadcast ground	1.3 ppb in surface water	0.85 ppb per lb/acre	Michael and Neary 1993
1.7 kg/ha, granular, spot application	442 ppb in surface water	291 ppb per lb/acre	Michael and Neary 1993
0.8 to 2.2 kg a.i./ha, Velpar L, broadcast ground, 3 sites	0, 130, and 680 ppb in surface water	0, 66.2, and 347 ppb per lb/acre	Michael and Neary 1993
0.8 kg a.i./ha, Velpar Gridball, aerial over stream	2,400 ppb after direct spray of stream and adjacent areas	3,363 ppb per lb/acre	Miller and Bace 1980

Table 3-8: Summary of field studies assessing water contamination after the application of hexazinone (see Appendix 7 for details; granular applications shaded for convenience).

Application	Maximum Concentration	Water Contamination Rate	Reference
1.02 kg/ha, Velpar (NOS), clay loam soil.	38 ppb in ground water after irrigation	38 ppb per lb/ac	Miller et al. 1995
1.7 kg a.i./ha, clay pellets, aerial application	N.D. [< 1ppb]	<0.65 ppb per lb/acre	Neary 1983
1.68 kg a.i./ha, pellets, spot applications	442 ppb in storm runoff water	295 ppb per lb/acre	Neary et al. 1983
2.24 kg a.i./ha to surface soils, ^{14}C-labeled hexazinone	60.6 ppb in soil water	30 ppb per lb/acre	Stone et al. 1993
Monitoring from Maine, no application rate	0.14 to 2.15 ppb in ground water 0.13 to 3.8 ppb in surface water	N/A	(U.S. EPA/OPP 2002h, p. 37)
2.76-3.0 kg a.i./ha, Velpar L, spotgun	85 ppb in surface water	31 ppb per lb/acre	Williamson 1988

Table 3-9: Concentrations of hexazinone in surface water used in this risk assessment (see Section 3.2.3.4.6 for discussion).

At application rate:	**2**	**lb/acre**	
		Peak Concentration (ppb or µg/L)	Longer Term Concentration (ppb or µg/L)
	Central	200	40
	Lower	1	0.02
	Upper [2]	800	140
Water contamination rate [1]	**mg/L per lb/acre applied**		
		Peak Concentration (mg/L per lb/acre)	Longer Term Concentration (mg/L per lb/acre)
	Central	1.00e-01	2.00e-02
	Lower	5.00e-04	1.00e-05
	Upper	4.00e-01	7.00e-02

[1] Water contamination rates – concentrations in units of mg/L expected at an application rate of 1 lb/acre.
[2] Encompasses normal variability but may not encompass extreme or accidental exposures. These are addressed in different worksheet scenarios. See discussion for Worksheet D05 in Section 3.2.3.4.1 and discussion of Miller and Bace (1980) in Section 3.2.3.4.5.

Table 4-1: Summary of field studies reporting adverse effects in terrestrial plants (see Appendix 6 for details)

Application Rate (lb a.i./acre)	Effects	Reference(s)
< 1	No effect on alfalfa or an increase in nectar production in alfalfa.	Curry et al. 1995
	Reduction in number of oaks (target species) in pine stand.	Long and Flinchum 1992
	Increased pine mortality after 1 year possibly due to insect predation.	Pehl and Shelnutt 1990
1 to < 2	Decreased plant biomass but only in first growing season.	Blake et al. 1987
	Decreased plant species diversity during first year.	Brockway et al. 1998
	Tolerated by pines in third growing season	Haywood 1994
	No effect to modest reduction in blueberries depending on timing of application	Jensen and Specht 2002
2 to < 3	Decrease in water oaks after 7 years	Boyd et al. 1995
	Decreased woody plant cover and/or grasses	Brockway et al. 1998; Reynolds and Roden 1995, 1996; Yarborough et al. 1986; Wilkins et al. 1993; Zutter et al.1988
	Some mortality in pine but an increase in overall productivity of pine due to decrease competition.	Glover et al. 1991
3 or more	Increased plant species diversity after one year	Brooks et al. 1993
	Adverse effects on a number of agricultural plants during first year.	Coffman et al. 1993
	Reduced hardwood production	Haywood 1995; Shiver et al. 1990
	Increased pine production	Loyd et al. 2002
	Reduced uptake of soil nutrients by pine	Maynard 1997
	Increase pine growth due to decreased competition from other vegetation	McDonald et al. 1994; Miller 1999; Pitt et al. 1999; Pollack et al. 1990

Table 4-2: Summary of modeled concentrations of hexazinone in entire 60 inch soil column (all units are mg/kg or ppm).

Annual Rainfall (inches)	Rainfall per Event (inches)[1]	Clay		Loam		Sand	
		Average	Maximum	Average	Maximum	Average	Maximum
		Concentration per lb/acre applied (from GLEAMS)					
5	0.14	0.0266	0.0566	0.0232	0.0517	0.0238	0.0522
10	0.28	0.0295	0.0594	0.0277	0.0565	0.0238	0.0522
15	0.42	0.0273	0.0573	0.0265	0.0551	0.0284	0.0584
20	0.56	0.0269	0.0571	0.0276	0.057	0.03	0.0594
25	0.69	0.0263	0.0561	0.0291	0.0593	0.0288	0.057
50	1.39	0.0237	0.0511	0.0316	0.0609	0.0196	0.0453
100	2.78	0.0192	0.0386	0.027	0.0532	0.0111	0.0445
150	4.17	0.0159	0.0348	0.0237	0.0482	0.00765	0.0442
200	5.56	0.0135	0.0336	0.0216	0.0462	0.00582	0.0436
250	6.94	0.0117	0.0326	0.0202	0.0453	0.00473	0.0427
Application rate:		**2**	lbs/acre				
		Concentration at above application rate					
5	0.14	0.0532	0.1132	0.0464	0.1034	0.0476	0.1044
10	0.28	0.059	0.1188	0.0554	0.113	0.0476	0.1044
15	0.42	0.0546	0.1146	0.053	0.1102	0.0568	0.1168
20	0.56	0.0538	0.1142	0.0552	0.114	0.06	0.1188
25	0.69	0.0526	0.1122	0.0582	0.1186	0.0576	0.114
50	1.39	0.0474	0.1022	0.0632	0.1218	0.0392	0.0906
100	2.78	0.0384	0.0772	0.054	0.1064	0.0222	0.089
150	4.17	0.0318	0.0696	0.0474	0.0964	0.0153	0.0884
200	5.56	0.027	0.0672	0.0432	0.0924	0.01164	0.0872
250	6.94	0.0234	0.0652	0.0404	0.0906	0.00946	0.0854

[1] Rain is assumed to occur at the same rate every 10th day – i.e., 36 rainfall events per year.

Table 4-3: Summary of modeled concentrations of hexazinone in top 12 inches of soil column (all units are mg/kg or ppm).

Annual Rainfall (inches)	Rainfall per Event (inches)[1]	Clay		Loam		Sand	
		Average	Maximum	Average	Maximum	Average	Maximum
		Concentration per lb/acre applied (from GLEAMS)					
5	0.14	0.133	0.283	0.116	0.258	0.119	0.261
10	0.28	0.147	0.297	0.139	0.282	0.119	0.261
15	0.42	0.137	0.286	0.125	0.266	0.0962	0.239
20	0.56	0.131	0.28	0.115	0.254	0.0701	0.225
25	0.69	0.125	0.272	0.104	0.244	0.0544	0.22
50	1.39	0.102	0.234	0.0677	0.224	0.0255	0.203
100	2.78	0.0752	0.164	0.0418	0.215	0.0124	0.168
150	4.17	0.0602	0.149	0.0329	0.21	0.00826	0.14
200	5.56	0.0503	0.145	0.0284	0.206	0.00624	0.119
250	6.94	0.0432	0.143	0.0257	0.203	0.00507	0.116
Application rate:		**2**	lbs/acre				
		Concentration at above application rate					
5	0.14	0.266	0.566	0.232	0.516	0.238	0.522
10	0.28	0.294	0.594	0.278	0.564	0.238	0.522
15	0.42	0.274	0.572	0.25	0.532	0.1924	0.478
20	0.56	0.262	0.56	0.23	0.508	0.1402	0.45
25	0.69	0.25	0.544	0.208	0.488	0.1088	0.44
50	1.39	0.204	0.468	0.1354	0.448	0.051	0.406
100	2.78	0.1504	0.328	0.0836	0.43	0.0248	0.336
150	4.17	0.1204	0.298	0.0658	0.42	0.01652	0.28
200	5.56	0.1006	0.29	0.0568	0.412	0.01248	0.238
250	6.94	0.0864	0.286	0.0514	0.406	0.01014	0.232

[1] Rain is assumed to occur at the same rate every 10th day – i.e., 36 rainfall events per year.

Table 4-4: Summary of the cumulative loss from soil runoff and sediment loss as a proportion of the application rate based on GLEAMS modeling.

Annual Rainfall (inches)	Rainfall per Event (inches)[1]	Clay	Loam	Sand
5	0.14	0	0	0
10	0.28	0	0	0
15	0.42	0.05	0	0
20	0.56	0.0893	0	0
25	0.69	0.126	0	0
50	1.39	0.268	0.000151	0
100	2.78	0.447	0.00457	0
150	4.17	0.552	0.0043	0
200	5.56	0.622	0.00337	0
250	6.94	0.671	0.00265	0

[1] Rain is assumed to occur at the same rate every 10th day – i.e., 36 rainfall events per year.

Table 4-5: Summary of modeled maximum depth of hexazinone in the soil column [1].

Annual Rainfall (inches)	Rainfall per Event (inches)[2]	Clay	Loam	Sand
5	0.14	6.5	6.5	6.5
10	0.28	6.5	6.5	6.5
15	0.42	18	42	60
20	0.56	24	54	60
25	0.69	24	60	60
50	1.39	30	60	60
100	2.78	36	60	60
150	4.17	36	60	60
200	5.56	36	60	60
250	6.94	36	60	60

[1] Based on a 60 inch soil column for the vadose zone. Values of 60 indicate that penetration may exceed 60 inches.
[2] Rain is assumed to occur at the same rate every 10th day – i.e., 36 rainfall events per year.

Table 4-6: Summary of hexazinone toxicity values used in ecological risk assessment (all amounts expressed as a.i.)

Organism	Endpoint	Toxicity Value	Reference
Mammals (Rats and Rabbits)	Acute NOAEL, maternal toxicity	100 mg/kg	Mullin 1987 [1]
	Chronic NOAEL, toxicity	5 mg/kg/day	Dalgard 1991
Birds (Bobwhite Quail)	Acute NOAEL, 1000 ppm, 5-day dietary	550 mg/kg	Dudeck and Bristol 1980 [2]
	Chronic NOAEL, 1000 ppm, Reproduction	150 mg/kg/day	Beavers et al. 1991a
Terrestrial Invertebrates			
Honey bee	NOEC for mortality	1075 mg/kg	Hoxter et al. (1989)
Terrestrial Plants - Pre-emergence assay (soil treatment)			
Sensitive (tomato)	NOEC, all effects	0.000348 lb/acre	McKelvey and Heldreth (1994)
Tolerant (corn)	NOEC, all effects	0.0234 lb/acre	McKelvey and Heldreth (1994)
Terrestrial Plants - Post-emergence assay (direct spray)			
Sensitive (cucumber)	NOEC, all effects	0.00391 lb/acre	McKelvey and Heldreth (1994)
Tolerant (corn)	NOEC, all effects	0.0625 lb/acre	McKelvey and Heldreth (1994)
Fish Acute			
Sensitive (Fathead minnow)	NOEC for mortality	160 mg/L	Sleight 1973
Tolerant (Trout)	NOEC for mortality	370 mg/L	Sleight 1973
Fish Chronic			
Sensitive/Tolerant (Fathead Minnows)	NOEC, egg-and-fry development	17 mg/L	Pierson 1990a
Aquatic Invertebrates, Acute			
Sensitive (*Daphnia*)	NOEC	20.5 mg/L	Hutton 1989c
Tolerant (oysters embryos)	NOEC	320 mg/L	Heitmuller 1976 [3]
Aquatic Invertebrates, Chronic			
Sensitive (*Daphnia*)	NOEC, reproduction	10 mg/L	Schneider 1977
Tolerant (NOS)	NOEC, reproduction	160 mg/L	Relative potency [4]
Aquatic Algae			
Sensitive (*Selenastrum capricornutum*)	NOEC, 5-day growth	0.004 mg/L	Forbis 1989
Tolerant (*Anabaena flos-aquae*)	NOEC, 5-day growth	0.15 mg/L	Thompson 1994

Aquatic Macrophytes			
Sensitive/Tolerant (*Lemna minor*)	NOEC, 7-day growth	0.012 mg/L	Peterson et al. 1997

[1] U.S. EPA/OPP (2002g,h) use the developmental NOAEL of 400 mg/kg/day as basis for acute RfD. The lower maternal NOAEL is used in the current Forest Service risk assessment.
[2] U.S. EPA/OPP (1994a) uses an LD_{50} value of 2251 mg/kg to characterized acute toxicity.
[3] NOEC values of up to 1000 mg/L reported for larger invertebrates.
[4] Chronic NOEC for daphnids multiplied by the ratio of the acute NOEC for tolerant species divided by the acute NOEC for daphnids.

Appendix 1: Acute toxicity of hexazinone and hexazinone formulations to experimental mammals [Subsections include Oral, Dermal, Intraperitoneal, Inhalation, and Ocular]

Species	Exposure	Response	Reference
		ORAL	
Dogs			
Dog, beagle, male, one animal only	Hexazinone, 1000 mg/kg, 1 day, single dose, gelatin capsule, 95.8% active	Vomiting, tremors, salivation, and rapid respiration 10-20 minutes post dosing; all signs of toxicity, except diarrhea, disappeared the day after treatment, and the dog survived with no further signs of toxicity	Kennedy 1984
Dog, beagle, male, one animal per dose	2250 or 3400 mg/kg, 1 day, single dose, gelatin capsule	Prominent clinical signs of toxicity that included lacrimation for up to 1 day after treatment; dogs survived and showed no signs of toxicity 15 days after treatment.	Kennedy 1984
Guinea pigs			
Guinea pigs, male, bw ≈ 500 g, 10/dose	700, 850, 900, 1000 mg/kg, single dose, gavage, 98+% pure technical grade, vehicle not specified	LD_{50} 860 (420-1260) mg/kg. 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.	Kennedy 1984
Rats			

Appendix 1: Acute toxicity of hexazinone and hexazinone formulations to experimental mammals [Subsections include Oral, Dermal, Intraperitoneal, Inhalation, and Ocular]

Species	Exposure	Response	Reference
Rats, outbred albino (*Rattus norvegicus*), 5M/5F	Pronone 25G. Single dose (limit test) of 5,000 mg formulation/kg bw with 14-day observation period. (Dose of about 1250 mg a.i./kg bw).	Tremors and lachypnea on Day 1. No mortality or other indications of toxicity.	Fitzgerald 1990a, MRID 41710001
Rats, Sprague-Dawley, 5M/5F	Pronone 10G, 5000 mg/kg as formulation. (Dose of about 500 mg a.i. /kg bw).	No mortality. Depression, tremors, and/or ataxia. Red stains on nose and/or eyes. One animal did not gain weight through 14-day observation period.	Gluck 1983a, MRID 43840702
Rat, Crl-CD, male, rats weighed 227-272 g	500, 550, 600, 1200, 1400, 1600, or 2000 mg/kg. 98+% technical grade. Vehicle was a 10-15% suspension in 15:85 acetone:corn oil	LD_{50}: 1690 (1560-1880) mg a.i./kg 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.	Kennedy 1984

Appendix 1: Acute toxicity of hexazinone and hexazinone formulations to experimental mammals [Subsections include Oral, Dermal, Intraperitoneal, Inhalation, and Ocular]

Species	Exposure	Response	Reference
Rats, Sprague-Dawley, male and female, 209-216 g males and 200-214 g females	Pronone 10G. Authors assumed 100% a.i. for dosing. [This formulation is 10% a.i.] 5000 mg/kg doses by gavage in a saline vehicle. Corresponds to 500 mg a.i./kg.	Depression, tremors and ataxia at one hour post-dosing. Signs of toxicity (rough coat, depression) in some animals during the first day. No mortality or gross signs of toxicity.	Gargus et al. 1983c, MRID 43840705. Resubmitted by Gluck 1983a, MRID 43840702
Rats, Crl:CD, Male and Female, 10/dose	Velpar 75 DF (75% a.i.), 500, 1000, 1500, and 2000 mg/kg bw. Doses expressed as test material (formulation)	LD_{50} Males: 1300 (1110-1350) mg/kg [Corresponds to approximately 975 (833-1010) mg a.i./kg] LD_{50} Females: 1100 (900-1400) mg/kg [Corresponds to approximately 825 (675-1050) mg a.i./kg] No mortality in any animals at 500 mg/kg. At doses of 1000 mg/kg and higher, decreased body weight and oral discharges (NOS). Convulsions seen at 1500 mg/kg and higher.	Redgate and Sarver 1986, MRID 00164208 Sarver 1995a, MRID 43784725 (minor corrections)

Appendix 1: Acute toxicity of hexazinone and hexazinone formulations to experimental mammals [Subsections include Oral, Dermal, Intraperitoneal, Inhalation, and Ocular]

Species	Exposure	Response	Reference
Rats, Crl:CD, Male and Female, 5M/5F per dose	75% hexazinone formulation (appears to be Velpar DF). Doses of 1000, 1500, and 2000 mg/kg as *test substance* – i.e., the formulation and not a.i.	Combined LD_{50}: 1310 (560-1800) mg/kg [Corresponds to approximately 982 (420-1350) mg a.i./kg] Males somewhat less sensitive than females but separate LD_{50} values not derived by authors. At doses of 1000, 1500, and 2000 mg/kg, combined morality rates of 3/10, 6/10 and 8/10, respectively. Signs of toxicity included lung noise, stained or wet perineum, hunched appearance, ocular discharge, and red-stained face.	Finlay 1994c, MRID 43697710
Rats, Crl:CD, Male and Female, 10/dose	Hexazinone t.g.a.i. (98 purity). Doses of 250, 750, 1000, and 1500 mg/kg bw.	LD_{50} Males: 1100 (810-1800) mg/kg. LD_{50} Females: 1200 (1000-2000) mg/kg. No mortality in males or females at 250 mg/kg. Slight loss of body weight in animals with signs of toxicity.	Sarver 1989, MRID 41235004
Rats, Crl:CD, Male and Female, 5/dose	Velpar formulation (NOS) containing 90% hexazinone. Doses of 500, 1000, and 1500 mg/kg by gavage.	No mortality at 500 mg/kg. 6/10 died at 1000 and 5000 mg/kg. Reported LD_{50} of 1100 (500-5000) mg/kg. [Corresponds to approximately 990 (450-4500) mg a.i./kg] Authors cite Finney (1971) but it is unclear how or if probit analysis was done. Convulsions, ataxia, lethargy, oral discharge, hunched, partially closed eyes, wet or yellow-stained perineum.	Filliben 1994a, MRID 43459401

Appendix 1: Acute toxicity of hexazinone and hexazinone formulations to experimental mammals [Subsections include Oral, Dermal, Intraperitoneal, Inhalation, and Ocular]

Species	Exposure	Response	Reference
Rats, Crl:CD, Male and Female, 5/dose	Velpar L (25% hexazinone). Doses of 4000, 5000, or 6000 mg/kg by gavage. Dose appear to be expressed as formulation.	Mortality rates of 5/10, 6/10, and 6/10 at doses of 4000, 5000, or 6000 mg/kg. Calculated LD_{50} of 4120 mg/kg (approximately 1030 mg a.i./kg). Signs of toxicity included lethargy, spasms, oral discharge, convulsions, tremors, and hunched posture.	Finlay 1994b, MRID 43466601
Rats, Sprague-Dawley, 5M/5F, 205-228 g	Bo-rid V-4 Liquid Weed Killer , a 0.5% liquid formulation of hexazinone. Single oral dose of 5000 mg/kg (25 mg a.i./kg)	No mortality or signs of toxicity.	Wolfe and Rice 1981b
		DERMAL	
Rabbits, New Zealand White, n=6	Hexazinone, 98% purity, 0.5 g applied to intact and abraded skin for 24 hours. Observation period of 4 days.	Primary irritation scores of 0.5 to 1.5 based on Day 1 and Day 3 readings. No irritation by Day 4. This study is used by U.S. EPA/OPP 2002g to classify hexazinone as a mild (Category IV) skin irritant.	Dashiell and Henry 1982b, MRID 00106004
Rabbits, New Zealand White, 5M/5F	Hexazinone (90%). Dose of 5000 mg/kg for 24 hours with a 4 day observation period.	No mortality. Weight loss of up to 5% in 9/10 animals. Moderate or severe erythema by no edema by 1 hour. Slight to mild erythema with some scaling up to 5 days. 9/10 rabbits had no effects after 12 days.	Filliben 1994b, MRID 43784706
Rabbits, New Zealand White, 5M/5F	Velpar ULW, dose of 5000 mg/kg as *test substance* for 24 hours	No mortality. Weight losses up to 5% of initial body weight in 5 animals on Day 1 after dosing. Moderate erythema and slight edema in some animals.	Filliben 1994c, MRID 43784726

Appendix 1: Acute toxicity of hexazinone and hexazinone formulations to experimental mammals [Subsections include Oral, Dermal, Intraperitoneal, Inhalation, and Ocular]

Species	Exposure	Response	Reference
Rabbits, New Zealand White, 4M/2F	Velpar (NOS), 0.5 g on back for 4 hours.	Erythema but no edema. No irritation by 6 days after exposure.	Filliben 1994d, MRID 43784709
Rabbits, New Zealand White, 5M/5F	75% hexazinone formulation (appears to be Velpar DF). Dose of 5000 mg/kg as *test substance* – i.e., the formulation and not a.i.	No mortality. Slight weight loss (<5%) in some animals. Slight to moderate erythema and slight edema in some animals. No dermal effects after 8 days.	Finlay 1994d, MRID 43697711
Rabbits, New Zealand White, 5M/5F	Velpar L, 5000 mg/kg as formulation to shaved and intact skin for 24 hours	No mortality. Weight loss (about 8%) on Day 1 after dosing. Weight loss (about 4%) in 3 animals on Day 14. Initial slight to mild erythema.	Finlay 1994g, MRID 43784716
Rabbits, New Zealand White, 3M/3F	75% hexazinone formulation (appears to be Velpar DF). 0.5 g for 4 hours.	Erythema and edema in some animals. Moderate skin irritant.	Finlay 1994f, MRID 43697714
Rabbits, New Zealand White, 5M/1F	Velpar L. 0.5 g for 4 hours.	Erythema but no edema in some animals at 48 hours. No effects at 72 hours.	Finlay 1994h, MRID 43697718
Rabbits, New Zealand White, males and females	Pronone 25G. Single dose (limit test) of 5,000 mg/kg bw with 14-day observation period.	No mortality or other signs of systemic toxicity. No skin irritation.	Fitzgerald 1990b, MRID 41710002
Rabbits, New Zealand White, males and females	Pronone 25G. Single dose (limit test) of 5,000 mg/kg bw with 14-day observation period.	No mortality or other signs of systemic toxicity. No skin irritation.	Fitzgerald 1991a, MRID 41876101 and Fitzgerald 1991b, MRID 44381301

Appendix 1: Acute toxicity of hexazinone and hexazinone formulations to experimental mammals [Subsections include Oral, Dermal, Intraperitoneal, Inhalation, and Ocular]

Species	Exposure	Response	Reference
Rabbits, New Zealand White, female (n=6)	Pronone 25G (25% hexazinone). 0.5 g applied to unabraded skin for 4 hours. 72 hour observation period	No dermal irritation or signs of toxicity.	Fitzgerald 1991d, MRID 41724501
Rabbits, New Zealand White, M/5 and F/5	Pronone 10G (10% hexazinone). 2000 mg/kg bw or 200 mg a.i./kg. Applied in moistened gauze covering. Unabraded clipped skin for 24 hours.	No mortality or other signs of systemic toxicity. No decrease in body weight. Erythema at all abraded sites and 4/5 intact sites.	Gargus et al. 1983a, MRID 00131360
Rabbits, New Zealand White, males and females	Pronone 10G. Authors assumed 100% a.i. for dosing. [It is really only 10% a.i.] 500 mg with poultice for 4 hours, after which the test material was cleared from the application site by washing.	No signs of primary skin irritation or other dermal effects over a 72-hour observation period.	Gargus et al. 1983d, MRID 0031363, resubmitted by Gluck 1983f, MRID 44047204
Rabbits, New Zealand White, 5M/5F	Pronone 10G. 0.5 g (as formulation) on skin for 4 hours.	No signs of irritation or other dermal effects.	Gluck 1983c, MRID 43840705
Rabbits, New Zealand White, males and females	Pronone 10G. Authors assumed 100% a.i. for dosing. [It is really only 10% a.i.] 2000 mg/kg doses corresponds to 200 mg a.i./kg. Both abraded and intact skin. Test material moistened with water.	Redness of skin in all abraded sites and 4 of 5 intact sites. Mild to well-defined. Slight edema in some animals that resolved by Day 3.	Groves 1983a, MRID 44047202

Appendix 1: Acute toxicity of hexazinone and hexazinone formulations to experimental mammals [Subsections include Oral, Dermal, Intraperitoneal, Inhalation, and Ocular]

Species	Exposure	Response	Reference
Rabbits, New Zealand White, 5M/5F	Pronone 10G. 2000 mg/kg as formulation to intact and abraded skin	No mortality. Normal weight gain. Erythema in abraded sites. Edema in abraded and some intact sites.	Groves 1983b, MRID 43840703
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 the treated area was washed with tap water; application site was observed daily for 14 days .	Rabbits showed transient signs 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
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. ***Continued below***	No skin irritation or evidence of dermal sensitization in any of the treated guinea pigs	Kennedy 1984

Continued from above: 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.

Appendix 1: Acute toxicity of hexazinone and hexazinone formulations to experimental mammals [Subsections include Oral, Dermal, Intraperitoneal, Inhalation, and Ocular]

Species	Exposure	Response	Reference
Guinea Pigs, Male, Hartley	Hexazinone formulation (NOS). [In MRID series with Velpar DF]	No dermal sensitization.	Moore 1994a, MRID 43697715
Guinea Pigs, Male, Hartley	Sample characterized only as H-20749	No dermal sensitization.	Moore 1994b, MRID 43784710
Guinea Pigs, Male, Hartley	Velpar L.	No dermal sensitization.	Moore 1994c, MRID 43697719
Guinea Pigs, Male, Hartley	Velpar ULW	No dermal sensitization.	Moore 1995, MRID 43784730
Guinea pigs, Hartley, Male and Female	300 mg/site. Identified in study only as 17,705. Identified by U.S. EPA 2002g as t.g.a.i. hexazinone.	No dermal sensitization.	Pharmakon Research Internationa l 1989, MRID 41235005
Guinea pigs, Hartley, Male and Female	Pronone 25G. Single dose of 0.4 g for induction and challenge. Applied once per week for three weeks.	No dermal sensitization.	Fitzgerald 1990c, MRID 41710003
New Zealand White Rabbits, 3M/3F	Velpar 75 DF. 0.5 g applied to abraded and intact skin for 24 hours	Erythema and edema. Mild dermal irritation (Category IV).	Sarver 1995b, MRID 43784729
New Zealand White Rabbits, 5M/5F	Velpar 75 DF. 2000 mg/kg applied to abraded skin with occlusion for 24 hours. No untreated or sham controls.	No mortality or dermal irritation. Slight (1-2%) weight loss on Day 1. No clinical signs of toxicity.	Vick and Sarver 1986a, MRID 00164209

Appendix 1: Acute toxicity of hexazinone and hexazinone formulations to experimental mammals [Subsections include Oral, Dermal, Intraperitoneal, Inhalation, and Ocular]

Species	Exposure	Response	Reference
New Zealand White Rabbits, 3M/3F	Velpar 75 DF. 0.5 g applied to abraded and intact sites on skin of each animal. Skin washed after 24 hours.	Slight to moderate erythema and slight edema in intact and abraded sites. No dermal irritation after 7 days.	Vick and Sarver 1986b, MRID 00164210
Guinea pigs, Male Duncan Hartley albino.	Velpar 75 DF, 5% and 50% solutions. Standard protocol for primary irritation followed by induction and challenge.	Mild erythema on challenge with 50% solution but not with 5% solution. Not classified as skin sensitizer. [Consistent with classification by U.S. EPA/OPP 2002g]	Vick and Henry 1986, MRID 00164211
New Zealand White Rabbits, 5M/5F	Bo-rid V-4 Liquid Weed Killer , a 0.5% liquid formulation of hexazinone. 2000 mg/kg bw (10 mg a.i./kg bw) applied to abraded skin.	Slight erythema in 7 animals on Day 1 and in 5 animals on Day 3. No mortality.	Wolfe et al. 1981b
New Zealand White Rabbits, 5M/5F	Bo-rid V-4 Liquid Weed Killer , a 0.5% liquid formulation of hexazinone. 0.5 mL applied to abraded skin and covered.	No signs of skin irritation.	Wolfe and Rice 1981c
INTRAPERITONEAL			
Rat, Crl-CD, male, 3 groups of 10 rats per dose	98+% technical grade hexazinone in a 7-10% saline suspension	LD_{50}: 530 (300-570) mg/kg	Kennedy 1984
INHALATION			

Appendix 1: Acute toxicity of hexazinone and hexazinone formulations to experimental mammals [Subsections include Oral, Dermal, Intraperitoneal, Inhalation, and Ocular]

Species	Exposure	Response	Reference
Rats, Crl:CD, 5M/5F	75% hexazinone formulation (appears to be Velpar DF). Exposure to 5.2 mg/L for 4 hours as *test substance* – i.e., the formulation and not a.i.	No mortality. Nasal or ocular discharges, stained perineum, and rough fur. Transient and slight decreases in body weight. Normal body weight by end of 14-day observation period.	Bamberger 1994a, MRID 43697712
Rats, Crl:CD, 5M/5F	Hexazinone (90.9%). Not clear if this is a t.g.a.i. or formulation. Exposure to 5.0 mg/L for 4 hours as *test substance*	No mortality. Slight weight loss one day after exposure in four males and four females. No weight loss by end of study. Signs of toxicity included lung noise, nasal and ocular discharge, and stained perineum.	Bamberger 1994b, MRID 43784707
Rats, Crl:CD, 5M/5F	Velpar ULW. Exposure to 5.3 mg/L for 4 hours as *test substance*	No mortality. Transient and very slight weight loss (up to 1.1%) after treatment but no effect on body weight be end of study. Nasal and ocular discharges and stained fur.	Bamberger 1994c, MRID 43784727
Rats, Sprague-Dawley, 5M/5F	Hexazinone, t.g.a.i., 3.94 mg/L for 4.5 hours.	No mortality. Shallow respiration and decreased movement. Hexazinone accumulated on the fur. Eye and mouth discharges. No signs of toxicity after 4 days.	Shapiro 1990, MRID 41756701
Rats, male, 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

Appendix 1: Acute toxicity of hexazinone and hexazinone formulations to experimental mammals [Subsections include Oral, Dermal, Intraperitoneal, Inhalation, and Ocular]

Species	Exposure	Response	Reference
Rats, Crl:CD, 5M/5F per concentration	Velpar L, 4.0, 5.8, or 7.5 mg/L for 4 hours.	No mortality at two lower concentrations. 1/5 males and 1/5 females died at the highest concentration on the day of exposure. Males rats exhibited weight loss (up to 12%) up to 3 days after exposure. Transient body weight loss in females. Signs of toxicity included alopecia, nasal and ocular discharges, wet and stained fur. Four females rats evidenced weakness and one female rat exhibited gasping (7.5 mg/L). At lower concentrations, 1 female in each group exhibited weakness.	Finlay 1995, MRID 43784717
Rats, male, 200-300 g, 10/group	1-hour exposure to 5.14 (±2.51) mg/L hexazinone particles suspended in 20 L glass cylinder	0/10 died	Kennedy 1984
Rats, male, 200-300 g	1-hour exposure to 7.48 (±0.95) mg/L hexazinone particles suspended in 20 L glass cylinder	0/10 died	Kennedy 1984
Rats, 10M/10F, 261-338g	Bo-rid V-4 Liquid Weed Killer , a 0.5% liquid formulation of hexazinone. 6.06 micrograms/L for 4 hours.	No signs of toxicity in 14 day observation period.	Wolfe et al. 1981a

Appendix 1: Acute toxicity of hexazinone and hexazinone formulations to experimental mammals [Subsections include Oral, Dermal, Intraperitoneal, Inhalation, and Ocular]

Species	Exposure	Response	Reference
		OCULAR	
Rabbits, New Zealand White, males, n=9	Hexazinone, 5% formulation as liquid concentrate (Does not correspond to formulations covered in this risk assessment.). 0.1 mL in right eye.	Moderate eye irritation: mild corneal cloudiness, moderate iritis, and moderate conjunctivitis in unwashed eyes (n=6). Slight corneal cloudiness (1/3) and moderate conjunctivitis (3/3) in washed eyes.	Dashiell and Hall 1982, MRID 00106005
Rabbits, New Zealand White, males, n=9	Hexazinone, 98% purity, 0.1 mL (42 mg) applied to right eye. Observation period of 28 days.	In unwashed eyes (n=6), mild to moderate corneal opacity and moderate iritis. Classified as severe eye irritant by Dashiell and Henry (1982) and this classification is confirmed by U.S. EPA/OPP 2002g.	Dashiell and Henry 1982a, MRID 00106003
Rabbits, New Zealand White, 1M/5F	Velpar (NOS). 38 mg (0.1 mL) in right eye. No washing. Observed for up to 21 days.	Corneal opacity, iritis, chemosis, and conjunctival redness and discharge. Corneal opacity persisted in 2 animals up to Day 21.	Filliben 1994c, MRID 43784708
Rabbits, New Zealand White, male, n=6	75% hexazinone formulation (appears to be Velpar DF). 0.1 mL (44 mg) of formulation in right eye. Observation period of up to 21 days.	Conjunctival chemosis and redness, iritis, and corneal opacity for up to 72 hours. Effects persisted in one animal throughout the 21 day observation period.	Finlay 1994e, MRID 43697713
Rabbits, New Zealand White, female (n=6)	Pronone 25G (25% hexazinone). 0.1 mL applied to the left eye of each animal.	No eye irritation – i.e., no effects on corneal opacity, no signs of iritis, chemosis or discharge over 72 hour observation period.	Fitzgerald 1991e, MRID 41724502

Appendix 1: Acute toxicity of hexazinone and hexazinone formulations to experimental mammals [Subsections include Oral, Dermal, Intraperitoneal, Inhalation, and Ocular]

Species	Exposure	Response	Reference
Rabbits, New Zealand White, males and females	Pronone 10G. Authors assumed 100% a.i. for dosing. [It is really only 10% a.i.] 48 mg of a 2% solution in placed into left eye. Right eye used for control.	Corneal opacity and iritis over 24 to 48 hours. No eye irritation at 7 days after dosing.	Gargus et al. 1983b, MRID 00131361. Resubmitted by Gluck 1983e, MRID 44047203
Rabbits, New Zealand White, 5M/5F	Pronone 10G. 48 mg (as formulation) in left eye.	Corneal opacity, iritis, and conjunctival irritation. No irritation noted by Day 7.	Gluck 1983b, MRID 43840704
Rabbits, New Zealand White, 2 males and 4 females	Velpar 75DF, 0.1 mL in right eye of each animal. Left eye used as control.	Mild to moderate corneal opacity, iritis, and moderate conjunctival redness. Copious blood-tined discharge in all animals. Corneal effects persisted up to end of study (Day 21). Classified as moderate eye irritant by authors.	Grandizio and Henry 1986, MRID 00164212
Rabbits, New Zealand White, 3 male and 3 female	Velpar L, 0.1 mL in right eye. Left eye used as control.	Corneal opacity that persisted to Day 21. Iritis, conjunctival redness, chemosis and discharge in all animals over a 48 hour period.	Finlay 1994a, MRID 43465401
Rabbits, New Zealand White, 2 male and 4 female	Velpar 75 DF, 40 mg (0.1 mL) is right eye. Left eye used as control.	Corneal opacity, conjunctival redness and chemosis, ocular discharge. Corneal opacity persisted in one animal to Day 21.	Henry 1995, MRID 43784728

Appendix 1: Acute toxicity of hexazinone and hexazinone formulations to experimental mammals [Subsections include Oral, Dermal, Intraperitoneal, Inhalation, and Ocular]

Species	Exposure	Response	Reference
2 albino rabbits	48 mg powder (NOS) 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 vascularization 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 inflamation of the iris; eye was normal within 7 days.	Kennedy 1984

Appendix 1: Acute toxicity of hexazinone and hexazinone formulations to experimental mammals [Subsections include Oral, Dermal, Intraperitoneal, Inhalation, and Ocular]

Species	Exposure	Response	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 inflamation of the iris; four of the six treated eyes had mild to moderate corneal cloudiness with vascularization in the lower portion of the cornea, which persisted 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
New Zealand White Rabbits, M/F	Bo-rid V-4 Liquid Weed Killer , a 0.5% liquid formulation of hexazinone. 0.1 mL in left eye.	No ocular effects in washed or unwashed eyes	Wolfe and Rice 1981a

Appendix 2: Systemic Toxicity of hexazinone after repeated administrations. **[Subsections include: Short term multiple gavage, Short term dietary, Developmental (Teratology) Studies, Reproduction Studies, Subchronic Dietary (15 days to 90 days), Chronic Dietary (>90 days), Multiple Exposure Dermal Studies]**

Species	Exposure	Response	Reference
Short Term Multiple Gavage (other than developmental studies)			
Rat, Crl-CD, male, n=6	0 or 300 mg/kg/day for 10 days (5 days/week for 2 weeks, 89.3% a.i. in corn oil	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	Kennedy 1984
Rat, Crl-CD, male, n=6	0 or 300 mg/kg/day for 10 days (5 days/week for 2 weeks, 98% pure in corn oil	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	Kennedy 1984
Developmental (Teratogenicity) Studies			
Rats, ChR-CD female	Dietary exposure to hexazinone (97.5 %) at concentrations of 0, 200, 1000, and 5000 ppm (equivalent to doses of 18.9, 94.5, and 482.0 mg/kg) on Days 6 to 15 of gestation.	Decreased body weights, body weight gains, and decreased food efficiency at 5000 ppm. No maternal effects at 1000 ppm. No effect on offspring at any concentration. **Classified as Unacceptable/Upgradable by U.S. EPA 2002g because of reporting deficiencies.**	Culik et al. 1974. MRID 00114486. Also summarized by Kennedy and Kaplan 1984

Appendix 2: Systemic Toxicity of hexazinone after repeated administrations. **[Subsections include: Short term multiple gavage, Short term dietary, Developmental (Teratology) Studies, Reproduction Studies, Subchronic Dietary (15 days to 90 days), Chronic Dietary (>90 days), Multiple Exposure Dermal Studies]**

Species	Exposure	Response	Reference
Mated Sprague-Dawley rats	Daily gavage doses of 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. ***Continue on next page***	Mullin 1987, MRID 40397501

Mullin 1987, continued from previous page: 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 and developmental 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. **U.S. EPA/OPP (2002g) classified this study as acceptable with a maternal NOAEL of 100 mg/kg and a LOAEL of 400 mg/kg. The developmental NOAEL set at 400 mg/kg/day. 900 mg/kg/day classified as LOAEL based on decreased female fetal weight, and increased incidence of kidneys with no papilla (malformation), and an increased incidence of misaligned sternebrae (variation). The U.S. EPA/OPP (2002g,h) use the 400 mg/kg/day NOAEL for reproductive effects as the basis for the acute RfD.**

Appendix 2: Systemic Toxicity of hexazinone after repeated administrations. **[Subsections include: Short term multiple gavage, Short term dietary, Developmental (Teratology) Studies, Reproduction Studies, Subchronic Dietary (15 days to 90 days), Chronic Dietary (>90 days), Multiple Exposure Dermal Studies]**

Species	Exposure	Response	Reference
22 female New Zealand white rabbits.	Gavage doses of 0, 20, 50, 125, and 175 mg/kg/day on Days 7-28 of gestation.	Decreased food consumption and decreased body weight gain, decreased food consumption, and diarrhea in dams in the 125 and 175 mg/kg dose groups. Maternal toxicity, including mortality and abortions, as well as decreased fetal weight at 125 mg/kg/day. At 175 mg/kg, all but one dam died. No toxicity at 20 or 50 mg/kg/day. **Classified by U.S. EPA 2002h as acceptable with a maternal and developmental NOAEL of 50 mg/kg and a maternal and developmental LOAEL of 125 mg/kg.**	Munley 2002, MRID 45677801
17 female New Zealand white rabbits (weighing 3.0-5.5g)	Gavage doses of 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 This appears to summarize Serota et al. 1980. See entry below.

Appendix 2: Systemic Toxicity of hexazinone after repeated administrations. **[Subsections include: Short term multiple gavage, Short term dietary, Developmental (Teratology) Studies, Reproduction Studies, Subchronic Dietary (15 days to 90 days), Chronic Dietary (>90 days), Multiple Exposure Dermal Studies]**

Species	Exposure	Response	Reference
Pregnant New Zealand white rabbits	Daily gavage doses of 0, 20, 50, or 125 mg/kg/day hexazinone on days 6-19 of gestation. Dosing volume of 1 mL/kg.	Compared to concurrent controls, no treatment-related changes in mortality, clinical signs, body weights, gross pathology, fetal weights, sex ratios, pre-implantation or post-implantation losses, or the number of corpora lutea, implantations, resorptions, live fetuses, or dead fetuses were observed (U.S. EPA 2002g). Maternal effects observed only at 125 mg/kg/day included increased incidence of depression, increased discharge from the eyes; decreased body weight gain, decreased food consumption, and increased resorptions. ***Continued below.***	Serota et al. 1980 MRID 00028863

Continued from above: Developmental effects observed only at 125 mg/kg/day included decreased fetal body weight gain and delayed ossification of the extremities. NOELs for maternal and developmental effects = 50 mg/kg/day; LOAEL for maternal and developmental effects = 125 mg/kg/day. **This study was classified as Unacceptable/Upgradable by U.S. EPA (2002g,h) because of reporting deficiencies, specifically the inability to determine the relationship of the gross incidence of abnormalities to differences in the incidence of abnormalities among different litters.**

Appendix 2: Systemic Toxicity of hexazinone after repeated administrations. **[Subsections include: Short term multiple gavage, Short term dietary, Developmental (Teratology) Studies, Reproduction Studies, Subchronic Dietary (15 days to 90 days), Chronic Dietary (>90 days), Multiple Exposure Dermal Studies]**

Species	Exposure	Response	Reference
Reproduction Studies			
Rats, Sprague-Dawley	Dietary exposure to 0, 200, 2000, or 5000 ppm hexazinone for two generations. Groups of 29 to 30 males and females. Standard 2-generation reproduction study. Based on food consumption, doses in F0 generation were 11.8, 117, and 294 mg/kg/day, respectively, for males and 14.3, 143, and 383 mg/kg/day, respectively, for females. In treated F1 groups, the doses were 15.3, 154, and 399 mg/kg/day, respectively, for males and 17.7, 180, and 484 mg/kg/day, respectively, for females. F0 and F1 parental animals were administered test or control diet for 73 or 105 days, respectively, prior to mating, throughout mating, gestation, and lactation, and until necropsy.	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. See Section 3.1.9.2. for additional details. NOELs for systemic effects and reproductive toxicity = 200 ppm; LOELs for systemic effects and reproductive toxicity were = 2000 ppm (100 mg/kg/day). **U.S. EPA/OPP 2002g made the following classifications:** NOAEL for systemic toxicity and reproductive effect is 200 ppm (11.8-15.3 mg/kg/day for males and 14.3-17.7 mg/kg/day for females) with a corresponding LOAEL of 2000 ppm (117-154 mg/kg/day for males and 143-180 mg/kg/day for females).	Mebus 1991, MRID 42066501

Appendix 2: Systemic Toxicity of hexazinone after repeated administrations. **[Subsections include: Short term multiple gavage, Short term dietary, Developmental (Teratology) Studies, Reproduction Studies, Subchronic Dietary (15 days to 90 days), Chronic Dietary (>90 days), Multiple Exposure Dermal Studies]**

Species	Exposure	Response	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
Subchronic Dietary (15 days to 90 days)			
Dogs, beagle, male and female, 4/sex/dose, 10-18 months old	0, 200, 1000, or 5000 ppm in the diet for 90 days During 1st week 5000 ppm group ate 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	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.	Kennedy and Kaplan 1984

Appendix 2: Systemic Toxicity of hexazinone after repeated administrations. **[Subsections include: Short term multiple gavage, Short term dietary, Developmental (Teratology) Studies, Reproduction Studies, Subchronic Dietary (15 days to 90 days), Chronic Dietary (>90 days), Multiple Exposure Dermal Studies]**

Species	Exposure	Response	Reference
Mouse, CD-1, male and female, n=10/sex/group.	0, 250, 500, 1250, 2500, or 10,000 ppm in the diet for 56 days. hexazinone 95% pure	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	Kennedy and Kaplan 1984
Rats, Crl-CD, male and female, 16/sex/group, weanling	0, 200, 1000, or 5000 ppm in the diet for 90 days in 1% corn oil. white crystalline solid (>98% pure)	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.	Kennedy and Kaplan 1984

Appendix 2: Systemic Toxicity of hexazinone after repeated administrations. **[Subsections include: Short term multiple gavage, Short term dietary, Developmental (Teratology) Studies, Reproduction Studies, Subchronic Dietary (15 days to 90 days), Chronic Dietary (>90 days), Multiple Exposure Dermal Studies]**

Species	Exposure	Response	Reference
Chronic Dietary (>90 days)			
Mouse, CD-1, male and female, n=10/sex/group. Animals were 4 weeks old. Males weighed 23-33 g; females weighed 18-26 g.	0, 200, 2500, or 10,000 ppm for 730 days. 95% pure (1st 18 months)/99% pure (last 6 months). Based on measured food consumption, the exposures were equivalent to 28, 366 and 1635 mg/kg/day in males and 0, 34, 450 and 1915 mg/kg/day in females.	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.... ***Continued below***.	Goldenthal and Trumball 1981, MRID 00079203. Slone 1992, MRID 42509301. Slone 1994, MRID 43202901 (Also summarized in Kennedy and Kaplan 1984 and U.S. EPA/OPP 2002g)

Appendix 2: Systemic Toxicity of hexazinone after repeated administrations. **[Subsections include: Short term multiple gavage, Short term dietary, Developmental (Teratology) Studies, Reproduction Studies, Subchronic Dietary (15 days to 90 days), Chronic Dietary (>90 days), Multiple Exposure Dermal Studies]**

Species	Exposure	Response	Reference

Addition notes on above study: 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.

EPA Classification of Carcinogenicity: *Under the conditions of this study, evidence of carcinogenic potential was equivocal: a positive trend test for neoplasia was observed in female mice, but no significant difference was determined by pair-wise comparison*. Study is classified as acceptable. (U.S. EPA/OPP 2002g, pp. 16-17).

EPA Assessment of Toxicity: The NOAEL is 28 mg/kg/day for males and 450 mg/kg/day for females. LOAEL is 366 mg/kg/day for males 1915 mg/kg/day for females.

Rats, Crl-CD, male and female, 16/sex/group	0, 200, 1000, or 2500 ppm in the diet for 730 days 94.0% active ingredient (first 14 months)/ 95.8% active ingredient (remainder of study)	Decreased body weights in females at 1000 ppm and in males and females at 2500 ppm, compared with controls. The decreased body weights in females could not be associated with a decrease in food consumption and was attributed to a decrease in food conversion efficient. A decrease in food conversion efficiency in male rats was noted only in the 1000 ppm exposure group. ***Continued below***.	Kaplan et al. 1977. MRID 00108638 (From Kennedy and Kaplan 1984 and U.S. EPA/OPP 1994a, 2002g,h)

Appendix 2: Systemic Toxicity of hexazinone after repeated administrations. **[Subsections include: Short term multiple gavage, Short term dietary, Developmental (Teratology) Studies, Reproduction Studies, Subchronic Dietary (15 days to 90 days), Chronic Dietary (>90 days), Multiple Exposure Dermal Studies]**

Species	Exposure	Response	Reference

Addition notes on above study:
Food consumption was slightly less among males rats 2500 ppm during final 3 months of treatment.

No overt 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. Male rats also evidenced a dose-related increase in the incidence of thyroid adenomas but the increase was not statistically significant based on pair-wise comparisons (i.e., the Fischer Exact test).

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.

EPA Classification of Carcinogenicity: *Under the conditions of this study, carcinogenic potential of hexazinone is considered negative*. Study is classified as acceptable. (U.S. EPA/OPP 2002g, pp. 18).

EPA Classification of Toxicity: NOAEL is 10.2 mg/kg/day for males and 12.5 mg/kg/day for females.
The LOAEL is 53.3 mg/kg for males and 67.5 mg/kg/day for females.

Dogs, beagles, 5M/5F per does	Dietary concentrations of 0, 200, 1500, or 6000 ppm for 1 year. Based on measured food consumption, doses in males were 5.00, 41.24, and 161.48 mg/kg/day. The corresponding doses in females were 4.97, 37.57, and 166.99 mg/kg/day.	**U.S. EPA/OPP 2002g classifies low dose (5.00 and 4.97 mg/kg/day) as NOAEL and mid-dose (41.24 and 37.57 mg/kg/day) as LOAEL. This study is used as the basis for the chronic RfD**. No mortality at any dose level.	Dalgard 1991, MRID 42162301

Appendix 2: Systemic Toxicity of hexazinone after repeated administrations. **[Subsections include: Short term multiple gavage, Short term dietary, Developmental (Teratology) Studies, Reproduction Studies, Subchronic Dietary (15 days to 90 days), Chronic Dietary (>90 days), Multiple Exposure Dermal Studies]**

Species	Exposure	Response	Reference

Addition notes on above study:
High dose: Statistically significant decrease in body weight in females (16.7% less than control animals). A substantial decrease in body weight in males (19.4% less than controls) but this decrease was not statistically significant. Food consumption was affected (data from Appendix 5B). Decreased food consumption (not statistically significant) in males – an average total food consumption of 96.8 kg over the course of the study compared to 108.1 kg in controls or a 10.3% decrease from controls. Statistically significant decreased food consumption seen in females – an average total food consumption of 81.5 kg over the course of the study compared to 104.8 kg in controls or a 22.2% decrease from controls. Decreases in RBC counts, hemoglobin, and hematocrit. Significant changes in several liver parameters and some liver pathology (change in gross appearance and aplasia). Several of the changes in blood chemistry and tissue weights may have been secondary to changes in body weight.

Mid Dose: Decreased body weight in males (not statistically significant). Changes in some liver parameters in males and females.

Low Dose: No effects.

DERMAL, Multiple Exposures

6 male rabbits (weighing between 2 and 2.5 kg)	0, 70, 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.	Kennedy 1984
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

Appendix 2: Systemic Toxicity of hexazinone after repeated administrations. **[Subsections include: Short term multiple gavage, Short term dietary, Developmental (Teratology) Studies, Reproduction Studies, Subchronic Dietary (15 days to 90 days), Chronic Dietary (>90 days), Multiple Exposure Dermal Studies]**

Species	Exposure	Response	Reference
5 male and 5 female New Zealand white rabbits per dose	0, 50, 400, or 1000 mg/kg/day Hexazinone technical (>98%) in distilled water, 6 hours/day for 21 consecutive days.	Dermal irritation in all groups, including controls. No signs of toxicity and no changes in hematology, gross pathology, organ weights, or body weights.	Malek 1989 MRID 41309005

Appendix 3: Toxicity of hexazinone and hexazinone formulations to birds

Species	Exposure	Effects	Reference
Single Dose Gavage			
Bobwhite quail, 20 weeks old, 5M/5F per dose	Single gavage doses of hexazinone in corn oil of 0, 398, 631,1000, 1590, and 2510 mg/kg.	No mortality in control group or at doses of 1000 mg/kg or less. 2/10 died at 1590 mg/kg and 6/10 died at 2510 mg/kg. LD_{50}: 2258 (1628-3130) mg/kg ***Continued below.***	Fink et al. 1978, MRID 00073988

Continued from above: Birds which eventually died exhibited depression (reduced activity and response to stimuli), incoordination, weakness, loss of righting reflex, lower limb rigidity, and clonic convulsions. At 1000 mg/kg (non-lethal exposure), all birds showed signs of depression, wing droop, loss of coordination and lower limb weakness. All birds at this dose recovered by Day 2. At 631 mg/kg, these signs of toxicity were seen in one bird. No frank signs of toxicity at lower dose.

During first seven days after dosing, a reduction in food consumption seen at doses of 1000, 1590, and 2510 mg/kg. As a % of control and going from lowest to highest dose, food consumption 105%, 82%, 54%, 45%, and 39%. [Additional details tabulated.]

Quail, bobwhite, male, 20 weeks old, fasted 15 hours before dosing	398, 631, 1000, 1590, or 2510 mg/kg body weight. Single dose in corn oil with 14-day observation period	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. ***Continued below.***	Kennedy 1984 This appears to be a summary of Fink et al. 1978, MRID 00073988. See above entry.

Species	Exposure	Effects	Reference
Continued from above: 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.			
Acute Dietary			
Mallards, 10-15 days old, 10 birds per concentration	Dietary concentrations of 0, 312.5, 625, 1250, 2500, and 5000 ppm. 5 days of exposure with a 3 day observation period	No mortality, signs of toxicity, or gross pathology. No effect on body weight or food consumption. Based on terminal values (Tables III and IV of study), the birds appear to have consumed food at a rate of about 25% of their body weight.	Fletcher 1973a, MRID 00104981
Quail, bobwhite, male, 2 weeks old, 10 birds per concentration	Dietary concentrations of 0, 312.5, 625, 1250, 2500, and 5000 ppm. 5 days of exposure with a 3 day observation period	1/10 birds died at concentrations of 312.5 ppm and 625 ppm but no birds died at higher concentrations. No signs of toxicity are reported. When compared to pooled controls (0/50), the 1/10 mortality is not significant using the Fisher exact test (p=0.166). No effect on body weight or food consumption. Based on terminal values (Tables III and IV of study), the birds appear to have consumed food at a rate of about 22% of their body weight.	Fletcher 1973b, MRID 00107878

Appendix 3: Toxicity of hexazinone and hexazinone formulations to birds

Species	Exposure	Effects	Reference
Quail, bobwhite, male, 2 weeks old, n=10/group	0, 625, 1250, 2500, 5000, or 10,000 ppm in the diet for 5 days. 98+% pure technical grade. Treated diets provided for 5 days with basal diets given to all groups for last 3 days.	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.	Kennedy 1984
Quail, bobwhite, male, 2 weeks old, n=10/group	0, 625, 1250, 2500, 5000, or 10,000 ppm in the diet for 5 days. 98+% pure technical grade. Treated diets provided for 5 days with basal diets given to all groups for last 3 days.	This is a replicate of the above study. 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.	Kennedy 1984

Appendix 3: Toxicity of hexazinone and hexazinone formulations to birds

Species	Exposure	Effects	Reference
Quail, bobwhite, male, 2 weeks old, n=10/group	0, 156, 312, 625, 1250, 2500, or 5000 ppm in the diet for 5 days. 98+% pure technical grade. Treated diets provided for 5 days with basal diets given to all groups for last 3 days.	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. The greatest response, 3/10, is not significantly different from the control response, 1/10 [p=0.105 using the Fisher Exact test]. Body weight loss was 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. Based on body weight (Table 2) and food consumption data (Table 3) in the report, the birds consumed about 0.22 of their body weight per day.	Dudeck and Bristol 1980, MRID 00072663 (Also summarized in Kennedy 1984)

Appendix 3: Toxicity of hexazinone and hexazinone formulations to birds

Species	Exposure	Effects	Reference
Reproduction Studies			
Quail, Northern bobwhite	1-Generation reproduction study. Dietary concentrations of 0, 100, 300, and 1000 ppm for 20 weeks. Body weights of birds were about 0.2 kg and food consumption was about 0.030 kg /day over the course of the study. Thus, the food consumption factor was 0.15 of body weight per day.	No mortality or signs of toxicity. No effect on reproductive parameters at any concentration. Increased food consumption at 1000 ppm. This effect was associated with increased body weight gains (Table 1, p. 30 of study). For 14-day survivors (hatchlings) the control body weights were 21 ±3 g and the100 ppm group was 19 ±3 g (Table 5A. p. 39 of study and Appendix XI, pp. 90-93 for pen means). This is about a 10% decrease in body weight on average. There was no effect on survival. Average 14-Day survivor body weights at 300 ppm and 1000 ppm were 20 ± 3 and 22 ±3 grams. Here the ± symbol is used to designate the standard deviation of the pen means. U.S. EPA/OPP 1994d appears to classify the NOEC from this study as <100 ppm based on "effects to the 14-Day survivors weight" (U.S. EPA/OPP 1994d, p. 14) but uses an NOEC of 1000 ppm for risk characterization (U.S. EPA/OPP 1994d, pp. 32-33).	Beavers et al. 1991a, MRID 41764901

Appendix 3: Toxicity of hexazinone and hexazinone formulations to birds

Species	Exposure	Effects	Reference
Mallard ducks	1-Generation reproduction study. Dietary concentrations of 0, 100, 300, and 1000 ppm for 20 weeks. Body weights of birds were about 1.1 kg and food consumption was about 0.200 kg /day.	At 1000 ppm, males evidenced a slight reduction in body weight. Also at 1000 ppm, a slight (statistically insignificant) drop in hatchability was noted. Authors classified the NOEC at 300 ppm. U.S. EPA/OPP 1994d classified the NOEC at >1000 ppm.	Beavers et al. 1991b, MRID 41764902 and corrections in Beavers et al 1991c, MRID 41938001

Mixture Studies not included in Appendix: Palmer et al. 1996 MRID 44112701;

Appendix 4: Effects of hexazinone and hexazinone formulation to terrestrial invertebrates and soil microorganisms (sorted alphabetically by author within each group).

Organism	Exposure	Observations	Reference
		Terrestrial Invertebrates	
Mites	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. The effect on mites appeared to be secondary to the effect on vegetation.	Badejo and Akinyemiju 1993, 1994
Honey bee	Hexazinone, 98% pure. Contact assay at 0, 13, 22, 36, 60, and 100 micrograms/bee. Two control grous	In pooled (untreated and acetone solvent) controls, mortality was 1/100. The one dead control bee occurred in the negative control. Mortality in dosed groups (lowest to highest) was 2/50, 4/50, 1/50, 2/50, and 4/50. Using the pooled controls, the highest response is statistically significant using the Fisher Exact Test (1/100 vs 4/50, p=0.04251). Not pooling controls, the highest response is marginal (0/50 vs 4/50, p=0.058732) The dose-response relationship is not statistically significant.	Hoxter et al. 1989, MRID 41216502
Honey bees	Hexazinone, t.g.a.i. Topical applications of 20, 30, 40, 50, and 60 ug/bee.	At 48 hours, mortality of 5% in the 30 and 4 ug/bee groups and 10% in the 10, 50, and 60 ug/bee groups. No clear dose-response relationship.	Meade 1978, MRID 00076963

Appendix 4: Effects of hexazinone and hexazinone formulation to terrestrial invertebrates and soil microorganisms (sorted alphabetically by author within each group).

Organism	Exposure	Observations	Reference
		Soil Microorganisms	
General microbial community in soil, as indicated by microbial biomass, basal respiration, and utilization of 95 C compounds	- Field study in Northern California - Three replicate paired plots of 70 m^2 at three ponderosa pine plantations, designated randomly for hexazinone or control treatment - Hexazinone (Velpar) applied at recommended field rate of 3 kg a.i./ha - Litter and mineral soil (0-15 cm depth) collected on days 1, 7, 30, 100, and 191 - Samples analyzed for microbial biomass, basal respiration, and utilization of 95 C compounds - Two *in situ* measurements made on each sampling date: net N mineralization at 0-15 cm depth and surface CO_2 efflux	- Microbial biomass virtually identical between hexazinone and control plots, with no significant main effect or treatment x time interaction found - No significant effect of hexazinone on basal or *in situ* respiration - N availability unaffected by hexazinone - Data and results not given for utilization of 95 C compounds	Busse et al. 2001
Fungal and bacterial populations	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.	No effect on populations 2 and 6 months after application; carbon dioxide evolution was not affected by any of the three application rates.	Chakravarty and Chatarpaul 1990

Appendix 4: Effects of hexazinone and hexazinone formulation to terrestrial invertebrates and soil microorganisms (sorted alphabetically by author within each group).

Organism	Exposure	Observations	Reference
Five species of ectomycorrhizal fungi	Concentrations of 0, 0.005, 0.05, 0.5, 12.5, 25, 50, 250, and 500 ug/L in growth medium.	No effect on any species at concentrations of 0.5 ug/L (ppb) or less. Inhibition in all species at concentrations of 50 ug/L (ppb) or greater.	Chakravarty and Chatarpaul 1990
Ectomycorrhizal fungi: *Cenococcum geophilum; Pisolithus tinctorius; Hebeloma longicaudum*	- Laboratory study - Hexazinone at 0, 1, 10, 100, 1000, 5000, and 10,000 ppm a.i. in agar to which agar discs of fungi were added - Four replicates per herbicide-fungus treatment plus four controls - All were incubated in the dark at 24°C; *P. tinctorius* for 26 days, *C geophilum* and *H. longicaudum* for 48 days - Data subject to Fisher's Least Significant Difference test	-Hexazinone significantly reduced the radial growth of each species at concentrations of 1000 ppm - Growth of all species completely inhibited at ≥5000 ppm - *C. geophilum* was slowest growing and least sensitive fungi, with radial growth greater than or no different from controls at concentrations ≤100 ppm - *H. longicaudum* had radial growth greater than or no different from controls at 1 and 10 ppm , but significantly reduced growth at 100 ppm - *P. tinctorius* was most sensitive fungi, with radial growth significantly reduced at 1, 10 and 100 ppm	Estok et al. 1989
Mixed populations of soil fungi and bacteria	Hexazinone in soils (3 types) at a concentration of 10 ppm. 8 week incubation period with observations at weeks 1, 2, 4, and 10.	No reduction in fungal or bacterial populations over 10 week period. A transient increase in fungal populations at 4 weeks in one soil (Illinois) that returned to normal at week 8.	Krause 1975
8 species of soil fungi in agar cultures	Hexazinone at 1, 10, 100, and 1000 ppm in agar with a 64 hour period of exposure.	No growth inhibition at 1 or 10 ppm. Inhibition of a *Fusarium* sp (20%) and a *Pythium* sp (50%) at 100 ppm. At 1000 ppm, inhibition (20% to 100%) in all species.	Krause 1975

Appendix 4: Effects of hexazinone and hexazinone formulation to terrestrial invertebrates and soil microorganisms (sorted alphabetically by author within each group).

Organism	Exposure	Observations	Reference
54 Strains of Ectomycorrhizal Fungi	- Laboratory study - Technical grade, Du Pont hexazinone dissolved in acetone, added to liquefied agar media to a final concentration of 1 ppm - "Non-pesticide" controls used but use of vehicle control not specified - Two different agar culture media used; modified Hagem's and modified Melin-Norkrans'(MMN) - Inoculated fungi were incubated at 18 ± 1°C for 2-8 weeks	- Hexazinone stimulated the growth of one strain of *S. bovinus* and one unidentified ectomycorrhizal fungi strain (values not given; as determined by comparison with controls), but otherwise had no effect on mycorrhizal growth.	Laatinkainen and Heinonen-Tanski 2002
Ectomycorrhizal fungus *Hymenoscyphus ericae*	- Laboratory study - Cultures of *H. ericae* grown on Petri dishes of MMN medium containing 0, 2, 7, 20, 60, or 540 ppm hexazinone as supplied by dilutions of Velpar L, 25% a.i. (dilution solvent not indicated; solvent control not indicated) - 10 replicates at each concentration incubated at 20-24°C - Measurements of colony size made every three days	- Average daily growth rate for the replicates of each concentration was nearly linear against log concentration between 7 ppm and 540 ppm - Slightly higher growth rate at 7 ppm than 0 ppm observed in earlier days of experiment, but was no longer evident when experiment ended 29 days after inoculation	Litten et al. 1985

Appendix 4: Effects of hexazinone and hexazinone formulation to terrestrial invertebrates and soil microorganisms (sorted alphabetically by author within each group).

Organism	Exposure	Observations	Reference
Ectomycorrhizal fungus *Hymenoscyphus ericae*	- Laboratory study - Cultures of *H. ericae* grown on Petri dishes of MMN medium containing 0, 5, 10, 15, 20, 25, or 30 ppm hexazinone - 8 replicates at each concentration incubated for 42 days (temp not given) - Measurements of colony size made every 7 days for 42 day - Data subject to regression analysis	- Growth of colony diameter significantly decreased as hexazinone concentration increased (R^2=0.973)	Litten et al. 1985
Mixed soil microorganisms	Laboratory study in which hexazinone (as Velpar L) was applied (to pots containing soil samples, forest soil (L-H horizons) at rates equivalent to2, 4, or 8 kg a.i./ha.	During the 150-day, 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 in the L-H horizons of mixed wood cutovers.	Maynard 1993

Appendix 4: Effects of hexazinone and hexazinone formulation to terrestrial invertebrates and soil microorganisms (sorted alphabetically by author within each group).

Organism	Exposure	Observations	Reference
Fungi and bacteria	- Laboratory study - Flanagan silt loam, Myakka sand, and Keyport silt loam collected from fields cultivated but not treated with herbicides within last 5 yrs. - Soil in flasks treated with 10 ppm hexazinone (solvent not indicated) - Untreated replicates as controls; solvent control not indicated - Incubated for 8 weeks at ambient temperature - Replicates sampled after 1,2,4, and 8 weeks to determine fungal and bacterial populations as total number per gram of soil	- In general, microorganism populations were similar (statistical significance not given) in treated and untreated soils - Highest populations of fungi and bacteria were in the Flanagan silt loam, lowest in the Keyport silt loam -Distribution of fungi types similar (statistical significance not given) between treated and untreated soils	Rhodes et al. 1980

Appendix 4: Effects of hexazinone and hexazinone formulation to terrestrial invertebrates and soil microorganisms (sorted alphabetically by author within each group).

Organism	Exposure	Observations	Reference
Nitrifying bacteria	- Laboratory study - Keyport silt loam and Fallsington sandy loam (both at pH 7.0) inoculated with garden soil (source/type unidentified) as source of nitrifying bacteria, then treated with: - 200 ppm ammonium sulfate and 0, 5 or 20 ppm hexazinone (99% purity) - Soil controls without ammonium sulfate or hexazinone -Incubated at 5°C for up to 5 weeks - Total nitrate detected as a measure of nitrifying bacteria was determined after 0, 7, 14, 21,and 35 days	- No effect on soil-nitrifying process was observed (statistical difference not given)	Rhodes et al. 1980

Appendix 5: Toxicity tests of hexazinone to terrestrial plants

Plant	Exposure	Response	Reference
Red pine (*Pinus resinosa*) inoculated with ectomycorrhiza (*Laccaria laccata*)	- Greenhouse study - Hexazinone as Velpar L surface-applied to pots of peat/vermiculite at 1, 2, and 4 kg/ha - 4 month old *P. resinosa* seedlings with or without inoculations of *L. laccata* were planted in pots 8 wks after treatment - Control pots treated with distilled water before planting - Seedlings evaluated for growth and mycorrhization at 2 and 6 mos. after planting - Data subjected to Duncan's new multiple range test	- At 4 kg/ha Velpar L, cumulative mortality after 6 mos. greater in inoculated seedlings (67%) than uninoculated (52%) (statistical significance not given) - At 1 and 2 kg/ha there was a general reduction (significant)in growth; at 4 kg/ha all measurements of growth reduced (significant) - At 2 and 4 kg/ha, mycorrhization of seedlings decreased significantly compared with controls at 2 and 6 mos. - At 1 kg/ha, mycorrhization of seedlings decreased significantly at 2 but not 6 mos.	Chakravarty and Chatarpaul 1988

Appendix 5: Toxicity tests of hexazinone to terrestrial plants

Plant	Exposure	Response	Reference
Lodgepole pine (Pinus contorta var. latifolia) White spruce (Picea glauca)	- Greenhouse study - Hexazinone as granular Pronone 5G surface-applied to pots of peat/vermiculite at 1,2, and 4 kg a.i./ha - 6 month old pine and spruce with naturally occurring mycorrhizae were planted in pots at 1,4, and 9 wks after treatment - Control pots treated with clay granules - Seedlings evaluated for growth and mycorrhization at 2,4, and 6 mos. after planting - Data subjected to ANOVA and Scheffe's test for multiple comparisons	- Seedling mortality occurred at all concentrations and decreased over time (data given only for seedlings planted 9 wks after treatment) - No seedling mortality at 6 mos. after planting - At 2 and 4 kg a.i./ha, significant reduction in shoot and root growth in both pine and spruce - At 1 kg a.i./ha, no significant reduction in shoot and root growth - At 2 and 4 kg a.i./ha, significant reduction in total number of short roots and mycorrhization - At 1 kg a.i./ha, significant reduction in total number of short roots and mycorrhization for first 4 mos., then no significant difference from control at 6 mos.	Chakravarty and Sidhu 1987
Cacti (5 species), seed-ground or grafts	Application rates of 3 and 6 lbs a.i./acre.	Decreased survival at both application rates in all species.	Crosswhite et al. 1993, MRID 43329501

Appendix 5: Toxicity tests of hexazinone to terrestrial plants

Plant	Exposure	Response	Reference
Loblolly pine (Pinus taeda)	- Laboratory study - Hexazinone applied as soil drench at 0 and approximately 0.00014, 0.014, 0.14, 1.4 and 11.4 kg a.i./ha to container-grown pine seedlings - Photosynthetic rates (µmol CO_2 m^2s^{-1}) of needles and whole plants and chlorophyll-a fluorescence of needles determined on 1,3, 7 and 14 days after treatment - Data subjected to ANOVA, Duncan's mean separation, and Student's t-test	- 1 day after treatment of hexazinone at > 1.4 kg a.i./ha, seedlings showed partial or complete inhibition of photosynthetic rate and electron transport, which remained unchanged during the following 13 days - At sublethal concentrations (<1.4 kg a.i./ha) photosynthetic rate increased for 7 days after treatment; then returned to control values by Day 14 - Sublethal concentrations (<1.4 kg a.i./ha) had little effect on chlorophyll-a fluorescence kinetics	Johnson and Stelzer 1991
Tier 2 greenhouse assays, 10 plant species	pre- and post emergence applications	Most sensitive species: Pre-emergence: Cotton, EC_{25} < 0.01 kg a.i./ha Post-emergence: Cocklebur and Sugarbeet, EC_{25} 0.011 kg a.i./ha Least sensitive species: Pre-emergence: Rice and Nutsedge, EC_{25} 0.13 kg a.i./ha Post-emergence: Corn, EC_{25} 0.052 kg a.i./ha	Leavitt 1988, MRID 41216501

Appendix 5: Toxicity tests of hexazinone to terrestrial plants

Plant	Exposure	Response	Reference
Glasshouse pots of *Stellaria media* L, *Polygonum lapathifolium* L., *Poa annua* L., and turnip.	Rates of 0.2, 0.6, or 1.8 kg a.i./ha (incorporated or surface applied)	Significantly lower weights of all four species. At the lower application rates, hexazinone had a greater effect on the organic fine sandy loam than on the peat. Furthermore, incorporation was more effective than surface application.	May 1978
Tier 1 and Tier 2 greenhouse assays, 10 plant species (4 monocots and 6 dicots	Hexazinone (purity reported as 100.2%). Tier 1: 12 lbs/acre Tier 2: 0.00206 lb a.i./acre to 1.5 lb a.i./acre for seedling emergence and 0.000977 to 0.5 lb a.i./acre for vegetative vigor.	Seed germination: 12 lbs/acre resulted in no significant inhibition. Seedling emergence: Most sensitive, Tomato NOEC for height of 0.000348 lb a.i./acre. Least sensitive, Soybeans and Corn, NOEC for height and shoot weight of 0.0234 lb a.i./acre. Vegetative vigor: Most sensitive, Cucumber NOEC for all endpoints of 0.00391 lb a.i./acre. Least sensitive, Corn, NOEC for shoot weight of 0.0625 lb a.i./acre. U.S. EPA rejected cucumber data because thiram was used as a seed treatment. McKelvey (1995) states that interaction with thiram is implausible.	McKelvey and Heldreth 1994, MRID 43162501 McKelvey 1995, MRID 43605001

Appendix 5: Toxicity tests of hexazinone to terrestrial plants

Plant	Exposure	Response	Reference
Unidentified seeds from the forest floor, location unspecified	- Laboratory study - Hexazinone as Velpar L or granular Pronone 10 was added to forest floor substrate at 0, 10, 50, 100, 500, 1000, and 5000 ppm dry weight - 29 days after treatment, seedlings were grouped and counted - Data subjected to ANOVA and Dunnett's multiple-range test	- Velpar L caused significant reduction of seed germination only at 5000 ppm - Pronone 10 significantly reduced germination at all concentrations, with absence of germination occurring in one group of seedlings at 5000 ppm	Morash and Freedman 1989

Appendix 5: Toxicity tests of hexazinone to terrestrial plants

Plant	Exposure	Response	Reference
Ceanothus velutinus, C. Integerrimus, Rubus ursinus, and *R. parviflorus*	- Greenhouse study - Hexazinone applied at 0, 0.56 1.12, 1.68, 2.24, and 3.36 kg a.i./ha over seeds of all four plant types planted in sandy loam-filled pots - Number seeds/pot germinated and alive recorded for 9 wks - After 9 wks, dry weights were determined for plants/pot - Data subjected to binomial logistic and linear regression	- Counts of live germinants dropped for all rates of hexazinone after day 22 for *C. velutinus, C. integerrimus*, and *R. parviflorus*, and very few plantlets developed true leaves - Counts of live germinants of *R. ursinus* did not drop for the duration of the experiment, and there was a general increase in numbers of seedlings with true leaves - At 0.56 kg a.i./ha, *C. velutinus* had a 20% chance of survival - At 1.12 kg a.i./ha, *C. velutinus* had <10% chance of survival - At 1.68 kg a.i./ha, *C. integerrimus* and *R. parviflorus* had <10% chance of survival - At rates over 2.24 kg a.i./ha, *R . ursinus* had <10% chance of survivorship - Dry weight was reduced at 1.68 kg a.i./ha by 59% (*C. integerrimus*), 74% (*C. velutinus*), and ≤50% for both *Rubus* sp.	Rose and Ketchum 2002

Appendix 5: Toxicity tests of hexazinone to terrestrial plants

Plant	Exposure	Response	Reference
Lodgepole pine (*Pinus contorta* var. *latifolia)* and White spruce *(Picea glauca)*	- Laboratory study - Hexazinone as Velpar L (25%- a.i.) or granular Pronone 5G (5%a.i.) applied at 0, 0.1, 1.0, 10, 50, and 100 µl/l to seedlings with or without inoculations of *Suillus tomentosus* grown in flasks containing vermiculite/MMN - Hexazinone added to 3 month old seedlings - Seedlings evaluated for growth and mycorrhization 6 mos. after treatment - Data subjected to ANOVA and Scheffe's test for multiple comparisons	- 0 seedling mortality at hexazinone (both formulations) concentrations ≤10 µl/l - 80-100% seedling mortality at hexazinone concentrations >10 µl/l - First significant reduction of growth in pine seedlings seen at 0.1 µl/l Velpar and 10.0 µl/l Pronone 5G - First significant reduction of growth in spruce seedlings seen at 0.1 µl/l Velpar and 0.1 µl/l Pronone 5G - Mycorrhization significantly reduced at all concentrations (except 0.1 µl/l Pronone 5G) (both formulations) in both pine and spruce - Phytotoxicity enhanced by the presence of *S. tomentosus*	Sidhu and Chakravarty 1990

Appendix 5: Toxicity tests of hexazinone to terrestrial plants

Plant	Exposure	Response	Reference
Lodgepole pine (*Pinus contorta* var. *latifolia)* and White spruce (*Picea glauca)*	- Greenhouse study - Hexazinone as Velpar L (25%- a.i.) applied at 2.4 and 4.8 kg a.i./ha to pots of peat/vermiculite - Hexazinone as granular Pronone 5G (5%a.i.) applied at 1, 2, and 4 kg a.i./ha to pots of peat/vermiculite - Control pots treated with distilled water (Velpar L) or blank granules (Pronone 5G) - 6 month old seedlings with or without inoculations of *Suillus tomentosus* planted in pots six months after treatment - Seedlings evaluated for growth and mycorrhization at 2, 4, and 6 mos. after planting - Data subjected to ANOVA and Scheffe's test for multiple comparisons	- Herbicide damage and seedling mortality were similar for Velpar L and Pronone 5G - Seedlings inoculated with S. tomentosus were more sensitive than the untreated seedlings to hexazinone at rates > 1 kg a.i./ha - Pine seedling mortality was 20% (inoculated) and 13% (uninoculated) planted 2 mos. after Velpar L at 2.4 kg a.i./ha - Spruce seedling mortality was 17% (inoculated) and 10% (uninoculated) planted 2 mos. after Velpar L at 2.4 kg a.i./ha - Pine seedling mortality was 13% (inoculated) and 10% (uninoculated) planted 2 mos. after Pronone 5G at 2 kg a.i./ha - Spruce seedling mortality was 12% (inoculated) and 8% (uninoculated) planted 2 mos. after Pronone 5G at 2 kg a.i./ha - At 1 kg a.i./ha Pronone 5G, general reduction in growth of inoculated seedlings - At 2 and 4 kg a.i./ha Pronone 5G, and 2.4 and 4.8 kg a.i./ha Velpar L, significant reductions in growth and mycorrhization at 2, 4, and 6 mos. after planting	Sidhu and Chakravarty 1990

Appendix 6: Summary of field or field simulation studies on the effects of 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
Hexazinone (NOS) applied to sandy soils. Application rate not specified.	Decreased mixed microarthropod populations, by about one-third, in top 7.5 cm of soil. Low populations persisted after hexazinone had dissipated from the soil. Other differences are apparent up to 112 days after application. [Note: Concentrations of hexazinone in soil are not reported. No statistical analyses are presented and it is not clear if any the differences are statistically significant.]	Badejo and Adejuyigbe 1994
Hexazinone (NOS) applied to sandy soils at an application rate of 1 kg/ha.	General decreases in the populations of mites at soil depths of up to 22.5 cm for up to 112 days after application. [Note: No statistical analyses are presented and it is not clear if any the differences are statistically significant. Concentrations of hexazinone in soil are not reported.]	Badejo and Akinyemiju 1993
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*). ***Continued below.***	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

Appendix 6: Summary of field or field simulation studies on the effects of hexazinone formulations

Application	Observations	Reference
Continued from above: 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.		
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*). ***Continued below.***	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
Continued from above: 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.		
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

Appendix 6: Summary of field or field simulation studies on the effects of 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®). ***Continued below.***	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

Continued from above: Applications 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..

Appendix 6: Summary of field or field simulation studies on the effects of hexazinone formulations

Application	Observations	Reference
1.1 kg a.i. granular hexazinone /ha broadcast evenly upon Florida sandhills soil (Astatula series; low in organic matter, nutrients, and water retention); 1.1 and 2.2 kg a.i. liquid hexazinone spot sprayed in a 2mx2m spot-grid upon soil; and control plot that received no hexazinone Treatment timed so rainfall occurred within 2 wks following application Study site located on Riverside Island in the Ocala National Forest, Florida	Turkey oak foliar cover declined by 83% at broadcast and liquid spot 1.1 kg/ha applications, and by 92% at liquid spot 2.2 kg/ha application (which caused a concurrent and only significant increase (89%) in wiregrass cover) Hexazinone significantly reduced the foliar cover of all oaks, while their cover doubled on control plots Only the liquid spot 2.2 kg/ha application rate caused a significant decline in shrub cover Only the liquid spot 1.1 and 2.2 kg/ha applications resulted in significant reductions of total woody plant cover 2 yrs. after application During the first year after 1.1. kg/ha broadcast application, there was a 56% decline in forb cover, but forb cover recovered during the 2nd and 3rd years The liquid spot 1.1 and 2.2 kg/ha treatments resulted in increases in forb cover during all three years During the first year, species richness was generally unaffected by hexazinone (non-significant increases in the number of plant species) except the 1.1 kg/ha broadcast treatment which resulted in a significant 28% decline in species richness All hexazinone treatments caused a decline in plant species diversity during the first year Both of the liquid spot applications resulted in a significant decline in plant species evenness that continued throughout the study period	Brockway et al. 1998

Appendix 6: Summary of field or field simulation studies on the effects of hexazinone formulations

Application	Observations	Reference
Field study in Northern California. Three replicate paired plots of 70 m^2 at three ponderosa pine plantations, designated randomly for hexazinone or control treatment. Hexazinone (Velpar) applied at recommended field rate of 3 kg a.i./ha (2.7 lb a.i./acre).	Arthropods collected at monthly intervals for three months post-treatment from three pitfall traps installed on each plot. No significant differences in numbers of mites, spiders, beetles, or springtails between hexazinone and control treatments.	Busse et al. 2001
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. ***Continued below.***	Only potato tolerated residual hexazinone through the last planting (436 days after application). Corn did not tolerate hexazinone 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

Continued from above: 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.

Hexazinone (NOS) was applied at a rate of 0.5 or 1.0 kg/ha. ***Continued below:***	Hexazinone did not injure the alfalfa or significantly affect nectar sugar production.	Curry et al. 1995

Appendix 6: Summary of field or field simulation studies on the effects of hexazinone formulations

Application	Observations	Reference
Continued from above: Applied 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 (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 production in early August.	Curry et al. 1995
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. ***Continued below.***	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
Continued from above: Velpar L 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.		

Appendix 6: Summary of field or field simulation studies on the effects of hexazinone formulations

Application	Observations	Reference
Broadcast application of hexazinone (NOS) at 1 lb a.i./acre 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 production 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). ***Continued below.***	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
Continued from above: Applied 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 was applied at 1.0 kg/ha with a plot sprayer to plots of lowbush blueberry (*Vaccinium augustifolium*) in Nova Scotia Effect on weed species also determined Applications were made in early, mid- and late May from 1992 to 1996	Tolerance of lowbush blueberries to hexazinone was dependent (significantly) on timing of application: % injury averaged <2% for applications made before May 25, and 37% for applications made after May 25 (>40% yield reduction)	Jensen and Specht 2002

Appendix 6: Summary of field or field simulation studies on the effects of hexazinone formulations

Application	Observations	Reference
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
Velpar ULW, 3.5 to 4 lb a.i./acre to pine sites	Increase growth of pine when compared to treatment with other herbicides.	Loyd et al. 2000
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 in the 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

Appendix 6: Summary of field or field simulation studies on the effects of hexazinone formulations

Application	Observations	Reference
Hexazinone (a Pronone 10G) at application rates of 2 and 4 kg a.i./ha.	Reduced uptakes of soil nutrients by plants secondary to the the phytotoxicity of hexazinone. No substantial changes in total nutrient pool in soil.	Maynard 1997
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

Appendix 6: Summary of field or field simulation studies on the effects of hexazinone formulations

Application	Observations	Reference
Hexazinone as Velpar L and Pronone 10G was applied to four study locations in Georgia: 3.9 kg a.i./ha at McElroy site (sandy clay loam), 3.4 kg a.i./ha at Hill and Ellington sites (loamy sand), and 2.8 kg a.i./ha at Grimsley site (fine sandy loam to loamy sand) Untreated control used at each site	Total species richness and richness by growth form, species diversity did not significantly differ from controls 11 years after hexazinone treatments Velpar L treatment resulted in significantly higher basal area (m^2/ha) for pines (doubled) and lower basal area for hardwoods (halved) compared to controls Velpar L treatment resulted in a significantly higher importance value (55%) in *Pinus taeda* than in controls, and a significantly lower importance value (2.5%) in *Quercus stellata* *Lespedeza bicolor* was completely absent from the Velpar L plots	Miller et al. 1999
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. Various application rates depending on soil.	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

Appendix 6: Summary of field or field simulation studies on the effects of 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

Appendix 6: Summary of field or field simulation studies on the effects of hexazinone formulations

Application	Observations	Reference
Hexazinone as Velpar L applied at 0, 1, 2, and 4 kg a.i./ha applied to sandy loam plots which were then planted 1 and 12 mos. later with container Jack pine, container black spruce, or bare-root black spruce Study area in Ontario, Canada Crop and noncrop vegetation assessed within plots over 5 growing seasons	Hexazinone treatment had a positive effect on jack pine diameter growth, with responses directly proportional to dose, and stem volumes increased in porportion to dose as well; authors suggest this is largely related to herbaceous weed control Jack pine planted 1 mo. after the 2 and 4 kg a.i./ha treatments averaged 12% lower age 4 survival than trees planted 1 yr after treatment When compared 5 growing seasons after treatment, container black spruce planted 1 mo. after treatment averaged 30 cm^3 in control and 1 kg a.i./ha plots and 137 cm^3 in 4 kg a.i./ha plots (responses curvilinear related to dose); black spruce planted 12 mos. after treatment averaged 6 cm^3 in the low-rate areas, and 28 cm^3 in the 4 kg a.i./ha plots (responses proportional to dose) Container black spruce planted 1 mo. after treatment averaged 83% survival at age 4, irrespective of hexazinone dose, and those planted 12 mos. after 2 and 4 kg a.i./ha treatments averaged a similar 84%; those planted 12 mos. after 0 and 1 kg a.i./ha averaged 70%. Authors suggest this is due higher levels of herbaceous competition in these low dose areas Bareroot black spruce responded positively (increased diameter and height growth) to treatment; volume responses were proportional to herbicide dose in all cases Bareroot black spruce survival was not affected by hexazinone	Pitt et al. 1999

Appendix 6: Summary of field or field simulation studies on the effects of hexazinone formulations

Application	Observations	Reference
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

Appendix 6: Summary of field or field simulation studies on the effects of hexazinone formulations

Application	Observations	Reference
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

Appendix 6: Summary of field or field simulation studies on the effects of hexazinone formulations

Application	Observations	Reference
Hexazinone as Velpar L (2 kg a.i./ha), Pronone 5G (2 kg a.i./ha) and Pronone 10G (1, 2, and 4 kg a.i./ha) was applied to 0.5 ha plots in a clear-cut area of loams and clays in New Brunswick, Canada Controls and half of each plot were planted 1 mo. and 12 mos. after treatment with bare root black spruce seedlings	Survival of seedlings planted 1 mo. after treatment was less than controls, but stem volume was significantly greater than most control seedlings 5 growing seasons after planting Survival and stem volume of seedlings planted 1 yr after treatment were greater than that for most control seedlings 5 growing seasons after planting Five years after planting there were no significant differences in survival or stem volume related to formulation Survival of seedlings decreased over time for all formulations and was lowest for Velpar L, but, concurrently, seedling stem volume was highest for Velpar L over of the black spruce's dominant competitor, raspberry, increased over time for all treatments and was lowest for the Velpar L formulation (55%) 6 growing seasons after treatment	Reynolds and Roden 1996
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

Appendix 6: Summary of field or field simulation studies on the effects of hexazinone formulations

Application	Observations	Reference
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 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 under-planted 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

Appendix 6: Summary of field or field simulation studies on the effects of hexazinone formulations

Application	Observations	Reference
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
Hexazinone applied to plots within commercial lowbush blueberry (*Vaccinium augustifolium*) fields at five locations in Maine at the rate of 0, 1.1, 2.2, and 4.5 kg/ha	There was a significant linear increase in grass control in the year of treatment and 2 yrs. after treatment; the greatest difference was from 0 to 1.1 kg/ha, with an increase in control from 0 to 90% At 1.1 kg/ha, stand/plot was reduced significantly for meadowsweet (*Spiraea latifolia*) from 490 stems without treatment to 21 stems, and for goldenrod (*Solidago spp.*)stand/plot was reduced significantly from 146 stems without treatment to 9 stems Blueberry injury increased with increasing hexazinone rate, from 10% at 1.1 kg/ha to 40% at 4.5 hg/ha Blueberry stand per 0.1 m^2 increased from 0 to 2.2 kg/ha, but then declined at 4.5 kg/ha	Yarborough et al. 1986

Appendix 6: Summary of field or field simulation studies on the effects of hexazinone formulations

Application	Observations	Reference
Hexazinone applied to plots within commercial lowbush blueberry (*Vaccinium augustifolium*) fields at 13 locations in Maine at the rate of 0, 0.6, 1.1, and 2.2 kg/ha	At 0.6 kg/ha hexazinone, 80% of grass was controlled Grass control increased and numbers of goldenrod and meadowsweet stems decreased with an increase in hexazinone rate At 0.6 kg/ha, stand/plot was reduced for meadowsweet from 257 stems without treatment to 77, and for goldenrod from 72 stems without treatment to 20 stems Although the authors state that blueberry injury increased with an increase in hexazinone rate, the injury was 10% at 0.6, 1.1, and 2.2 kg/ha	Yarborough et al. 1986
Hexazinone was applied to three 1-year-old clearcuts in north central Florida. ***Continued below.***	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 on the hydric hammock site, where all tended to decrease with increasing hexazinone rates.	Wilkins et al. 1993

Continued from above: 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).

Appendix 6: Summary of field or field simulation studies on the effects of hexazinone formulations

Application	Observations	Reference
Hexazinone as ½-cc 10% pellets, 1-cc 10% pellets, and 20% granules was applied at 0, 1.12, 1.68, and 2.24 kg a.i./ha to 0.04 ha sandy loam plots of newly planted and 1 yr. old loblolly pine (*Pinus taeda*) alongside 2yr old hardwoods in Alabama	22 weeks after hexazinone application, average crown reduction of hardwoods was significantly greater than for the controls (51%, 54%, and 33% at 1.12 kg/ha for 1-cc pellet, ½-cc pellet and granular, respectively) , and increased with increasing rate At 1.12 kg a.i./ha, hardwood mortality was 43% for 1-cc pellet, 32% for ½ -cc pellet, and 10% for granular formulation Hardwood density decreased with increasing hexazinone rate, and was similar for the two pellet formulations and greater for the granules Hardwood composition changed 5 growing seasons after treatment, with percentage of red oaks, white oaks and sumacs decreasing in the study area, and percentage of flowering dogwood, hickories, and *Vaccinium* spp. increasing for most of the treatments	Zutter et al. 1988

Appendix 7: Summary of field or field simulation studies on the environmental fate of hexazinone.

Application	Observations	Reference
Velpar L applied at 12 lbs a.i./acre to sites in Delaware (loam) and Mississippi (silt loam) applied to bare soil. Samples taken for up to 540 days.	Soil halftimes of 123 and 154 days. Soil dissipation reasonably fit a simple exponential curve. Hexazinone not detected in any soil cores at 75-90 cm over entire period. Some detectable concentrations are 60-75 cm. No metabolites detected below 30 cm.	Bollin 1992a
Velpar L applied at 12 lbs a.i./acre to sites in California. Samples taken for up to 540 days.	Soil halftime of 140 days. Soil dissipation reasonably fit a simple exponential curve although an outlier was noted at Day 60. Hexazinone was detected in any soil cores at 75-90 cm from Day 0 to Day 60. The Day 0 detection was attributed to core contamination. No metabolites detected below 30 cm at any time.	Bollin 1992b
Liquid hexazinone (Velpar L®) applied at 2.0 kg a.i./ha to Fleming Creek experimental 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 1ppb; the highest hexazinone concentration in stream water was 14ppb in a 1-hour period during high stream discharge after a heavy rainfall of 5.6 cm; hexazinone was stable in incubated stream water, with 50% disappearance of the compound over several years. In soil, hexazinone 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

Appendix 7: Summary of field or field simulation studies on the environmental fate of hexazinone.

Application	Observations	Reference
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
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. 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. ***Continued below:***	Feng 1987

Appendix 7: Summary of field or field simulation studies on the environmental fate of hexazinone.

Application	Observations	Reference
Continued from above: 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.		
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

Appendix 7: Summary of field or field simulation studies on the environmental fate of hexazinone.

Application	Observations	Reference
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
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. Release was described by the following equation: $\log(\boldsymbol{y}) = 1.83 - 0.996 \log(\boldsymbol{t}) - 0.62 \log(\boldsymbol{r})$ where $\boldsymbol{y}$ is the % remaining, $\boldsymbol{t}$ is time in days after application and $\boldsymbol{r}$ is rainfall in mm.	Feng et al. 1989a

Appendix 7: Summary of field or field simulation studies on the environmental fate of hexazinone.

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
General monitoring study on pesticides in an agricultural water basin in Italy, 1992 to 1995	Most hexazinone concentrations were < 0.03 ppb. The maximum concentrations for the years surveyed was 0.08 ppb.	Griffini et al. 1997
Small-scale prospective groundwater monitoring after Velpar L applications at a rate of 0.75 lb a.i./acre	In ground water (12 feet) at 366 DAT. Highest conc at 9.2 ppb. Highest concentration of metabolite was 12.9 ppb. Dissipation halftime of 22 days in upper 2 feet of soil.	Hanson et al. 2000, MRID 45132801

Appendix 7: Summary of field or field simulation studies on the environmental fate of hexazinone.

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 (16 µg/L), the maximum runoff concentration was about 4 mg/m^3, and the maximum residues on leaves was <1.0 mg/kg.	Lavy et al. 1989

Appendix 7: Summary of field or field simulation studies on the environmental fate of hexazinone.

Application	Observations	Reference
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 Ul vapron), was applied from a Bell JetRanger 206B helicopter fitted with a 10.9 m boom spray on December 16, 1981.	Of the 69 stream water 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 stream water 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

Appendix 7: Summary of field or field simulation studies on the environmental fate of hexazinone.

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 maximum 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

Appendix 7: Summary of field or field simulation studies on the environmental fate of hexazinone.

Application	Observations	Reference
Hexazinone formulated as Velpar L (liquid) and Velpar ULW (granular). Applied to two adjacent watersheds (predominately loam soil) within one day of each other in Alabama at 6.72 kg a.i./ha [6 lb a.i./acre] by helicopter. Samples of water, sediment, foliage, litter, soil, and stream water collected over a 1 year period.	Halftimes on plants in the range 26-59 days for granular formulation and 19-36 days for liquid formulation. Except for litter, vegetation residues on plants were much higher after liquid formulation than after granular formulation. See Table 3-3 of risk assessment for details residues in environmental sampes.	Michael 1992, MRID 42336401

Continued below:

Michael 1992, continued: Hexazinone consistently detected at in soil at 30-40 cm but rarely detected at 60 cm or more. Soil halftimes of 55-77 days except for soil under litter (275 days). Metabolites B, D, G, and H were most common. Dissipation was bimodal for ULV formulation and exponential (first-order) for Velpar L. This probably reflect slow release from granular formulation.

Hourly peak concentrations in stream water after storm events were 145-230 for Velpar L and 56-76 ppb for Velpar ULV after rainfalls of 18 to 26 mm (0.7 to 1 inches) (Table 15 of study).

Daily average concentrations in streams had peaks of about 35-65 ppb for Velpar L and about 40-125 ppb for Velpar ULV. The 125 peak for Velpar ULV occurred one day after application and could have been due to washoff of pellets into streamwater. Excluding this point, the highest concentration from Velpar ULV application was about 65 ppb (Figure 18 of study).

Peak concentrations of hexazinone in top 15 cm (about 5.7 inches) of soil were 4.29 ppm for Velpar L (DAT 7) and 3.26 ppm for Velpar ULV (DAT 3) (date from Tables 30 and 31 of study).

Hexazinone at pesticide mixing/loading facility in Hawaii	At one site, hexazinone could be detected in soil at depths of 244 to 274 cm (about 96 to 108 inches).	Miles et al. 1990

Appendix 7: Summary of field or field simulation studies on the environmental fate of hexazinone.

Application	Observations	Reference
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 stream water (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 groundwater 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
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 treated in 1980 were free of residues.	Neary 1983

Appendix 7: Summary of field or field simulation studies on the environmental fate of hexazinone.

Application	Observations	Reference
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 ppb 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.
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 at application rates of 3-3.5 lb a.i./acre to forest sites in California	Detectable residues in various plants used by native Americans. Residues detected in about 50% of the on-site samples at concentrations up to 10 ppm with reporting limits of 0.05 to 0.2 ppm. Much lower concentrations found outside of treatment area.	Segawa et al. 1997
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 plant species 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

Appendix 7: Summary of field or field simulation studies on the environmental fate of hexazinone.

Application	Observations	Reference
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
General monitoring study of ground water in four watersheds in Denmark.	No detectable concentrations of hexazinone.	Spliid and Koppen 1998
Hexazinone spiked with ^{14}C-labeled 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 hexazinone at 150 cm by almost 3-fold.	Stone et al. 1993

Appendix 7: Summary of field or field simulation studies on the environmental fate of hexazinone.

Application	Observations	Reference
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
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 8: Laboratory studies on the environmental fate of hexazinone

Data Summary	Reference
Aquatic Sediment Halftimes	
Aerobic aquatic sediment halftimes of > 2 months in both sterile and non-sterile sediment.	Chrzanowski 1991, MRID 41811801
Aerobic aquatic sediment, natural sunlight, 37-44 days Aerobic aquatic sediment, sterile sediment, 103-122 days Aerobic aquatic sediment, dark, 187-330 days	Chrzanowski 1996, MRID 44196301
Anaerobic aquatic sediment halftime of 230 days in non-sterile sediment and 1500 days in sterile sediment.	Hawkins et al. 1990c, MRID 41807402
Hydrolysis	
Stable at pH 5, 7, and 9 at 25 deg. C over a period of 8 weeks.	Chrzanowski 1990, MRID 41587301
Photolysis, Aqueous	
No significant degradation during 30 days of study (equivalent to 69 days in natural sunlight).	Hawkins et al. 1989a, MRID 41300801
Photolysis, Soil	
Halftime of 82 days	Hawkins et al. 1989b, MRID 41300802
Soil Degradation/Dissipation	
Degradation halftime of about 216 days in non-sterile soil and 1440 days in sterile soil.	Hawkins et al. 1990b, MRID 41807401
Degradation halftime in sandy loam (pH 7.87) of 47 days Degradation halftime in sandy loam (pH 4.65) of 91 days	Calderon et al. 2004
22 days (dissipation)	Hanson et al. 2000
90 days (recommended value)	Knisel and Davis 2000
4.8 to 15.4 days (first-order rates of 0.045 to 0.142 day^{-1}) in forestry nursery soils	Torstensson and Stenstrom 1990

Appendix 8: Laboratory studies on the environmental fate of hexazinone

Data Summary	Reference
88 days (recommended value) 216 days (dark, sandy loam) 39-54 days (Silt loam) 27-72 days (Sandy loam)	USDA/ARS 1995
60 - 230 days under aerobic and anaerobic conditions.	U.S. EPA/OPP 2002h

Appendix 8: Laboratory studies on the environmental fate of hexazinone

Data Summary	Reference
Soil Binding (Kd, Ko/c)	
Sandy Loam (Toledo): 0.42 (0.34-0.51) (3.15% OM, pH 7.87) Sandy Loam (Burgos): 0.63 (0.54-0.72)(1.36% OM, pH 4.65)	Calderon et al. 2004
Ko/c of 54, recommended value	Knisel and Davis 2000
A Kd of 0.94 estimated from field tracer experiment.	Pang and Close 2001
Sandy Loam (CA): 0.24/41 (1% OM, pH 6.4, 25°C) Sandy Loam (MD): 0.45/27 (2.1% OM, pH 6.4, 25°C) Sandy Loam (NJ): 0.18/34 (0.9% OM, pH 6.4, 25°C) Sandy Loam (ID): 0.56/74 (1.3% OM, pH 8.3, 25°C) Silt Loam (IL): 1.03/41 (4.3% OM, pH 5.4, 25°C) Silt Loam (IL): 0.53/38 (2.4% OM, pH 6.8, 25°C) Loam (CA): 10.8/<300 (0.8% OM, pH 8, 25°C) Loam (CA): 0.59/54 (1.9% OM, pH 7.7, 25°C) Note: Average Ko/c of 44.1, excluding the <300 value.	USDA/ARS 1995

Appendix 9: Toxicity of hexazinone to fish and amphibians (sort within groups by species and author) [Unless otherwise noted, all concentrations are expressed a mg a.i./L for assays on hexazinone and as mg formulation/L for assays on formulations. The major exception in the study by Wan et al. 1988. For this study, results on hexazinone formulations are based on measured levels of hexazinone in water – i.e., mg a.i./L]

Organism	Exposure	Effects	Reference
FISH - ACUTE			
Bluegill sunfish	Static, hexazinone t.g.a.i (95% purity). Concentrations of 0, 158, 211, 263, 329, 395, 461, 526, 592, and 658 mg a.i./L. 10 fish per concentration.	No mortality at 211 mg/L of less. 48-hour LC_{50}: 505 (450-539) mg/L.	DuPont De Nemours 1976, MRID 00047178
Bluegill sunfish	static, Velpar L (25% a.i.). Concentrations of 77, 130, 210, 360, 600, and 1000 mg formulation/L. 10 fish per concentration. **Aeration on last 2 days due to falling oxygen levels in water**.	NOEC (no mortality) at 600 mg formulation/L, equivalent to 150 mg a.i./L. Mortality at 1000 mg formulation was 20% (2/10) on Day 4, not statistically significant from control group (0/10).	Hutton 1989a, MRID 41235001
Bluegill sunfish	Liquid formulation containing 25% hexazinone. (Appears to be Velpar L but this is not specified) Concentrations (as formulation) of 0, 100, 250, 500, 600, 700, 800, 900, 1000, 1250 mg/L. 10 fish per concentration.	Mortality rates (going from control to highest concentration) of 0, 10, 0, 20, 20, 10, 50, 20, 90, 90%. LC_{50}: 925 (782-1049) mg formulation/L. about 230 (220 - 262) mg a.i./L Severe **oxygen depletion** attributed to an ingredient in the formulation rather than hexazinone itself.	Schneider 1976a, MRID 00076959

Appendix 9: Toxicity of hexazinone to fish and amphibians (sort within groups by species and author) [Unless otherwise noted, all concentrations are expressed a mg a.i./L for assays on hexazinone and as mg formulation/L for assays on formulations. The major exception in the study by Wan et al. 1988. For this study, results on hexazinone formulations are based on measured levels of hexazinone in water – i.e., mg a.i./L]

Organism	Exposure	Effects	Reference
Bluegill sunfish	Hexazinone, t.g.a.i., static conditions	24-hour LC_{50} = 425 (366-493) mg/L 48-hour LC_{50} = >370 <420 mg/L 96-hour LC_{50} = >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	Sleight 1973, MRID 00104980 Also summarized in Kennedy 1984
Carp (*Leuciscus idus melanotus*)	96 hour exposure with aeration to hexazinone concentrations of 0, 300, 350, 400, 450, 500, 550, 600, or 650 mg/L.	96-hour LC_{50} = 340 mg/L All fish died within 24 hours at concentrations of 450 mg/L or higher. No mortality at 24 hours at concentrations of 300 mg/L. One fish died at 300 mg/L by 48 hours.	Okolimna 1980a MRID 00076960
Fathead minnow	static exposure to hexazinone for 96 hours; pH 7.1	24-hour LC_{50} = 453 (369-556) mg/L 48-hour LC_{50} = 370-490 mg/L 96-hour LC_{50} = 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	Sleight 1973, MRID 00104980 Also summarized in Kennedy 1984

Appendix 9: Toxicity of hexazinone to fish and amphibians (sort within groups by species and author) [Unless otherwise noted, all concentrations are expressed a mg a.i./L for assays on hexazinone and as mg formulation/L for assays on formulations. The major exception in the study by Wan et al. 1988. For this study, results on hexazinone formulations are based on measured levels of hexazinone in water – i.e., mg a.i./L]

Organism	Exposure	Effects	Reference
Salmon, Chinook	96-hour exposure to Velpar® L (25% Hex/L liquid product).	24-hour LC_{50} = 1096 mg a.i./L 48-hour LC_{50} = 1096 mg a.i./L 72-hour LC_{50} = 1096 mg a.i./L 96-hour LC_{50} = 1096 mg a.i./L LC_{50} change (24-96 hours) = 0%	Wan et al. 1988 [1]
Salmon, Chum	96-hour exposure to Velpar® L (25% Hex/L liquid product)	24-hour LC_{50} = 934 mg a.i./L 48-hour LC_{50} = 934 mg a.i./L 72-hour LC_{50} = 934 mg a.i./L 96-hour LC_{50} = 934 mg a.i./L LC_{50} change (24-96 hours) = 0%	Wan et al. 1988 [1]
Salmon, Chum	96-hour exposure to hexazinone (95% Hex)	24-hour LC_{50} = 321 mg/L 48-hour LC_{50} = 288 mg/L 72-hour LC_{50} = 288 mg/L 96-hour LC_{50} = 285 mg/L LC_{50} change (24-96 hours) = 11%	Wan et al. 1988
Salmon, Coho	96-hour exposure to hexazinone (95% Hex)	24-hour LC_{50} = 290 mg/L 48-hour LC_{50} = 282 mg/L 72-hour LC_{50} = 265 mg/L 96-hour LC_{50} = 246 mg/L LC_{50} change (24-96 hours) = 15%	Wan et al. 1988
Salmon, Coho	96-hour exposure to Velpar® L (25% Hex/L liquid product)	24-hour LC_{50} = 1192 mg a.i./L 48-hour LC_{50} = 1131 mg a.i./L 72-hour LC_{50} = 1041 mg a.i./L 96-hour LC_{50} = 923 mg a.i./L LC_{50} change (24-96 hours) = 23%	Wan et al. 1988 [1]
Salmon, Chinook	96-hour exposure to hexazinone (95% Hex)	24-hour LC_{50} = 394 mg a.i./L 48-hour LC_{50} = 323 mg a.i./L 72-hour LC_{50} = 318 mg a.i./L 96-hour LC_{50} = 317 mg a.i./L LC_{50} change (24-96 hours) = 20%	Wan et al. 1988 [1]

Appendix 9: Toxicity of hexazinone to fish and amphibians (sort within groups by species and author) [Unless otherwise noted, all concentrations are expressed a mg a.i./L for assays on hexazinone and as mg formulation/L for assays on formulations. The major exception in the study by Wan et al. 1988. For this study, results on hexazinone formulations are based on measured levels of hexazinone in water – i.e., mg a.i./L]

Organism	Exposure	Effects	Reference
Salmon, Pink	96-hour exposure to Pronone 10G (10% Hex/kg granular product)	24-hour LC_{50} = 1760 mg a.i./L 48-hour LC_{50} = 1621 mg a.i./L 72-hour LC_{50} = 1559 mg a.i./L 96-hour LC_{50} = 1408 mg a.i./L LC_{50} change (24-96 hours) = 20%	Wan et al. 1988 [1]
Salmon, Pink	96-hour exposure to hexazinone (95% Hex)	24-hour LC_{50} = 309 mg/L 48-hour LC_{50} = 280 mg/L 72-hour LC_{50} = 280 mg/L 96-hour LC_{50} = 236 mg/L LC_{50} change (24-96 hours) = 24%	Wan et al. 1988
Salmon, Pink	96-hour exposure to Velpar® L (25% Hex/L liquid product)	24-hour LC_{50} = 978 mg a.i./L 48-hour LC_{50} = 839 mg a.i./L 72-hour LC_{50} = 728 mg a.i./L 96-hour LC_{50} = 676 mg a.i./L LC_{50} change (24-96 hours) = 31%	Wan et al. 1988 [1]
Rainbow trout (*Salmo gairdneri*)	96-hour exposure to Velpar L (25%). Concentrations of 58, 82, 120, 170, 240, 340, 490, 700, and 1000 mg/L. All concentration expressed as formulation. No aeration.	24-hour LC_{50} = not calculated due to insufficient mortality 48-hour LC_{50} = 1000 (850-22000) mg/L 72-hour LC_{50} = 850 (690 - 1300) mg/L 96-hour LC_{50} = 610 (490 - 730) mg/L No mortality at 58 mg/L, 120 mg/L or 170 mg/L. 1/10 mortality at 82 mg/L. All LC_{50} values expressed as formulation.	Hutton 1989b, MRID 41235002

Appendix 9: Toxicity of hexazinone to fish and amphibians (sort within groups by species and author) [Unless otherwise noted, all concentrations are expressed a mg a.i./L for assays on hexazinone and as mg formulation/L for assays on formulations. The major exception in the study by Wan et al. 1988. For this study, results on hexazinone formulations are based on measured levels of hexazinone in water – i.e., mg a.i./L]

Organism	Exposure	Effects	Reference
Rainbow trout	96 hour exposure with aeration to hexazinone concentrations of 0, 200, 250, 300, 350, 400, 450, or 500 mg/L.	96-hour LC_{50} = 322 mg/L All fish died within 24 hours at concentrations of 450 mg/L or higher. No mortality at concentrations of 250 mg/L over the 96-hour period.	Okolimna 1980b, MRID 00076961
Rainbow trout	Hexazinone, t.g.a..i., static conditions	24-h LC_{50}: 401 (326-492) mg/L 48-h LC_{50}: 388 (307-490) mg/L 96-h LC_{50}: >320 but <420 mg/L NOEC: 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	Sleight 1973, MRID 00104980 Also summarized in Kennedy 1984
Rainbow trout	96-hour exposure to hexazinone (95% Hex)	24-hour LC_{50} = 320 mg a.i./L 48-hour LC_{50} = 286 mg a.i./L 72-hour LC_{50} = 271 mg a.i./L 96-hour LC_{50} = 257 mg a.i./L LC_{50} change (24-96 hours) = 20%	Wan et al. 1988 [1]
Rainbow trout	96-hour exposure to Pronone 10G (10% granular product)	24-hour LC_{50} = 2513 mg a.i./L 48-hour LC_{50} = 2084 mg a.i./L 72-hour LC_{50} = 2043 mg a.i./L 96-hour LC_{50} = 1964 mg a.i./L LC_{50} change (24-96 hours) = 22%	Wan et al. 1988 [1]
Rainbow trout	96-hour exposure to Velpar® L (25% liquid product)	24-hour LC_{50} = 962 mg a.i./L 48-hour LC_{50} = 889 mg a.i./L 72-hour LC_{50} = 875 mg a.i./L 96-hour LC_{50} = 872 mg a.i./L LC_{50} change (24-96 hours) = 10%	Wan et al. 1988 [1]

Appendix 9: Toxicity of hexazinone to fish and amphibians (sort within groups by species and author) [Unless otherwise noted, all concentrations are expressed a mg a.i./L for assays on hexazinone and as mg formulation/L for assays on formulations. The major exception in the study by Wan et al. 1988. For this study, results on hexazinone formulations are based on measured levels of hexazinone in water – i.e., mg a.i./L]

Organism	Exposure	Effects	Reference
Rainbow trout	96-hour exposure to Carrier P (Pronone 10G carrier)	24-hour LC_{50} = >2000 mg carrier/L 48-hour LC_{50} = >2000 mg carrier/L 72-hour LC_{50} = >2000 mg carrier/L 96-hour LC_{50} = >2000 mg carrier/L LC_{50} 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 LC_{50} = 4330 mg carrier/L 48-hour LC_{50} = 4330 mg carrier/L 72-hour LC_{50} = 4330 mg carrier/L 96-hour LC_{50} = 4330 mg carrier/L LC_{50} change (24-96 hours) = 0%	Wan et al. 1988
Sockeye salmon	96-hour exposure to hexazinone (95% Hex)	24-hour LC_{50} = 363 mg/L 48-hour LC_{50} = 332 mg/L 72-hour LC_{50} = 318 mg/L 96-hour LC_{50} = 317 mg/L LC_{50} change (24-96 hours) = 13%	Wan et al. 1988
Sockeye salmon	96-hour exposure to Velpar® L (25% Hex/L liquid product)	24-hour LC_{50} = 1167 mg a.i./L 48-hour LC_{50} = 974 mg a.i./L 72-hour LC_{50} = 927 mg a.i./L 96-hour LC_{50} = 925 mg a.i./L LC_{50} change (24-96 hours) = 20%	Wan et al. 1988 [1]

Appendix 9: Toxicity of hexazinone to fish and amphibians (sort within groups by species and author) [Unless otherwise noted, all concentrations are expressed a mg a.i./L for assays on hexazinone and as mg formulation/L for assays on formulations. The major exception in the study by Wan et al. 1988. For this study, results on hexazinone formulations are based on measured levels of hexazinone in water – i.e., mg a.i./L]

Organism	Exposure	Effects	Reference
FISH - Longer-term			
Fathead minnow	eggs and fry study, t.g.a.i. hexazinone, Concentrations of 0, 9.3, 17, 35.5, 74.5, 150, and 308 mg/L	NOEC of 17 mg/L. Higher concentrations resulted in decreased numbers of normal hatchlings and decreased survival of hatchlings.	Pierson 1990a, MRID 41406001
Bluegill sunfish	0.1 and 1.0 mg/L ^{14}C-hexazinone for 4 weeks. Note: Rhodes specifies that the term *carcass* refers to the fillet or edible portion.	No signs of toxicity over 4 week exposure periods. BCF first reported for Day 3: 1 for carcass, 1.3 for liver, and 2 for viscera. Maximum BCF at 14 days: 2.1 for carcass, 5 for liver, and 5.5 for viscera.	Rhodes 1974, MRID 00064265
AMPHIBIANS			
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

[1] All concentrations reported by Wan et al. 1988 that involve hexazinone or hexazinone formulations are based on measured levels of hexazinone in water – i.e., mg a.i./L. Aeration prior to placing fish in test water but aeration during the bioassays does not appear to have been conducted.

Appendix 10: Toxicity of hexazinone to aquatic invertebrates

Organism	Exposure	Effects	Reference
ACUTE			
Daphnia magna	Hexazinone (95%). Concentrations of 0, 1, 10, 50, 100, 150, 175, 200, 225, 250, and 300 mg/L for 48 hours.	No mortality in controls (0/20). Mortality rates of 4%, 0%, and 4% at 1, 10, 50 mg/L respectively. Concentration related increases in mortality at higher concentrations. 48-h LC_{50}: 151.6 (125.2-172.8) mg/L	Schneider 1976b, MRID 00116269 Also summarized in Kennedy 1984
Daphnia magna	Velpar L (25% a.i.), Concentrations of 0, 82, 120, 170, 240, 340, 490, 700, 1000 mg/L as formulation for 48-hours. Static.	48-hour LC_{50} = 400 (320-500) mg formulation/L [equivalent to 110 (83-130) mg a.i./L] No mortality at lowest concentration, 82 mg/L (20.5 mg a.i./L).	Hutton 1989c, MRID 41235003
13 species of stream macro-invertebrates	Velpar L (25% a.i.) at a single concentration for each species that varied from 70 mg a.i./L to 80 mg a.i./L. Exposures in an artificial stream channel lasted for 1 hour. Observation period of 48 hours.	Mortality rates of 0% in 8 of 13 species. The highest mortality rates (corrected for control responses) were 14% and this was seen in two species of Ephemeroptera, an *Isonychia* sp and *Epeorus vitrea*.	Kreutzweiser et al. 1992
Eastern oysters (embryos)	48-hour exposure in natural sea water containing 0, 100, 180, 320, 560, and 1000 mg/L hexazinone; pH 8 (±0.05); salinity 21%	No effects on embryos at concentrations up to and including 320 mg/L. No normally developed animals were observed after exposure to 560 or 1000 mg/L. NOEC: 320 mg/L	Heitmuller 1976, MRID 00047164 (also summarized in Kennedy 1984)

Appendix 10: Toxicity of hexazinone to aquatic invertebrates

Organism	Exposure	Effects	Reference
Grass shrimp	96-hour exposure in natural sea water containing 0, 100, 180, 320, 560 mg/L hexazinone; pH 8 (±0.05); salinity 22%; temperature 19 (±1)°C	No mortality at 56 mg/L 24-hour LC50 = 241 (±95-607) mg/L; 48-hour LC50 = 94 (±50-176) mg/L; At 96 hours, all organisms died at concentrations of 100 mg/L or higher. No organism died at 56 mg/L.	Heitmuller 1976, MRID 00047164 (also summarized in Kennedy 1984)
Fiddler crabs	96-hour exposure in natural sea water at hexazinone concentrations of 0, 10, 100, 500, or 1000 mg/L.; pH 8 (±0.05); salinity 26%; temperature 19 (±1)°C	No mortality at any concentrations.	Heitmuller 1976, MRID 00047164 (also summarized in Kennedy 1984)

Appendix 10: Toxicity of hexazinone to aquatic invertebrates

Organism	Exposure	Effects	Reference
REPRODUCTION STUDIES			
Daphnia magna	Measured concentrations hexazinone (>98% purity) of 0, 4.3, 12, 29, 81, 210 and 500 mg/L for 21 days	Significant reduction in the number of offspring produced and the length of the offspring at 81 mg/L and 210 mg/L. NOEC of 29 mg/L.	Pierson 1990b, MRID 41406002
Daphnia magna	21 day exposure to hexazinone (89.3%) at nominal concentrations of 0.01, 0.1 1, 5, 10, 20, and 30 mg/L.	LC_{50} of 33.1 (28.1-36.9) mg/L. Reproductive impairment seen only at the highest concentration, 30 mg/L. Delay in time to reproduction at 5 mg/L and 10 mg/L but no change in number of offspring produced.	Schneider 1977, MRID 00114038

Appendix 11: Toxicity of hexazinone to algae and macrophytes

Organism	Chemical	Effects	Reference
Algae			
Anabaena flos-aquae (Lyng) (blue-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	Hexazinone (98%) at concentrations of 0, 0.7, 0.9, 1.2, 1.5, and 2 mg/L. 2.014 mg/L for 3 days	EC_{50} values based on decrease of chlorophyll (a) 3-Day: 2.014 mg/L 5-Day: 2.375 mg/L 7-Day: 2.752 mg/L	Abou-Waly et al. 1991

Appendix 11: Toxicity of hexazinone to algae and macrophytes

Organism	Chemical	Effects	Reference
Anabaena flos-aquae	Hexazinone (reported purity of 100.1%) concentrations of 0.15, 0.29, 0.66, 1.4, and 3.1 mg/L for 5 days.	5-Day: EC_{25} of 0.16 (0.02-0.24) mg/L **5-Day NOEC for cell density of 0.15 mg/L.** **Least sensitive species**	Thompson 1994, MRID 43302701

Note on Thompson 1994: Details of the calculation of the EC_x values are given only as: "linear interpolation of the initial measured test concentrations against measured parameter". Additional details are not provided. The NOEC is virtually identical to the EC_{25} because the dose-response is flat at 0.29 mg/L – i.e., the cell is essentially identical to the controls – and very steep at 0.66 mg/L – the cell density is much less than the controls.

Selenastrum capricornutum (green alga)	Hexazinone (98%) at concentrations of 0, 0.7, 0.9, 1.2, 1.5, and 2 mg/L. 2.014 mg/L for 3 days	EC_{50} values based on decrease of chlorophyll (a) 3-Day: 0.056 mg/L 5-Day: 0.085 mg/L 7-Day: 0.126 mg/L	Abou-Waly et al. 1991b
Selenastrum capricornutum	Hexazinone concentrations of 0.004, 0.008, 0.016, 0.032, and 0.064 mg/L for 5 days.	Endpoints based on cell counts. 24 h-EC_{50}: 0.014 (0.012-0.017) mg/L 5 day-EC_{50}: 0.0068 (0.0063-0.0072) mg/L **5-Day NOEC: 0.004 mg/L.** **Most sensitive species.**	Forbis 1989, MRID 41287001
Selenastrum costatum (Marine algae)	Hexazinone (reported as 100.1% purity) concentrations of 0.0041, 0.0069, 0.013, 0.025, 0.039, and 0.073 mg/L for 5 days.	NOEC for all endpoints: 0.0041 mg/L. EC_{25} for cell density (most sensitive endpoint) of 0.025 mg/L.	Baer 1994a, MRID 43225102 Baer 1994b, MRID 434000401

Appendix 11: Toxicity of hexazinone to algae and macrophytes

Organism	Chemical	Effects	Reference
Navicula pelliculosa (freshwater diatom)	Hexazinone (reported purity of 100.1%) concentrations of 2.8, 3.5, 12, 23, and 46 ug/L for 5 days.	NOEC for cell density of 0.0035 mg/L with an EC_{25} of 0.0076 (0.0052-0.01) mg/L	Thompson 1994, MRID 43302701
Periphyton (spp. not identified) colonized in the field	- Laboratory study - Periphyton exposed to 0, 0.4, 2, 10, and 50 µg/L hexazinone (grade not given) for 1 hr and 24 hrs - Incubated at 16°C and light intensity 250 $\mu Em^{-2}s^{-1}$ - Photosynthetic activity measured by assimilation of ^{14}C for 1 hr at end of exposure period	- After 1 hr exposure, photosynthesis was stimulated compared to controls (statistical significance not given) at 0.0004, 0.002, and 0.010 mg/L hexazinone and inhibited at 0.050 mg/L; NEC and EC_{50} could not be determined - After 24 hr exposure, no stimulating effect was observed; NEC = 0.00229 mg/L and EC_{50} = 0.033 mg/L hexazinone	Gustavson et al. 2003
Dinoflagellates in coral *Seriatopora hystrix*	Laboratory study comparing several different herbicides at concentrations of <1 ppb to 1000 ppb.	Approximate EC_{50} for hexazinone (read from Figure 1, p. 153) is 0.009 mg/L.	Jones and Kerswell 2003

Appendix 11: Toxicity of hexazinone to algae and macrophytes

Organism	Chemical	Effects	Reference
Diatoms *Cyclotella meneghiana* and *Nitzschia sp.*; Green algae *Scenedesmus quadricauda* and *Selenastrum capricornutum;* Cyanobacteria *Microcystis aeruginosa, Pseudoanabaena sp., Oscillatoria sp., Aphanizomenon flos-aquae,* and *Anabaena inaequalis* - All species from established laboratory cultures	- Laboratory study - 2.867 mg/L hexazinone (grade not given) in ASTM Type 1 water added to algae in test medium - Controls were algae in test medium and distilled water - Incubated for 6 hrs. with hexazinone, ^{14}C added, then incubated another 16 hrs (temp not given) - ^{14}C uptake determined as measure of growth	- Hexazinone caused >75 % inhibition of growth, (significantly different from controls) as measured by i n all test species except the nitrogen-fixing cyanobacterium *A. inaequalis*, which had 58% inhibition of growth	Peterson et al. 1994

Appendix 11: Toxicity of hexazinone to algae and macrophytes

Organism	Chemical	Effects	Reference
Diatoms *C. meneghiana* and *Nitzschia sp.*; Green algae *S. quadricauda* and *S. capricornutum;* Cyanobacteria *M. aeruginosa, Pseudoanabaena sp., Oscillatoria sp., A. flos-aquae,* and *A. inaequalis;* - All species from established laboratory cultures	- Laboratory study - 0, 0.0014, 0.014, 0.143, 1.433, and 2.867 mg/l hexazinone (98% technical a.i.) in ASTM Type I water added to algae in medium - Incubated 6 hrs with hexazinone, then ^{14}C added and incubation continued another 16 hrs -Diatoms incubated at 15°C, algae and cyanobacteria at 25°C; both at light intensity of 75µEcm^{-2}s^{-1}	- At concentrations <2.867 mg/l hexazinone, inhibition of ^{14}C uptake was >90% (relative to controls, statistical significance not given) in 8/10 algae species - Green algae most sensitive to hexazinone; ^{14}C uptake was inhibited by over 10% at the lowest test concentration of 0.0014 mg/l hexazinone - Cyanobacteria least sensitive to hexazinone; slight inhibition or stimulation at < 0.014 mg/l hexazinone (data not given) - Mean concentrations at which 50% inhibition of ^{14}C uptake occurred were calculated from regression equations: EC_{50}= 0.01(green algae), 0.05 (diatoms), and 0.06 (cyanobacteria) mg/l hexazinone.	Peterson et al. 1997
Selenastrum capricornutum	24.5 (±14.5-33.1) µg/L for 96 hours	EC_{50}	St-Laurent et al. 1992

Appendix 11: Toxicity of hexazinone to algae and macrophytes

Organism	Chemical	Effects	Reference
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} **Lowest reported 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
Phytoplankton community	Velpar 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	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

Appendix 11: Toxicity of hexazinone to algae and macrophytes

Organism	Chemical	Effects	Reference
Periphyton, mixed	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 0.145-0.432 mg/L. Periphyton chlorophyll-a-specific productivity decreased by 80% during the addition of hexazinone , but returned to normal within 24 hours. The 4-hour EC_{50} value for chlorophyll-a-specific productivity was 0.0036 mg/L, which is lower than published bioassay results for single species.	Schneider et al. 1995
Selenastrum capricornutum	24.5 (SD = 3) µg/L Velpar L (25% a.i.) for 4 days; mode of action was apparently through blockage of photosynthesis	EC_{50}: 0.0245 mg formulation/L or 0.0061 mg a.i./L	Williamson 1988
Selenastrum capricornutum	22.5 (±15.91-31.50) µg/L Velpar L (25% a.i.) for 18 days	EC_{50}: 0.0225 mg formulation/L or 0.0056 mg a.i./L	Williamson 1988

Appendix 11: Toxicity of hexazinone to algae and macrophytes

Organism	Chemical	Effects	Reference
Macrophytes			
Duckweed *Lemna minor*, obtained from pond in Saskatoon, Saskatchewan, Canada	- 2.867 mg/L hexazinone (grade not given) in ASTM Type 1 water or distilled water (as control) added to single plant (three mature leaves) in medium and distilled water -Exposure lasted 7 days - Growth measured by counting leaves	- Hexazinone caused 100% growth inhibition (significantly different from controls)	Peterson et al. 1994
Duckweed *Lemna minor*, obtained from pond in Saskatoon, Saskatchewan, Canada	0, 0.0014, 0.014, 0.143, 1.433, and 2.867 mg/l Hexazinone (98% technical a.i.) in ASTM Type I water added to single plant (three mature leaves) in medium and ASTM Type I water -Exposure lasted 7 days -Growth measured by counting leaves	Hexazinone caused 80% growth inhibition at 0.143 mg/l (as relative to controls; statistical significance not given) Mean concentration at which 50% inhibition of growth occurred was calculated from regression equation; EC_{50}= 0.07 mg/l hexazinone. An NOEC is not reported. Based on Figure 3a (p. 128), the NOEC appears to be about 0.012 mg/L.	Peterson et al. 1997

Appendix 11: Toxicity of hexazinone to algae and macrophytes

Organism	Chemical	Effects	Reference
Duckweed *Lemna gibba*, USDA culture	Hexazinone concentrations (reported as 100.2% purity) of 0.026, 0.042, 0.057, 0.072, and 0.088 mg/L with exposure period of 14 days.	Frond Count: NOEC <0.026 mg/L, EC_{25} of 0.027 (0.023-0.030) mg/L. Biomass: NOEC <0.026 mg/L, EC_{25} of 0.033 (0.029-0.036) mg/L. At lowest concentration, 0.026 mg/L, frond count was reduced by about 26% and biomass was reduced by about 14%.	Kannuck and Sloman 1994, MRID 43225101

Appendix 12: GLEAMS Modeling to Approximate Granular Applications of Hexazinone

See Section 3.2.3.4.3 for discussion. The numbering used in these tables corresponds to the numbering used in the tables incorporated in the body of the risk assessment.

Table 3-6: Summary of modeled concentrations in streams (all units are ug/L or ppb per lb/acre applied) [**Strm01**]

Annual Rainfall (inches)	Clay		Loam		Sand	
	Average	Maximum	Average	Maximum	Average	Maximum
5	0	0	0	0	0	0
10	0	0	0	0	0	0
15	0.329	31.5	0	0	0.02	0.958
20	0.563	67.9	2.62E-07	3.19E-05	0.333	7.16
25	0.76	107	0.00938	0.478	0.793	11.8
50	1.27	268	0.413	6.33	1.98	41.4
100	1.4	435	0.887	24	2.14	67.3
150	1.28	418	0.891	22.9	1.79	76.4
200	1.14	373	0.821	18.4	1.5	78.9
250	1.02	334	0.745	14.8	1.28	78.4

Table 3-7: Summary of modeled concentrations in ponds (all units are ug/L or ppb per lb/acre applied) **[Pond01]**

Annual Rainfall (inches)	Clay		Loam		Sand	
	Average	Maximum	Average	Maximum	Average	Maximum
5	0	0	0	0	0	0
10	0	0	0	0	0	0
15	26.5	41.3	0	0	0.47	2.21
20	27.5	68.2	3.35E-06	1.53E-05	8.28	15.2
25	28.2	92.5	0.0567	0.416	17.2	25.1
50	27.9	182	4.06	6.68	31.6	46.9
100	24.2	329	8.55	10.8	27.1	64.5
150	20.5	344	8.32	13.4	22	69.1
200	17.7	325	7.44	13.1	18.4	70.1
250	15.5	302	6.58	11.8	15.8	69.2

Table 4-2: Summary of modeled concentrations in the entire 60 inch soil column (all units are mg/kg soil or ppm per lb/acre applied)**[Soil]**

Annual Rainfall (inches)	Clay		Loam		Sand	
	Average	Maximum	Average	Maximum	Average	Maximum
5	0.0291	0.0618	0.0244	0.0535	0.0252	0.0542
10	0.0323	0.0648	0.0286	0.058	0.0269	0.0556
15	0.03	0.0636	0.0275	0.0568	0.0291	0.0593
20	0.0295	0.0638	0.0286	0.0586	0.0305	0.0605
25	0.0288	0.0638	0.0299	0.0608	0.0296	0.0589
50	0.026	0.0641	0.0325	0.0627	0.0209	0.0471
100	0.0211	0.0631	0.0276	0.0554	0.0121	0.046
150	0.0174	0.0613	0.024	0.0502	0.00834	0.0458
200	0.0148	0.0599	0.0219	0.0479	0.00636	0.0458
250	0.0128	0.0589	0.0205	0.0469	0.00518	0.0458

Table 4-3: Summary of modeled concentrations in the top 12 inches of the soil column (all units are mg/kg soil or ppm per lb/acre applied)**[Soil12]**

Annual Rainfall (inches)	Clay		Loam		Sand	
	Average	Maximum	Average	Maximum	Average	Maximum
5	0.146	0.309	0.122	0.268	0.126	0.271
10	0.161	0.324	0.143	0.29	0.135	0.278
15	0.149	0.316	0.132	0.276	0.114	0.256
20	0.143	0.313	0.122	0.264	0.0893	0.237
25	0.137	0.309	0.111	0.254	0.0722	0.231
50	0.112	0.297	0.0735	0.232	0.0357	0.229
100	0.0825	0.284	0.0451	0.229	0.0171	0.229
150	0.0661	0.278	0.0351	0.229	0.0113	0.229
200	0.0553	0.275	0.0302	0.229	0.00851	0.229
250	0.0475	0.272	0.0273	0.229	0.00693	0.229

Table 4-4: Summary of modeled maximum depth of chemical in the soil column and days to maximum ()**[SoilMaxDepth]**

Annual Rainfall (inches)	Clay		Loam		Sand	
	Depth	Julian Day	Depth	Julian Day	Depth	Julian Day
5	6.5	1991181	6.5	1991181	6.5	1991181
10	6.5	1991181	6.5	1991181	6.5	1991181
15	24	1994004	36	1993001	60	1992361
20	24	1992002	54	1994071	60	1991321
25	24	1991294	60	1993021	60	1991251
50	36	1995004	60	1991271	60	1991181
100	36	1993003	60	1991201	60	1991181
150	42	1995004	60	1991181	60	1991181
200	42	1995004	60	1991181	60	1991181
250	42	1995005	60	1991181	60	1991181

Table 4-5: Summary of the cumulative loss from soil runoff and sediment as a proportion of the application rate **[PropRunoSed]**

Annual Rainfall (inches)	Clay	Loam	Sand
5	0	0	0
10	0	0	0
15	0.0546	0	0
20	0.0975	0	0
25	0.138	0	0
50	0.293	0.00032	0
100	0.488	0.0176	0
150	0.603	0.0262	0
200	0.679	0.0294	0
250	0.733	0.0306	4.49E-05

Appendix 13: GLEAMS Modeling with Negligible Degradation to Simulate Exposures to Total Hexazinone Metabolites

See Section 3.2.3.4.3 for discussion. The numbering used in these tables corresponds to the numbering used in the tables incorporated in the body of the risk assessment.

Table 3-6: Summary of modeled concentrations in streams (all units are ug/L or ppb per lb/acre applied) [**Strm01**]

Annual Rainfall (inches)	Clay		Loam		Sand	
	Average	Maximum	Average	Maximum	Average	Maximum
5	0	0	0	0	0	0
10	0	0	0	0	0	0
15	0.369	29.6	9.56E-08	2.05E-05	0.807	32
20	0.586	63.3	0.0376	2.6	3.14	73.9
25	0.764	99.5	0.353	16.1	3.89	62.3
50	1.21	249	2.35	40.2	3.74	75.4
100	1.31	404	2.19	32.9	2.82	88.3
150	1.21	388	1.74	27.1	2.13	91
200	1.08	347	1.43	24.8	1.7	89.1
250	0.961	310	1.22	22.7	1.41	86.4

Table 3-7: Summary of modeled concentrations in ponds (all units are ug/L or ppb per lb/acre applied) **[Pond01]**

Annual Rainfall (inches)	Clay		Loam		Sand	
	Average	Maximum	Average	Maximum	Average	Maximum
5	0	0	0	0	0	0
10	0	0	0	0	0	0
15	41.8	48.1	6.16E-07	1.43E-05	24.1	113
20	39.7	67.9	0.329	2.79	92.3	224
25	39.1	90.1	3.39	18.3	109	194
50	35.7	172	26.9	59.7	83.2	97.9
100	29.5	305	26.3	37.1	49.5	89.1
150	24.7	320	20.7	25.9	35.7	85
200	21.1	302	16.8	19.9	28.1	81.7
250	18.5	280	14.1	16.5	23.3	78.1

Table 4-2: Summary of modeled concentrations in the entire 60 inch soil column (all units are mg/kg soil or ppm per lb/acre applied)**[Soil]**

Annual Rainfall (inches)	Clay		Loam		Sand	
	Average	Maximum	Average	Maximum	Average	Maximum
5	0.129	0.231	0.121	0.216	0.121	0.216
10	0.13	0.232	0.122	0.218	0.121	0.216
15	0.122	0.22	0.121	0.217	0.117	0.202
20	0.117	0.211	0.122	0.218	0.088	0.129
25	0.112	0.204	0.12	0.211	0.0657	0.0937
50	0.0945	0.173	0.0835	0.121	0.0287	0.0474
100	0.0718	0.129	0.0486	0.0707	0.0136	0.0452
150	0.0579	0.107	0.0374	0.0556	0.00877	0.0449
200	0.0483	0.0932	0.0321	0.0498	0.00648	0.0442
250	0.0411	0.083	0.0289	0.0475	0.00518	0.0433

Table 4-3: Summary of modeled concentrations in the top 12 inches of the soil column (all units are mg/kg soil or ppm per lb/acre applied)**[Soil12]**

Annual Rainfall (inches)	Clay		Loam		Sand	
	Average	Maximum	Average	Maximum	Average	Maximum
5	0.646	1.15	0.604	1.08	0.605	1.08
10	0.649	1.16	0.609	1.09	0.605	1.08
15	0.58	1.02	0.477	0.777	0.211	0.334
20	0.503	0.855	0.329	0.5	0.114	0.242
25	0.44	0.733	0.244	0.374	0.0779	0.226
50	0.283	0.458	0.105	0.237	0.0303	0.206
100	0.177	0.277	0.0544	0.218	0.0136	0.17
150	0.134	0.225	0.0405	0.213	0.00888	0.142
200	0.108	0.204	0.0341	0.209	0.00663	0.121
250	0.091	0.191	0.0304	0.206	0.00535	0.116

Table 4-4: Summary of modeled maximum depth of chemical in the soil column and days to maximum **[SoilMaxDepth]**

Annual Rainfall (inches)	Clay		Loam		Sand	
	Depth	Julian Day	Depth	Julian Day	Depth	Julian Day
5	6.5	1991181	6.5	1991181	6.5	1991181
10	6.5	1991181	6.5	1991181	6.5	1991181
15	30	1994004	54	1995001	60	1992101
20	36	1994312	60	1993121	60	1991271
25	42	1995003	60	1992201	60	1991221
50	54	1995005	60	1991261	60	1991181
100	60	1995004	60	1991191	60	1991181
150	60	1994299	60	1991181	60	1991181
200	60	1994299	60	1991181	60	1991181
250	60	1994339	60	1991181	60	1991181

Table 4-5: Summary of the cumulative loss from soil runoff and sediment as a proportion of the application rate **[PropRunoSed]**

Annual Rainfall (inches)	Clay	Loam	Sand
5	0	0	0
10	0	0	0
15	0.0612	0	0
20	0.101	0	0
25	0.139	0	0
50	0.28	0.000156	0
100	0.455	0.00465	0
150	0.561	0.00437	0
200	0.631	0.00343	0
250	0.681	0.00269	0