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Control/Eradication Agents for the Gypsy Moth - Risk Comparison – Final Report

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ACRONYMS, ABBREVIATIONS, AND SYMBOLS

a.i.	active ingredient
Ach	acetylcholine
AChE	acetylcholinesterase
AEL	adverse-effect level
APHIS	Animal and Plant Health Inspection Service
ARS	Agricultural Research Station
BCF	bioconcentration factor
B.t.k.	*Bacillus thuringiensis* var. *kurstaki*
BIU	Billions of international units
bw	body weight
4-CA	4-chloroaniline
ChE	pseudo-cholinesterase
CNS	central nervous system
DFB	diflubenzuron
EC_x	concentration causing X% inhibition of a process
EIS	environmental impact statement
FH	Forest Health
FS	Forest Service
FTU	forestry toxic units
HQ	hazard quotient
IRIS	Integrated Risk Information System
IU	international units
kg	kilogram
L	liter
LdNPV	gypsy moth (*Lymantria dispar*) nucleopolyhedrosis virus
lb	pound
LC_{50}	lethal concentration, 50% mortality
LD_{50}	lethal dose, 50% mortality
LD_{95}	lethal dose, 95% mortality
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
MSDS	material safety data sheet
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level

ACRONYMS, ABBREVIATIONS, AND SYMBOLS (*continued*)

NRC	National Research Council
OPP	Office of Pesticide Programs
ORD	Office of Research and Development
OTS	Office of Toxic Substances
PIB	polyhedral inclusion body
ppm	parts per million
PVC	polyvinyl chloride
RfD	reference dose
RQ	risk quotients
UF	uncertainty factor
U.S.	United States
U.S. EPA	U.S. Environmental Protection Agency
USDA	United States Department of Agriculture

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	5/9 (°F-32)
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)	ug/square centimeter (ug/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
1×10^{-10}	0.0000000001	One in ten billion
1×10^{-9}	0.000000001	One in one billion
1×10^{-8}	0.00000001	One in one hundred million
1×10^{-7}	0.0000001	One in ten million
1×10^{-6}	0.000001	One in one million
1×10^{-5}	0.00001	One in one hundred thousand
1×10^{-4}	0.0001	One in ten thousand
1×10^{-3}	0.001	One in one thousand
1×10^{-2}	0.01	One in one hundred
1×10^{-1}	0.1	One in ten
1×10^{0}	1	One
1×10^{1}	10	Ten
1×10^{2}	100	One hundred
1×10^{3}	1,000	One thousand
1×10^{4}	10,000	Ten thousand
1×10^{5}	100,000	One hundred thousand
1×10^{6}	1,000,000	One million
1×10^{7}	10,000,000	Ten million
1×10^{8}	100,000,000	One hundred million
1×10^{9}	1,000,000,000	One billion
1×10^{10}	10,000,000,000	Ten billion

EXECUTIVE SUMMARY

OVERVIEW

The current document provides a comparison of the risks posed by the gypsy moth itself to the risks posed by the different control agents as well as a comparison of risks among the various control agents. The agents used in control programs include *Bacillus thuringiensis* var. *kurstaki* (*B.t.k.*), the gypsy moth nucleopolyhedrosis virus (LdNPV), diflubenzuron, tebufenozide, DDVP, and disparlure.

The gypsy moth itself poses the clearest risks in both the human health and ecological risk assessments. If the gypsy moth is not controlled, population outbreaks will occur and humans will be exposed to large numbers of gypsy moth larvae. If this occurs, a substantial number of individuals will experience skin irritation that is sufficiently severe to warrant medical attention. No more serious effects are likely. Ecologically, the gypsy moth will clearly damage some terrestrial vegetation and may directly affect some other species of moths. Because of the obvious importance of vegetation to the existence and habitat of most animals, defoliation by the gypsy moth will have numerous secondary effects.

Most of the control agents also pose risks and raise concerns, the nature and certainty of which are highly variable. In applications used to control the gypsy moth, *B.t.k.* is associated with irritant effects in humans; however, the severity of these effects appears to be less than those associated with exposure to the gypsy moth itself. The potential for *B.t.k.* to cause more serious human health effects is considered but appears to be remote. *B.t.k.* may also cause adverse effects in nontarget *Lepidoptera*. Concern for this effect is heightened because some of the *Lepidoptera* that may be adversely affected include at least on endangered species. Diflubenzuron does not appear to present any substantial risk to human health, and this assessment encompasses 4-chloroaniline, a potential carcinogen that is formed in the degradation of diflubenzuron. Diflubenzuron, however, is a rather nonspecific insecticide and is likely to impact both terrestrial and aquatic arthropods. Tebufenozide is a somewhat more specific insecticide but is used at higher application rates that may lead to high exposures in some terrestrial mammals. The likelihood of observing adverse effects, however, is unclear. Tebufenozide may also impact some nontarget moths and butterflies but should not adversely affect any aquatic species. Although DDVP is a broad spectrum insecticide and can be highly toxic to humans, adverse human health and ecological effects are not expected under normal conditions of use. If DDVP is improperly handled, exposures could substantially exceed prudent levels. For disparlure, exposure estimates for aquatic invertebrates approach a level of concern. More significantly, there is substantial uncertainty in the risk characterization of disparlure because of the limited acute toxicity data, the lack of chronic toxicity data, and the high likelihood that many species will be exposed to this compound.

Unlike all of the other agents considered in this risk assessment, there is no basis for asserting that the use of LdNPV to control or eradicate gypsy moth populations is likely to cause any adverse effects in any species other than the gypsy moth.

PROGRAM DESCRIPTION

The USDA control programs for the gypsy moth are intended to limit damage to forests that can be substantially impacted by gypsy moth outbreaks. Two biological agents that are pathogenic to the gypsy moth are used in broadcast applications: *B.t.k.* and LdNPV. In addition, three chemical agents are used in broadcast applications: diflubenzuron, tebufenozide, and disparlure. Diflubenzuron and tebufenozide are both insecticides, and, as discussed in subsequent sections of the this document, are quite similar with respect to their toxicological properties. The major difference between the two is that application rates for tebufenozide are higher than those for diflubenzuron and this is a controlling factor in the comparative risk assessment for these two agents. Disparlure is a gypsy moth pheromone that is used in broadcast applications to disrupt mating and in population monitoring programs to attract the male gypsy moth to sampling traps. In the past, disparlure was used in a slow-release flake formulation. DDVP is not used in broadcast applications and is used only as a PVC formulated product in milk carton traps used in mass trapping operations.

The USDA adopted various intervention strategies roughly categorized as suppression, eradication, and slow-the-spread. Suppression programs have relied predominantly on *B.t.k.* and diflubenzuron. Slow-the-Spread programs rely predominantly on the use of disparlure flakes and secondarily on *B.t.k.* applications. Eradication efforts rely predominantly on *B.t.k.* NPV is used in all three strategies but is used on very few acres relative to *B.t.k.*, diflubenzuron, and disparlure flakes.

HUMAN HEALTH RISK ASSESSMENT

Hazard Identification – The gypsy moth, *B.t.k.*, and LdNPV are similar not only because they are biological agents but also because the primary effect associated with each agent is irritation. The gypsy moth causes more pronounced and severe irritation relative to either *B.t.k.* or LdNPV. Of the chemical agents used in gypsy moth control programs, diflubenzuron and tebufenozide are similar to each other in that both cause adverse effects on blood. The risk assessment of diflubenzuron is somewhat more involved than that of tebufenozide because diflubenzuron is degraded to 4-chloroaniline, a compound that is classified as a carcinogen. DDVP and disparlure, the other two chemicals used in gypsy moth control programs, have toxicologic profiles that are very different from each other as well as diflubenzuron or tebufenozide. DDVP is a a well-characterized neurotoxin which was studied extensively in mammals. Disparlure, an insect attractant, was not tested extensively for toxicological effects in mammals.

Exposure Assessment – The exposure assessments of the biological agents differ substantially from those of the chemical agents in terms of how the exposures are expressed. Because of the available exposure and toxicity data, different measures of exposure are used for each of the biological agents – i.e., the gypsy moth, *B.t.k.*, and LdNPV. For the chemical agents, all exposure assessments are based on the amount or concentration of the chemical to which an individual or population might be exposed via ingestion, dermal contact, or inhalation. Differences among the chemical agents are dictated largely by differences in how the chemicals are used and, to a lesser extent, on the available toxicity data.

A very different set of exposure assessments is conducted for each of the biological agents. Both *B.t.k.* and LdNPV may also be applied in broadcast applications and the routes of plausible exposure are the same as those for the chemicals applied in broadcast applications – i.e., oral, dermal, and inhalation. For *B.t.k.*, however, the most directly relevant data used to characterize risk are based on actual applications of *B.t.k.* formulations where exposure is best characterized as an application rate. For the assessment of the potential for serious adverse effects, exposures are measured in colony forming units (cfu). LdNPV differs from all of the other agents in that no clear hazard potential can be identified; consequently, the most meaningful measure of exposure is, in some respects, moot. Those exposures that are quantified in the human health risk assessment for LdNPV are based on the mass of the formulation, Gypchek. Exposures to the gypsy moth itself are based on an indirect measure of exposure, egg masses/acre, because this is the expression of exposure that is used in the dose response assessment.

Differences in the exposure assessments among the chemicals used in USDA programs primarily reflect differences in how the chemicals are applied, what routes of exposure are most substantial, and the nature of the toxicity data. Diflubenzuron, tebufenozide, and disparlure may be applied in aerial broadcast applications and multiple routes of exposure (oral, dermal, and inhalation) are plausible. No chronic exposures for disparlure are conducted, however, because no chronic toxicity data are available on this chemical. DDVP, on the other hand, is used only in milk carton traps and exposures will be minimal under normal conditions, although much higher exposures are possible if the traps are not assembled properly or if individuals tamper with the traps.

Dose-Response Assessment – Dose-response assessments are typically based on an RfD, an estimate of a dose or exposure that is not likely to induce substantial adverse effects in humans. The RfD, in turn, is typically based on a NOAEL (no observed adverse effect level) divided by an uncertainty factor. Risk is then characterized as a hazard quotient (HQ), which is the estimated level of exposure divided by the RfD. If the HQ is below unity—i.e., the exposure is less than the RfD —there is no credible risk. If the HQ is above unity, risk is characterized based on dose-response or dose-severity relationships. The quality of the dose-response assessment depends on the quality of the individual studies, the relevance of the studies to potential human exposures, and the strength of the dose-response relationship.

As in the exposure assessments, the dose-response assessments for the biological agents differ substantially from each other as well as from those of the chemical agents. The dose-response assessment for the gypsy moth itself is based on only a single study; however, the study involves two human populations and demonstrates a clear dose-response relationship. Thus, confidence in the dose-response assessment is high. Two endpoints are considered for *B.t.k.*, irritant effects and more serious toxic effects. While the irritant effects are well documented, there is no apparent dose-response relationship and confidence in the dose-response assessment is classified as medium. The dose-response assessment for more serious effects is based on a single study on mice involving intratracheal exposures. While a clear dose-response relationship is apparent, confidence in the dose-response assessment is low because intratracheal exposures have marginal

(if any) relevance to human exposures, the response was not independently replicated, and the observed response might be an artifact. For LdNPV, no endpoint of concern can be identified. Although the individual studies conducted on LdNPV are somewhat dated, the weight of evidence for LdNPV as well as other similar viruses clearly indicates that no systemic effects in humans are anticipated. Thus, confidence in the dose-response assessment for LdNPV is classified as high.

Following standard practices in USDA risk assessments, risk assessment values available from U.S. EPA are adopted directly unless there is a compelling basis for doing otherwise. This approach is taken because the U.S. EPA will typically devote substantial resources and expertise to the development of risk assessment values and it is not feasible to duplicate this effort in risk assessments prepared for the USDA. In addition, the U.S. EPA has the legislative mandate to develop risk values for pesticides and it is sensible for the USDA to administratively defer to U.S. EPA in this area. When risk values are not available from U.S. EPA, the methods used by U.S. EPA are employed to derive surrogate values. Except for disparlure, chronic RfD values are available from U.S. EPA and these values are used directly. For 4-chloroaniline, the U.S. EPA also derived a cancer potency factor as well as a chronic RfD and these values are used directly in the risk assessment. For DDVP, the U.S. EPA derived an acute RfD, and this value is also adopted in the current risk assessment. A complication with DDVP, however, is that this agent is contained within a PVC strip, which substantially impacts the bioavailability of DDVP. In order to consider this detail quantitatively, a single and somewhat marginal study on the toxicity of DDVP in a PVC strip is used, and confidence in this dose-response assessment is, in turn, marginal. Unlike all of the other chemicals considered in this comparative risk assessment, very little toxicity data are available on disparlure. The U.S. EPA did not derive an RfD for this chemical, and the toxicity data available on disparlure are insufficient to derive a surrogate RfD. Thus, confidence in the dose-response assessment for disparlure is marginal.

Risk Characterization – Of the agents considered in this risk assessment, the gypsy moth and DDVP are clearly agents of marked concern, although the nature of the concerns is different. If the gypsy moth is not controlled, population outbreaks will occur and humans will be exposed to large numbers of gypsy moth larvae. If this occurs, a substantial number of individuals will experience irritant effects that are sufficiently severe to cause these individuals to seek medical attention. No more serious effects are likely. For DDVP, the potential for risk is clear but the likelihood of observing risk seems to be remote. Under normal conditions and proper handling, levels of exposure to DDVP will be negligible and risk will be inconsequential. Workers who mishandle a DDVP-PVC strip and/or members of the general public who handle a DDVP-PVC strip may be exposed to levels of DDVP that are far above acceptable levels. While such exposures are clearly to be avoided, they are not likely to cause frank signs of toxicity. This conclusion is consistent with human experience in the use of DDVP resin strips.

Diflubenzuron and tebufenozide are agents of marginal concern. Under most foreseeable conditions of exposure—i.e., exposure scenarios that might be characterized as typical—exposure levels will be far below levels of concern. At the upper ranges of plausible

exposure – levels that might be characterized as extreme— the hazard quotients for diflubenzuron approach a level of concern (HQs between 0.1 and 0.5 for both diflubenzuron and its 4-chloroaniline metabolite). For tebufenozide, the highest hazard quotient is 1.5, which is characterized as undesirable; however, exposure is not likely to cause overt signs of toxicity. The somewhat higher hazard quotients for tebufenozide, compared with those of diflubenzuron, are due solely to higher application rates.

Among the agents of minimal concern, *B.t.k.* is somewhat problematic. Based on the risk for serious adverse effects, there is clearly no cause for concern (the highest HQ is 0.04). As detailed in the dose-response assessment, this lack of concern is reenforced by a very aggressive and protective interpretation of the available toxicity data. Nonetheless, there is some residual concern with irritant effects. These effects are quite plausible in accidental cases of gross over-exposure – e.g., splashing a formulation into the eye. These kinds of concern are minimal and are common to almost all chemical or biological agents. The more troubling concern involves studies of workers and non-workers who report irritant effects, primarily throat irritation. Whether or not these effects should be attributed to the *B.t.k.* exposure is unclear.

The risk characterization for LdNPV and disparlure is unequivocal. Based on the available information, there is no basis for asserting that any serious adverse effects are plausible. Again, various accidental exposures, including splashing the agent into the eyes, could cause transient irritant effects.

ECOLOGICAL RISK ASSESSMENT

Hazard Identification – Unlike the human health risk assessment, in which the potential effects of the biological agents were similar, the ecological effects profile of each of the biological agents considered in this risk assessment are quite distinct. The gypsy moth will primarily affect sensitive trees, and these effects may be substantial. Because of the obvious importance of vegetation to the existence and habitat quality of most animals, a large number of secondary effects may be produced in many other groups of organisms. There is little indication, however, that the gypsy moth will have marked direct effects on groups of organisms other than sensitive plants. LdNPV, on the other hand, is not likely to have any effect on any species other than the gypsy moth. *B.t.k.* is toxic to nontarget *Lepidoptera* as well as the gypsy moth and some other lepidopteran species. There is very little indication that direct effects on other groups of organisms are plausible. Thus, the potential effects of all of the biological agents are considered relatively specific, with LdNPV showing the greatest degree of specificity (only the gypsy moth), followed by the gypsy moth itself (several types of plants) and *B.t.k.* (several types of *Lepidoptera*).

The chemical agents also differ in specificity: disparlure is most specific, tebufenozide is relatively specific to *Lepidoptera*, diflubenzuron is less specific and may affect many arthropods, and DDVP is a nonspecific biocide toxic to many groups of animals, especially arthropods and vertebrates. As a pheromone, disparlure is almost as specific as LdNPV. It will attract the gypsy moth and two other closely related species, the nun moth (*Lymantria monacha*) and the pink

gypsy moth (*Lymantria fumida*). As with the gypsy moth, both of these *Lymantria* species are forest pests, and adverse effects on these species are not a substantial concern for this risk assessment. In addition, the pink gypsy moth is native to Japan and is not found in the United States. A major qualification with the assessment of the specificity of disparlure is that, as in the human health risk assessment, the information on the toxicity of disparlure to nontarget species is very limited. At least in *Daphnia magna*, a commonly used test species in aquatic toxicity studies, the toxicity of disparlure is relatively high. Both diflubenzuron and tebufenozide are clearly toxic to mammals and at least some arthropods. In mammals, both chemicals will cause adverse effects in blood (methemoglobinemia), as detailed in the human health risk assessment. In both terrestrial and aquatic arthropods, both chemicals will interfere with growth and development. Because of differences in the mechanism of action of diflubenzuron and tebufenozide, tebufenozide appears to be somewhat more selective. Effects in birds have been clearly demonstrated for tebufenozide but not for diflubenzuron. While somewhat speculative, it seems plausible to assert that both diflubenzuron and tebufenozide are likely to affect the blood of birds in a way similar to that seen in mammals. In terms of the mechanism of action, DDVP is a general neurotoxin. In all animals that have nervous systems that involve acetylcholinesterase (AChE) and use acetylcholine (ACh) as a neurotransmitter (a substance necessary to make the nerves work properly), DDVP will be toxic, and sufficiently high exposures to DDVP will be lethal. The definition of *sufficiently high*, however, is critical and variable. Although DDVP is not selective mechanistically, differences in sensitivity among species are substantial. For instance, insects are much more sensitive than mammals or other higher organisms to DDVP exposure. This difference in sensitivity is what characterizes DDVP as an effective insecticide that can be used safely.

Exposure Assessment – Diflubenzuron, tebufenozide, LdNPV, and disparlure may be applied in broadcast applications, which means that the potential for exposure is high and, in many cases, unavoidable. Disparlure, in addition to being used in broadcast applications, is used in traps as an attractant. Under those conditions of use, exposure to disparlure will be variable and primarily incidental. Exposures to the gypsy moth itself also vary, depending on the state of the gypsy moth population—i.e., from low level infestation to outbreak conditions.

Some differences between the human health exposure assessment and the ecological exposure assessment, however, are notable. Table 4-2 does not give a measure of exposure for each agent. This is because the measure of exposure will vary both among agents and among the target groups for each agent. For example, exposures to the gypsy moth are measured as egg masses/acre in the human health risk assessment and this is the same measure of exposure used for terrestrial vegetation. As in the human health risk assessment, egg masses/acre are used as the measure of exposure because this is the primary determinant in the dose-response assessment for plants. For all other species, however, effects from the gypsy moth are likely to be secondary rather than primary. Thus, the exposure assessment for these indirectly affected species is based on defoliation – i.e., the result of the dose-response assessment for terrestrial vegetation is used as the exposure assessment for most other groups of organisms.

Other differences in the exposure assessments for nontarget species are mostly superficial. For each of the chemical agents, the mass of the chemical is typically used as the measure of exposure. Depending on the group, the measure of exposure may be expressed as dose (mg agent/kg bw for most terrestrial species), concentration (mg agent/L of water for aquatic species), or simply as application rate (lb agent/acre). This last measure is used primarily when field studies are the basis for the dose-response assessment.

As in the human health risk assessment, different measures of exposure are used for each of the biological agents. For *B.t.k.*, most of the exposures are characterized simply as an application rate in units of BIU/acre. However, colony forming units are used for some of the mammalian exposure scenarios. Also as in the human health risk assessment, no clear hazard potential is identified for LdNPV. The very few exposure scenarios that are quantified in the ecological risk assessment for LdNPV are based on the mass of the formulation, Gypchek.

The level of detail used in the exposure assessments for the different chemicals reflects both differences in use patterns and the nature of the available toxicity data. Full sets of exposure assessments in several groups of animals are developed for diflubenzuron and tebufenozide. As in the human health risk assessment, the exposure assessment for diflubenzuron is elaborated by the consideration of 4-chloroaniline and the exposure assessment for tebufenozide is elaborated by the consideration of multiple applications.

Disparlure, which also may be applied in aerial broadcast applications, has a much more restricted set of exposure scenarios on far fewer groups of organisms. This difference is due completely to the sparse toxicity data available on this compound. In other words, while a very elaborate set of exposure scenarios could be prepared, these scenarios would serve little purpose because they could not be combined with a dose-response assessment to characterize risk. The exposure assessment for DDVP is also restricted but this restriction is due to the very limited exposures that are plausible because DDVP is used only in milk carton traps and exposures for nontarget species will be minimal under normal conditions.

Dose-Response Assessment – In general, confidence in any dose-response relationship is enhanced if a clear dose-response relationship can be demonstrated and both effect and no-effect exposures have been identified. In the case of LdNPV, however, there is simply no indication that LdNPV or the Gypchek formulation will cause toxicity in any nontarget species at any dose level. All of the risk values for LdNPV are based on no-effect concentrations or doses. While additional studies could be conducted at higher doses and while these studies would enhance confidence in the risk assessment, the NOAEL and NOEC values that have been identified are far above any plausible exposures. Thus, while based on limited data in terms of dose-effect characterization, the dose-response assessment for LdNPV is adequate for risk characterization.

For most of the other agents, the dose-response assessments are reasonably good for the species of greatest concern. Dose-response assessments for DDVP are derived only for mammals, fish, and aquatic invertebrates. This limited approach is taken with DDVP because of the limited use

of DDVP in programs to control the gypsy moth. The DDVP is contained in a PVC strip that is placed in a milk carton trap that includes disparlure as an attractant for the gypsy moth. This type of use limits potential exposure to most nontarget species. A formal dose-response assessment is not conducted for terrestrial invertebrates. This is not due to any lack of data. The toxicity of DDVP to insects and many other invertebrates is very well characterized. DDVP is such a potent insecticide that no formal dose-response assessment is needed. Insects and many other species that enter the trap are likely to be killed by exposure to DDVP.

Disparlure is the other agent for which a full set of dose-response assessments is not developed. As discussed in the hazard identification, this is due to the very limited data that are available on the toxicity of disparlure to nontarget species.

Relatively full dose-response assessments on groups of greatest concern are given for the gypsy moth, *B.t.k.*, diflubenzuron and its 4-chloroaniline metabolite, and tebufenozide. For the gypsy moth, the effect of primary concern is damage to vegetation. While data are available on both lethality in trees as well as defoliation, defoliation is used as the sublethal effect of primary concern. A dose-response assessment is also given for nontarget lepidopterans. While effect and no-effect levels can be identified, the significance of this effect is questionable. In terms of direct effects, terrestrial vegetation is the primary target of concern.

The primary nontarget group of concern for *B.t.k.* involves *Lepidoptera*. A relatively rich set of studies is available in which the sensitivities of nontarget *Lepidoptera* as well as some other insects can be quantified reasonably well based on studies involving exposures that encompass the application rates used to control the gypsy moth. Sensitive nontarget lepidoptera include larvae of the endangered Karner blue butterfly as well as several other types of moths.

Similar types of information are available on diflubenzuron and tebufenozide, and dose-response assessments can be made for the species of primary concern. For both chemicals, this includes nontarget *Lepidoptera* and aquatic invertebrates. Other terrestrial arthropods are also considered for diflubenzuron. In addition, because of the standard tests required by U.S. EPA for the registration of most pesticides, adequate toxicity data are available on mammals, birds, and fish. The toxicity data base for diflubenzuron is somewhat more extensive and sensitivities in nontarget organisms are somewhat better defined in both laboratory and field studies than is the case with tebufenozide.

Risk Characterization – Ecological risk assessments involve, at least implicitly, considerations of thousands of different species and relationships among these species and their habitats. Invariably, however, data are available on only a small subset of these species and field studies provide only limited insight into the complex interrelationships and secondary effects among species. Thus, as in the human health risk assessments, ecological risk assessments cannot offer a guarantee of safety. They can and do offer a means to identify whether or not there is a basis for asserting that adverse effects are plausible and what the nature of these effects might be.

Within these limitations, only LdNPV clearly qualifies as an agent of minimal concern. While there are limitations in the available studies on LdNPV, there is simply no basis for asserting that LdNPV will adversely affect any species except the gypsy moth.

Agents of marked concern included the gypsy moth, *B.t.k.*, and diflubenzuron. The types of concern with each of these agents, however, are quite different. For both the gypsy moth and *B.t.k.*, the concerns are narrow. The gypsy moth will clearly damage some terrestrial vegetation. *B.t.k.* is likely to affect sensitive *Lepidoptera*. Concern with the use of diflubenzuron is broader and includes effects on both terrestrial and aquatic invertebrates.

The designation of the gypsy moth as an agent of marked concern is obvious. The effects of gypsy moth larvae on forests are extremely well documented and well understood. In sensitive forest stands—i.e., stands in which oak, birch, and other favored species predominate —gypsy moth larvae can cause substantial defoliation and tree mortality. While some other lepidopteran species also may be directly affected by exposure to the gypsy moth, most of the other effects caused by the gypsy moth will be secondary. Reductions in populations of squirrels, mice, and other mammals which may be sensitive to changes in the availability of acorns are likely and have been well documented. Substantial secondary adverse effects on other groups of animals – i.e., birds, reptiles, and aquatic species – cannot be ruled out but have not been convincingly or consistently demonstrated.

Diflubenzuron is also clearly an agent of marked concern. Exposures to diflubenzuron at application rates used in gypsy moth control programs will adversely affect both terrestrial and aquatic invertebrates that rely on chitin for their exoskeleton. This effect is demonstrated in controlled toxicity studies as well as multiple field studies.

B.t.k. is considered an agent of marked concern because recent studies convincingly demonstrate that adverse effects in nontarget *Lepidoptera* will occur in the applications of *B.t.k.* used to control the gypsy moth. Concern is heightened because some of the *Lepidoptera* that may be adversely affected include at least one endangered species.

Tebufenozide, DDVP, and disparlure are all classified as agents of marginal concern. For tebufenozide, the numeric expressions of risk may be less relevant than a more qualitative assessment. The highest risk is associated with the consumption of contaminated vegetation by a large mammal after two applications at the highest labeled application rate. It is not clear, however, that any frank signs of toxicity would be seen. Risks to nontarget *Lepidoptera* may be of greater concern, but the available data are insufficient to quantify potential risk. Risks to other invertebrates, both terrestrial and aquatic, appear to be insubstantial. DDVP is of marginal concern in that highly localized effects may be expected: nontarget insects entering a milk carton trap or some aquatic invertebrates affected by the accidental contamination of a small body of water with a pest strip. In both cases, the effects would be relatively minor, in terms of the number of organisms affected. Marginal concern for disparlure is associated with the relatively high toxicity of this agent to *Daphnia*. The very limited information on the toxicity of disparlure

argues for a persistent level of vigilance for this agent that may be applied to large areas in broadcast applications.

1. INTRODUCTION

The USDA is preparing an update to the 1995 Environmental Impact Statement (EIS) for the Cooperative Gypsy Moth Management Program (USDA 1995). As part of this effort, updated risk assessments were developed on each of the chemical and biological control agents that are used in the USDA programs:—i.e., *Bacillus thuringiensis* var. *kurstaki* (*B.t.k.*) (SERA 2004a), the gypsy moth nucleopolyhedrosis virus (LdNPV) (SERA 2004b), diflubenzuron (SERA 2004c), tebufenozide (SERA 2004f), DDVP (SERA 2004e), and disparlure as an active ingredient in materials used to attract the gypsy moth (SERA 2004d). In addition, a separate risk assessment was prepared on the gypsy moth (*Lymantria dispar*) itself.

The current document not only compares the risks posed by the gypsy moth itself with the risks posed by the different control agents, but also compares the risks associated with the various control agents. The risk comparison is structured like the individual risk assessments and includes comparisons of uses (Section 2), potential human health effects (Section 3), and potential ecological effects (Section 4). As in the individual risk assessments, each of the comparative risk assessment sections (Sections 3 and 4) has four major subsections, including an identification of the hazards associated with the agents, an assessment of potential exposure, an assessment of the dose-response relationships, and a characterization of the risks associated with each agent.

Each of the individual risk assessments cited above are complex, detailed, and often very large documents. The risk comparison does not attempt to summarize this information again in detail. Instead, it focuses on discussing the nature and quality of the data that support each step of the risk assessments and the uncertainties and limitations in the conclusions that are reached. Thus, with few exceptions, individual studies are not discussed or referenced in the current document. The exceptions primarily involve relatively recent studies that substantially impact the assessment of risk. Most of these studies involve *B.t.k.* (Herms et al. 1995; Hernandez et al. 1999, 2000; Peacock et al. 1998; Petrie et al. 2003).

2. PROGRAM DESCRIPTION

2.1. Overview

The USDA control programs for the gypsy moth are intended to limit damage to forests that can be substantially impacted by gypsy moth outbreaks. Two biological agents that are pathogenic to the gypsy moth are used in broadcast applications: *B.t.k.* and LdNPV. In addition, three chemical agents are used in broadcast applications: diflubenzuron, tebufenozide, and disparlure. Diflubenzuron and tebufenozide are both insecticides and, as discussed in subsequent sections of the this document, have similar toxicologicalal properties. The major difference between the two is that application rates for tebufenozide are higher than those for diflubenzuron, which is a controlling factor in the comparative risk assessment for these two agents. Disparlure is a gypsy moth pheromone used in broadcast applications to disrupt mating and in population monitoring programs to attract the male gypsy moth to sampling traps. In the past, disparlure was used in a slow-release flake formulation. DDVP is not used in broadcast applications and is used only as a PVC formulated product in milk carton traps used in mass trapping operations.

The USDA adopted various intervention strategies roughly categorized as suppression, eradication, and slow-the-spread. Suppression programs have relied predominantly on *B.t.k.* and diflubenzuron. Slow-the-Spread programs rely predominantly on the use of disparlure flakes and secondarily on *B.t.k.* applications. Eradication efforts rely predominantly on *B.t.k.* NPV is used in all three strategies but is used on very few acres relative to *B.t.k.*, diflubenzuron, and disparlure flakes.

2.2. Control Agents

Gypsy moth is a pest species that can cause substantial damage to some forests. In the eastern United States, most hardwood forests are classified as susceptible to gypsy moth infestation and as many as 12.5 million acres have been defoliated in a single season. The gypsy moth is found throughout much of New England and south to Virginia and west to portions of Wisconsin.

In past years, USDA employed chemical and biological agents in gypsy moth control programs. The biological control agents consist of *B.t.k.* and LdNPV. Both of these biological agents are pathogenic to the gypsy moth. The chemicals that may be used in the control of the gypsy moth include diflubenzuron, tebufenozide, and disparlure. Diflubenzuron and tebufenozide are used as direct insecticidal control agents, similar to the uses of *B.t.k.* and LdNPV. All of these agents are used in broadcast aerial or ground applications.

DDVP and disparlure are used in mass trapping. Disparlure attracts the male gypsy moth to a large milk carton trap and the DDVP kills insects that enter the trap. While DDVP functions as an insecticide in the trap, it is not considered a control agent for the gypsy moth because mass trapping is used only in population surveys. Disparlure, in a flake formulation, is also used in broadcast aerial applications. While the disparlure does not cause any direct toxic effects to the gypsy moth, the mass application of disparlure will impair the ability of the male gypsy moth to

find female gypsy moths and thus will limit the ability of gypsy moth populations to propagate. Thus, disparlure is used as a control agent.

All of the agents used in gypsy moth control programs are applied in various types of formulations—i.e., the active ingredient combined with various other chemicals or materials. To the extent possible, these materials are discussed in each of the individual risk assessments. Specific information on inerts, however, is classified as CBI (confidential business Information) under Section 7(d) and Section (10) of FIFRA, and this information cannot be specifically disclosed in a risk assessment. In terms of a comparative risk assessment, however, the most important distinctions involve the formulations of *B.t.k.* and LdNPV in complex mixtures and the use of DDVP in polyvinyl chloride (PVC) strips.

B.t.k. and LdNPV are both applied as very complex mixtures that are not fully or clearly defined. *B.t.k.* is cultured or grown in a medium containing water and nutrients, including sugars, starches, proteins, and amino acids. The nutrients, which are, themselves, chemically complex consist of variable biological materials, including animal foodstuffs, various flours, yeasts, and molasses. Similarly, LdNPV is prepared by isolating the virus from infected gypsy moth larvae. The active material consists of the virus, gypsy moth parts, and residual materials used to isolate and purify the virus. Complex mixtures can pose substantial difficulties in a risk assessment; however, the data on *B.t.k.* and LdNPV involve adequate studies on the toxicity of the complex mixtures. This is particularly true for *B.t.k.* in which much of the information on risk is based on applications of commercial formulations in the field.

DDVP is used only in a PVC strip. Each strip contains 590 mg of DDVP and 89.25% inerts, which consist primarily of the PVC in the strip and plasticizers. The limited use of DDVP and its containment in the PVC strip have a major impact on the risk posed by DDVP, relative to the other compounds used in gypsy moth control programs. This impact is discussed at some length in the DDVP risk assessment and in subsequent sections of this document.

2.3. Application Rates

Application rates for the different control agents differ substantially both in magnitude and, for the biological agents, in the manner in which the application rate is expressed.

For *B.t.k.*, application rates are expressed in billions of international units (BIU), which is a measure of the activity or potency of the formulation rather than an expression of mass. The range of application rates used in USDA programs is 20-40 BIU/acre. For LdNPV, the recommended application rate is 0.43 oz Gypchek/acre for suppression and 1.08 oz Gypchek/acre for eradication. The application rate of 0.43 oz/acre corresponds to about $4x10^{11}$ PIB (polyhedral inclusion bodies)/acre and the application rate of 1.08 oz/acre corresponds to about $1x10^{12}$ PIB/acre.

Broadcast application rates are expressed in units of lb a.i./acre. For diflubenzuron, the range of labeled application rates is 0.0078-0.0624 lbs a.i./acre. For tebufenozide, higher labeled

application rates are permitted: 0.03-0.12 lbs/acre. Multiple applications of tebufenozide are also permitted, and the maximum annual application rate is 0.24 lb a.i./acre. The application rates for tebufenozide may vary among USDA programs—i.e., suppression, eradication, and slow-the-spread. For the tebufenozide risk assessment, a range of application rates—i.e., 0.015- 0.12 lb a.i./acre—are considered. All exposure assessments are conducted at the maximum application rate of 0.12 lb/acre, assuming that two applications are made with three days between applications. This worse-case scenario involves the use of two applications that reach the maximum annual application rate of 0.24 lb/acre and the shortest interval between applications. As noted in Section 3.4, the higher application rates for tebufenozide, compared with application rates for diflubenzuron, are the determining factor in the risk comparison. The application rate for disparlure is about 0.064 lb a.i./acre, near the maximum application rate allowed for diflubenzuron. Disparlure, however, is always applied in a slow-release formulation, either flakes or microspheres. DDVP is not applied in broadcast applications. Accordingly, the application rate is not a meaningful measure of exposure for this agent.

2.4. Use Statistics

In order to minimize the ecological effects and human health effects of gypsy moth infestations, the USDA adopted various intervention strategies roughly categorized as suppression, eradication, and slow-the-spread (Liebhold and McManus 1999). Suppression efforts are conducted by the USDA Forest Service in areas of well established gypsy moth infestations to combat or interdict periodic gypsy moth population outbreaks. Eradication efforts are conducted by USDA/APHIS to eliminate gypsy moth populations in areas where new populations of the gypsy moth are found. Slow-the-Spread, as the name implies, is a program to reduce the expansion of gypsy moth populations from areas of established populations to adjacent non-infested areas.

The use of the various control agents in USDA programs is summarized in Table 2-1. This table gives the total number of acres treated with each of the control agents between 1995 and 2003. Suppression programs rely predominantly on *B.t.k.* and diflubenzuron. Slow-the-Spread programs rely predominantly on the use of disparlure flakes and secondarily on *B.t.k.* applications. Eradication efforts rely predominantly on *B.t.k.* NPV is used in all three strategies but is used on very few acres relative to *B.t.k.*, diflubenzuron, and disparlure flakes. As discussed in the risk assessment on NPV, the production of Gypchek is very expensive and the application of this agent is currently limited to areas that are considered environmentally sensitive. As noted above, tebufenozide is not used in gypsy moth programs but may be used in the future. Given the similarities between tebufenozide and diflubenzuron, the use of tebufenozide is likely to be similar to that of diflubenzuron—i.e., primarily in suppression programs.

3. HUMAN HEALTH RISK ASSESSMENT

3.1. HAZARD IDENTIFICATION

3.1.1. Overview

An overview of the comparative hazard identification for the gypsy moth and the agents used in USDA programs to control the gypsy moth is given in Table 3-1. The gypsy moth, *B.t.k.*, and LdNPV are similar not only because they are biological agents but also because the primary effect associated with each agent is irritation. The gypsy moth causes more pronounced and severe irritation relative to either *B.t.k.* or LdNPV. Of the chemical agents used in gypsy moth control programs, diflubenzuron and tebufenozide are similar to each other in that both cause adverse effects on blood. The risk assessment of diflubenzuron is somewhat more involved than that of tebufenozide because diflubenzuron is degraded to 4-chloroaniline, a compound that is classified as a carcinogen. DDVP and disparlure, the other two chemicals used in gypsy moth control programs, have toxicological profiles that are very different from each other as well as from diflubenzuron or tebufenozide. DDVP is a well-characterized neurotoxin and the toxicity of DDVP in mammals has been studied extensively. Disparlure is an insect attractant that has not been extensively tested for toxicological effects in mammals.

3.1.2. Biological Agents

The biological agents—i.e., *B.t.k.*, LdNPV, and the gypsy moth itself—present similar toxicological profiles. All three agents are irritants and cause similar irritant effects. The most likely effect from exposure to the gypsy moth is skin irritation. Gypsy moth larvae, as well as the larvae of many species of *Lepidoptera*, cause skin irritation in humans. The skin reactions seem to be associated with contact with small fine hairs that stick out from the body of the larva. Other effects associated with exposure to gypsy moth larvae include eye and respiratory irritation; however, these effects are not as well documented as the dermal effects.

LdNPV also causes irritant effects. It is likely that the irritant effects are due at least in part to the presence of body parts of gypsy moth larvae in LdNPV preparations. Based on the available animal data, there is clear evidence that Gypchek, the commercial formulation of LdNPV, can cause eye irritation. There is little indication, however, that Gypchek is likely to cause dermal or respiratory irritation, which may have something to do with the processing of the gypsy moth parts during the preparation of Gypchek.

The irritant effects of *B.t.k.* are probably due to the formulation of the bacteria rather than the bacteria itself. As noted in Section 2, commercial preparations of *B.t.k.* are very complex mixtures of the bacteria, fermentation byproducts, and adjuvants. *B.t.k.* formulations, however, are not strong irritants to either the eyes or the skin, except in the cases of accidental and gross contamination of the eyes. Instead, the most consistent effect appears to be irritation of the respiratory tract, particularly the throat.

The irritant effects of the gypsy moth appear to be notably more severe than those of *B.t.k.* The wheals and rashes that result from exposure to the gypsy can cause severe itching which may

persist from several days to two weeks. Moreover, these effects can be severe enough to cause the affected individual to seek medical treatment. The relatively consistent set of epidemiology studies following *B.t.k.* applications note a very different outcome. Despite many reports of irritant effects among exposed individuals, there is not a corresponding increase in the incidence of individuals seeking medical care. Thus, unlike the case in severe gypsy moth infestations, the severity of the irritant effects does not appear to be severe enough for individuals to seek medical care.

There is very little indication that these biological agents will be associated with other more serious effects. LdNPV and Gypchek formulations of LdNPV were tested in relatively standard toxicity studies as well as in pathogenicity studies with no indication of serious effects even at very high doses. The gypsy moth has not been formally tested in human or animal studies; on the other hand, this species has infested North America for more than 100 years and no cases of frank adverse effects associated with gypsy moth exposure are to be found in the available literature. Hence, there appears to be no risk of serious adverse effects from exposure to LdNPV, Gypchek, or the gypsy moth itself.

The potential for *B.t.k.* to produce serious adverse effects is somewhat more complicated than the assessment of LdNPV and the gypsy moth. As discussed in the *B.t.k.* risk assessment, severe adverse effects associated with exposure to *B.t.k.* are not reported in any of several epidemiology studies or standard animal toxicity studies on *B.t.k.* or formulations of *B.t.k.* A recent study by Hernandez et al. (2000), however, reports mortality in mice after intranasal instillations of *B.t.k.* Intranasal instillations of bacteria are analogous to inhalation exposures in that the bacteria are inhaled and transported to the lungs during the course of the study. This route of exposure is used to screen qualitatively for potential toxic effects, particularly for biological agents, and is not commonly used in a quantitative risk assessment because of uncertainties in extrapolating from intranasal doses to inhalation exposures that may occur in humans. In the *B.t.k.* risk assessment, some very conservative assumptions are made in the application of the Hernandez et al. (2000) study to provide an estimate of risk. As with LdNPV and the gypsy moth, this analysis (considered further in Sections 3.3 and 3.4) suggests that the risk of adverse effects is likely to be very low under foreseeable conditions of exposure.

The Hernandez et al. (2000) study also reports that pre-treatment of mice with an influenza virus substantially increased mortality in mice exposed to various doses of *B.t.k.*, again by intranasal instillation. This effect raises concern about the susceptibility of individuals who have influenza or other viral respiratory infections to severe adverse responses to *B.t.k.* exposure. The viral enhancement of bacterial infections is not uncommon and the enhancement of *B.t.k.* toxicity by a viral infection is, in some respects, not surprising. The relevance of this observation to public health cannot be assessed well at this time. No such effects are reported in the epidemiology studies conducted to date. It is, however, not clear that the epidemiology studies would detect such an effect or that such an effect is plausible under the anticipated exposure levels (typical or extreme) used in programs to control the gypsy moth. The viral enhancement of *B.t.k.* toxicity is likely to be an area of further study in the coming years.

3.1.3. Chemical Agents

In terms of potential human health effects, diflubenzuron and tebufenozide are similar to one another in that both cause adverse effects on blood. DDVP and disparlure, the other two chemicals used in gypsy moth control programs, have toxicological profiles that are very different from one another as well as from diflubenzuron or tebufenozide. The toxicity of DDVP, which is a well-characterized neurotoxin, has been studied extensively in mammals. Disparlure is an insect attractant that has not been extensively tested for toxicologicalal effects in mammals.

3.1.3.1. Diflubenzuron and Tebufenozide – For both diflubenzuron and tebufenozide, the most sensitive effect in mammals involves damage to hemoglobin, a component in red blood cells that is responsible for transporting oxygen throughout the body. If this function is impaired, either because of damage to hemoglobin or lack of oxygen in the air, serious adverse effects (i.e., equivalent to suffocation) can occur. Both diflubenzuron and tebufenozide cause the formation of methemoglobin, a form of hemoglobin that is not able to transport oxygen. Both chemicals causes other effects on the blood; however, methemoglobinemia is the most sensitive effect—that is, the effect that occurs at the lowest dose.

While effects on the blood are well documented, there is less of an indication that diflubenzuron or tebufenozide will cause other specific forms of toxicity. Neither diflubenzuron nor tebufenozide appears to be carcinogenic, mutagenic, neurotoxic or immunotoxic. Furthermore, these chemicals do not appear to cause birth defects or affect endocrine function in laboratory mammals. Diflubenzuron does not appear to cause reproductive effects. Tebufenozide, on the other hand, is associated with adverse reproductive effects in experimental mammals. These reproductive effects, however, occur at doses higher than those associated with methemoglobinemia. Neither diflubenzuron nor tebufenozide have a high order of acute oral toxicity. Diflubenzuron is relatively nontoxic by oral administration, with reported single-dose LD_{50} values ranging from greater than 4640 to greater than10,000 mg/kg. Similarly, single oral gavage doses of tebufenozide at 2000 mg/kg caused no observable signs of toxicity in mice or rats.

Diflubenzuron is degraded to 4-chloroaniline in the environment. While most chemicals are metabolized in some way, the formation of 4-chloroaniline from diflubenzuron must be and is explicitly considered in the risk assessment because 4-chloroaniline is classified as a carcinogen. This is the only identified carcinogen associated with any of the agents used to control the gypsy moth.

3.1.3.2. DDVP – DDVP is an organophosphorus insecticide that works by inhibiting cholinesterase. Inhibition of this enzyme in mammalian systems produces a variety of systemic effects, including salivation, urination, lacrimation, convulsions, increased bronchial secretions, respiratory depression, and even death. The nature and magnitude of the toxic effects produced by a given exposure to DDVP by any route are directly related to the dose and rate at which the exposure occurs.

In the case of the USDA programs for the management of the gypsy moth, the use of milk carton traps containing Vaportape II (slow-release of DDVP from PVC strips) precludes rapid exposures to high doses of DDVP. The decrease in toxicity of DDVP in a PVC formulation has been studied directly. For the technical grade liquid DDVP, the acute oral LD_{50} in young pigs is about 160 mg/kg and signs of toxicity in these animals were consistent with the general signs of acetylcholinesterase (AChE) inhibition. In a similar bioassay using a PVC formulation, no deaths occurred at doses up to 1000 mg/kg. This key study on the comparative toxicity of DDVP and DDVP-PVC formulations is discussed further in the dose-response assessment (Section 3.3).

DDVP is a very well studied compound and threshold doses for cholinesterase inhibition are well characterized. Short-term animal studies using technical grade DDVP indicate that oral exposures to doses below about 0.5 mg/kg-day (or inhalation exposures to 1-2 mg/m^3) do not result in meaningful reductions in cholinesterase activity. Experiments in laboratory mammals exposed to DDVP during pregnancy (by oral or inhalation route) did not show any effect on fertility or health of the offspring, even at levels that produced maternal toxicity. The latest evaluation of data from assays for carcinogenicity and genetic toxicity classify DDVP as a "suggestive" carcinogen and determined that a quantitative assessment of cancer risk is not applicable. The literature contains some data suggesting that contact dermatitis (as well as cross-sensitization to other pesticides) may occur; although, this appears to be an infrequent occurrence in the general population.

3.1.3.3. Disparlure – In the registration of most pesticides, the U.S. EPA requires a relatively standard set of toxicity data covering multiple routes and durations of exposure as well as a number of specific endpoints of concern (e.g., carcinogenicity, reproductive toxicity, neurotoxicity, etc.). These requirements have been applied to diflubenzuron, tebufenozide, and DDVP but not to disparlure. Because of the apparently low toxicity of most pheromones to mammals and because of the low concentrations that are expected in the environment, U.S. EPA requires less rigorous testing of insect pheromones than is required of insecticides (U.S. EPA 2004).

The prudence of these assumptions may be argued but this issue is beyond the scope of the current risk assessment except to note that the application rate for disparlure is somewhat higher than the application rate for diflubenzuron—i.e., up to 0.0624 lbs a.i./acre for diflubenzuron and about 0.064 lb a.i./acre for disparlure (see Section 2). Nonetheless, as noted in Section 2, disparlure is always applied in a slow-release formulation (either flakes or microspheres) and the limited available monitoring data (Section 3.2), do support the assumption that exposures to disparlure are likely to be very low.

In terms of the hazard identification, the result of the U.S. EPA position and the more general lack of concern with the toxicity of insect pheromones is that the toxicity of disparlure to mammals has not been studied extensively. Except for some standard acute toxicity studies in laboratory mammals, few data are available regarding the biological activity of disparlure in mammals. Results of acute exposure studies for oral, dermal, ocular, and inhalation exposure to

disparlure show no indication of adverse effects. The acute toxicity of disparlure in mammals is very low. The LD_{50} of a single dose administered to rats by gavage exceeds 34,600 mg/kg. No studies investigating the effects of chronic exposure of mammals to disparlure or studies investigating the effects of disparlure on the nervous system, immune system, reproductive system, or endocrine system were identified. The carcinogenic potential of disparlure has not been assessed. In a single study on mutagenicity, there was no indication that disparlure is mutagenic.

A case report of an accidental exposure indicates that disparlure may persist in humans for years. This case report concerns an individual involved in the early testing of disparlure who came into contact with the chemical. For more than 10 years after exposure to disparlure, the individual tended to attract male gypsy moths. This nuisance effect is the only well documented result of exposures to disparlure that might occur in USDA programs.

3.2. EXPOSURE ASSESSMENT

3.2.1. Overview

A summary of the exposure assessments for each of the agents covered in the risk assessment is given in Table 3-2. The exposure assessments of the biological agents differ substantially from those of the chemical agents in terms of how the exposures are expressed. Different measures of exposure are used for each of the biological agents—i.e., the gypsy moth, *B.t.k.*, and LdNPV. For the chemical agents, all exposure assessments are based on the amount or concentration of the chemical to which an individual or population might be exposed via ingestion, dermal contact, or inhalation. Differences among the chemical agents are dictated largely by differences in how the chemicals are used and, to a lesser extent, on the available toxicity data.

A very different set of exposure assessments is conducted for each of the biological agents. Both *B.t.k.* and LdNPV may also be applied in broadcast applications and the routes of plausible exposure are the same as those for the chemicals applied in broadcast applications—i.e., oral, dermal, and inhalation. For *B.t.k.*, however, the most directly relevant data used to characterize risk are based on actual applications of *B.t.k.* formulations where exposure is best characterized as an application rate. For the assessment of the potential for serious adverse effects, exposures are measured in colony forming units (cfu). LdNPV differs from all of the other agents in that no clear hazard potential can be identified. Thus, the most meaningful measure of exposure is in some respects moot. Those exposures that are quantified in the human health risk assessment for LdNPV are based on the mass of the formulation, Gypchek. Exposures to the gypsy moth itself are based on an indirect measure of exposure, egg masses/acre, because this is the expression of exposure that is used in the dose-response assessment.

Differences in the exposure assessments among the chemicals used in USDA programs primarily reflect differences in how the chemicals are applied, what routes of exposure are most substantial, and the nature of the available toxicity data. Diflubenzuron, tebufenozide, and disparlure may be applied in aerial broadcast applications that lead to multiple routes of exposure (oral, dermal, and inhalation). No chronic exposures for disparlure are conducted, however, because no chronic toxicity data are available on this chemical. DDVP, on the other hand, is used only in milk carton traps and exposures will be minimal under normal conditions, although much higher exposures are possible if the traps are not assembled properly or if individuals tamper with the traps.

3.2.2. Biological Agents

The exposure assessments for the biological agents —i.e., the gypsy moth, *B.t.k.*, and LdNPV differ substantially from each other, and these differences are largely dictated by the nature of the toxicity data available on each agent and the resulting dose-response assessments (Section 3.3.2).

3.2.2.1. Gypsy Moth – For the gypsy moth, the most direct and relevant measure of human exposure is probably the number of larvae per unit area or tree because it is contact with the larvae that causes skin irritation, the adverse effect typically associated with the gypsy moth. Nonetheless, the available dose-response data are based on studies in which exposure is

quantified as the number of eggs masses/acre. Accordingly, egg masses/acre is the exposure measure used in this risk assessment. As long as gypsy moth populations remain sparse, the larvae usually eat only a small proportion of the foliage of even their most favored host species, and contacts with people are rare. In such cases, egg masses generally do not exceed 50 egg masses/acre. During full-scale outbreaks, densities of about 5000 egg masses/acre are common and densities greater than 20,000 egg masses/acre are occasionally recorded. In such outbreaks, the numbers of gypsy moth larvae can reach up to 50,000 larvae per tree and exposure to the larvae will be essentially unavoidable for individuals near infested trees.

3.2.2.2. B.t.k. **–** The exposure assessment for *B.t.k.* is unusual in two respects. First, the most directly relevant data used to characterize risk are based on actual applications of *B.t.k.* formulations where exposure is best characterized as an application rate. As summarized in Section 3.3.2, epidemiology studies are available that report responses in populations after applications of *B.t.k.* in the range of those used in USDA programs to control the gypsy moth—i.e., 20-40 BIU/acre. Thus, these studies are used directly in the risk characterization and explicit exposure assessments and dose-response assessments are not needed.

Second, the apparent lack of a specific mechanism of toxicity for *B.t.k.* makes selecting the most appropriate measure of exposure somewhat arbitrary. The potency of *B.t.k.* is often expressed as BIU or FTU and exposures or application rates are expressed in units of BIU or FTU per acre. Although these units may be meaningful expressions of exposure for the gypsy moth, they are not necessarily or even likely to be a meaningful measures of human exposure. Exposure data are available, however, on *colony forming units* or cfu. When *B.t.k.* formulations are applied, either by aerial spray or ground spray, one or more viable spores contained in droplets or particulates is suspended in the air and deposited on sprayed surfaces. These droplets may be collected, either by air sampling or direct deposition, onto various types of filters. The filters are then cultured in a nutrient medium under conditions conducive to bacterial growth. As the bacteria grow, visible masses of bacteria, referred to as colonies, appear on the media. The significance of cfu as a measure of human exposure is limited because there is little indication that *B.t.k.* is a human pathogen. Consequently, the number of viable spores, albeit an important measure of exposure for the gypsy moth, does not appear to be toxicologicalally significant to humans. In this respect, cfu, like BIU, are of limited significance.

Nonetheless, at least for short-term exposures, cfu can be used as a practical measure of relative exposure to a *B.t.k.* formulation. Based on cfu, ground workers may be exposed to much higher concentrations of *B.t.k.* than other groups—i.e., 200,000-15,800,000 cfu/m^3. Much lower exposures, 400-11,000 cfu/m^3, have been measured in workers involved in aerial applications. During spray operations, members of the general public may be exposed to concentrations in the ranging from about 200-4000 cfu/m^3.

3.2.2.3. LdNPV **–** Given the failure to identify any hazard associated with LdNPV or the Gypchek formulation, there is little need to conduct a detailed exposure assessment for Gypchek. Gypchek contains gypsy moth parts, and these constituents, like the gypsy moth larvae

themselves, cause irritant effects in humans. The use of Gypchek, however, will not substantially increase the overall adverse effects of gypsy moth exposure in infested areas. On the contrary, the use of Gypchek will decrease the potential for human exposure to gypsy moth larvae by reducing larval populations. Based on simple physical processes associated with the application of any pesticide, it is possible to construct any number of exposure scenarios for Gypchek. The risk assessment for LdNPV focuses on one extreme exposure scenario involving the accidental spray of a home garden. While Gypchek is not intentionally applied to such vegetation, the inadvertent spray scenario is plausible. Based on this accidental exposure scenario, the estimated dose to an individual is 0.034 mg Gypchek/kg bw, with an upper range of 0.66 mg Gypchek/kg bw.

3.2.3. Chemical Agents

3.2.3.1. Diflubenzuron and Tebufenozide – Diflubenzuron and tebufenozide are applied in broadcast applications. The available data regarding the toxicity and environmental fate of these chemicals support a standard set of exposure scenarios involving worker exposure (both routine and accidental) and exposures of the general public to direct spray, dermal contact with contaminated vegetation, as well as the acute and longer-term consumption of contaminated food and water. For both of these chemicals, all exposure assessments are conducted at the maximum application rates. For diflubenzuron, all exposure assessments are conducted at the maximum single application rate for diflubenzuron of 0.0625 lb/acre, which is also the maximum amount that can be applied in a single season. The exposure assessments of tebufenozide are somewhat more elaborate because both single and multiple applications must be modeled—i.e., one or two applications at 0.12 lb/acre. While diflubenzuron is modeled at only the single maximum application rate, the exposure assessment for diflubenzuron is made elaborate by the quantitative consideration of the formation of 4-chloroaniline as an environmental metabolite. As noted in Section 3.1, the quantitative consideration of this metabolite is necessary because 4-chloroaniline is classified as a carcinogen and cancer risk is considered quantitatively in the risk characterization.

The exposure patterns for both diflubenzuron and tebufenozide are similar. For workers, three types of application methods are modeled: directed ground spray, broadcast ground spray, and aerial spray. In these general applications, the maximum exposures to workers are similar: 0.009 mg/kg/day for diflubenzuron and 0.02 mg/kg/day for tebufenozide. The differences in worker exposure levels merely reflect the differences in application rates for the two chemicals. Accidental dermal exposures for workers can be much higher: 0.4 mg/kg/day for diflubenzuron and 4 mg/kg/day for tebufenozide. These differences in exposure levels reflect the differences in the concentrations of the two chemicals used in field solutions as well as the differences in the estimated dermal absorption rates.

For members of the general public, the exposure profiles for diflubenzuron and tebufenozide are also similar. The maximum acute exposure levels for both chemicals are associated with contaminated water in an accidental spill scenario: doses of 1.5 mg/kg bw for diflubenzuron and 1.2 mg/kg bw for tebufenozide. Longer-term exposure to both agents, which involves the

consumption of contaminated fruit rather than water, will result in much lower levels of exposure: 0.002 mg/kg/day for diflubenzuron and 0.03 mg/kg/day for tebufenozide. Like workers, members of the general public can be at risk of dermal exposure to diflubenzuron or tebufenozide, and dermal exposure concentrations can be estimated quantitatively. Estimates of dermal exposure, however, are lower than estimates of oral exposure: a maximum of 0.05 mg/kg bw for diflubenzuron and about 0.4 mg/kg bw for tebufenozide.

Exposure assessments for 4-chloroaniline as an environmental metabolite of diflubenzuron are made only for members of the general public. Workers are not considered at risk because significant amounts of 4-chloroaniline are not likely to form during the application of diflubenzuron. For the general public, estimates of exposure to 4-chloroaniline from contaminated vegetation are likely to be about a factor of 50 below the corresponding estimates of exposure to diflubenzuron. The lower estimate of exposure to 4-chloroaniline is due to its expected rapid dissipation from diflubenzuron deposited on vegetation. In water, however, estimated concentrations of 4-chloroaniline are likely to be equal to or greater than anticipated water concentrations of diflubenzuron under certain circumstances. Finally, peak exposures to 4-chloroaniline differ from peak exposures to diflubenzuron in the environment, usually occurring at different times (later after the application of diflubenzuron) and under different conditions of precipitation. These differences are due to the relatively slow rate in the formation of 4-chloroaniline from diflubenzuron in soil.

3.2.3.2. Disparlure – Disparlure is like diflubenzuron and tebufenozide in that all three can be applied by aerial broadcast and multiple routes of acute and longer-term exposure are possible. The exposure assessment for disparlure, however, is much less elaborate than those for diflubenzuron and tebufenozide because of the very limited toxicity data base on disparlure. As discussed in Section 3.3 (Dose-Response Assessment), the U.S. EPA did not derive RfD values for acute or chronic exposure and the available toxicity data do not support the derivation of surrogate values. Thus, in the absence of toxicity data, an elaborate exposure assessment would not be useful in evaluating risk.

For disparlure, dermal exposure is most likely to be the predominant route for occupational exposure and is a possible route of exposure for the general public. A case report involving the accidental exposure of a worker to disparlure indicates that the only notable effect in the worker was the persistent attraction of gypsy moths. Since the available acute systemic toxicity of disparlure in mammals appears to be very low, the absence of dermal absorption data does not add significant uncertainty to this risk assessment. While dermal exposure of workers is expected to be non-toxic, dermal exposure is likely to cause the persistent attraction of gypsy moths.

Both workers and the public may be exposed to disparlure by inhalation, and the magnitude of the exposure can be estimated from available monitoring studies. At application rates more than 15 times the normal application rate (i.e., about 200 g a.i./acre compared with 29.1 g/acre), peak air concentrations ranged from 0.022 to 0.030 $\mu g/m^3$. Adjusted to the normal application rate,

these values correspond to about 0.003-0.004 $\mu g/m^3$, which is far below the air concentration of 5.0 mg/L —equivalent to 5000 µg/L or 5,000,000 $\mu g/m^3$—that did not cause mortality or signs of toxicity in experimental animals.

3.2.3.3. DDVP – Unlike the other chemicals used in gypsy moth control programs, DDVP is not applied in broadcast applications. DDVP is used only in a PVC strip that is placed in milk carton traps. Consequently, exposures of both workers and members of the general public should be negligible under normal conditions—i.e., the workers use proper procedures during assembly of the traps and members of the general public do not tamper with the traps. The risk assessment for DDVP does develop exposure scenarios for both workers and members of the general public to encompass improper handling of the DDVP strips by workers or tampering with the traps by members of the general public. These exposures, however, should be considered atypical, and some are extreme.

During assembly, the central estimate of dermal exposures in workers not wearing gloves leads to an absorbed dose of about 0.0008 mg/kg with a range of about 0.0003 mg/kg to 0.004 mg/kg. Inhalation exposures in workers may be highly variable depending on the ventilation rates in an enclosed space and the number of traps that are handled. Based on the handling and transport of 75 traps, inhalation exposures could be as high as 0.6 mg/m^3 in an enclosed and unventilated room and as high as 1.8 mg/m^3 in the passenger compartment of a vehicle. These exposure assessments are based on several site-specific and situation-specific assumptions intended to reflect plausible upper bounds of exposure.

Exposure assessments are also developed for children who might come in contact with an accidentally discarded or misplaced DDVP strip. Estimated dermal doses are much higher than those for workers: a central estimate of about 0.02 mg/kg with a range of 0.003-0.1 mg/kg. Oral exposures from a small child sucking on the pest strip are about a factor of 10 higher than dermal exposures: a central value of about 0.2 mg/kg with a range of 0.04-0.6 mg/kg.

Under normal circumstances, the use of DDVP in PVC strips is not likely to result in contamination of water or other materials that might be consumed by members of the general public. Nonetheless, an exposure assessment is developed for the accidental contamination of a small pond by a pest strip. In this scenario, dose estimates range from about 0.000003 to 0.00007 mg/kg with a central estimate of about 0.00001 mg/kg.

3.3. DOSE-RESPONSE ASSESSMENT

3.3.1. Overview

A summary of the dose-response assessments for each of the agents covered in the risk assessment is given in Table 3-3. Dose-response assessments are typically based on an RfD, an estimate of a dose or exposure that is not likely to induce substantial adverse effects in humans. The RfD, in turn, is typically based on a NOAEL (no-observed-adverse-effect level) divided by an uncertainty factor. Risk is then characterized as a hazard quotient (HQ) which is the estimated level of exposure divided by the RfD. If the HQ is below unity—i.e., the exposure is less than the RfD —there is no credible risk. If the HQ is above unity, risk is characterized based on dose-response or dose-severity relationships. The quality of the dose-response assessment depends on the quality of the individual studies, the relevance of the studies to potential human exposures, and the strength of the dose-response relationship.

As in the exposure assessments (see Section 3.2), the dose-response assessments for the biological agents differ substantially from one another as well as from those of the chemical agents. The dose-response assessment for the gypsy moth itself is based on only one study; however, the study involves two human populations, and a demonstrates a clear dose-response relationship. Thus, confidence in the dose-response assessment is high. Two endpoints are considered for *B.t.k.*, irritant effects and more serious toxic effects. While the irritant effects are well documented, there is no apparent dose-response relationship and confidence in the dose-response is classified as medium. The dose-response assessment for more serious effects is based on a single study in mice that involves intranasal exposures. Although the study demonstrates a clear dose-response relationship, confidence in the dose-response assessment is low because intranasal exposures have marginal (if any) relevance to human exposure, the response was not independently replicated, and the observed response may be an artifact. For LdNPV, no endpoint of concern can be identified. Although the individual studies conducted on LdNPV are all somewhat dated, the weight of evidence for LdNPV and similar viruses clearly indicates the unlikelihood of systemic effects in humans after exposure to LdNPV. Thus, confidence in the dose-response assessment for LdNPV is classified as high.

Following standard practices in USDA risk assessments, risk assessment values available from U.S. EPA are adopted directly unless there is a compelling basis for doing otherwise. This approach is taken because the U.S. EPA will typically devote substantial resources and expertise to the development of risk assessment values and it is not feasible to duplicate this effort in risk assessments prepared for the USDA. In addition, the U.S. EPA has the legislative mandate to develop risk values for pesticides and it is sensible for the USDA to administratively defer to U.S. EPA in this area. When risk values are not available from U.S. EPA, the methods used by U.S. EPA are employed to derive surrogate values. Except for disparlure, chronic RfD values are available from U.S. EPA and these values are used directly. For 4-chloroaniline, the U.S. EPA derived a cancer potency factor as well as a chronic RfD, and these values are used directly in the risk assessment. For DDVP, the U.S. EPA derived an acute RfD, and this value is also adopted in the current risk assessment. A complication with DDVP, however, is that this agent is contained within a PVC strip, which substantially impacts its bioavailability. In order to consider

this matter quantitatively, a single and somewhat marginal study regarding the toxicity of DDVP in a PVC strip is used, and confidence in the dose-response assessment is, in turn, marginal. Unlike all of the other chemicals considered in this comparative risk assessment, very little toxicity data are available on disparlure. The U.S. EPA did not derive an RfD for this chemical, and the available toxicity data are insufficient to derive a surrogate RfD. Thus, confidence in the dose-response assessment for disparlure is marginal.

3.3.2. Biological Agents

3.3.2.1. Gypsy Moth – The dose-response assessment for human health effects is based on reports of skin irritation in two populations: one with low exposure (an average of 32 egg masses/acre) and the other with high exposure (an average of 3809 egg masses/acre). The low-exposure group exhibited no increase in skin irritation. Accordingly, 32 egg masses/acre is taken as a NOAEL (no-observed-adverse-effect level) for humans and is used as a surrogate RfD for exposure to the gypsy moth in a manner analogous to the use of RfD values for control agents. The high exposure group had a significant increase in skin irritation, and, based on a dose-response model developed by U.S. EPA, egg mass densities up to128 egg masses/acre are not likely to cause a detectable increase in skin irritation or rashes.

While the dose-response relationship is based on only two exposure levels, the strength of the dose-response relationship is strong. Typically, an association is judged to be statistically significant if the *p*-value (the probability that the association occurred by chance) is 0.05 or less. For the study on which these dose-response relationships are based, p-values are on the order of 0.0004 or less for most groups. The only exception involves individuals over the age of 59 years. In this group, it is unclear if the lack of a significant response is related to a lesser sensitivity to the gypsy moth or less exposure—i.e., less time spent outdoors.

In addition to these quantitative estimates of response, the severity of the response is important, particularly in a comparison of effects caused by exposure to the gypsy moth and effects caused by exposure to the agents used to control the gypsy moth. Dermal responses to the gypsy moth are sufficiently severe to have generated numerous case reports. While precise statistics are not available, it does appear that the severity of the skin irritation is sufficient to cause appreciable numbers of affected individuals to seek medical care. While exposure to the gypsy moth is associated with irritation to the eyes and respiratory tract, quantitative dose-response relationships for these endpoints cannot be developed.

3.3.2.2. B.t.k. – Two types of dose-response assessments are presented for *B.t.k.*, one for irritant effects and the other systemic toxicity. There is relatively high confidence that formulations of *B.t.k.* will cause various types of irritant effects in humans and experimental animals; however, confidence in the quantitative assessment of these effects is limited by a very weak dose-dependency in the incidence of the response. The quantitative assessment for systemic toxic effects is extremely tenuous because it is based on a very conservative interpretation of a single study using a route of exposure (intratracheal instillation) that typically is not used in quantitative risk assessments.

The estimate for irritant effects is actually a set of observations rather than a formal dose-response assessment. Several epidemiology studies were conducted after *B.t.k.* applications at rates within the range of those used in USDA programs to control the gypsy moth—i.e., 20-40 BIU/acre. Two key epidemiology studies, one involving workers (Cook 1994) and the other involving members of the general public (Petrie et al. 2003), suggest that irritant effects, particularly throat irritation, may be reported in groups of humans during or after applications of *B.t.k.* In the worker study, the data demonstrate a statistically significant increase in the incidence of irritant effects in workers. The significantly increased effects include generalized dermal irritation (dry or itchy skin and chapped lips), irritation to the throat, and respiratory irritation (cough or tightness). Furthermore, the overall incidence of all symptoms combined was increased significantly among the workers, compared with the controls . In the study involving the general public, several types of irritant effects are reported; however, the only effect that is clearly statistically significant involves throat irritation ($p=0.002$).

Confidence in accepting whether these reports are biologically significant, however, is reduced by the apparent lack of a strong dose-response relationship. The workers were exposed to up to about 16 million cfu/m^3 and the reported incidence of throat irritation is about 24%. In the study involving members of the general public, no measures of exposure are given. Based on monitoring data from similar applications, however, it is likely that members of the general public may have been exposed to air concentrations ranging from approximately 100 to 4000 cfu/m^3 during or shortly after aerial applications of *B.t.k.* This range is a factor of 3950 to 158,000 less than exposures in the worker study. The apparent incidence of throat irritation in the study on members of the general public, however, is about 19%. Thus, while these much lower exposures lead to a somewhat lesser response, the dose-response relationship appears weak. Nonetheless, these studies are taken together to characterize risk semi-quantitatively, as discussed further in Section 3.4.

There is essentially no information indicating that oral, dermal, or inhalation exposure to *B.t.k.* or *B.t.k.* formulations will cause serious adverse health effects. Extremely severe inhalation exposures that coat the test species with commercial formulations of *B.t.k.* are associated with decreased activity, discolored lungs, and other effects but not mortality. Although the animal data are consistent with data regarding human exposure *B.t.k.*, the animal studies are all based on single concentrations and cannot be used in a meaningful dose-response assessment.

Few studies (David 1990; Hernandez et al. 1999,2000) report mortality after exposure to *B.t.k.,* and these studies, while related to inhalation toxicity, involve atypical routes of exposure. One such study (David 1990) was conducted on a *B.t.k.* Dipel formulation after intratracheal instillations. Intratracheal instillations of bacteria are analogous to inhalation exposures in that the bacteria is essentially inserted into the lungs. Toxic responses including death were observed in treated animals, and the time-to-clearance (estimated from linear regression) was prolonged. Hernandez et al. (1999, 2000) assayed the toxicity of *B.t.k.* after intranasal instillations in mice. This method of dosing is also analogous to inhalation exposures in that the material is deposited in nasal passages and the *B.t.k.* is gradually transported to the lungs by inhalation. Doses of 10^2,

10^4, and 10^6 cfu/mouse caused only local inflamation. A dose of 10^8 cfu/mouse resulted in 80% lethality.

In terms of the human health risk assessment, the data from Hernandez et al. (1999, 2000) are not directly useful. Furthermore, the route of exposure (intranasal instillation) makes any use of these data somewhat tenuous. Concern with the use of this atypical route of exposure in a dose-response assessment is exacerbated because the Hernandez et al. (2000) study does not specify whether or not the instillations were adjusted to a constant volume. If the installations were not adjusted to a constant volume, it is possible that the observed dose-response relationship could be due to differences in volumetric bronchial obstruction or a combination of bronchial obstruction and *B.t.k.*

Notwithstanding these reservations, the Hernandez et al. (1999, 2000) studies provide the best dose-response data available in experimental mammals. Based on a consideration of the Hernandez et al. (2000) study and the estimates of equivalent human exposures, it seems plausible that cumulative exposures up to $1.4x10^{10}$ cfu/m^3 x hour will not cause adverse effects in humans. This estimate is supported by the worker study (Cook 1994) from which an apparent NOAEL of $3x10^8$ cfu/m^3 x hours for adverse health effects in humans can be calculated, and this value is used quantitatively to characterize the potential for serious adverse effects in humans.

3.3.2.3. LdNPV **–** The dose-response assessment for LdNPV and its formulation as Gypchek is extremely simple, compared with the other biological and chemical agents, except disparlure, used to control the gypsy moth. Due to the lack of systemic toxic effects associated with any plausible route of exposure (i.e., oral, dermal, or inhalation), the U.S. EPA did not derive an acute or chronic RfD for Gypchek. Although this approach is reasonable, the risk assessment for LdNPV, which is used in the EIS, derives a surrogate acute RfD of 26 mg/kg bw. The surrogate RfD, which is based on an experimental acute NOAEL of 2600 mg/kg bw in rats and an uncertainty factor of 100, provides a quantitative basis for comparison between the extremely low risks associated with the application of Gypchek and the risks posed by the other gypsy moth control agents. Confidence in this value is limited because no adverse effect levels were identified—i.e., the true NOAEL for Gypchek may be higher than 2600 mg/kg. This uncertainty in the LdNPV risk assessment is relatively minor, given that even extreme exposures are far below any level of concern (Section 3.4).

Technical grade Gypchek is an eye irritant. While not quantitatively considered in the risk assessment, the distinction between the irritant properties of technical grade Gypchek and the lack of eye irritation associated with Gypchek formulations applied in the field is emphasized in order to highlight areas in which prudent handling practices are likely to be most important.

3.3.3. Chemical Agents

3.3.3.1. Diflubenzuron and Tebufenozide **–** As discussed in the hazard identification and the exposure assessment, diflubenzuron and tebufenozide are similar to one another in terms of their toxicological profiles. Both chemicals were tested in a similar and relatively standard set of

toxicity studies required by the U.S. EPA for the registration of pesticides. Their most sensitive endpoint, hematological effects (including methemoglobin formation and several other endpoints characteristic of hemolytic anemia) was observed in all mammalian species tested.

Quantitatively, the similarities between diflubenzuron and tebufenozide are further expanded and even more striking in the dose-response assessment. The U.S. EPA derived RfDs for both compounds and the values are virtually identical: 0.02 mg/kg/day for diflubenzuron and 0.018 mg/kg/day for tebufenozide. Even this minor difference is an artifact of rounding. The U.S. EPA agency-wide workgroup, which derived the RfD for diflubenzuron, typically rounds all RfDs to one significant place. The U.S. EPA Office of Pesticides, which derived the RfD for tebufenozide, often reports RfDs to two significant places. If the agency-wide criteria had been applied to tebufenozide, the two RfDs would be identical—i.e., 0.02 mg/kg/day. Since the molecular weights of diflubenzuron (310 g/mole) and tebufenozide (352 g/mole) are so similar, the RfDs would be identical even when expressed in moles—i.e., $7x10^{-5}$ mMoles/kg/day for diflubenzuron and $5x10^{-5}$ mMoles/kg/day for tebufenozide.

The RfDs for both chemicals are based on dietary studies in rats, and the respective NOAELs are quite similar: 2 mg/kg/day for diflubenzuron and 1.5-2.4 mg/kg/day for tebufenozide. Again, these minor differences are an artifact of the way in which the dietary concentrations (i.e., mg agent/kg diet) used in the studies were converted to dose estimates expressed as mg/kg bw/day based on food consumption. Both RfDs are also based on an uncertainty factor of 100, a factor of 10 for interspecies differences—i.e., extrapolation of animal data to humans—and a factor of 10 for intraspecies variability—i.e., individuals who might be most sensitive to the chemical. For both chemicals, the U.S. EPA determined that an additional uncertainty factor of 10 for the protection of infants and children, a factor that must be considered under the Food Quality Protection Act (FQPA), is not required. Finally, confidence in both RfDs is high, which is stated explicitly in the Agency wide RfD for diflubenzuron and is implicit in the discussion of the chronic RfD for tebufenozide derived by the U.S. EPA Office of Pesticides—i.e., no data gaps are identified.

The acute dose-response assessments on diflubenzuron and tebufenozide prepared by U.S. EPA are similar in that the U.S. EPA elected not to derive an acute RfD for either compound. This approach is taken because the agency concluded that no endpoint for acute dietary exposure could be identified for either chemical. U.S. EPA identifies an acute NOAEL of 10,000 mg/kg bw for diflubenzuron and an acute oral NOAEL of 2000 mg/kg bw for tebufenozide. For the USDA risk assessments on gypsy moth control agents, surrogate acute RfDs are derived for both chemicals according to the methods typically employed by the U.S. EPA, because many areas of greatest concern involve potential acute effects after accidental or incidental exposures.

For diflubenzuron, a surrogate acute RfD of 100 mg/kg could be derived using the NOAEL of 10,000 mg/kg identified by U.S. EPA. A more conservative approach is taken, however, using the NOAEL of 1118 mg/kg from an acute study (single dose) in which Dimilin 4L, a formulation containing petroleum oil, was used. The resulting surrogate acute RfD is 11 mg/kg. A similar

approach is taken for tebufenozide. Rather than using an acute NOAEL of 2000 mg/kg, a NOAEL of 1000 mg/kg/day in pregnant rats and rabbits, identified by U.S. EPA, is used to derive a surrogate acute RfD of 10 mg/kg/day. Like the chronic RfDs, the acute RfDs are nearly identical.

The dose-response assessment for diflubenzuron is somewhat more complicated than that for tebufenozide because of the need to consider 4-chloroaniline quantitatively. As noted in the hazard identification (see Section 3.1), 4-chloroaniline is an environmental metabolite of diflubenzuron and 4-chloroaniline has been classified as a potential human carcinogen. The U.S. EPA derived a chronic RfD for 4-chloroaniline of 0.004 mg/kg/day, and this value is used to characterize risks from 4-chloroaniline for longer-term exposures. This RfD is based on a chronic oral LOAEL of 12.5 mg/kg/day using an uncertainty factor of 3000, three factors of 10 for interspecies extrapolation, sensitive subgroups, and the use of a LOAEL with an additional factor of 3 due to the lack of reproductive toxicity data. As with diflubenzuron, the U.S. EPA has not derived an acute RfD for 4-chloroaniline. For 4-chloroaniline, a conservative approach is taken in which a surrogate acute RfD of 0.03 mg/kg is based on a subchronic (90-day) NOAEL of 8 mg/kg/day. Consistent with the approach taken by U.S. EPA for the chronic RfD, an uncertainty factor of 300 is used. For cancer risk, the U.S. EPA proposes a human cancer potency factor for 4-chloroaniline of 0.0638 $(mg/kg/day)^{-1}$. This potency factor is used to calculate a dose of $1.6x10^{-5}$ mg/kg/day that could be associated with a plausible upper limit of cancer risk of 1 in 1 million.

3.3.3.2. Disparlure – As noted in the hazard identification (see Section 3.1.3.3), the U.S. EPA does not require extensive testing of insect pheromones, including disparlure. This approach is taken because insect pheromones are generally regarded as nontoxic to mammals and because these pheromones are commonly employed in very low environmental concentrations. While the merits of this approach may be argued, the result is that there is little information regarding the toxicity of disparlure, and no RfD values, acute or chronic, have been or can be derived.

The only information that can be used to assess the consequences of exposure to disparlure are LD_{50} or LC_{50} values: an oral LD_{50} value greater than 34,600 mg/kg; a dermal LD_{50} value greater than 2025 mg/kg, and an inhalation LC_{50} value greater than 5 mg/L · 1 hour. Notably, each of the values is expressed as "greater than". In other words, less than half of the organisms died at the specified exposure. In the case of disparlure, these values are actually NOEC values for mortality in that none of the animals died during any of the exposures.

3.3.3.3. DDVP – Like diflubenzuron and tebufenozide, and perhaps to an even greater extent, DDVP has an extensive toxicology data base that has been evaluated by numerous government organizations, including U.S. EPA, the Agency for Toxic Substances and Disease Registry (ATSDR), National Institute for Occupational Safety and Health (NIOSH), Occupational Safety and Health Administration, and the World Health Organization. As noted above, these sources are used when possible for selecting levels of acceptable exposure. Because all of the scenarios

considered in this risk assessment involve only acute exposures, only acute exposure criteria are considered.

The acute RfD established by the U.S. EPA for oral and dermal exposure to DDVP, 0.0017 mg/kg, is used for the risk characterization. The RfD is based an acute oral NOAEL of 0.5 mg/kg from a rat study, and the application of an uncertainty factor of 300. Acute exposure criteria proposed by other groups are comparable to but somewhat higher than the acute RfD. Because some of the accidental acute exposures may substantially exceed the acute RfD, some attempt is made to characterize the consequences of high oral exposures. A human NOAEL of 1 mg/kg for AChE inhibition has been identified. While this NOAEL is not used to modify the acute RfD, it can be used to assess plausible consequences of exceeding the RfD. The human data on DDVP, although extensive, are not sufficient to identify a minimal lethal dose. For the current risk assessment, the lowest reported lethal dose (16 mg/kg) is used to assess the plausibility of observing serious adverse effects in cases of accidental overexposure to DDVP.

A number of inhalation criteria are available for DDVP. Since potentially significant inhalation exposures are likely only in workers, the occupational exposure criterion of 0.1 mg/m^3 proposed by American Conference of Governmental Industrial Hygienists is used. This value is a factor of 10 below the occupational criteria proposed by NIOSH and OSHA.

A major factor and a major complication in the dose-response assessment of DDVP involves the formulation of DDVP in a PVC strip. Some of the accidental exposures considered in this risk assessment involve a small child gaining access to a DDVP-PVC strip and being subject to both oral and dermal exposure. While there is little doubt that the PVC strip will slow the rate of exposure and reduce the risk, this is extremely difficult to quantify. Despite the availability of numerous studies regarding the toxicity of DDVP itself, the number of studies regarding the toxicity of DDVP-PVC strips is relatively small. By far the most relevant study is that conducted by Stanton et al. (1979), which clearly indicates that DDVP in a PVC formulation will be much less toxic than unformulated DDVP. The extent of the difference in toxicity can only be semi-quantitatively characterized. For unformulated DDVP, the LD_{50} value was 157 (113–227) mg/kg with no mortality observed at 56 mg/kg. For the DDVP-PVC formulation, no deaths occurred at doses of up to 1000 mg/kg, although signs of toxicity consistent with AChE inhibition were observed at doses of 320 and 1000 mg/kg. Neither tremors nor salivation were observed at doses of 240 or 180 mg/kg. Stanton et al. (1979) do not provide comparative data on the extent of AChE inhibition in unformulated DDVP and the DDVP-PVC formulation.

3.4. RISK CHARACTERIZATION

3.4.1. Overview

Risk characterization is the process of comparing the exposure assessment with the dose-response assessment to express the level of concern regarding a specific exposure scenario or set of scenarios. For systemic toxic effects, risk characterizations are presented as hazard quotients (HQs). A hazard quotient is the ratio of a projected level of exposure divided by some index of an acceptable exposure, such as an RfD. If the HQ is substantially less than one – i.e., the level of exposure is less than the level of acceptable exposure—there is no apparent cause for concern. If the hazard quotient is greater than unity, there is cause for concern.

Because the hazard quotient does not describe dose-response or dose-severity relationships, a comparison of the magnitudes of the hazard quotients among different agents may not be a reliable index of relative risk and other types of information need to be considered. Hazard quotients that are close to a level of concern—i.e., between about 0.1 and 10—may be more difficult to interpret because of uncertainties in both the exposure estimates as well as the dose-response relationships. While the range from 0.1 to 10 is somewhat arbitrary in terms of classifying the nature of concern, this is similar to the approach recently adopted by ATSDR (2004) in which concern for interactions of chemicals is triggered when individual hazard quotients exceed a value of 0.1.

In order to reflect these gradations of concern in the general interpretation of hazard quotients, the comparative risk characterization is not organized by biological and chemical agents (as in the previous sections) but is organized by the nature of the hazard quotients: agents of marked concern (HQ>10), agents of marginal concern (HQ>0.1 but <10), and agents of ***minimal*** concern (HQ<0.1). The word ***minimal*** is emphasized because of the inherent limitation in all risk assessments. Risk assessments can never prove absolute safety—i.e., it is impossible to prove the negative, that something does not exist, in this case risk. Risk assessments, however, can be and are used to determine whether or not there is a basis for asserting that risk is plausible.

An overview of the comparative risk characterization is summarized in Table 3-4 and illustrated in Figure 3-1. Of the agents considered in this risk assessment, the gypsy moth and DDVP are clearly agents of marked concern, although the nature of the concerns is different. If the gypsy moth is not controlled, population outbreaks will occur and humans will be exposed to large numbers of gypsy moth larvae. If this occurs, a substantial number of individuals will experience irritant effects that are sufficiently severe to cause these individuals to seek medical attention. No more serious effects are likely. For DDVP, the potential for risk is clear but the likelihood of observing risk seems to be remote. Under normal conditions and proper handling, exposures to DDVP will be negligible and risk will be inconsequential. Workers who mishandle a DDVP-PVC strip or members of the general public who handle a DDVP-PVC may be exposed to levels of DDVP that are far above levels that would be considered acceptable. While such exposures clearly should be avoided, it seems unlikely that they would result in frank signs of toxicity. This conclusion is consistent with human experience in the use of DDVP resin strips.

Diflubenzuron and tebufenozide are agents of marginal concern. Under most foreseeable conditions of exposure—i.e., exposure scenarios that might be characterized as typical—levels of exposure will be far below levels of concern. At the upper ranges of plausible exposure— levels that might be characterized as extreme—the hazard quotients for diflubenzuron approach a level of concern (HQs between 0.1 and 0.5 for both diflubenzuron and its 4-chloroaniline metabolite). For tebufenozide, the highest hazard quotient is 1.5, indicating that, although unlikely to cause overt signs of toxicity, the exposure would be characterized as undesirable. The somewhat higher hazard quotients for tebufenozide are attributed solely to the higher application rates for this compound, compared with diflubenzuron.

Among the agents of minimal concern, *B.t.k.* is somewhat problematic. Based on the risk for serious adverse effects, there is clearly no cause for concern (the highest HQ is 0.04). As discussed in the dose-response assessment, this lack of concern is reenforced by a very aggressive and protective interpretation of the available toxicity data. Nonetheless, there is some residual concern with irritant effects. These effects are quite plausible in accidental cases of gross overexposure—e.g., splashing a formulation into the eye. These kinds of concern are minimal and are common to almost all chemical or biological agents. The more troubling concern involves studies of workers and non-workers who report irritant effects, primarily throat irritation. Whether or not these effects should be attributed to the *B.t.k.* exposure is unclear.

The risk characterization for LdNPV and disparlure is unequivocal. Based on the available information, there is no plausible basis for concern that exposure will cause serious adverse effects. Again, various accidental exposures, such as splashing the agent into the eyes, might cause transient irritant effects.

3.4.2. Agents of Marked Concern

3.4.2.1. Gypsy Moth – Although the quantitative dose-response assessment is based on only one study, the study demonstrates a clear dose-response relationship and is supported by less quantitative reports of irritant effects associated with exposure to the gypsy moth as well as other lepidopteran larvae. In sparse to moderate infestations—i.e., egg mass densities of more than 500 egg masses/acre—adverse effects involving skin irritation are not likely to be detectable in populations of exposed humans. Nonetheless, some individuals who have contact with gypsy moth larvae might develop skin irritation. In heavy gypsy moth infestations—i.e., from more than 500 to 5000 egg masses/acre—the occurrence of adverse skin reactions is expected to be hight, and the effects are likely be severe enough to cause some individuals to seek medical attention. In extreme outbreaks—i.e., greater than 5000 egg masses/acre— the effects will be qualitatively similar to those of severe infestations but may affect up to one-third of the population. Heavy infestations or extreme outbreaks may cause ocular and respiratory effects in some people; nonetheless, there is no way to quantify the likelihood of observing these effects. Similarly, severe infestations are often considered to be a nuisance and cause aesthetic damage to the environment. Both of these factors can lead to stress in some individuals. Young children may be a group at special risk from effects of gypsy moth exposure; however, it is not clear whether children are more sensitive than adults to the effects of gypsy moth exposure or whether

responses in children appear greater because children spend more time outdoors compared with adults.

3.4.2.2. DDVP – In most cases, exposures to both workers and members of the general public should be negligible. If workers take prudent steps to limit both dermal and inhalation exposures, the likelihood of exposures to DDVP reaching a level of concern appears to be very low. Similarly, members of the general public should not be exposed to substantial amounts of DDVP. The DDVP is contained within a PVC strip to ensure that the active ingredient is slowly released over a long period of time. The strip, in turn, is placed within a trap and the trap is placed so that it will not be accessed except in the case of intentional tampering or trap monitoring.

Nonetheless, the risk assessment for DDVP develops exposure scenarios for both workers and members of the general pubic, which are intended to illustrate the potential effects of mishandling or tampering with DDVP strips. For workers, the greatest risks are associated with inhalation exposures from assembling the traps in enclosed and poorly ventilated spaces or transporting the traps in the passenger compartments of vehicles. These risks can be readily avoided. Dermal exposures can also lead to lesser but sill undesirable levels of exposure. For members of the general public, all of the exposure scenarios are accidental and some are extreme. The most likely of these is the accidental contamination of a small body of water. This scenario leads to exposures that are below the level of concern by a factor of about 25. If a child were to come into contact with a DDVP strip, however, both dermal and oral exposures could substantially exceed a level of concern. Although such exposures clearly should be avoided, it seems unlikely that they would result in frank signs of toxicity. This conclusion is consistent with human experience in the use of DDVP resin strips.

3.4.3. Agents of Marginal Concern

3.4.3.1. Diflubenzuron – The risk characterization for potential human health effects associated with the use of diflubenzuron is relatively unambiguous: none of the hazard quotients reach a level of concern at the highest application rate that could be used in USDA programs. In that many of the exposure assessments involve very conservative assumptions—that is, assumptions that tend to overestimate exposure—and because the dose-response assessment is based on similarly protective assumptions, there is no plausible basis for concluding that this use of diflubenzuron poses a hazard to human health.

Notwithstanding the above assertion, it is worth noting that the greatest relative risk concerns the contamination of water with 4-chloroaniline rather than exposure to diflubenzuron itself. The highest hazard quotient for diflubenzuron is 0.1, a factor of 10 below a level of concern. Since this hazard quotient is based on toxicity, an endpoint that is considered to have a population threshold, it is reasonable to assert that the risk associated with exposure to diflubenzuron is essentially zero.

Such is not the case with 4-chloroaniline, which is classified as a probable human carcinogen and is an environmental metabolite of diflubenzuron. For 4-chloroaniline, the highest hazard quotient is 0.4, below the level of concern by a factor of only 2.5. The scenario of greatest concern involves cancer risk from drinking contaminated water. This risk would be most plausible in areas with sandy soil and annual rainfall rates ranging from about 50 to 250 inches. The central estimate of the hazard quotient for the consumption of water contaminated with 4-chloroaniline and based on a cancer risk of 1 in 1million is 0.09, which is 10 times lower than the level of concern.

3.4.3.2. Tebufenozide – The similarities between tebufenozide and diflubenzuron have been emphasized throughout this comparative risk assessment. As noted in the dose-response assessment, the toxicities of these two compounds are virtually identical. While both diflubenzuron and tebufenozide are classified as agents of marginal concern—i.e., risk quotients between 0.1 and 10 —tebufenozide does exceed the level of concern, whereas diflubenzuron does not. This difference is due to the higher application rates that may be used with tebufenozide. These higher application rates for tebufenozide increase the levels of exposure, which results in somewhat higher hazard quotients for tebufenozide, compared with diflubenzuron.

Nonetheless, as with diflubenzuron, there is no clear indication that adverse effects are likely to result from exposure to tebufenozide. At the maximum application rate considered in this risk assessment, two applications at 0.12 lb/acre spaced three days apart, there is little indication that adverse effects on human health are likely and only one scenario exceeds a risk quotient of 1. Based on central estimates of exposure— those that might be considered typical and expected—hazard quotients including workers and members of the general public range from 0.00003 to 0.03, below a level of concern by factors ranging from approximately 30 to 33,000. At the upper range of plausible exposures, the hazard quotient for ground spray workers reaches a level of concern—i.e., a hazard quotient of 1. For members of the general public, the upper range of exposure leads to a hazard quotient of 1.5 for the longer-term consumption of contaminated vegetation following two applications at 0.12 lb/acre. Because of the linear relationship between exposure and application rate, two applications at 0.08 lb/acre would reach but not exceed a level of concern. With a single application at the maximum rate of 0.12 lb/acre, the hazard index is 0.8, below the level of concern. While the longer-term consumption of contaminated vegetation is probably not a likely scenario, it is a standard exposure scenario used in USDA risk assessments to consider the longer-term consumption of food items, like berries, that might be sprayed during the broadcast application of a pesticide. This risk assessment suggests that two applications at 0.08 lb/acre or more should be avoided in areas where members of the general public might consume contaminated fruits or other contaminated vegetation.

3.4.4. Agents of Minimal Concern

3.4.3.1. B.t.k. – The risk characterization regarding exposure to *B.t.k.* and its formulations is generally consistent with that of the previous USDA risk assessment as well as more recent risk assessments conducted by the U.S. EPA and the World Health Organization: *B.t.k.* and its

formulations are likely to cause irritation to the skin, eyes, and respiratory tract; however, serious adverse health effects are implausible. Whether irritation is caused by *B.t.k.* in typical field applications used to control the gypsy moth is uncertain. While epidemiology studies involving self-reporting of symptoms do suggest that reports of irritant effects are to be expected, the biological plausibility of these effects is called into question because of an insubstantial dose-dependency for the irritant effect.

B.t.k. applications to control or eradicate the gypsy moth are not expected to cause serious adverse health effects in humans. At the extreme upper range of exposure in ground workers, exposure levels are estimated to be below the functional human NOAEL for serious effects by a factor of 25. For members of the general public, exposure levels are estimated to be below the functional human NOAEL by factors ranging from about 28,000 to 4,000,000 [4 million]. This assessment is based on reasonably good monitoring data, conservative exposure assumptions, and an aggressive and protective use of the available toxicity data. Based on these data, it is not likely that overt signs of toxicity will be observed in any group— ground workers, aerial workers, or members of the general public—exposed to *B.t.k.* as the result of gypsy moth control and eradication programs conducted by the USDA.

There is no documented evidence of a subgroup of individuals who are more sensitive than most members of the general public to *B.t.k.* formulations. According to a recent epidemiology study, asthmatics are not likely to be affected adversely by aerial applications of *B.t.k.* The literature on *B.t.k.* includes one anecdotal claim of a severe allergy to a carbohydrate in a *B.t.k.* formulation; however, neither the claim nor observations of similar effects are substantiated in the available published epidemiology studies. On the other hand, *B.t.k.* formulations are complex mixtures, and the possibility that individuals may be allergic to some of the components in the formulations is acknowledged by a state health service.

As noted in Section 3.1, pre-treatment with an influenza virus substantially increased mortality in mice exposed to various doses of *B.t.k.* Although the relevance of this observation to public health cannot be assessed well at this time, the viral enhancement of *B.t.k.* toxicity is likely to be an area of further study in the coming years.

3.4.3.2. LdNPV (Gypchek) **–** There is no plausible basis for concern that either workers or members of the general public are at risk of adverse effects from the use of Gypchek to control the gypsy moth. This statement follows from the failure to identify any hazard associated with exposures to Gypchek or LdNPV and is essentially identical to the risk characterization given by the U.S. EPA.

As discussed in both the exposure and dose-response assessments, the current risk assessment extends the U.S. EPA risk assessment by proposing a surrogate acute RfD and presenting a very conservative exposure assessment based on the accidental spray of a home garden. This approach is taken simply to facilitate the comparison of risks (or lack of risk) associated with Gypchek to the risks associated with other agents used to control the gypsy moth. Based on a

relatively standard dose-response assessment and very conservative exposure assumptions, plausible exposures to Gypchek are below a level of concern by factors ranging from about 50 to more than 750. While more typical exposures—i.e., incidental exposure to Gypchek in water or air—are not provided, they will be substantially less than the range of accidental exposure scenarios used to quantify risk.

3.4.3.3. Disparlure – Although there are studies regarding the acute toxicity of disparlure in laboratory animals, the lack of subchronic and chronic toxicity data precludes a quantitative characterization of risk. The available data regarding the acute toxicity of disparlure indicate that the potential hazard from exposure to the compound is low.

The reliance on acute toxicity data introduces uncertainties into the risk assessment of disparlure that are quite different from the other better studied agents, and these uncertainties cannot be quantified. Other uncertainties in this analysis are associated with the exposure assessment and involve environmental transport and dermal absorption. These uncertainties are relatively minor compared with the lack of subchronic or chronic toxicity data. Thus, while there is no reason to believe that longer-term exposure to disparlure will produce adverse effects, this assumption can not be substantiated due to the lack of chronic toxicity data. The significance of this uncertainty is at least partially offset by the very low exposures that are plausible given the limited use of disparlure. For example, as noted in the dose-response assessment, inhalation exposures of mice to 5 mg/L (5,000,000 $\mu g/m^3$) for 1 hour caused no mortality or signs of toxicity. As noted in the exposure assessment, likely concentrations of disparlure in air after applications comparable to those used in programs to control the gypsy moth are likely to be on the order of 0.004 $\mu g/m^3$, a factor of 1,250,000,000 (1.25 billion) below the apparent NOEC for acute toxicity. This relationship is consistent with the general assumption made by the U.S. EPA that exposures to insect pheromones will be far below levels of concern (U.S. EPA 2004).

4. ECOLOGICAL RISK ASSESSMENT

4.1. HAZARD IDENTIFICATION

4.1.1. Overview

An overview of the comparative hazard identification is given in Table 4-1. Unlike the human health risk assessment, in which the potential effects of the biological agents are similar, each of the ecological effects profiles of the biological agents considered in this risk assessment is quite distinct. The principal effect of the gypsy moth is damage to sensitive trees, which can be substantial. Because of the obvious importance of vegetation to the existence and habitat of most animals, defoliation by the gypsy moth will have numerous secondary effects in many other groups of organisms. There is, however, no indication that the gypsy moth will have direct effects on groups of organisms other than sensitive plants. LdNPV, on the other hand, is unlikely to have effects on species other than the gypsy moth. *B.t.k.* is toxic to nontarget *Lepidoptera* as well as the gypsy moth and some other lepidopteran species, but is unlikely to have direct effects on other groups of organisms. Thus, the potential effects of all of the biological agents are considered relatively specific, with LdNPV showing the greatest degree of specificity (only the gypsy moth), followed by the gypsy moth itself (several types of plants) and *B.t.k.* (several types of *Lepidoptera*).

The chemical agents also differ in specificity: disparlure is most specific, tebufenozide is relatively specific to *Lepidoptera*, diflubenzuron is less specific and may affect many arthropods, and DDVP is a nonspecific biocide toxic to most groups of animals. As a pheromone, disparlure is almost as specific as LdNPV. It will attract the gypsy moth and two other closely related species, the nun moth (*Lymantria monacha*) and the pink gypsy moth (*Lymantria fumida*). Like the gypsy moth, both of these *Lymantria* species are forest pests, and adverse effects on these species are not a substantial concern for this risk assessment. In addition, the pink gypsy moth is native to Japan and is not found in the United States. A major qualification regarding the specificity of disparlure is the limited amount of information available on nontarget species. The data that are available indicate that the relative toxicity of disparlure to *Daphnia magna*, a commonly used test species in aquatic toxicity studies, is high. Diflubenzuron and tebufenozide are clearly toxic to mammals and at least some arthropods. In mammals, exposure to either chemicals causes adverse effects in blood (methemoglobinemia), as discussed in the human health risk assessment. In terrestrial and aquatic arthropods, exposure to either chemical interferes with growth and development. Because of differences in the mechanism of action of diflubenzuron and tebufenozide, the toxicity of tebufenozide appears to be somewhat more selective. For instance, effects in birds have been clearly demonstrated for tebufenozide but not for diflubenzuron. Nonetheless, it is plausible to speculate that both diflubenzuron and tebufenozide are likely to cause adverse hematological effects in birds, similar to those observed in mammals exposed to these chemicals. In terms of its mechanism of action, DDVP is a general neurotoxin. In all animals that have nervous systems that involve acetylcholinesterase (AChE) and use acetylcholine (ACh) as a neurotransmitter (a substance necessary to make the nerves work properly), DDVP will be toxic and sufficiently high exposures to DDVP will be lethal. The definition of *sufficiently high*, however, is critical and variable. Although DDVP is not selective

mechanistically, differences in sensitivity among species are substantial. Insects are much more sensitive than mammals or other higher organisms to DDVP. This difference in sensitivity is what characterizes DDVP as an effective insecticide that can be used safely.

4.1.2. Biological Agents

4.1.2.1. Gypsy Moth – The clearest primary effect of gypsy moth infestations is on terrestrial plants, primarily trees. Various instars of the gypsy moth larvae will feed on host trees and can cause extensive defoliation which can kill some of the infested trees. On a larger scale, the extensive defoliation and/or death of trees may result in secondary changes to vegetation, which will, in turn, affect other forms of vegetation as well as various animal species (primarily related to changes in habitat). Gypsy moth larvae appear to have definite food preferences; oak, birch, poplar, and apple trees seem to be their favorite food sources. While both the European and Asian gypsy moth cause similar types of damage (i.e., defoliation), their feeding preferences are somewhat different, with the Asian gypsy moth preferring a wider range of vegetation. Heavy defoliation is much more common among the oaks than among trees that are not particularly favored as food by the gypsy moth. For susceptible oaks, the effects of infestations on tree mortality varies according to the initial condition of the stand and the number of infestations. Generally, gypsy moth infestations result in mortality of less than 15% of total basal area—i.e., mortality of trees involving 15% the total area of the tree trunks near the ground. When heavy defoliation is followed by massive overstory mortality, existing shrub and herb cover increase dramatically due to increases in available light, moisture, and nutrients. Extensive loss of the existing canopy will also favor the growth of tree species that are intolerant to shade and will shift the forest ecosystem towards earlier successional stages.

The only other groups of organisms likely to be affected directly by the gypsy moth are some and probably very few other lepidopteran species, including the northern tiger swallowtail butterfly. The mechanisms for direct adverse effects on other lepidopteran species may include bacterial contamination of the leaves by gypsy moth larvae and a decrease in the nutritional value of the leaves damaged by the gypsy moth. Most studies, however, do not indicate substantial direct effects on other insects, including *Lepidoptera*. In some cases, increases may be seen in populations of insect predators of the gypsy moth.

There is no evidence in the literature of direct adverse effects of the gypsy moth on most groups of animals. Indirect effects, associated with damage to vegetation, may be of substantial consequence to some species, including squirrels, mice, and other mammals that rely on acorns. Although some mammals consume insects, including the gypsy moth, there is no evidence that gypsy moth outbreaks have a substantial impact on insectivorous mammals. Similarly, birds and aquatic species are not likely to be affected directly or adversely by the gypsy moth. In some species of birds, gypsy moth infestations and subsequent defoliation may be beneficial, especially for those species favoring dead wood as a habitat.

4.1.2.2. B.t.k. – The hazard identification for mammals is closely related to the hazard identification for the human health risk assessment in that both are based, in part, on numerous

standard toxicity studies in experimental mammals. Although *B.t.k.* may persist in mammals for several weeks after exposure, there is little indication that oral or dermal exposure leads to serious adverse effects. Most inhalation studies do not suggest a potential for adverse effects even at *B.t.k.* concentrations much greater than those likely to be encountered in the environment. The lack of a positive hazard identification is supported by field studies which demonstrate a lack of adverse effects in populations of mammals after applications of *B.t.k.*

Toxicity studies in birds are limited to standard acute exposures required by U.S. EPA for product registration. The studies all involve either single-dose gavage administration or five daily dose gavage administrations, and none of the studies reports signs of toxicity or pathogenicity at single oral doses up to 3333 mg formulation/kg bw or at multiple oral doses up to 2857 mg formulation/kg bw. Due to the lack of toxicity of *B.t.k.* formulations as well as other *B.t.* strains, the U.S. EPA did not require chronic or reproductive toxicity studies in birds. This apparent lack of toxicity is supported by numerous field studies in birds. In one field study, a transient decrease in abundance was noted in one species, the spotted towhee (*Pipilo maculatus*). This observation is inconsistent with other field studies on *B.t.k.,* and, according to the investigators, may be an artifact of the study design.

The mechanism of action of *B.t.k.* in *Lepidoptera* is relatively well characterized. *B.t.k.* vegetative cells produce spores and crystals. After the insect consumes the crystals, toxins are formed that attach to the lining of the mid-gut of the insect and rupture the cell walls. The *B.t.k.* spores germinating in the intestinal tract enter the body cavity through the perforations made by the crystal toxins and replicate causing septicemia and eventually death. While various strains of *B.t.* are often characterized as selective pesticides, *B.t.k.* is toxic to several species of target and nontarget *Lepidoptera*. Sensitive nontarget *Lepidoptera* include larvae of the Karner blue butterfly, two species of swallowtail butterflies, a promethea moth, the cinnabar moth, and various species of Nymphalidae, Lasiocampidae, and Saturniidae.

While some nontarget lepidopteran species appear to be as sensitive as target species to *B.t.k.*, most studies indicate that effects in other terrestrial insects are likely to be of minor significance. There is relatively little information regarding the toxicity of *B.t.k.* or *B.t.k.* formulations to terrestrial invertebrates other than insects. Some oil-based *B.t.k.* formulations may be toxic to some soil invertebrates; however, the toxicity is attributable to the oil in the formulation and not to *B.t.k.* There is no indication that *B.t.k.* adversely affects terrestrial plants or soil microorganisms.

The U.S. EPA classifies *B.t.k.* as virtually non-toxic to fish, and this assessment is consistent with the bulk of experimental studies reporting few adverse effects in fish exposed to *B.t.k.* concentrations that exceed environmental concentrations associated with the use of *B.t.k.* in USDA programs. Although there are no data regarding the toxicity of *B.t.k.* or its formulations to amphibians, other strains of *B.t.* appear to have low toxicity to amphibians. The effects of *B.t.k.* on aquatic invertebrates is examined in standard laboratory studies and in numerous field studies. At concentrations high enough to cause decreases in dissolved oxygen or increased biological

oxygen demand, *B.t.k.* may be lethal to certain aquatic invertebrates, like *Daphnia magna*. Most aquatic invertebrates, however, seem relatively tolerant to *B.t.k.* This assessment is supported by several field studies that have failed to note remarkable effects in most species after exposures that substantially exceed expected environmental concentrations. As with effects on terrestrial plants, the toxicity of *B.t.k.* to aquatic plants has not been tested.

The U.S. EPA's Office of Pesticides (U.S. EPA/OPP 1998) has raised concerns that some batches of *B.t.* may contain heat labile exotoxins that are toxic to *Daphnia*. The production of these toxins is an atypical event thought to be associated with abnormal or poorly controlled production processes. The U.S. EPA requires manufacturers to submit a daphnid study on each new manufacturing process to demonstrate that heat labile exotoxin levels are controlled.

4.1.2.2. LdNPV **–** Similar to the hazard identification for the human health risk assessment, the hazard identification for nontarget wildlife species fails to identify any adverse effects of concern—i.e., there is no indication that LdNPV or the Gypchek formulation of LdNPV has the potential to cause adverse effects in any nontarget species. The mammalian toxicity data base for LdNPV is reasonably complete and indicates that LdNPV is not pathogenic or otherwise toxic to mammals. One specific study conducted on wildlife mammals that may consume contaminated gypsy moth larvae indicates no adverse effects in mice, shrews, and opossums. Relative to the large number available studies in mammals, few studies are available in birds but the results of these studies are nearly identical to those in mammals indicating that exposures to LdNPV at levels substantially higher than those likely to occur in the environment will not be associated with adverse effects. Based on bioassays of LdNPV on numerous nontarget insect species and supported by the generally high species specificity of related baculoviruses, the hazard identification for LdNPV in nontarget insects is strikingly similar to that in birds and mammals. There is no indication LdNPV will cause adverse effects in nontarget insects at any level of exposure. Relatively few studies regarding the toxicity of LdNPV have been conducted in fish or aquatic invertebrates; nevertheless, these studies are consistent with studies in terrestrial species, indicating a lack of toxicity to fish and aquatic invertebrates. No data are available on the effects of LdNPV on amphibians, aquatic or terrestrial plants, or other microorganisms. While this lack of information does, by definition, add uncertainty to this risk assessment, there is no basis for asserting that effects on these or other organisms are plausible.

4.1.3. Chemical Agents

4.1.3.1. Diflubenzuron and Tebufenozide **–** The toxicity of diflubenzuron and tebufenozide is well characterized in most groups of animals, including mammals, birds, terrestrial invertebrates, fish, and aquatic invertebrates. In general, both of these compounds are much more toxic to some invertebrates, specifically arthropods, than to vertebrates or other groups of invertebrates.

This differential toxicity of these two compounds involves fundamentally different and well understood mechanisms of action, with tebufenozide being somewhat more selective than diflubenzuron. Toxicity of diflubenzuron to sensitive invertebrate species is based on the inhibition of chitin synthesis. Chitin is a polymer (repeating series of connected chemical

subunits) of a glucose-based molecule and is a major component of the exoskeleton, outer body shell, of all arthropods. The inhibition of the formation of chitin disrupts the normal growth and development of insects and other arthropods. Both terrestrial and aquatic arthropods are affected, but there seems to be some substantial differences in sensitivity. The toxicity of tebufenozide to sensitive invertebrates is based on the mimicking of 20-hydroxyecdysone, an invertebrate hormone that controls molting. The effectiveness of tebufenozide in mimicking 20-hydroxyecdysone activity, however, appears to vary markedly among orders and species of invertebrates. In general, moths are sensitive to tebufenozide but other insects are much less sensitive.

The most sensitive effects in wildlife mammalian species and possibly other vertebrates exposed to diflubenzuron or tebufenozide are likely to be the same as those in experimental mammals (i.e., effects on the blood). The major difference between the hazard identification for diflubenzuron and tebufenozide concerns potential reproductive effects. As noted in the comparative human health risk assessment, tebufenozide may cause reproductive effects in mammals, while this effect has not been noted for diflubenzuron. Similarly, the reproductive effects of tebufenozide but not diflubenzuron are of concern for birds, although the data are somewhat inconsistent. The available studies on tebufenozide include a reproduction study investigating effects in mallard ducks and two reproduction studies investigating effects in bobwhite quail. In one of the quail studies, dietary concentrations of 300 and 1000 ppm caused reproductive effects. The effects were not observed in that study at 100 ppm; moreover, the effects were not observed in the more recent quail study or in the study on mallard ducks. A field study regarding the effects of tebufenozide on reproductive performance in birds noted trends that were not statistically significant but, nonetheless, suggestive of adverse reproductive effects in a warbler species. Thus, consistent with the interpretation by the U.S. EPA, reproductive effects in both mammals and birds are considered endpoints of concern for tebufenozide. For diflubenzuron, there is only one relatively old report of reproductive effects in birds and the effects reported have not been noted in other studies. Thus, also consistent with the approach taken by U.S. EPA, reproductive effects are not identified as an endpoint of concern for diflubenzuron.

Terrestrial invertebrates appear to be much more sensitive to diflubenzuron and tebufenozide than are vertebrates, and tebufenozide appears to affect a narrower group of invertebrates than does diflubenzuron. The terrestrial species most sensitive to diflubenzuron are arthropods, a large group of invertebrates, including insects, crustaceans, spiders, mites, and centipedes. In terrestrial organisms, the species most sensitive to diflubenzuron include lepidopteran and beetle larvae, grasshoppers, and other herbivorous insects. More tolerant species include bees, flies, parasitic wasps, adult beetles, and sucking insects. Tebufenozide is toxic to a much narrower range of terrestrial insects. In general, moths are sensitive to tebufenozide but other insects are much less sensitive.

Both diflubenzuron and tebufenozide are also more toxic to aquatic invertebrates than they are to fish. U.S. EPA has classified diflubenzuron as practically non-toxic to fish, with LC_{50} values that

range from 25 to 500 mg/L. Tebufenozide is somewhat more toxic to fish, with LC_{50} values that range from 2.2 to 6.5 mg/L for fish, categorized as moderately toxic using the U.S. EPA classification system. Invertebrates are affected at much lower concentrations and the relative potency of the two compounds is reversed, with diflubenzuron being substantially more toxic than tebufenozide to aquatic invertebrates. The NOEC values in invertebrates for diflubenzuron are as low as 0.3 µg/L in acute studies and 0.04 µg/L in longer-term studies. Tebufenozide is substantially less toxic to invertebrates, with NOEC values as low as 120 µg/L in acute studies and 3.5 µg/L in longer-term studies.

4.1.3.2. DDVP – Although DDVP is a general neurotoxin, the available data suggest that invertebrates are more sensitive than other organisms to DDVP. For example, the oral LD_{50} in honey bees is 0.29 mg/kg bee, and the topical LD_{50} is 0.65 mg/kg bee. Although DDVP is also toxic to birds, the oral LD_{50} value is about 10 mg/kg for the most sensitive species. Short-term repeat dose studies in mammals found that oral exposures to doses below about 0.5 mg/kg-day or inhalation exposures to 1–2 mg/m³ generally do not result in adverse effects. Thus, no effects are apparent in experimental mammals at doses that are clearly lethal to bees.

Aquatic animals are also sensitive to DDVP. As with terrestrial animals, invertebrates appear to be more sensitive than vertebrates. The lowest reported LC_{50} value in fish is approximately 0.2 mg/L. Some aquatic invertebrates are much more sensitive than fish to DDVP. For daphnids, the most sensitive group of invertebrate species, reported EC_{50} values range from 0.00007 to 0.00028 mg/L.

Most of the toxicity data on ecological receptors is limited to free DDVP, rather than a slow-release formulation like the Vaportape II product used in USDA programs to control the gypsy moth. Hence, the toxicity values reported for indicator species are likely to be conservative (i.e., suggest greater toxicity), as compared with Vaportape II. Although U.S. EPA assessed the ecological effects of DDVP, the exposures assessed are not specific to formulations in which DDVP is encapsulated in PVC resin. In general, aside from those organisms that enter the milk carton trap or those that remove the PVC strip form the trap, toxicity resulting from exposure of ecological receptors to DDVP in Vaportape II milk carton traps is not likely.

4.1.3.3. Disparlure – There is very little information regarding the toxicity of disparlure to nontarget wildlife species. As noted in the human health risk assessment, the U.S. EPA does not require extensive testing of insect pheromones. Thus, the only studies available are acute studies in bobwhite quail, mallard ducks, rainbow trout, bluegill sunfish, *Daphnia magna*, and Eastern oysters. No chronic exposure studies were identified.

Results of acute gavage and dietary exposure studies in mallard ducks and bobwhite quail show that disparlure has very low toxicity in these species, with no mortalities observed following exposure to up to 2510 mg/kg in bobwhite quail. Limited data are available regarding the toxicity disparlure to aquatic animals. Relative to mammals and birds, *Daphnia* appear to the

most sensitive species tested, with an LC_{50} value of 0.098 mg/L. In rainbow trout, 20% mortality was noted at a concentration of 100 mg/L.

4.2. EXPOSURE ASSESSMENT

4.2.1. Overview

Table 4-2 summarizes the exposure assessments on nontarget species for each of the agents covered in the risk assessment. Table 4-2 is similar to the corresponding table for the human health risk assessment (see Table 3-2) because the applications and uses for each control agent are identical. Since diflubenzuron, tebufenozide, LdNPV, and disparlure can be applied in broadcast applications, exposure potential is high and in many cases unavoidable, as is true for the human health risk assessment. When disparlure is used as an attractant in traps, exposures will be variable and primarily incidental. Exposures to the gypsy moth itself are also variable and depend on the extent of the gypsy moth population, which can range from low level infestation to outbreak conditions.

There are, however, notable differences between the human health exposure assessment and the ecological exposure assessment. Unlike Table 3-2, Table 4-2 does not provide measures of exposure for each agent, because the measures of exposure for ecological effects vary not only among the control agents but also among the target groups for each agent. For example, exposures to the gypsy moth are measured as egg masses/acre in the human health risk assessment, which is the same measure of exposure used for terrestrial vegetation, because it is the primary determinant in the dose-response assessment for plants. For all other species, however, effects from the gypsy moth are most likely to be secondary, which means the exposure assessment for these indirectly affected species is based on defoliation—i.e., the result of the dose-response assessment for terrestrial vegetation is used as the exposure assessment for most other groups of organisms.

Other differences in the exposure assessments for nontarget species are mostly superficial. For each of the chemical agents, the mass of the chemical is typically used as the measure of exposure. Depending on the group, the measure of exposure may be expressed as dose (mg agent/kg bw for most terrestrial species), concentration (mg agent/L of water for aquatic species), or simply as application rate (lb agent/acre). This last measure is used primarily when field studies are the basis for the dose-response assessment.

As in the human health risk assessment, different measures of exposure are used for each of the biological agents. For *B.t.k.*, most of the exposures are characterized simply as an application rate in units of BIU/acre. Nevertheless, colony forming units are used for some of the mammalian exposure scenarios. Also as in the human health risk assessment, no clear hazard potential is identified for LdNPV. The very few exposure scenarios that are quantified in the ecological risk assessment for LdNPV are based on the mass of the formulation, Gypchek.

The level of detail used in the exposure assessments for the different chemicals reflects differences in the use patterns and the nature of the available toxicity data. Full sets of exposure assessments in several groups of animals are developed for diflubenzuron and tebufenozide. As in the human health risk assessment, the exposure assessment for diflubenzuron is elaborated by

the consideration of 4-chloroaniline and the exposure assessment for tebufenozide is elaborated by the consideration of multiple applications.

Disparlure, which may also be applied in aerial broadcast applications, has a much more restricted set of exposure scenarios on far fewer groups of organisms. This difference is due completely to the sparse toxicity data available on this compound. In other words, while a very elaborate set of exposure scenarios could be prepared, these scenarios would serve little purpose because they could not be combined with a dose-response assessment to characterize risk. The exposure assessment for DDVP is also restricted due to the limited number of plausible exposures, given that DDVP is used only in milk carton traps and minimal exposures for nontarget species are anticipated under ordinary conditions.

4.2.2. Biological Agents

4.2.2.1. Gypsy Moth – As in the human health risk assessment, the exposure metameter is dictated by the data used to formulate the dose-response assessment—i.e., egg mass density is the exposure metameter for terrestrial invertebrates and plants because it is the measure on which the dose-response assessment is based. Egg mass densities ranging from 5 to 5000 egg masses/acre are used to estimate responses in terrestrial plants and invertebrates.

Most wildlife species are not affected directly by exposure to the gypsy moth but are more likely to experience indirect effects due to changes in habitat or other environmental conditions secondary to defoliation. Consequently, the exposure assessment for most wildlife species is almost identical to the dose-response assessment for terrestrial plants which is expressed as defoliation caused by gypsy moth larvae. For this exposure assessment, categories of defoliation are defined as normal background defoliation (<30% defoliation), moderate defoliation (30-60% defoliation), and high or severe defoliation (>60% defoliation).

4.2.2.2. B.t.k. – Based on the hazard identification, exposure assessments are presented for three groups: small mammals, terrestrial insects, and aquatic species. While a number of different exposure scenarios could be developed for terrestrial mammals, the only positive hazard identification for *B.t.k.* involves inhalation exposures. As in the human health risk assessment, inhalation exposures ranging from 100 to 5000 cfu/m^3 are used to assess potential risks of serious adverse effects in terrestrial vertebrates. These concentrations are applied to a 20 g mouse and correspond to inhaled doses of 0.00336-0.168 cfu/mouse. While there is no basis for asserting that any oral and/or dermal exposures are likely to cause adverse effects in terrestrial vertebrates, an extremely conservative exposure assessment is developed for combined oral (water and vegetation) and dermal (direct spray) exposures that yields an estimated maximum dose of about 184 mg/kg body weight. For terrestrial insects, the toxicity values used to assess the consequences of observing effects is given in units of BIU/ha. Consequently, the exposure assessment for this group is simply the range of application rates used in USDA programs —i.e., approximately 49-99 BIU/ha. For aquatic organisms, toxicity data are expressed in several different units such as mg formulation/L, IU/L, and cfu/L. Based on application rates used in USDA programs and conservative assumptions concerning the depth of water over which *B.t.k.*

might be sprayed, concentrations in water would be expected to be at or below 0.24 mg formulation/L. As discussed in the hazard identification, there is no basis for asserting that adverse effects in birds, plants, soil microorganisms, or soil invertebrates other than insects are of plausible concern. Consequently, explicit exposure assessments are not conducted for those groups.

4.2.2.3. LdNPV – Numerous wildlife species might be exposed to Gypchek or LdNPV as a result of ground and aerial applications of the Gypchek formulation. The need for any formal risk assessment is questionable, however, because neither Gypchek nor LdNPV appear to cause systemic adverse effects. Nonetheless, to provide some basis for comparing the potential risks of Gypchek with other agents used to control the gypsy moth, two extreme exposure assessments are developed: one for a terrestrial herbivore consuming contaminated vegetation and the other for aquatic organisms in a small pond directly sprayed with Gypchek at the highest application rate. For the terrestrial herbivore, the dose estimates range from 1.1 to 3.2 mg Gypchek /kg bw. For aquatic organisms, concentrations are expressed in units of PIB/L because this unit is used in the corresponding toxicity studies. For a small pond directly sprayed with Gypchek at the highest application rate, the estimated initial concentration is 2.5×10^5 PIB/L. Several less extreme exposure assessments could be developed but they would not alter the risk assessment given that the extreme exposure assessments are substantially below any level of concern.

4.2.3. Chemical Agents

4.2.3.1. Diflubenzuron and Tebufenozide – As in the human health risk assessment, the exposure assessments for diflubenzuron and tebufenozide are similar. The same set of exposure scenarios are used with the same set of potential target species. The difference in their application rates dominates the quantitative difference in projected exposure to these two chemicals: a single application rate of 0.0625 lb/acre for diflubenzuron and one or two applications at 0.12 lb/acre for tebufenozide. As a result of the higher application rate for tebufenozide, all exposures are higher for tebufenozide than for diflubenzuron. Also as in the human health risk assessment, the exposure assessments for diflubenzuron are elaborated to include 4-chloroaniline as an environmental metabolite of diflubenzuron.

Not withstanding the quantitative differences in the application rates, the patterns of exposure for terrestrial species for diflubenzuron and tebufenozide are similar except for the maximum acute exposure. For diflubenzuron, this exposure is associated with direct spray of a small mammal and could reach 10 mg/kg. For tebufenozide, the maximum acute exposure is associated with a fish-eating bird and could be as high as 85 mg/kg. For other acute and longer-term exposures, the consumption of contaminated vegetation results in higher levels of exposure to both compounds than does the consumption of contaminated water. Estimates of longer-term daily doses for a small mammal consuming contaminated vegetation at the application site range up to 0.005 mg/kg for diflubenzuron and 0.08 mg/kg/day for tebufenozide. The consumption of contaminated water by a small mammal results in estimated doses of up to 0.00001 mg/kg/day for diflubenzuron and 0.0002 mg/kg/day for tebufenozide. Exposures of terrestrial organisms to 4-chloroaniline as a degradation product of diflubenzuron tend to be much lower than the doses

for diflubenzuron. The highest acute exposure to 4-chloroaniline is about 0.2 mg/kg, the approximate dose for the consumption of contaminated water by a small mammal and the consumption of contaminated fish by a predatory bird. The highest longer term exposure to 4-chloroaniline is 0.0002 mg/kg/day, the dose associated with the consumption of contaminated vegetation by a large bird.

As dicussed in Section 4.3, the toxicity data on terrestrial invertebrates are much more extensive for diflubenzuron than tebufenozide, which is directly related to differences in the numbers of field studies available on diflubenzuron (many), compared with tebufenozide (very few). The difference reflects the long-time, extensive use of diflubenzuron, compared with tebufenozide, which is a more recently introduced insecticide. For both chemicals, exposure of terrestrial invertebrates is generally expressed as an application rate from a field study, and no formal exposure assessment is given.

Exposures of aquatic organisms to diflubenzuron or tebufenozide are based essentially on the same information used to assess the exposures of terrestrial species from contaminated water. At the maximum application rates, the upper range of the expected peak concentration in surface water is estimated at 16 µg/L for diflubenzuron and 40 µg/L for tebufenozide.

4.2.3.2. Disparlure – Given the apparent low acute toxicity of disparlure and the lack of any chronic toxicity data, an exposure assessment for terrestrial species would not add to the assessment of risk. Acute exposure studies in *Daphnia* and rainbow trout show that aquatic animals appear more sensitive than terrestrial animals to disparlure. Therefore, an exposure assessment for aquatic species is made based on aerial spray of a pond at an application rate of 29.1 g a.i./acre, with an estimated concentration in pond water of 0.0072 mg a.i./L.

4.2.3.3. DDVP – As in the human health risk assessment, exposure of terrestrial mammals to DDVP from the VaporTape strips used in milk carton traps is likely to be negligible under most circumstances. Nonetheless, it is conceivable that some mammals such as racoons or bears could easily access and tamper with the milk carton trap. Depending on the proportion of the DDVP strip that is consumed, doses (as DDVP in the PVC strip) are estimated to range from 10.5 mg/kg (10% of strip) to 105 mg/kg (100% of strip) and the central estimate is taken as 31.6 mg/kg (30% of strip). In addition, contamination of water with a pest strip is plausible, although probably rare, and is considered in a manner similar to the corresponding scenario in the human health risk assessment (see Section 3.2.3.4). This scenario is based on the consumption of contaminated water by a small mammal, and the dose to the animal is estimated at about 0.00003 mg/kg with a range from 0.000009 to 0.00009 mg/kg. Other exposure scenarios for terrestrial vertebrates, while possible, seem far less plausible and are not considered quantitatively. No quantitative exposure assessments for terrestrial invertebrates are developed because the milk carton trap will attract only male gypsy moths. Nontarget insects that incidentally enter the trap are likely to be killed by exposure to the DDVP vapor. Exposures to aquatic species are based on the same water concentrations used for terrestrial species: 0.000177 mg/L with a range from 0.000059 to 0.00059 mg/L.

4.3.3. DOSE-RESPONSE ASSESSMENT

4.3.3.1. Overview

An overview of the dose-response assessment for groups of nontarget species is presented in Table 4-3. The information in this table categorizes the data descriptively rather than in terms of data quality. The categories reflect whether the data are sufficient to quantify risk or quantitatively characterize differences in sensitivity among several species in the designated group (●), whether the dose-response assessment is based on both an effect and no-effect level (■), whether the dose-response assessment is based only on a no-effect level (□), or whether the assessment is based only on an effect level (○). These categories are reasonable measures of data quality for all of the agents covered in this risk assessment except LdNPV.

All of the risk values for LdNPV are based on no- effect concentrations or doses. In general, confidence in any dose-response relationship is enhanced if a clear dose-response relationship can be demonstrated and both effect and no-effect exposures have been identified. In the case of LdNPV, however, there is simply no indication that LdNPV or the Gypchek formulation will cause toxicity in any nontarget species at any dose level. While additional studies could be conducted at higher doses and while these studies would enhance confidence in the risk assessment, the NOAEL and NOEC values that have been identified are far above any plausible exposures. Thus, while based on limited data in terms of the dose-effect characterization, the dose-response assessment for LdNPV is adequate for risk characterization.

For most of the other agents, the dose-response assessments are reasonably good for the species of greatest concern. As noted in Table 4-3, dose-response assessments for DDVP are derived only for mammals, fish, and aquatic invertebrates. As discussed in the exposure assessment, this limited approach is taken with DDVP because of the limited use of DDVP in programs to control the gypsy moth. The DDVP is contained in a PVC strip that is placed in a milk carton trap that includes disparlure as an attractant for the gypsy moth. This type of use limits potential exposure for most nontarget species. A formal dose-response assessment is not conducted for terrestrial invertebrates. This is not due to any lack of data. The toxicity of DDVP to insects and many other invertebrates is very well characterized. DDVP is such a potent insecticide that no formal dose-response assessment is needed. Insects and many other species that enter the trap are likely to be killed by exposure to DDVP.

Disparlure is the other agent for which a full set of dose-response assessments are not conducted. As discussed in the hazard identification, this is due to the limited amount of data regarding the toxicity of disparlure to nontarget species.

Relatively full dose-response assessments on groups of greatest concern are given for the gypsy moth, *B.t.k.*, diflubenzuron and its 4-chloroaniline metabolite, and tebufenozide. For the gypsy moth, the effect of primary concern is damage to vegetation. While data are available on both lethality in trees as well as defoliation, defoliation is used as the sublethal effect of primary concern. A dose-response assessment is also given for nontarget lepidopterans. While effect and

no-effect levels can be identified, the significance of this effect is questionable. In terms of direct effects, terrestrial vegetation is the primary target of concern.

Lepidoptera are the primary nontarget group of concern for *B.t.k.* exposure. A relatively rich set of studies is available regarding the sensitivities of nontarget *Lepidoptera* and some other insects. The sensitivities of the nontarget insects can be quantified reasonably well from exposures that encompass the application rates used in USDA programs to control the gypsy moth. Sensitive nontarget *Lepidoptera* include larvae of the endangered Karner blue butterfly as well as several other types of moths.

Similar types of information are available on diflubenzuron and tebufenozide, and dose-response assessments can be made for the species of primary concern. For both chemicals, this includes nontarget *Lepidoptera* and aquatic invertebrates. Other terrestrial arthropods are also considered for diflubenzuron. In addition, because of the standard tests required by U.S. EPA for the registration of most pesticides, adequate toxicity data are available on mammals, birds, and fish. The toxicity data base for diflubenzuron is somewhat more extensive and sensitivities in nontarget organisms are somewhat better defined in both laboratory and field studies than is the case with tebufenozide.

4.3.2. Biological Agents

4.3.2.1. Gypsy Moth – As in the human health risk assessment for the gypsy moth, the dose measure for the gypsy moth is egg masses/acre. Quantitative dose-response assessments can be made for both terrestrial plants and sensitive species of *Lepidoptera*. The dose-response assessments for terrestrial plants are based on a relatively simple quantitative model for the relationship of egg mass density and vegetation type to defoliation. Three broad categories of vegetation (sensitive, intermediate, and tolerant) are used to characterize the susceptibility of forest stands to gypsy moth induced defoliation. Estimated LOAEL values based on 30% defoliation, which is considered the lower range of moderate defoliation, are approximately 125 egg masses/acre for sensitive stands, 1000 egg masses/acre for intermediate stands, and 7000 egg masses/acre for tolerant stands. The corresponding NOAEL values, defined as 10% defoliation, are estimated as 12, 20, and 125 egg masses/acre for sensitive, intermediate, and tolerant forest stands.

The effects of gypsy moth exposure on sensitive terrestrial invertebrates, including some species of *Lepidoptera*, are less well documented and less well characterized, compared with the effects on terrestrial plants. Nonetheless, available studies indicate that the NOAEL for adverse effects in certain other species of *Lepidoptera* are lower than the NOAEL for sensitive forest stands—— i.e., about 6-72 egg masses/acre for some *Lepidoptera*. No quantitative dose-response assessment is presented for other groups of organisms—e.g., mammals, birds, and soil or aquatic organisms. The impact of gypsy moth exposure on these species is most likely to result in indirect effects secondary to defoliation. This is discussed further in the risk characterization.

4.3.2.2. B.t.k. – As summarized in Table 4-3, exposure assessments are presented for four groups: mammals, terrestrial insects, fish, and invertebrates. While a number of different exposure scenarios could be developed for terrestrial mammals, the only positive hazard identification for *B.t.k.* involves inhalation exposures. As in the human health risk assessment, inhalation exposures of 100-5000 cfu/m^3 are used to assess potential risks of serious adverse effects in terrestrial vertebrates. These concentrations are applied to a 20 g mouse and correspond to inhaled doses of 0.00336-0.168 cfu/mouse. While there is no basis for asserting that any oral and/or dermal exposures are likely to cause adverse effects in terrestrial vertebrates, an extremely conservative exposure assessment is developed for combined oral (water and vegetation) and dermal (direct spray) exposures that yields an estimated maximum dose of approximately 184 mg/kg body weight.

For terrestrial insects, the toxicity values used to assess the consequences of observing effects is given in units of BIU/ha over a range of applications similar to those used in gypsy moth control programs. The magnitude of response to *B.t.k.* in sensitive nontarget species appears similar to that of the gypsy moth. Tolerant species appear to be about 30-fold less sensitive than the gypsy moth to B.t.k.. The designations of sensitive and tolerant species are not intended to imply absolute ranges on tolerance among all possible insects. Instead, the dose-response assessments for this group simply indicate that some nontarget species, such as the Karner blue butterfly and cinnabar moth, appear to be as sensitive to *B.t.k.* as target species such as the gypsy moth and cabbage looper. The range of sensitivities among various insect species appears to follow a continuum, and it is possible that some species may be more or less sensitive to *B.t.k.* than those insects on which toxicity data are available.

For aquatic organisms, toxicity data are expressed in several different units such as mg formulation/L, IU/L, and cfu/L. Based on application rates used in USDA programs and conservative assumptions concerning the depth of water over which *B.t.k.* might be sprayed, concentrations in water would be expected to be at or below 0.24 mg formulation/L. Toxicity values for fish are 1.4 mg formulation/L (an LOEC for sensitive species) and 1000 mg formulation/L (an NOEC for tolerant species). For aquatic invertebrates, the NOEC values for sensitive and tolerant species are 0.45 and 36 mg/L, respectively.

4.3.2.3. LdNPV – Because no hazards can be identified for any species, a quantitative dose-response assessment is not required. Consequently, no dose-response assessments were proposed by U.S. EPA and none were used in the previous gypsy moth risk assessment for Gypchek. In order to provide a quantitative comparison of the risks of using Gypchek relative to the other agents, dose-response assessments are made for both terrestrial mammals and aquatic species. For terrestrial mammals, the NOAEL of 2600 mg/kg bw is used. This is the same NOAEL that serves as the basis for the surrogate acute RfD for LdNPV in the human health risk assessment for this agent. For aquatic species, only NOEC values are available, and the highest NOEC of $8x10^9$ PIB/L is used to characterize risk.

4.3.3. Chemical Agents

4.3.3.1. Diflubenzuron and Tebufenozide – As summarized in Table 4-3, the dose-response assessments for diflubenzuron and tebufenozide are far more complete, in terms of the number of groups encompassed, than are the corresponding assessments for other agents considered in this risk assessment. This difference reflects both the nature of the available data and an assessment of the need to characterize risk quantitatively. Despite their specific modes of action in target species, diflubenzuron and tebufenozide induce toxicological responses in many different groups of animals. Furthermore, both chemicals are used in broadcast aerial applications, making exposure to many different groups of organisms likely.

Both diflubenzuron and tebufenozide are relatively non-toxic to mammals and birds. As noted in the human health risk assessment, the acute and chronic toxicities of these two chemicals in mammals appear to be virtually identical in terms of NOAELs. This is also true for birds. The toxicity values used in the ecological risk assessment for mammals are identical to those used in the human health risk assessments: an acute NOAEL of 1118 mg/kg and a chronic NOAEL of 2 mg/kg/day for diflubenzuron and an acute NOAEL of 1000 mg/kg and a chronic NOAEL of 1.8 mg/kg/day for tebufenozide. The differences between the values for the chemicals are clearly insubstantial. For birds, the acute NOAEL for diflubenzuron is taken as 2500 mg/kg and the longer-term NOAEL is taken as 110 mg/kg/day. For tebufenozide, the values are again very similar: an acute NOAEL of 2150 mg/kg and a longer-term NOAEL of 15 mg/kg/day. For both chemicals, the longer-term NOAEL is taken from standard assays on reproduction.

In terms of potential effects on terrestrial invertebrates, the data set for diflubenzuron is much richer than the data set for tebufenozide. Many laboratory toxicity studies and field studies have been conducted on diflubenzuron. Field studies are used in the dose-response assessment of diflubenzuron because the standard toxicity studies are extremely diverse and many are not directly applicable to a risk assessment. Despite the difficulty and uncertainty in interpreting some of the field studies, the relatively large number of field studies on diflubenzuron appears to present a reasonably coherent pattern that is at least qualitatively consistent with the available toxicity data and probably a more realistic basis on which to assess risk to nontarget species. The most sensitive species appear to be grasshoppers which may be adversely affected at an application rate of about 0.02 lb/acre [22 g/ha]. Somewhat high application rates—in the range of 0.027-0.031 lb/acre [30 to 35 g/ha]—will adversely affect macrolepidoptera and some beneficial parasitic wasps. At the maximum application rate considered in this risk assessment—0.062 lb/acre [70 g/ha]—some additional herbivorous insects are likely to be affected. No adverse effects in several other groups of insects are expected at this or much higher application rates. Honeybees are among the most tolerant species and are not likely to be adversely affected at application rates of up to 0.35 lb/acre [400 g/ha]. Invertebrates that do not synthesize chitin are also relatively tolerant to diflubenzuron.

Although there are fewer and generally less detailed field studies on tebufenozide, compared with diflubenzuron, it appears to be less toxic to nontarget species (e.g., lacewing). In general, the field studies indicate that tolerant insect species are not affected by tebufenozide at application

rates up to 0.24 lb/acre. The true NOEC may be higher – i.e., an LOEC has not been identified for tolerant species of terrestrial insects. Conversely, application rates as low as 0.03 lb/acre have been shown to have adverse effects on sensitive nontarget insects, primarily *Lepidoptera*. A NOEC for sensitive species was not identified.

For both diflubenzuron and tebufenozide, the toxicity values for aquatic species follow a pattern similar to that for terrestrial species: arthropods appear to be much more sensitive than fish or non-arthropod invertebrates. Both compounds are about equally toxic to fish with virtually identical chronic NOEC values: 0.05 mg/L for diflubenzuron and 0.048 mg/L for tebufenozide.

There are major and substantial differences regarding the toxicity of diflubenzuron and tebufenozide to aquatic invertebrates. Diflubenzuron is much more toxic. In acute toxicity studies, the NOEC for the most sensitive species is 0.0003 mg/L diflubenzuron, which is 400 times less than the corresponding NOEC of 0.12 mg/L for tebufenozide. Chronic toxicity studies indicate a similar pattern. The NOEC for the most sensitive species is 0.00004 mg/L for diflubenzuron and 0.0035 mg/L for tebufenozide. The difference is a factor of about 90 [0.0035 mg/L / 0.00004 mg/L]. Even though the number of available NOEC values is greater for diflubenzuron (seven acute and seven chronic), compared with tebufenozide (three acute and two chronic), and variability can be expected to increase as the number of species tested increases, it is unlikely that the apparent differences in toxicity are artifacts of sample size. For example, based on acute and chronic NOEC values in *Daphnia*, which are available for both compounds, diflubenzuron is more toxic than tebufenozide by a factor of about 2700 in acute studies and a factor of 725 in chronic studies. The toxicity to aquatic invertebrates is one of the few areas in which diflubenzuron and tebufenozide differ remarkably, and this difference has an impact on the risk characterization (Section 4.4).

4.3.3.2. Disparlure – The limited amount of toxicity data on disparlure precludes making a standard dose-response assessment for terrestrial species. Disparlure is identical or similar to pheromones produced by other species of moths and is able to attract male nun moths. Since, however, there are no quantitative data available regarding the efficacy of disparlure in nontarget moths, a dose-response assessment for this effect in a nontarget species of moths cannot be made. For aquatic species, NOEC values and limited data on effect levels are available from acute exposure studies in rainbow trout and *Daphnia*. No LC_{50} values are available in fish. The dose-response assessment is limited to NOEC values of 10 mg/L in trout and 300 mg/L in bluegills. The only information on toxic effects in fish consists of a report of 20% mortality in trout after acute exposure to disparlure at 100 mg/L. Thus, disparlure does not appear to be highly toxic to fish. *Daphnia magna* are much more sensitive with a 48-hour LC_{50} of 0.098 mg/L and an NOEC for mortality of 0.017 mg/L. Based on the LC_{50} value, disparlure is classified as highly toxic to aquatic invertebrates.

4.3.3.3. DDVP – Given the limited nature of the use of DDVP in programs to control the gypsy moth and consequent limited number of exposure assessments, the dose-response assessment for DDVP is relatively simple. For terrestrial mammals, a value of 240 mg/kg from a study using

DDVP in a PVC formulation is used for direct exposure to the DDVP-PVC strip—i.e., a raccoon tampering with a milk carton trap and consuming all or part of the DDVP strip. At the dose of 240 mg/kg, no mortality or frank signs of AChE inhibition were observed. For the contaminated water scenario, the NOAEL of 0.5 mg/kg from a study involving exposure to free or unformulated DDVP is used. This NOAEL is from the study that forms the basis for the acute RfD used in the human health risk assessment. Although DDVP is classified as highly toxic to fish, the estimated levels of acute exposure for fish are far below the 30-day NOEC of 0.03 mg/L. Thus, this value is used for all fish and no attempt is made to consider differences in sensitivity among fish. A somewhat different approach is taken with aquatic invertebrates, some of which are more sensitive than fish to DDVP by a factor of more than 2500. Risks to sensitive species of aquatic invertebrates —i.e., daphnids and other small arthropods—are characterized based on the lowest reported LC_{50} value, 0.00007 mg/L from a 48-hour bioassay in *Daphnia pulex*. Some other groups of aquatic invertebrates, such as snails, appear to be much less sensitive than small arthropods. Risks to such tolerant species are based on a LC_{50} value of 21 mg/L in a freshwater snail.

4.4. RISK CHARACTERIZATION

4.4.1. Overview

The comparative risk characterization for the ecological risk assessment is expressed similarly to that in the human health risk assessment. Numerically, the risk characterizations are given as hazard quotients (HQs), the level of exposure divided by some measure of effect, typically an NOAEL or NOEC. As in the human health risk assessment, the comparative risk characterization for ecological effects typically categorizes concern with the agents as marked (HQ>10), marginal (HQs between about 0.1 and 10), and minimal (HQ<0.1). One exception is made for *B.t.k.*, which is classified as an agent of marked concern although the highest HQ is 9.4.

An overview of the comparative risk characterization is summarized in Table 4-4 for terrestrial species and Table 4-5 for aquatic species. The risk characterizations are illustrated in Figure 4-1 (terrestrial) and Figure 4-2 (aquatic). As in the human health risk assessment, the HQs for each agent are presented as a range. The upper end of the range is typically the highest hazard quotient associated with a plausible exposure scenario. The lower end of the range is not necessarily the lowest HQ calculated in each of the risk assessments. For some agents, the lower range is taken from sets of exposure scenarios that provide similar HQs for exposures that may be regarded as typical. For these agents, the lowest HQs reported in the individual risk assessments are close to zero. In some cases, the numerical expressions of risk do not adequately convey the potential for hazard. These cases are noted in Figures 4-1 and 4-2 with comments.

Ecological risk assessments involve, at least implicitly, considerations of thousands of different species and the relationships among these species and their habitats. Invariably, however, data are available on only a small subset of these species and field studies provide only limited insight into the complex interrelationships and secondary effects among species. Thus, as in the human health risk assessments, ecological risk assessments cannot offer a guarantee of safety. They can and do offer a means to identify whether or not there is a basis for asserting that adverse effects are plausible and what the nature of these effects might be.

Within these limitations, only LdNPV clearly qualifies as an agent of minimal concern. While there are limitations in the available studies on LdNPV, there is simply no basis for asserting that LdNPV will adversely affect any species except the gypsy moth.

Agents of marked concern include the gypsy moth, *B.t.k.*, and diflubenzuron. The types of concern with each of these agents, however, are quite different. For both the gypsy moth and *B.t.k.*, the concerns are narrow. The gypsy moth clearly will damage some terrestrial vegetation. *B.t.k.* is likely to affect sensitive *Lepidoptera*. Concern with the use of diflubenzuron is broader and includes effects on both terrestrial and aquatic invertebrates.

The designation of the gypsy moth as an agent of marked concern is obvious. The effects of gypsy moth larvae on forests are extremely well documented and well understood. In sensitive forest stands—i.e., stands in which oak, birch, and other favored species predominate —gypsy moth larvae can cause substantial defoliation and tree mortality. While some other lepidopteran

species also may be directly affected by exposure to the gypsy moth, most of the other effects caused by the gypsy moth will be secondary. Reductions in populations of squirrels, mice, and other mammals which may be sensitive to changes in the availability of acorns are likely and have been well documented. Substantial secondary adverse effects on other groups of animals—i.e., birds, reptiles, and aquatic species—cannot be ruled out but have not been convincingly or consistently demonstrated.

Diflubenzuron is also clearly an agent of marked concern. Exposures to diflubenzuron at application rates used in gypsy moth control programs will adversely affect both terrestrial and aquatic invertebrates that rely on chitin for their exoskeleton. This has been demonstrated in controlled toxicity studies as well as multiple field studies.

The designation of *B.t.k.* as an agent of marked concern is somewhat judgmental. As noted in Table 4-4, the highest hazard quotient is 9.4. Based on this HQ and the classification scheme used generally, *B.t.k.* would be classified as an agent of marginal concern. However, recent studies convincingly demonstrate that adverse effects in nontarget *Lepidoptera* will occur in the applications of *B.t.k.* used to control the gypsy moth. Concern is heightened because some of the *Lepidoptera* that may be adversely affected include at least one endangered species.

Tebufenozide, DDVP, and disparlure are all classified as agents of marginal concern. For tebufenozide, the numerical expressions of risk may be less relevant than a more qualitative assessment. The highest HQ is 4 and is associated with the consumption of contaminated vegetation by a large mammal after two applications of the compound at the highest labeled application rate. While this exposure would be considered undesirable, it is not clear that any frank signs of toxicity would be seen. Risks to nontarget *Lepidoptera* may be of greater concern but the available data are insufficient to quantify potential risk. Risks to other invertebrates, both terrestrial and aquatic, appear to be insubstantial. DDVP is of marginal concern in that highly localized effects may be expected: nontarget insects entering a milk carton trap or some aquatic invertebrates affected by the accidental contamination of a small body of water with a pest strip. In both cases, the effects would be relatively minor, in terms of the number of organisms affected. Marginal concern for disparlure is associated with the relatively high toxicity of this agent to *Daphnia* and is reenforced by the very scant data on the toxicity of an agent that may be applied to large areas in broadcast applications.

4.4.2. Agents of Marked Concern

4.4.2.1. Gypsy Moth – The best documented and most obvious effect of the gypsy moth will be on terrestrial vegetation, particularly forest stands in which sensitive species of trees predominate. In some respects, the risk characterization for terrestrial vegetation is essentially a restatement of the hazard identification. In other words, the effects of gypsy moth larvae on forests is extremely well documented and relatively well understood. In sensitive forest stands—i.e., stands in which oak, birch, and other favored species predominate —gypsy moth larvae can cause substantial defoliation. In forest stands in which tree species that are not favored by gypsy moth larvae predominate —e.g., hemlock, various types of pine, black locust

and white ash—even relatively high exposures, as measured by egg mass density, may not result in substantial defoliation. The risk assessment for direct effects on forests should be at least qualitatively influenced by the current range of the gypsy moth, which has not yet extended to some forests in the southeast that may be among the most sensitive to gypsy moth exposure. Thus, unless measures to contain the gypsy moth are successful, the southeastern oak forests may suffer serious damage in future infestations.

Some other lepidopteran species also may be directly affected by exposure to the gypsy moth. Most studies, however, suggest that substantial adverse effects in terrestrial insects are unlikely and effects in some insect species, including some other *Lepidoptera*, may be beneficial.

Because the gypsy moth may substantially damage some forests in severe infestations or outbreaks, secondary effects in other species of wildlife are plausible. Reductions in populations of squirrels, mice, and other mammals which may be sensitive to changes in the availability of acorns are likely. Substantial adverse effects on other groups of animals—i.e., birds, reptiles, and aquatic species—cannot be ruled out but have not been convincingly demonstrated.

4.4.2.2. B.t.k. – Terrestrial insects are the only organisms likely to be adversely affected by exposure to *B.t.k.* or its formulations. Separate dose-response curves can be generated for both sensitive and tolerant terrestrial insects. At the application rates used to control gypsy moth populations, mortality rates among sensitive terrestrial insects are likely to range from approximately 80% to 94% or more. All sensitive terrestrial insects are *Lepidoptera* and include some species of butterfly, like the endangered Karner blue and some swallowtail butterflies and promethea moths.

The effects in sensitive species have been convincingly demonstrated in the study by Herms et al. (1997). In this study, the toxicity of Foray 48B was assayed in larvae of both the gypsy moth and the Karner blue butterfly, an endangered species of butterfly indigenous to the northern United States (Minnesota to New Hampshire). Bioassays in both species involved applications of Foray 48B to vegetation (wild lupine leaves for the Karner blue and white oak leaves for the gypsy moth) at treatment levels equivalent to either 30-37 BIU/ha per ha (low dose) or 90 BIU/ha (high dose). A negative control consisted of untreated vegetation. The insect larvae (either 1st or 2nd instar for the Karner blue and 2nd instar for the gypsy moth) were placed on the vegetation 7 to 8 hours after treatment and allowed to feed for 7 days. Survival rates for Karner blue larvae were: 100% for controls, 27% at the 30-37 BIU/ha treatment rate, and 14% at the 90 BIU/ha treatment rate. Survival rates for gypsy moth larvae were: 80% for controls; 33% for low-dose treatment, and 5% for high-dose treatment. Based on a statistical analyses of these data, the gypsy moth and Karner blue appear to be equally sensitive to *B.t.k.* This study is supplemented by the series of bioassays conducted by Peacock et al. (1998) which suggest that various other lepidopteran species may be as sensitive as the gypsy moth to *B.t.k.*.

For some *Lepidoptera*, sensitivity to *B.t.k.* is highly dependent on developmental stage. This is particularly evident for the cinnabar moth, where late instar larvae are very sensitive to *B.t.k.* and

early instar larvae are very tolerant to *B.t.k*. Given the mode of action of *B.t.k.*—i.e., it must be ingested to be highly toxic to the organism— effects on even the most sensitive species will occur only if exposure coincides with a sensitive larval stage of development. In tolerant species, including non-lepidopteran insects and certain larval stages of some *Lepidoptera*, the anticipated mortality rates are much lower (on the order of less than 1% to about 4%).

The risk characterization for terrestrial mammals is unambiguous: under foreseeable conditions of exposure, adverse effects are unlikely to be observed. Similarly, based on a very conservative exposure assessment for aquatic species, effects in fish and aquatic invertebrates appear to be unlikely. As discussed in the hazard identification, effects in birds, plants, soil microorganisms, or soil invertebrates other than insects are not of plausible concern. Thus, quantitative risk characterizations for these groups are not conducted. For oil-based formulations of *B.t.k.* (or any other pesticide), effects in some soil invertebrates are plausible.

4.4.2.3. Diflubenzuron – While the data base supporting the risk assessment of diflubenzuron is large and somewhat complex, the risk characterization is relatively simple and unequivocal. Diflubenzuron is an effective and general insecticide. Application rates used to control the gypsy moth are likely to have effects on some nontarget terrestrial insects. Species at greatest risk include grasshoppers, various macrolepidoptera (including the gypsy moth), other herbivorous insects, and some beneficial predators to the gypsy moth. These species are at risk because of the mode of action of diflubenzuron (i.e., inhibition of chitin) and the behavior of the sensitive insects (the consumption of contaminated vegetation or predation on the gypsy moth). Some aquatic invertebrates may also be at risk but the risks appear to be less than risks to terrestrial insects. The risk characterization for aquatic invertebrates is highly dependant on site-specific conditions. If diflubenzuron is applied when drift or direct deposition in water is not controlled well or in areas where soil losses from runoff and sediment to water are likely to occur, certain aquatic invertebrates are at risk of acute adverse effects, and exposure could cause longer-term effects on more sensitive species.

Direct effects of diflubenzuron on other groups of organisms—that is, mammals, birds, amphibians, fish, terrestrial and aquatic plants, microorganisms, and non-arthropod invertebrates—do not appear to be plausible. Nontarget species that consume the gypsy moth or other invertebrates adversely affected by diflubenzuron may be at risk of secondary effects (for example, a change in the availability of insect prey). There is no indication that 4-chloroaniline formed from the degradation of diflubenzuron will have an adverse effect on any terrestrial or aquatic species.

4.4.3. Agents of Marginal Concern

4.4.3.1. Tebufenozide – The use of tebufenozide to control the gypsy moth may result in adverse effects in nontarget *Lepidoptera* but these effects have not been well characterized or clearly demonstrated. There is little indication that other species will be impacted under normal conditions of use even at the highest application rate. Tebufenozide is an insecticide that is effective in controlling populations of lepidopteran pests. No data, however, are available on

toxicity to nontarget *Lepidoptera*. For the risk assessment of this compound, the assumption is made that nontarget *Lepidoptera* may be as sensitive as target *Lepidoptera* to tebufenozide. Thus, adverse effects in nontarget *Lepidoptera* would be expected after applications that are effective for the control of lepidopteran pest species.

There is no indication that short-term exposures to tebufenozide will cause direct adverse effects in any terrestrial vertebrates or non-lepidopteran invertebrates even at the upper range of plausible exposures or as a result of accidental exposures. Similarly, direct adverse effects from longer-term exposures in birds and mammals appear to be unlikely under most conditions. Effects on birds due to a decrease in available prey—i.e., terrestrial invertebrates—are considered plausible. In extreme cases, exposure levels in some large mammals might exceed the NOEC, but would remain below levels associated with frank signs of toxicity. This point is reflected in the HQ of 4 for a large mammal consuming contaminated vegetation after two applications of tebufenozide at the highest labeled rate. Under normal conditions of use, tebufenozide is not likely to cause adverse effects in aquatic species; however, in the case of a large accidental spill into a relatively small body of water, adverse effects might be expected in aquatic vertebrates, invertebrates, and plants.

4.4.3.2. DDVP – As in the human health risk assessment of DDVP, typical exposures and consequent risks to nontarget species should be negligible. The containment of the DDVP within a slow-release PVC strip combined with the target specific nature of pheromone baited traps should reduce the risks of inadvertent effects on nontarget species. Other insects and arthropods that may inadvertently enter the trap will probably be killed by DDVP vapor. While such inadvertent contact may occur, it is not likely to have a substantial impact on the number of nontarget insects or arthropods.

Because of the limited use of DDVP, a relatively small number of exposure scenarios —all of which might be considered accidental or incidental—are developed. For terrestrial mammals, contact with the pest strip could occur by an animal directly tampering with a trap or by an animal consuming water accidentally contaminated with a DDVP strip. Adverse effects would not be expected in either case. In the case of accidental contamination of a small body of water with a DDVP strip, concentrations of DDVP in the water would be below the level of concern for fish by factors ranging from about 50 to 500. Some aquatic invertebrates, however, might be affected. For the most sensitive species of aquatic invertebrates —i.e., small aquatic arthropods like daphnids—exposure levels could substantially exceed laboratory LC_{50} values by factors of up to about 8. Exposures to tolerant aquatic invertebrates—like snails—would be below a level of concern by a substantial margin—i.e., factors ranging from about 30,000 to 300,000.

The exposure assessments that serve as the bases for these risk characterizations are highly dependent on specific conditions—i.e., how much DDVP was in the strip at the time that the contamination occurred and the size of the body of water that was contaminated. Because the hydrolysis of DDVP in water is rapid, the estimates of adverse effects in some aquatic

invertebrates would probably apply only to a very limited area near the pest strip rather than to the larger area of the body of water that is contaminated.

4.4.3.3. Disparlure – There is little data available on terrestrial and aquatic animals to allow for a quantitative characterization of risk. The lack of chronic toxicity data in any species adds uncertainty to any risk characterization. Thus, for both terrestrial and aquatic species, the potential for the development of toxicity from long-term exposure to disparlure cannot be ruled out. Concern with the lack of toxicity data on disparlure is exacerbated by the fact that this compound may be applied to large areas in broadcast applications.

Nonetheless, based on the available data, clear hazards to nontarget species have not been identified. Disparlure may disrupt mating in some moths other than the gypsy moth. The two species that are known to be affected, however, are both forest pests like the gypsy moth and only one of these other species is native to North America. For aquatic species, hazard quotients for both rainbow trout and *Daphnia* are below one, although the hazard quotient of 0.4 for *Daphnia* approaches one. Thus, while 0.4 is below the level of concern of one, there is uncertainty in the risk characterization because of the limited acute toxicity data, the lack of chronic toxicity data, and the high likelihood that many species will be exposed to this compound.

4.4.4. Agent of Minimal Concern: Gypchek

Unlike all of the other agents considered in this risk assessment, there is no basis for asserting that the use of Gypchek to control or eradicate gypsy moth populations is likely to cause any adverse effects in any species other than the gypsy moth. While no pesticide is tested in all species under all exposure conditions, the data base on LdNPV and related viruses is reasonably complete and LdNPV has been tested adequately for pathogenicity in a relatively large number of species, particularly terrestrial invertebrates. LdNPV appears to be pathogenic and toxic to the gypsy moth and only to the gypsy moth.

For Gypchek, quantitative expressions of risk are in some respects more difficult because clear LOEC values are not defined—i.e., if an agent is not shown to cause an effect, the threshold for effects is not a meaningful concept. Nonetheless, general but very conservative exposure assessments demonstrate that plausible upper ranges of exposures are clearly below any level of concern by a factor of 1000 for terrestrial species and 30,000 for aquatic species.

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Tables

Table 2-1: Total use of control agents by numbers of acres treated between 1995 and 2003

	Suppression (Total acres)	Eradication (Total acres)	Slow-the-Spread (Total acres)	Grand Total (Acres)
B.t.k.	1,484,486	1,057,201	367,722	2,909,409
NPV	36,518	7,376	9,140	53,034
Diflubenzuron	657,671	6	6,883	664,560
Tebufenozide	0	0	0	0
Disparlure flakes	0	60,090	1,567,199	1,627,289
Mass Traps *	0	1,912	0	1,912

* Mass traps contain DDVP in a PVC strip and disparlure as an attractant.

Table 3-1: Comparative hazard identification for potential effects in humans

Endpoint	Agents used in Gypsy Moth Program						
	Gypsy Moth	*B.t.k.*	LdNPV	DFB	Tebufen-ozide	DDVP	Dispar-lure
Lethality	○	□	○	□	□	● [a]	○
Sub-lethal effects							
Irritation	●	●	■	□	○	■	□
Blood				●	●	○ [b]	
Carcinogenicity				■ [c]	○	□	
Neurotoxicity		○	○	□	○	●	
Immunotoxicity		○	○	○	○	□	
Reproduction				○	■	■	
Endocrine Effects					○	□	
Pathogenicity		□ [d]	○	N/A	N/A	N/A	N/A

[a] Risks are mitigated by formulation in PVC.
[b] Excluding inhibition of plasma and RBC AChE.
[c] An environmental metabolite, 4-chloroanaline, poses a carcinogenic risk.
[d] *B.t.k.* itself does not appear to be pathogenic. Possible enhancement of influenza virus.

Key:		
	●	Effect/risk demonstrated in humans
	■	Effect is plausible
	□	Marginal evidence for potential effect
	○	No plausible basis for risk
	Blank	No data are available

Table 3-2: Comparative exposure assessment for human health effects

Agent	Measure of Exposure	Plausibility of Exposure	Comments
Gypsy moth	Eggs masses per acre	Variable	Exposure potential is high during outbreaks and decreases as intensity of infestation decreases.
B.t.k.	Application rate and cfu/m^3 x hour	High	During broadcast applications, exposure potential is high and can be reasonably well characterized.
LdNPV	mass of formulation	High	During broadcast applications, exposure potential is high and can be reasonably well characterized.
Diflubenzuron	mass of chemical	High	Can persist on vegetation and water contamination is plausible.
Tebufenozide	mass of chemical	High	Can persist on vegetation and water contamination is plausible.
DDVP	mass of chemical	Very low	Except in cases of intentional or incidental tampering with a trap, exposures will be very low.
Disparlure	mass of chemical	Variable	Very little compound is used in traps and exposures are likely to be very low.

Table 3-3: Comparative dose-response assessment for human health effects

Agent	Toxicity Value	Endpoint	Quality	Comment
Gypsy Moth	Acute	Irritation	●	Based on human data with a clear dose-response relationship.
B.t.k.	Acute	Irritation	■	Based on human data but no dose-response relationship is apparent.
		Toxicity	□	Based on a single study in mice using a marginally relevant route of exposure.
LdNPV	Acute	None	●	High confidence because no endpoint of concern can be identified.
Diflubenzuron	Acute	Blood	■	No EPA acute RfD. Conservative approach based on petroleum formulation.
	Chronic	Blood	●	Agency-wide EPA RfD adopted by OPP.
4-Chloroaniline*	Acute	Blood	■	No EPA acute RfD. Conservative approach based on 90-day study.
	Chronic	Blood	□	EPA chronic RfD. Confidence classified as low by EPA.
	Cancer Potency	Cancer	■	EPA cancer potency factor
Tebufenozide	Acute	Repro	■	No EPA acute RfD. Based on reproduction studies in two species
	Chronic	Blood	■	EPA/OPP chronic RFD.
DDVP	Acute	Neuro	●/□	For DDVP itself, value is based on an EPA acute RfD. For DDVP in PVC strip, the value is based on marginal data.
Disparlure	Acute	N/A	□	No acute RfD can be derived.

Key for quality of Toxicity Values:

●	High
■	Medium
□	Low

* An environmental metabolite of diflubenzuron.

Table 3-4: Comparative risk characterization for human health effects [a]

Agent	Hazard Quotient (HQ) [b]		Comments
	Lower	Upper	
Gypsy Moth	**1.6**	**625**	Irritant effects (dermal, ocular, and/or respiratory) are well documented. Lower range is based on sparse infestations, where effects might be seen in about 1% of the population. Upper range is based on major outbreaks where responses might be seen in about 40% of the population.
B.t.k.	0	0.04	HQs are for serious adverse effects, which are highly unlikely to occur. Irritant effects could be reported in about 20% of exposed individuals – both workers and members of the general public.
LdNPV	0	0.02	No risks are plausible. Upper range of HQ is calculated from a free-standing NOAEL.
Diflubenzuron			
Workers	0.05	0.5	The upper range is associated with the upper range of plausible exposures in ground spray applications. Under typical conditions, the HQ will be about 0.05.
Public	0.09	0.1	This narrow range of HQs reflects the higher HQ for any longer term exposure (0.09) and the highest HQ for acute exposures (0.1). Most other HQs are below 0.01.
4-Chloroaniline as an environmental metabolite of diflubenzuron			
Toxicity	0.02	0.4	Lower value is based on acute consumption of contaminated water (peak concentration) by child. Upper range based on acute consumption of contaminated fish by subsistence populations after accidental spill. Other HQs are insubstantial.
Cancer	0.09	0.4	HQs based on cancer risk of 1 in 1 million. Both lower and upper are based on consumption of contaminated water (central and upper ranges). Other scenarios lead to much lower risks.
Tebufenozide	0.03	**1.5**	Lower range is based on the central estimate of contaminated fruit (longer-term) after 2 applications. Highest HQ is for the upper range of longer-term consumption of contaminated fruit following 2 applications at the highest application rate. Other HQs are much less than 0.03.
DDVP	0	**380**	Lower range of risk is essentially zero because exposures are unlikely. Upper range is based on oral exposure from a child tampering with the strip. Likelihood of clinically significant effects seems remote.
Disparlure	0	0	No potential risk can be identified.

[a] See Figure 3-1 for illustration.

[b] Hazard quotients less than 0.01 are given as zero. For *B.t.k.*, the lower range of the HQ is 0.000036. For NPV and disparlure, risks are essentially zero. For DDVP, exposure is unlikely and the risk is also essentially zero except for accidental exposures.

Table 4-1: Comparative hazard identification for potential effects in nontarget species

Endpoint	Agents used in Gypsy Moth Program						
	Gypsy Moth	*B.t.k.*	LdNPV	DFB	Tebufen-ozide	DDVP	Dispar-lure
Terrestrial species							
Mammals	■	○	○	●	●	●	○
Birds	■	○	○	□	■	●	○
Nontarget *Lepidoptera*	■	●	○	●	●	●	■*
Other arthropods	□	○	○	●	●	●	○
Other invertebrates	□	□	○	○	○	●	○
Plants	●	○	○	○	○	○	
Microorganisms	■	○		□			
Aquatic species							
Fish	□	○	○	□	□	●	○
Invertebrates	□	■	○	●	●	●	■
Plants	□	○	○	□	■		
Microorganisms	■	○		□			

* Effects in other pest *Lepidoptera* pest species only.

Key:		
	●	Direct effects demonstrated in species of concern
	■	Effects are plausible
	□	Marginal evidence for effect
	○	No plausible basis for risk
	Blank	No data are available

Table 4-2: Comparative exposure assessment for ecological effects

Agent	Plausibility of Exposure	Primary Route	Comments
Gypsy moth	Variable	N/A	Exposure potential is high during outbreaks and decreases as intensity of infestation decreases.
B.t.k.	High	Oral	During broadcast applications, exposure potential is high.
LdNPV	High	Oral	During broadcast applications, exposure potential is high and can be reasonably well characterized.
Diflubenzuron	High	Oral	Can persist on vegetation and water contamination is plausible.
Tebufenozide	High	Oral	Can persist on vegetation and water contamination is plausible.
DDVP	Very low	Inhalation /Oral	Except in cases of insects entering the trap or other animals tampering with trap, exposures will be very low.
Disparlure	Variable	Variable	Very little compound is used in traps and exposures are likely to be very low.

Table 4-3: Comparative dose-response assessment for potential effects in nontarget species

Endpoint	Agents used in Gypsy Moth Program							
	Gypsy Moth	*B.t.k.*	Ld-NPV	DFB	4-CA	Tebufen-ozide	DDVP	Dispar-lure
Terrestrial species								
Mammals		■/□ [a]	□	■	■	■	■	
Birds		□		■	■	■		
Nontarget *Lepidoptera*	■	●		●		○		
Other arthropods				●		□		
Other invertebrates				□		○		
Plants	●							
Microorganisms				■				
Aquatic species								
Fish		□/○ [b]	□	○/■ [c]	□	■	■	■
Invertebrates		□	□	●	□	■	○	■
Plants				□	□	□		
Microorganisms				□	○			

[a] NOEC value only for oral exposure. NOEC and LOEC for inhalation.
[b] NOEC value only for tolerant species. LOEC only for sensitive species.
[c] Effect level only for acute exposures.

Descriptive Key:		
	●	Effect and no-effect levels clearly identified. Response or differences in sensitivities among species can be quantified.
	■	Effect and no-effect levels identified.
	□	Based on no-effect level only.
	○	Based on effect level only.
	Blank	No quantitative dose-response assessment is made.

Table 4-4: Comparative risk characterization for terrestrial species [a]

Agent	Hazard Quotient (HQ) [b]		Comments
	Lower	Upper	
Gypsy Moth	0.25	**400**	All HQs based on defoliation. Lower HQ based on low infestation (5 egg masses/acre) in intermediate stands. Upper HQ based on damage to sensitive stands in an outbreak (up to 83% defoliation). Effects secondary to defoliation will occur in some animal populations.
B.t.k.	0.36	**9.4**	All HQs based on lethality to terrestrial invertebrates using 10% as a benchmark. A maximum mortality of 3.6% for tolerant invertebrates and 94% for sensitive invertebrates
LdNPV	0	0	No toxicity to terrestrial species is likely. The upper range of the HQ is 0.001 and is based on the consumption of contaminated vegetation and an acute free-standing NOAEL in mammals.
Diflubenzuron	0.18	**32**	All HQs based on responses in terrestrial invertebrates. The lower range is based on tolerant species and the upper range on sensitive species.
4-Chloroaniline	0	0.02	The upper range based on the consumption of fish by a predatory bird after an accidental spill (acute scenario).
Tebufenozide	0	**4**	The upper range is based on the consumption of contaminated vegetation by a large mammal after 2 applications at the maximum application rate. While not quantified, effects on some nontarget *Lepidoptera* are possible.
DDVP	0	0	Typically, exposures will be minimal. Insects entering the traps are likely to be killed.
Disparlure	0	0	No potential hazard can be identified except possible mating disruption in other pest *Lepidoptera*.

[a] See Figure 4-1 for illustration. Note that the magnitude of the HQ among different agents is not a measure of relative risk or severity of effects. See text for discussion.
[b] Hazard quotients less than 0.01 are given as zero. For tebufenozide, the lower range of the HQ is 0.0002. For 4-chloroaniline the lower range of the HQ is 0.00002. For NPV and disparlure, lower range of the HQs are essentially zero. For DDVP, exposure is unlikely and the risk is also essentially zero except for accidental exposures.

Table 4-5: Comparative risk characterization for aquatic species [a]

Agent	Hazard Quotient (HQ) [b]		Comments
	Lower	Upper	
Gypsy Moth	0	0	No basis for asserting that adverse effects will be observed.
B.t.k.	0	0.5	All HQs based on aquatic invertebrates. Lower range is 0.007 for tolerant species. The upper range is based on sensitive species
LdNPV	0	0	No basis for asserting that adverse effects will be observed. The upper range is 0.00003 and is based on a free-standing NOEC.
Diflubenzuron	0	**5**	Upper range is based on acute effects in sensitive aquatic invertebrates (*Daphnia*) after peak exposures.
4-Chloroaniline	0	0.2	Upper range is based on acute exposures to aquatic invertebrates and aquatic plants.
Tebufenozide	0	0.4	Upper range is based on longer-term toxicity in sensitive aquatic invertebrates.
DDVP	0	0 **8**	No risks are plausible in normal use. The HQ for aquatic invertebrates could reach up to 8 in accidental exposures.
Disparlure	0	0.4	Upper range based on acute exposures to sensitive aquatic invertebrates (*Daphnia*).

[a] See Figure 4-1 for illustration. Note that the magnitude of the HQ among different agents is not a measure of relative risk or severity of effects. See text for discussion.
[b] Hazard quotients less than 0.01 are given as zero.

Figures

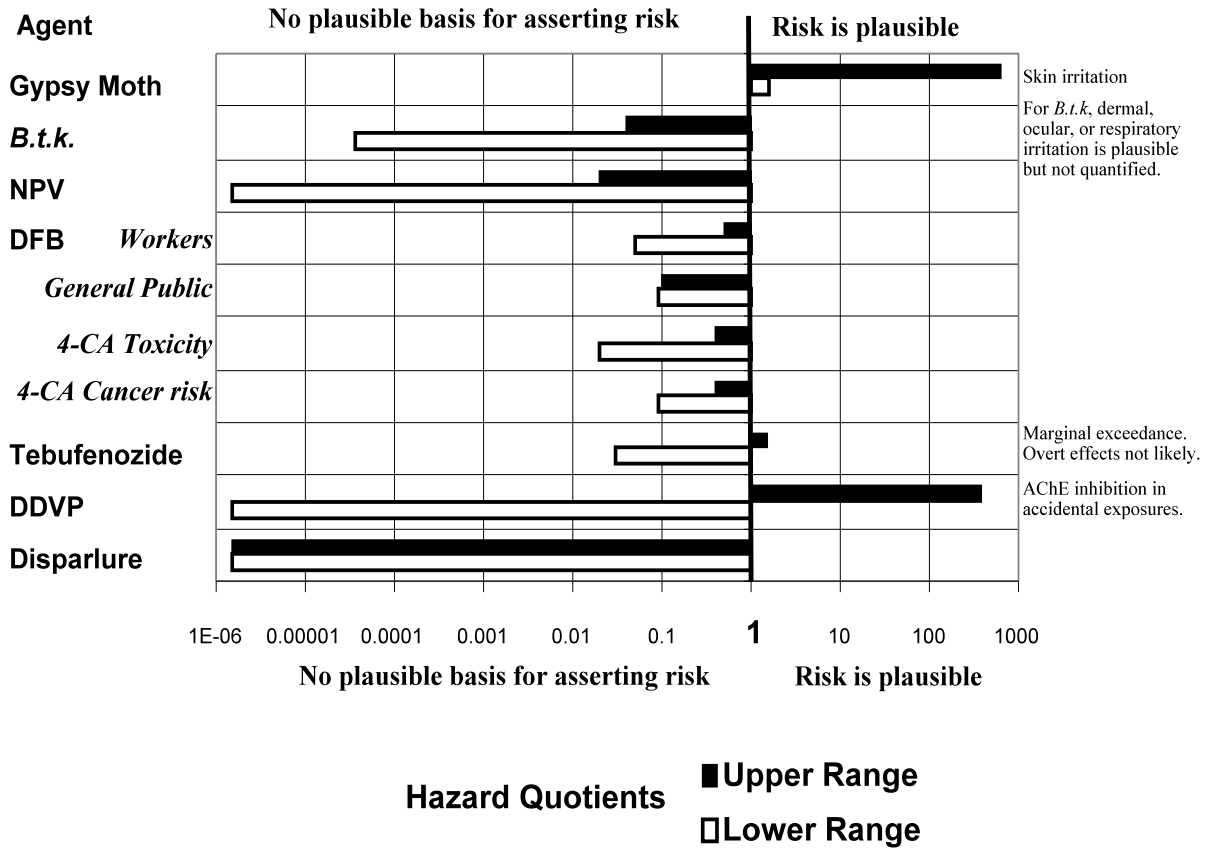

Figure 3-1: Risk comparison for potential human health effects.

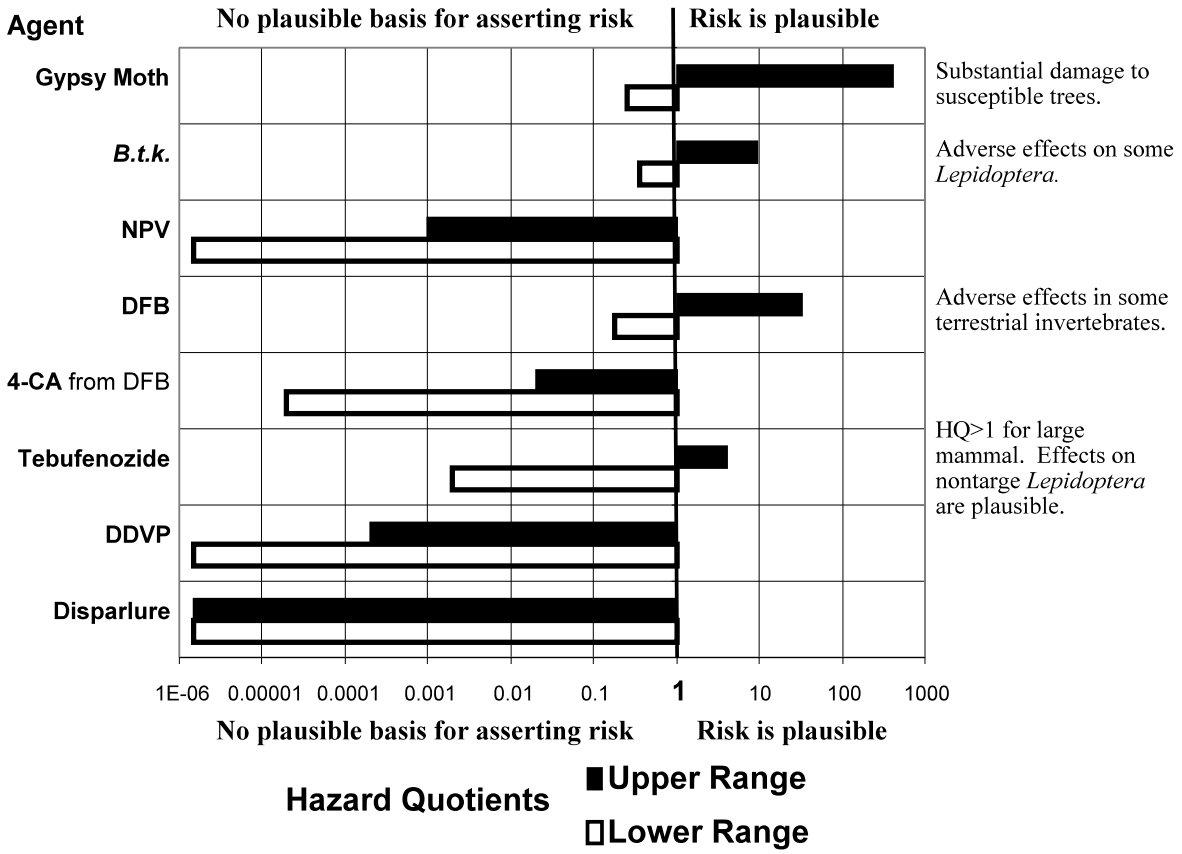

Figure 4-1: Risk comparison for potential effects in terrestrial species.

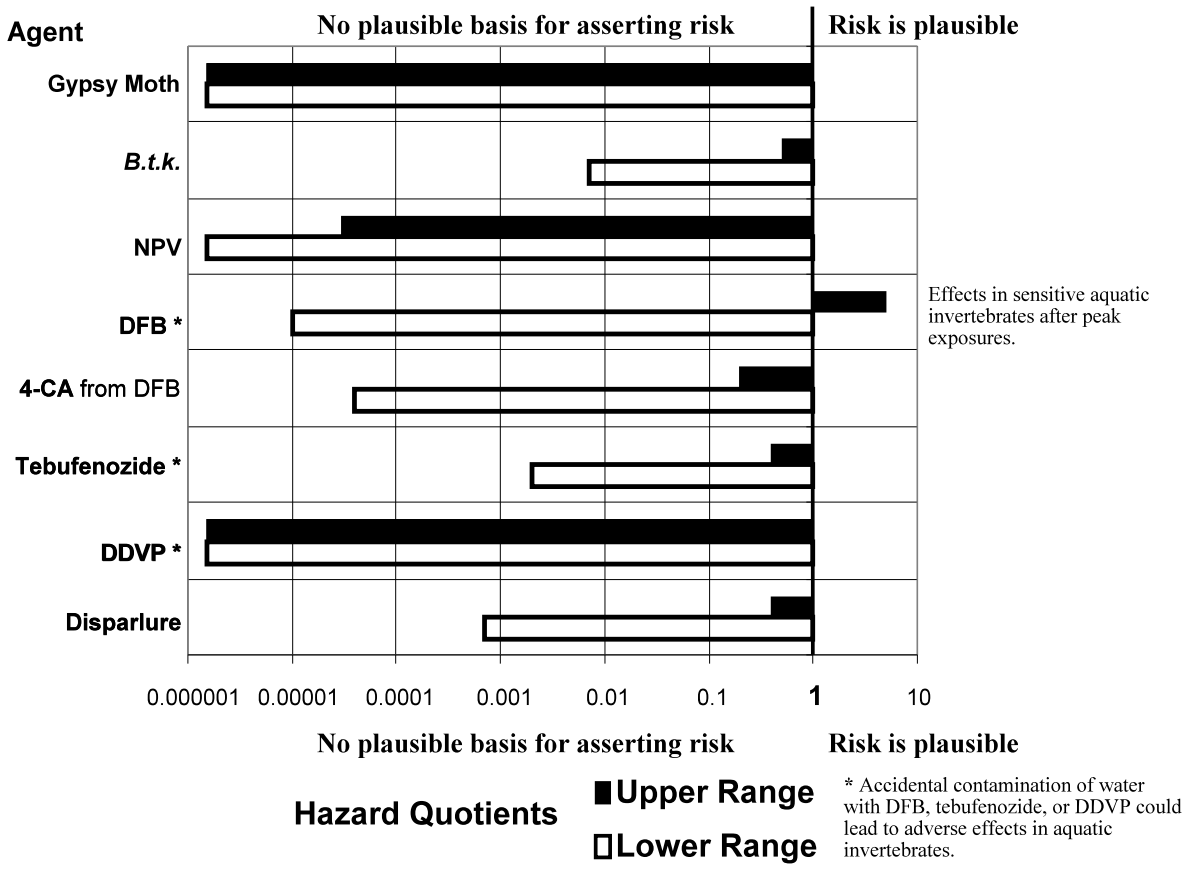

Figure 4-2: Risk comparison for potential effects in aquatic species.