

# Appendix D

## Site Specific Human Health Risk Assessment

### Fred's Fire Reforestation Final Environmental Impact Statement Eldorado National Forest

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### Section 1 – Introduction

The purpose of this analysis is to assess the site-specific risks to human health and safety of using five different herbicides for the control of grasses, forbs, and woody brush, and the control and eradication of the noxious weeds yellow starthistle and tall whitetop on the Eldorado National Forest. The herbicides examined are glyphosate, triclopyr, hexazinone, clopyralid, and chlorsulfuron. This analysis is based on the planned application rates for each of these herbicides that are proposed for ground-based application under the proposed action (Alternative 1). The application methods and application rates are based on silvicultural prescriptions prepared for the treatment units, and are on file at the Placerville Ranger District office. Table D-1 summarizes the herbicide formulations that are planned for use for Alternative 1, the expected rates per acre, and the additives planned for use.

**Table D-1 - Herbicide Formulations, Application Rates and Additives**

Herbicide Formulation	Application Rate (pounds/acre)	Additives
<b>Site Preparation and Release Treatments</b>		
glyphosate (Accord or equivalent formulation)	2.7 - 4.8 lbs/acre (ae)	NPE-based or silicone/MSO blend surfactant, Colorfast Purple dye
hexazinone (granular - Pronone or equivalent formulation)	2.0 - 3.0 lbs/acre (ae)	none
triclopyr (Garlon 4 or equivalent formulation)	1.6 - 2.4 lb./acre (ae)	MSO-based or silicone/MSO blend surfactant, Colorfast Purple dye
<b>Noxious Weed Treatments</b>		
glyphosate (Accord or equivalent formulation)	2.7 lbs/acre (ae)	NPE-based or silicone/MSO blend surfactant, Colorfast Purple dye
chlorsulfuron (Telar)	0.047 – 0.14 lbs./acre (ai)	NPE-based or silicone/MSO blend surfactant, Colorfast Purple dye

ae – acid equivalent, ai – active ingredient

Rates for hexazinone vary depending on soil texture and organic matter. The lower rates are for soils with higher sand content and lower organic matter, while the higher rates are for soils with higher silt content and organic matter. In addition to the specific herbicides, an additive (NPE-based surfactant, MSO-based surfactant, or a silicone/MSO blend surfactant), and a colorant (such as Colorfast Purple) may be utilized. NPE-based surfactants, MSO-based surfactants, and silicone/MSO blend surfactants are spreader/activators that improve the activity and penetration of the herbicide by reducing surface tension, allowing the herbicide mixture to spread evenly over the surface of vegetation. A colorant is added to indicate where the herbicide has been applied.

This risk assessment examines the potential health effects on all groups of people who might be exposed to any of the five herbicides proposed to be used. Those potentially at risk fall into two groups: workers and members of the public. Workers include applicators, supervisors, and other personnel directly involved in the application of herbicides. The public includes other forest workers, forest visitors, and nearby residents who could be exposed through the drift of herbicide spray droplets, through contact with sprayed vegetation, or by eating, or placing in the mouth, food items or other plant materials, such as berries or shoots growing in or near treated areas, by eating game or fish containing herbicide residues, or by drinking water that contains such residues.

The analysis of the potential human health effects of the use of chemical herbicides was accomplished using the methodology generally accepted by the scientific community (National Research Council, 1983, United States Environmental Protection Agency, 1986). In essence, the risk assessment consists of comparing doses, based on site-specific herbicide use levels, that people might receive from applying the herbicides (worker doses) or from being near an application site (public doses) with the United States Environmental Protection Agency's (U. S. EPA) established Reference Doses (RfD), a level of exposure considered protective of lifetime or chronic exposures. The site-specific risk assessment also examines the potential for these treatments to cause synergistic effects, cumulative effects, and effects on sensitive individuals, including women and children.

Details regarding the specific methods used to prepare the Syracuse Environmental Research Associates, Inc. (SERA) Human Health Risk Assessments referenced in this document are provided in SERA (2007), while detailed explanations of specific methods used in estimating occupational exposure are provided in SERA (1998). The risk assessment has five major sections: an introduction (Section 1); an identification of the hazards associated with each herbicide and its commercial formulations (Section 2); an assessment of potential exposure to the product (Section 3); an assessment of the dose-response relationships (Section 4); and a characterization of the risks associated with plausible levels of exposure (Section 5).

Risk assessments are usually expressed with numbers; however, the numbers are far from exact. *Variability* and *uncertainty* may be dominant factors in any risk assessment, and these factors should be expressed. Within the context of a risk assessment, the terms *variability* and *uncertainty* signify different conditions.

*Variability* reflects the knowledge of how things may change. Variability may take several forms. For this risk assessment, three types of variability are distinguished: *statistical*, *situational*, and *arbitrary*. *Statistical variability* reflects, at least, apparently random patterns in data. For example, various types of estimates used in this risk assessment involve relationships of certain physical properties to certain biological properties. In such cases, best or maximum likelihood estimates can be calculated as well as upper and lower confidence intervals that reflect the statistical variability in the relationships. *Situational variability* describes variations depending on known circumstances. For example, the application rate or the applied concentration of a herbicide will vary according to local conditions and goals. As discussed in the following section, the limits on this variability are known and there is some information to indicate

what the variations are. In other words, *situational variability* is not random. *Arbitrary variability*, as the name implies, represents an attempt to describe changes that cannot be characterized statistically or by a given set of conditions that cannot be well defined. This type of variability dominates some spill scenarios involving either a spill of a chemical on to the surface of the skin or a spill of a chemical into water. In either case, exposure depends on the amount of chemical spilled and the area of skin or volume of water that is contaminated.

*Variability* reflects knowledge of or at least an explicit assumption about how things may change, while *uncertainty* reflects a lack of knowledge. For example, the focus of the human health dose-response assessment is an estimation of an “acceptable” or “no adverse effect” dose that will not be associated with adverse human health effects. For most chemicals, however, this estimation regarding human health must be based on data from experimental animal studies, which cover only a limited number of effects. Generally, judgment, not analytical methods, is the basis for the methods used to make the assessment. Although the judgments may reflect a consensus (i.e., be used by many groups in a reasonably consistent manner), the resulting estimations of risk cannot be proven analytically. In other words, the estimates regarding risk involve uncertainty. The primary functional distinction between variability and uncertainty is that variability is expressed quantitatively, while uncertainty is generally expressed qualitatively.

In considering different forms of variability, almost no risk estimate presented in this document is given as a single number. Usually, risk is expressed as a central estimate and a range, which is sometimes very large. Because of the need to encompass many different types of exposure as well as the need to express the uncertainties in the assessment, this risk assessment involves numerous calculations. Most of the calculations are relatively simple, however, some of the calculations are cumbersome. These calculations are contained in worksheets in the project file, and are based on the worksheets contained in the various SERA risk assessments.

## **Section 2 – Hazard Analysis**

The hazards associated with using each of the herbicides were determined by a thorough review of available toxicological studies. The reviews are contained in other documents and are referenced here as needed. A considerable body of information has been compiled in a group of risk assessments completed by SERA (authored by Dr. Patrick Durkin, PhD) under contract to the Forest Service, the risk assessment contained in the programmatic Region 5 Final EIS Vegetation Management for Reforestation (USDA 1989), and the risk assessment contained in the Herger-Feinstein Quincy Library Group Forest Recovery Act Final Supplemental EIS (USDA, 2003b). Another source of information on toxicity are the background statements contained in Forest Service Agricultural Handbook No. 633 (USDA, 1984). Current peer-reviewed articles from the open scientific literature, as well as recent U. S. EPA documents are also used to update the information contained in these documents. Toxicity information for the surfactants being considered for use are summarized in USDA, 2003a and USDA, 2007. Additional information on toxicity is contained in Williams, et al (2000). Current peer-reviewed articles from the open scientific literature, as well as recent U.S. EPA documents are also used to update information contained in these documents. All of these documents are incorporated by reference into this risk assessment.

The toxicological database for each herbicide was reviewed for acute, subchronic, and chronic effects on test animals. Because of the obvious limitations on the testing of chemicals on humans, judgments about the potential hazards of pesticides to humans is necessarily based in large part on the results of toxicity tests on laboratory animals. Where such information is available, information on actual human poisoning incidents and effects on human populations supplement these test results. For a background discussion of the various toxicological tests and endpoints, refer to USDA (1989, pages F-7 to F-18).

A note specific to impurities and metabolites – virtually no chemical synthesis yields a totally pure product. Technical grade herbicides, as with other technical grade products, undoubtedly contain some impurities. The U. S. EPA defines the term impurity as “...any substance ... in a pesticide product other than an active ingredient or inert ingredient, including un-reacted starting materials, side reaction products, contaminants, and degradation products” (40 CFR 158.153(d)). To some extent, concern for impurities in technical grade products is reduced by the fact that the existing toxicity studies on these herbicides were conducted with the technical grade product. Thus, if toxic impurities are present in the technical grade product, they are likely to be encompassed by the available toxicity studies on the technical grade product. An exception to this general rule involves carcinogens, most of which are presumed to act by non-threshold mechanisms. Because of the non-threshold assumption, any amount of a carcinogen in an otherwise non-carcinogenic mixture may pose a carcinogenic risk. As with contaminants, the potential effect of metabolites on a risk assessment is often encompassed by the available *in vivo* toxicity studies under the assumption that the toxicological consequences of metabolism in the species on which toxicity studies are available will be similar to those in the species of concern (humans in this case). Uncertainties in this assumption are encompassed by using an uncertainty factor in deriving the RfD and may sometimes influence the selection of the study used to derive the RfD. Unless otherwise specifically referenced, all data and test results are from the references listed at the herbicide heading.

### **Chlorsulfuron (Reference: SERA, 2004a)**

**Acute and Chronic Exposures** - Although no information is available on the toxicity of chlorsulfuron to humans, the toxicity of chlorsulfuron has been relatively well characterized in mammals. All of this information is contained in unpublished studies submitted to the U.S. EPA as part of the registration process for chlorsulfuron.

In experimental mammals, the acute oral LD<sub>50</sub> for chlorsulfuron is greater than 5,000 milligrams per kilogram of body weight (mg/kg), which indicates a low order of oral toxicity. Acute exposure studies of chlorsulfuron and chlorsulfuron formulations give similar results, indicating that formulations of chlorsulfuron are not more toxic than chlorsulfuron alone.

Similar adverse effects are observed following both subchronic and chronic exposure to chlorsulfuron in tested mammals. The most common and sensitive signs of acute, subchronic, and chronic toxicity are weight loss and decreased body weight gain. The only other commonly noted effects are changes in various hematological parameters and general gross pathological changes to several organs. None of these changes, however, suggest a clear or specific target organ toxicity. While observations of weight loss and decreased weight gain suggest that chlorsulfuron could be associated with an underlying change in metabolism, studies specifically investigating the effects of chlorsulfuron on metabolism have not been conducted. The U.S. EPA used a 1-year feeding study in rats, with a NOEL of 5 mg/kg/day, to derive an RfD for chlorsulfuron; body weight loss and decreased weight gain were used as the most sensitive effects.

**Effects on the Skin and Eyes** - Chlorsulfuron is classified as a moderate eye irritant, but as a non-irritant to the skin. The results of several acute dermal studies show that formulations containing up to 80% chlorsulfuron produced only mild skin irritation. Dermal application of chlorsulfuron to intact and abraded skin produced mild redness in rabbits that resolved within 4-6 days. Dermal application of chlorsulfuron did not produce skin irritation or a sensitization response in guinea pigs. Application to the eyes of rabbits produced mild irritant effects to the cornea and conjunctiva. Transient, mild corneal clouding and mild to no conjunctival swelling and discharge were observed in rabbits following a single application of 0.1 milliliter (mL) of a 75% formulation. No signs of irritation of the iris were observed. In another study, a single application to the eyes produced transient slight corneal clouding, conjunctivitis,

and swelling of the iris. Eyes returned to normal within 4 days. Studies on the systemic toxicity of chlorsulfuron following dermal exposure have been conducted in rabbits. Dermal exposure to doses up to 3,400 mg/kg were not associated with any signs of significant systemic toxicity in rabbits based on standard acute bioassays with 14-day observation periods. The only signs of systemic toxicity reported in these studies were an initial weight loss and diarrhea.

**Reproductive and Teratogenic Effects** - Two gavage teratogenicity studies have been conducted in rabbits and rats and two dietary reproduction studies have been conducted in rats. Chlorsulfuron is not teratogenic, but is toxic to embryos at high exposure levels. An increase in the number of fetal resorptions and a decrease in fetal viability, indicating embryo toxicity, were observed in rabbits exposed to 75 mg/kg/day. Teratogenic effects were not observed in any dose group. Exposure of rats for three-generations to chlorsulfuron did not result in significant treatment-related effects. The only adverse effect on reproductive function reported was a slightly decreased fertility index in rats exposed to 125 mg/kg/day. The NOEL for reproductive effects in rats is 25 mg/kg/day. Other than weight loss, no significant maternal toxicity was reported in these studies. Thus, chlorsulfuron does not appear to have significant adverse effects on reproductive function. Chlorsulfuron is listed as a developmental toxicant by the state of California under Proposition 65 (the Safe Drinking Water and Toxic Enforcement Act of 1986).

**Carcinogenicity and Mutagenicity** - Chlorsulfuron has been tested for mutagenicity in a number of different test systems and has been assayed for carcinogenic activity in rats and mice. No evidence of carcinogenic activity was found in any of the chronic toxicity studies conducted on chlorsulfuron. Chlorsulfuron was classified as having "no evidence of carcinogenicity" based upon lack of evidence of carcinogenicity in rats and mice (U.S. EPA 2002e).

Results of *in vitro* mutagenicity studies in several *Salmonella typhimurium* bacteria strains and in Chinese hamster ovary cells show that chlorsulfuron is not mutagenic, either with or without metabolic activation. Negative results were also obtained from genotoxicity studies in rat liver cell cultures. In addition, *in vivo* studies in rats show that chlorsulfuron at exposure levels up to 250 mg/kg/day for 10 weeks does not produce dominant lethal mutations.

**Other Toxic Endpoints** – There is very little direct information on which to assess the immunotoxic potential of chlorsulfuron. Results of long-term exposure studies in dogs and mice show that chlorsulfuron may produce changes to immune system function. Increases in lymphocytes and eosinophils (a type of white blood cell that can increase with allergy and other infections) were observed in female dogs exposed for 6 months to 25 or 125 mg/kg/day chlorsulfuron. Effects were not seen at the 5 mg/kg/day dose or in male dogs at any dose. In mice, neutrophilic granulocytes (a type of white blood cell) were decreased and lymphocyte counts were increased in female mice exposed to 250, or 375 mg/kg/day chlorsulfuron for 3 months. These effects were not observed in female mice at lower doses or in male mice at any dose. While results of these studies suggest that exposure to chlorsulfuron may produce changes in immune system parameters, the observations in these studies do not provide conclusive evidence supporting the immunotoxic potential of chlorsulfuron.

Virtually any chemical, including chlorsulfuron, will cause signs of neurotoxicity in severely poisoned animals and thus can be classified as an indirect neurotoxicant. This is the case for chlorsulfuron in that exposure to acute high doses of chlorsulfuron produces lethargy and weakness. This does not, however, implicate chlorsulfuron as a direct neurotoxicant.

Chronic, lifespan, and multigenerational bioassays in mammals and acute and subchronic studies on aquatic organisms and wildlife did not reveal endocrine effects. Any endocrine related effects would have been detected in this definitive array of required tests (U.S. EPA, 2002f). Both weight loss and weight gain are observed in animals treated with chlorsulfuron, implying a change in metabolic status. However, there is no evidence to suggest that changes in weight are due to effects of chlorsulfuron on the endocrine system. Decreased pituitary and thyroid weights were observed in male dogs exposed to chlorsulfuron for

26 weeks. However, these changes were not considered to be treatment related. With the exception of a slight decrease in the fertility index in rats exposed to 125 mg/kg/day chlorsulfuron in a three-generation reproductive study, there is no evidence that chlorsulfuron produces adverse effects on the reproductive endocrine system. Thus, no evidence for chlorsulfuron producing direct effects on the endocrine system was found.

**Inhalation Exposures** – There is only one inhalation toxicity study of chlorsulfuron. Acute (4 hour) inhalation of chlorsulfuron at relatively high concentration levels (5.9 mg/L) in dust did not result in any systemic adverse effects to rats considered to be treatment related. While no systemic effects were noted from necropsy performed after exposure, microscopic changes to the mucus membrane in the nasal cavity, including atrophy of the secreting cells of the nasal gland and minor changes to the nasal cavity skin cells, were noted in some of the rats. These histological findings were consistent with chronic inflammation of the lining of the nose or with post-injury repair processes.

**Impurities** – No information has been encountered in the published or unpublished literature on impurities in chlorsulfuron.

**Metabolites** - The elimination of chlorsulfuron has been studied in rats, goats, dairy cows, and hens. In rats, chlorsulfuron exhibits first order elimination kinetics, with an estimated half-life of <6 hours. In all mammalian species studied, chlorsulfuron and its metabolites are extensively and rapidly cleared by a combination of excretion and metabolism. Most of the chlorsulfuron is excreted in urine or feces in the form of the unchanged compound. Due to its rapid elimination, metabolism of chlorsulfuron in animals is minimal. The major metabolite identified in the urine of rats is 2-chlorobenzenesulfonamide (a hydrolysis product), although other minor metabolites have also been identified in urine. Conjugation products, mainly N-glucuronides, have also been identified in the urine of goats. No studies investigating the toxicity of the chlorsulfuron metabolites produced by mammals were identified in the published literature or unpublished studies. There is no evidence that the metabolites of chlorsulfuron as identified in either the plant, or animal metabolism studies are of any toxicological significance (U.S. EPA, 2002f).

**Inerts** - The formulation of chlorsulfuron used by the Forest Service contains materials other than chlorsulfuron that are included as adjuvants to improve either efficacy or ease of handling and storage. The identity of these materials is confidential. The inerts were disclosed to the U.S. EPA and were reviewed in the preparation of SERA, 2004a. All that can be disclosed explicitly is that none of the additives are classified by the U.S. EPA as toxic.

## **Clopyralid (Reference: SERA, 1999, 2004b)**

**Acute and Chronic Exposures** - Although no information is available on the toxicity of clopyralid to humans, the toxicity of clopyralid has been relatively well characterized in mammals. All of this information is contained in unpublished studies submitted to the U.S. EPA as part of the registration process for clopyralid.

Two different manufacturing processes may be used for clopyralid: the penta process and the electrochemical process. The limited available information indicates that technical grade clopyralid samples from the electrochemical process may be somewhat more toxic (median lethal dose (LD<sub>50</sub>) values in the range of about 3000 mg/kg) than the penta process (LD<sub>50</sub> > 5000 mg/kg). These differences, however, are not substantial and may be due to random variability.

The available data do not suggest that Transline would be more or less toxic than clopyralid following acute oral exposure. Carreon and New (1981, as referenced in SERA 2004b) reported an LD<sub>50</sub> >5000 mg/kg for a formulation with no deaths at a dose level of 5000 mg/kg; lethargy was the only treatment-related effect.

Clopyralid also has a low order of chronic toxicity. On chronic or subchronic exposures, no effects have been observed in laboratory mammals at doses of 50 mg/kg/day or less. At doses of 100 mg/kg/day or greater, various effects have been observed in different species and different bioassays. These effects include weight loss, changes in the weight of the liver and kidney, thickening of epithelial tissue, irritation of the lungs, and decreases in red blood cell counts.

Up until 2001, U.S. EPA had used a chronic No Observed Adverse Effect Level (NOAEL) of 50 mg/kg/day to establish the RfD. This was based on a chronic exposure study in rats (Humiston et al, 1977, as referenced in SERA, 1999) that showed decreases in body weight in females at the next highest dose tested (150 mg/kg/day). In 2001, U.S. EPA changed the chronic NOAEL to 15 mg/kg/day (U.S. EPA, 2001), based on another chronic study in rats that also showed effects at 150 mg/kg/day (thickening of epithelial tissue), but a NOAEL of 15 mg/kg/day (Barna-Lloyd et al, 1986, as referenced in SERA, 1999). This second study did not have a 50 mg/kg/day dose level. This change is currently under discussion between the clopyralid registrant and the U.S. EPA. However, for this risk assessment, the value of 15 mg/kg/day will be used as the chronic NOAEL, for the establishment of the RfD.

**Effects on the Skin and Eyes** - After direct instillation into the eyes, both penta and electrochemical process clopyralid can cause persistent damage to the eyes. The damage is characterized as slight to marked redness, swelling of the conjunctiva, and discharge with reddening of the iris and moderate to marked opacity of the cornea.

Other than signs of transient redness of the skin shortly after application, there is no evidence to suggest that clopyralid is a potent skin irritant. Neither the penta process clopyralid nor electrochemical process clopyralid causes skin sensitization.

Studies on formulations comparable or equivalent to Transline have been conducted for dermal irritation and for ocular irritation. These studies indicate that the irritant effects of Transline are comparable to those of technical grade clopyralid.

The available toxicity studies suggest that dermal exposure to 2000 mg/kg clopyralid was not associated with any signs of systemic toxicity in rabbits based on standard acute/single application bioassays with 14-day observation periods. The available data suggest that the dermal absorption of clopyralid is poor. No systemic effects were reported by a dermal study in which New Zealand white rabbits were exposed to 2000 mg/kg clopyralid for 24 hours.

The systemic effects from dermal exposure to the formulation may be influenced by the presence of other adjuvants which may alter the rate at which the parent chemical moves through the skin. The available data do not suggest that the Transline formulation has greater potential for persistent systemic toxicity than clopyralid, although lethargy was observed following acute dermal exposure.

**Reproductive and Teratogenic Effects** - Two gavage teratogenicity studies have been conducted in rabbits, one gavage teratogenicity study has been conducted in rats, and four dietary reproduction studies have been conducted in rats. Other than a decrease in maternal body weight, which is consistent with the information on the subchronic and chronic toxicity of clopyralid, these studies report few signs of toxicity in dams or offspring. At doses that cause no signs of maternal toxicity - i.e., doses below about 100 mg/kg/day - no reproductive or teratogenic effects are apparent. The available data suggest that clopyralid does not produce developmental effects at doses that do not produce maternal toxicity. U.S. EPA has established a reproductive NOAEL of >1,500 mg/kg/day (U.S. EPA, 2002b).

**Carcinogenicity and Mutagenicity** - Several chronic bioassays have been conducted on clopyralid in mice, rats, and dogs and no evidence of carcinogenic activity has been detected. U.S. EPA has placed clopyralid in Group E (no evidence of carcinogenicity). In addition, clopyralid is inactive in several different standard bioassays of mutagenicity.

Although none of the bioassays have shown that clopyralid has carcinogenic potential, technical grade clopyralid does contain low levels of the impurities hexachlorobenzene and pentachlorobenzene. Hexachlorobenzene has shown carcinogenic activity in three mammalian species and has been classified as a potential human carcinogen by the U.S. EPA. Pentachlorobenzene is not classifiable as to human carcinogenicity based on lack of available human and animal data. The risk of cancer from these contaminants is considered qualitatively and quantitatively in this risk assessment.

**Other Toxic Endpoints** – Clopyralid can be classified as an indirect neurotoxicant but not as a direct neurotoxicant. At high acute doses that produce a broad spectrum of toxicological effects, clinical signs of clopyralid poisoning include neurotoxicity, indicated by ataxia, tremors, convulsions, and weakness. Similar effects at high doses have been seen in birds. These reports, however, do not implicate clopyralid as a direct neurotoxicant. No studies designed specifically to detect impairments in motor, sensory, or cognitive functions in animals or humans exposed to clopyralid have been reported in the open literature or in the studies submitted to the U.S. EPA to support the registration of clopyralid. In addition, none of the studies in the clopyralid database reported histopathologic changes in nervous tissue.

There is very little direct information on which to assess the immunotoxic potential of clopyralid. The only studies specifically related to the effects of clopyralid on immune function are skin sensitization studies. While these studies provide information about the potential for clopyralid to act as a skin sensitizer, they provide no information useful for directly assessing the immuno-suppressive potential of clopyralid. The toxicity of clopyralid has been examined in numerous acute, subchronic, and chronic bioassays. Although many of these studies did not focus on the immune system, changes in the immune system were not observed in any of the available studies.

Clopyralid has not been tested for activity as an agonist (activator) or antagonist of the major hormone systems (e.g., estrogen, androgen, thyroid hormone), nor have the levels of circulating hormones been measured following clopyralid exposures. Thus, all inferences concerning the potential effect of clopyralid on endocrine function must be based on inferences from standard toxicity studies. The available toxicity studies have not reported any histopathologic changes in endocrine tissues that have been examined as part of the standard battery of tests.

**Inhalation Exposures** - Two relatively detailed inhalation studies have been submitted to U.S. EPA in support of registration of clopyralid. At nominal concentrations of 1 mg/L or greater over 4-hour exposure periods, the only effects noted were labored breathing and red stains around the openings of the nasal cavity. After a two-week recovery period, there was discoloration of the lungs in rats exposed to nominal concentrations of 1.2 mg/L but not in rats exposed to nominal concentrations of 5.5 mg/L. Although the author did not attribute the changes in the lungs to clopyralid exposure, these changes are consistent with effects noted in a one-year dietary study in dogs. In this study, low-dose (100 mg/kg/day), mid-dose (320 mg/kg/day), and high-dose (1000 mg/kg/day) animals evidenced atypical nodules in the lungs. The study authors attributed these findings to the inhalation of food particles containing clopyralid with subsequent irritation of the lungs from direct clopyralid contact.

No occupational exposure criteria have been found for clopyralid. While any effects on the lungs are of substantial concern, such effects have not been seen at lower dietary dose levels in other species. The current RfD for clopyralid is based on a NOAEL of 15 mg/kg/day from a two-year rat feeding study. This NOAEL is a factor of 6 below the lowest dose associated with lung effects in dogs (100 mg/kg/day).

**Impurities** - Technical grade clopyralid contains hexachlorobenzene and pentachlorobenzene as contaminants. Nominal or average concentrations of hexachlorobenzene are less than 2.5 parts per million (ppm). Nominal or average concentrations of pentachlorobenzene are less than 0.3 ppm. The U.S. EPA has classified hexachlorobenzene as a probable human carcinogen for which the data are adequate to consider risk quantitatively.

**Metabolites** – Metabolism studies indicate that clopyralid is not extensively metabolized in mammals and birds, with 79-96% of the administered dose being excreted unchanged in the urine during the first 24 hours, and nearly complete elimination within 120 hours. This is similar to the pattern seen in plants that generally suggests that clopyralid is not extensively metabolized, although it may be conjugated to form a methyl ester. U.S. EPA does not consider any clopyralid metabolites to be of toxic significance (U.S. EPA, 1999).

**Inerts** - The commercial formulation of clopyralid used by the Forest Service (Transline<sup>®</sup>) is formulated as the monoethanolamine salt – i.e., monoethanolamine is considered part of the active ingredient. Transline<sup>®</sup> also contains isopropyl alcohol and polyglycol as adjuvants.

No studies specifically mentioning Transline<sup>®</sup>, were located in the search of the studies submitted to U.S. EPA for product registration. Dow AgroSciences (2003, as referenced in SERA 2004b) provided clarification of this issue and identified the studies submitted to U.S. EPA that were accepted as relevant to Transline<sup>®</sup>. These studies do not indicate any substantial differences between Transline<sup>®</sup> and clopyralid. This is consistent with the publicly available information on the three inerts contained in Transline<sup>®</sup>, two of which are approved for use as food additives (monoethanolamine and isopropyl alcohol).

The other inert in Transline<sup>®</sup> is Polyglycol 26-2. This compound is classified by the U.S. EPA as a List 3 inert. In other words, there is insufficient information to categorize this compound as either hazardous (Lists 1 or 2) or non-toxic (List 4). Notwithstanding this classification, surfactants such as Polyglycol 26-2 are surface active agents that can disrupt cellular membranes and lead to a number of different adverse effects. In an *in vitro* study on energy production in sub-mitochondrial particles derived from a marine alga, Oakes and Pollak (1999, as referenced in SERA 2004b) noted that Polyglycol 26-2 inhibited oxidative function in the submitochondrial preparations at a concentration of about 0.01%. While this study clearly indicates that Polyglycol 26-2 will impact mitochondrial function *in vitro*, the implications for potential effects in humans at plausible levels of exposure are not apparent.

### **Glyphosate (References: USDA, 1984; USDA, 1989; SERA, 2003a, Williams, et al, 2000)**

**Acute and Chronic Exposures** - The toxicity of glyphosate is relatively well characterized in both experimental mammals and humans, although the mechanism of action is not clear. The acute toxicity of glyphosate is relatively low, with oral LD<sub>50</sub> values in rats and mice ranging from approximately 2,000 to 6,000 mg/kg. Most of the human experience with glyphosate involves the consumption of large quantities of glyphosate during attempted suicides. The signs of toxicity are generally consistent with massive mucosal irritation and tissue degeneration. In addition, glyphosate may interfere with normal metabolic biochemical functions.

The chronic toxicity of glyphosate has been well characterized in laboratory mammals. One of the more consistent signs of subchronic or chronic exposure to glyphosate is loss of body weight. This effect has been noted in mice, rats, and rabbits. Other signs of toxicity seem general and non-specific. A few studies report changes in liver weight, blood chemistry that would suggest mild liver toxicity, or liver pathology. Changes in pituitary weight have also been observed. Signs of kidney toxicity, which might be expected based on the acute toxicity of glyphosate, have not been reported consistently and are not severe. As summarized by the National Toxicology Program (NTP) (1992, as referenced in SERA, 2003a), various hematological changes have been observed but are not considered severe and are attributed to mild dehydration.

**Effects on the Skin and Eyes** - Glyphosate formulations used by the Forest Service are classified as either non-irritating or only slightly irritating to the skin and eyes in standard assays required for product registration. Based on several eye and skin irritation studies submitted to the U.S. EPA as part of the

registration process, the U.S. EPA classifies glyphosate as mildly irritating to the eyes (Category III) and slightly irritating to the skin (Category IV). The free acid of glyphosate is severely irritating to the eyes but the isopropylamine (IPA) salt of glyphosate, the form that is in all formulations used by the USDA Forest Service, is nonirritating to the skin and eyes. Although glyphosate is an irritant, there are no data indicating that the compound causes sensitization in animals or humans. POEA and other surfactants used in glyphosate formulations may be severely irritating to the eyes, skin, and other mucosal surfaces, such as the gastrointestinal tract and the lungs.

**Carcinogenicity and Mutagenicity** – Based on standard animal bioassays for carcinogenic activity *in vivo*, there is no basis for asserting that glyphosate is likely to pose a substantial risk. The Reregistration Eligibility Decision (RED) document (U.S. EPA, 1993) on glyphosate indicates that glyphosate is classified as Group E: Evidence of non-carcinogenicity for humans. Tumors have been observed in some of the earlier chronic toxicity studies. U.S. EPA determined that the studies conducted before 1990 were insufficient for evaluating the potential carcinogenicity of glyphosate because the observed responses were equivocal or the dose levels were inappropriate (i.e., the highest dose used was not the maximum tolerated dose). A recent epidemiology study in Sweden (Hardell and Eriksson, 1999, as referenced in SERA 2003a) reported an increased cancer risk of non-Hodgkin lymphoma (NHL) in individuals in Sweden who have a history of exposure to glyphosate. The increased risk was not statistically significant. A review of the Hardell and Eriksson study was done by U.S. EPA, which concluded that the study does not change their risk assessment for the current uses of glyphosate.

According to the U.S. EPA classification of carcinogens and their assessment of the available data, glyphosate is not carcinogenic to humans. Given the marginal mutagenic activity of glyphosate and the failure of several chronic feeding studies to demonstrate a dose-response relationship for carcinogenicity and the limitations in the available epidemiology study, the Group E classification given by the U.S. EPA appears to be reasonable. As with any compound that has been studied for a long period of time and tested in a large number of different systems, some equivocal evidence of carcinogenic potential is apparent and may remain a cause of concern, at least in terms of risk perception. While these concerns are understandable, there is no compelling basis for challenging the position taken by the U.S. EPA and no quantitative risk assessment for cancer is conducted as part of the current analysis.

A formulation of glyphosate, Roundup<sup>®</sup>, has been shown to cause an increase in chromosomal aberrations in a plant (*Allium* spp.) associated with cell abnormalities in spindle fiber, DNA adduct formation in mice, and single strand breaks in mice. None of the *in vivo* studies using mammalian species or mammalian cell lines have reported mutagenic activity. Two studies (Vyse and Vigfusson 1979, Vigfusson and Vyse 1980, as referenced in SERA, 2003a) report a significant increase in sister chromatid exchanges in human white blood cells *in vitro*. The authors of these studies conclude from their results that glyphosate is, at most, slightly mutagenic. In addition, some positive assays in the fruit fly have been reported as well as positive results in white blood cell cultures. Based on the weight of evidence of all available studies, U.S. EPA concluded that glyphosate is not mutagenic. More recent studies do not provide data that challenges the U.S. EPA assessment (Williams et al. 2000).

**Reproductive and Teratogenic Effects** - Glyphosate has been subject to multi-generation reproduction studies as well as teratology studies. There is no indication from these studies that glyphosate induces teratogenic effects (i.e., birth defects) in soft tissues at doses up to 3,500 mg/kg/day. The only abnormal development was delayed bone development (ossification). In the teratology studies, the observed signs of toxicity - respiratory and gastrointestinal effects - were similar to those observed in acute toxicity studies and occurred at dose levels that were also comparable. In a multi-generation reproduction study in rats, effects to the kidney were observed in male pups at 30 mg/kg/day but not at 10 mg/kg/day. This effect is consistent with the acute toxicity of glyphosate rather than a specific reproductive effect. In a subsequent study, no such effects were observed at doses up to 1,500 mg/kg/day. In the glyphosate RED (U.S. EPA, 1993), U.S. EPA concluded that the lack of renal effects in the second study indicated that the effects seen in the first study were not glyphosate-related. Previous to this, the U.S. EPA had based the

RfD for glyphosate on the 10 mg/kg/day NOAEL for this effect. Based on this re-interpretation of results, the NOEL for developmental effects was set at 500 mg/kg/day. The multi-generation reproduction studies found no effect on reproductive capacity. In another study using rabbits, developmental toxicity was not observed at maternal doses up to 350 mg/kg/day, but maternal effects were seen at this dose. The maternal NOEL in this study was 175 mg/kg/day; this is the value U.S. EPA has used to establish the current RfD.

The only other specific and consistent effect of glyphosate involves effects on the testicles. In an NTP study, relative testicular weights in mice were increased. In rats, there was a 20% decrease in sperm counts at the two highest dose levels, 1,678 and 3,398 mg/kg/day. Given the absence of specific testicular pathology in either species, the NTP concluded that there was no evidence of adverse effects on the reproductive system of rats or mice. This finding is consistent with the bulk of other animal studies, in which no adverse effects on the testes are reported, although an increase in testicular weight - relative and absolute - was observed in mice at 3,465–7,220 mg/kg/day. A study by Yousef et al., (1995, as referenced in SERA 2003a) suggests that more serious effects are plausible. Substantial decreases in libido, ejaculate volume, sperm concentrations, semen initial fructose and semen concentration, as well as increases in abnormal and dead sperm were observed in rabbits. In contrast, in multi-generation reproduction studies, no effects on reproductive performance have been observed at dietary levels equivalent to doses of 1,500 mg/kg/day. The basis for the inconsistency between the Yousef et al., 1995 study and all other studies that have assessed the reproductive effects of glyphosate cannot be identified unequivocally. As discussed in Williams, et al, 2000, the authors describe the Yousef study as having serious deficiencies in design, conduct, and reporting, such that “the data from [the Yousef] study cannot be used to support any meaningful conclusions”. In addition, the method of administration of the glyphosate in the Yousef study is not representative of likely human exposures. In a subsequent study, Yousef also demonstrated a reduction in sperm motility after direct exposure of sperm to glyphosate. The mechanism of this effect is not clear, but may be related to the ability of glyphosate to inhibit cellular energy production.

Numerous epidemiological studies have examined relationships between pesticide exposures or assumed pesticide exposures in agricultural workers and reproductive outcomes. Very few studies, however, have attempted to characterize exposures, either qualitatively or quantitatively, to specific pesticides. Of those studies that have specifically addressed potential risks from glyphosate exposures, adverse reproductive effects have not been associated with glyphosate exposure.

**Other Toxic Endpoints** – No neurotoxic effects have been seen in any *in vivo* or *in vitro* studies. Glyphosate has been specifically tested for neurotoxicity in rats after both acute and chronic exposures and in hens. In all three assays, glyphosate was negative for signs of neurotoxicity. U.S. EPA has determined that there is no evidence of neurotoxicity in any of the exposure studies conducted (U.S. EPA, 2000b). Large-scale controlled epidemiological studies of glyphosate exposure and neurological outcomes have not been reported. A small clinical investigation found no evidence for neurological effects among forest workers who mixed and sprayed Roundup during a workweek. The clinical case literature of acute glyphosate intoxication is reasonably extensive and does not provide evidence for glyphosate being an acute neurotoxicant in humans. Several long-term experimental studies examined various endpoints of neurotoxicity (brain morphology) in dogs, mice, or rats and did not find evidence of neurotoxicity. An acute study found no effect of glyphosate exposure on nervous system reflexes in dogs. Studies conducted in various bird species did not find evidence for neurological effects. One study reported a case of Parkinsonism in an adult male who was exposed to glyphosate (Barbosa et al 2001 as referenced in SERA 2003a). This study stands in contrast to the abundant case literature that suggests glyphosate is not a neurotoxicant in humans. Any direct connection between glyphosate exposure and onset of Parkinsonism from this one study cannot be established, as the effects could be coincidental. There appears to be no evidence for glyphosate being a neurotoxicant in humans or other species.

Schiffman et al. (1995, as referenced in SERA 2003a) conducted a study of the effects of glyphosate on taste response in gerbils. This study appears to be the only reported investigation of the effects of glyphosate on sensory mechanisms. Glyphosate (1 or 10 micromolar concentration (mM)) applied to the tongue of anesthetized gerbils decreased taste receptor response to table salt, sugars, and acids. These tests on glyphosate involved exposure periods of one minute and were conducted along with tests on ten other pesticides, with one-minute rinses between each agent. The mechanism of this effect on the taste response has not been investigated and the implications in terms of dietary preferences in the field cannot be assessed. The effect could have been produced by a general biochemical alteration in the epithelial cells of the tongue, including the specialized cells that detect taste (glyphosate has been shown to produce injury to the oral cavity), by chemical injury to the tongue, or by a direct neurotoxic effect on the sensory nerve endings. Thus, effects reported in Schiffman et al. (1995) cannot be classified clearly as a glyphosate-induced neurologic effect.

Based on results from the available studies in humans and experimental studies in rodents, glyphosate does not appear to be an immunotoxicant in humans or other animals. This conclusion is supported not only by an extensive set of standard mammalian bioassays on toxicity but also by an *in vivo* assay specifically designed to detect humoral immune response and an *in vitro* assay specifically designed to detect cell-mediated immune response.

Epidemiological studies and clinical cases have not found evidence for allergic reactions or sensitization to dermal exposures to glyphosate formulations. Two human experimental studies provide evidence that Roundup® is not a dermal allergen or sensitizing agent. Tests conducted in guinea pigs provide further support for glyphosate not being a dermal sensitizing agent. Several long-term experimental studies have examined the effects of exposure to glyphosate on lymphoid tissue morphology and blood leukocyte counts; treatment-related effects were not observed.

Three specific tests on the potential effects of glyphosate on the endocrine system have been conducted and all of these tests reported no effects. That glyphosate is not an endocrine disruptor is reinforced by epidemiological studies that have examined relationships between occupational farm exposures to glyphosate formulations and risk of spontaneous miscarriage, fecundity, sperm quality, and serum reproductive hormone concentrations. The studies have not found positive associations between exposure to glyphosate formulations and any reproductive or endocrine outcomes. The clinical case literature does not provide evidence for glyphosate being an endocrine active agent. Several long-term experimental studies have examined the effects of exposure to glyphosate on endocrine organ morphology, reproductive organ morphology, and reproductive function; treatment-related effects were not observed.

Notwithstanding the negative results on endocrine function, the current RfD for glyphosate is based on reproductive effects. In addition, glyphosate has not undergone an extensive evaluation for its potential to interact or interfere with the estrogen, androgen, or thyroid hormone systems (i.e., assessments on hormone availability, hormone receptor binding or post-receptor processing (EDSTAC 1998, as referenced in SERA 2003a)). Thus, the assessment of the potential endocrine effects of glyphosate cannot be overly interpreted.

**Inhalation Exposures** – Because of the low volatility rate for glyphosate and the available inhalation toxicity studies on a number of glyphosate formulations, the U.S. EPA waived the requirement of an acute inhalation study for technical grade glyphosate in the re-registration of glyphosate. The acute inhalation LC<sub>50</sub> value of the isopropylamine salt of glyphosate is >6.37 mg/L – i.e., no mortality in any of five rats of each sex exposed to this concentration for four hours (Mcguirk 1999a, as referenced in SERA 2003a). The short-term (typically 4 hours) inhalation LC<sub>50</sub> values for various glyphosate formulations range from >1.3 mg/L to >7.3 mg/L. The lowest LC<sub>50</sub> value that is not designated with a greater than (>) symbol is 2.6 mg/L, the reported LC<sub>50</sub> value for several glyphosate formulations (refer to SERA 2003a).

**Impurities** - Glyphosate contains small amounts of a nitrosamine, N-nitrosoglyphosate (NNG). Certain groups of nitrosoamines have served as model compounds in some of the classical studies on chemical

carcinogenicity. While there is a general concern for the carcinogenic potential of nitroso compounds, the contribution of specific nitroso compounds to carcinogenic risk is difficult to quantify. Monsanto has conducted an apparently extensive series of tests on NNG. A summary of the studies stated that NNG is relatively non-toxic, is rapidly excreted without undergoing any chemical change, does not bioaccumulate, is not mutagenic, and does not cause birth defects or cancer in laboratory test species.

**Metabolites** – Glyphosate is metabolized to a minor extent in animals, to aminomethylphosphonate (AMPA). In mammals, only very small amounts of AMPA, less than 1% of the absorbed dose, are formed. In addition, AMPA is formed in environmental media such as water and soil as a breakdown product of glyphosate. The approach of examining the potential importance of the metabolism of a chemical agent by a mammal is common in the risk assessment of xenobiotics, which generally involve the formation of one or more mammalian metabolites, some of which may be more toxic than the parent compound. Usually, the parent compound is selected as the agent of concern because the toxicology studies and monitoring studies provide information about the agent. Thus, the dose measure for the risk assessment is most clearly expressed in terms of the parent compound. In cases where a toxic metabolite is known to be handled differently by humans, this simple approach may be modified. There is no indication that such a modification is necessary for glyphosate. Thus, in terms of assessing direct exposures to technical grade glyphosate, the inherent exposures to AMPA as a metabolite are encompassed by the existing toxicity data on glyphosate.

This approach does not, however, encompass concern for exposures to AMPA as an environmental metabolite. The U.S. EPA has assessed the potential consequences of exposures to AMPA as an environmental metabolite. Based on this review, the U.S. EPA concluded that only the glyphosate parent is to be regulated and that AMPA is not of toxicological concern regardless of its levels in food. The position taken by the U.S. EPA is supported by more extensive reviews. The position taken by U.S. EPA appears to be reasonable and is well supported. Consequently, in this risk assessment, AMPA is not quantitatively considered in the dose-response and exposure assessments.

**Inerts** – The only listed inert ingredient in Rodeo<sup>®</sup> and Accord<sup>®</sup> is water (46% to 58%), although it is likely that small amounts of isopropylamine and related organic acids of glyphosate also are present.

### **Hexazinone (USDA 1984, USDA 1989, SERA 2002, SERA 2005)**

**Acute and Chronic Exposures** - The toxicity of hexazinone has been relatively well-characterized in a number of standard bioassays that are required by U.S. EPA for the registration on pesticides. Acute oral toxicity studies indicate the oral LD<sub>50</sub> for hexazinone in mammals is in the range of 1000 mg/kg. The reported acute oral LD<sub>50</sub> values range from 860 mg/kg (guinea pig) to 1200 mg/kg (rat). Generally, the signs of toxicity in various mammalian species are similar, including tearing, salivation, vomiting, tremors/ataxia/weakness, diarrhea, and increased rates of respiration and/or labored breathing.

Several standard subchronic and chronic bioassays were conducted on hexazinone and none of the studies suggest a specific mode of toxic action. Most of the reported effects from longer-term exposures are limited to decreases in body weight, increases in liver weight, and changes in blood enzyme levels associated with liver toxicity. Body weight decreases are typically slight and appear to be related primarily with decreases in food consumption rather than changes in food conversion efficiency. Although decreases in body weight appear to be non-specific rather than secondary to an identifiable mode of toxic action, this endpoint is used by the U.S. EPA as the critical effect for hexazinone (i.e., the toxic effect that occurs at the lowest dose level). The study selected by the U.S. EPA for the chronic RfD is the 1-year feeding study in dogs, which involved feeding male and female beagles diets with concentrations of hexazinone of 0, 200, 1500, and 6000 ppm. Decreases in body weight were noted in the mid- and high-dose groups.

**Effects on the Skin and Eyes** - Hexazinone is a severe irritant to the eyes but has a much lesser effect on the skin. Both powdered and liquid formulations of hexazinone as well as technical grade hexazinone are shown to be moderate to severe eye irritants. U.S. EPA classifies hexazinone as a severe eye irritant, and this classification is amply supported by the available data.

Eye damage may include corneal injury with opacity as well as conjunctivitis. In one study, corneal damage in rabbits persisted up to 28 days after exposure, at which time the study was terminated. The corneal damage, however, seems to be restricted to unwashed eyes. Most of the studies indicate that longer-term and potentially irreversible ocular effects are observed only in unwashed eyes after the instillation of hexazinone. Granular formulations, however, appear to be less irritating than hexazinone or the other hexazinone formulations, causing no or transient irritation, with complete recovery by the seventh day.

Based on human experience, in a California study (Spencer, as referenced in SERA 2005), workers applying Pronone 10G using a belly grinder exhibited eye irritation and upper respiratory tract irritation (reported burning sensations in mouth, nose and throat, coughing, spitting) at the highest operational levels of exposure. No attempt was made to determine if the potential effects were attributable to hexazinone or the clay matrix used in Pronone formulation. These effects were transient and did not persist after exposure was terminated. It is important to recognize that the product applied in this study was recognized as defective, with excessive dustiness. As a result of this study, the USFS, Region 5 established additional requirements for protective equipment when applying granular hexazinone formulations via belly grinder. In addition, this direction instructs applicators not to continue applications if excessive dustiness is seen.

Technical hexazinone is classified as a mild skin irritant. Some formulations of hexazinone, including granular formulations, appear to cause little if any irritant effects. are much less irritating to the skin. The threshold for systemic toxicity after dermal exposure seems to be comparable to the threshold for skin irritation. In other words, levels of hexazinone that are sufficient to cause systemic toxic effects are associated with only mild reddening of the skin. Furthermore, skin sensitization studies on hexazinone are negative.

Based on a comparison of acute oral and dermal LD<sub>50</sub> values, it appears that the dermal absorption rate is much less than the rate of absorption after oral exposure. Oral LD<sub>50</sub> values for hexazinone generally range from about 500 to 3500 mg/kg. Conversely, dermal exposure to as much as 7,500 mg/kg is not associated with mortality. Based on a comparison of the acute oral and dermal toxicity of hexazinone, the U.S. EPA waived the registration requirement for a dermal penetration study for this compound

**Carcinogenicity and Mutagenicity** - U.S. EPA conducted a review of two unpublished studies on the potential carcinogenicity of hexazinone. In a study using rats, no statistically significant increases in tumor incidences were observed except for a dose-related trend in C-cell thyroid tumors. Interpretation of the study by the U.S. EPA is as follows: *Under the conditions of this study, carcinogenic potential of hexazinone is considered negative.* Similar results were noted in the study using mice. Although no statistically significant increase in the incidence of malignant tumors was observed in terms of pair-wise comparisons, a number of liver endpoints did evidence a statistically significant dose-response relationship. This study was classified by the U.S. EPA as follows: *evidence of carcinogenic potential was equivocal: a positive trend test for neoplasia was observed in female mice, but no significant difference was determined by pair-wise comparison.* Based on the weight of evidence, the U.S. EPA concluded that hexazinone should be classified Class D, not classifiable as to human carcinogenicity. Consequently, the U.S. EPA did not conduct a quantitative risk assessment for carcinogenicity associated with exposures to hexazinone. The World Health Organization has not evaluated the carcinogenicity of hexazinone.

The decision of U.S. EPA to decline to conduct a quantitative risk assessment for the carcinogenicity of hexazinone is supported by the lack of mutagenic activity of hexazinone in several *in vivo* and *in vitro* bioassays, although one bioassay for chromosomal damage was positive. Hexazinone yielded negative results in the Ames assay, the Chinese hamster ovary cell HGPRT assay, a chromosome aberration assay using bone marrow cells from rats, and an assay for unscheduled DNA synthesis in rat hepatocytes. In a chromosome aberration assay using Chinese hamster ovary cells, however, there was a significant increase in the number of structural chromosomal aberrations.

This risk assessment will defer to the position taken by the U.S. EPA and no quantitative risk assessment for carcinogenicity will be proposed.

**Reproductive and Teratogenic Effects** - U.S. EPA classifies 400 mg/kg/day as the lowest observed adverse effect level (LOAEL) for rats based on an increase in fetuses with kidney abnormalities and/or delayed ossification. No such effects were seen at 100 mg/kg/day, the dose classified as a NOAEL. Similarly, in rabbits, increased resorptions were noted at 125 mg/kg/day but not at lower doses (20 or 50 mg/kg/day). In multi-generation feeding studies at dietary levels up to 5000 ppm, no effects were noted on reproductive capacity. However, in a more recent multi-generation feeding study in rats, decreased pup survival was noted at 250 mg/kg/day but not at 10 mg/kg/day or 100 mg/kg/day. At 100 mg/kg/day, however, decreases in pup weight as well as maternal body weight were observed. This no effect level for decreased pup weight (at a dose of 10 mg/kg) is only a factor of two greater than the no effect level for changes in adult body weight in the study on which the RfD is based. The NOEL of 5 mg/kg/day on which the RfD is based is, nonetheless, below any of the effect levels for reproductive toxicity or teratogenic effects.

**Other Toxic Endpoints** –There is no evidence for hexazinone having a direct neurotoxic effect in humans or other animals (SERA 2002). Studies designed specifically to detect impairments in motor, sensory, or cognitive functions in mammals or other species exposed sub-chronically or chronically to hexazinone have not been conducted because the clinical and experimental toxicology experience with hexazinone provide no reason to suspect a neurotoxicity potential. Thus, the effort and expense associated with the conduct of specific studies to assay for neurotoxicity do not appear to be justified.

Nonetheless, acute toxicity studies conducted in various mammalian species and in quail have observed lethargy, impaired coordination, weakness, labored respiration, and tremors in animals exposed to lethal or near-lethal dose levels of hexazinone. These studies indicate that acutely lethal or near-lethal exposures to hexazinone may exert either direct or indirect neurological effects. If hexazinone were a direct neurotoxic agent, however, neurologic effects would be expected in longer-term experimental studies in which exposures were well below lethal levels. However, studies conducted in rodents, dogs, and birds have not provided evidence of neurotoxicity, even at the maximum tolerated dose. Neurologic endpoints evaluated in these studies were limited to brain, spinal cord and peripheral nerve morphology and observation of the animals for gross abnormalities in movement or balance. Nevertheless, these studies suggest that the acute neurological effects of hexazinone observed at near lethal doses may indeed be secondary to cardiovascular or respiratory trauma from treatment-induced injuries to other organs.

There is very little direct information on which to assess the immunotoxic potential of hexazinone (SERA 2002). Hexazinone has been tested for skin sensitization and caused no signs of skin sensitization in guinea pigs (U.S. EPA 1984, as referenced in SERA 2002). A lack of activity as a skin sensitizer has also been reported in Kennedy (1984, as referenced in SERA 2002) and SERA (2005). The negative sensitization of hexazinone does not decrease or in any way impact concern for potential immune suppression. The only information with which to assess the potential immune suppressive effects of hexazinone is largely indirect. Hexazinone has been subject to a large number of standard toxicity studies required for pesticide registration by the U.S. EPA (U.S. EPA 1984, as referenced in SERA 2005). Although these studies are not designed to specifically detect changes in immune function, significant effects on immune function would likely be evidenced by observable changes in lymphoid tissue as well

as changes in differential blood cell counts. No such effects are reported in the hexazinone RED. The only changes in blood noted in any of the toxicity studies involve blood enzymes that are indicative of damage to liver cells.

The U.S. EPA RfD for hexazinone (0.05 mg/kg/day) is based on a NOAEL of 5 mg/kg/day. This NOAEL is based on the most sensitive effect – histological evidence and biochemical indicators of liver damage. While this study and other chronic studies on hexazinone cannot rule out the possibility of immunologic effects, they provide no evidence that such effects occurred. If such immunologic effects had occurred, changes in differential blood cell counts and/or pathological changes in lymphoid tissues would be expected along with some indication of increased susceptibility to infection. No such effects have been noted. Thus, there is no plausible basis for asserting that the current RfD established by U.S. EPA should be revised to accommodate concern for potential effects on the immune system.

Hexazinone has not undergone evaluation for its potential to interact or interfere with the estrogen, androgen, or thyroid hormone systems (i.e., assessments on hormone availability, hormone receptor binding or post-receptor processing). The U.S. EPA has not yet adopted standardized screen tests for endocrine disruptors.

Hexazinone as well as a number of other herbicides were found to influence the activity of estrogen in the E-SCREEN assay. This test system uses a human breast cell line and measures estrogen-induced proliferation in the number of these cells and the inhibition or enhancement of this proliferation by the test agent. Additional inferences concerning the potential effect of hexazinone on endocrine function must be based on results from standard toxicity studies. The U.S. EPA has concluded that: In the available toxicity studies on hexazinone, there was no evidence of endocrine disruptor effects. While this statement is substantially correct, some studies have suggested that hexazinone exposures may be associated with reductions in food conversion efficiency – i.e., reduced body weights that cannot be directly attributed to decreases in food consumption. This effect has been demonstrated clearly in female rats in three studies and in male rats in one study. The decrease in food conversion efficiency in male rats was not dose-related – i.e., it was noted in the 1000 ppm exposure group but not the 2500 ppm exposure group.

In addition, Kaplan et al. (1987, as referenced in SERA 2005) reported a statistically significant dose-related increase in thyroid C-cell adenomas in male rats. The differences were not statistically significant, however, based on comparisons of incidence of these adenomas in any exposed group relative to the incidence in the matched control group. The occurrence of thyroid tumors is noteworthy because thyroid adenomas can secrete thyroxine (also known as thyroid hormone or T), which causes weight loss through an increase of the basal metabolic rate, thereby leading to a hyperthyroid state (Hansen 1998 as referenced in SERA 2005). While hexazinone may not directly disrupt the endocrine system, thyroid adenomas may secondarily cause of weight loss through alteration of thyroid function. The development of adenomas seen in this study, however, cannot be clearly related to the more commonly seen decrease in food conversion efficiency noted in other studies.

As noted by U.S. EPA/OPP (2002, as referenced in SERA 2005), the EPA may elect to have hexazinone screened for effects on endocrine function once standardized screening assays have been developed. Such tests would help to clarify any possible endocrine involvement associated with exposure to hexazinone.

**Inhalation Exposures** - Inhalation of hexazinone is not a typical route of exposure. The lowest reported inhalation LC<sub>50</sub> for hexazinone is about 4 mg/L or 4 g/m<sup>3</sup> and no adverse effects were observed after repeated exposure to 2 mg/L. These air concentrations are far below any plausible exposure during brown-and-burn operations. Nonetheless, no information is available regarding the combustion products of hexazinone. Given the implausibility of significant residues of hexazinone on treated vegetation, this adds relatively little to uncertainties associated with this risk assessment. On the other hand, hexazinone is a respiratory irritant. As documented in the study by Spencer et al. (1996) workers applying a granular formulation of hexazinone have exhibited upper respiratory tract irritation (reported burning sensations in mouth, nose and throat, coughing, spitting) at the highest operational levels of exposure.

**Impurities** - There is no information available in the open literature on the identity or toxicity of any impurities in hexazinone. The U.S. EPA, however, has reviewed the information on the impurities and determined that there are no reported impurities of toxicological concern in hexazinone.

**Metabolites** - Hexazinone is virtually completely metabolized in mammals, with little parent product recovered in tissue. The primary metabolic pathway in rats and humans appears to be hydroxylation, (adding a hydroxyl group (OH), resulting in oxidation), with lesser amounts of hexazinone undergoing deamination (the loss of an amine group) and demethylation (the loss of a methyl group (CH<sub>3</sub>)). There is relatively little information available regarding the toxicity of the metabolites. One study reports that the approximate lethal dose for the metabolites is about 5000 mg/kg, which is substantially greater than the LD<sub>50</sub> for hexazinone in rats. Any uncertainty with the estimates of the toxicity of the metabolites of hexazinone does not have a significant impact on this risk assessment. The toxicity studies on which the hazard identification and subsequent dose-response assessment are based involve *in vivo* exposure to hexazinone and the subsequent formation of hexazinone metabolites. Therefore, the toxicological effects, if any, of the metabolites are likely to be captured by animal toxicology studies involving exposure to hexazinone.

**Inerts** - The major component of granular formulations of hexazinone appears to be montmorillonite clay (U.S. EPA inert list 4A). The other inert ingredients are listed in the Hexazinone Herbicide Information Profile (USDA 1992). Based on the acute toxicity of these formulations relative to technical grade hexazinone, there is no indication that the carriers contribute to the toxicity of the granular formulations of hexazinone. The granular formulations of hexazinone appear to be less toxic than hexazinone itself. U.S. EPA considers none of the other inert ingredients hazardous (on inert lists 1 or 2).

## **Triclopyr**

**(References: USDA, 1984; USDA, 1989; U.S. EPA, 1998; SERA 2002, 2003b)**

**Acute and Chronic Exposures** - Triclopyr has a low order of acute lethal potency. Oral LD<sub>50</sub> values range from 600 to 1,000 mg/kg. The signs and symptoms of acute oral intoxication generally include lethargy, impaired coordination, weakness, labored respiration, and tremors. Anorexia and diarrhea have also been observed in rodents and domestic animals. Similar signs and symptoms are associated with triclopyr acid, triclopyr butoxyethylester (BEE), and triclopyr triethylamine salt (TEA). The few available studies regarding histopathology and clinical chemistry data on triclopyr suggest that the liver and kidney are the primary target organs in acute intoxication.

The kidney appears to be the most sensitive target organ for triclopyr, and the dog was initially thought to be the most sensitive species. The lowest effect level for triclopyr is 2.5 mg/kg/day in the dog. In this study, this dose was associated with decreased urinary excretion, determined by means of a phenolsulfonphthalein (PSP) dye excretion test, as well as reduced absolute and relative kidney weights. The inhibition of PSP excretion in the dog could be attributed to competition between triclopyr and PSP for elimination via anion transport. U.S. EPA does not consider PSP excretion appropriate for establishing a NOEL. In the absence of other toxic effects, the 2.5 mg/kg/day dose in the dog study was classified as a NOEL by U.S. EPA. This determination formed the basis of U.S. EPA's provisional acceptable daily intake of 0.025 mg/kg/day. In a follow-up study, the dose of 2.5 mg/kg/day was associated with a statistically significant increase in serum urea nitrogen and creatinine in male dogs. These effects were also evident but more pronounced at 5 mg/kg/day. The NOEL for this effect was 0.5 mg/kg/day. This resulted in the lowering of the provisional U.S. EPA/OPP RfD to 0.005 mg/kg/day using the 0.5 mg/kg/day dose group as the NOEL for effects on kidney function. However, in the 1998 triclopyr RED (U.S. EPA, 1998), U.S. EPA determined that these two studies, while showing statistically significant results, did not represent a toxic response to triclopyr, but rather a physiologic response of the

dog, based on the dog's limited ability to excrete organic acids at higher plasma concentrations. They used the lack of histopathological changes in the kidneys as support for this decision.

In rodents, kidney effects - hematological and histopathological changes and increased kidney weight - have been observed after subchronic exposure to triclopyr doses as low as 7 mg/kg/day for 90 days. The highest NOEL below the 7 mg/kg/day AEL for kidney effects in rodents is 5 mg/kg/day for 90 days. This result is supported by additional NOAELs of 5 mg/kg/day for exposure periods ranging from 90 days to 2 years. All of these NOAELs are based on the lack of tissue pathology in the kidney rather than tests of kidney function. In 1998, U.S. EPA determined that the RfD would be based upon the NOEL of 5 mg/kg/day, from a two-generation reproduction study (U.S. EPA, 1998).

The other general systemic toxic effects of triclopyr are un-remarkable. At high doses, signs of liver damage may be apparent as well as decreases in food consumption, growth rate, and gross body weight.

**Effects on the Skin and Eyes** - Exposure to triclopyr formulations may cause irritation to the skin and eyes. Technical grade triclopyr is classified as only slightly irritating (Category IV). Triclopyr TEA is not a primary skin irritant but has been shown to cause delayed contact sensitization in some studies. Triclopyr BEE has also been shown to cause delayed contact hypersensitivity. Triclopyr BEE causes more severe skin irritation than triclopyr acid or TEA. This may be due to the more rapid absorption of triclopyr BEE.

Ocular exposure appears to follow a different pattern with triclopyr TEA being much more irritating than triclopyr acid or triclopyr BEE.

Triclopyr is poorly absorbed by the skin, and very high doses (>2,000 mg/kg) applied to the skin have not caused death or other signs of toxicity, except weight loss. This result suggests that triclopyr, like many herbicides, is less readily absorbed after dermal exposure than after oral exposure.

There have been repeated dosing studies on triclopyr. Three of these studies involve applications of Garlon<sup>®</sup> 4 - i.e., triclopyr BEE. The only study reporting systemic toxic effects involved rats that received dermal doses of 24, 240, and 480 mg a.i./kg/day, 5 days per week for 3 weeks. A significant decrease in food intake and growth was observed in males at all dose levels and a significant decrease in food efficiency was observed in males at all dose levels and in females at the highest dose. Based on a review of these and other studies, the U.S. EPA/OPP classified the dermal NOAEL for multiple exposures to triclopyr as greater than 1,000 mg/kg.

**Reproductive and Teratogenic Effects** - Triclopyr has been subject to several teratogenicity studies, and two multi-generation reproduction studies. At sufficiently high doses, triclopyr can cause adverse reproductive effects as well as birth defects. A consistent pattern with triclopyr, however, is that adverse reproductive effects as well as teratogenic effects occur only at doses that are maternally toxic. At doses that do not cause maternal toxicity, there is no apparent concern for either reproductive or teratogenic effects.

The most significant study is the two-generation reproduction study by Vedula et al. (1995 as referenced in SERA 2003b). This study is the basis of the current RfD

At substantially higher doses – i.e., greater than or equal to 100 mg/kg/day, triclopyr has been shown to result in birth defects. Most of the abnormalities have been indicative of delayed growth and have been associated with maternal toxicity. Based on several studies with triclopyr BEE and triclopyr TEA, these two forms of triclopyr appear to be equally toxic, consistent with the basic position adopted by U.S. EPA.

**Carcinogenicity and Mutagenicity** - In 1995, U.S. EPA's Carcinogenicity Peer Review Committee (CPRC) classified triclopyr as a Group D chemical (not classifiable as to human carcinogenicity). This decision was based on increases in mammary tumors in female mice and rats and adrenal tumors in male rats. The CPRC felt that the evidence was marginal (not entirely negative, but yet not convincing), and when combined with lack of genotoxicity and mutagenicity and lack of carcinogenicity of structural analogs, supported the Group D classification. The decision by U.S. EPA to classify triclopyr as Group D is accompanied automatically by a decision not to derive a cancer potency factor for triclopyr and hence, in terms of a risk assessment, the potential carcinogenicity of triclopyr is not considered quantitatively.

There is concern however, since triclopyr has been shown to cause the same type of tumors in two species. In addition, while all cancers are a public health concern, the particular tumor type noted in rats and mice (breast cancer) is a common and important form of cancer in humans. Nonetheless, it is worth noting that none of the dose groups in either rats or mice evidenced a statistically significant pair-wise increase in breast tumors. In other words, the magnitude of the response was not substantial. The other important factor considered by U.S. EPA is the apparent lack of mutagenic activity of triclopyr. Only one study indicated any form of mutagenic activity and the other standard assays for genotoxicity were negative. This is an important point because even if the U.S. EPA had decided to classify triclopyr as a carcinogen, it is plausible that a threshold dose-response assessment would be conducted. In the current risk assessment, a threshold-based approach is used for standard toxicity and this approach is based on the most sensitive endpoint – effects on the kidney.

**Other Toxic Endpoints** - There is no evidence for triclopyr being a direct neurotoxicant in humans or other species. Studies designed specifically to detect impairments in motor, sensory, or cognitive functions in mammals or other species exposed sub-chronically or chronically to triclopyr have not been reported. This is not surprising, since the undertaking of such studies on a substance for which the clinical and experimental toxicology experience provide no reason to suspect a neurotoxicity potential, would be highly unusual. Experiments conducted in fish suggest possible effects of triclopyr on behavior when exposures are at or near lethal levels. As is the case with mammals, these studies provide no evidence that triclopyr is a direct neurotoxicant.

Acute toxicity studies conducted in various mammalian species have observed lethargy, impaired coordination, weakness, labored respiration, and tremors in animals exposed to lethal or near-lethal dose levels of triclopyr. Direct neurotoxic activity is expected in longer-term experimental studies in which exposures were well below lethal levels. However, studies conducted in rodents, dogs, monkeys, birds, and amphibians have not provided evidence of direct neurotoxicity, even at the maximum tolerated dose. Neurological endpoints evaluated in these studies may have been limited to brain morphology and observation of the animals for gross abnormalities in movement or balance. Nevertheless, these studies suggest that the acute neurological effects of triclopyr observed at near lethal doses may indeed be secondary to cardiovascular trauma from treatment-induced injuries to other organs, possibly kidney and liver. Studies designed specifically to detect impairments in motor, sensory, or cognitive functions in mammals exposed sub-chronically or chronically to triclopyr have not been reported. Two studies found evidence for possible neurological effects of triclopyr in fish. The effects observed included lethargy, hypersensitivity to light stimuli, and avoidance behavior but were only observed at lethal or near-lethal exposure levels. In the absence of any signs of direct neurotoxicity in other species, these observations are consistent with indirect neurological effects secondary to general poisoning.

There is very little direct information on which to assess the immunotoxic potential of triclopyr. The only studies specifically related to the immune effects of triclopyr are skin sensitization studies conducted

on triclopyr BEE and the triclopyr TEA salt. For both of these forms of triclopyr, skin sensitization was observed following standard protocols accepted by the U.S. EPA (1998, as referenced in SERA, 2003b). While these studies provide support for asserting that triclopyr may cause skin sensitization, they provide no information useful for directly assessing immune suppressive potential of triclopyr. The toxicology of triclopyr has been examined in subchronic, chronic, and multi-generation studies in rodents and in subchronic studies in dogs. In these reviews of the toxicity of triclopyr, morphologic abnormalities in lymphoid tissues have not been reported.

Triclopyr has not undergone evaluation for its potential to interact or interfere with the estrogen, androgen, or thyroid hormone systems (i.e., assessments on hormone availability, hormone receptor binding, or post-receptor processing). However, extensive testing in experimental animals provides reasonably strong evidence that triclopyr is not an endocrine disruptor. No epidemiological studies of health outcomes of triclopyr have been reported, and there is no clinical case literature on human triclopyr intoxication. Several long-term experimental studies in dogs, rats, and mice have examined the effects of exposure to triclopyr on endocrine organ morphology, reproductive organ morphology, and reproductive function; treatment-related effects on these endpoints were not observed.

**Inhalation Exposures** – There is very little information regarding the inhalation toxicity of triclopyr. Three studies on the inhalation toxicity of triclopyr have been reviewed involving technical grade triclopyr as well as triclopyr BEE and triclopyr TEA. No mortality was observed in any animals. The only study not summarized in U.S. EPA (1998) is the recent report by Carter (2000, as referenced in SERA 2003b) on technical grade triclopyr. The results of this study – i.e., an LC<sub>50</sub> of greater than 2.56 mg/L – is essentially equivalent to the reported LD<sub>50</sub> value of 2.6 mg/L for triclopyr TEA. Based on these results, the U.S. EPA classified inhalation exposures to not be of toxicological concern.

**Metabolites** - Triclopyr is not extensively metabolized in humans or experimental mammals. In a study involving rats, >90% of the administered dose of triclopyr acid was recovered in the urine as un-metabolized triclopyr. The remainder was identified as the metabolite 3,5,6-trichloro-2-pyridinol (TCP) and possible conjugates. TCP acute and chronic toxicity is similar to triclopyr. TCP has an acute NOEL of 25 mg/kg/day (compared to 30 mg/kg/day for triclopyr) and a chronic NOEL of 3 mg/kg/day, from a 1-year dog study (compared to a NOEL of 5 mg/kg/day for triclopyr). TCP is also the major metabolite of the insecticide chlorpyrifos. Because of the toxicity of TCP, it will be considered in this risk assessment, specifically in Section 5 (Cumulative Effects).

**Inerts** –Garlon® 4 contains the butoxyethyl ester (BEE) of triclopyr (61.6%) as well as inerts (38.4%) that include deodorized kerosene.

As reviewed by U.S. EPA, triclopyr BEE hydrolyzes to triclopyr acid and 2-butoxyethanol. There is an extensive database on the toxicity of 2-butoxyethanol. The acute oral maximum residue level (MRL) for 2-butoxyethanol is 0.4 mg/kg/day and the intermediate MRL for 2-butoxyethanol is 0.07 mg/kg/day. The acute MRL for 2-butoxyethanol is on the same order as the acute RfD for triclopyr (1 mg/kg/day) and the intermediate MRL for 2-butoxyethanol is similar to the intermediate and chronic RfD for triclopyr (0.05 mg/kg/day). In terms of a practical impact on the risk assessment, the most relevant factor is that 2-butoxyethanol will mineralize very rapidly in the environment – i.e., be completely degraded to CO<sub>2</sub>. This is not the case for triclopyr or TCP, a metabolite of triclopyr. Thus, the comparable toxicity of 2-butoxyethanol to triclopyr has relatively little impact on this risk assessment. Because triclopyr and the TCP metabolite of triclopyr persist in the environment much longer than 2-butoxyethanol, it is triclopyr and the TCP metabolite that are the major quantitative focus of the risk assessment. This approach is identical to the position taken by U.S. EPA.

Garlon® 4 causes substantially less acute toxicity in mammals than does triclopyr (oral LD<sub>50</sub> values in rats = 2,140-2,460 mg/kg (1,540-1,770 mg a.e./kg)). U.S. EPA classifies deodorized kerosene as a List 3 Inert. The toxicity of kerosene was reviewed recently by the Agency for Toxic Substances and Disease Registry (ATSDR). At sufficiently high doses, kerosene can cause many gastrointestinal, central nervous

system (CNS), and renal effects. The acute lethal dose of kerosene for humans ranges from approximately 2,000 to 12,000 mg/kg; the acute oral LD<sub>50</sub> values in experimental mammals range from approximately 16,000 to 23,000 mg/kg. In experimental mammals, acute oral LD<sub>50</sub> values for triclopyr range from approximately 600 to 1,000 mg/kg. Thus, the acute lethal potency of kerosene is approximately 16 times less than the acute lethal potency of triclopyr. Given the relative potency of kerosene, the acute effects associated with exposure to Garlon® 4 are probably attributable to triclopyr and not to kerosene.

In contrast, the material safety data sheet for Garlon® 4 specifies that inhalation exposure to its vapors may cause central nervous system (CNS) depression attributable to kerosene. CNS depression is consistent with inhalation exposure to kerosene. No monitoring data are available regarding kerosene levels during the application of Garlon® 4. One study monitored triclopyr in air at levels ranging from approximately 5 to 15 µg/m<sup>3</sup>, based on the personal breathing zone air of workers involved in backpack sprays. If kerosene in Garlon® 4 is present at a concentration of ≤20%, the corresponding concentration of kerosene in the air would range from approximately 1 to 3 µg/m<sup>3</sup>. The NOAEL for neurological effects in experimental mammals after exposure to kerosene, which ranged from 14 days to 1 year, is approximately 100 mg/m<sup>3</sup>; the NIOSH TLV for petroleum distillates is 350 mg/m<sup>3</sup>. Thus, plausible levels of exposure to kerosene during applications of Garlon® 4 are approximately 30,000-100,000 below the NOEL for kerosene in experimental mammals and a factor of 120,000-350,000 below the TLV for petroleum distillates. Although some components of kerosene are known to be carcinogenic to humans (e.g., benzene) kerosene is not classified as a carcinogen, and quantitative risk assessments have not been conducted on kerosene. Exposure to Garlon® 4 may present a hazard, based on the toxicity of triclopyr. Relative to those concerns, the presence of kerosene in Garlon® 4 is not toxicologically significant.

## **Nonylphenol Polyethoxylate**

**(References: USDA, 2003a)**

**Introduction:** The primary active ingredient in many of the non-ionic surfactants used by the Forest Service is a component known as nonylphenol polyethoxylate (NPE). NPE is found in these commercial surfactants at rates varying from 20 to 80%. NPE is formed through the combination of ethylene oxide with nonylphenol, and may contain small amounts of un-reacted nonylphenol. Nonylphenol (NP) is a material recognized as hazardous by the U.S. EPA (currently on U.S. EPA's inerts list 2). Both NP and NPE exhibit estrogen-like properties, although they are much weaker than the natural estrogen estradiol. Because of the potential for exposure to nonylphenol, as well as the demonstrated estrogenicity of these compounds, a comprehensive consideration of NPE is warranted.

In the production of NPE, various numbers of ethoxylate groups are attached to a nonylphenol (NP) molecule, through a reaction of NP with ethylene oxide. The properties of the particular NPE depend upon the number of ethoxylate groups that are attached, and this number can vary from just a few, up to about a hundred. The most common NPE used in surfactants for pesticide is a mixture that has, as a majority, 8-10 ethoxylate groups attached.<sup>1</sup> But it is important to understand that there is a bell-shaped distribution curve around 9 ethoxylate groups in such a mixture, and that other longer and shorter-chain NPEs also exist in the mixture. An average of 8-10 ethoxylate groups makes these surfactants highly water-soluble.

**Acute and Chronic Exposures:** - Various NPEs have been acutely tested in rats, rabbits, mice, and guinea pigs. NP4E, NP5E, NP6E and NP9E are classified as slightly toxic to practically non-toxic to

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<sup>1</sup> In this risk assessment, the average number of ethoxylate groups and the NPE will be combined into a standard shorthand. For example NP9E will represent a nonylphenol polyethoxylate with an average of 9 ethoxylate groups. Unless otherwise stated, NP9E will represent the average surfactant ingredient, even though these surfactants may contain an average of 8 to 10 ethoxylate groups.

mammals and are placed in EPA toxicity category III or IV (tested LD<sub>50</sub> values ranging from 620 to 7,400 mg/kg). In comparison with these NPEs, the acute toxicity of NP is somewhat higher (tested LD<sub>50</sub> values in rats ranging from 580 to 1,620 mg/kg).

Based on subchronic and chronic testing, it appears that the liver and kidney are the organs most likely to be affected by exposures to NPE and NP. In 90-day subchronic studies in rats and dogs, exposure to NP9E resulted in slight reductions of polysaccharide in the liver, increased relative liver, kidney, or spleen weight, and decreased weight gain; in rats the NOELs range from about 10-20 mg/kg/day. In 90-day subchronic studies in rats, the oral toxicity of NP6E resulted in a male rat NOEL of 40 mg/kg/day based on increased liver to body weight ratios at 200 mg/kg/day; in females this effect was noted at 1,000 mg/kg/day. In a 90-day subchronic test with beagles, the NOEL for NP4E and NP6E was 40 mg/kg/day; emesis was evident at 200 mg/kg/day, with relative liver weight being affected at highest dose (1,000 mg/kg/day). In a 2-year chronic exposure test of NP9E in dogs, there was an increase in relative liver weight at a dose of 88 mg/kg/day, with a NOEL of 28 mg/kg/day.

In a 90-day subchronic study, rats exposed to NP in feed had a NOAEL of 650 ppm (50 mg/kg/day) based on small decreases in body weight and food consumption.

NP and NPE have been determined to be weakly estrogenic in both *in vitro* and *in vivo* tests involving aquatic and terrestrial organisms. Non-reproductive effects appear to be the more sensitive endpoint. The NOAEL for chronic effects is assumed to be 10 mg/kg/day based on kidney effects in rats.

**Effects on the Skin and Eyes** -. NP9E is considered minimally to severely irritating to rabbit skin; acute dermal LD<sub>50</sub> of 2,830 mg/kg. Acute dermal LD<sub>50</sub> of NP5E in rabbits is greater than 2,000 mg/kg; with NP6E in rabbits, the acute dermal LD<sub>50</sub> exceeds 3,000 mg/kg. Both NP5E and NP6E are considered at most, slightly toxic to rabbits via dermal exposure. NP5E and NP6E are skin irritants in rabbits; NP6E is not a skin sensitizer in guinea pigs. Dermal acute toxicity assessment of NP in rabbits gives LD<sub>50</sub> values > 2,000 mg/kg. NP is considered moderately to severely irritating to rabbit skin.

NP9E is considered moderately to severely irritating to rabbit eyes. The ocular irritation potential of NP6E was evaluated in a Draize test using rabbits; the eyes were not rinsed. NP5E and NP6E are considered severe ocular irritants. NP is considered moderately to severely irritating to rabbit eyes.

Exposure data for NP9E in humans is limited to its use as a component of spermicides and in cosmetics and cleaning products. Incidents of vaginal irritation, irritation of the urinary tract, and allergic contact dermatitis have been reported. Contact dermatitis and contact photosensitivity has been reported in humans following exposure to NP6E, NP10E, and NP12E in consumer products NP2E and NP4E were evaluated as a skin sensitizer on humans; there was no sensitization with a 5% solution of NP2E, but sensitization was seen with NP2E at 10% dilution and NP4E at 10% dilution.

In one study on rats, NP9E was administered dermally to females during gestational days 6-15 at doses of 0, 50, or 500 mg/kg/day. There were no dose-related reproductive or teratogenic effects following this dermal exposure, although there was a decrease in feeding in dams exposed to the highest dose.

**Reproductive and Teratogenic Effects** - NP and NPE have been determined to be weakly estrogenic in both *in vitro* and *in vivo* tests involving aquatic and terrestrial organisms. In comparison to the natural estrogen 17-beta-estradiol, NP is approximately 1,000 - 100,000 times weaker in eliciting estrogenic responses. NP9E is less potent than NP, by 1 to 3 orders of magnitude. In general, estrogenic effects appear to decrease with increasing ethoxylate number.

NP increased uterine weight in immature or ovariectomized rats (the ovaries are removed) and in mice following oral administration of 75 mg/kg/day and above and following subcutaneous and intraperitoneal administration, with a NOAEL of 37.5 mg/kg/day. With NP4E and NP9E, no evidence of estrogenic activity was observed in rats *in vivo* as evidenced by a lack of the stimulation of uterine growth following oral exposure of ovariectomized females at doses up to 1000 mg/kg/day for 3 or 4 days. *In vivo* tests in

mammals have shown that high chronic dietary levels of NPE need to be administered to show any estrogenic effects (on the order of hundreds or thousands of ppm).

Because of the demonstrated estrogenicity of NP, there have been many studies completed concerning potential reproductive effects of exposure. There are relatively few reproductive tests completed concerning NP9E or other NPEs.

In a multi-generation reproduction study in rats, a 200-ppm daily dose of NP (the lowest dose tested) in the diet (12-18 mg/kg/day in males; 16-21 mg/kg/day in non-lactating females, 27-30 mg/kg/day in lactating females) was the LOEL based on kidney effects (Chapin et al 1999, as referenced in USDA 2003a). No developmental effects were seen at any exposure level, however a range of effects on endocrine-regulated endpoints were observed at 650 and 2,000 ppm in females (increased estrous cycle length, accelerated vaginal opening, increase in relative weights of uterus and vagina). There were no consistent detectable effects on male reproductive parameters (*ibid*). A reproductive NOEL of 200 ppm (~12-40 mg/kg/day) was determined. The authors conclude that NP at low doses would appear to pose a greater hazard to the kidneys than to the reproductive system of male or female rats (*ibid*).

In a multi-generation study in rats where they were continuously exposed to NP via oral gavage at doses of 0, 2, 10, and 50 mg/kg/day, the authors concluded that the reproductive NOAEL for all three generations would be 10 mg/kg/day (Nagao et al, 2001, as referenced in USDA 2003a). In this study, the F0 generation (6 week-old males and 13 week old females at the beginning of the test) showed no dose-related reproductive effects after exposure to NP at any dose. However effects were seen at the 50 mg/kg/day dose in the F1 generation. Although there were no treatment related effects on mating ability or fertility, there were effects to hormone levels in the F1 males and females at the highest dose, although the authors caution against assuming this is treatment related due to inconsistent changes in various related hormones and an absence of effect to the thyroid. There was also a significant decrease in both absolute and relative ovary weight and an acceleration of vaginal opening. There was a significant decrease in the number of implants and live pups born to F1 females in the highest dose group. Histopathologic examination found no treatment related effects to the testes, and spermatogenesis was normal; there was no effect on male fertility in any generation at any dose, which agrees with the findings in Chapin et al 1999.

De Jager et al 1999 (as referenced in USDA 2003a) provided oral doses of NP to female rats during gestation through weaning and to the male offspring from point of weaning through mating to determine both maternal effects and effects to male reproduction. There were no offspring born to the highest dose group (400 mg/kg/day). There were adverse effects to body and testicular mass and decreased seminiferous tubule diameter at 100 and 250 mg/kg/day dose levels (NOEL < 100 mg/kg/day). There were no significant effects to sperm count, or testis/body weight ratio at 100 mg/kg/day. In Nagao et al 2000 (as referenced in USDA 2003a), after subcutaneous injection of 500 mg/kg/day on post-natal days 1-5, rats were evaluated for reproductive function after puberty. There were effects to reproductive function in females, assumed to be the result of effects to the estrous cycle and histopathological alterations to the ovaries and uterus. In males, there was a decrease in germ cells in the seminiferous tubules, and an increase in degenerated germ cells was noted in the epididymides (*ibid*). There were no effects to sperm motility or plasma testosterone (*ibid*).

NP9E was injected (intraperitoneal) into 9-10 week old male mice at doses of 20, 40, 50, 60 mg/kg/day for 5 days along with a positive and negative control to study the effects on sperm (Johnson 1999, as referenced in USDA 2003a). Evaluations were completed 35 days after injections were completed. The authors concluded that NP9E did not increase the frequency of morphologically abnormal sperm (NOEL > 60 mg/kg/day). No reproductive or developmental effects were observed following oral exposure during gestation to 600 mg/kg/day NP10E in mice. In another study, NP10E was administered subcutaneously to 7-week old female rats at dose levels of 2 and 20 mg/kg/day for 15 weeks (Aso et al 1999a, as referenced in USDA 2003a). There were no effects to reproductive ability and no effects to

fetuses (external, skeletal or visceral effects). The same authors conducted another study in which NP10E was administered subcutaneously to female rats at dose levels of 5, 20, and 80 mg/kg/day from date of offspring birth through day 21 after birth to explore the effects on offspring from lactation exposure. There were no effects to physical development or reproductive ability, however there were growth effects at the highest dose. The authors consider 20 mg/kg/day to be the NOEL, based on growth effects to both the dams and offspring.

Oral exposure in rats to NP9E on gestation days 6-15 indicated teratogenic NOEL at 50 mg/kg/day based on litter size decrease, pre-implantation loss, and skeletal anomalies seen in fetuses after maternal exposures to 250 and 500 mg/kg/day. These doses of 250 and 500 mg/kg/day were also maternally toxic, based on decreases in maternal weight gain.

The relationship between birth defects and use of NP9E as a spermicide was examined in an epidemiological study involving 462 women (426 of whom had used spermicides containing NP9E or OP9E in the first four months of pregnancy). Limb reduction deformities, neoplasms, Down's syndrome, and hypospadias (birth defect of the penis) did not occur in excess in children whose mothers were exposed to spermicides (Shapiro et al 1982, as referenced in USDA 2003a). Although this provides no quantitative information, it is useful in that it is a study involving human health.

**Carcinogenicity and Mutagenicity** - NP9E was not mutagenic in the Ames test (either with or without metabolic activation) or on the unscheduled DNA synthesis assay (adult rat liver cells). NP9E did not induce malignant transformations (*in vitro*) in rat liver cells. In one study NP9E did induce malignant transformations in BALB/3T3 cells, but this was not duplicated in another study. NP10E was not mutagenic in the Ames test (either with or without activation). NP4E showed no evidence of genotoxicity in tests of reverse mutation in bacteria or in unscheduled DNA repair studies in rat primary liver cells. NP4E did not induce micronuclei in the bone marrow cells of mice following intraperitoneal injection. NP did not show any initiating activity for BALB/3T3 cell transformation, implying that NP did not cause any genetic alteration that was inherited by daughter cells. In another study, NP did cause transformation of pre-treated BALB/3T3 cells in the promotion phase, but not in the initiation phase, indicating that NP may cause the enhancement of carcinogenesis *in vivo* (Sakai 2001, as referenced in USDA 2003a). NP was consistently negative in bacterial tests of mutagenicity, although it induced DNA damage in human sperm, lymphocytes, and MCF-7 breast cancer cells exposed *in vitro*.

No evidence of carcinogenicity was reported in 2-year chronic oral toxicity studies of NP9E with rats and dogs. Intravaginal dosages of NP9E in rats, up to 20 times the rates recommended for use in humans as a spermicide, for 2 years, indicated no carcinogenicity.

No chronic toxicity studies with NP were found with the exception of the two multi-generation studies discussed above (Chapin et al 1999; Nagao et al 2001). There was no indication of carcinogenesis in either of these two studies. As paraphrased from European Union 2002 (as referenced in USDA, 2003a), carcinogenicity of NP has not been directly studied, however, some information on the carcinogenic potential can be derived from other data. On the basis of information currently available it is unlikely that NP is mutagenic, so concerns for cancer caused by a genotoxic mechanism are low. Considering the potential for carcinogenicity by a non-genotoxic mechanism, no evidence of sustained cell proliferation or hyperplasia was seen in the standard repeated exposure toxicity studies. Overall, there are low concerns for carcinogenicity by a non-genotoxic mechanism.

**Other Toxic Endpoints** - Some xenoestrogenic chemicals may also have an effect on the immune system; estradiol and diethylstilbestrol have shown both types of effects. In one study using female mice, the mice were injected with 0.2 ml of 0.2% NP9E daily (approximately 130 mg/kg/day) for 24 days followed by a challenge with sheep red blood cells. There were no effects to white blood cell counts, primary and secondary anti-SRBC titers, and serum immunoglobulin M (IgM) and serum immunoglobulin G (IgG) concentrations.

Indirect observations of potential immunotoxicity can be developed from *in vivo* studies that conduct histopathological examinations of body tissues that are part of the immune system such as the lymphoid tissues (lymphocytes), thymus, spleen, bone marrow, and lymph nodes (SERA 2002). In Nagao et al, 2001, after continuous exposure to NP (oral gavage) at 50 mg/kg/day in rats, there was a decrease in both relative and absolute thymus weight, but no histopathologic alterations observed in this organ; these effects were not seen at the next lower dose of 10 mg/kg. In the same study, after exposure of males to 250 mg/kg/day over several months, reduced thymus was observed in most of the males, and upon histopathologic examination, there was atrophy with pyknosis (reduction in the nucleus) and a reduction in lymphocyte number. Based on this observation, it was felt that the reduced thymus weights seen at 50 mg/kg were likely related to the exposure to NP (*ibid*).

In a subchronic study in rats exposed to NP, there was no effect to spleen weight, and histopathological examinations of sternum bone marrow, the spleen, mandibular and mesenteric lymph nodes, and the thymus revealed no treatment related changes after a 90-day exposure to NP in male and female rats up to 129 (males) and 149 mg/kg/day (females) (Cunny et al 1997, as referenced in USDA 2003a). In the multigeneration study by Chapin et al 1999, there were no effects to the spleen, in terms of relative weight, in any generation at any NP dose tested (up to 2,000 ppm).

There are few studies that look at neurological effects of exposure to NP9E or the other NPEs. After subcutaneous injection of NP10E in the female rats at 2 and 20 mg/kg/day for 15 weeks, effects to offspring that were conceived and delivered during the maternal exposure period showed no effects in several behavior tests (open field test, water maze test), nor showed any effects in several reflex response assessments (righting on surface, negative geotaxis, corneal or pinna reflex).

There are several *in vivo* studies that look at the neurological effects of exposure to NP. In a recent multigenerational study by Flynn et al. (2002 as referenced in USDA 2003a), rats were exposed to NP in the diet at rates of 0, 25, 200, 750 ppm (equivalent to 0, 2, 16, 60 mg/kg/day) over two generations (F<sub>0</sub>, F<sub>1</sub>). Females in each of three generations (F<sub>0</sub>, F<sub>1</sub>, F<sub>2</sub>) were tested at several points during their lives using a water maze test. The study showed that two generations of dietary exposure to NP did not significantly alter the water maze performance in young adult or middle-aged female rats. This suggests that chronic dietary exposure to NP does not cause gross alterations in spatial learning and memory in female rats.

In Nagao et al 2001, performance in behavioral tests (open field activity, water maze, and running wheel activity) was assessed, as was the development of neural reflexes (righting response, cliff-drop aversion response, negative geotaxis) in developing pups. There were no significant effects seen in any of these parameters in the F<sub>1</sub> or F<sub>2</sub> generations after lifetime exposures to up to 50 mg/kg/day NP via oral gavage. There was an increase in salivation in F<sub>0</sub> males at 50 mg/kg.

Pregnant rats were exposed to NP in the diet at 0, 25, 500, and 2,000 ppm and after weaning, their offspring were exposed to the same diet until postnatal day 77. At several points during the growth of the offspring, behavioral tests were conducted to assess effects of NP exposure. There were no consistent NP-related effects in open-field activity, running wheel activity, play behavior, or intake of a saccharin-flavored solution. Intake of a sodium-flavored solution as well as water intake was increased at the 2,000 ppm level in offspring. The authors note that increased sodium solution intake has been seen in experiments after developmental exposure to other estrogenic compounds (such as genistein and estradiol), indicating that this may be an estrogenic response. Male rats exposed to NP during development and weaning (through maternal dosing), and after weaning (oral gavage) showed no signs of behavioral abnormalities when exposed to NP up to 250 mg/kg/day through post natal day 70.

Indirect observations of potential neurotoxicity can be developed from *in vivo* studies that conduct histopathological examinations of body tissues that are part of the nervous system such as the spinal cord, the brain, peripheral nerves (such as the sciatic nerve) (SERA 2002). In the study by Cunny et al, 1997, there were no effects seen to the brain or brainstem in terms of absolute weight or based upon



monitored for metabolites. The NP9E was completely metabolized by the rats and these metabolites were primarily excreted in feces and secondarily in urine (all radioactivity being excreted within 48 hours after injection). Analysis of urinary metabolites 24 hours after an intravenous dose indicated the presence of highly polar neutral and acidic species.

Doerge et al 2002 (as referenced in USDA 2003a) analyzed for NP metabolites in rats after feeding over 2 generations at levels of 1.5, 12, and 45 mg/kg/day. Glucuronides were identified as the primary metabolite, with lesser amounts of NP-aglycone and NP-catechol. Glucuronides are not active as an estrogen receptor (nor as anti-estrogens, androgens, or anti-androgens) while the NP-aglycone and NP-catechol are expected to continue to act as estrogen mimics. After a 50 mg/kg oral dose, there was rapid absorption and elimination of NP in both males and females (elimination halftimes of 3.1 to 4.0 hours). In a human exposure experiment to NP, radio-labeled NP was injected intravenously (14 µg/kg) or given orally (66 µg/kg) to two human volunteers to study metabolism and excretion. Elimination from the blood was rapid, with no detectable residue after 10 hours through either method of exposure. Only a relatively small percentage of NP or glucuronide or sulphate conjugates were detectable in the urine or feces (approximately 10% of the dose), suggesting further metabolism to compounds unidentified in this study or storage in tissues, likely lipids.

**Inerts** – NP9E-based surfactants also commonly include an alcohol (such as butyl or isopropyl alcohol), making up about 10% of the mixture; a silicone defoamer (about 1% of the mixture); and water. The NP9E makes up the majority of the formulation, often around 80% of the formulation. Most of these inert ingredients are on U.S. EPA list 4B (considered safe in pesticide formulations).

## **Section 3 – Exposure Assessment**

### **Workers**

Pesticide applicators are the individuals most likely to be exposed to a pesticide during application. Two types of worker exposure assessments are considered: general and accidental/incidental. The term general exposure assessment is used to designate those exposures that involve estimates of absorbed dose based on the handling of a specified amount of a chemical during specific types of applications. The accidental/incidental exposure scenarios involve specific types of events that could occur during any type of application.

The USDA Forest Service has generally used an absorption-based model for worker exposure modeling, in which the amount of chemical absorbed is estimated from the amount of chemical handled. Absorption based models have been used by the USDA Forest Service because of two common observations from field studies. First, most studies that attempt to differentiate occupational exposure by route of exposure indicate that dermal exposure is the dominant route of exposure for pesticide workers. Second, most studies of pesticide exposure that monitored both dermal deposition and chemical absorption or some other method of bio-monitoring noted a very poor correlation between the two values (e.g., Cowell et al. 1991, Franklin et al. 1981, Lavy et al. 1982, all as referenced in SERA 2007). In this exposure assessment for workers, the primary goal is to estimate absorbed dose so that the absorbed dose estimate can be compared with available information on the dose-response relationships for the chemical of concern.

In past risk assessments for the USDA Forest Service, exposure rates were by the estimated dermal absorption rate, typically using 2,4-D as a surrogate chemical when compound-specific data were not available (USDA 1989). In 1998, SERA conducted a detailed review and re-evaluation of the available

worker exposure studies that can be used to relate absorbed dose to the amount of chemical handled per day (SERA 1998). This review noted that there was no empirical support for a dermal absorption rate correction. Two factors appear to be involved in this unexpected lack of association: 1) algorithms for estimating dermal absorption rates have large margins of error; and, 2) actual levels of worker exposure are likely to be far more dependent on individual work practices or other unidentified factors than on differences in dermal absorption rates.

workers, the use of the arithmetic mean rather than some other measure of central tendency, like the geometric mean, has no marked effect on the risk assessment.

The application rates are based on the planned application rates for each of these herbicides under the proposed action (Alternative 1) and are based on previous experience using these herbicides on the Eldorado National Forest (refer to Table D-3). Rates are expressed as either acid equivalents (ae) or active ingredient (ai). Similarly, the application rates are based on Eldorado National Forest experience. The typical application rate is 20-25 gallons per acre of herbicide mixture applied, with the lowest dilution being 10 gallons per acre, and the highest being 30 gallons per acre. For hexachlorobenzene, the application rate is based on the application rate for clopyralid and the percentage of hexachlorobenzene in clopyralid.

**Table D-3: Herbicide and Nonylphenol Polyethoxylate Application Rates to be used on the Freds Fire (Including the Incidental Rate of Application of the Impurity Hexachlorobenzene)**

Herbicide	Application Rate Typical (lb/ac)	Application Rate Lowest (lb/ac)	Application Rate Highest (lb/ac)
Chlorsulfuron	0.062 ai	0.047 ai	0.062 ai
Clopyralid	0.25 ae	0.10 ae	0.25 ae
Glyphosate	3.2 ae	2.7 ae	4.8 ae
Hexazinone	3.0 ae	2.0 ae	3.0 ae
Triclopyr (BEE)	2.0 ae	1.6 ae	2.4 ae
Nonylphenol polyethoxylate	1.3 ai	1.1 ai	2.0 ai
Hexachlorobenzene	0.00000625 ai	0.0000025 ai	0.00000625 ai

The central estimate of the amount handled per day is calculated as the product of the central estimates of the acres treated per day and the application rate. The ranges for the amounts handled per day are calculated as the product of the range of acres treated per day and the range of application rates. Similarly, the central estimate of the daily-absorbed dose is calculated as the product of the central estimate of the exposure rate and the central estimate of the amount handled per day. The ranges of the daily-absorbed dose are calculated as the range of exposure rates and the ranges for the amounts handled per day. The lower and upper limits are similarly calculated using the lower and upper ranges of the amount handled, acres treated per day, and worker exposure rate.

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

The available literature does not include quantitative methods for characterizing exposure or responses associated with splashing a solution of a chemical into the eyes; furthermore, there appear to be no reasonable approaches to modeling this type of exposure scenario quantitatively. Consequently, accidental exposure scenarios of this type are considered qualitatively in the risk characterization.

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

For this risk assessment, two exposure scenarios are developed for each of the two types of dermal exposure, and the estimated absorbed dose for each scenario is expressed in units of mg chemical/kg body weight.

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

For both scenarios (the hand immersion and the contaminated glove), the assumption of zero-order absorption kinetics is appropriate. Following the general recommendations of U.S. EPA (1992, as referenced in SERA 2007), Fick's first law is used to estimate dermal exposure.

Exposure scenarios involving chemical spills on to the skin are characterized by a spill on to the lower legs as well as a spill on to the hands. In these scenarios, it is assumed that a solution of the chemical is spilled on to a given surface area of skin and that a certain amount of the chemical adheres to the skin. The absorbed dose is then calculated as the product of the amount of the chemical on the surface of the skin (i.e., the amount of liquid per unit surface area multiplied by the surface area of the skin over which the spill occurs and the concentration of the chemical in the liquid) the first-order absorption rate, and the duration of exposure. For both scenarios, it is assumed that the contaminated skin is effectively cleaned after 1 hour. As with the exposure assessments based on Fick's first law, this product (mg of absorbed dose) is divided by bodyweight (kg) to yield an estimated dose in units of mg chemical/kg body weight. The specific equation used in these exposure assessments is taken from SERA (2007).

See Tables F-4a to F-4g for the results of worker exposure calculations. (Actual calculations are displayed on worksheets contained in the project file and are based on the referenced SERA risk assessments and USDA (2003a).

**Table D-4a. Summary of Worker Exposure Scenarios – Chlorsulfuron**

Scenario	Typical Dose (mg/kg/day)	Lower Range (mg/kg/day)	Upper Range (mg/kg/day)
General Exposure (dose in mg/kg/day)			
Backpack Application	8.45E-04	1.69E-05	4.2E-03
Accidental/Incidental Exposures (dose in mg/kg/event)			
Immersion of Hands - 1 Minute	2.58E-07	4.42E-08	7.73E-07
Contaminated Gloves - 1 Hour	1.55E-05	2.65E-06	4.64E-05
Spill on Hands - 1 Hour	9.68E-06	9.41E-07	4.84E-05
Spill on Lower Legs - 1 Hour	2.38E-03	2.32E-06	1.19E-04

**Table D-4b. Summary of Worker Exposure Scenarios – Clopyralid**

Scenario	Typical Dose (mg/kg/day)	Lower Range (mg/kg/day)	Upper Range (mg/kg/day)
General Exposure (dose in mg/kg/day)			
Backpack Application	1.51E-03	3.60E-05	7.50E-03
Accidental/Incidental Exposures (dose in mg/kg/event)			

Immersion of Hands - 1 Minute	4.08E-07	1.06E-07	1.56E-06
Contaminated Gloves - 1 Hour	2.45E-05	6.34E-06	9.36E-05
Spill on Hands - 1 Hour	7.26E-05	1.50E-05	3.57E-04
Spill on Lower Legs - 1 Hour	1.79E-04	3.69E-05	8.79E-04

**Table D-4c. Summary of Worker Exposure Scenarios – Glyphosate**

Scenario	Typical Dose (mg/kg/day)	Lower Range (mg/kg/day)	Upper Range (mg/kg/day)
General Exposure (dose in mg/kg/day)			
Backpack Application	2.90E-02	9.72E-04	1.44E-01
Accidental/Incidental Exposures (dose in mg/kg/event)			
Immersion of Hands - 1 Minute	5.70E-06	1.18E-06	2.39E-05
Contaminated Gloves - 1 Hour	3.42E-04	7.10E-05	1.44E-03
Spill on Hands - 1 Hour	7.48E-04	2.00E-04	1.82E-03
Spill on Lower Legs - 1 Hour	1.84E-03	4.92E-04	4.49E-03

**Table D-4d. Summary of Worker Exposure Scenarios – Hexazinone**

Scenario	Typical Dose (mg/kg/day)	Lower Range (mg/kg/day)	Upper Range (mg/kg/day)
General Exposure (dose in mg/kg/day)			
Backpack Application	1.81E-02	7.20E-04	9.00E-02
Accidental/Incidental Exposures (dose in mg/kg/event)			
Immersion of Hands - 1 Minute	2.44E-03	1.58E-03	3.83E-03
Contaminated Gloves - 1 Hour	1.47E-01	9.50E-02	2.30E-01
Spill on Hands - 1 Hour	NA	NA	NA
Spill on Lower Legs - 1 Hour	NA	NA	NA

**Table D-4e. Summary of Worker Exposure Scenarios – Triclopyr BEE**

Scenario	Typical Dose (mg/kg/day)	Lower Range (mg/kg/day)	Upper Range (mg/kg/day)
General Exposure (dose in mg/kg/day)			
Backpack Application	1.45E-02	5.76E-04	7.20E-02
Accidental/Incidental Exposures (dose in mg/kg/event)			
Immersion of Hands - 1 Minute	1.57E-02	8.45E-03	2.88E-02
Contaminated Gloves - 1 Hour	9.45E-01	5.07E-01	1.73E+00
Spill on Hands - 1 Hour	3.70E-02	2.49E-04	6.06E-02
Spill on Lower Legs - 1 Hour	9.12E-02	6.13E-04	1.49E-01

**Table D-4f. Summary of Worker Exposure Scenarios – NPE**

Scenario	Typical Dose (mg/kg/day)	Lower Range (mg/kg/day)	Upper Range (mg/kg/day)
General Exposure (dose in mg/kg/day)			
Backpack Application	0.012	0.0004824	0.06
Accidental/Incidental Exposures (dose in mg/kg/event)			
Immersion of Hands - 1 Minute	0.00017	0.0000624	.00044
Contaminated Gloves - 1 Hour	0.010	0.0037440	0.026
Spill on Hands - 1 Hour	5.4 E-5	0.0000077	0.00069
Spill on Lower Legs - 1 Hour	0.00013	0.0000189	0.0017

**Table D-4g. Summary of Worker Exposure Scenarios – Hexachlorobenzene**

Scenario	Typical Dose (mg/kg/day)	Lower Range (mg/kg/day)	Upper Range (mg/kg/day)
General Exposure (dose in mg/kg/day)			
Backpack Application	3.8E-09	9 E-11	1.9 E-08
Accidental/Incidental Exposures (dose in mg/kg/event)			
Immersion of Hands - 1 Minute	4.68E-07	1.44E-07	1.50E-06
Contaminated Gloves - 1 Hour	2.81E-05	8.64E-06	9.00E-05
Spill on Hands - 1 Hour	6.27E-09	1.35E-09	2.74E-08
Spill on Lower Legs - 1 Hour	1.54E-08	3.33E-09	6.75E-08

### General Public

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

There are permanent residences or second homes within a ¼ mile of some of the proposed treatment areas, containing an estimated 250 residents. These residences are located along the South Fork of the American River. All other treatment areas are greater than ¼ mile from permanent human habitation. Any exposure from an herbicide spray project, due to drift, to residents living beyond ¼ mile from treatment sites would be negligible (USDA 1989, pages F-79 to F-81). According to recent work completed by the Department of Pesticide Regulation (DPR), exposure to native plant material collectors can be essentially eliminated if they remain at least 100 feet from the treated areas (Goh, K., as referenced in Bakke, 2000). In DPR's study (Segawa et al, 2001), herbicides were detected in 19 of 227 (8%) samples taken outside both aerial and ground-based herbicide application units, the majority of these positive samples (90%) were within 70 feet of the sampled unit edge, and all positive samples had concentrations of herbicides less than or equal to 2.68 parts per million. This study did not determine whether these detected amounts were due to drift or errors in application. This would indicate that with

ground-based applications, negligible amounts of off-site movement due to drift would be expected beyond 75 to 100 feet from the unit edge.

The proposed units are near or within parts of the Eldorado National Forest used for dispersed recreation, which might include activities such as hiking, hunting, fishing, woodcutting, berry-picking, or collection of plant materials for basket weaving. The public generally will pass through or near these units while participating in these activities. This dispersed use is estimated to be around 10-30 people per year on any given unit. Assuming each of the units could have people in them at the same time would represent 400 to 1200 people per year.

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

**Direct Spray** -- Direct sprays involving ground applications are modeled in a manner similar to accidental spills for workers. In other words, it is assumed that the individual is sprayed with a solution containing the compound and that an amount of the compound remains on the skin and is absorbed by first-order kinetics. As with the similar worker exposure scenarios, the first-order absorption kinetics are estimated from the empirical relationship of first-order absorption rate coefficients to molecular weight and octanol-water partition coefficients (SERA 2007).

For direct spray scenarios, it is assumed that during a ground application, a naked child is sprayed directly with the herbicide. The scenario also assumes that the child is completely covered (that is, 100% of the surface area of the body is exposed), which makes this an extremely conservative exposure scenario that is likely to represent the upper limits of plausible exposure. An additional set of scenarios are included involving a young woman who is accidentally sprayed over the feet and legs. For each of these scenarios, some standard assumptions are made regarding the surface area of the skin and body weight.

**Dermal Exposure from Contaminated Vegetation** -- In this exposure scenario, it is assumed that the herbicide is sprayed at a given application rate and that an individual comes in contact with sprayed vegetation or other contaminated surfaces at some period after the spray operation. For these exposure scenarios, some estimates of dislodgeable residue and the rate of transfer from the contaminated vegetation to the surface of the skin must be available. No such data are directly available for these herbicides, and the estimation methods of Durkin et al. (1995, as referenced in SERA 2007) are used. Other estimates used in this exposure scenario involve estimates of body weight, skin surface area, and first-order dermal absorption rates.

**Contaminated Water** - Water can be contaminated from runoff, as a result of leaching from contaminated soil, from a direct spill, or from unintentional contamination from applications. For this risk assessment, the two types of estimates made for the concentration of these herbicides in ambient water are acute/accidental exposure from an accidental spill and longer-term exposure to the herbicides in ambient water that could be associated with the typical application of this compound to a 100-acre treatment area.

The acute exposure scenario assumes that a young child (2- to 3-years old) consumes 1 L of contaminated water (a range of 0.6 to 1.5L) shortly after an accidental spill of 200 gallons of a field solution into a pond that has an average depth of 1 m and a surface area of 1000 m<sup>2</sup> or about one-quarter acre. Because this

scenario is based on the assumption that exposure occurs shortly after the spill, no dissipation or degradation of the herbicide is considered. This is an extremely conservative scenario dominated by arbitrary variability. The actual concentrations in the water would depend heavily on the amount of compound spilled, the size of the water body into which it is spilled, the time at which water consumption occurs relative to the time of the spill, and the amount of contaminated water that is consumed. It is also unlikely that ponds would be the waterbody receiving any herbicides in this project. Flowing streams are the more likely recipients, so dilution would occur. For these reasons, a second scenario is developed in which a stream is contaminated through drift, runoff, or percolation and a child consumes water from that stream. For the level of herbicide in this stream, an assumption of the short-term water contamination rate is developed (Table D-5a).

Water monitoring results following herbicide applications in Region 5 (USDA, 2001) were used to estimate concentrations of glyphosate, hexazinone, and triclopyr in water. For hexazinone, the lower, central, and upper estimates are based on the 50<sup>th</sup>, 90<sup>th</sup>, and 99<sup>th</sup> percentile results from Region 5 monitoring. For triclopyr the lower estimate is taken as zero (no detect) and the central estimate is taken as 3 ppb, which is rounded up from the highest detection in non-accidental or erroneous applications. For glyphosate the lower estimate is taken as zero. The SERA estimate was used for the upper estimate of triclopyr, and the central and upper estimate for glyphosate. For the other chemicals concentrations of these herbicides in water used levels derived from the SERA Risk Assessments.

The scenario for chronic exposure to these herbicides from contaminated water assumes that an adult (70 kg male) consumes contaminated ambient water for a lifetime. There are some monitoring studies available on many of these herbicides that allow for an estimation of expected concentrations in ambient water associated with ground applications of the compound over a wide area (glyphosate, hexazinone, and triclopyr). For the others, such monitoring data does not exist. For those herbicides without monitoring data, for this component of the exposure assessment, estimates of levels in ambient water were made based on the GLEAMS (Groundwater Loading Effects of Agricultural Management Systems) model.

GLEAMS is a root zone model that can be used to examine the fate of chemicals in various types of soils under different meteorological and hydro-geological conditions (Knisel et al. 1992, as referenced in SERA 2001). SERA (2001) illustrated the general application of the GLEAMS model to estimating concentrations in ambient water. The results of the GLEAMS modeling runs are displayed in the respective SERA risk assessments.

The specific estimates of longer-term concentrations of these herbicides in water that are used in this risk assessment are summarized in Table D-5b. These estimates are expressed as the water contamination rates (WCR) in mg/L (ppm) per pound of active ingredient or acid equivalent applied. The values in Tables F5a and F5b must be multiplied by the rates of application in Table D-3 (with the exception of NPE, which already encompasses a range of application rates). It is important to note that water monitoring conducted in the Pacific Southwest Region since 1991, involving glyphosate, triclopyr, and hexazinone has not shown levels of water contamination as high as these for normal (i.e., not accidental) applications (USDA 2001). This indicates that, at least for these herbicides, the assumptions in this risk assessment provide for a conservative (i.e. protective) assessment of risk. In addition, water monitoring involving clopyralid and hexachlorobenzene conducted on the Eldorado National Forest between 2002 and 2006 have not shown levels of water contamination as high as these for normal (i.e., not accidental) applications (USDA 2003c, 2006). Based on these samples, the assumptions in this risk assessment provide for a conservative (i.e. protective) assessment of risk for these two chemicals.

**Table D-5a: Short-Term Water Contamination Rates (WCR) of Herbicides, Nonylphenol Polyethoxylate, and the Hexachlorobenzene Impurity (in mg/L per lb applied)**

Herbicide	Typical WCR	Low WCR	High WCR
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Chlorsulfuron	0.1	0.01	0.2
Clopyralid	0.02	0.005	0.07
Glyphosate	0.02	0.0	0.4
Hexazinone	0.005	0.003	0.1
Triclopyr	0.003	0.0	0.4
Nonylphenol Polyethoxylate	0.012	0.0031	0.031
Hexachlorobenzene	0.09	0.001	0.3

**Table D-5b: Longer-Term Water Contamination Rates (WCR) of Herbicides, Nonylphenol Polyethoxylate, and the Hexachlorobenzene Impurity (in mg/L per lb applied)**

Herbicide	Typical WCR	Low WCR	High WCR
Chlorsulfuron	0.0006	0.0001	0.0009
Clopyralid	0.007	0.001	0.013
Glyphosate	0.001	0.0001	0.008
Hexazinone	0.02	0.00001	0.07
Triclopyr	0.03	0.008	0.05
Nonylphenol Polyethoxylate	0.007	0.0	0.014
Hexachlorobenzene	0.0005	0.00003	0.001

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

spraying of plants collected by Native Americans for basketweaving or medicinal use. These scenarios assume that vegetation is directly sprayed and that no washing of vegetation occurs. Again, in most instances and particularly for longer-term scenarios, treated vegetation would probably show signs of damage from herbicide exposure, thereby reducing the likelihood of consumption that would lead to significant levels of human exposure. Notwithstanding that assertion, it is conceivable that individuals could consume contaminated vegetation.

Two sets of exposure scenarios are provided: one for the consumption of contaminated fruit and the other for the consumption of contaminated vegetation. One of the more plausible scenarios involves the consumption of contaminated berries after treatment along a road or some other area in which wild berries grow. A second scenario is the consumption of contaminated vegetation after treatment. The two accidental exposure scenarios developed for each exposure assessment include one scenario for acute exposure and one scenario for longer-term exposure. In both scenarios, the concentration of herbicide on contaminated vegetation is estimated using the empirical relationships between application rate and concentration on vegetation developed by Hoerger and Kenaga (1972, as referenced in SERA 2007) as modified by Fletcher et al (1994, as referenced in SERA 2007). For the acute exposure scenario, the estimated residue level is taken as the product of the application rate and the residue rate. This approach, however, is not applicable to granular formulations of hexazinone, where the formulation will not tend to adhere to the surface of vegetation. For granular formulations, the residue rates from Fletcher et al. (1994) are divided by a factor of 25 based difference in residues on vegetation between granular and liquid formulations (Michael, 1992, as referenced in SERA, 2005). For the longer-term exposure scenario, a duration of 90 days is used and the dissipation on the vegetation is estimated based on the estimated or established foliar halftimes.

For hexachlorobenzene, the estimated residue level is taken as the product of the bioconcentration factor in vegetation and the long-term concentration in soil. The bioconcentration factor in vegetation is established as 19 (ATSDR 1998, as referenced in SERA 2004). GLEAMS is used to estimate concentrations in soil.

See Tables F-6a to F-6g for the results of public exposure calculations. (Actual calculations are displayed on worksheets contained in the project file and are based on the referenced SERA risk assessments and USDA (2003a).

**Table D-6a. Summary of Public Exposure Scenarios – Chlorsulfuron**

Scenario	Typical Dose (mg/kg/day)	Lower Range (mg/kg/day)	Upper Range (mg/kg/day)
Acute/Accidental Exposures (dose in mg/kg/day)			
Direct Spray, Entire Body, Child	3.66E-04	3.55E-05	1.83E-03
Direct Spray, Lower Legs, Woman	3.67E-05	3.57E-06	1.84E-04
Dermal Exposure, Contaminated Vegetation	5.32E-05	3.15E-06	2.64E-04
Contaminated Fruit	1.65E-03	5.52E-04	2.61E-02
Contaminated Vegetation	2.27E-02	1.58E-03	1.89E-01
Contaminated Water, Spill	3.19E-02	9.72E-03	4.78E-02
Contaminated Water, Stream	1.05E-03	2.15E-05	3.16E-03
Consumption of Fish, General Public	9.57E-04	4.78E-04	9.57E-04
Consumption of Fish, Subsistence Populations	4.66E-03	2.33E-03	4.66E-03
Chronic/Longer Term Exposures (dose in mg/kg/day)			

Contaminated Fruit	6.93E-04	2.32E-04	1.10E-02
Contaminated Vegetation	9.54E-03	6.66E-04	7.95E-02
Consumption of Water	2.40E-06	9.38E-08	4.32E-06
Consumption of Fish, General Public	1.80E-08	1.01E-09	2.70E-08
Consumption of Fish, Subsistence Population	1.46E-07	8.14E-09	2.19E-07

**Table D-6b. Summary of Public Exposure Scenarios – Clopyralid**

Scenario	Typical Dose (mg/kg/day)	Lower Range (mg/kg/day)	Upper Range (mg/kg/day)
Acute/Accidental Exposures (dose in mg/kg/day)			
Direct Spray, Entire Body, Child	2.74E-03	5.66E-04	1.35E-02
Direct Spray, Lower Legs, Woman	2.75E-04	5.68E-05	1.35E-03
Dermal Exposure, Contaminated Vegetation	3.48E-04	2.66E-05	1.67E-03
Contaminated Fruit	2.94E-03	1.18E-03	4.67E-02
Contaminated Vegetation	4.05E-02	3.38E-03	3.38E-01
Contaminated Water, Spill	6.83E-02	4.17E-02	1.02E-01
Contaminated Water, Stream	3.76E-04	2.29E-05	1.97E-03
Consumption of Fish, General Public	2.05E-03	2.05E-03	2.05E-03
Consumption of Fish, Subsistence Populations	9.99E-03	9.99E-03	9.99E-03
Chronic/Longer Term Exposures (dose in mg/kg/day)			
Contaminated Fruit	1.19E-03	3.79E-04	2.46E-02
Contaminated Vegetation	1.63E-02	1.09E-03	1.78E-01
Consumption of Water	5.00E-05	2.00E-06	1.11E-04
Consumption of Fish, General Public	2.50E-07	1.43E-08	4.64E-07
Consumption of Fish, Subsistence Population	2.03E-06	1.16E-07	3.76E-06

**Table D-6c. Summary of Public Exposure Scenarios – Glyphosate**

Scenario	Typical Dose (mg/kg/day)	Lower Range (mg/kg/day)	Upper Range (mg/kg/day)
Acute/Accidental Exposures (dose in mg/kg/day)			
Direct Spray, Entire Body, Child	2.82E-02	7.54E-03	6.89E-02
Direct Spray, Lower Legs, Woman	2.84E-03	7.58E-04	6.92E-03
Dermal Exposure, Contaminated Vegetation	5.70E-03	9.68E-04	1.38E-02
Contaminated Fruit	5.64E-02	3.18E-02	8.96E-01
Contaminated Vegetation	7.78E-01	9.11E-02	6.48E+00
Contaminated Water, Spill	1.08E+00	5.56E-01	1.62E+00
Contaminated Water, Stream	7.22E-03	0.00E+00	2.17E-01

Consumption of Fish, General Public	1.23E-02	1.04E-02	1.23E-02
Consumption of Fish, Subsistence Populations	6.01E-02	5.06E-02	6.01E-02
Chronic/Longer Term Exposures (dose in mg/kg/day)			
Contaminated Fruit	3.09E-02	1.74E-02	4.90E-01
Contaminated Vegetation	4.26E-01	4.99E-02	3.55E+00
Consumption of Water	1.37E-04	5.40E-06	1.32E-03
Consumption of Fish, General Public	2.61E-07	1.47E-08	2.08E-06
Consumption of Fish, Subsistence Population	2.11E-06	1.19E-07	1.69E-05

**Table D-6d. Summary of Public Exposure Scenarios – Hexazinone**

Scenario	Typical Dose (mg/kg/day)	Lower Range (mg/kg/day)	Upper Range (mg/kg/day)
Acute/Accidental Exposures (dose in mg/kg/day)			
Direct Spray, Entire Body, Child			
Direct Spray, Lower Legs, Woman			
Dermal Exposure, Contaminated Vegetation	5.60E-04	1.75E-04	1.14E-03
Contaminated Fruit	1.41E-03	9.41E-04	2.24E-02
Contaminated Vegetation	1.94E-02	8.10E-03	1.62E-01
Contaminated Water, Spill	1.36E+00	3.33E-01	4.09E+00
Contaminated Water, Stream	1.13E-03	2.75E-04	3.38E-02
Consumption of Fish, General Public	4.10E-02	1.64E-02	8.19E-02
Consumption of Fish, Subsistence Populations	2.00E-01	7.98E-02	3.99E-01
Chronic/Longer Term Exposures (dose in mg/kg/day)			
Contaminated Fruit	5.94E-04	3.96E-04	9.42E-03
Contaminated Vegetation	8.18E-03	3.41E-03	6.82E-02
Consumption of Water	1.71E-03	4.00E-07	7.20E-03
Consumption of Fish, General Public	1.80E-05	6.00E-09	6.30E-05
Consumption of Fish, Subsistence Population	1.46E-04	4.86E-08	5.10E-04

**Table D-6e. Summary of Public Exposure Scenarios – Triclopyr**

Scenario	Typical Dose (mg/kg/day)	Lower Range (mg/kg/day)	Upper Range (mg/kg/day)
Acute/Accidental Exposures (dose in mg/kg/day)			
Direct Spray, Entire Body, Child	1.40E+00	9.40E-03	2.29E+00
Direct Spray, Lower Legs, Woman	1.41E-01	9.44E-04	2.30E-01
Dermal Exposure, Contaminated Vegetation	1.71E-01	1.13E-03	2.20E-01
Contaminated Fruit	7.46E-03	4.97E-03	8.27E-02

Contaminated Vegetation	3.89E-01	5.40E-02	3.24E+00
Contaminated Water, Spill	5.46E-01	3.33E-01	8.20E-01
Contaminated Water, Stream	5.41E-04	0.00E+00	1.08E-01
Consumption of Fish, General Public	9.84E-04	9.84E-04	9.84E-04
Consumption of Fish, Subsistence Populations	4.80E-03	4.80E-03	4.80E-03
Chronic/Longer Term Exposures (dose in mg/kg/day)			
Contaminated Fruit	3.65E-03	1.87E-03	5.45E-02
Contaminated Vegetation	1.90E-01	2.03E-02	2.14E+00
Consumption of Water	2.06E-03	2.56E-04	4.11E-03
Consumption of Fish, General Public	6.17E-07	1.10E-07	1.03E-06
Consumption of Fish, Subsistence Population	5.00E-06	8.89E-07	8.33E-06

**Table D-6f. Summary of Public Exposure Scenarios – Nonylphenol Polyethoxylate**

Scenario	Typical Dose (mg/kg/day)	Lower Range (mg/kg/day)	Upper Range (mg/kg/day)
Acute/Accidental Exposures (dose in mg/kg/day)			
Direct Spray, Entire Body, Child	0.0020	0.00029	0.026
Direct Spray, Lower Legs, Woman	0.00020	2.9 E-5	0.0026
Dermal Exposure, Contaminated Vegetation	0.00038	3.5 E-5	0.0048
Contaminated Fruit	0.024	0.016	0.37
Contaminated Water, Spill	0.46	0.28	0.68
Contaminated Water, Stream	0.00094	0.00014	.0035
Consumption of Fish, General Public	0.014	0.014	0.014
Consumption of Fish, Subsistence Populations	0.067	0.067	0.067
Chronic/Longer Term Exposures (dose in mg/kg/day)			
Contaminated Fruit	0.00037	2.5 E-4	0.006
Consumption of Water	0.00020	0	0.00048
Consumption of Fish, General Public	1.0 E-6	0	2.0 E-6
Consumption of Fish, Subsistence Population	8.1 E-6	0	1.6 E-5

**Table D-6g. Summary of Public Exposure Scenarios – Hexachlorobenzene**

Scenario	Typical Dose (mg/kg/day)	Lower Range (mg/kg/day)	Upper Range (mg/kg/day)
Acute/Accidental Exposures (dose in mg/kg/day)			
Direct Spray, Entire Body, Child	2.37E-07	5.10E-08	1.04E-06
Direct Spray, Lower Legs, Woman	2.38E-08	5.13E-09	1.04E-07
Dermal Exposure, Contaminated Vegetation	7.46E-09	7.14E-10	1.65E-08

Contaminated Fruit	1.34E-08	5.35E-09	9.90E-08
Contaminated Water, Spill	1.71E-07	1.04E-07	2.56E-07
Contaminated Water, Stream	4.23E-09	1.15E-11	2.11E-08
Consumption of Fish, General Public	1.03E-05	1.03E-05	1.03E-05
Consumption of Fish, Subsistence Populations	5.00E-05	5.00E-05	5.00E-05
Chronic/Longer Term Exposures (dose in mg/kg/day)			
Contaminated Fruit	5.19E-10	4.79E-11	4.58E-09
Consumption of Water	8.93E-12	1.50E-13	2.14E-11
Consumption of Fish, General Public	8.93E-10	2.14E-11	1.79E-09
Consumption of Fish, Subsistence Population	7.23E-09	1.74E-10	1.45E-08

## **Section 4 – Dose Response Assessment**

### **Chlorsulfuron**

The U.S. EPA derived a chronic RfD for chlorsulfuron of 0.05 mg/kg/day. This RfD is currently listed on the U.S. EPA IRIS web site. This RfD is based on a two-year rat feeding study. The rats were given chlorsulfuron in the diet at concentrations of 100, 500 and 2,500 ppm for two years. Treatment related adverse effects of decreases in mean body weights and weight in male rats occurred at the 500 ppm and 2,500 ppm dose level. No frank signs of toxicity were seen at the 100 ppm or higher dose levels. Dose related effects on various hematological parameters were observed in males; however, these effects were observed during the first year. The investigators indicated that although the findings suggest the presence of reticulocytosis, reticulocyte counts were not measured. Consequently, the investigators concluded that in the absence of clarifying data, the biological significance of these hematological effects is unclear. No other behavioral, nutritional, clinical, hematological, gross, or histopathological abnormalities were observed. In deriving the RfD, the U.S. EPA accepted the 100 ppm dose as a NOAEL and estimated the daily intake as 5 mg/kg/day and used an uncertainty factor of 100.

The U.S. EPA Office of Pesticide Programs has recently proposed a lower chronic RfD of 0.02 mg/kg/day, which appears to be based on the identical study used by U.S. EPA in deriving the RfD of 0.05 mg/kg/day. The difference in the two RfDs is accounted for by an additional uncertainty factor required under the FQPA. Citing a three-generation reproduction study in which effects “...considered of questionable toxicological significance...” were noted at 125 mg/kg/day, the U.S. EPA selected an FQPA uncertainty factor of 3. Thus, the chronic NOAEL of 5 mg/kg/day was divided by 300 – factors of 10 for extrapolating from animals to humans, 10 for extrapolating to sensitive individuals within the human population, and 3 for accounting for differences in children as required by FQPA. This value was rounded to one significant decimal to yield the RfD of 0.02 mg/kg/day. For this risk assessment, the lower and more recent RfD of 0.02 mg/kg/day will be used to characterize all risks involving chronic or longer-term exposures.

The NOAEL of 5 mg/kg/day for chronic toxic effects is below the NOAEL of 25 mg/kg/day for reproductive effects. Thus, doses at or below the RfD will be below the level of concern for reproductive effects.

The U.S. EPA did not explicitly derive an acute/single dose RfD for chlorsulfuron. Nonetheless, for several short-term exposure scenarios the U.S. EPA recommends that an acute RfD be 0.25 mg/kg/day. This acute RfD appears to be based on a developmental study in rabbits with decreased body weight gains at 200 mg/kg/day. As with the chronic RfD, the NOAEL of 75 mg/kg/day was divided by an uncertainty

factor of 300. Consistent with U.S. EPA, this risk assessment will use the short term RfD of 0.25 mg/kg/day to characterize all risks acute or short-term exposures.

Chlorsulfuron is listed by the state of California on its Groundwater Protection List and is a reproductive toxicant under Proposition 65 (the Safe Drinking Water and Toxic Enforcement Act of 1986).

### **Clopyralid**

Up until 2001, U.S. EPA had established a provisional RfD of 0.5 mg/kg/day. This RfD was based on a two-year rat feeding study in which groups of male and female rats were administered clopyralid in the diet for 2 years at concentrations that resulted in daily doses of 0 (control), 5, 15, 50 or 150 mg/kg/day. No gross signs of toxicity, changes in organ or body weight, or histopathologic effects attributable to treatment were seen at doses of 50 mg/kg/day or lower. At 150 mg/kg/day, the only effect noted was a decrease in the body weight of the female rats. Thus, the U.S. EPA designated the dose of 50 mg/kg/day as a NOAEL and used an uncertainty factor of 100 (10 for species-to-species extrapolation and 10 for sensitive subgroups in the human population) to derive the RfD of 0.5 mg/kg/day. In 2001, U.S. EPA changed the chronic NOAEL to 15 mg/kg/day, based on a study in rats showing effects at 150 mg/kg/day. This change is currently under discussion between the clopyralid registrant and the U.S. EPA, however, for this risk assessment, the value of 15 mg/kg/day will be used as the chronic NOAEL, resulting in a chronic RfD of 0.15 mg/kg/day.

Based on these data, the critical effect - i.e., the adverse effect that will occur at the lowest dose level - is somewhat ambiguous. At a factor of 3 to 10 above the chronic NOAEL, effects have been reported on body weight, liver weight, and the gastric epithelium. Decreases in body weight and changes in organ weight are commonly observed in chronic toxicity studies and can indicate either an adaptive or toxic response. Changes in epithelial tissue are less commonly observed and the toxicological significance of this effect is unclear.

U.S. EPA has established an acute oral RfD of 0.75 mg/kg, based on a maternal NOEL of 75 mg/kg/day in rats in a developmental toxicity test (U.S. EPA, 2001). This value can be used as an indicator of short-term risk.

There are no drinking water standards established for clopyralid, either by U.S. EPA or CalEPA.

Although the two chlorinated benzenes should be regarded as much more potent toxicologically than clopyralid, the chlorinated benzenes do not appear to be present in a significant quantity with respect to systemic toxicity. In addition, all of the toxicity studies on clopyralid used the technical grade clopyralid and thus encompass the likely toxic contribution of the chlorinated benzene contaminants.

### **Glyphosate**

The U.S. EPA Office of Pesticide Programs has established a provisional RfD of 2 mg/kg/day for glyphosate (U.S. EPA, 2000b). This is based on the maternal NOAEL of 175 mg/kg/day from a rabbit developmental study and an uncertainty factor of 100 (10 for sensitive individuals and 10 for species to species extrapolation). The RfD of 2 mg/kg/day is a rounding of the 1.75 mg/kg/day value to one significant digit.

The U.S. EPA has also derived an RfD for glyphosate of 0.1 mg/kg/day (U.S. EPA/IRIS 1990, as referenced in SERA 2003a). This RfD was originally derived in 1990 by the U.S. EPA Integrated Risk Information System (IRIS) workgroup and is the current RfD posted on IRIS. This RfD is based on a dietary 3-generation reproduction study. In this study, rats were exposed to glyphosate in the diet with resulting dose rates of 0, 3, 10 and 30 mg/kg/day. No signs of maternal toxicity were observed. The only effect in offspring was an increase in the incidence of unilateral renal tubular dilation in male pups from the F3b mating. Thus, the NOAEL was identified as 10 mg/kg/day and an uncertainty factor of 100 was applied to derive an RfD of 0.1 mg/kg/day.

Unlike the two RfD values proposed by the U.S. EPA, the ADI proposed by WHO (1994, as referenced in SERA 2003a) is not based on a reproductive toxicity study. Instead, WHO (1994) selected a life-time feeding study in rats. This study involved dietary concentrations of 0, 30, 100, or 300 ppm for 26 months which corresponded to approximate daily doses of 0, 3.1, 10.3, or 31.5 mg/kg/day for males and 0, 3.4, 11.3, or 34.0 mg/kg/day for females. No effects were seen at any dose levels and thus WHO (1994) used a NOAEL of 31.5 mg/kg/day and uncertainty factor of 100. Rounding to one significant digit, the recommended ADI was set at 0.3 mg/kg/day.

The U.S. EPA/OPP will sometimes derive acute RfD values that can be used to assess risks associated with very short-term exposures – i.e., accidental spills. No acute RfD has been proposed, however, for glyphosate.

For the current risk assessment, the RfD of 2 mg/kg/day derived by U.S. EPA/OPP (1993) will be used as the basis for characterizing risk from longer term exposures in this risk assessment. For short-term exposures, the value of 2 mg/kg/day recommended by U.S. EPA/ODW (1992, as referenced in SERA 2003a) will be used. Since this is identical to the chronic RfD, this approach is equivalent to applying the same RfD to be short-term and long-term exposures. Given the lack of a significant dose-duration relationship for glyphosate, this approach seems appropriate.

The U.S. EPA Office of Water has established a lifetime health advisory level (HA) of 0.7 mg/L (700 ppb) and a 10-day HA of 20 mg/L (20 ppm) for glyphosate in drinking water (U.S. EPA, 2006). The lifetime HA is an estimate of acceptable drinking water levels for a contaminant at which adverse health effects would not be expected to occur, even over a lifetime of exposure. The 10-day HA is designed to be protective of a child consuming 1 liter of water a day. These are not legally enforceable Federal standards, but serve as technical guidance to assist others. In addition, U.S. EPA has set a Maximum Contaminant Level (MCL) of 0.7 mg/L. This is an enforceable standard for drinking water quality. The state of California has also established a Public Health Goal (PHG) of 1 mg/L (1 ppm), based on a similar analysis as U.S. EPA (CalEPA, 1997). The PHG describes a level of contamination at which adverse health effects would not be expected to occur, even over a lifetime of exposure.

## **Hexazinone**

In the process of reregistration, a 2-year feeding study in dogs was submitted to the U.S. EPA. In this study, doses of 41 and 38 mg/kg/day in males and females, respectively, were associated with changes in clinical chemistry and histopathology. The NOEL for these effects was 5 mg/kg/day. Based on this NOEL and using an uncertainty factor of 100 for species-to-species extrapolation (10) and sensitive subgroups (10), the Office of Pesticides derived an RfD of 0.05 mg/kg/day. The U.S. EPA determined that an additional uncertainty factor for the protection of infants and children is not required because of the information indicating that hexazinone does not have developmental or reproductive effects at doses below those associated with the same effect in dams. Hence, the RfD should protect against effects in both dams and offspring.

Based on developmental studies in rats and rabbits, the U.S. EPA identified acute dietary exposures to women of child bearing age as a potential concern and derived an acute RfD of 4 mg/kg. For the general population, no acute RfD was proposed because ... no appropriate endpoint attributable to a single-dose [was] identified in the database (U.S. EPA, as referenced in SERA, 2005). The RfD of 4 mg/kg is based on the developmental NOAEL of 400 mg/kg/day with an uncertainty factor of 100.

The U.S. EPA Office of Water has established a lifetime health advisory level (HA) of 0.4 mg/L (400 ppb) and a 10-day HA of 2 mg/L for hexazinone in drinking water (U.S. EPA 2006).

## **Triclopyr**

The U.S. EPA has established a chronic RfD for triclopyr at 0.05 mg/kg/day (U.S. EPA 1998). The U.S. EPA has concluded that the triethylamine acid (TEA) and butoxyethyl ester (BEE) of triclopyr are toxicologically equivalent; thus, this RfD is applicable to both forms of triclopyr. The RfD is based on a two-generation reproduction study in rats, with a NOEL of 5.0 mg/kg/day, the lowest dose tested. At the next dose level (25 mg/kg/day), an increased incidence of proximal tubular degeneration of the kidneys was observed in parental rats. An uncertainty factor of 100 was applied to this NOEL.

Under the Food Quality Protection Act (FQPA), the U.S. EPA is required to evaluate whether or not an additional uncertainty factor is required for the protection of children. The parental NOAEL of 5 mg/kg/day is below any adverse reproductive effects. Consequently, the U.S. EPA (1998) has determined that no additional FQPA uncertainty factor is required.

In the most recent pesticide tolerance for triclopyr, the U.S. EPA has recommended an acute RfD of 1 mg/kg/day for the general population (U.S. EPA 2002a). This appears to be based on the NOAEL of 100 mg/kg/day from a study in which rats were administered gavage doses of triclopyr BEE on days 6 through 15 of gestation. At 300 mg/kg/day, toxic responses included signs of marked maternal toxicity, overt clinical signs in a few dams, mean body weight loss and decreased mean body weight gain, decreased mean feed consumption, increased mean water consumption, and increased mean liver and kidney weights. In addition, fetal effects included both skeletal and soft-tissue malformations. This acute RfD is not applicable to females between the ages of 13-50 years – i.e., of childbearing age. For these individuals, the U.S. EPA recommends an acute RfD of 0.05 mg/kg/day, equivalent to the chronic RfD. This is based on a chronic 2-generation reproduction study with a NOAEL of 5 mg/kg/day and an increased incidence of defects in offspring at the next dose level of 25 mg/kg/day. In the triclopyr RED (U.S. EPA 1998), U.S. EPA considers a value of 30 mg/kg/day as a measure of acute dietary risk, based on a developmental toxicity study in rabbits administered triclopyr BEE. At the next highest dose (100 mg/kg/day), effects included parental mortality as well as decreased number of live fetuses, increased number of fetal deaths, and increased number of fetal and/or litter incidence of skeletal anomalies and variants. The 30 mg/kg/day NOEL is supported by a number of other teratogenicity studies as well as a multi-generation reproduction study.

For risk characterization, this risk assessment will adopt the most recent RfD values recommended by U.S. EPA – i.e., 1 mg/kg for acute exposures in the general population and 0.05 mg/kg/day for exposure scenarios of one month to a lifetime. Also consistent with the approach taken by U.S. EPA, the acute RfD of 1 mg/kg/day will be applied to the general population, but not to women of child-bearing age.

Some exposure scenarios for the general public and workers yield estimates that are above the current chronic (and adult female acute) RfD of 0.05 mg/kg/day or above the acute RfD of 1.0 mg/kg/day for the general population. Consequently, some attempt must be made to characterize the consequences of exposures above the RfD. The RfD is intended to be a conservative estimate and does not explicitly incorporate information on dose-duration or dose-severity relationships. In other words, doses below the RfD, regardless of the duration of exposure, are of no substantial concern as long as the RfD is based on a sound set of data. The assumption that exposures above the RfD will result in adverse human health effects is not necessarily correct, particularly when the duration of exposure is substantially less than a lifetime. All exposure scenarios considered in this risk assessment are less than lifetime. Triclopyr rapidly dissipates or degrades, and high levels of exposure generally occur only over short periods. Workers may be exposed repeatedly during an application program in a particular season and may use triclopyr formulations over the course of a career but exposures at occupational levels will be intermittent and less than lifetime.

The most sensitive effect, and the effect on which the chronic RfD is based, involve kidney toxicity. All of the kidney effects noted in rats are based on histopathological changes or increased kidney weight. The effect and no effect levels based on changes in kidney weight in rats after chronic exposure are very similar to those for subchronic exposures.

The issue of species sensitivity is important in assessing the use of a 10-fold factor for species-to-species extrapolation, as used in the RfD for triclopyr. For many chemicals, differences in species sensitivity are apparent and generally indicate that small animals are less sensitive than large animals. Triclopyr does not follow this pattern: there is no apparent relationship between body weight and toxicity measured as acute oral LD<sub>50</sub> values. The lack of consistent species differences in sensitivity suggests that U.S. EPA's use of an uncertainty factor of 10 for species-to-species extrapolation may be conservative. For assessing effects of exposures, an uncertainty factor of three will also be used as a range-bounding value.

Using data from acute studies on various species, including cattle and ponies, SERA (1996b) concluded that taking an approach analogous to that for the RfD, 60 mg/kg might be taken as a conservative 1-day NOAEL. Dividing by 100, as is done with the RfD, yields the adjusted value of 0.6 mg/kg for a reference 1-day exposure that should not be associated with adverse effects. As with the RfD, a 3-fold higher value, 1.8 mg/kg, could be proposed based on a less conservative but still protective species extrapolation.

From SERA (1996b), the AEL of 75 mg/kg, based on the data in cattle, yields a corresponding AEL range for humans of 0.75-2.25 mg/kg. This range of doses would not be associated with acute signs of toxicity but would be regarded as undesirable because adverse effects on the kidney might occur. The minimum dose associated with mortality in experimental mammals is 252 mg/kg in rabbits. After applying an uncertainty factor of 100, the estimated dose associated with concern for acute lethal effects in humans is 2.5 mg/kg, with an upper range of 7.5 mg/kg.

**Dose-severity relationships used for triclopyr risk characterization.**

Dose (mg/kg/day)	Plausible Effect
2.5 – 7.5	potentially lethal doses, especially at upper end of range, overt signs or symptoms of toxicity after acute exposures
0.75 to 2.25	with longer term exposure, probable effects on kidneys, offspring; acute exposures at upper end may also result in kidney effects, other clinical effects
0.05 to 0.75	nature and severity of toxic effects for chronic exposures are uncertain in general population; potential developmental effects in offspring of women
≤1.8	no effects anticipated with one-time exposures
≤0.05	no effects anticipated with chronic exposures.

**Nonylphenol Polyethoxylate**

At present there are no existing State or Federal human exposure guidelines for NP9E or NP. U.S. EPA has not established an RfD. Since it appears that NP could be a component of the NP9E mixture, NP could be a metabolite of NPE, and that NP appears to be more toxic in mammalian systems, one method of establishing a human threshold value would be to utilize NP toxicity studies to establish a benchmark level for use in assessing risks of exposure.

The use of the LOEL value of 12 mg/kg/day for NP from the study by Chapin et al. (1999, as referenced in USDA 2003) as a functional NOAEL value is the approach utilized by the Canadian government. However, the more recent multi-generation study by Nagao et al. (2001, as referenced in USDA 2003) provides a NOEL value of 10 mg/kg/day for NP.



As noted previously, clopyralid is not classified as a carcinogen. While it can be argued that the technical grade clopyralid used in the standard bioassays encompasses any toxicologic effects that could be caused by hexachlorobenzene, this argument is less compelling for carcinogenic effects because, for most cancer causing agents, the cancer risk is conservatively viewed as a non-threshold phenomenon - i.e., zero risk is achieved only at zero dose.

The potency factor of  $1.6 \text{ (mg/kg/day)}^{-1}$  is intended for application to lifetime daily doses. Many of the exposure assessments used in this risk assessment involve much shorter periods of time. Following the approach recommended by U.S. EPA this risk assessment assumes that the average daily dose over a lifetime is the appropriate measure for the estimation of cancer risk. Thus, the lifetime potency of  $1.6 \text{ (mg/kg/day)}^{-1}$  is scaled linearly when applied to shorter periods of exposure. As calculated in SERA (2004b), the potency parameter for a one-day exposure is  $0.000063 \text{ (mg/kg/day)}^{-1}$ . Thus, the lifetime risk associated with a single dose of 0.001 mg/kg would be calculated as  $6.3 \times 10^{-8}$  or 6.3 in one hundred million. This method of estimating cancer risk from short-term exposures is used in the next section for hexachlorobenzene.

No explicit dose response estimate is made for the potential carcinogenic effects of pentachlorobenzene. This is consistent with the approach taken by the U.S. EPA (1988b, as referenced in SERA 2004b) and reflects the fact the available data on pentachlorobenzene are inadequate to classify this compound as a carcinogen or to estimate carcinogenic potency.

## **Section 5 - Risk Characterization**

A quantitative summary of the risk characterization for workers associated with exposure to these herbicides is presented in Tables F-7a-1 to F-7g-1. The quantitative risk characterization is expressed as the hazard quotient, which is the ratio of the estimated exposure doses from Tables F-4a to F-4g to the RfD. The quantitative hazard characterization for the general public associated with exposure to these herbicides is summarized in Tables F-7a-2 to F-7g-2. Like the quantitative risk characterization for workers, the quantitative risk characterization for the general public is expressed as the hazard quotient, which again is the ratio of the estimated exposure doses from Tables F-6a to F-6g to the RfD.

As a standard for formatting, numbers greater than 1.0 are expressed in standard decimal notation and smaller numbers are expressed in scientific notations - e.g.,  $7 \text{ E-7}$  equivalent to  $7 \times 10^{-7}$  or 0.0000007.

The only reservation attached to this assessment is that associated with any risk assessment: Absolute safety cannot be proven and the absence of risk can never be demonstrated. No chemical has been studied for all possible effects and the use of data from laboratory animals to estimate hazard or the lack of hazard to humans is a process that contains uncertainty. Prudence dictates that normal and reasonable care should be taken in the handling of these herbicides.

### **Chlorsulfuron**

**Workers** -The toxicity data on chlorsulfuron allows for separate dose-response assessments for acute and chronic exposures. For acute exposures, the hazard quotients are based on U.S. EPA's recommended acute RfD of 0.25 mg/kg/day. For chronic exposures, the hazard quotients are based on the proposed chronic RfD from U.S. EPA of 0.02 mg/kg/day.

Given the very low hazard quotients for both general occupational exposures as well as accidental exposures, the risk characterization for workers is unambiguous. None of the exposure scenarios approach a level of concern.

While the accidental exposure scenarios are not the most severe one might imagine, they are representative of reasonable accidental exposures. Given that the highest hazard quotient for any of the

accidental exposures is a factor of about 5,000 below the level of concern, more severe and less plausible scenarios would be required to suggest a potential for systemic toxic effects.

The hazard quotients for general occupational exposure scenarios are somewhat higher than those for the accidental exposure scenarios. Nonetheless, the upper limit of the hazard quotients (HQ=0.2) is below the level of concern - i.e., a hazard quotient of 1. As previously discussed, these upper limits of exposure are constructed using the highest anticipated application rate, the highest anticipated number of acres treated per day, and the upper limit of the occupational exposure rate. If any of these conservative assumptions were modified the hazard quotients would drop substantially. The simple verbal interpretation of this quantitative characterization of risk is that even under the most conservative set of exposure assumptions, workers would not be exposed to levels of chlorsulfuron that are regarded as unacceptable. Under typical application conditions, levels of exposure will be far below levels of concern.

Mild irritation to the skin and eyes can result from exposure to relatively high levels of chlorsulfuron- i.e., placement of chlorsulfuron directly onto the eye or skin. From a practical perspective, eye or skin irritation is likely to be the only overt effect as a consequence of mishandling chlorsulfuron. These effects can be minimized or avoided by prudent industrial hygiene practices during the handling of the compound.

**General Public** – As with the corresponding worksheet for workers, the hazard quotients for acute exposure are based on an acute oral RfD of 0.25 mg/kg/day and the hazard quotients for chronic exposures are based on a proposed chronic RfD of 0.02 mg/kg/day.

None of the acute scenarios exceed a level of concern. The consumption of contaminated vegetation has a hazard quotient of 0.8, at the upper level. As previously discussed, these upper limits of exposure are constructed using the highest anticipated application rate, the highest anticipated number of acres treated per day, and the upper limit of the occupational exposure rate. If any of these conservative assumptions were modified the hazard quotients would drop substantially.

The longer-term consumption of contaminated vegetation after application of the highest dose yields a hazard quotient that is greater than unity (HQ= 4) at the highest dose. At typical and lower levels of exposure, this scenario yields hazard quotients below a level of concern. This scenario may be extremely conservative in that it does not consider the limited projected use of this herbicide on this project or the likelihood that such treated vegetation in older treated areas are expected to be dead, dying, chlorotic, brittle or deformed and hence undesirable to consume in the long-term.

**Table D-7a-1. Summary of Risk Characterization for Workers – Chlorsulfuron**

Chronic RfD = 0.02 mg/kg/day Acute RfD = 0.25 mg/kg/day			
Scenario	Hazard Quotient <sup>1</sup>		
	Typical	Lower	Upper
General Exposures			
Backpack Application	0.04	.0008	0.2
Accidental/Incidental Exposures			
Immersion of Hands - 1 Minute	1E-06	2E-07	3E-06
Contaminated Gloves - 1 Hour	6E-05	1E-05	2E-04
Spill on Hands - 1 Hour	4E-05	4E-06	2E-04
Spill on Lower Legs - 1 Hour	1E-04	9E-06	5E-04

<sup>1</sup> Hazard quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

**Table D-7a-2. Summary of Risk Characterization for the Public – Chlorsulfuron**

Chronic RfD = 0.02 mg/kg/day Acute RfD = 0.25 mg/kg/day			
Scenario	Hazard Quotient <sup>1</sup>		
	Typical	Lower	Upper
Acute/Accidental Exposures			
Direct Spray, Entire Body, Child	1E-03	1E-04	7E-03
Direct Spray, Lower Legs, Woman	1E-04	1E-05	7E-04
Dermal Exposure, Contaminated Vegetation	2E-04	1E-05	1E-03
Contaminated Fruit	7E-03	2E-03	0.1
Contaminated Vegetation	9E-02	6E-03	0.8
Contaminated Water, Spill	0.1	4E-02	0.2
Contaminated Water, Stream	4E-03	9E-05	1E-02
Consumption of Fish, General Public	4E-03	2E-03	4E-03
Consumption of Fish, Subsistence Populations	2E-02	9E-03	2E-02
Chronic/Longer Term Exposures			
Contaminated Fruit	3E-02	1E-02	0.5
Contaminated Vegetation	0.5	3E-02	4
Consumption of Water	1E-04	5E-06	2E-04
Consumption of Fish, General Public	9E-07	5E-08	1E-06
Consumption of Fish, Subsistence Population	7E-06	4E-07	1E-05

<sup>1</sup> Hazard quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

## Clopyralid

**Workers** -The toxicity data on clopyralid allows for separate dose-response assessments for acute and chronic exposures. For acute exposures, the hazard quotients are based on U.S. EPA's acute oral RfD of 0.75 mg/kg/day (U.S. EPA 2001). For chronic exposures, the hazard quotients are based on the provisional chronic RfD from U.S. EPA of 0.15 mg/kg/day. Given the very low hazard quotients for both general occupational exposures as well as accidental exposures, the risk characterization for workers is unambiguous; none of the exposure scenarios approaches a level of concern.

While the accidental exposure scenarios are not the most severe one might imagine, they are representative of reasonable accidental exposures. Given that the highest hazard quotient for any of the accidental exposures is a factor of about 1,000 below the level of concern, more severe and less plausible scenarios would be required to suggest a potential for systemic toxic effects. The hazard quotients for general occupational exposure scenarios are somewhat higher than those for the accidental exposure scenarios. Nonetheless, the upper limit of the hazard quotients for backpack application is below the level of concern - i.e., a hazard index of 1. As previously discussed, these upper limits of exposure are constructed using the highest anticipated application rate, the highest anticipated number of acres treated per day, and the upper limit of the occupational exposure rate. If any of these conservative assumptions were modified the hazard quotients would drop substantially. The simple verbal interpretation of this quantitative characterization of risk is that even under the most conservative set of exposure assumptions, workers would not be exposed to levels of clopyralid that are regarded as unacceptable. Under typical application conditions, levels of exposure will be far below levels of concern.

Irritation and damage to the skin and eyes can result from exposure to relatively high levels of clopyralid - i.e., placement of clopyralid directly onto the eye or skin. From a practical perspective, eye or skin irritation is likely to be the only overt effect as a consequence of mishandling clopyralid. These effects can be minimized or avoided by prudent industrial hygiene practices during the handling of clopyralid.

**General Public** – As with the corresponding worksheet for workers, the hazard quotients for acute exposure are based on an acute oral RfD of 0.75 mg/kg/day and the hazard quotients for chronic exposures are based on a provisional chronic RfD of 0.15 mg/kg/day.

For the acute/accidental scenarios, the exposure resulting from the consumption of contaminated vegetation is the scenario with the highest hazard quotient (HQ = 0.5) at the upper level. As previously discussed, these upper limits of exposure are constructed using the highest anticipated application rate, the highest anticipated number of acres treated per day, and the upper limit of the occupational exposure rate. If any of these conservative assumptions were modified the hazard quotients would drop substantially.

For the other acute/accidental scenarios, the exposure resulting from the consumption of contaminated water by a child is the scenario with the highest hazard quotient (HQ = 0.1), a factor of 10 below a level of concern. It must be noted that the exposure scenario for the consumption of contaminated water is an arbitrary scenario: scenarios that are more or less severe, all of which may be equally probable or improbable, easily could be constructed. All of the specific assumptions used to develop this scenario have a simple linear relationship to the resulting hazard quotient. Thus, if the accidental spill were to involve 20 rather than 200 gallons of a field solution of clopyralid, all of the hazard quotients would be a factor of 10 less. Nonetheless, this and other acute scenarios help to identify the types of scenarios that are of greatest concern and may warrant the greatest steps to mitigate. For clopyralid, such scenarios involve oral (contaminated water) rather than dermal (spills or accidental spray) exposure.

For chronic scenarios, the consumption of contaminated vegetation has a hazard quotient slightly above unity (HQ = 1.2). At typical and lower levels of exposure, this scenario yields hazard quotients below a level of concern. As previously described, this scenario may be extremely conservative in that it does not consider the limited projected use of this herbicide on this project or the likelihood that such treated vegetation in older treated areas are expected to be dead, dying, chlorotic, brittle or deformed and hence undesirable to consume in the long-term. However, this scenario points out the importance of directing the herbicide onto the targeted vegetation and avoiding non-target deposition through overspray.

**Table D-7b-1. Summary of Risk Characterization for Workers – Clopyralid**

Chronic RfD = 0.15 mg/kg/day Acute RfD = 0.75 mg/kg/day			
Scenario	Hazard Quotient <sup>1</sup>		
	Typical	Lower	

Chronic RfD = 0.15 mg/kg/day Acute RfD = 0.75 mg/kg/day			
Scenario	Hazard Quotient <sup>1</sup>		
	Typical	Lower	Upper
Acute/Accidental Exposures			
Direct Spray, Entire Body, Child	4E-03	8E-04	2E-02
Direct Spray, Lower Legs, Woman	4E-04	8E-05	2E-03
Dermal Exposure, Contaminated Vegetation	5E-04	4E-05	2E-03
Contaminated Fruit	4E-03	2E-03	6E-02
Contaminated Vegetation	5E-02	5E-03	0.5
Contaminated Water, Spill	9E-02	6E-02	0.1
Contaminated Water, Stream	5E-04	3E-05	3E-03
Consumption of Fish, General Public	3E-03	3E-03	3E-03
Consumption of Fish, Subsistence Populations	1E-02	1E-02	1E-02
Chronic/Longer Term Exposures			
Contaminated Fruit	8E-03	3E-03	0.2
Contaminated Vegetation	0.1	7E-03	<b>1.2</b>
Consumption of Water	3E-04	1E-05	7E-04
Consumption of Fish, General Public	2E-06	1E-07	3E-06
Consumption of Fish, Subsistence Population	1E-05	8E-07	3E-05

<sup>1</sup> Hazard quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

## Glyphosate

**Workers** - Given the low hazard quotients for both general occupational exposures as well as accidental exposures, the risk characterization for workers is unambiguous. None of the exposure scenarios exceed a level of concern.

While the accidental exposure scenarios are not the most severe one might imagine, they are representative of reasonable accidental exposures. Given that the highest hazard quotient for any of the accidental exposures is a factor of about 500 below the level of concern, more severe and less plausible scenarios would be required to suggest a potential for systemic toxic effects. The hazard quotients for these acute occupational exposures are based on a chronic RfD. This adds an additional level of conservatism and, given the very low hazard quotients for these scenarios, reinforces the conclusion that there is no basis for asserting that systemic toxic effects are plausible.

The hazard quotients for general occupational exposure scenarios are somewhat higher than those for the accidental exposure scenarios. Nonetheless, the upper limits of the hazard quotients are below the level of concern - i.e., a hazard index of 1. As previously discussed, these upper limits of exposure are constructed using the highest anticipated application rate, the highest anticipated number of acres treated per day, and the upper limit of the occupational exposure rate. If any of these conservative assumptions were modified the hazard quotients would drop substantially. The simple verbal interpretation of this quantitative characterization of risk is that even under the most conservative set of exposure assumptions, workers would not be exposed to levels of glyphosate that are regarded as unacceptable. Under typical backpack application conditions, levels of exposure will be at least 100 times below the level of concern.

Glyphosate and glyphosate formulations are skin and eye irritants. Quantitative risk assessments for irritation are not normally derived, and, for glyphosate specifically, there is no indication that such a derivation is warranted.

**General Public** - For chronic scenarios, the consumption of contaminated vegetation has a hazard quotient above unity (HQ = 1.8) at the upper level. At typical and lower levels of exposure, this scenario yields hazard quotients below a level of concern. As previously described, this scenario may be extremely conservative in that it does not consider the limited projected use of this herbicide on this project or the likelihood that such treated vegetation in older treated areas are expected to be dead, dying, chlorotic, brittle or deformed and hence undesirable to consume in the long-term. However, this scenario points out the importance of directing the herbicide onto the targeted vegetation and avoiding non-target deposition through overspray. As detailed in Table D-6c, the upper range of exposure scenario involves a dose of 3.55 mg/kg bw. While this is an unacceptable level of exposure, it is far below doses that would likely result in overt signs of toxicity. As detailed in SERA (2003a), a dose of 184 mg/kg as Roundup – i.e., glyphosate plus surfactant – was not associated with any overt signs of toxicity in humans – and mild signs of toxicity were apparent at doses of 427 mg/kg, over 100 times higher than the upper range of 3.55 mg/kg in the consumption of contaminated vegetation scenario.

None of the other longer-term exposure scenarios approach a level of concern. Although there are several uncertainties in the longer-term exposure assessments

**Table D-7c-1. Summary of Risk Characterization for Workers – Glyphosate**

RfD = 2.0 mg/kg/day			
Scenario	Hazard Quotient <sup>1</sup>		
	Typical	Lower	Upper
General Exposures			
Backpack Application	1E-02	5E-04	7E-02
Accidental/Incidental Exposures			
Immersion of Hands - 1 Minute	3E-06	6E-07	1E-05
Contaminated Gloves - 1 Hour	2E-04	4E-05	7E-04
Spill on Hands - 1 Hour	4E-04	1E-04	9E-04
Spill on Lower Legs - 1 Hour	9E-04	2E-04	2E-03

worker exposures to hexazinone are likely to exceed exposures that would generally be regarded as acceptable if workers do not follow prudent handling practices that will minimize exposure.

For accidental scenarios, no scenarios result in HQ values exceeding 1. While the accidental exposure scenarios are not the most severe one might imagine, they are representative of reasonable accidental exposures. The highest hazard quotient for any of the accidental exposures is a factor of about 10 below the level of concern. The hazard quotients for these acute occupational exposures are based on a chronic RfD. This adds an additional level of conservatism to the risk assessment.

As stated, hexazinone is a severe eye irritant. Quantitative risk assessments for irritation are not usually derived, and, for hexazinone specifically, the available data do not support any reasonable quantitative dose-response modeling. Nonetheless, human experience with this compound (Spencer et al. 1996) indicates that such effects are clearly plausible for granular formulations. As described in Section 2, workers applying Pronone 10G [on the Eldorado National Forest] using a belly grinder exhibited transient eye irritation and upper respiratory tract irritation (reported burning sensations in mouth, nose and throat, coughing, spitting) at the highest operational levels of exposure. These effects did not persist after exposure was terminated. It is important to recognize that the product applied in this study was recognized as defective, with excessive dustiness. As a result of this study, the USFS, Region 5 established additional requirements for protective equipment when applying granular hexazinone formulations via belly grinder. In addition, this direction instructs applicators not to continue applications if excessive dustiness is seen.

While skin irritation could also occur, it would probably be less severe than effects on the eyes.

**General Public** - For the acute/accidental scenarios, none exceed a level of concern. The consumption of contaminated water after a spill by a child or by consuming fish found in such contaminated waters, at the upper dose estimates equals the level of concern (HQ=1). The exposure scenarios involving contaminated water are arbitrary scenarios: scenarios that are more or less severe, all of which may be equally probable or improbable, easily could be constructed. All of the specific assumptions used to develop this scenario have a simple linear relationship to the resulting hazard quotient. Thus, if the accidental spill were to involve 20 rather than 200 gallons of a field solution of hexazinone, all of the hazard quotients would be a factor of 10 less. A further conservative aspect to the water contamination scenario is that it represents standing water, with no dilution or decomposition of the herbicide. This is unlikely in a forested situation where flowing streams are more likely to be contaminated in a spill, rather than a standing pond of water. The contaminated stream scenario presents a more realistic scenario for potential operational contamination of a stream; the HQ values are well below 1 (HQ = 0.008). The greatest practical consequence of a direct spray probably would be eye irritation, which could be severe

Of the longer-term scenarios, the consumption of unwashed vegetation after application of the highest dose yields a hazard quotient of 1.4. This scenario may be extremely conservative in that it does not consider the effects of washing contaminated vegetation or the likelihood that such treated vegetation in older treated areas are expected to be dead, dying, chlorotic, brittle or deformed and hence undesirable to consume in the long-term.

**Table D-7d-1. Summary of Risk Characterization for Workers – Hexazinone**

Chronic RfD = 0.05 mg/kg/day Acute RfD = 4.0 mg/kg/day			
Scenario	Hazard Quotient <sup>1</sup>		
	Typical	Lower	Upper
General Exposures			
Backpack Application	0.4	1E-02	1.8

Accidental/Incidental Exposures			
Immersion of Hands - 1 Minute	6E-04	4E-04	1E-03
Contaminated Gloves - 1 Hour	4E-02	2E-02	6E-02
Spill on Hands - 1 Hour	Not applicable to granular formulations		
Spill on Lower Legs - 1 Hour	Not applicable to granular formulations		

<sup>1</sup> Hazard quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

**Table D-7d-2. Summary of Risk Characterization for the Public – Hexazinone**

Chronic RfD = 0.05 mg/kg/day Acute RfD = 4.0 mg/kg/day			
Scenario	Hazard Quotient <sup>1</sup>		
	Typical	Lower	Upper
Acute/Accidental Exposures			
Direct Spray, Entire Body, Child	Not applicable to granular formulations		
Direct Spray, Lower Legs, Woman	Not applicable to granular formulations		
Dermal Exposure, Contaminated Vegetation	1E-04	4E-05	3E-04
Contaminated Fruit	4E-04	2E-04	6E-03
Contaminated Vegetation	5E-03	2E-03	4E-02
Contaminated Water, Spill	0.3	8E-02	<b>1.0</b>
Contaminated Water, Stream	3E-04	7E-05	8E-03
Consumption of Fish, General Public	1E-02	4E-03	2E-02
Consumption of Fish, Subsistence Populations	5E-02	2E-02	1E-01
Chronic/Longer Term Exposures			
Contaminated Fruit	1E-02	8E-03	0.2
Contaminated Vegetation	0.2	7E-02	<b>1.4</b>
Consumption of Water	3E-02	8E-06	0.1
Consumption of Fish, General Public	4E-04	1E-07	1E-03
Consumption of Fish, Subsistence Population	3E-03	1E-06	1E-02

<sup>1</sup> Hazard quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

## Triclopyr

**Workers** – The toxicity data on triclopyr allows for separate dose-response assessments for acute and chronic exposures. For acute exposures, the hazard quotients are based on an acute NOAEL of 100 mg/kg/day from a gestational study in rats resulting in a provisional acute RfD of 1 mg/kg/day. For women of childbearing age, the acute RfD is based on the reproductive study resulting in the NOAEL of 5 mg/kg/day - the basis for the chronic RfD. For chronic exposures, the hazard quotients are based on the provisional chronic RfD from U.S. EPA of 0.05 mg/kg/day.

Typical and lower estimates of exposure for all groups of workers approach, but don't exceed, a level of concern. At the upper application range, exposure levels slightly exceed the level of concern, with hazard quotients of 1.4. The health consequences of these exposure levels are uncertain but would be expected to be minimal. It is also important to keep in mind that the chronic RfD is based on daily, lifetime exposures, which are unlikely for a worker.

The accidental exposure scenario of wearing gloves contaminated with triclopyr for 1 hour exceeds the RfD for upper exposure levels (HQ = 1.7). Although it is unlikely that a one-time exposure to triclopyr at this level would result in toxic effects, this scenario indicates that adequate worker hygiene practices are important. As stated above, workers applying triclopyr only occasionally would be at much lower risk of such an accident. If a worker applies triclopyr often, and is sloppy with industrial hygiene, some effects to the kidney are plausible. The simple verbal interpretation of this quantitative characterization of risk is that under the most conservative set of accidental exposure assumptions, workers could be exposed to levels of triclopyr that are regarded as unacceptable. If triclopyr is not applied at the highest application and concentration rate or if appropriate steps are taken to ensure that workers are not exposed to the maximum plausible rates (i.e., worker hygiene practices) the risk to workers would be substantially reduced.

**General Public** – As with the corresponding worksheet for workers, the hazard quotients for acute exposure are based on acute RfD of 1.0 mg/kg/day and the hazard quotients for chronic exposures are based on the chronic RfD from U.S. EPA of 0.05 mg/kg/day. For women of childbearing age, the acute RfD is 0.05 mg/kg/day.

One acute/accidental scenario (the consumption of contaminated vegetation) exceeds a level of concern at all levels of exposure (HQ = 1 to 65). These findings suggest that in the unlikely event that someone had a vegetable garden growing in proximity to a treatment area that triclopyr was applied, especially at the typical or maximum application rates, adult females who consume the vegetables from such gardens could be at risk. At the typical level of exposure, the consumption of contaminated vegetation could lead to acute exposures where the nature and severity of effects are uncertain. At the upper level of exposure, the consumption of contaminated vegetation could lead to a one-time dose of 3.2 mg/kg which could result in overt signs or symptoms of toxicity after acute exposures. The plausibility of the existence of this scenario is limited by several important factors. First, the areas proposed for treatment with triclopyr are well removed (> 1 mile) from private residences, and hence, vegetable gardens. Secondly, unless the triclopyr contamination were to occur immediately before picking, it is plausible that the accidental contamination would kill the plants or diminish their capacity to yield consumable vegetation. Thirdly, this scenario is extremely conservative in that it does not consider the effects of washing contaminated vegetation in reducing doses. Finally, signs at likely access points informing the public that an area has been sprayed and the presence of dye on vegetation would reduce the potential that freshly sprayed material would be consumed.

In the other acute/accidental scenarios involving triclopyr, based on the high exposure assumptions, four of the acute/accidental scenarios reach or slightly exceed a level of concern (i.e., child sprayed, woman sprayed on lower legs, exposure to sprayed vegetation, and consumption of contaminated fruit). Based on the dose-severity relationship for triclopyr, at these levels of acute exposure ( $\leq 1.8$  mg/kg), it is unlikely that there would be any adverse health effects associated with a one-time exposure.

Two longer term scenarios exceed a level of concern - the consumption of unwashed fruit and the consumption of unwashed vegetation. While the consumption of fruit slightly exceeds a hazard quotient of 1 at only the upper level of exposure, the consumption of vegetation exceeds a level of concern at both the typical and upper exposure level. At the highest application rate, the estimated dose at the upper level of exposure could be about 2.1 mg/kg/day. This value is in the range that, with longer term exposure, could result in effects on kidneys or offspring. As previously discussed, these upper limits of exposure are constructed using the highest anticipated application rate, the highest anticipated number of acres treated per day, and the upper limit of the occupational exposure rate. If any of these conservative assumptions were modified the hazard quotients would drop substantially. This is a standard scenario used in all Forest Service risk assessments and is extremely conservative – i.e., it assumes that vegetation that has been directly sprayed is harvested and consumed for a prolonged period of time. In addition, this scenario does not consider the effects of washing contaminated vegetation or the likelihood that such

treated vegetation in older treated areas are expected to be dead, dying, chlorotic, brittle or deformed and hence undesirable to consume in the long-term.

TCP is of concern to the human health risk assessment both because it is a metabolite of triclopyr and because the aggregate risks of exposure to TCP from the breakdown of both triclopyr and chlorpyrifos must be considered. While the U.S. EPA has not derived a formal RfD for TCP, the RED on triclopyr (U.S. EPA 1998, p. 31) as well as the RED on chlorpyrifos (U.S. EPA 2001b, as referenced in SERA 2003b) use a chronic value of 0.03 mg/kg/day for the risk characterization for TCP. In the more recent pesticide tolerances for triclopyr (U.S. EPA 2002a), a somewhat lower value is used for the risk characterization of TCP: a dose of 0.012 mg TCP/kg/day derived using an uncertainty factor of 1000 and data from a chronic study in dogs in which changes in clinical chemistry at a dose of 48 mg/kg/day (LOAEL) but no effects at 12 mg/kg/day (NOAEL). For acute effects, the pesticide tolerances for triclopyr (U.S. EPA 2002a) use an acute value of 0.025 mg/kg/day based on a developmental toxicity study in rabbits with NOAEL of 25 mg/kg/day and a corresponding LOAEL of 100 mg/kg/day in which an increased incidence of hydrocephaly and dilated ventricles were noted in rabbits.

For both acute and chronic exposures the uncertainty factor for TCP is set at 1,000. This value is comprised of the factors of 10 to account for uncertainties in species-to-species extrapolation and another factor of 10 to encompass sensitive individuals in the population as well as an additional factor of 10 for the potentially higher sensitivity of children – i.e., the FQPA uncertainty factor. For the current risk assessment, the values used for risk characterization are identical to the most recent and conservative values proposed by U.S. EPA: 0.025 mg/kg/day for acute exposures and 0.012 mg/kg/day for chronic exposures.

**Table D-7e-1. Summary of Risk Characterization for Workers – Triclopyr**

Chronic RfD = 0.05 mg/kg/day Acute RfD = 1.0 mg/kg/day			
Scenario	Hazard Quotient <sup>1</sup>		
	Typical	Lower	Upper
General Exposures			
Backpack Application	0.3	1E-02	1.4
Accidental/Incidental Exposures			
Immersion of Hands - 1 Minute	2E-02	8E-03	3E-02
Contaminated Gloves - 1 Hour	0.9	0.5	1.7
Spill on Hands - 1 Hour	4E-02	2E-04	6E-02
Spill on Lower Legs - 1 Hour	9E-02	6E-04	0.1

<sup>1</sup> Hazard quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

**Table D-7e-2. Summary of Risk Characterization for the Public – Triclopyr**

Chronic RfD = 0.05 mg/kg/day Acute RfD = 1.0 mg/kg/day			
Scenario	Hazard Quotient <sup>1</sup>		
	Typical	Lower	Upper
Acute/Accidental Exposures			
Direct Spray, Entire Body, Child	1.4	9E-03	2
Direct Spray, Lower Legs, Woman	3	2E-02	5
Dermal Exposure, Contaminated Vegetation	3	2E-02	4

Contaminated Fruit	0.1	1E-01	<b>1.7</b>
Contaminated Vegetation	<b>8</b>	<b>1.1</b>	<b>65</b>
Contaminated Water, Spill	0.5	0.3	0.8
Contaminated Water, Stream	5E-04	0E00	0.1
Consumption of Fish, General Public	1E-03	1E-03	1E-03
Consumption of Fish, Subsistence Populations	5E-03	5E-03	5E-03
Chronic/Longer Term Exposures			
Contaminated Fruit	7E-02	4E-02	<b>1.1</b>
Contaminated Vegetation	<b>4</b>	0.4	<b>43</b>
Consumption of Water	4E-02	5E-03	8E-02
Consumption of Fish, General Public	1E-05	2E-06	2E-05
Consumption of Fish, Subsistence Population	1E-04	2E-05	2E-04

<sup>1</sup> Hazard quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

### Nonylphenol Polyethoxylate

**Workers** - Given the low hazard quotients for accidental exposure, the risk characterization is reasonably unambiguous. None of the accidental exposure scenarios exceed a level of concern. While the accidental exposure scenarios are not the most severe one might imagine (e.g., complete immersion of the worker or contamination of the entire body surface for a prolonged period of time) they are representative of reasonable accidental exposures. Confidence in this assessment is diminished by the lack of information regarding the dermal absorption kinetics of NP9E in humans. Nonetheless, the statistical uncertainties in the estimated dermal absorption rates, both zero-order and first-order, are incorporated into the exposure assessment and risk characterization.

The upper limit of general worker exposure scenarios approach, but don't exceed, a level of concern (HQ = 0.7). The simple verbal interpretation of this quantitative characterization of risk is that under the most conservative set of exposure assumptions, workers should not be exposed to levels of NP9E that are regarded as unacceptable.

NP9E can cause irritation and damage to the skin and eyes. Quantitative risk assessments for irritation are not derived; however, from a practical perspective, eye or skin irritation is likely to be the only overt effect as a consequence of mishandling NP9E. These effects can be minimized or avoided by prudent industrial hygiene practices during the handling of NP9E.

**General Public** –Although there are several uncertainties in the longer-term exposure assessments for the general public, the upper limits for hazard indices are sufficiently far below a level of concern that the risk characterization is relatively unambiguous: based on the available information and under the foreseeable conditions of application, there is no route of exposure or scenario suggesting that the general public will be at any substantial risk from longer-term exposure to NP9E.

For the acute/accidental scenarios, exposure resulting from the consumption of contaminated water from a spill is of greatest concern. Exposure resulting from the consumption of contaminated vegetation is of somewhat less concern. None of the other acute exposure scenarios represent a risk of effects to the public from NP9E exposure.

Acute or accidental exposure scenarios involving consumption of contaminated water or consumption of contaminated vegetation represent some risk of effects. None of the other acute exposure scenarios represent a risk of effects to the public from NP9E exposure. At typical rates of application, the drinking of contaminated water after a spill (HQ = 4.6) approaches the level that could present a risk of subclinical

effects to the liver and kidney (HQ values between 5 and 10). The upper HQ of 6.8 represents an increasing risk of clinical effects to the kidney, liver, and other organ systems. The exposure scenario for the consumption of contaminated water is an arbitrary scenario: scenarios that are more or less severe, all of which may be equally probable or improbable, easily could be constructed. All of the specific assumptions used to develop this scenario have a simple linear relationship to the resulting hazard quotient. Thus, if the accidental spill were to involve 20 rather than 200 gallons of a field solution of NP9E, all of the hazard quotients would be a factor of 10 less. This scenario involving water contamination assumes that a small pond is affected, rather than a creek or river as would be more likely in this forested setting. The contaminated stream scenario presents a more realistic scenario for potential operational contamination of a stream; the HQ values are substantially below one

At high application rates only (HQ = 3.7) the short-term consumption of fruit also approaches the level that could present a risk of subclinical effects to the liver and kidney (HQ values between 5 and 10). At the typical rate of application, the HQ is less than one. Signing and the presence of dye on vegetation would reduce the potential of freshly sprayed material to be consumed.

The public exposure scenario involving the consumption of fruit, both short-term (above) and long-term, most closely proxies the use of native material by basketweavers. The highest estimated HQ value for the long-term exposure scenario is 0.7. Plant materials in older treated areas are expected to be dead, dying, chlorotic, brittle or deformed and hence undesirable and very unlikely to be selected for basketweaving, medicine or food (Segawa, R., et al, 2001), reducing the likelihood of additive doses.

**Table D-7f-1. Summary of Risk Characterization for Workers – Nonylphenol Polyethoxylate**

RfD = 0.10 mg/kg/day			
Scenario	Hazard Quotient <sup>1</sup>		
	Typical	Lower	Upper
General Exposures			
Backpack Application	0.12	0.0048	0.7
Accidental/Incidental Exposures			
Immersion of Hands - 1 Minute	0.0017	0.0006240	0.0044
Contaminated Gloves - 1 Hour	0.1	0.0374400	0.26
Spill on Hands - 1 Hour	0.0005	0.0000768	0.0069
Spill on Lower Legs - 1 Hour	0.0013	0.0001893	0.017

<sup>1</sup> Hazard quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

**Table D-7f-2. Summary of Risk Characterization for the Public – Nonylphenol Polyethoxylate**

RfD = 0.10 mg/kg/day			
Scenario	Hazard Quotient <sup>1</sup>		
	Typical	Lower	Upper
Acute/Accidental Exposures			
Direct Spray, Entire Body, Child	0.02	0.0029	0.26
Direct Spray, Lower Legs, Woman	0.002	0.00029	0.026
Dermal Exposure, Contaminated Vegetation	0.004	0.00035	0.048

Contaminated Fruit	0.24	0.16	3.7
Contaminated Water, Spill	4.6	2.8	6.8
Contaminated Water, Stream	0.009	0.001	0.035
Consumption of Fish, General Public	0.14	0.14	0.14
Consumption of Fish, Subsistence Populations	0.67	0.67	0.67
Chronic/Longer Term Exposures			
Contaminated Fruit	0.004	0.0025	0.06
Consumption of Water	0.002	0	0.005
Consumption of Fish, General Public	1 E-5	0	2 E-5
Consumption of Fish, Subsistence Population	8 E-5	0	0.00016

<sup>1</sup> Hazard quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

## Hexachlorobenzene

**Workers** –The toxicity data on hexachlorobenzene allows for separate dose-response assessments for acute and chronic exposures. For acute exposures, the hazard quotients are based on ATSDR's short-term MRL of 0.008 mg/kg/day (ATSDR 1998, as referenced in SERA 2004). For chronic exposures, the hazard quotients are based on the chronic RfD from U.S. EPA of 0.0008 mg/kg/day.

For general worker exposures, the hazard quotients associated with hexachlorobenzene are approximately two to three orders of magnitude below the corresponding hazard quotients for clopyralid. Similarly, hazard quotients associated with accidental scenarios are consistently lower for hexachlorobenzene than the corresponding scenarios for clopyralid. Thus, for the reasonably diverse exposure scenarios covered in this risk assessment, the amount of hexachlorobenzene in technical grade clopyralid is not toxicologically significant.

The cancer risks presented in Table D-7g-3 are presented as the estimated exposure divided by the lifetime dose associated with a cancer risk of 1 in one million. Thus, the interpretation of these hazard quotients is identical to that of hazard quotients for toxicity – i.e., if the hazard quotient is below unity, the cancer risk is below 1 in one million. As indicated in Table D-7g-3, none of the cancer risks in workers exceed 1 in one million.

While there are substantial uncertainties involved in any cancer risk assessment, the verbal interpretation of the numeric risk characterization derived in this risk assessment is relatively simple. Using the assumptions and methods typically applied in Forest Service risk assessments, there is no plausible basis for asserting that the contamination of clopyralid with hexachlorobenzene will result in any substantial risk of cancer in workers applying clopyralid under normal circumstances.

While the chronic cancer potency could be scaled linearly and the cancer risk associated with short term exposures could be calculated, this sort of extrapolation is highly uncertain and, more importantly, ignores the normal background exposures to hexachlorobenzene from other sources. For example background levels of exposure to hexachlorobenzene are in the range of 0.000001 mg/kg/day or  $1 \times 10^{-6}$  mg/kg/day. As summarized in Table D-4g, even the upper range general worker exposure values are below this background dose – i.e.,  $1.9 \times 10^{-8}$  mg/kg/day. As discussed in the next section, the upper range of the longer term exposure scenarios for the general public are substantially below the background dose – i.e., about  $5 \times 10^{-9}$  to  $2 \times 10^{-11}$ . Thus, there is no basis for asserting that the presence of pentachlorobenzene or hexachlorobenzene in clopyralid will impact substantially the cancer risk under conditions characteristic of applications made in this project.

As indicated in Section 2, all of these risk characterizations are based on the typical or average 2.5 ppm concentration of hexachlorobenzene in technical grade clopyralid. This is the upper range of hexachlorobenzene that may be expected in technical grade clopyralid and thus the actual risks are probably much lower than those given in these tables.

While there are substantial uncertainties involved in any cancer risk assessment, the verbal interpretation of the numeric risk characterization derived in this risk assessment is relatively simple. Using the assumptions and methods typically applied in Forest Service risk assessments, there is no plausible basis for asserting that the contamination of clopyralid with pentachlorobenzene or hexachlorobenzene will result in any substantial risk of cancer in workers applying clopyralid under normal circumstances.

The above discussion is not to suggest that general exposures to hexachlorobenzene – i.e., those associated with normal background exposures that are not related to Forest Service applications of clopyralid – are acceptable. At background exposure levels of about  $1 \times 10^{-6}$  mg/kg/day, the background risk associated with exposure to hexachlorobenzene would be 0.0000016 or about 1 in 625,000.

**General Public** –As with the corresponding worksheet for workers, the hazard quotients for acute exposure are based on the short-term MRL of 0.008 mg/kg/day and the hazard quotients for chronic exposures are based on the U.S. EPA RfD of 0.0008 mg/kg/day.

All exposure scenarios result in hazard quotients that are below unity - i.e., the level of exposure is below the RfD for chronic exposures and below the MRL for acute exposures. In addition, all of the acute exposure scenarios result in hazard quotients that are substantially below the corresponding hazard quotient for clopyralid. The highest acute hazard quotient for hexachlorobenzene is about 0.006, the upper range of the hazard quotient associated with the consumption of contaminated fish by subsistence populations. The consumption of fish contaminated with hexachlorobenzene is a primary exposure scenario of concern because of the tendency of hexachlorobenzene to bio-concentrate from water into fish. For chronic exposures, the highest chronic HQ is about 0.00002, the upper range of the hazard quotient associated with the consumption of fish by subsistence populations. This is also consistent with the general observation that exposure to hexachlorobenzene occurs primarily through the consumption of contaminated food.

As with worker exposures, none of the hazard quotients for cancer risk levels of 1 in 1-million exceed unity. As indicated in Table D-6g, the highest longer-term exposure rate associated with Forest Service programs is  $1.45 \times 10^{-8}$  mg/kg/day – i.e., the upper range of exposure for the consumption of contaminated fish by subsistence populations. This is below the typical background exposure by a factor of about 70.

No explicit dose response assessment is made for the potential carcinogenic effects of pentachlorobenzene, another impurity in clopyralid. Based on the comparison of apparent toxic potencies and the relative amounts of both hexachlorobenzene and pentachlorobenzene in clopyralid, a case could be made for suggesting that pentachlorobenzene may double the cancer risk over that associated with hexachlorobenzene. Given the extremely low levels of estimated cancer risk, this has essentially no impact on the risk characterization.

The simple verbal interpretation of this risk characterization is that, in general, the contamination of clopyralid with hexachlorobenzene and pentachlorobenzene does not appear to pose a risk to the general public. This is consistent with the conclusions reached by the U.S. EPA (1995a, as referenced in SERA, 1999).

As indicated in Section 2, all of these risk characterizations are based on the typical or average 2.5 ppm concentration of hexachlorobenzene in technical grade clopyralid. This is the upper range of hexachlorobenzene that may be expected in technical grade clopyralid and thus the actual risks are probably much lower than those given in these tables

**Table D-7g-1. Summary of Risk Characterization for Workers – Hexachlorobenzene**

Chronic RfD = 0.0008 mg/kg/day Acute MRL = 0.008 mg/kg/day			
Scenario	Hazard Quotient <sup>1</sup>		
	Typical	Lower	Upper
General Exposures			
Backpack Application	5 E-6	1 E-7	2 E-5
Accidental/Incidental Exposures			
Immersion of Hands - 1 Minute	6E-05	2 E-5	2E-04
Contaminated Gloves - 1 Hour	4E-03	1E-03	1E-02
Spill on Hands - 1 Hour	8E-07	2 E-7	3E-06
Spill on Lower Legs - 1 Hour	2E-06	4 E-7	8E-06

<sup>1</sup> Hazard quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

**Table D-7g-2. Summary of Risk Characterization for the Public – Hexachlorobenzene**

Chronic RfD = 0.0008 mg/kg/day Acute MRL = 0.008 mg/kg/day			
Scenario	Hazard Quotient <sup>1</sup>		
	Typical	Lower	Upper
Acute/Accidental Exposures			
Direct Spray, Entire Body, Child	3E-05	6E-06	1E-04
Direct Spray, Lower Legs, Woman	3E-06	6E-07	1E-05
Dermal Exposure, Contaminated Vegetation	9E-07	9E-08	2E-06
Contaminated Fruit	2E-06	7E-07	1E-05
Contaminated Water, Spill	2E-05	1E-05	3E-05
Contaminated Water, Stream	5E-07	1E-09	3E-06
Consumption of Fish, General Public	1E-03	1E-03	1E-03
Consumption of Fish, Subsistence Populations	6E-03	6E-03	6E-03
Chronic/Longer Term Exposures			
Contaminated Fruit	6E-07	6E-08	6E-06
Consumption of Water	1E-08	2E-10	3E-08
Consumption of Fish, General Public	1E-06	3E-08	2E-06
Consumption of Fish, Subsistence Population	9E-06	2E-07	2E-05

<sup>1</sup> Hazard quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

**Table D-7g-3. Summary of Cancer Risk Assessment for Workers – Hexachlorobenzene – Relative to Risk Level of 1 in 1 Million**

Adjusted Cancer Potency Parameter = 6.26 E-5 (mg/kg/day) <sup>-1</sup>			
Scenario	Cancer Risk Divided by 1 in 1 Million		
	Typical	Lower	Upper

General Exposures			
Backpack Application	6E-03	1E-04	3E-02

**Table D-7g-4. Summary of Cancer Risk Assessment for Public – Hexachlorobenzene Relative to Risk Level of 1 in 1 Million**

Adjusted Cancer Potency Parameter = 6.25 E-7 (mg/kg/day) <sup>-1</sup>			
Scenario	Cancer Risk Divided by 1 in 1 million		
	Typical	Lower	Upper
Chronic/Longer Term Exposures			
Contaminated Fruit	8E-04	8E-05	7E-03
Consumption of Water	1E-05	2E-07	3E-05
Consumption of Fish, General Public	1E-03	3E-05	3E-03
Consumption of Fish, Subsistence Population	1E-02	3E-04	2E-02

## Cumulative Effects

The proposed use of herbicides could result in cumulative doses of herbicides to workers or the general public. Cumulative doses to the same herbicide result from (1) additive doses resulting from various routes of exposure from this project and (2) additive doses if an individual is exposed to other herbicide treatments.

Additional sources of exposure include: use of herbicides on adjacent private lands, use of herbicides on adjacent National Forest System lands, or home use by a worker or member of the general public. Reported past use of glyphosate, hexazinone, chlorsulfuron, triclopyr, and clopyralid (1999-2006) in El Dorado County is displayed in Table D-8, below, by total use and Forestland use. Hexazinone is used primarily for forestland. Glyphosate is primarily used in forestland (41%), other crops, right-of-way, and landscape maintenance. Chlorsulfuron is primarily used in right-of-way and landscape maintenance. Triclopyr is primarily used in forestland (28%), right-of-way, and landscape maintenance. Clopyralid is primarily used for forestland (14%), rangeland, landscape maintenance, and right-of-way. We assume that there would not be any extensive changes in these use patterns into the near future.

**Table D-8 Reported Herbicide Use (lbs active ingredient) in El Dorado County (1999-2006)**

	Forestland Total								
Chemical	1999	2000	2001	2002	2003	2004	2005	2006	Total
Chlorsulfuron	0	0	0	0	0	0	0	0	0
Glyphosate	7,881	5,324	7,231	3,709	3,183	2,561	6,471	6,271	42,631
Clopyralid	51	0	89	88	14	51	24	18	335
Hexazinone	3,081	2,569	3,778	3,554	1,772	5,549	1,474	4,895	26,672
Triclopyr	541	770	633	978	69	67	532	50	3,640
	All Reported Uses								
Chemical	1999	2000	2001	2002	2003	2004	2005	2006	Total
Chlorsulfuron	3	3	4	7	3	8	23	46	97
Glyphosate	13,054	9,482	11,113	9,596	10,640	14,927	15,508	19,921	104,241
Clopyralid	178	103	376	400	468	222	224	372	2,343
Hexazinone	3,154	2,695	3,826	3,559	1,559	5,673	1,523	4,935	26,924
Triclopyr	1,336	1,504	1,521	1,904	2,101	1,076	1,900	1,438	12,780

Source - California Department of Pesticide Regulation, Annual (1999-2004) Pesticide Use Reports for El Dorado County, accessed on line at <http://www.cdpr.ca.gov/docs/pur/purmain.htm> on August 30, 2006(updated7/31/2008).

Additional sources of exposure on National Forest Lands – Past use on the Eldorado National Forest (1999-2005) of glyphosate, hexazinone, triclopyr, and clopyralid are displayed in Table D-9, below. Chlorsulfuron hasn't been used on the Eldorado National Forest. R-11 surfactant is assumed to have been used in all glyphosate and clopyralid applications. There is the potential for exposure from projects on the Eldorado National Forest involving the herbicides proposed for use on this project. They include the Yellow Starthistle Control Project (clopyralid and glyphosate), Spotted Knapweed Control Project (glyphosate), PG and E/SMUD Transmission line (clopyralid), Star Fire Reforestation Project (glyphosate), 2004 Vegetation Management in Conifer Plantations (glyphosate, clopyralid, and

hexazinone) and Bosworth Forest Health project (glyphosate and triclopyr). This project would add an estimated maximum of 33,000 lbs (AI) of glyphosate, 280 lbs (AI) of hexazinone and 25 lbs (AI) of clopyralid, 240 lbs (AI) triclopyr, and < 1 lb. of chlorsulfuron over the life of the project. We assume that there would not be any extensive changes in these use patterns into the near future, with the following exception. Use of glyphosate and triclopyr on NFS land may increase over 1999-2005 levels for due to its possible use for reforestation on the Power Fire and the Big Grizzly Fuel Reduction Project.

**Table D-9 – Herbicide Use (lbs active ingredient) Eldorado National Forest (1999-2005)**

Year	Clopyralid	Glyphosate	Triclopyr	Hexazinone
1999	0	8,017	0	122
2000	0	3,315	395	180
2001	1	2,979	0	0
2002	46	940	612	0
2003	11	770	31	0
2004	27	4,978	0	0
2005	13	2,370	27	0

Eldorado National Forest includes portions of Alpine, Amador, El Dorado, and Placer Counties.

It is conceivable that workers or members of the public could be exposed to herbicides as a result of treatments on surrounding private forestlands or treatments on National Forest System Lands. Glyphosate and hexazinone have been used on Sierra Pacific Industries land (Barr, 2009). Where individuals could be exposed by more than one route, the risk of such cases can be quantitatively characterized by adding the hazard quotients for each exposure scenario. For example, using glyphosate as an example, the typical levels of exposure for a woman being directly sprayed on the lower legs, staying in contact with contaminated vegetation, eating contaminated fruit, and consuming contaminated fish leads to a combined hazard quotient of 0.04. Similarly, for all of the chronic glyphosate exposure scenarios, the addition of all possible pathways lead to hazard quotients that are substantially less than one. Similar scenarios can be developed with the other herbicides. This risk assessment specifically considers the effect of repeated exposure in that the chronic RfD is used as an index of acceptable exposure. Consequently, repeated exposure to levels below the toxic threshold should not be associated with cumulative toxic effects.

Since these herbicides persist in the environment for a relatively short time (generally less than 1 year), do not bio-accumulate, and are rapidly eliminated from the body, additive doses from re-treatments in subsequent years are not anticipated. According to recent work completed by the California Department of Pesticide Regulation, some plant material contained hexazinone residues for up to 2.5 years after treatment, triclopyr residues up to 1.5 years after treatment, and glyphosate up to 66 weeks after treatment; however, these levels were less than 1 part per million (Segawa et al. 2001). Since repeat treatments in this project are at one or more years into the future, it is likely that any residue from an application would be substantially degraded between applications. It is possible that residues from the initial herbicide application could still be detectable during subsequent re-treatments, but these plants would represent a low risk to humans as they would show obvious signs of herbicide effects as so would be undesirable for collection.

The information in Table D-8 indicates that these herbicides are also used outside of forestlands in El Dorado County. In order to consider the cumulative effects of these other uses, U.S. EPA has developed the theoretical maximum residue contribution (TMRC). The TMRC is an estimate of maximum daily exposure to chemical residues that a member of the general public could be exposed to from all published and pending uses of a pesticide on a food crop. Adding the TMRC to this project’s dose estimate can be used as an estimate of the cumulative effects of this project with theoretical background exposure levels of these herbicides. The result of doing this doesn’t increase the HQ values appreciably.

Herbicide	TMRC (mg/kg/day)	% of RfD	Data Source
Chlorsulfuron	0.00386	19.3	US EPA 2002f
Clopyralid	0.00903	6.0	US EPA 1999
Glyphosate	0.02996	1.5	US EPA 2000a
Hexazinone	0.0035	7.0	US EPA 1994
Triclopyr	0.00105	2.1	US EPA 2002a

Cumulative effects can be caused by the interaction of different chemicals with a common metabolite or a common toxic action. With the exception of triclopyr and chlorpyrifos discussed below, none of the other herbicides have been demonstrated to share a common metabolite with other pesticides. Although concern has been expressed about a possible link between the toxic effects of other triazine herbicides, such as atrazine, and the herbicide hexazinone, no studies on hexazinone have supported such a link. These two herbicides, while having some commonality in chemical structure, are dissimilar enough chemically that common toxic action is not expected.

As previously stated, the primary metabolite of triclopyr is TCP. TCP is also the primary metabolite of an insecticide called chlorpyrifos. U.S. EPA (1998, 2002a) considered exposures to TCP from both triclopyr and chlorpyrifos in their general dietary and drinking water exposure assessments. In the RED on triclopyr (U.S. EPA 1998) the provisional chronic RfD for TCP is 0.03 mg/kg/day, about the same as the 0.05 mg/kg/day for triclopyr. For acute exposures in this risk assessment, the corresponding values are 1 mg/kg/day for triclopyr and 0.25 mg/kg/day for TCP. The U.S. EPA estimated dietary exposures at the upper 99.5% level for a young woman – i.e., the most sensitive population in terms of potential reproductive effects, the endpoint of greatest concern for triclopyr. The upper range of acute exposure to triclopyr was estimated at 0.012 mg/kg/day and the upper range of exposure to chlorpyrifos was estimated at 0.016 mg/kg/day. Thus, making the assumption that both triclopyr and chlorpyrifos are totally converted to TCP, the total exposure is about 0.028 mg/kg/day, a factor of 8.9 below the level of concern. For chronic exposures, the U.S. EPA based the risk assessment on infants – i.e., individuals at the start of a lifetime exposure. The dietary analysis indicated that the total exposure expressed as a fraction of the RfD was 0.044 for TCP from triclopyr and 0.091 for TCP from chlorpyrifos for a total of 0.135 or a factor of about 7.4 below the level of concern [ $1 \div 0.135 = 7.4$ ]. Based on this assessment, the U.S. EPA (1998) concluded that:

*...the existing uses of triclopyr and chlorpyrifos are unlikely to result in acute or chronic dietary risks from TCP. Based on limited available data and modeling estimates, with less certainty, the Agency concludes that existing uses of triclopyr and chlorpyrifos are unlikely to result in acute or chronic drinking water risks from TCP. Acute and chronic aggregate risks of concern are also unlikely to result from existing uses of triclopyr and chlorpyrifos. – U.S. EPA (1998, p. 34).*

This conclusion, however, is based primarily on the agricultural uses of triclopyr – i.e., estimated dietary residues – and does not specifically address potential exposures from forestry applications. In forestry applications, the primary concern would be the formation of TCP as a soil metabolite. TCP is more persistent than triclopyr in soil and TCP is relatively mobile in soil (U.S. EPA 1998) and could contaminate bodies of water near the site of application. In order to assess the potential risks of TCP formed from the use of triclopyr, the TCP metabolite was modeled in the SERA risk assessment (SERA 2003b) along with triclopyr. The results for TCP are summarized in SERA (2003b) Table 3-10 for a small stream and Table 3-11 for a small pond.

There is very little monitoring data with which to assess the plausibility of the modeling for TCP. As discussed by U.S. EPA (1998, p. 65), TCP is seldom detected in surface water after applications of triclopyr that result in triclopyr concentrations of up to about 25µg/L, with a limit of detection (LOD) for TCP of 10 µg/L. Thompson et al. (1991, as referenced in SERA 2003b) examined the formation of TCP from triclopyr in a forest stream. Consistent with the results reported by U.S. EPA, these investigators failed to detect TCP (LOD=50 µg/L) in stream water with concentrations of triclopyr up to 140 µg/L. This is at least consistent with the GLEAMS modeling of both triclopyr and TCP. As indicated in SERA (2003b), the maximum modeled concentrations of triclopyr in stream water range from about 161 to 428 µg/L (for sandy and clay soils respectively) and the corresponding maximum modeled concentration of TCP in stream water range from about 5 to 11 µg/L. Thus, given the LOD of 50 µg/L in the study by Thompson et al. (1991, as referenced in SERA 2003b), the failure to find TCP in stream water is consistent with the GLEAMS modeling.

While triclopyr and chlorpyrifos would not be commonly applied together in forestry applications, at least one formulation of chlorpyrifos, Nufos 4E, is labeled for forestry applications and may be applied at a rate of 1 lb/acre for the control of insect pests in tree nurseries and plantations. In order to assess potential exposures to TCP from the application of both triclopyr and chlorpyrifos at the same site, GLEAMS was used to model the application of chlorpyrifos at 1 lb per acre under the same conditions used for triclopyr (SERA 2003b). It should be noted that the maximum concentrations for TCP in water do not necessarily reflect simultaneous application of triclopyr and chlorpyrifos. Because triclopyr and chlorpyrifos degrade at different rates, maximum concentration in soil, and hence maximum runoff to water, will occur at different times. Thus, in order to provide the most conservative estimate of exposure to TCP, the maximum concentrations reflect applications of triclopyr and chlorpyrifos spaced in such a way as to result in the maximum possible concentrations of TCP in water. As modeled, concentrations of TCP in a small stream could reach up to 11 ppb from the use of triclopyr at a rate of 1 lb/acre and up to 68 ppb in a small stream from the use of triclopyr at a rate of 1 lb/acre and chlorpyrifos at a rate of 1 lb/acre.

The current RfD for TCP used by U.S. EPA (2002a) is 0.012 mg/kg/day for chronic exposure and 0.025 mg/kg/day for acute exposure. The child is the most exposed individual, consuming 1L of water per day at a body weight of 10 kg. Thus, based on the chronic RfD of 0.012 mg/kg/day, the associated concentration in water would be 0.12 mg/L or ppm [ $0.012 \text{ mg/kg/day} \times 10 \text{ kg/1 L/day}$ ] which is in turn equivalent to 120 ppb. Since the peak exposure to TCP in water is below the concentration associated with the chronic RfD, there is no basis for asserting that the use of triclopyr with or without the use of chlorpyrifos will result in hazardous exposures of humans to TCP.

Recent studies have shown drift of chlorpyrifos, and other insecticides, from agricultural lands in the Sacramento/San Joaquin Valley to the Sierra Nevada range (McConnell et al. 1998). In El Dorado County, chlorpyrifos use in 2004 totaled 181 pounds, primarily used in wine grapes, landscape maintenance, and structural pest control. Levels of chlorpyrifos have been measured in watercourses in the Sierra Nevada as high as 13 ng/L (0.013 µg/L or ppb). These upper levels have been measured in the southern Sierra. As a comparison, the use of chlorpyrifos in Fresno County was over 291,000 pounds, 1,600 times higher in 2004 than El Dorado County. This would indicate that it is unlikely that such high aquatic levels of chlorpyrifos would be found in the Eldorado National Forest area as a result of atmospheric movement. Assuming that 100% of measured chlorpyrifos would degrade to TCP (an over-exaggeration of the rate of degradation), this would add 0.013 ppb of TCP. If this amount is added to the modeled peak exposure of 68 ppb, it would not result in any appreciable increase in risk.

Estrogenic effects (a common toxic action) can be caused by additive amounts of NP, NPE, and their breakdown products. In other words, an effect could arise from the additive dose of a number of different xenoestrogens, none of which individually have high enough concentrations to cause effects (USDA 2003a). This can also extend out to other xenoestrogens that biologically react the same. Additive effects, rather than synergistic effects, are expected from combinations of these various estrogenic substances.

Other sources of exposure to NP and NPEs include personal care products (skin moisturizers, makeup, deodorants, perfumes, spermicides), detergents and soaps, foods, and from the environment away from the forest herbicide application site. In Environment Canada 2001 (as referenced in USDA, 2003a), the authors made estimates of these background exposures assuming a 100 percent dermal absorption rate of NP and NPs. This assumption was based on the inadequacy of the one *in vitro* study of absorption in human skin that showed absorption rates below 1%. Based on a review of the literature on surfactants and absorption (USDA, 2002) it would appear that a 100% figure is extremely conservative. The use of a 1% absorption rate would appear to be a realistic figure; the 100% figure should be considered a worst-case figure.

Contributions from the air, water, soil, and food of NP and NPEs in adult Canadians was estimated at 0.034 mg/kg/day (Environment Canada 2001, as referenced in USDA, 2003a). The contribution of NP and NPEs from the exposure to skin moisturizers, makeup, deodorant, fragrances, detergents, cleaners, paints, and spermicides are also estimated in Environment Canada (2001, as referenced in USDA, 2003a). Both of these exposure sources are based on very small sample sizes and should be considered worst-case. Using the skin absorption figure of 100%, and the highest concentration estimates, these products contribute up to 27.0 mg/kg/day, assuming each is used every day. If a 1% dermal absorption figure is used, this total would be 0.27 mg/kg/day. In another study from Europe, the daily human exposure to NP is estimated at 0.002 mg/kg/day (2 µg/kg/day) as a worst-case assumption (note that this estimate does not include the ethoxylates) (Bolt 2001, as referenced in USDA, 2003b).

In addition to xenoestrogens, humans are exposed to various phytoestrogens, which are hormone-mimicking substances naturally present in plants. In all, more than 300 species of plants in more than 16 families are known to contain estrogenic substances, including beets, soybeans, rye grass, wheat, alfalfa, clover, apples, and cherries. Background exposures of Europeans to natural phytoestrogens (isoflavones (daidzein, genistein) and lignans), mainly from soybeans and flaxseed, is estimated at 4.5-8 mg/kg body weight for infants on soy-based formulae, and up to 1 mg/kg body weight for adults (USDA, 2003a). In East Asian populations where soy-based foods are more commonly consumed, estimates of intake of phytoestrogens are in the range of 50-100 mg/kg/day (*ibid*). Some might consider that the contribution from these natural phytoestrogens should be disregarded, as the human species has adapted over time to daily exposures to such compounds. However, at a biochemical level, these phytoestrogens can react similarly to the estrogenic xenoestrogens, such as NP.

From Section 2, based on the studies by Chapin et al. and Nagao et al., the lowest reproductive NOAEL for NP is 10 mg/kg/day from these studies in rats. Assuming a 100X safety factor to convert to a human reproductive NOAEL would result in a value of 0.10 mg/kg/day. Adding together the contributions from the worst-case background environment and consumer products, as described in Environment Canada 2001, there would be a background dose to a female worker of 27.034 mg/kg/day (assuming 100% dermal absorption) or 0.304 mg/kg/day (assuming 1% dermal absorption). Using a derived NP human NOEL of 0.10 mg/kg/day (as described in USDA, 2003b) these exposure estimates result in hazard quotients of 270 to 3. In terms of this risk assessment, the non-acute contribution of NP9E (backpack workers exposure ranged from 0.01 to 0.07 mg/kg/day) would contribute up to 0.7 to any hazard quotient. At typical application rates, the worker exposure would add 0.1 to the HQ. For the public chronic exposures at the upper range of application, the doses of NP9E would add 0.00002 to 0.06 to any HQ. These may be negligible depending upon the background exposures, lifestyles, absorption rates, and other potential chemical exposures that are used to determine overall risk to environmental xenoestrogens.

## **Inert Ingredients, Additives, Synergistic Effects, and Sensitive Individuals**

### **Inert Ingredients**

The issue concerning inert ingredients, additives, and the toxicity of formulations is discussed in USDA 1989 (pages 4-116 to 4-119). The approach used in USDA, 1989, the SERA Risk Assessments, and this site-specific analysis to assess the human health effects of inert ingredients and full formulations has been to: (1) compare acute toxicity data between the formulated products (including inert ingredients) and their active ingredients alone; (2) disclose whether or not the formulated products have undergone chronic toxicity testing; and (3) identify, with the help of EPA and the chemical companies, ingredients of known toxicological concern in the formulated products and assess the risks of those ingredients.

Researchers have studied the relationships between acute and chronic toxicity and while the biological end-points are different, relationships do exist and acute toxicity data can be used to give an indication of overall toxicity (Zeise, et al., 1984). The court in NCAP v. Lyng, 844 F.2d 598 (9th Cir 1988) decided that this method of analysis provided sufficient information for a decisionmaker to make a reasoned decision. In SRCC v. Robertson, Civ.No. S-91-217 (E.D. Cal., June 12, 1992), and again in CATS v. Dombeck, Civ. S-00-2016 (E.D. Cal., Aug 31, 2001), the district court upheld the adequacy of the methodology used in USDA 1989 for disclosure of inert ingredients and additives.

The EPA has categorized approximately 1200 inert ingredients into four lists. Lists 1 and 2 contain inert ingredients of toxicological concern (USDA 1989, 4-116). List 3 includes substances for which EPA has insufficient information to classify as either hazardous (List 1 and 2) or non-toxic (List 4). List 4 contains non-toxic substances such as corn oil, honey and water. Use of formulations containing inert ingredients on List 3 and 4 is preferred on vegetation management projects under current Forest Service policy.

Since most information about inert ingredients is classified as "Confidential Business Information" the Forest Service asked EPA to review thirteen herbicides for the preparation of USDA, 1989 (includes glyphosate, triclopyr, and hexazinone) and the commercial formulations and advise if they contain inert ingredients of toxicological concern (Inerts List 1 or 2)(USDA, 1989, Appendix F, Attachment B). The U.S. EPA determined that there were no inerts on List 1 or 2, with the exception of kerosene in certain formulations triclopyr. Kerosene has since been moved to List 3. In addition, the CBI files were reviewed in the development of most of the SERA risk assessments. Information has also been received from the companies who produce the herbicides and spray additives.

Butoxyethanol (or EGBE) has been assessed for human health risk as an impurity in the Garlon 4 formulation of triclopyr (Borrecco and Neiss, 1991). In that risk assessment, the addition of butoxyethanol did not substantially increase the risk to human health over the risk of using the active ingredient of triclopyr. The amount of butoxyethanol in Garlon 4 is listed as 0.3% in that assessment.

Comparison of acute toxicity (LD<sub>50</sub> values) data between the formulated products (including inert ingredients) and their active ingredients alone shows that the formulated products are generally less toxic than their active ingredients (USDA 1989, USDA, 1984, SERA risk assessments).

While these formulated products have not undergone chronic toxicity testing like their active ingredients, the acute toxicity comparisons, the EPA review, and our examination of toxicity information on the inert ingredients in each product leads us to conclude that the inert ingredients in these formulations do not

significantly increase the risk to human health and safety over the risks identified for the active ingredients.

## **Adjuvants**

The use of the NPE-based surfactants (such as R-11) is analyzed in this risk assessment, and its use under typical conditions should result in acceptable levels of risk to workers and the public. As with the herbicides, eye and skin irritation may be the only manifestations of exposure seen in the absence of spills and accidents. The exposure to ethylene oxide as a contaminant of NPE-based surfactants should also be at acceptable levels of risk.

### **Colorfast® Purple Colorant (SERA, 1997b)**

The active ingredients in Colorfast Purple are acetic acid, dipropylene glycol, and Basic Violet 3. The exact amounts of the ingredients in this product are considered proprietary. Acetic acid, a major component of vinegar, is on the EPA's list 4A of inerts. Dipropylene glycol is on EPA's list 3 of inerts. None of the ingredients in this product are known to be on EPA List 1 or 2. Basic Violet 3 dye is the colorant in Colorfast Purple. Most of the information about its toxicological effects are attributed to the chloride salt, commonly referred to as Gentian Violet. Gentian Violet is used as an antifungal agent, a treatment for oral infections, and as laboratory reagent and stain (SERA, 1997b). Based on the MSDS no toxic chemicals are present that are subject to the reporting requirement of the Emergency Planning and Community Right-to-Know Act (EPCRA, also referred to as SARA Title III) and 40 CFR 372 (Toxic Chemical Release Reporting: Community Right-to-Know). In a Study by Littlefield et al (in SERA, 1997b) marked carcinogenic activity was observed in mice, and is the basis for a qualitative cancer risk assessment in SERA (1997b). Based on SERA, 1997b, risk characterization leads to typical cancer risks for workers of  $4.7 \times 10^{-7}$  or 1 in 2.1 million. For the public, the consumption of sprayed berries yielded an estimated single exposure risk of 1 in 37 million to 1 in 294 million. For public exposures, it is expected that the dye would reduce exposures both to itself and to the other chemicals it might be mixed with (herbicide and other adjuvants) as the public would be alerted to the presence of treated vegetation.

### **Hi-Light® Blue (USDA, 2007)**

Hi-Light® Blue dye is not required to be registered as a pesticide; therefore it has no signal word associated with it. It is mildly irritating to the skin and eyes. It would likely be considered a Category III or IV material and have a Caution signal word if it carried one.

Hi-Light® Blue is a water-soluble dye that contains no listed hazardous substances. It is considered to be virtually non-toxic to humans. The dye used in Hi-Light® Blue is commonly used in toilet bowl cleaners and as a colorant for lakes and ponds (SERA 1997b).

### **MSO and Silicone/MSO blend surfactant (USDA, 2007)**

Surfactants consisting of vegetable oil and a blend of silicone-based surfactant and vegetable oil are proposed for use. A brief discussion of silicone-based and oil-based surfactants is below. An analysis of the ingredients in these adjuvants did not identify any of specific toxic concern with the exception of the ingredients discussed in this risk assessment (ibid). None were on U.S. EPA Inerts Lists 1 or 2.

The primary summary statement that can be made is that the more common risk factors for the use of these adjuvants are through skin or eye exposure. These adjuvants all have various levels of irritancy associated with skin or eye exposure. This points up the need for good industrial hygiene practices while utilizing these products, especially when handling the concentrate, such as during mixing. The use of chemical resistant gloves and goggles, especially while mixing, should be observed.

### Silicone-Based Surfactants

Also known as organosilicones, these are increasing in popularity because of their superior spreading ability. This class contains a polysiloxane chain. Some of these are a blend of non-ionic surfactants (NIS) and silicone while others are entirely silicone. The combination of NIS and a silicone surfactant can increase absorption into a plant so that the time between application and rainfall can be shortened. This is known as rainfastness. The surfactants extreme spreading ability may lead to droplet coalescence and subsequent runoff if applied at inappropriately high rates.

Based on a review of the current research, it would appear that surfactants have the potential to affect terrestrial insects. However, as is true with many toxicity issues, it would appear that any effect is dose related. The research does indicate that the silicone-based surfactants, because of their very effective spreading ability, may represent a risk of lethality through the physical effect of drowning, rather than through any toxicological effects. Silicone surfactants are typically used at relatively low rates and are not applied at high spray volumes because they are very effective surfactants. Hence it is unlikely that insects would be exposed to rates of application that could cause the effects noted in these studies. Other surfactants, which are less effective at reducing surface tension, can also cause the drowning effect. But as with the silicones, exposures have to be high, to the point of being unrealistically high, for such effects.

### Vegetable Oils

The methylated seed oils are formed from common seed oils, such as canola, soybean, or cotton. They act to increase penetration of the herbicide. These are comparable in performance to crop oil concentrates. In addition, silicone-seed oil blends are also available that take advantage of the spreading ability of the silicones and the penetrating characteristics of the seed oils.

The U.S. Food and Drug Administration (FDA) considers methyl and ethyl esters of fatty acids produced from edible fats and oils to be food grade additives (CFR 172.225). Because of the lack of exact ingredient statements on these surfactants, it is not always clear whether the oils that are used in them meet the U.S. FDA standard.

## Synergistic Effects

Synergistic effects (multiplicative) are those effects resulting from exposure to a combination of two or more chemicals that are greater than the sum of the effects of each chemical alone (additive). See pages 4-111 through 4-114 in USDA 1989, for a detailed discussion on synergistic effects.

Instances of chemical combinations that cause synergistic effects are relatively rare at environmental exposure levels. Reviews of the scientific literature on toxicological effects and toxicological interactions of agricultural chemicals indicate that exposure to a mixture of pesticides is more likely to lead to additive rather than synergistic effects (US EPA 2000c; ATSDR 2004; Kociba and Mullison 1985). The literature review by ATSDR (2004) cited several studies that found no synergistic effects for mixtures of four, eight, and nine chemicals at low (sub-toxic) doses. In assessing health risk associated with drinking water, Crouch et al. (1983) reach a similar conclusion when they stated:

"...in most cases we are concerned with small doses of one pollutant added to a sea of many pollutants. For those small doses a multiplicative effect is not expected."

EPA (1986) concludes:

"There seems to be a consensus that for public health concerns regarding causative (toxic) agents, the additive model is more appropriate than any multiplicative model."

Synergism generally has not been observed in toxicological tests involving combinations of commercial pesticides. The herbicide and additives proposed for this project have not shown synergistic effects in humans who have used them extensively in forestry and other agricultural applications. However, synergistic toxic effects of herbicide combinations, combinations of the herbicides with other pesticides such as insecticides or fertilizers, or combinations with naturally occurring chemicals in the environment are not normally studied. Based on the limited data available on pesticide combinations involving these herbicides, it is possible, but unlikely, that synergistic effects could occur as a result of exposure to the herbicides considered in this analysis.

It is not anticipated that synergistic effects would be seen with the herbicides and the adjuvants that might be added to them. Based on a review of several recent studies, there is no demonstrated synergistic relationship between herbicides and surfactants (Abdelghani et al 1997; Henry et al 1994; Lewis 1992; Oakes and Pollak 1999, 2000 as referenced in USDA 2002). Synergistic effects are not expected from multiple exposures to NP, NPEs, and their breakdown products (Payne et al 2000, Environment Canada 2001, as referenced in USDA 2003b).

However, even if synergistic or additive effects were to occur as a result of the proposed treatment, these effects are dose responsive (Dost 1991). This means that exposures to the herbicide plus any other chemical must be significant for these types of effects to be of a biological consequence. As Dost explains:

"While there is little specific published study of forestry herbicides in this particular regard, there is a large body of research on medical drugs, from which principles arise that govern such interactions. Amplifications of effect are not massive; one chemical cannot change the impact of another by hundreds or thousands of times. Rarely will such change be more than a few fold. This difference can be dangerous when dealing with drugs that are already at levels intended to significantly alter bodily functions, but is insignificant when both compounds are at the very low levels of exposure to be found associated with an herbicide treatment."

Based on the very low exposure rates estimated for this alternative, synergistic or additive effects, if any, are expected to be insignificant.

Although the combination of surfactant and herbicide might indicate an increased rate of absorption through the skin, a review of recent studies indicates this is not often true (Ashton et al 1986; Boman et al 1989; Chowan and Pritchard 1978; Dalvi and Zatz 1981; Eagle et al 1992; Sarpotdar and Zatz 1986; Walters et al 1993, 1998; Whitworth and Carter 1969 as referenced in USDA 2002). For a surfactant to increase the absorption of another compound, the surfactant must affect the upper layer of the skin. Without some physical effect to the skin, there will be no change in absorption as compared to the other compound alone. The studies indicate that in general non-ionic surfactants have less of an effect on the skin, and hence absorption, than anionic or cationic surfactants. Compound specific studies indicate that the alkylphenol ethoxylates generally have little or no effect on absorption of other compounds. In several studies, the addition of a surfactant actually decreased the absorption through the skin. It would appear that there is little support for the contention that the addition of surfactants to herbicide mixtures would increase the absorption through the skin.

#### Herbicide-Specific Interaction Data

The manufacturers recommend that chlorsulfuron formulations be mixed with a non-ionic surfactant. There is no published literature or information in the US EPA files that would permit an assessment of toxicological effects or risk assessment of chlorsulfuron mixed with a surfactant (SERA, 2004a).

Clopyralid may be applied in combination with other herbicides, particularly in combination with picloram. There are no data in the literature suggesting that clopyralid will interact, either synergistically or antagonistically with this or other compounds (SERA, 1999).

There is very little information available on the interaction of glyphosate with other compounds. The available data do not suggest a synergistic interaction between glyphosate and the POEA surfactant found in some formulations (e.g., Roundup) from plausible routes of exposure (SERA 1996a).

There is very little information available on the interaction of triclopyr with other compounds. The available data do not suggest a synergistic interaction between the triclopyr active ingredient and the other components in the commercial triclopyr formulations of Garlon 4 (SERA 1996b).

There is very little information available on the interaction of hexazinone with other compounds. The available data suggest that hexazinone may be metabolized by and may induce cytochrome P-450 (SERA 1997a). This is a very important enzyme in the metabolism of many endogenous as well as xenobiotic compounds. Thus, it is plausible that the toxicity of hexazinone may be affected by and could affect the toxicity of many other agents. The nature of the potential effect (i.e., synergistic or antagonistic) would depend on the specific compound and perhaps the sequence of exposure.

## **Sensitive Individuals**

The uncertainty factors used in the development of the RfD takes into account much of the variation in human response. The uncertainty factor of 10 for sensitive subgroups is sufficient to ensure that most people will experience no toxic effects. "Sensitive" individuals are those that might respond to a lower dose than average, which includes women and children. The National Academy of Sciences report entitled Pesticides in the Diets of Infants and Children (NAS 1993) found that quantitative differences in toxicity between children and adults are usually less than a factor of approximately 10-fold. An uncertainty factor of 10 may not cover individuals that may be sensitive to herbicides because human susceptibility to toxic substances can vary by two to three orders of magnitude. Factors affecting individual susceptibility include diet, age, heredity, preexisting diseases, and life style. Individual susceptibility to the herbicides proposed in this project cannot be specifically predicted. Unusually sensitive individuals may experience effects even when the HQ is equal or less than 1. Further information concerning risks to sensitive individuals can be found on pages 4-114 through 4-116 in USDA, 1989.

There is no information to suggest that specific groups or individuals may be especially sensitive to the systemic effects of chlorsulfuron. Due to the lack of data in humans, the likely critical effect of chlorsulfuron in humans cannot be identified clearly. In animals the most sensitive effect of chlorsulfuron appears to be weight loss. There is also some evidence that chlorsulfuron may produce alterations in hematological parameters. However, it is unclear if individuals with pre-existing diseases of the hematological system or metabolic disorders would be particularly sensitive to chlorsulfuron exposure. Individuals with any severe disease condition could be considered more sensitive to many toxic agents.

The 1996 Food Quality Protection Act requires that U.S. EPA evaluate an additional 10X safety factor, based on data uncertainty or risks to certain age/sex groupings. U.S. EPA has evaluated chlorsulfuron against this standard and has recommended a 3X additional safety factor be used for the protection of infants and children. This additional 3X safety factor is factored into the acute and chronic RfD's of this risk assessment as it applies to chlorsulfuron.

The likely critical effect of clopyralid in humans cannot be identified clearly (SERA 2004b). Clopyralid can cause decreased body weight, increases in kidney and liver weight, decreased red blood cell counts, as well as hyperplasia in gastric epithelial tissue (*ibid*). These effects, however, are not consistent among species or even between different studies in the same species (*ibid*). Thus, it is unclear if individuals with pre-existing diseases of the kidney, liver, or blood would be particularly sensitive to clopyralid exposures, although individuals with any severe disease condition could be considered more sensitive to many toxic agents. There are no data or case reports on idiosyncratic responses to clopyralid (*ibid*).

No reports were encountered in the glyphosate literature leading to the identification of sensitive subgroups. There is no indication that glyphosate causes sensitization or allergic responses, which does not eliminate the possibility that some individuals might be sensitive to glyphosate as well as many other chemicals (SERA 2003a).

Because triclopyr may impair glomerular filtration, individuals with pre-existing kidney diseases are likely to be at increased risk (SERA 1996b). Because the chronic RfD for triclopyr is based on reproductive effects, women of child-bearing age are an obvious group at increased risk (SERA 2003b). This group is given explicit consideration and is central to the risk characterization.

Because hexazinone was demonstrated to induce fetal resorptions, pregnant women are an obvious group at increased risk (SERA 2005). This group is given explicit consideration and is central to the risk characterization. There are no other reports in the literature suggesting subgroups that may be sensitive to hexazinone exposure. There is no indication that hexazinone causes sensitization or allergic responses (*ibid*).

NP9E can cause increases in kidney and liver weight, and effects to kidney function and structure. Thus, individuals with pre-existing conditions that involve impairments of the kidney or liver may be more sensitive to this compound. There is some indication that sensitive individuals may develop contact allergies. People with a history of skin allergic reactions to soaps and detergents may be especially sensitive to dermal exposures of NP9E-based surfactants.

The potential of NP9E to induce reproductive effects described in section 2 should be considered low. Based on the available dose/duration/severity data, it appears that exposure levels below those associated with the most sensitive effect (i.e., kidney effects) are not likely to be associated with reproductive toxicity. However, as shown in the exposure scenarios, there is the potential for acute exposures to be in the range (considering a 100X safety factor) where effects to the developing fetus may occur, therefore women of child-bearing age could be considered a sensitive population.

## Worksheets

All worksheets related to the information noted in this document can be found in the Project Record and are hereby incorporated by reference.

## Glossary

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

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

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

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

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

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

**Ataxia** -- inability to coordinate muscle activity; loss of balance

**Bioconcentration factor (BCF)** -- The concentration of a compound in an aquatic organism divided by the concentration in the ambient water of the organism.

**Cancer potency parameter** -- A model-dependent measure of cancer potency  $(\text{mg/kg/day})^{-1}$  over lifetime exposure. [Often expressed as  $a_{q1}$  \* which is the upper 95% confidence limit of the first dose coefficient ( $q_1$ ) from the multistage model.]

**Carcinogen** -- A chemical capable of inducing cancer.

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

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

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

**Creatine** -- An organic acid composed of nitrogen. It supplies the energy required for muscle contraction.

**Creatinine** -- The end product of the metabolism of creatine. It is found in muscle and blood and is excreted in the urine.

**Dams** -- A term used to designate females of some species such as rats.

**Degraded** -- Broken down or destroyed.

**Dermal** -- Pertaining to the skin.

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

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

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

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

**Endogenous** -- Growing or developing from or on the inside.

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

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

**Estrogenic** – a substance that induces female hormonal activity.

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

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

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

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

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

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

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

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

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

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

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

**Hematological** -- Pertaining to the blood.

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

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

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

**Humoral** – of, or related to, elements in the blood.

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

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

**Hyperplasia** – An abnormal increase in the number of cells composing a tissue or organ.

**Immunotoxic** – damaging to the immune system.

**In vivo** -- Occurring in the living organism.

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

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

**Intraperitoneal** -- Injection into the abdominal cavity.

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

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

**LC<sub>50</sub> (lethal concentration<sub>50</sub>)** -- A calculated concentration of a chemical in air or water to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

**LD<sub>50</sub> (lethal dose<sub>50</sub>)** -- The dose of a chemical calculated to cause death in 50% of a defined experimental animal population over a specified observation period. The observation period is typically 14 days.

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

**Lymphatic** -- Pertaining to lymph, a lymph vessel, or a lymph node.

**Lymph** -- A clear water fluid containing white blood cells. Lymph circulates throughout the lymphatic system, removing bacteria and certain proteins from body tissue. It also is responsible for transporting fat from the small intestine and supplying mature lymphocytes to the blood.

**Lymphocyte** -- white blood cell involved in immune system.

**Malignant** -- Cancerous.

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

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

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

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

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

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

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

**No-observed-effect level (NOEL)** -- The dose of a chemical at which no treatment-related effects were observed.

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

**Octanol-water partition coefficient ( $K_{ow}$ )** -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

**Ocular** -- Pertaining to the eye.

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

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

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

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

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

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

**Pup** -- The offspring or young of various animal species.

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

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

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

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

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

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

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

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

**Sensitization** -- A condition in which one is or becomes hypersensitive or reactive to an agent through repeated exposure.

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

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

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

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

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

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

**Terrestrial** -- Anything that lives on land as opposed to living in an aquatic environment.

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

**Thymus** -- A small gland that is the site of T-cell production. The gland is composed largely of lymphatic tissue and is situated behind the breastbone. The gland plays an important role in the human immune system.

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

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

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

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

**Xenobiotic** -- A substance not naturally produced within an organism; substances foreign to an organism.

**Xenoestrogen** -- An estrogen not naturally produced within an organism.

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