Appendix F:

Human Risk Assessment

Appendix F: Human Health Risk Assessment Table of Contents

Appendix F: Human Health Risk Assessment Table of Contents 1
Section 1 - Introduction 3
Section 2 - Hazard Analysis 5
Chlorsulfuron (Reference: SERA, 2004a) 6
Clopyralid (Reference: SERA, 1999, 2004b) 9
2,4-D (References: USDA 1984; USDA 1989; SERA 1998a; U.S. EPA 2000c, 2004a, 2005) 14
Dicamba (References: USDA 1984; USDA 1989; SERA 2004c) 21
Glyphosate (References: USDA, 1984; USDA, 1989; SERA, 2003a) 25
Triclopyr (References: USDA, 1984; USDA, 1989; SERA 2002, 2003b; U.S. EPA, 1998b) 33
Nonylphenol Polyethoxylate (References: USDA, 2003a) 40
Section 3 – Exposure Assessment 49
Workers 49
General Public 56
Section 4 – Dose Response Assessment 63
Chlorsulfuron 63
Clopyralid 64
2,4-D 65
Dicamba 67
Glyphosate 69
Triclopyr 70
Nonylphenol Polyethoxylate 73
Hexachlorobenzene 74
Section 5 - Risk Characterization 75
Chlorsulfuron 75
Clopyralid 78
2,4-D 80
Dicamba 82
Glyphosate 84
Triclopyr 87
Nonylphenol Polyethoxylate 90
Hexachlorobenzene 92
Cumulative Effects 95
Inert Ingredients 103
Adjuvants 105
Silicone-Based Surfactants 106
Oils 106
Synergistic Effects 107
Herbicide-Specific Interaction Data 109
Sensitive Individuals 110
Worksheets 113

Appendix F: Human Health Risk Assessment

Section 1 - Introduction

The purpose of this analysis is to assess the risks to human health of using six different herbicides for the control and eradication of noxious weeds on the Modoc National Forest. The herbicide active ingredients assessed are chlorsulfuron, clopyralid, 2,4-D, dicamba, glyphosate, and triclopyr. For a description of uses and formulations, refer to Appendix E – Herbicide Descriptions.

This risk assessment examines the potential health effects on all groups of people who might be exposed to any of the six herbicides that might potentially be used in treating noxious weeds on the Modoc National Forest. 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 forests, 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 of risk assessment generally accepted by the scientific community (National Research Council 1983, U.S. EPA 1986). In essence, this pesticide risk assessment consists of comparing doses that people may get from applying the pesticides (worker doses) or from being near an application site (public doses) with the U.S. Environmental Protection Agency's (U.S. EPA) established Reference Doses (RfD), a level of exposure considered protective of lifetime or chronic exposures.

Details regarding the specific methods used to prepare the Syracuse Environmental Research Associates, Inc. (SERA) human health risk assessments referenced are documented in SERA (2000b), while detailed explanations of specific methods for estimating occupational exposure are provided in SERA (1998b). Basically, 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 an 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 for this EIS, and are based on the worksheets contained in the various SERA risk assessments.

Additives, or adjuvants, to the formulations that might be used when herbicides are applied are not considered in detail in this risk assessment, with the exception of surfactants containing nonylphenol polyethoxylate as an active ingredient. Additives might involve surfactants and colorants. Many of the formulated herbicides require the use of added surfactants; such information is on the herbicide label. Surfactants increase the ability of the herbicide to be absorbed into plant tissues. Colorants are used to indicate that a plant or area has been treated, for several reasons, including avoiding waste of materials by retreating, to allow people to avoid treated areas in short term, and to be more effective by treating all target vegetation.

Section 2 - Hazard Analysis

The hazards associated with using each of the herbicides were determined by a thorough review of available toxicological studies. These 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, as well as in a risk assessment contained in the programmatic Region 5 Final EIS *Vegetation Management for Reforestation* (USDA 1989) and in the programmatic *Herger Feinstein Quincy Library Group Forest Recovery Act Final SEIS* (USDA 2003b). Another source of information on toxicity is 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 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, sub-chronic, and chronic effects to test animals. Because of the obvious limitations on the testing of chemicals on humans, judgments about the potential hazards of pesticides to humans are 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 F18).

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 EPA defines the term impurity as "…any substance…in a pesticide product other than an active ingredient or an 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 herbicides 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 is assumed to pose some 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, human 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_{50} 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 was 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.

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 is 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_{50}) values in the range of about 3000 mg/kg) than the penta process (LD_{50} > 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_{50} >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, 1999b).

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

No studies specifically mentioning Transline®, 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®. These studies do not indicate any substantial differences between Transline® and clopyralid. This is consistent with the publicly available information on the three inerts contained in Transline®, two of which are approved for use as food additives (monoethanolamine and isopropyl alcohol).

The other inert in Transline® 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) 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.

2,4-D (References: USDA 1984; USDA 1989; SERA 1998a; U.S. EPA 2000c, 2004a, 2005)

Acute and Chronic Exposures - 2,4-D has a low order of acute toxicity to mammals, with oral LD_{50} values ranging from approximately 69 mg a.e./kg (100 mg butyl ester/kg) in cattle to 1800 mg/kg (2000 mg sodium salt/kg) in rats. Although the mode of action of 2,4-D as a plant toxin is well understood, the mode of action of 2,4-D toxicity in mammals is not clear. After acute lethal exposure, the signs of toxicity in humans include convulsions, vomiting, congestion of various organs, and degenerative changes in nerve cells. In non-lethal but toxic oral exposure to 2,4-D, the signs and symptoms of toxicity in humans include irritation to mouth, throat, and gastrointestinal tract, vomiting, chest and abdominal pain, diarrhea, muscle twitches, tenderness, and stiffness. Similar signs of acute toxicity were observed in monkeys and pigs exposed to 2,4-D. With the possible exception of neurotoxicity (see below), none of these signs or symptoms suggests a highly specific mode of toxic action in mammals.

Following subchronic oral exposure at dose levels of 2,4-D above the threshold of saturation for renal clearance, the primary target organs are the eye (retinal degeneration, cataract formation), thyroid (increased thyroid weight, changes in thyroid hormones, and follicular cell enlargement), kidney (loss of absorptive capacity), adrenals (enlargement), and ovaries/testes (decrease in size and weight). These changes are also observed following exposure to the amine salts and esters of 2,4-D. At high concentrations *in vitro*, 2,4-D may affect cellular energy processes and interfere with other enzymes involved in cellular energy, calcium regulation, protein and DNA synthesis, and polyamine synthesis. It is plausible that the target organ specificity of 2,4-D is related to active transport processes in certain organs.

There are no substantial or systematic differences in toxicity between different formulations of 2,4-D (amine or esters), when expressed as acid equivalents. 2,4-D and its amine salts (diethanolamine, dimethylamine, isopropylamine, and triisopropanolamine) and esters (butoxyethyl ester, ethylhexyl ester, and isopropyl ester) are not acutely toxic via the oral route of exposure (Toxicity Category III).

The current chronic RfD listed on U.S. EPA's Integrated Risk Information System (IRIS) for 2,4-D is based on the study by Serota et al (1983b as referenced in SERA 1998a) using Fisher 344

rats. This is the RfD used in SERA 1998a. The RfD was last revised on May 5, 1988. In the subchronic dietary study by Serota et al. (1983b), rats were exposed to daily doses of 1, 5, 15, or 45 mg/kg bw/day 2,4-D for 90 days. The investigators observed dose-related increases in kidney weight (males and females) and thyroid weight (males only) as well as decreases in mean hemoglobin, percentage of red blood cells, red blood cell levels, and immature red blood cells levels (males only). The increase in thyroid weight was associated with an increase in the levels of the thyroid hormone thyroxine in the blood of male rats. In addition, levels of various enzymes associated with liver function were decreased rather than increased. The U.S. EPA considered the dose of 1 mg/kg/day the NOAEL, identifying the critical effects as "hematologic, hepatic, and renal toxicity". Although the RfD record indicates that the effects on the thyroid and thyroid hormone levels were taken into consideration, the record also indicates that these effects "were not considered to be treatment related".

In 2000, the U.S. EPA wrote a toxicology disciplinary chapter as part of the reregistration eligibility decision document for 2,4-D (U.S. EPA 2000c). There is no discussion of the 1983 subchronic study discussed above. In this 2000 document, a proposed chronic RfD is based on a 2-year combined chronic toxicity/carcinogenicity study in rats in which rats were fed 2,4-D acid in the diet at doses of 0, 5, 75, and 150 mg/kg/day. The NOAEL from this study is 5 mg/kg/day. The LOAEL of 75 mg/kg/day is based on decreased body-weight gain (females) and food consumption (females), alterations in hematology (decreased red blood cells (females), hemoglobin (females), platelets (both sexes)) and clinical chemistry parameters (increased creatinine (both sexes), alanine and aspartate aminotransferase (males), alkaline phosphatase (both sexes), decreased thyroid hormones (both sexes), glucose (females), cholesterol (both sexes), and triglycerides (females)), increased thyroid weights (both sexes at study termination), decreased testes and ovarian weights, and microscopic lesions in the lungs (females). At the high-dose level, there were microscopic lesions in the eyes, liver, adipose tissue, and lungs. There was no treatment-related increase in the incidence of any tumor.

There is no strong time-response relationship for 2,4-D. The similarities in doses associated with similar subchronic and chronic effects can be explained, in part, by the pharmacokinetics of 2,4-D. Like other phenoxy-herbicides, such as 2,4,5-T and Silvex, 2,4-D is absorbed rapidly, distributed within the body, bound to endogenous proteins, and rapidly eliminated. Thus, steady-state levels are reached relatively fast and there is little difference with regard to body burdens in subchronic and chronic studies. A point to be made however is that tests using dogs have shown that dogs have a limited capacity to eliminate organic acids, such as 2,4-D and triclopyr. Because of this, toxicity tests

involving dogs may not be representative of human toxic responses because of the longer residence times of 2,4-D in the dog.

Effects on the Skin and Eyes - 2,4-D is an organic acid. Like all organic acids, 2,4-D in aqueous solution can be highly irritating to the eyes and can also cause skin irritation. 2,4-D and its amine salts and esters are not acutely toxic via the dermal routes of exposure. 2,4-D and its amine salts and esters are not skin irritants and none is a skin sensitizer. The acid and amine salt forms of 2,4-D are considered severe eye irritants, but the ester forms are not eye irritants. More unusual, however, is the potential for an effect on the eyes through systemic absorption. In subchronic and chronic feeding studies in rats, degenerative changes in eyes (cataracts, retinal degeneration) were noted in several studies.

Carcinogenicity and Mutagenicity – 2,4-D is classified as a Group D chemical (not classifiable as to human carcinogenicity). Chronic toxicity tests in rats and mice did not indicate any significant increases in tumors. There are many epidemiology studies that examine the association between exposure to 2,4-D (and other phenoxy herbicides) and the development of various forms of cancer. These studies are the subject of several reviews sponsored or prepared by industries associated with the manufacture and/or distribution of 2,4-D as well as a 1996 review sponsored by the USDA.

In 1994, the Science Advisory Board of the U.S. EPA reviewed the agency's analysis of 2,4-D carcinogenicity and concluded that while there is some evidence that cancer may occur in excess in populations which are likely to be exposed to 2,4-D, the data are not sufficient to conclude that there is a cause and effect relationship between the exposure to 2,4-D and cancer.

The U.S. EPA (EPA/OPP Cancer Peer Review Committee) classified 2,4-D as a Category D chemical (i.e., not classifiable as to human carcinogenicity) in 1996. The U.S. EPA requested further histopathological examinations of rat brain tissues and mouse spleen tissues. These exams were submitted and reviewed and in March 1999, the US EPA decided that it would continue to classify 2,4-D as a Group D carcinogen. The U.S. EPA has twice recently reviewed epidemiological studies linking cancer to 2,4-D. In the first review, completed January 14, 2004, U.S. EPA concluded there is no additional evidence that would implicate 2,4-D as a cause of cancer. The second review of available epidemiological studies occurred in response to comments received during the public comment period for the 2,4-D RED. This report, dated December 8, 2004, found that none of the more recent epidemiological studies definitively linked human cancer cases to 2,4-D (US EPA 2005).

Much of the controversy concerning the potential carcinogenicity of 2,4-D involves exposure to Agent Orange, a mixture of 2,4-D, 2,4,5-T, and TCDD (dioxin) used as a herbicide during the

Vietnam war. In the early 1990's, the National Academy of Sciences' Institute of Medicine reviewed the available epidemiology data on the effects of exposure to Agent Orange and concluded "there is limited/suggestive evidence for *no* association between exposure to phenoxy-herbicides and brain tumors". In the current reregistration effort, U.S. EPA is developing another review of the risks of dioxin in 2,4-D and has submitted its findings to the National Academy of Sciences for review.

Reproductive and Teratogenic Effects – At relatively high doses associated with fetotoxicity or maternal toxicity, 2,4-D might induce fetal malformations. Developmental toxicity was observed in the rat, as evidenced by the increased incidence of skeletal malformations and variations observed at the same dose level that resulted in maternal toxicity, indicated by decreased body-weight gain.

One occupational exposure study reports an association between 2,4-D exposure and sperm damage; however, the data in the study do not support the association. At best, the study shows that the incidence of sperm anomalies in a group of pesticide applicators was higher than in a group of individuals who did not apply pesticides. Whether exposure to 2,4-D was the cause of the observed effects cannot be verified by the data presented in the study. Although some animal studies support an association between 2,4-D exposure and male reproductive impairment, reproductive effects seem to be much less sensitive endpoints than the effects on which the RfD derived by U.S. EPA is based.

Other Toxic Endpoints – In experimental animals, 2,4-D exposure is associated with myotonia: the development of tonic muscle spasms in which the muscle remains contracted for a prolonged period. This endpoint may reflect a neurotoxic rather than muscular effect because removing the nerve from the muscle results in a blockage of the myotonic response. Both 2,4-D sodium salt and 2,4-D butyl ester were shown to affect brain levels of neurotransmitters in rats. Rats, however, may be atypically sensitive to the neurotoxic effects of 2,4-D. In all species tested, only rats showed evidence of histopathological changes in the brain. Subchronic exposure to 2,4- D acid was associated with changes in neurological function. Specific nerve damage (destruction of the nerve's myelin sheath) was associated with exposure to the n-butyl ester of 2,4-D but not the amine salt. Clinical signs of neurotoxicity (ataxia, decreased motor activity, inability to relax muscles, prostration, impaired/loss of the righting reflex, and skin cold to the touch) were observed in pregnant rabbits following exposure to 2,4-D and its amine salts and esters. Neuropathology (retinal degeneration) was observed following 2,4-D exposure in several studies in female rats. A lack of coordination and slight gait abnormalities (forepaw flexing or knuckling) were observed following acute dosing and increased forelimb grip strength was observed following chronic exposure to 2,4-D at dose levels that exceeded the threshold of saturation of renal clearance.

There is some evidence that certain forms of 2,4-D may cause immunological effects; however, most of the studies involve exposure to the n-butyl ester of 2,4-D, and it is not clear whether the observed responses are attributable to the 2,4-D part of the molecule or the formation of n-butanol. At acutely toxic levels, the n-butyl ester was shown to inhibit immune function in mice, assayed as antibody production against sheep red blood cells. Subtoxic doses, however, had no effect. Thus, the suppression of antibody production may be secondary to other toxic effects.

2,4-D affects thyroid hormone regulation following oral exposure, and there is a concern for endocrine disruption. Effects on the gonads in rats and dogs are seen following exposure to 2,4-D and/or its amine salts and esters. Although there are data on thyroid hormone levels in the adult animal, there are no data with respect to thyroid hormones in the young; therefore, there is no information on whether the young are more sensitive with respect to this endpoint. There is no developmental neurotoxicity (DNT) study available on 2,4-D, and U.S. EPA has called for a DNT study in the recent reregistration effort. There have been no studies on 2,4-D that specifically assess its endocrine disruption potential, and there are no data on other hormonal effects. As already stated, thyroid effects have been observed in the rat following subchronic and chronic exposure to 2,4-D and its amine salts and esters. Additionally, there is some concern for immunotoxicity following exposure to 2,4-D. There are clear NOAELs for each of the above-mentioned effects, which occur only at high-dose levels; above the doses selected for overall risk assessment. Therefore, there are no residual uncertainties with regard to these effects. However, U.S. EPA concluded that a two-generation reproduction study using current protocols is required to address the concern for thyroid effects (comparative assessment between the young and adult animals) and immunotoxicity, as well as a more thorough assessment of the gonads and reproductive/developmental endpoints. Because of these data gaps, U.S. EPA in its current reregistration documents, calls for an additional 10X safety factor for database uncertainty when developing the acute and chronic RfDs.

Inhalation Exposures – The acute toxicity data indicate that 2,4-D or its amine or ester formulations are not highly acutely toxic via the inhalation route of exposure. The rat LC_{50} value for 2,4-D acid is >1.79 mg/L (Toxicity Category 3) while the ester and amine formulations all exceeded 3.5 mg/L (Toxicity Category 4). Clinical signs of toxicity observed during inhalation exposure were decreased activity and closed eyes. Signs observed at the end of and during the week after inhalation exposure were salivation, tearing from the eyes, nasal discharge, labored breathing, dried red or brown material around eyes and nose, matted fur, and staining of the fur in the anogenital region. There were no significant findings *post mortem*.

Impurities - There is little published information on the impurities in commercial formulations of 2,4-D. Hansen et al. (1971, as referenced in SERA 1998a) reported that a commercial sample of 2,4-D contained low concentrations of monochlorophenoxyacetic acid (0.1%), 2,6-dichlorophenoxyacetic acid (2.3%), 2,4,6-trichlorophenoxyacetic acid (0.2%), and bis(2,4-dichlorophenoxy)-acetic acid (0.7%). Because the toxicity studies on 2,4-D used in SERA 1998 were conducted with technical grade 2,4-D, it is likely that the toxicity of the minor impurities is encompassed by the studies used as the basis for this risk assessment.

One concern regarding the use of 2,4-D is the possibility of contamination with chlorinated dioxins, such as 2,3,7,8-TCDD. Agent Orange, which is a mixture of 2,4-D and 2,4,5-T, was used during the Vietnam War, and it did contain 2,3,7,8-TCDD. Moreover, commercial formulations of 2,4,5-T have been known to contain 2,3,7,8-TCDD. 2,4-D formulations, however, were shown not to contain 2,3,7,8-TCDD. Thus, it appears that 2,3,7,8-TCDD contamination in commercial preparations of herbicides containing 2,4-D is attributable to the contamination of 2,4,5-T with 2,3,7,8-TCDD rather than the presence of 2,3,7,8-TCDD in 2,4-D. As stated, U.S. EPA is currently developing a new review of risks presented by dioxin in 2,4-D.

Some commercial samples of 2,4-D amine have been shown to contain polychlorinated dibenzo-p-dioxins, chiefly di-, tri-, and non-2,3,7,8-tetrachlorinated isomers. Most samples contained <1 µg/L, and the highest concentration of any dioxin in the samples of 2,4-D amine was 0.32 mg/L. All but one of the 2,4-D esters, however, were found to contain dioxin residues, and the levels were much higher, ranging from 0.1 to 23 mg/L.

Metabolites -The metabolism and excretion of 2,4-D have been investigated in a number of species including humans. In general, 2,4-D undergoes limited metabolism primarily involving minor conjugation of the parent acid that is then excreted in the urine. No detectable metabolites of 2,4-D have been reported in the rat; i.e., only the parent acid is found in rat urine. In addition to 2,4-D itself, 2,4-D conjugates have been found in the urine of dogs, humans, mice, and hamsters following oral exposure.

Although 2,4-D does not appear to be metabolized extensively in mammals; the compound degrades in the environment to form the metabolite, 2,4-dichlorophenol. Although 2,4-dichlorophenol was not detected in vegetation or water samples after the application of 2,4-D, it has been detected in aqueous sediments at approximately the same concentrations as 2,4-D. 2,4-Dichlorophenol is a toxic metabolite. The RfD for 2,4-dichlorophenol is 0.003 mg/kg/day based on impaired immunological function. The RfD for 2,4-dichlorophenol is approximately the same as the RfD for 2,4-D that is used in this risk assessment (refer to Section 4). Because there is no indication that workers or the general

public will be exposed to substantial amounts of 2,4-dichlorophenol, the formation of this compound in sediment as part of the environmental degradation process does not contribute substantially to the risks associated with the use of 2,4-D.

Inerts – EPA reviews have not identified any inerts on EPA list 1 or 2 in the 2,4-D amine formulation (Weedar 64). The Weedone 638 label mentions petroleum distillates as being in the formulation. The current material safety data sheet (MSDS) also mentions two inerts: propylene glycol and titanium oxide (both on EPA list 4B). Heavy aromatic naptha ("other petroleum hydrocarbons") was identified in a 1988 letter from the USDA Forest Service Washington office to the Regions as the carrier for Weedone 638. Information from a Rhone-Poulenc 1995 MSDS (as described in NCAP, 2000) lists the following inerts for the Weedone 638 formulation of 2,4-D: methanol (CAS 67-56-1, EPA inert list 3), butoxyethanol (111-76-2, list 2), xylene (1330-20-7, list 2), and naphthalene (91-20-3, list 3).

EPA considers xylene to be a potentially toxic inert ingredient, with an oral RfD of 2 mg/kg/day, and is considered fetotoxic and teratogenic in mice at high doses, but EPA stated that the calculated RfD should be protective of these effects. EPA has not reached a conclusion on the carcinogenicity of xylene (USDA, 1997). In USDA, 1997, a human health risk assessment analyzed the risk of using xylene (an inert in two pesticides analyzed in that assessment). The conclusion from that assessment was that the proposed use of pesticides containing xylene did not represent a risk to either the public or the workers. Assuming that xylene makes up about 10% of the Weedone 638 formulation, and knowing that the RfD for xylene is 200 times higher than the value for 2,4-D, it would be unlikely that the RfD for xylene would be exceeded in the scenarios analyzed in this risk assessment. The lack of knowing the actual percentage of xylene in Weedone 638, as well as the lack of consensus on the carcinogenic potential of xylene adds some uncertainty to this risk assessment.

Butoxyethanol (or EGBE) has been assessed for human health risk as an impurity in the Garlon 4 formulation of triclopyr (Borrecco and Neisess, 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. As the actual amount of butoxyethanol in Weedone 638 is not known, there is some uncertainty in this risk assessment, however the toxicity of EGBE is a factor of 20 times lower than 2,4-D, and assuming that EGBE makes up less than 1% of Weedone 638, it is unlikely that the addition of EGBE represents a significantly increased hazard over the use of 2,4-D itself.

Dicamba (References: USDA 1984; USDA 1989; SERA 2004c)

Acute and Chronic Exposures – Dicamba is relatively nontoxic by oral administration, with single-dose LD_{50} values ranging from approximately 750 to 3,000 mg/kg in rats. Signs of neurotoxicity (e.g., decreased activity, ataxia, loss of coordination) were the main systemic effects in the LD_{50} assays, although gross pathologic changes (e.g., in liver, kidneys and lungs) have been noted in animals that died.

There are no clear indications that the dimethylamine (DMA) salt (e.g., Banvel®), sodium salt or methyl ester derivatives differ significantly from the toxicity of dicamba, or that the toxicity of these forms differs significantly between species or sexes. No information was located on the acute toxicity of the diglycolamine (DGA) salt (e.g., Vanquish®). The similar ranges of oral LD_{50} values for the different forms of dicamba are consistent with pharmacokinetic and chemical evidence for toxicological equivalence, i.e., data showing that dicamba rapidly dissociates in aqueous environments regardless of its form as free acid or salt. Intraperitoneal injections appear to be much more hazardous than oral (or inhalation or dermal) exposure, suggesting that the low acute toxicity by normal exposure routes might be due in part to the kinetics of absorption.

A large number of standard subchronic and chronic toxicity studies have been conducted on dicamba with reported NOAELs ranging from about 50 to 500 mg/kg/day depending on the endpoints assayed and species tested.

Effects on the Skin and Eyes - Mild and transient skin irritation occurred at the application site in some of the studies of the DMA and sodium salts after a dermal dose of 5,050 mg/kg. The local eye, nasal and skin effects observed in the acute inhalation and dermal studies are consistent with results of skin and eye irritation assays. Eye exposure is classified as being mildly to moderately irritating. Dermal exposure to dicamba appears to present no substantial acute toxicity. No mortality, clinical signs of toxicity and/or effects on body weight gain were observed in rats and rabbits dermally exposed to dicamba, the DMA or sodium salts or the methyl ester in single applications of 1,000-5,050 mg/kg (highest tested dose levels). Mild and transient skin irritation occurred at the application site in some of the studies of the DMA and sodium salts.

Subchronic dermal toxicity was studied in rabbits exposed to the DMA, DGA and isopropanolamine (IPA) salts of dicamba. Skin irritation was induced by the DMA salt tested as Banvel®. There were no compound-related changes in behavior and appearance, body weight, hematology, blood chemistry, urinalysis indices, or organ weights in either study. Comprehensive histological examinations were performed that only showed change in the skin at the application site that was consistent with the dermal irritation. In contrast to Banvel®, repeated dermal exposures to the

DGA salt or IPA salt caused no skin irritation in rabbits. There were no clinical signs of toxicity or effects on body weight, hematology, blood chemistry, urinalysis indices, organ weights, or histology in these studies.

Carcinogenicity and Mutagenicity – There are no epidemiology studies or case reports that demonstrate or suggest that exposure to dicamba leads to cancer in humans.

Reproductive and Teratogenic Effects – Dicamba has been tested for its ability to cause birth defects (i.e., teratogenicity) as well as its ability to cause reproductive and developmental impairment. Rabbits were more sensitive to dicamba than rats, with a NOAEL of 3 mg/kg/day for both maternal toxicity and reproductive effects. The reproductive NOAEL in rats was 400 mg/kg/day, a dose that caused signs of toxicity in dams. The 3 mg/kg/day NOAEL in rabbits is the basis of the U.S. EPA RfD on dicamba. Another type of reproduction study involves exposing more than one generation of the test animal to the compound. Three such studies, all in rats, have been conducted on dicamba. The 500 ppm dietary NOAEL determined in these studies was used by the U.S. EPA Office of Pesticide Programs (OPP) in setting the chronic RfD used in setting pesticide tolerances for dicamba.

Other Toxic Endpoints – One study was located that specifically addresses the potential toxic effects of repeated exposures to dicamba in humans. These investigators noted an increased incidence of acetylcholinesterase inhibition in farm workers using herbicides, including dicamba, and found that 3,6-dichloro-2-methoxy benzoic acid, the major component in dicamba, causes inhibition of both plasma and red blood cell cholinesterase *in vitro*, using red cells and plasma from human blood samples.

Neurobehavioral effects of lower dose levels of dicamba were comprehensively evaluated in rats using Functional Observational Battery (FOB) and open-field locomotor activity tests following acute or subchronic exposure. Similar effects were observed in both studies, including body tone rigidity in response to handling and touch, abnormal righting reflex, and impaired gait. Other effects included increased salivation and impaired respiration, flattened and/or raised posture, decreased rearing frequency, increased tail flick latency, decreased forelimb grip strength, hypoalertness and decreased locomotor activity in the acute study, and increased latency to first step in the subchronic study. No NOAEL was identified in the single dose study, indicating that the acute neurotoxicity LOAEL is 300 mg/kg. The subchronic study identified a neurotoxicity NOAEL of 472 mg/kg/day and LOAEL of 768 mg/kg/day.

Clinical signs of neurotoxicity, including ataxia, body stiffening and decreased motor activity, occurred in maternal rats treated with 400 mg/kg/day by gavage on days 0-19 of gestation, and rabbits

administered ≥150 mg/kg/day by capsule on gestation days 6-18. These LOAELs, like the 300 mg/kg LOAEL in the single dose rat study, are lower than the subchronic neurotoxicity NOAEL of 472 mg/kg/day in rats. The lower neurotoxicity LOAELs in the acute and developmental studies is likely related to the bolus methods of oral exposure (gavage or capsule) compared to diet in the subchronic study.

There is very little direct information on which to assess the immunotoxic potential of dicamba. The only studies specifically related to the effects of dicamba on immune function are skin sensitization studies. Nonetheless, the toxicity of dicamba 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 (which could potentially be manifest as increased susceptibility to infection compared to controls) were not observed in any of the available long-term animal studies. Typical subchronic or chronic animal bioassays conduct morphological assessments of the major lymphoid tissues, including bone marrow, major lymph nodes, spleen and thymus (thymus weight is usually measured as well), and white blood cell counts. These assessments can detect signs of inflammation or injury indicative of a direct toxic effect of the chemical on the lymphoid tissue. Changes in cellular physical and chemical properties of lymphoid tissue and blood, indicative of a possible immune system stimulation or suppression, can also be detected. None of these effects have been noted in any of the longer term toxicity studies.

Dicamba has not been tested for activity as a stimulator or antagonist of the major hormone systems (e.g., estrogen, androgen, thyroid hormone), nor have the levels of these circulating hormones been measured following dicamba exposures. Thus, any judgments concerning the potential effect of dicamba on endocrine function must be based on inferences from standard toxicity studies. The major endocrine glands in the body include the adrenal, hypothalamus, pancreas, parathyroid, pituitary, thyroid, ovary, and testis. None of the longer term or short-term toxicity studies reports effects in any of these organs.

Inhalation Exposures – Inhalation exposure to dicamba appears to present no substantial acute toxicity. Subchronic inhalation toxicity was evaluated in rats that were exposed to an aerosol of dicamba DMA salt as Banvel® 4S for 6 hours/day, 5 days/week for 2 weeks. Histopathological changes in the lungs occurred at ≥0.202 mg/L. The lung pathology in all exposure groups indicates that the LOAEL is 0.202 mg/L and a NOAEL cannot be identified.

Impurities - Information on impurities in technical grade dicamba have been disclosed to the U.S. EPA and this information was obtained and reviewed as part of the development of SERA 2004c. Because this information is classified as confidential business information, detail of the

information submitted to U.S. EPA cannot be disclosed in this risk assessment. If toxic impurities are present in technical dicamba, they are likely to be encompassed by the available toxicity studies using technical grade dicamba.

Some published information is available on the impurities in dicamba. A pharmacokinetics study indicates that the main impurity is 3,5-dichloro-2-methoxy benzoic acid. In a worker exposure study analysis of technical grade dicamba contained the major (3,6-dichloro) and minor (3,5-dichloro) isomers.

There is some indication that the impurities in dicamba may be more toxic than dicamba itself. Edson and Sanderson (1965, as referenced in SERA 2004c) note that "pure" dicamba was less toxic than technical grade dicamba to female rats. Nonetheless, all of the toxicology studies on dicamba involve technical grade dicamba, which is presumed to be the same as or comparable to the active ingredient in the formulations used by the Forest Service. Thus, if toxic impurities are present in technical dicamba, they are likely to be encompassed by the available toxicity studies using technical grade dicamba.

Metabolites - Following gavage or subcutaneous exposure, approximately 93% and 96% of the administered ^{14}C-dicamba, respectively, was excreted unmetabolized in the urine within 24 hours of dosing. With dietary exposure, urinary and fecal excretion approached 96% and 4% of the rate of intake. Dicamba was excreted unchanged in the urine. Similarly, following a single oral dose of 100 mg/kg of radiocarbon-labeled dicamba in rats, mice, rabbits and dogs, 67-83% of the radioactivity was eliminated in the urine as parent compound within 48 hours. About 1% of the administered dose was metabolized to 3,6-dichlorosalicylic acid (3,6-DCSA) and another 1% to an unidentified metabolite.

The pharmacokinetics of radiocarbon-labeled dicamba were compared in rats following a single gavage dose as the free acid or its dimethylamine, isopropylamine or diglycolamine salt in normal saline. Evaluation for 24 hours following dosing showed that there were no statistically significant differences between dicamba and the three amine salt forms. Parent dicamba was the major excreted compound, accounting for 92-94% of the urinary radiocarbon and 75-80% of the fecal radiocarbon. 3,6-DCSA was a minor metabolite (≈0.5 - 0.6% and ≈3-4% of the urinary and fecal radiocarbon, respectively), and unidentified metabolites accounted for <1 % of the urinary radiocarbon. The results of this study indicate that dicamba rapidly dissociated *in vivo* regardless of its form as free acid or an amine salt.

Inerts - The identity of inerts in both Banvel® and Vanquish® has been disclosed to the U.S. EPA and this information has been reviewed as part of the development of SERA 2004c. This information, however, is protected under Section 10 of FIFRA. Other than to state that no apparently hazardous materials have been identified, which is consistent with the MSDS for both Banvel® and Vanquish®, the information on the inerts in these formulations cannot be detailed.

The potential toxicological significance of inerts in Banvel® can be inferred from a comparison of the toxicity data on Banvel® with corresponding toxicity data on dicamba. The acute oral LD_{50} value for Banvel® in rats is 1,028-2,629 mg/kg and the corresponding value for the DMA salt of dicamba is 1,707-2,900 mg/kg. The dermal LD_{50} values for both Banvel® and the DMA salt of dicamba are >2,000 mg/kg and the inhalation LC_{50} value for both Banvel®l and the DMA salt of dicamba are >200 mg/L. Thus, in terms of acute lethal potency, no substantial differences are apparent between the active ingredient in Banvel® (the DMA salt of dicamba) and the Banvel® formulation. However, Banvel® causes severe skin irritation but the DMA salt of dicamba caused no irritation or only slight irritation.

For Vanquish®, commercial searches of the studies available in the FIFRA confidential business information (CBI) files as well as supplemental searches that were kindly provided by the U.S. EPA Office of Pesticide Programs did not identify specific mammalian toxicity studies using Vanquish®. Some data are available comparing the toxicity of the IPA salt, the active ingredient in Vanquish® to other forms of dicamba in birds. The LD_{50} value of a formulation of the IPA salt of dicamba in bobwhite quail is 1,373 mg/kg and the corresponding value for dicamba is 216 mg/kg.

Glyphosate (References: USDA, 1984; USDA, 1989; SERA, 2003a)

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_{50} 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 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 Erikkson, 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 Erikkson 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®, 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.

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 nay 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_{50} 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_{50} values for various glyphosate formulations range from >1.3 mg/L to >7.3 mg/L. The lowest LC_{50} value that is not designated with a greater than (>) symbol is 2.6 mg/L, the reported LC_{50} 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 – Certain formulations of glyphosate (Roundup® for example) contain a polyethoxylated tallow amine (POEA) surfactant at levels of ~15% (150 g/L) or contain a phosphate ester neutralized POEA surfactant (for example, Roundup Pro®) at a level of ~14.5%. There is some uncertainty in the interpretation of the toxicity data on Roundup® concerning the potential significance of these POEA surfactants, however the available toxicity information on Roundup® are adequate for the identification of toxic thresholds. It appears from an assessment of the data that POEA is less acutely toxic to mammals than glyphosate or Roundup®.

There is little information available on the subchronic or chronic toxicity of POEA. In a developmental toxicity test in rats, Farmer et al (2000b as referenced in SERA 2003a), exposed rats to glyphosate (0, 300, 1,000, or 3,500 mg/kg/day) and both the POEA (0, 15, 100, 300 mg/kg/day) and the phosphate ester neutralized POEA surfactant (0, 15, 50, 150 mg/kg/day) on days 6-15 of gestation. For glyphosate, severe maternal poisoning was observed at 3,500 mg/kg/day and this was associated with reduced fetal body weights and hardening of the cartilage around the sternum, as well

as fetal death. The NOAEL for both maternal and fetal toxicity was 1,000 mg glyphosate/kg/day. The surfactants also caused mortality in dams at the highest doses tested: 300 mg/kg/day for POEA and 150 mg/kg/day for neutralized POEA. In addition, a dose of 100 mg POEA/kg/day caused mild clinical signs of toxicity and decreased food consumption in dams. No fetotoxic effects were reported at any dose level. Thus, in repeated dosing, the NOAEL for glyphosate of 1,000 mg/kg/day was substantially higher than the NOAEL for either POEA (15 mg/kg/day) or neutralized POEA (50 mg/kg/day).

POEA contains the contaminant 1,4-dioxane, which has been classified by U.S. EPA as a probable human carcinogen, Class B2: Probable human carcinogen, and has been given a cancer potency factor (referred to by U.S. EPA as a slope factor) of 0.011 $(mg/kg/day)^{-1}$. Borrecco and Neisess (1991) derived toxicity-based criteria for 1,4-dioxane and used the information to calculate margins of safety for exposure to 1,4-dioxane. At the time of that analysis it was assumed that dioxane is present in Roundup® at a level of approximately 0.03% or 300 mg/L (300 ppm). This is about a factor of 0.00084 less than the level of glyphosate in Roundup®. This is likely an over-estimate of the concentration of dioxane, based on information from the manufacturer (*ibid*).

From Borrecco and Neisess, (1991), the risks of cancer from the exposure to 1,4-dioxane were considered negligible for occupationally exposed individuals, based on an acceptable standard of risk of 1 in 1 million. Since the Borrecco and Neisess paper was written, the amount of 1,4-dioxane that was assumed present in the glyphosate formulation by the authors, has been determined to be much lower (correspondence between Borrecco and M. Lemon, Monsanto Company, 1995). Hence, the margins of safety in Borrecco and Neisess can be considered conservative. In addition, an evaluation of non-cancer toxicity indicated that exposures to 1,4-dioxane would result in acceptable levels of risk (Borrecco and Neisess 1991). As the risks from 1,4-dioxane are considered in Borrecco and Neisess, (1991), and risks are considered acceptable, given the conservative assumptions of exposure, it will not be further analyzed or discussed in this Risk Assessment. Based on the analysis in Borrecco and Neisess (1991) and according to the available toxicity data, dioxane does not present unique toxic effects; therefore, its toxicity is likely to be encompassed by the available toxicity data on Roundup®. Dioxane does not present cancer risks to workers at levels considered unacceptable.

Another potential impurity in the POEA surfactant is un-reacted ethylene oxide. Ethylene oxide may be present in any ethoxylated surfactant as a residue of the manufacturing process. Ethylene oxide is a potential carcinogen. Refer to the discussion in Appendix 2 of USDA (2003a) for a discussion of the cancer risk of ethylene oxide in surfactants. The low amount of ethylene oxide in such surfactants, combined with the physical properties of ethylene oxide, make cancer risks low.

Since the late 1990's, patent protection for glyphosate expired, resulting in a strong increase in the number of commercial formulations available for purchase. Most of the hazard analyses done to date have involved Roundup ®, Rodeo®, or Accord® formulations. Inerts in the Roundup® formulation other than the surfactant discussed above, are isopropylamine (0.5%), related organic acids of glyphosate (1.5%), and water (41.6%). The only listed inert ingredient in Rodeo® and Accord® is water (46% to 58%), although it is likely that small amounts of isopropylamine and related organic acids of glyphosate also are present.

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

Acute and Chronic Exposures - Triclopyr has a low order of acute lethal potency. Oral LD_{50} 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, 1998b), 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, 1998b).

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® 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 on triclopyr. In this study, male and female rats were exposed to triclopyr in the diet at concentrations resulting in doses of 0, 5, 25, or 250 mg/kg/day, except that the first generation males in the high dose group were exposed only to concentrations resulting in a daily dose of 100 mg/kg/day. The 5 mg/kg/day dose groups evidenced no adverse effects in parents or offspring. At 25 mg/kg/day, kidney effects were noted only in adult animals. At 250 mg/kg/day, parental effects included decreased food consumption and body weights as well as histopathologic changes in the liver and kidney. Fetotoxic effects – decreased pup survival and litter sizes – were noted only at 250 mg/kg/day. This dose also resulted in decreased parental fertility. Because no effects were observed at this dose on spermatogenesis or the testes, the decreased fertility was attributed to effects on the female rats.

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 genotoxicty 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_{50} of greater than 2.56 mg/L – is essentially equivalent to the reported LD_{50} 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® 3A contains the triethylamine salt of triclopyr (44.4%) as well as emulsifiers, surfactants, and ethanol. 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 TEA dissociates extremely rapidly to triclopyr acid and triethanolamine and triclopyr BEE hydrolyzes to triclopyr acid and 2-butoxyethanol. Relatively little information is available on the toxicity of triethanolamine. This compound is classified as a list 3 inert by U.S. EPA. The List 3 classification reflects the limited toxicity data on triethanolamine and indicates that U.S. EPA was not able to classify this compound as toxic (List 1), potentially toxic (List 2), or essentially non-toxic (Lists 4a or 4b). 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 both triethanolamine and 2-butoxyethanol will mineralize very rapidly in the environment – i.e., be completely degraded to CO_2. This is not the case for triclopyr or TCP, a metabolite of triclopyr. Thus, the uncertainties associated with the toxicity of triethanolamine and the comparable toxicity of 2-butoxyethanol to triclopyr have relatively little impact on this risk assessment. Because triclopyr and the TCP metabolite of triclopyr persist in the environment much longer than triethanolamine or 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.

The toxicity of ethanol is extremely well characterized in humans, and the hazards of exposure include intoxication from acute exposure as well as liver cirrhosis and fetal alcohol syndrome. For chronic exposure, the alcohol contained in Garlon® 3A will not be of toxicological significance because of the rapid breakdown of alcohol in the environment and the relatively high levels of alcohol associated with chronic alcohol poisoning. Similarly, alcohol is not likely to pose an acute toxic hazard. Each milliliter (mL) of Garlon® 3A contains 0.01 mL of ethanol. Therefore, 1,480 mL, or approximately 1.5 liters (L), of Garlon® 3A must be consumed to equal the amount of alcohol contained in 1 ounce of an alcoholic beverage. The same amount of Garlon® 3A contains approximately a lethal dose for triclopyr in humans. Thus, compared with the active ingredient, which is triclopyr, the amount of ethanol in Garlon® 3A is not toxicologically significant in terms of potential toxicity.

The acute toxicity of Garlon® 3A is substantially less than the acute toxicity of triclopyr. The acute oral LD_{50} of triclopyr to rats is approximately 713 mg/kg. The corresponding values for Garlon® 3A range from approximately 2,140 to 2,830 mg/kg or from approximately 1,540 to 2,040 mg a.e./kg. This suggests that components in Garlon® 3A antagonize the acute toxicity of triclopyr.

Like Garlon® 3A, Garlon® 4 causes substantially less acute toxicity in mammals than does triclopyr (oral LD_{50} 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_{50} values in experimental mammals range from approximately 16,000 to 23,000 mg/kg. In experimental mammals, acute oral LD_{50} 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 $\mu g/m^3$, 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 $\mu g/m^3$. 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^3; the NIOSH TLV for petroleum distillates is 350 mg/m^3. 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.[1] 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 mammals and are placed in EPA toxicity category III or IV (tested LD_{50} values ranging from 620 to 7,400 mg/kg). In comparison with these NPEs, the acute toxicity of NP is somewhat higher (tested LD_{50} 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

[1] 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.

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_{50} of 2,830 mg/kg. Acute dermal LD_{50} of NP5E in rabbits is greater than 2,000 mg/kg; with NP6E in rabbits, the acute dermal LD_{50} 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_{50} 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 reveled 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_0, F_1). Females in each of three generations (F_0, F_1, F_2) 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_1 or F_2 generations after lifetime exposures to up to 50 mg/kg/day NP via oral gavage. There was an increase in salivation in F_0 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 microscopic examination of the tissues after subchronic 90-day exposures to NP up to 149 mg/kg/day in male or female rats.

Impurities – To some extent, concern for impurities in technical grade NPE is reduced by the fact that the existing toxicity studies on NPE 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 potential carcinogen in an otherwise non-carcinogenic mixture may represent a carcinogenic risk. This is the situation with NPE. NPE may contain ethylene oxide and 1,4-dioxane as impurities. U.S. EPA considers ethylene oxide to be a probable human carcinogen for which the data are adequate to consider risk quantitatively.

Ethylene oxide has been found in NP9E at low levels, <3.6 to 12.2 mg/L (ppm), in the unreacted form as a residual from the manufacturing process. Depending upon processing methods, this can be reduced essentially to zero. Ethylene oxide is used in the production of many chemicals, including ethoxylates, and used as a hospital sterilant, but most use is for the production of ethylene glycol. Ethylene oxide is likely present in many products that contain ethoxylates, such as surfactants containing linear alcohol ethoxylates. Unreacted levels of ethylene oxide in these products should reduce with time due to reaction, storage, further pumping, and other processing.

Ethylene oxide has been described as a probable human carcinogen with sufficient evidence in experimental animals to support a finding as a carcinogen; it is also a mutagen (refer to USDA, 2003a, Appendix 2). Ethylene oxide has a high vapor pressure and high water solubility, and at normal room temperature and pressure is a gas. Because of its high vapor pressure and high water solubility it is not expected to bio-accumulate or accumulate in soil or sediment. Metabolism of ethylene oxide in larger mammals is primarily through hydrolysis to ethylene glycol, which in turn is converted to oxalic acid, formic acid, and CO_2. While a detailed review of ethylene oxide is beyond the scope of this risk assessment, adequate information is available on ethylene oxide to quantify the carcinogenic risk associated with the use of NP9E. This discussion of risk is contained in USDA (2003a, Appendix 2). Based on conservative assumptions concerning exposure, the carcinogenic risks to workers from ethylene oxide are at acceptable levels. Ethylene oxide will not be discussed further in this risk assessment.

1,4-dioxane has also been found as an impurity in NP9E at low levels (<4.5 to 5.9 ppm). 1,4-dioxane has also been classified as a carcinogen. Borrecco and Neisess 1991 conducted a risk assessment of the impurity 1,4-dioxane in the surfactant in Roundup® formulations of glyphosate. In that risk assessment, they assumed a concentration of 1,4-dioxane at 0.03% in the Roundup® formulation, which is about two orders of magnitude greater concentration than found in NP9E. Borrecco and Neisess used a systemic NOEL of 9.6 mg/kg/day and a cancer potency value of 0.0076 mg/kg/day. With the higher percentage of 1,4-dioxane assumed in Roundup®, they concluded that the risk of acute, chronic, or reproductive effects would be acceptably low, even at maximum labeled rates for Roundup®. They included a cancer risk assessment written by Heydens 1989, which looked at the increased risk of cancer caused by the use of surfactants that contained 1,4-dioxane as a

contaminant. Heydens, using a cancer potency value of 0.0076 mg/kg/day, and a 300 ppm contamination rate, determined that the risk of cancer from 1,4-dioxane was well below the 1 in 1 million threshold considered acceptable. Heydens concluded that the carcinogenic risk from exposure to 1,4-dioxane is negligible for occupationally exposed individuals. As these two documents have adequately considered the risk of 1,4-dioxane, this impurity will not be considered further in this risk assessment.

It is important to note that chronic studies involving NP9E have not determined cancer to be an endpoint in mammals.

Metabolites – Based on one study of NP9E, it appears to be rapidly metabolized and excreted (Walter et al 1988, as referenced in USDA 2003a). After injection of NP9E into female rats, bile and urine were 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 likely to be the individuals who are most exposed to a pesticide during the application process. 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 2000b). 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.

Initially, risk assessments for the USDA Forest Service adjusted the exposure rate 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 1998b). 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.

Thus, in the absence of data to suggest an alternative approach, no corrections for differences in dermal absorption rate coefficients or other indices of dermal absorption seem to be appropriate for adjusting occupational exposure rates. Although pesticide application involves many different job activities, exposure rates can be defined for three categories: directed foliar applications (including cut surface, streamline, and direct sprays) involving the use of backpacks or similar devices,

broadcast hydraulic spray applications, and broadcast aerial applications. While these may be viewed as crude groupings, the variability in the available data does not seem to justify further segmenting the job classifications - e.g., hack-and-squirt, injection bar.

See Tables F3-3a to F3-3i 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).

General Exposures - As described in SERA (2000b), worker exposure rates are expressed in units of milligrams (mg) of absorbed dose per kilogram (kg) of body weight per pound of chemical handled (mg/kg/lb applied). The exposure rates used in this risk assessment are based on worker exposure studies on nine different pesticides with molecular weights ranging from 169 to 416 and the base-10 log of the octanol water coefficient (log K_{ow}) values at pH 7 ranging from –2.90 to 6.50 (SERA 1998b, Table 1). The estimated exposure rates (Table F3-1) are based on estimated absorbed doses in workers as well as the amounts of the chemical handled by the workers (SERA 1998b, Table 5). Exposure rates are shown as milligrams of chemical per kilogram of body weight per pound of active ingredient (ai) applied. The molecular weight and log K_{ow} of the six herbicides considered in this risk assessment are within the range of pesticides studied in SERA (1998b). Although the molecular weight of NP9E is outside this range, the values derived in SERA (1998b), should be conservative for this use, because larger molecules would tend to be absorbed at lower rates. As described in SERA (2000b), the ranges of estimated occupational exposure rates vary substantially among individuals and groups, (i.e., by a factor of 50 for backpack applicators and a factor of 100 for mechanical ground sprayers). It seems that much of the variability can be attributed to the hygienic measures taken by individual workers (i.e., how careful the workers are to avoid unnecessary exposures).

Table F3-1: Estimated Exposure Rates from Herbicides used to Treat Noxious Weed

Job Category	Typical (mg/kg/lb ai)	Lower (mg/kg/lb ai)	Upper (mg/kg/lb ai)
Ground Application	0.003	0.0003	0.01
Hydraulic Sprayer	0.0002	0.00001	0.0009

Source: SERA, 1998b, Table 5.

The estimated number of acres treated per hour for ground applications is taken from recent experiences in the Pacific Southwest Region. It is estimated that hydraulic ground spray workers will typically treat 2 to 6 acres per hour. Although this rate of treatment is substantially lower than the typical rates used in herbicide ground broadcast applications in other risk assessments, these lower

values are better estimates of plausible treatment rates for these herbicides given the types of equipment that will be used and the areas that will be treated.

The number of hours worked per day is expressed as a range, the lower end of which is based on an 8-hour workday with 1 hour at each end of the workday spent in activities that do not involve herbicide exposure. The upper end of the range, 8 hours per day, is based on an extended (10-hour) workday, allowing for 1 hour at each end of the workday to be spent in activities that do not involve herbicide exposure. It is recognized that the use of 6 hours as the lower range of time spent per day applying herbicides is not a true lower limit. It is conceivable and perhaps common for workers to spend much less time in the actual application of a herbicide if they are engaged in other activities. Thus, using 6 hours can be regarded as conservative. In the absence of any published or otherwise documented work practice statistics to support the use of a lower limit, this conservative approach is used.

The range of acres treated per hour and hours worked per day is used to calculate a range for the number of acres treated per day. For this calculation as well as others in this section involving the multiplication of ranges, the lower end of the resulting range is the product of the lower end of one range and the lower end of the other range. Similarly, the upper end of the resulting range is the product of the upper end of one range and the upper end of the other range. This approach is taken to encompass as broadly as possible the range of potential exposures. The central estimate of the acres treated per day is taken as the arithmetic average of the range. Because of the relatively narrow limits of the ranges for backpack and boom spray 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 range of application rates and the typical application rate are based on experience in the Pacific Southwest Region or, for those herbicides without much previous use in this Region, the rate is based on local recommendations (See Table F3-2). (Rates are expressed as either acid equivalents (ae) or active ingredient (ai).) Similarly, the typical dilution rates and ranges of dilution rates are largely based on Pacific Southwest Region experience. The typical dilution rate is 25 gallons per acre of herbicide mixture applied, with the lowest dilution being 20 gallons per acre, and the highest being 35 gallons per acre. For hexachlorobenzene, the application rate is based on the application rate for clopyralid and the percentage of hexachlorobenzene in clopyralid.

Table F3-2: Herbicide and Nonylphenol Polyethoxylate Application Rates to be used to Treat Noxious Weeds (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	0.047 ai	0.035 ai	0.062 ai
Clopyralid	0.25 ae	0.13 ae	0.25 ae
2,4-D	1.5 ae	0.5 ae	2.0 ae
Dicamba	1.0 ae	0.25 ae	2.0 ae
Glyphosate	2.5 ae	0.75 ae	3.75 ae
Triclopyr (both BEE and TEA)	1.0 ae	0.5 ae	1.5 ae
Nonylphenol polyethoxylate	1.7 ai	1.3 ai	2.3 ai
Hexachlorobenzene	0.000000625 ai	0.000000325 ai	0.000000625 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 2000b), Fick's first law is used to estimate dermal exposure.

Exposure scenarios involving chemical spills on to the skin are characterized by a spill onto 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 onto a given surface area of skin and that a certain amount of the chemical adheres to the skin. The absorbed dose is then calculated as the product of the amount of the chemical on the surface of the skin (i.e., the amount of liquid per unit surface area multiplied by the surface area of the skin over which the spill occurs and the concentration of the chemical in the liquid) the first-order absorption rate, and the duration of exposure. 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 (2000b).

Table F3-3a: 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	0.00028	1.3 E-5	0.0025
Boom Spray	0.00026	4.2 E-6	0.0027
Accidental/Incidental Exposures (dose in mg/kg/event)			
Immersion of hands, 1 minute	1.1 E-7	1.9 E-8	5.1 E-7

Contaminated Gloves, 1 hour	6.4 E-6	1.1 E-6	3.1 E-5
Spill on hands,1 hour	4.0 E-6	4.0 E-7	3.2 E-5
Spill on lower legs,1 hour	9.8 E-6	9.9 E-7	7.9 E-5

Table F3-3b: 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	0.0015	4.7 E-5	0.010
Boom Spray	0.0014	1.6 E-5	0.011
Accidental/Incidental Exposures (dose in mg/kg/event)			
Immersion of hands, 1 minute	4.1 E-7	3.9 E-8	1.9 E-6
Contaminated Gloves, 1 hour	2.4 E-5	2.3 E-6	0.00012
Spill on hands,1 hour	7.3 E-5	5.5 E-6	0.00045
Spill on lower legs,1 hour	0.00018	1.4 E-5	0.0011

Table F3-3c: Summary of Worker Exposure Scenarios – 2,4-D

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	0.0090	0.00018	0.080
Boom Spray	0.0084	6.0 E-5	0.086
Accidental/Incidental Exposures (dose in mg/kg/event)			
Immersion of hands, 1 minute	3.5 E-5	3.4 E-6	0.00014
Contaminated Gloves, 1 hour	0.0021	0.00020	0.0084
Spill on hands, 1 hour	0.00083	6.4 E-5	0.0041
Spill on lower legs, 1 hour	0.0020	0.00016	0.010

Table F3-3d: Summary of Worker Exposure Scenarios – Dicamba

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	0.0060	9.0 E-5	0.080
Boom Spray	0.0056	3.0 E-5	0.086
Accidental/Incidental Exposures (dose in mg/kg/event)			
Immersion of hands, 1 minute	3.2 E-5	2.4 E-6	0.00018
Contaminated Gloves, 1 hour	0.0019	0.00014	0.011
Spill on hands, 1 hour	0.00060	3.7 E-5	0.0045
Spill on lower legs, 1 hour	0.0015	9.2 E-5	0.011

Table F3-3e: 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	0.015	0.00027	0.15
Boom Spray	0.014	9.0 E-5	0.16
Accidental/Incidental Exposures (dose in mg/kg/event)			
Immersion of hands, 1 minute	3.6 E-6	1.9 E-7	2.8 E-5
Contaminated Gloves,1 hour	0.00022	1.2 E-5	0.0017
Spill on hands, 1 hour	0.00047	3.2 E-5	0.0021
Spill on lower legs, 1 hour	0.0012	8.0 E-5	0.0052

Table F3-3f: Summary of Worker Exposure Scenarios – Triclopyr TEA

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	0.0060	0.00018	0.060
Boom Spray	0.0056	6.0 E-5	0.065
Accidental/Incidental Exposures (dose in mg/kg/event)			
Immersion of hands, 1 minute	2.3 E-5	3.7 E-6	9.7 E-5
Contaminated Gloves, 1 hour	0.0014	0.00022	0.0058
Spill on hands, 1 hour	0.0064	0.00080	0.035
Spill on lower legs, 1 hour	0.016	0.0020	0.085

Table F3-3g: 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	0.0060	0.00018	0.060
Boom Spray	0.0056	6.0 E-5	0.065
Accidental/Incidental Exposures (dose in mg/kg/event)			
Immersion of hands, 1 minute	0.0079	0.0015	0.027
Contaminated Gloves, 1 hour	0.47	0.090	1.6
Spill on hands, 1 hour	0.018	4.4 E-5	0.057
Spill on lower legs, 1 hour	0.046	0.00011	0.14

Table F3-3h: 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	0.010	0.00048	0.093
Boom Spray	0.0093	0.00016	0.10
Accidental/Incidental Exposures (dose in mg/kg/event)			
Immersion of hands, 1 minute	0.00017	6.2 E-5	.00044
Contaminated Gloves, 1 hour	0.010	0.0037	0.026
Spill on hands, 1 hour	5.4 E-5	7.7 E-6	0.00069
Spill on lower legs, 1 hour	0.00013	1.9 E-5	0.0017

Table F3-3i: 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	3.8 E-9	1.2 E-10	2.5 E-8
Boom Spray	3.5 E-9	3.9 E-11	2.7 E-8
Accidental/Incidental Exposures (dose in mg/kg/event)			
Immersion of hands, 1 minute	4.7 E-7	5.3 E-8	1.8 E-6
Contaminated Gloves, 1 hour	2.8 E-5	3.2 E-6	0.00011
Spill on hands, 1 hour	6.3 E-9	5.0 E-10	3.4 E-8
Spill on lower legs, 1 hour	1.5 E-8	1.2 E-9	8.3 E-8

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.

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, water, and fish. Most of these scenarios should be regarded as extreme, some to the point of limited plausibility. The longer-term or chronic exposure scenarios parallel the acute exposure scenarios for the consumption of contaminated fruit, water, and fish but are based on estimated levels of exposure for longer periods after application. See Tables F3-5a to F3-5i for a summary of the general public exposure scenarios.

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 2000b).

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 2000b) 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^2 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 F3-4a).

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 2001b). SERA (2001b) 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 F3-4b. 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 F3-4a and F3-4b must be multiplied by the rates of application in Table F3-2 (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 and triclopyr 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 two herbicides, the assumptions in this risk assessment provide for a conservative (i.e. protective) assessment of risk.

Table F3-4a: 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
Chlorsulfuron	0.1	0.01	0.2
Clopyralid	0.02	0.005	0.07
2,4-D	0.15	0.13	0.42
Dicamba	0.003	0.00006	0.01
Glyphosate	0.02	0.001	0.4
Triclopyr	0.09	0.001	0.4
Nonylphenol Polyethoxylate	0.012	0.0031	0.031
Hexachlorobenzene	0.09	0.001	0.3

Table F3-4b: 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
2,4-D	0.002	0.001	0.004
Dicamba	0.00001	0.000005	0.00003
Glyphosate	0.001	0.0001	0.008
Triclopyr	0.03	0.008	0.05
Nonylphenol Polyethoxylate	0.007	0.00001	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 Calabrese and Baldwin (1993, as referenced in SERA 2000b).

Most of the herbicides in this risk assessment have BCF values for fish of 1 or less. There are three with BCF values greater than 1: chlorsulfuron (1-12), 2,4-D (40), and hexachlorobenzene (10,000). These values are generally determined from a standardized test that is required as part of the registration process.

For both the acute and longer-term exposure scenarios involving the consumption of contaminated fish, the water concentrations of the herbicides used are identical to the concentrations used in the contaminated water scenarios. The acute exposure scenario is based on the assumption that an adult angler consumes fish taken from contaminated water shortly after an accidental spill of 200 gallons of a field solution into a pond that has an average depth of 1 meter and a surface area of 1000 m^2 or about one-quarter acre. No dissipation or degradation is considered. Because of the available and well-documented information and substantial differences in the amount of caught fish consumed by the general public and native American subsistence populations (U.S. EPA 1996, as referenced in SERA 2000b), separate exposure estimates are made for these two groups. The chronic exposure scenario is constructed in a similar way.

Oral Exposure from Contaminated Vegetation - Under normal circumstances and in most types of applications, it is extremely unlikely that humans will consume, or otherwise place in their mouths, vegetation contaminated with these herbicides. Nonetheless, any number of scenarios could be developed involving either accidental spraying of crops, the spraying of edible wild vegetation, like berries, or the spraying of plants collected by Native Americans for basketweaving or medicinal use. 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.

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. The two accidental exposure scenarios developed for this 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 2000b) as modified by Fletcher et al (1994, as referenced in SERA 2003a). For the acute exposure scenario, the estimated residue level is taken as the product of the application rate and the residue rate. 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 assumption used is that there is no dissipation of the impurity in plants over the course of the chronic contaminated vegetation scenario. This is due to its long half-time in the soil (SERA 1999c). An additional consideration is the BCF in vegetation, established as 19 (ATSDR 1998, as referenced in SERA 1999c).

Although the duration of exposure of 90 days may appear to be somewhat arbitrarily chosen, it is intended to represent the consumption of contaminated vegetation that might be available over one season. Longer durations could be used for certain kinds of vegetation but would lower the estimated dose (i.e., would result in a less conservative exposure assessment). The central estimate of dose for the longer-term exposure period is taken as the time-weighted average of the initial concentration and concentration after 90 days. For the acute exposure scenario, it is assumed that a woman consumes 1 lb (0.4536 kg) of contaminated fruit. Based on statistics summarized in U.S. EPA (1996, as referenced in SERA 2000b), this consumption rate is approximately the mid-range between the mean and upper 95% confidence interval for the total vegetable intake for a 64 kg woman. The longer-term exposure scenario is constructed in a similar way, except that the estimated exposures include the range of vegetable consumption (U.S. EPA 1996, as referenced in SERA 2000b) as well as the range of concentrations on vegetation and the range of application rates for the herbicides.

Table F3-5a: 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	0.00015	1.5 E-5	0.0012
Direct Spray, lower legs, woman	1.5 E-5	1.5 E-6	0.00012
Dermal Exposure, contaminated vegetation	1.6 E-5	2.3 E-6	0.00011
Contaminated Fruit	0.00055	0.00041	0.012
Contaminated Water, spill, child	0.013	0.0042	0.032
Contaminated Water, stream, child	0.00035	1.6 E-5	0.0014
Consumption of Fish, general public	0.00039	0.00020	0.00063
Consumption of Fish, subsistence populations	0.0019	0.0010	0.0031
Chronic/Longer Term Exposures (dose in mg/kg/day)			
Contaminated Fruit	0.00023	0.00017	0.0049
Consumption of Water	8.1 E-7	7.0 E-8	1.9 E-6
Consumption of Fish, general public	6.0 E-9	7.5 E-10	1.2 E-8
Consumption of Fish, subsistence population	4.9 E-8	6.1 E-9	9.8 E-8

Table F3-5b: 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	0.0027	0.00021	0.017
Direct Spray, lower legs, woman	0.00027	2.1 E-5	0.0017
Dermal Exposure, contaminated vegetation	0.00035	3.6 E-5	0.0017
Contaminated Fruit	0.0029	0.0015	0.047
Contaminated Water, spill, child	0.068	0.015	0.13
Contaminated Water, stream, child	0.00038	3.0 E-5	0.0020
Consumption of Fish, general public	0.0020	0.00075	0.0026
Consumption of Fish, subsistence populations	0.010	0.0037	0.012
Chronic/Longer Term Exposures (dose in mg/kg/day)			
Contaminated Fruit	0.0012	0.00049	0.025
Consumption of Water	5.0 E-5	2.6 E-6	0.00011
Consumption of Fish, general public	2.5 E-7	1.9 E-8	4.6 E-7
Consumption of Fish, subsistence population	2.0 E-6	1.5 E-7	3.7 E-6

Table F3-5c: Summary of Public Exposure Scenarios – 2,4-D

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	0.031	0.0024	0.16
Direct Spray, lower legs, woman	0.0032	0.00024	0.016
Dermal Exposure, contaminated vegetation	0.0046	0.00046	0.018
Contaminated Fruit	0.018	0.0059	0.37
Contaminated Water, spill, child	0.41	0.059	1.02
Contaminated Water, stream, child	0.017	0.0030	0.095
Consumption of Fish, general public	0.49	0.12	0.82
Consumption of Fish, subsistence populations	2.4	0.57	4.0
Chronic/Longer Term Exposures (dose in mg/kg/day)			
Contaminated Fruit	0.0039	0.0013	0.083
Consumption of Water	8.6 E-5	1.0 E-5	0.00027
Consumption of Fish, general public	1.7 E-5	2.9 E-6	4.6 E-5
Consumption of Fish, subsistence population	0.00014	2.3 E-5	0.00037

Table F3-5d: Summary of Public Exposure Scenarios – Dicamba

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	0.023	0.0014	0.17
Direct Spray, lower legs, woman	0.0023	0.00014	0.017
Dermal Exposure, contaminated vegetation	0.0032	0.00025	0.020
Contaminated Fruit	0.012	0.0029	0.37
Contaminated Water, spill, child	0.27	0.030	1.02
Contaminated Water, stream, child	2.3 E-4	6.9 E-7	0.0023
Consumption of Fish, general public	0.0054	0.00097	0.014
Consumption of Fish, subsistence populations	0.026	0.0047	0.066
Chronic/Longer Term Exposures (dose in mg/kg/day)			
Contaminated Fruit	0.0017	0.00042	0.054
Consumption of Water	2.9 E-7	2.5 E-8	2.1 E-6
Consumption of Fish, general public	9.4 E-10	1.2 E-10	5.7 E-9
Consumption of Fish, subsistence population	7.6 E-9	9.6 E-10	4.6 E-8

Table F3-5e: 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	0.018	0.0012	0.080
Direct Spray, lower legs, woman	0.0018	0.00012	0.0080
Dermal Exposure, contaminated vegetation	0.0028	0.00024	0.010
Contaminated Fruit	0.029	0.0088	0.7
Contaminated Water, spill, child	0.68	0.090	1.9
Contaminated Water, stream, child	0.0038	3.4 E-5	0.17
Consumption of Fish, general public	0.0078	0.0017	0.014
Consumption of Fish, subsistence populations	0.038	0.0082	0.070
Chronic/Longer Term Exposures (dose in mg/kg/day)			
Contaminated Fruit	0.016	0.0048	0.38
Consumption of Water	7.1 E-5	1.5 E-6	0.0010
Consumption of Fish, general public	1.4 E-7	4.1 E-9	1.6 E-6
Consumption of Fish, subsistence population	1.1 E-6	3.3 E-8	1.3 E-5

Table F3-5f: Summary of Public Exposure Scenarios – Triclopyr TEA

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	0.24	0.030	1.3
Direct Spray, lower legs, woman	0.024	0.0030	0.13
Dermal Exposure, contaminated vegetation	0.030	0.0055	0.10
Contaminated Fruit	0.0031	0.0016	0.052
Contaminated Water, spill, child	0.27	0.059	0.77
Contaminated Water, stream, child	0.0068	2.3 E-5	0.068
Consumption of Fish, general public	0.00049	0.00017	0.00092
Consumption of Fish, subsistence populations	0.0024	0.00085	0.0045
Chronic/Longer Term Exposures (dose in mg/kg/day)			
Contaminated Fruit	0.0015	0.00058	0.034
Consumption of Water	0.00086	8.0 E-5	0.0026
Consumption of Fish, general public	2.6 E-7	3.4 E-8	6.4 E-7
Consumption of Fish, subsistence population	2.1 E-6	2.8 E-7	5.2 E-6

Table F3-5g: Summary of Public Exposure Scenarios – Triclopyr BEE

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	0.70	0.0017	2.2
Direct Spray, lower legs, woman	0.070	0.00017	0.22
Dermal Exposure, contaminated vegetation	0.066	0.00032	0.13
Contaminated Fruit	0.0031	0.0016	0.052
Contaminated Water, spill, child	0.27	0.059	0.77
Contaminated Water, stream, child	0.0068	2.3 E-5	0.068
Consumption of Fish, general public	0.00049	0.00017	0.00092
Consumption of Fish, subsistence populations	0.0024	0.00085	0.0045
Chronic/Longer Term Exposures (dose in mg/kg/day)			
Contaminated Fruit	0.0015	0.00058	0.034
Consumption of Water	0.00086	8.0 E-5	0.0026
Consumption of Fish, general public	2.6 E-7	3.4 E-8	6.4 E-7
Consumption of Fish, subsistence population	2.1 E-6	2.8 E-7	5.2 E-6

Table F3-5h: 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	0.00031	3.5 E-5	0.0057
Contaminated Fruit	0.020	0.016	0.44
Contaminated Water, spill, child	0.46	0.28	0.68
Contaminated Water, stream, child	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	0.00032	0.00025	0.0070
Consumption of Water	0.00020	2.0 E-7	0.00048
Consumption of Fish, general public	1.0 E-6	1.4 E-9	2.0 E-6
Consumption of Fish, subsistence population	8.1 E-6	1.2 E-8	1.6 E-5

Table F3-5i: 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	2.4 E-7	1.9 E-8	1.3 E-6
Direct Spray, lower legs, woman	2.4 E-8	1.9 E-9	1.3 E-7
Dermal Exposure, contaminated vegetation	7.5 E-9	9.5 E-10	1.6 E-8
Contaminated Fruit	1.3 E-8	7.0 E-9	9.9 E-8
Contaminated Water, spill, child	1.7 E-7	3.8 E-8	3.2 E-7
Contaminated Water, stream, child	4.2 E-9	1.5 E-11	2.1 E-8
Consumption of Fish, general public	1.0 E-5	3.8 E-6	1.3 E-5
Consumption of Fish, subsistence populations	5.0 E-5	1.8 E-5	6.2 E-5
Chronic/Longer Term Exposures (dose in mg/kg/day)			
Contaminated Fruit	5.2 E-10	6.2 E-11	4.6 E-9
Consumption of Water	8.9 E-12	2.0 E-13	2.1 E-11
Consumption of Fish, general public	8.9 E-10	2.8 E-11	1.8 E-9
Consumption of Fish, subsistence population	7.2 E-9	2.3 E-10	1.4 E-8

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.

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.

2,4-D

In 1988, the U.S. EPA derived a chronic RfD of 0.01 mg/kg/day for 2,4-D. The RfD is based on a NOAEL of 1 mg/kg/day using an uncertainty factor of 100 to account for species to species extrapolation and sensitive individuals in the human population. Since this RfD was developed, a significant amount of new information was made available and is under review by the U.S. EPA as part of the re-registration process for 2,4-D. The re-registration review has focused on different studies to establish both an acute and chronic RfD. The chronic RfD is based on a 2-year chronic toxicity study in rats with a NOAEL of 5 mg/kg/day. There are two acute RfDs developed, one for females of childbearing age, and one for the population as a whole. The acute RfD for women is based on a developmental toxicity study in rats that found skeletal abnormalities at the 75 mg/kg/day dose, while the next lowest dose of 25 mg/kg/day was the NOAEL. The acute RfD for the general

population is based on an acute neurotoxicity study in rats that had a NOAEL of 67 mg/kg/day. As discussed in the hazard identification, the potential effects of 2,4-D on the developing nervous system as well as the endocrine system were considered to be data gaps in the toxicity database for 2,4-D. Because of this, the U.S. EPA recommends an additional 10X uncertainty factor (for a total of 1000) in deriving the RfDs. The RfD that will be used for acute exposure scenarios involving women will be 0.025 mg/kg/day; for the general population, the acute RfD will be 0.067 mg/kg/day. The chronic RfD that will be used is 0.005 mg/kg/day.

2,4-D is considered a restricted-use pesticide within the state of California.

The U.S. EPA Office of Water has established a lifetime health advisory level (HA) of 0.07 mg/L (70 ppb) and a 10-day HA of 0.30 mg/L for 2,4-D in drinking water (U.S. EPA, 2004b). 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, a Maximum Contaminant Level (MCL) of 0.07 mg/L has been set by U.S. EPA. This is an enforceable standard for drinking water quality. The state of California has also established a Public Health Goal (PHG) of 0.07 mg/L (70 ppb), based on a similar analysis as U.S. EPA (CalEPA, 1997a). The PHG describes a level of contamination at which adverse health effects would not be expected to occur, even over a lifetime of exposure. The dimethylamine salt formulation of 2,4-D is listed by the state of California on its Groundwater Protection List.

An assessment of the dose/duration/severity data on 2,4-D suggests no apparent or, at least, no strong relationship between exposure duration and the severity of effects at a given dose. In other words, adverse effects, if they are to develop, will develop relatively fast and will not become more severe as the duration of exposure continues. This assessment is confirmed by categorical regression analysis in which the duration of exposure is statistically insignificant. The weak duration-response relationship for 2,4-D may be explained, in part, by the pharmacokinetics of 2,4-D. For compounds like 2,4-D that are eliminated rapidly, the time to approximate steady state is relatively brief. Although somewhat speculative, this explanation suggests that 2,4-D does not exert cumulative toxic damage (i.e., at low levels of exposure, the rate of injury is less than the rate of repair).

A qualitative summary of the dose-severity relationship based on these data is presented in the table below. The animal doses are presented as ranges. The column labeled “estimated human dose” is the animal dose divided by 10 (i.e., the uncertainty factor used for species to species extrapolation

in deriving RfDs). The column giving estimated human doses in the table does not incorporate an additional uncertainty factor for sensitive subgroups or for data uncertainty, which is incorporated into the RfD. The purpose of the table is to provide dose estimates associated with effects of varying severity. Effects like these in sensitive subgroups exposed to 2,4-D cannot be quantified from the available data.

Table F4-1: Dose-severity relationships used for 2,4-D risk characterization

Animal Dose (mg ae/kg/day)	Estimated Human Dose (mg ae/kg/day)	Plausible Effect
100 to 1,000	10 to 100	Frank neurological and/or reproductive effects, including teratogenic, are likely. Upper limit of the range will be lethal without prompt and effective medical intervention.
10 to 100	1 to 10	For chronic exposures - Subclinical signs of neurologic toxicity are likely and mild signs of toxicity are plausible. Degenerative or other pathological changes to several organs are likely. Upper limit of the range may be lethal. For acute exposures – Risk of prenatal effects (reduced ossification, resorptions), possible neurological (behavioral) effects; body weight loss.
1 to 10	0.1 to 1	For chronic exposures - A slight increase in thyroid weight and/or decrease in testicular weight may be noted. Possible decrease in whole body weight gain. Subclinical signs of neurologic toxicity are possible. Subclinical pathology to the kidney and liver. For acute exposures – No effects are likely,
<0.1 to 1	<0.01 to 0.1	For chronic exposures – No effects are likely For acute exposures – No effects are likely

Source: Table derived from SERA 1998a and U.S. EPA 2000c

Dicamba

The most recent chronic U.S. EPA RfD for dicamba is 0.045 mg/kg/day. This RfD was derived by the U.S. EPA/OPP in the re-evaluation of pesticide tolerances for dicamba required by the Food Quality Protection Act (FQPA). The RfD is based on the two-generation reproduction study in rats by Masters (1993, as referenced in SERA 2004c). The dietary NOAEL in this study was 500 ppm, corresponding to daily doses of in the range of 35-44 mg/kg/day. The dietary LOAEL, based on significantly decreased pup growth, was 1,500 ppm, corresponding to daily doses of 105-135 mg/kg/day. The RfD of 0.045 mg/kg/day proposed by U.S. EPA/OPP appears to be based on a rounding of the NOAEL to 45 mg/kg/day and the use of an uncertainty factor of 1000, 10 for species to species extrapolation, 10 for sensitive subgroups, and 10 as an FQPA uncertainty factor for the protection of children. It should be noted that FQPA requires the U.S. EPA to use an additional uncertainty factor of 10 to encompass concerns for exposures involving children unless the available toxicity data indicate that such an uncertainty factor is unnecessary. In an earlier version of the RfD development, the U.S. EPA/OPP had used an uncertainty factor of 300. It is unclear why the

uncertainty factor was increased to 1000 but this factor will be maintained for consistency with the U.S. EPA/OPP risk assessment and because it is more protective than the uncertainty factor of 300.

Prior to the RfD derived by U.S. EPA/OPP, the U.S. EPA had recommended a somewhat lower chronic RfD of 0.03 mg/kg/day. This RfD was based on a NOAEL of 3 mg/kg/day in a teratology study in rabbits (Goldenthal et al. 1978, as referenced in SERA 2004c). In a re-evaluation of the data, the U.S. EPA/OPP determined that the Goldenthal et al. (1978) study was not scientifically adequate and should not be the basis of the chronic RfD. Deficiencies of the study include the use of unhealthy rabbits, lack of clinical signs and individual necropsy data, inadequate number of pregnancies, lack of analytical data on dosing solutions, and the conduct of the study prior to GLP regulations. This re-evaluation of the study by Goldenthal et al. (1978) is supported by a more recent teratology study in rabbits by Hoberman (1992 as referenced in SERA 2004c). Hoberman (1992) failed to note any effects in dams or pups at a dose of 30 mg/kg/day. At 150 mg/kg/day, there were signs of maternal toxicity as well as an increase in the number of spontaneous abortions.

For this risk assessment, the most recent RfD – i.e., 0.045 mg/kg/day derived by the Office of Pesticides – will be used to characterize risk. Given the reasonable and well-documented concerns with the earlier teratology studies as well as the appropriate application of the FQPA uncertainty factors in the more recent RfD, the use of the more recent chronic RfD seems justified over the earlier and somewhat lower RfD.

For characterizing the risks for acute exposure scenarios, 1-day dietary RfD of 0.10 mg/kg/day, derived by U.S. EPA/OPP, is used. This acute RfD is based on a neurotoxicity study, which involved single-dose gavage exposures to rats at doses of 300, 600 or 1200 mg/kg. At the lowest dose tested, 300 mg/kg/day, a number of gross signs of neurotoxicity, including impaired gait and decreased forelimb grip strength, were apparent within 2.5 hours after dosing. Most effects were transient but decreased forelimb grip strength persisted for 7 days. Thus, 300 mg/kg/day was classified as an LOAEL. The RfD was derived by dividing the LOAEL by an uncertainty factor of 3000: 10 for species to species, 10 for sensitive subgroups, 10 for the use of a LOAEL, 3 for FQPA considerations. The use of the 300 mg/kg/day with an uncertainty factor of 10 for using the LOAEL functionally estimates the NOAEL at 30 mg/kg/day. Because the neurotoxicity study involved adult animals rather than neonate or young animals, the application of the FQPA uncertainty factor is clearly appropriate.

Dicamba is considered a restricted-use pesticide within the state of California.

The U.S. EPA Office of Drinking Water used the 3 mg/kg/day NOAEL from the teratology study to derive a 10-day health advisory for drinking water of 0.3 mg/L using an uncertainty factor of

100. This 10-day health advisory was also recommended for 1-day exposures. Thus, this is analogous to a 1-day RfD of 0.03 mg/kg/day, identical to the chronic NOAEL.

While the 1-day RfD of 0.03 mg/kg based on the Office Drinking Water 1-day health advisory is somewhat more conservative than the acute RfD of 0.10 mg/kg derived by U.S. EPA/OPP, the 1-day RfD derived by U.S. EPA/OPP is based on a single dose exposure and more clearly applies to several of the acute exposure scenarios developed in this risk assessment. Consequently, the 1-day RfD of 0.10 mg/kg is used to characterize the risks of short-term exposures.

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 (1993c) 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, 2004b). 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, 1997b). The PHG describes a level of contamination at which adverse health effects would not be expected to occur, even over a lifetime of exposure

Triclopyr

The U.S. EPA has established a chronic RfD for triclopyr at 0.05 mg/kg/day (U.S. EPA 1998b). 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 (1998b) 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 1998b), 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, the current 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_{50} 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.

Table F4-2: 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 2003a) as a functional NOAEL value is the approach utilized by the Canadian government. However, the more recent multigeneration study by Nagao et al. (2001 , as referenced in USDA 2003a) provides a NOEL value of 10 mg/kg/day for NP.

Utilizing a 10X safety factor for interspecies differences and a 10X safety factor for intraspecies differences provides a value of 0.10 mg/kg/day which should be protective of human health from chronic exposures to NP and NPEs. Since the toxicity of NPEs decreases with increasing numbers of ethoxylate groups, and that the general population is exposed to mixtures that include NPEs of longer chain lengths, this protective value, based on NP, should be considered conservative.

Another method would be to utilize the experimental values for NP9E, with the assumption that any testing involving the NP9E mixture would include minor amounts of NP and the short-chain NPEs. However there is a lack of chronic test results involving NP9E, and the subchronic test results are not much different than the corresponding values for NP. Hence the derived value of 0.10 mg/kg/day for NP will be used to assess risks of chronic human exposure.

For shorter-term exposures, 90-day subchronic tests involving NP9E in rats and beagles resulted in NOELs ranging from 10 to approximately 30 mg/kg/day. LOAELs from these same studies ranged upwards from 50 mg/kg/day. Slightly higher NOELs of 40 mg/kg/day were seen in 90-day sub-chronic studies with NP4E and NP6E. The use of the lowest sub-chronic NOEL of 10 mg/kg/day will be another conservative measure, considering that in these studies there is a considerable gap in dosing intervals between the NOEL and LOAEL levels determined in these studies. Again, using the same two safety factors as above, the human acute NOEL that will be used is 0.10 mg/kg/day. Based on the sub-chronic studies, however, short-term, or acute exposures to humans in the range of 0.1 to 0.4 mg/kg/day should not be associated with adverse health effects.

As regards the estrogenicity of NP and NPEs, it appears that most estrogenic effects are seen at relatively high exposure rates in mammals. The assessment level of 0.10 mg/kg/day should be

protective of any estrogenic or reproductive effects that NP and NPE exposure may represent in mammalian systems.

Hexachlorobenzene

The U.S. EPA RfD for hexachlorobenzene is 0.0008 mg/kg/day. This RfD is based on a 130-week feeding study in male and female rats that also included a 90-day exposure to offspring. The U.S. EPA judged the NOAEL for liver effects at a dose of 0.08 mg/kg/day with a LOAEL at 0.29 mg/kg/day. The U.S. EPA used an uncertainty factor of 100 to derive the RfD of 0.0008 mg/kg/day.

ATSDR has derived an acute Minimal Risk Level (MRL) for hexachlorobenzene of 0.008 mg/kg/day, a factor of 10 above the chronic RfD derived by U.S. EPA. The U.S. EPA Office of Drinking Water has derived a maximum contaminant level of 0.001 mg/L of drinking water and a 10-day health advisory of 0.05 mg/L in drinking water (U.S. EPA 2004b).

In addition to systemic toxicity, hexachlorobenzene has been shown to cause tumors of the liver, thyroid and kidney in three species of rodents - mice, rats, and hamsters. Based on a two-year feeding study in rats, the U.S. EPA derived a cancer slope factor for lifetime exposures of 1.6 $(mg/kg/day)^{-1}$. In other words, cancer risk over a lifetime (P) is calculated as the product of the daily dose (d) over a lifetime and the potency parameter (â) ($P = d \times â$). The lifetime daily dose associated with a given risk level is therefore: $d = P \div â$. Thus, the lifetime daily dose of hexachlorobenzene associated with a risk of one in one million is 0.000000625 mg/kg/day (6.25×10^{-7}).

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 $(mg/kg/day)^{-1}$ is intended to be applied 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 $(mg/kg/day)^{-1}$ is scaled linearly when applied to shorter periods of exposure. As calculated in SERA (1999), the potency parameter for a one-day exposure is 0.000063 $(mg/kg/day)^{-1}$. Thus, the lifetime risk associated with a single dose of 0.001 mg/kg would be calculated as 6.3×10^{-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 assessment is made for the potential carcinogenic effects of pentachlorobenzene. This is consistent with the approach taken by U.S. EPA and reflects the fact that the available data on pentachlorobenzene are inadequate to classify this compound as a carcinogen or to estimate carcinogenic potency. Because pentachlorobenzene and hexachlorobenzene are structurally and toxicologically similar and because the chronic RfD for both compounds are identical, a more conservative approach would be to assume that pentachlorobenzene is a carcinogen and that the carcinogenic potency of pentachlorobenzene is equal to that of hexachlorobenzene. If such an approach were taken, the cancer risks taken in this risk assessment would increase by a factor of about 0.1. In other words, pentachlorobenzene would be assumed to have the same potency but occurs at a ten-fold lower concentration relative to hexachlorobenzene. This relatively modest difference has little impact on the characterization of cancer risk.

Section 5 - Risk Characterization

A quantitative summary of the risk characterization for workers associated with exposure to these herbicides is presented in Tables F5-1a to F-10a. The quantitative risk characterization is expressed as the hazard quotient, which is the ratio of the estimated exposure doses from Tables F3-3a to F3-3i to the RfD. The quantitative hazard characterization for the general public associated with exposure to these herbicides is summarized in Tables F5-1b to F5-10b. 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 F3-5a to F3-5i 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 E-7 equivalent to 7×10^{-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 3,000 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=0.1) are 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 or longer-term exposure scenarios approach a level of concern. Although there are several uncertainties in the longer-term exposure assessments for the general public, the upper limits for hazard quotients 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 chlorsulfuron.

For the acute/accidental scenarios, the exposure resulting from the consumption of contaminated water by a child is the only scenario that approaches a level of concern (HQ=0.1 at upper level). 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 chlorsulfuron, 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 chlorsulfuron, such scenarios involve oral (contaminated water) rather than dermal (spills or accidental spray) exposure.

Table F5-1a: Summary of Risk Characterization for Workers – Chlorsulfuron

Chronic RfD = 0.02 mg/kg/day Acute RfD = 0.25 mg/kg/day			
Scenario	**Hazard Quotient[1]**		
	Typical	**Lower**	**Upper**
General Exposures			
Backpack application	1.E-02	6.E-04	1.E-01
Boom Spray	1.E-02	2.E-04	1.E-01
Accidental/Incidental Exposures			
Immersion of hands, 1 minute	4.E-07	8.E-08	2.E-06
Contaminated Gloves, 1 hour	3.E-05	5.E-06	1.E-04
Spill on hands. 1 hour	2.E-05	2.E-06	1.E-04
Spill on lower legs, 1 hour	4.E-05	4.E-06	3.E-04

[1] Hazard quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

Table F5-1b: 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[1]**		
	Typical	**Lower**	**Upper**
Acute/Accidental Exposures			
Direct Spray, entire body, child	6.E-04	6.E-05	5.E-03
Direct Spray, lower legs, woman	6.E-05	6.E-06	5.E-04
Dermal Exposure, contaminated vegetation	6.E-05	9.E-06	4.E-04
Contaminated Fruit	2.E-03	2.E-03	5.E-02
Contaminated Water, spill, child	5.E-02	2.E-02	1.E-01
Contaminated Water, stream, child	1.E-03	6.E-05	6.E-03
Consumption of Fish, general public	2.E-03	8.E-04	3.E-03
Consumption of Fish, subsistence populations	8.E-03	4.E-03	1.E-02
Chronic/Longer Term Exposures			
Contaminated Fruit	1.E-02	9.E-03	2.E-01
Consumption of Water	4.E-05	4.E-06	1.E-04
Consumption of Fish, general public	3.E-07	4.E-08	6.E-07
Consumption of Fish, subsistence population	2.E-06	3.E-07	5.E-06

[1] 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 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 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 are 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 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.

None of the acute or longer-term exposure scenarios approach a level of concern. Although there are several uncertainties in the longer-term exposure assessments for the general public, the upper limits for hazard quotients 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 clopyralid.

For the acute/accidental scenarios, the exposure resulting from the consumption of contaminated water by a child is the only scenario that approaches 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, only the consumption of contaminated fruit approaches a level of concern, and only at the upper levels of exposure. This scenario points out the importance of directing the herbicide onto the targeted vegetation and avoiding non-target deposition through overspray or drift.

Table F5-2a: Summary of Risk Characterization for Workers – Clopyralid

Chronic RfD = 0.15 mg/kg/day Acute RfD = 0.75 mg/kg/day			
Scenario	**Hazard Quotient[1]**		
	Typical	**Lower**	**Upper**
General Exposures			
Backpack application	1 E-2	3 E-4	7 E-2
Boom Spray	9 E-3	1 E-4	7 E-2
Accidental/Incidental Exposures			
Immersion of hands, 1 minute	5 E-7	5 E-8	3 E-6
Contaminated Gloves, 1 hour	3 E-5	3 E-6	2 E-4
Spill on hands. 1 hour	1 E-4	7 E-6	6 E-4
Spill on lower legs, 1 hour	2 E-4	2 E-5	1 E-3

[1] Hazard quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

Table F5-2b: Summary of Risk Characterization for the Public – Clopyralid

Chronic RfD = 0.15 mg/kg/day Acute RfD = 0.75 mg/kg/day			
Scenario	**Hazard Quotient[1]**		
	Typical	**Lower**	**Upper**
Acute/Accidental Exposures			

Direct Spray, entire body, child	4 E-3	3 E-4	2 E-2
Direct Spray, lower legs, woman	4 E-4	3 E-5	2 E-3
Dermal Exposure, contaminated vegetation	5 E-4	5 E-5	2 E-3
Contaminated Fruit	4 E-3	2 E-3	6 E-2
Contaminated Water, spill, child	9 E-2	2 E-2	2 E-1
Contaminated Water, stream, child	5 E-4	4 E-5	3 E-3
Consumption of Fish, general public	3 E-3	1 E-3	3 E-3
Consumption of Fish, subsistence populations	1 E-2	5 E-3	2 E-2
Chronic/Longer Term Exposures			
Contaminated Fruit	8 E-3	3 E-3	2 E-1
Consumption of Water	3 E-4	2 E-5	7 E-4
Consumption of Fish, general public	2 E-6	1 E-7	3 E-6
Consumption of Fish, subsistence population	1 E-5	1 E-6	3 E-5

[1] Hazard quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

2,4-D

Workers – For all accidental exposures, none of the scenarios exceeds a hazard quotient of one, although at the upper rates of exposure, a value of unity is approached. At the typical application rates, the hazard quotient slightly exceeds one with a value of 2 for both backpack and boom spray applications. At the upper rates of application, worker exposures greatly exceed a value of one, with hazard quotients of 16 and 17. One reason for these high hazard quotients is the additional 10X safety factor due to toxicity database gaps that is used to derive the RfD. As discussed in Section 4, and assuming that the missing studies don't change the conclusions, chronic human doses in the range of 0.08 to 0.09 mg/kg/day (upper range for workers) can result in some sub-clinical effects (effects to kidney, liver, testes, thyroid, body weight). At the typical exposures, effects to workers are unlikely, even with hazard quotients slightly exceeding unity.

As stated, some formulations of 2,4-D are severe eye irritants. Quantitative risk assessments for irritation are not usually derived, and, for 2,4-D specifically, the available data do not support any reasonable quantitative dose-response modeling. Splashing liquid formulations into the eye would probably cause severe eye irritation. While skin irritation could also occur, it would probably be less severe than effects on the eyes.

General Public - For the acute/accidental scenarios, the exposures resulting from the consumption of contaminated water after a spill by a child or by consuming fish found in such contaminated waters, at the typical application rates exceed the level of concern. The doses associated with these typical application rates ranges from 0.41 to 2.4 mg/kg per incident. Again, assuming that new studies don't change the current hazard discussions, levels of acute exposures from 1 to 3 mg/kg/day could result in prenatal effects, possible neurological effects, and body weight loss. These scenarios point out that spill prevention and the prevention of water contamination is a critical aspect of 2,4-D use.

At the upper exposure levels, all the acute/accidental public exposures approach or exceed the level of concern, with hazard quotients ranging from 0.6 to 60. As with the worker exposures, one reason for these high hazard quotients is the additional 10X safety factor due to toxicity database gaps that is used to derive the RfD. As stated, where the acute human exposures exceed about 1 mg/kg/day, potential subclinical effects could be seen. Based on the values in Table F-5c, the only upper range acute exposure scenarios that exceed this level of exposure (1 mg/kg/day) are the consumption of water and fish after a spill.

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 2,4-D, 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 water contamination. The HQ values for this scenario range from 0.04 to 1.4 with acute doses below 1 mg/kg/day so would not be expected to result in acute toxic effects.

Of the longer-term scenarios, only the consumption of unwashed berries immediately after application of the highest dose yields a hazard quotient that is substantially greater than unity. At the highest application rate of 2.0 lbs/acre, the estimated dose would be about 0.08 mg/kg/day. This value is in the range of which no chronic effects should be seen. This scenario may be considered conservative in that it does not consider the effects of washing contaminated vegetation, but again, it points out that oral exposures are of greater concern than dermal exposures. It also points out the importance of notifying the public of areas to be treated so that the collection of food products or basketry materials can be avoided.

Table F5-3a: Summary of Risk Characterization for Workers – 2,4-D

Chronic RfD = 0.005 mg/kg/day Acute RfD = 0.067 mg/kg/day (general population) Acute RfD = 0.025 mg/kg/day (women)			
Scenario	**Hazard Quotient[1]**		
	Typical	**Lower**	**Upper**
General Exposures			
Backpack application	2	4 E-2	16
Boom Spray	2	1 E-2	17
Accidental/Incidental Exposures			
Immersion of hands, 1 minute	5 E-4	5 E-5	2 E-3

Contaminated Gloves, 1 hour	3 E-2	3 E-3	1 E-1
Spill on hands, 1 hour	1 E-2	9 E-4	6 E-2
Spill on lower legs, 1 hour	3 E-2	2 E-3	2 E-1

[1] Hazard quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

Table F5-3b: Summary of Risk Characterization for the Public – 2,4-D

Chronic RfD = 0.005 mg/kg/day Acute RfD = 0.067 mg/kg/day (general population) Acute RfD = 0.025 mg/kg/day (women)			
Scenario	**Hazard Quotient[1]**		
	Typical	**Lower**	**Upper**
Acute/Accidental Exposures			
Direct Spray, entire body, child	5 E-1	4 E-2	2
Direct Spray, lower legs, woman	1 E-1	1 E-2	1
Dermal Exposure, contaminated vegetation	2 E-1	2 E-2	1
Contaminated Fruit	7 E-1	2 E-1	15
Contaminated Water, spill, child	6	1	15
Contaminated Water, stream, child	3 E-1	4 E-2	1
Consumption of Fish, general public	7	2	12
Consumption of Fish, subsistence populations	36	8	60
Chronic/Longer Term Exposures			
Contaminated Fruit	1	3 E-1	17
Consumption of Water	2 E-2	2 E-3	5 E-2
Consumption of Fish, general public	3 E-3	6 E-4	9 E-3
Consumption of Fish, subsistence population	3 E-2	5 E-3	7 E-2

[1] Hazard quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

Dicamba

Workers – For all accidental exposures, none of the scenarios exceeds a hazard quotient of one, although at the upper rates of exposure, a value of unity is approached. At the typical and lower application rates, the hazard quotients are below unity for both backpack and boom spray applications. At the upper application rate, the hazard quotient slightly exceeds one with a value of 2 for both backpack and boom spray applications. The simple verbal interpretation of this quantitative characterization of risk is that under a protective set of exposure assumptions, backpack and boom spray workers would not be exposed to levels of dicamba that are regarded as unacceptable at the typical application rate. At the maximum application rate, some workers could be exposed to levels of dicamba that would not be regarded as acceptable. It is unclear from the toxicity tests that form the basis for the RfD, if overt effects would be likely from this slight exceedance. These doses are below the 45 mg/kg/day rat NOAEL by a factor of ~560.

As discussed in Section 2, dicamba may be irritating to the eyes and cause mild and transient skin irritation. Quantitative risk assessments for skin and eye irritation are not derived; however, from a practical perspective, effects on the eyes and skin are likely to be the most common effects as a

consequence of mishandling dicamba. These effects can be minimized or avoided by prudent industrial hygiene practices during the handling of dicamba.

General Public - For the acute/accidental scenarios, the exposure resulting from the consumption of contaminated water after a spill by a child at the typical application rates slightly exceeds the level of concern (HQ = 3). As stated above for workers, it is uncertain from the toxicology studies whether such an acute exposure would result in any overt effects. At the upper exposure level, the consumption of contaminated water by a child exceeds the level of concern by an order of magnitude (HQ = 10). This level of exposure (approximately 1 mg/kg/day) may result in subclinical effects to a child, although the toxicity data do not clearly point to this conclusion. As stated in Section 4, the acute RfD is based on a single-dose neurotoxicity study in rabbits with an implied NOAEL of 30 mg/kg/day. Based on this study, there is a chance for some neurological effects to a child exposed at the upper application rates from drinking water after a spill.

At the upper exposure levels, two other acute/accidental public exposures slightly exceed the level of concern, with hazard quotients ranging from 1.7 to 4. Again, it is uncertain from the toxicology studies whether such acute exposures would result in any overt effects to adults.

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 dicamba, 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 water contamination; the HQ values are below 1 at all application rates.

Of the longer-term scenarios, only the consumption of unwashed berries immediately after application of the highest dose yields a hazard quotient that is greater than unity. At the highest application rate of 2 lbs ae/acre, the estimated dose would be about 0.05 mg/kg/day. Similar to the worker exposures, it is unclear from the toxicity tests that form the basis of the RfD, if overt effects would be likely. This dose is 833 times lower than the 45 mg/kg/day rat NOAEL on which the current RfD is based. This scenario may be considered conservative in that it does not consider the effects of washing contaminated vegetation, but again, it points out that oral exposures are of greater concern

than dermal exposures. It also points out the importance of notifying the public of areas to be treated so that the collection of food products or basketry materials can be avoided.

Table F5-4a: Summary of Risk Characterization for Workers – Dicamba

Chronic RfD = 0.045 mg/kg/day Acute RfD = 0.1 mg/kg/day			
Scenario	**Hazard Quotient[1]**		
	Typical	**Lower**	**Upper**
General Exposures			
Backpack application	1 E-1	2 E-3	2
Boom Spray	1 E-1	7 E-4	2
Accidental/Incidental Exposures			
Immersion of hands, 1 minute	3 E-4	2 E-5	2 E-3
Contaminated Gloves, 1 hour	2 E-2	1 E-3	1 E-1
Spill on hands, 1 hour	6 E-3	4 E-4	4 E-2
Spill on lower legs, 1 hour	1 E-2	9 E-4	1 E-1

[1] Hazard quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

Table F5-4b: Summary of Risk Characterization for the Public – Dicamba

Chronic RfD = 0.045 mg/kg/day Acute RfD = 0.1 mg/kg/day			
Scenario	**Hazard Quotient1**		
	Typical	**Lower**	**Upper**
Acute/Accidental Exposures			
Direct Spray, entire body, child	2 E-1	1 E-2	1.7
Direct Spray, lower legs, woman	2 E-2	1 E-3	2 E-1
Dermal Exposure, contaminated vegetation	3 E-2	2 E-3	2 E-1
Contaminated Fruit	1 E-1	3 E-2	4
Contaminated Water, spill, child	3	3 E-1	10
Contaminated Water, stream, child	2 E-3	7 E-6	2 E-2
Consumption of Fish, general public	5 E-2	1 E-2	1 E-1
Consumption of Fish, subsistence populations	3 E-1	5 E-2	7 E-1
Chronic/Longer Term Exposures			
Contaminated Fruit	4 E-2	9 E-3	1.2
Consumption of Water	6 E-6	6 E-7	5 E-5
Consumption of Fish, general public	2 E-8	3 E-9	1 E-7
Consumption of Fish, subsistence population	2 E-7	2 E-8	1 E-6

[1] 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 330 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 limit 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 125 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. As discussed in SERA, 2003a, glyphosate with the POEA surfactant, is about as irritating as standard dishwashing detergents, all purpose cleaners, and baby shampoos.

General Public - None of the longer-term exposure scenarios approach a level of concern. Although there are several uncertainties in the longer-term exposure assessments for the general public, the upper limits for hazard quotients 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 glyphosate.

For the acute/accidental scenarios, the exposure resulting from the consumption of contaminated water by a child, at the highest application rates, approaches the level of concern. None of the other acute/accidental exposures reach or exceed a hazard quotient of one. At the exposure level for a child drinking water, as per the discussion in Section 4, no effects would be anticipated for doses up to 20 mg/kg/day. It is important to realize that 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 glyphosate, 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 substantially below 1. 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 glyphosate, such scenarios involve oral (contaminated water) rather than dermal (spills or accidental spray) exposure.

Table F5-5a: Summary of Risk Characterization for Workers – Glyphosate

RfD = 2.0 mg/kg/day			
Scenario	**Hazard Quotient[1]**		
	Typical	**Lower**	**Upper**
General Exposures			
Backpack application	8 E-3	1 E-4	8 E-2
Boom Spray	7 E-3	5 E-5	8 E-2
Accidental/Incidental Exposures			
Immersion of hands, 1 minute	2 E-6	1 E-7	1 E-5
Contaminated Gloves, 1 hour	1 E-4	6 E-6	8 E-4
Spill on hands, 1 hour	2 E-4	2 E-5	1 E-3
Spill on lower legs, 1 hour	6 E-4	4 E-5	3 E-3

[1] Hazard quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

Table F5-5b: Summary of Risk Characterization for the Public – Glyphosate

RfD = 2.0 mg/kg/day			
Scenario	**Hazard Quotient[1]**		
	Typical	**Lower**	**Upper**
Acute/Accidental Exposures			
Direct Spray, entire body, child	9 E-3	6 E-4	4 E-2
Direct Spray, lower legs, woman	9 E-4	6 E-5	4 E-3
Dermal Exposure, contaminated vegetation	1 E-3	1 E-4	5 E-3
Contaminated Fruit	1 E-2	4 E-3	3 E-1
Contaminated Water, spill, child	3 E-1	5 E-2	9 E-1
Contaminated Water, stream, child	2 E-3	2 E-5	8 E-2
Consumption of Fish, general public	4 E-3	8 E-4	7 E-3
Consumption of Fish, subsistence populations	2 E-2	4 E-3	4 E-2
Chronic/Longer Term Exposures			
Contaminated Fruit	8 E-3	2 E-3	2 E-1
Consumption of Water	4 E-5	8 E-7	5 E-4
Consumption of Fish, general public	7 E-8	2 E-9	8 E-7
Consumption of Fish, subsistence population	5 E-7	2 E-8	7 E-6

[1] 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 1.2 and 1.3. 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.

None of the accidental scenarios for workers, involving triclopyr TEA exceed a level of concern.

The accidental exposure scenario of wearing gloves contaminated with triclopyr BEE for 1 hour exceeds the RfD for upper exposure levels (HQ = 1.6). Although it is unlikely that a one-time exposure to triclopyr BEE 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 BEE 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.

None of the longer-term exposure scenarios exceed the level of concern. Although there are several uncertainties in the longer-term exposure assessments for the general public, the upper limits for the chronic 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 triclopyr (either the BEE or TEA formulations).

In the 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, it is unlikely that there would be any adverse health effects associated with a one-time exposure.

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 1000. 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 F5-6a: Summary of Risk Characterization for Workers – Triclopyr TEA

Chronic RfD = 0.05 mg/kg/day Acute RfD = 1 mg/kg/day			
Scenario	**Hazard Quotient1**		
	Typical	**Lower**	**Upper**
General Exposures			

Backpack application	1 E-1	4 E-3	1.2
Boom Spray	1 E-1	1 E-3	1.3
Accidental/Incidental Exposures			
Immersion of hands, 1 minute	2 E-5	4 E-6	1 E-4
Contaminated Gloves, 1 hour	1 E-3	2 E-4	6 E-3
Spill on hands, 1 hour	6 E-3	8 E-4	3 E-2
Spill on lower legs, 1 hour	2 E-2	2 E-3	9 E-2

[1] Hazard quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

Table F5-6b: Summary of Risk Characterization for the Public – Triclopyr TEA

Chronic RfD = 0.05 mg/kg/day Acute RfD = 1 mg/kg/day			
Scenario	**Hazard Quotient[1]**		
	Typical	**Lower**	**Upper**
Acute/Accidental Exposures			
Direct Spray, entire body, child	2 E-1	3 E-2	1.3
Direct Spray, lower legs, woman	5 E-1	6 E-2	3
Dermal Exposure, contaminated vegetation	6 E-1	1 E-1	2
Contaminated Fruit	6 E-2	3 E-2	1.0
Contaminated Water, spill, child	3 E-1	6 E-2	8 E-1
Contaminated Water, stream, child	7 E-3	2 E-5	7 E-2
Consumption of Fish, general public	5 E-4	2 E-4	9 E-4
Consumption of Fish, subsistence populations	2 E-3	8 E-4	4 E-3
Chronic/Longer Term Exposures			
Contaminated Fruit	3 E-2	1 E-2	7 E-1
Consumption of Water	2 E-2	2 E-3	5 E-2
Consumption of Fish, general public	5 E-6	7 E-7	1 E-5
Consumption of Fish, subsistence population	4 E-5	6 E-6	1 E-4

[1] Hazard quotient is the level of exposure divided by the RfD, then rounded to one significant digit. NOTE: chronic RfD used for acute scenarios involving women.

Table F5-7a: Summary of Risk Characterization for Workers – Triclopyr BEE

Chronic RfD = 0.05 mg/kg/day Acute RfD = 1.0 mg/kg/day			
Scenario	**Hazard Quotient[1]**		
	Typical	**Lower**	**Upper**
General Exposures			
Backpack application	1 E-1	4 E-3	1.2
Boom Spray	1 E-1	1 E-3	1.3
Accidental/Incidental Exposures			
Immersion of hands, 1 minute	8 E-3	1 E-3	3 E-2
Contaminated Gloves, 1 hour	5 E-1	9 E-2	1.6
Spill on hands, 1 hour	2 E-2	4 E-5	6 E-2
Spill on lower legs, 1 hour	5 E-2	1 E-4	1 E-1

[1] Hazard quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

Table F5-7b: Summary of Risk Characterization for the Public – Triclopyr BEE

Chronic RfD = 0.05 mg/kg/day Acute RfD = 1.0 mg/kg/day			
Scenario	**Hazard Quotient[1]**		
	Typical	**Lower**	**Upper**
Acute/Accidental Exposures			
Direct Spray, entire body, child	7 E-1	2 E-3	2
Direct Spray, lower legs, woman	1.4	3 E-3	4

Dermal Exposure, contaminated vegetation	1.3	6 E-3	3
Contaminated Fruit	6 E-2	3 E-2	1.0
Contaminated Water, spill, child	3 E-1	6 E-2	8 E-1
Contaminated Water, stream, child	7 E-3	2 E-5	7 E-2
Consumption of Fish, general public	5 E-4	2 E-4	9 E-4
Consumption of Fish, subsistence populations	2 E-3	8 E-4	4 E-3
Chronic/Longer Term Exposures			
Contaminated Fruit	3 E-2	1 E-2	7 E-1
Consumption of Water	2 E-2	2 E-3	5 E-2
Consumption of Fish, general public	5 E-6	7 E-7	1 E-5
Consumption of Fish, subsistence population	4 E-5	6 E-6	1 E-4

[1] Hazard quotient is the level of exposure divided by the RfD, then rounded to one significant digit. NOTE: chronic RfD used for acute scenarios involving women.

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 approaches or just reaches the derived RfD. Given the conservative nature of the RfD itself, it is unlikely that there would be any signs of toxicity.

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 –Like the quantitative risk characterization for workers, the quantitative risk characterization for the general public is expressed as the hazard quotient using the derived RfD of 0.10 mg/kg/day.

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 and exposure resulting from the consumption of contaminated vegetation are of concern. None of the other acute exposure scenarios represent a risk of effects to the public from NP9E exposure.

The spill scenario represents the greatest risk, with an HQ of 5 for the typical application rate, and an HQ exceeding unity even with the lowest application rates. An HQ of 5 represents a risk of subclinical effects to the liver and kidney. The upper HQ of 7 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.

The consumption of contaminated vegetation also represents a risk of clinical effects at the high application rates only (HQ = 4). At the typical rate of application, the HQ is less than one. 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 NP9E, such scenarios involve oral rather than dermal exposure.

Table F5-8a: Summary of Risk Characterization for Workers – Nonylphenol Polyethoxylate

RfD = 0.10 mg/kg/day			
Scenario	**Hazard Quotient[1]**		
	Typical	**Lower**	**Upper**
General Exposures			
Backpack application	1 E-1	5 E-3	9 E-1
Boom Spray	9 E-2	2 E-3	1.0
Accidental/Incidental Exposures			
Immersion of hands, 1 minute	2 E-3	6 E-4	4 E-3
Contaminated Gloves, 1 hour	1 E-1	4 E-2	3 E-1
Spill on hands, 1 hour	5 E-4	8 E-5	7 E-3
Spill on lower legs, 1 hour	1 E-3	2 E-4	2 E-2

[1] Hazard quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

Table F5-8b: Summary of Risk Characterization for the Public – Nonylphenol Polyethoxylate

RfD = 0.10 mg/kg/day			
Scenario	**Hazard Quotient[1]**		
	Typical	**Lower**	**Upper**
Acute/Accidental Exposures			
Direct Spray, entire body, child	2 E-2	3 E-3	3 E-1
Direct Spray, lower legs, woman	2 E-3	3 E-4	3 E-2
Dermal Exposure, contaminated vegetation	3 E-3	3 E-4	6 E-2
Contaminated Fruit	2 E-1	2 E-1	4
Contaminated Water, spill, child	5	3	7
Contaminated Water, stream, child	9 E-3	1 E-3	4 E-2

Consumption of Fish, general public	1 E-1	1 E-1	1 E-1
Consumption of Fish, subsistence populations	7 E-1	7 E-1	7 E-1
Chronic/Longer Term Exposures			
Contaminated Fruit	3 E-3	3 E-3	7 E-2
Consumption of Water	2 E-3	2 E-6	5 E-3
Consumption of Fish, general public	1 E-5	1 E-8	2 E-5
Consumption of Fish, subsistence population	8 E-5	1 E-7	2 E-4

[1] 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, 1999). 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 F5-10a 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 F5-10a, 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 1×10^{-6} mg/kg/day. As summarized in Table F3-3i, even the upper range general worker

exposure values are below this background dose – i.e., in the range of 2×10^{-8} to 3×10^{-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 1×10^{-8} to 2×10^{-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 Forest Service programs.

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 hexachlorobenzene or pentachlorobenzene will result in any substantial risk of cancer in workers applying them 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 1×10^{-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 0.008, 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 bioconcentrate 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 subsistence consumption of fish. 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 F3-5i, the highest longer-term exposure rate associated with Forest Service programs is 1.4×10^{-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.

Table F5-9a: Summary of Risk Characterization for Workers – Hexachlorobenzene

Chronic RfD = 0.0008 mg/kg/day Acute MRL = 0.008 mg/kg/day			
Scenario	**Hazard Quotient[1]**		
	Typical	**Lower**	**Upper**
General Exposures			
Backpack application	5 E-6	1 E-7	3 E-5
Boom Spray	4 E-6	5 E-8	3 E-5
Accidental/Incidental Exposures			
Immersion of hands, 1 minute	6 E-5	2 E-5	2 E-4
Contaminated Gloves, 1 hour	4 E-3	1 E-3	1 E-2
Spill on hands, 1 hour	8 E-7	2 E-7	4 E-6
Spill on lower legs, 1 hour	2 E-6	5 E-7	6 E-5

[1] Hazard quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

Table F5-9b: 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[1]**		
	Typical	**Lower**	**Upper**
Acute/Accidental Exposures			
Direct Spray, entire body, child	3 E-5	8 E-6	2 E-4

Chronic RfD = 0.0008 mg/kg/day Acute MRL = 0.008 mg/kg/day			
Scenario	**Hazard Quotient[1]**		
	Typical	**Lower**	**Upper**
Direct Spray, lower legs, woman	3 E-6	8 E-7	2 E-5
Dermal Exposure, contaminated vegetation	9 E-7	1 E-7	2 E-6
Contaminated Fruit	2 E-6	9 E-7	1 E-5
Contaminated Water, spill, child	2 E-5	2 E-5	4 E-5
Contaminated Water, stream, child	5 E-7	2 E-9	3 E-6
Consumption of Fish, general public	1 E-3	2 E-3	2 E-3
Consumption of Fish, subsistence populations	6 E-3	8 E-3	8 E-3
Chronic/Longer Term Exposures			
Contaminated Fruit	6 E-7	8 E-8	6 E-6
Consumption of Water	1 E-8	2 E-10	3 E-8
Consumption of Fish, general public	1 E-6	3 E-8	2 E-6
Consumption of Fish, subsistence population	9 E-6	3 E-7	2 E-5

[1] Hazard quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

Table F5-10a: Cancer Risk Characterization for Workers – Hexachlorobenzene

Dose representing a risk of 1 in 1 million = 6.25 E-7 $(mg/kg/day)^{-1}$			
Scenario	**Hazard Quotient**		
	Typical	**Lower**	**Upper**
General Exposures			
Backpack application	6 E-3	2 E-4	4 E-2
Boom Spray	6 E-3	6 E-5	4 E-2

Table F5-10b: Cancer Risk Characterization for Public – Hexachlorobenzene

Dose representing a risk of 1 in 1 million = 6.25 E-7 $(mg/kg/day)^{-1}$			
Scenario	**Hazard Quotient**		
	Typical	**Lower**	**Upper**
Chronic/Longer Term Exposures			
Contaminated Fruit	8 E-4	1 E-4	7 E-3
Consumption of Water	1 E-5	3 E-7	3 E-5
Consumption of Fish, general public	1 E-3	4 E-5	3 E-3
Consumption of Fish, subsistence population	1 E-2	4 E-4	2 E-2

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 via various routes of exposure resulting from the management scenarios presented in Alternatives 2, 4, and 6 and (2) additive doses if an individual is exposed to other herbicide treatments. Alternative 6 proposes using significantly less herbicide (only 7.5% of the amounts proposed for Alternatives 2 and 4). Therefore, potentially cumulative doses under Alternative 6 would be far less than under Alternatives 2 or 4.

Additional sources of exposure include: use of herbicides on adjacent private timberlands or home use by a worker or member of the general public. Using Forest Service and State of California pesticide-use records (from 2002 and 2003), Table F5-11 displays the use of herbicides on public and

private timberlands, rangelands, and road rights-of-ways (the latter assumed to be primarily for noxious weed work) within the four-counties that make up the Modoc National Forest area (Lassen, Modoc, Shasta, and Siskiyou Counties).

Most of the remaining uses of 2,4-D, dicamba, and glyphosate are in agricultural applications. In these counties, 2,4-D and dicamba are used on grain crops such as wheat, barley, forage hay, and oats. Clopyralid is used for pasture restoration and in mint fields. Glyphosate is used in a variety of field, row, and orchard crops, such as wheat, alfalfa, onions, and apples.

Based on a comparison of Forest Service annual pesticide-use reports for 2002 and 2003, and California Department of Pesticide Regulation reports for 2002 and 2003, the majority of herbicides used on timberlands in the Modoc National Forest area are on private lands. The Modoc national forest has not been extensively involved in herbicide applications in the last five years (for 2002, there was minor use of clopyralid, 2,4-D, dicamba, glyphosate, and hexazinone, all for noxious weed control and in 2003 and 2004 there were no herbicides applied on the Modoc NF).

Table F5-11: Forestry, Range, and ROW Herbicide Applications within Modoc National Forest Counties – 2002 and 2003

Herbicide	Pounds of Active Ingredient Applied	Acres Treated1	Average Rate per Acre (lbs/ac) 2	Forestry, Range, and ROW Use (lbs) as a % of Total Use in the Counties
Chlorsulfuron	115	0	-	71
Clopyralid	1013	367	0.2	71
2,4-D	20,501	7,985	1.2	28
Dicamba	2,394	91	0.8	43
Glyphosate	37,328	16,175	1.1	50
Triclopyr	7,054	4,246	1.1	88

Sources – USFS, Region 5, 2002 and 2003 Pesticide Use Reports; California Department of Pesticide Regulation, 2002 and 2003 Annual Pesticide Use Reports for Lassen, Shasta, Modoc, and Siskiyou counties, accessed on line at http://www.cdpr.ca.gov/docs/pur/purmain.htm on November 9, 2004 and August 25, 2005

1 – Acres Treated are only for forestry and rangeland uses as these are the only categories that have acres reported in the CDPR database.

2 – Average rate per acre is based on forestry and rangeland uses only.

Table F5-12a: Total Forestry, Range, and ROW Herbicide Applications within Modoc National Forest Counties, Calendar Year 2002, in Pounds

Category	Lassen	Modoc	Shasta	Siskiyou
Forestry	14,478	8,637	20,804	12,665
Rangeland	1	0	46	94
Rights-of-Way	5,766	12,585	54,790	20,930

Source - California Department of Pesticide Regulation, 2002 Annual Pesticide Use Reports for Lassen, Shasta, Modoc, and Siskiyou counties, accessed on line at http://www.cdpr.ca.gov/docs/pur/purmain.htm on November 9, 2004. This table includes all herbicides used in 2002, not just the six proposed for use in this EIS.

Table F5-12b: Total Forestry, Range, and ROW Herbicide Applications within Modoc National Forest Counties, Calendar Year 2003, in Pounds

Category	Lassen	Modoc	Shasta	Siskiyou
Forestry	8,737	5,538	18,908	19,455
Rangeland	0	287	10	929
Rights-of-Way	2,214	6,180	12,944	17,369

Source - California Department of Pesticide Regulation, 2003 Annual Pesticide Use Reports for Lassen, Shasta, Modoc, and Siskiyou counties, accessed on line at http://www.cdpr.ca.gov/docs/pur/purmain.htm on August 25, 2005. This table includes all herbicides used in 2003, not just the six proposed for use in this EIS.

We assume that, with the exception of uses proposed under Alternatives 2, 4, and 6 there would not be any extensive changes in the use patterns displayed in Tables F5-11, F5-12a and F5-12b into the near future.

Other projects that potentially could involve herbicides within the planning area on National Forest lands might involve the restoration of wildfire areas, such as the recent Blue Fire. However, at this time, there are no other pesticide-related projects listed on the Modoc National Forest Schedule of Proposed Action.

Under Alternatives 2 and 4, it is estimated that from 300 to 1,500 acres would be treated annually. It is assumed that Alternatives 1, 3, and 5 would not involve any herbicide use in this analysis. Based on the pesticide use from 2002-2003 displayed in Table F5-11, Alternatives 2, 4, and 6 would result in at most a 10% increase in forest and rangeland acreage treated in the Modoc National Forest area. [Total acres from column 3 of Table F5-11 = 28,864 acres. (3,000 acres in Alts 2,4,6)/28,864 = 0.103 or approximately 10%.] This is an overestimation, as the acres for rights-of-ways are not included in the totals in Table F5-11.

It is conceivable that workers or members of the public could be exposed to herbicides as a result of treatments on surrounding public or private forestlands or from fire restoration efforts on Forest Service lands. Where individuals could be exposed by more than one route, the risk of such cases can be quantitatively characterized by simply 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 0.02. 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 triclopyr residues up to 1.5 years after treatment (glyphosate, up to 66 weeks), however, these levels were less than 1 part per million (Segawa et al. 2001). Based on the re-treatment schedule in Alternatives 2, 4, and 6, 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.

Table F5-11 indicates that several of these herbicides are used primarily outside of forestlands in the four county area. 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 (Table F5-13). Adding the TMRC to this project's chronic dose estimates 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 change the risk conclusions based on the project-related HQ values.

Table F5-13: TMRC values for US population as a whole

Herbicide	TMRC (mg/kg/day)	% of RfD	Data Source
Chlorsulfuron	0.00386	19.3	US EPA 2002f
Clopyralid	0.00903	6.0	US EPA 1999b
2,4-D	0.000168	3.4	U.S. EPA 2004a
Dicamba	0.01075	35.8	US EPA 1999a
Glyphosate	0.02996	1.5	US EPA 2000a
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.

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÷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 mg/kg/day × 10 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 the four-county Modoc National Forest area, chlorpyrifos use in 2002 totaled 5,800 pounds, primarily used in alfalfa, onion, mint, and walnut orchards in the agricultural valleys. 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 40 times higher in 2002 then the four Modoc National Forest counties combined. This would indicate that it is unlikely that such high aquatic levels of chlorpyrifos would be found in the Modoc 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.

When assessing cumulative effects of exposure to NP and NPEs, there must be some consideration of the contribution from other sources, such as 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 (2001a, as referenced in USDA 2003a), the authors made some estimates of these background exposures based on extrapolation of admittedly limited data and very conservative assumptions. One of the more critical, and extreme, assumptions made was that dermal absorption of NP and NPEs would be 100%. This assumption was based on the inadequacy of the one *in vitro* study of absorption in human skin that showed absorption rates below 1%. However, this would seem to be an extreme over-assessment of absorption and leads to estimates of exposure that greatly exceed the threshold value for kidney damage in rats from NP exposure of 12 mg/kg/day. 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 2001a, 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 (2001a). 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 1% dermal absorption is used, this total would be reduced to 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 2003a).

In addition to xenoestrogens, humans are exposed to various phytoestrogens, which are hormone-mimicking substances naturally present in plants. Specific compounds that have been identified as phytoestrogens include coumestrol, formononetin, daidzein, biochanin A, and genistein. 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. There is some indication that a soy-based diet could act to ameliorate the effects of exposure to NP.

From Section 2, the lowest reproductive NOAEL for NP is 10 mg/kg/day from studies in rats. Assuming a 100X safety factor to convert to a human reproductive NOAEL, this 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 (2001a), 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 the derived NP human NOEL of 0.10 mg/kg/day, these exposure estimates result in hazard quotients of 270 and 3. In terms of this risk assessment, the non-acute contribution of NP9E (worker exposure ranged from 0.00016 to 0.1 mg/kg/day) would contribute up to 1 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 0.07 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

The issue concerning inert ingredients 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 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 U.S. 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 decision maker 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 U.S. EPA has categorized approximately 1200 inert ingredients into four lists. Lists 1 and 2 contain inert ingredients of toxicological concern. List 3 includes substances for which U.S. 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” (CBI) the Forest Service asked U.S. EPA to review the thirteen herbicides for the preparation of USDA 1989 (includes 2,4-D, dicamba, glyphosate, hexazinone, and triclopyr) and the commercial formulations and advise if they contained 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 of 2,4-D and triclopyr, and xylenes and naptha in certain formulations of 2,4-D. 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.

The 2,4-D formulation Weedone 638 label mentions petroleum distillates as being in the formulation. The current material data safety sheet (MSDS) also mentions two inerts: propylene glycol and titanium oxide (both on EPA list 4B). Heavy aromatic naptha ("other petroleum hydrocarbons") was identified in a 1988 letter from the FS Washington office to the Regions as the carrier for Weedone 638. Information from a Rhone-Poulenc 1995 MSDS (as described in NCAP, 2000) lists the following inerts for the Weedone 638 formulation of 2,4-D: methanol (CAS 67-56-1, EPA inert list 3), butoxyethanol (111-76-2, list 2), xylene (1330-20-7, list 2), and naphthalene (91-20-3, list 3).

EPA considers xylene to be a potentially toxic inert ingredient, with an oral RfD of 2 mg/kg/day, and is considered fetotoxic and teratogenic in mice at high doses, but EPA stated that the calculated RfD should be protective of these effects. EPA has not reached a conclusion on the carcinogenicity of xylene (USDA, 1997). In USDA, 1997, a human health risk assessment analyzed the risk of using xylene (an inert in two pesticides analyzed in that assessment). The conclusion from that assessment was that the proposed use of pesticides containing xylene did not represent a risk to either the public or the workers. Assuming that xylene makes up about 10% of the Weedone 638 formulation, and knowing that the RfD for xylene is 200 times higher than the value for 2,4-D, it would be unlikely that the RfD for xylene would be exceeded in the scenarios analyzed in this risk assessment. The lack of knowing the actual percentage of xylene in Weedone 638, as well as the lack of consensus on the carcinogenic potential of xylene adds some uncertainty to this risk assessment.

Butoxyethanol (or EGBE) has been assessed for human health risk as an impurity in the Garlon 4 formulation of triclopyr (Borrecco and Neisess, 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. As the actual amount of butoxyethanol in Weedone 638 is not known, there is some uncertainty in this risk assessment, however the toxicity of EGBE is a factor of 20 times lower than 2,4-D, and assuming that EGBE makes up less than 1% of Weedone 638, it is unlikely that the addition of EGBE represents a significantly increased hazard over the use of 2,4-D itself.

Comparison of acute toxicity (LD50 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 U.S. 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 NPE-based surfactants is analyzed in this risk assessment, and their 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.

There is a colorant often used in foliar applications of these herbicides (Colorfast™ Purple) that contains a dye, Basic Violet 3 or Gentian Violet, considered to be a potential carcinogen. A risk assessment for the carcinogenic properties of this dye was completed (SERA 1997b). In SERA (1997b) the cancer risk to workers and the public is at acceptable levels of risk. 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. As the SERA (1997b) reference adequately analyzes for the health risks of utilizing this dye, it will not be discussed further in this risk assessment. Another colorant that could be used is Hi-Light™ Blue colorant. 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. It is considered to be virtually non-toxic to humans. Its effect on non-target terrestrial and aquatic species is unknown; however its use has not resulted in any known problems. The dye used in Hi-Light® Blue is commonly used in toilet bowl cleaners and as a colorant for lakes and ponds (SERA 1997b). The use of these colorants in the formulations would result in almost no increase in risk to the health and safety of the workers or public, and in fact the use of a dye can reduce exposures and hence the risks since treated vegetation can be avoided.

As for other adjuvants, as stated on page 2 and in USDA (2002), there is a considerable range of such products that might be considered for use. USDA (2002) provides an overview of the various types of adjuvants likely to be used in forest herbicide applications and provides acute toxicity data for many of the formulations used by the USFS. 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.

Oils

Adjuvants that are primarily oil-based have been gaining in popularity especially for the control of grassy weeds. Oil additives function to increase herbicide absorption through plant tissues and increase spray retention. They are especially useful in applications of herbicides to woody brush or tree stems to allow for penetration through the bark. Oil adjuvants are made up of either petroleum, vegetable, or methylated vegetable or seed oils plus an emulsifier for dispersion in water.

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 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). Refer to USDA (1989 pages 4-111 to 4-114) 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 2000; 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."

U.S. 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 a multiplicative model]."

Synergism has rarely been observed in toxicological tests involving combinations of these herbicides with other commercial pesticides. The herbicide mixtures proposed for this project have not shown synergistic effects in humans who have used them 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.

However, even if synergistic or additive effects were to occur as a result of the proposed treatment, these effects are dose dependent (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."

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).

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, then 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 of these herbicides.

Several of the six herbicides considered in this risk assessment can be combined with other herbicides to increase the range of effective control. Although combining any of these six herbicides with any other herbicide is not anticipated nor proposed under Alternatives 2 or 4, it is important to consider whether any of the six have shown synergistic effects when combined with other compounds. Studies of these six herbicides in combination with other compounds are not common, as toxicology studies generally involve the active ingredient. So to the extent that any studies exist, they

are important to consider for their insight into potential impacts of combinations. In addition, in Alternative 6, there are two mixtures proposed to be used (dicamba plus 2,4-D and chlorsulfuron plus 2,4-D), while in Alternative 7 the dicamba/2,4-D mixture is proposed for use.

The guidance resulting from the reviews and analyses of available information by both US EPA (2000) and ATSDR (2004) is that, in the absence of known toxicity information on the mixture, mixtures of herbicides that have similar modes of toxic action can be assumed to have additive effects. Further, effects from mixtures are not likely to occur where the dose from each chemical in the mixture is at least one order of magnitude below its respective RfD (i.e. HQ < 0.1), and the sum of individual HQs does not approach an additive HQ = 1. If only one component is present at a HQ>0.1, and if the HQ for that component exceeds unity, this situation is not considered a mixtures problem but should focus on the one chemical that exceeds an HQ of unity.

Looking at the Tables in this risk assessment that display the risk characterizations for chlorsulfuron, 2,4-D, and dicamba (Tables F-6a-1 and 2, F-6c-1 and 2, and F-6d-1 and 2), it is apparent that mixtures containing 2,4-D will represent some degree of risk represented by 2,4-D itself (several scenarios with HQ values > 1). None of the acute scenarios involving workers should represent a risk of additive effects when these two mixtures are considered. Central estimates for chlorsulfuron result in HQ values less than 0.1, even at the highest application rate of 0.0625 pounds/acre, which would indicate that a mixture of 2,4-D and chlorsulfuron should represent health risks that should focus on 2,4-D itself, and not on the mixture. However, since several of the dicamba HQ values also exceed 0.1 at the upper mixture rate of 1 lb ae/acre, there could be additive effects associated with this mixture (although, as stated below, there is some evidence that such interactions may not occur, as the mode of toxic action may be dissimilar between dicamba and 2,4-D). These additive effects of dicamba and 2,4-D would be more likely in public acute exposures and chronic worker exposures and would be unlikely in chronic public exposures or acute worker exposures.

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. According to the product label, the Telar formulation of chlorsulfuron may be applied in combination with other herbicides, such as 2,4-D, dicamba, or glyphosate. However, there are no animal data to assess whether chlorsulfuron will interact, either synergistically or antagonistically with 2,4-D or any other herbicide.

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, 1999a).

A commercial formulation of picloram and 2,4-D, Tordon 202C, has been shown to inhibit immune response in mice (SERA 1999c). While the design of this study does not permit the determination of which agent caused the immune response, this observation is relevant to some Forest Service activities because, picloram is often applied with 2,4-D (although the use of picloram is not proposed under this EIS, as it is not registered in California).

There is no substantial evidence that dicamba will interact with other compounds. A study by Moody et al. (1991, as referenced in SERA 2004c) indicates that dicamba does not induce cytochrome P-450 activity and does not substantially affect a variety of other xenobiotic metabolizing enzymes. Although this finding does not rule out the possibility that dicamba may be involved in toxicologically significant interactions, the induction of cytochrome P-450 is a major mechanism by which such interactions are known to occur.

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 3A or Garlon 4 (SERA 1996b).

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. As stated in National Academy of Sciences (NAS 1993), the quantitative differences in toxicity between children and adults are usually less than a factor of approximately 10-fold. An uncertainty factor of 10 for sensitive subgroups may not cover all 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 to or less than 1.

Further information concerning risks to sensitive individuals can be found in USDA (1989, pages 4-114 through 4-116).

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 1999a). Clopyralid can cause decreased body weight, increases in kidney and liver weight, deceased 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).

As reviewed by Mullison (1981, as referenced in SERA 1998a), there is anecdotal information (case histories) suggesting that some individuals may be sensitive to 2,4-D. These individuals may develop neuropathy/impaired nerve function after exposure to 2,4-D at levels that are not expected to cause adverse health effects in the general population. The effects reported in the case studies are debilitating, and recovery may be prolonged and incomplete. On the other hand, the case studies do not rule out the possibility that the neuropathy was caused by other unidentified agents. Probenecid enhances the acute toxicity of 2,4-D and 2,4,5-T to rats (Ylitalo et al. 1990, as referenced in SERA

1998a). This effect is attributable, in part, to the displacement of the phenoxy acids from proteins. Thus, individuals taking probenecid, as an adjuvant to penicillin therapy, may be more sensitive than others to the acute toxicity of 2,4-D. Laboratory studies demonstrate that there is substantial variation among individual animals within a species in their response to 2,4-D (Arnold and Beasley 1989 as referenced in SERA 1998a). Also, there is evidence of human variability regarding dermal absorption rates. Individuals who absorb 2,4-D more rapidly or eliminate the compound more slowly are likely to be more sensitive than others to 2,4-D exposure.

The only identified sensitive subgroup for dicamba appears to be children. Since the RfD for dicamba explicitly considers the increased sensitivity of children with an additional safety factor and since exposure assessments for children are conducted in the risk assessment, this sensitive subgroup is addressed in the current risk assessment.

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.

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 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. The Project Record is located at the Modoc National Forest Supervisor's Office, 800 West 12th Street, Alturas, CA. Phone 530-233-5811

References Cited

ATSDR (Agency for Toxic Substances and Disease Registry). 2004. Guidance Manual for the Assessment of Joint Toxic Action of Chemical Mixtures. US Department of Health Services, Public Health Service, ATSDR, Division of Toxicology. May 2004. 108 pages. On-line (accessed on May 26, 2005) at http://www.atsdr.cdc.gov/interactionprofiles/ipga.html.

Borrecco, J., Neisess, J. 1991. Risk assessment for the impurities 2-butoxyethanol and 1,4-dioxane found in Garlon 4 and Roundup herbicide formulations. Pacific Southwest Region, Forest Pest Management. Report No. R91-2. 33 pages.

California Environmental Protection Agency (CalEPA), 1997a. Public Health Goal for 2,4-Dichlorophenoxyacetic Acid in Drinking Water. Pesticide and Environmental Toxicology Section; Office of Environmental Health Hazard Assessment. December, 1997. 12 pages.

California Environmental Protection Agency (CalEPA), 1997b. Public Health Goal for Glyphosate in Drinking Water. Pesticide and Environmental Toxicology Section; Office of Environmental Health Hazard Assessment. December, 1997. 14 pages.

Crouch, E.A.C., R. Wilson, and L. Zeise. 1983. The risks of drinking water. *Water Resources Research* 19(6): 1359-1375

Dost, Frank N. 1991. Declaration in the case of SRCC et al v. Robertson, U.S. District Court for the Southeast District of California, CIV. No. 91-217-DFL-PAN. August 19, 1991. 24 pages.

DowElanco. 1994. Technical Information on Garlon Formulations. In: Focus Forestry. Volume 2, Issue 1 (Spring 1994). 6 pages.

Farmer, D.R., T.A. Kaempfe, W.F.Heydens, W.R. Kelce. 2000. Developmental toxicity studies with glyphosate and selected surfactants in rats. *Teratology*. June 2000. 61(6):446. Abstract.

Kociba, R.J. and W.R. Mullison. 1985. Toxicological interactions with ag chemicals. *Farm Supplier*. August.

McConnell, L, J. LeNoir, S. Datta, J. Seiber. 1998. Wet Deposition of Current Use Pesticides in the Sierra Nevada Mountain Range, California, USA. *Environmental Toxicology and Chemistry*, 17(10) 1908-1916.

National Academy of Sciences (NAS). 1993. Pesticides In the Diets of Infants and Children. National Academy Press. Washington, D.C.

Northwest Coalition for Alternatives to Pesticides (NCAP). 2000. Inert Ingedients in Commercial 2,4-D Products. Online (accessed May 9, 2000). Available from http://www.pesticide.org/24Dinert.html

National Research Council (NRC). 1983. Risk assessment in the Federal Government: Managing the Process. National Academy Press. Washington, D.C. No. 20647. 99 pages.

Segawa, R., C. Ando, A. Bradley, J. Walters, R. Sava, C. Gana, K. Goh. 2001. Dissipation and Off-site Movement of Forestry Herbicides in Plants of Importance to California Tribes. California Department of Pesticide Regulation. 11 pages.

SERA (Syracuse Environmental Research Associates, Inc.) 1996a. Selected Commercial Formulations of Glyphosate - Accord, Rodeo, and Roundup. Risk Assessment. Final Report. March 20, 1996. SERA TR 96-22-02-01b. 159 pages.

SERA (Syracuse Environmental Research Associates, Inc.) 1996b. Selected Commercial Formulations of triclopyr – Garlon 3A and Garlon 4 - Risk Assessment. Final Report. March 31, 1996. SERA TR 95-22-02-02a. 163 pages.

SERA (Syracuse Environmental Research Associates, Inc.). 1997b. Use and assessment of marker dyes used with herbicides. December 21, 1997. SERA TR 96-21-07-03b. 47 pages.

SERA (Syracuse Environmental Research Associates, Inc.) 1998a. 2,4-Dichlorophenoxyacetic acid Formulations - Human Health and Ecological Risk Assessment – Final Report. September 20, 1998. SERA TR 95-21-09-01d. 241 pages.

SERA (Syracuse Environmental Research Associates, Inc.) 1998b. A Reevaluation of Methods for Assessing Occupational Exposure in Pesticide Applicators. SERA TR 98-21-08-01d2. May 18, 1998. 45 pages

SERA (Syracuse Environmental Research Associates, Inc.) 1999. Clopyralid (Transline) – Final Report. April 11, 1999. SERA TR 99-21-11/12-01d. 236 pages.

SERA (Syracuse Environmental Research Associates, Inc.) 2000b. Preparation of Environmental Documentation and Risk Assessments. November 12, 2000. SERA MD 2000-10-01b. 82 pages.

SERA (Syracuse Environmental Research Associates, Inc.) 2001b. Documentation for the Use of GLEAMS and Auxiliary Programs in Forest Service Risk Assessments. July 6, 2001. SERA AT 2001-01b. 25 pages.

SERA (Syracuse Environmental Research Associates, Inc.) 2002. Neurotoxicity, immunotoxicity, and endocrine disruption with specific commentary on glyphosate, triclopyr, and hexazinone: final report. Prepared by P. Durkin, G. Diamond. February 14, 2002. SERA TR 01-43-08-04a. 68 pages.

SERA (Syracuse Environmental Research Associates, Inc.) 2003a. Glyphosate – Human Health and Ecological Risk Assessment – Final Report. March 1, 2003. SERA TR 02-43-09-04a. Fayetteville, New York. 281 pages.

SERA (Syracuse Environmental Research Associates, Inc.) 2003b. Triclopyr – Revised Human Health and Ecological Risk Assessments – Final Report. March 15, 2003. SERA TR 02-43-13-03b. Fayetteville, New York. 264 pages.

SERA (Syracuse Environmental Research Associates, Inc.) 2004a. Chlorsulfuron - Human Health and Ecological Risk Assessment – Final Report. November 21, 2004. SERA TR 04-43-18-01c. Fayetteville, New York. 180 pages.

SERA (Syracuse Environmental Research Associates, Inc.) 2004b. Clopyralid - Human Health and Ecological Risk Assessment – Final Report. December 5, 2004. SERA TR 04-43-17-03c. Fayetteville, New York. 154 pages.

SERA (Syracuse Environmental Research Associates, Inc.) 2004c. Dicamba - Human Health and Ecological Risk Assessment – Final Report. November 24, 2004. SERA TR 04-43-17-06d. Fayetteville, New York. 179 pages.

United States Department of Agriculture (USDA), Forest Service. 1984. Pesticide Background Statements: Volume 1. Herbicides. Agriculture Handbook 633. Washington, D.C.

United States Department of Agriculture (USDA), Forest Service. 1989. Final Environmental Impact Statement - Vegetation Management for Reforestation. USDA Forest Service, Pacific Southwest Region. Vallejo, California.

United States Department of Agriculture (USDA), Forest Service. 1992b. Risk Assessment for Herbicide Use in Forest Service Regions 1, 2, 3, 4, and 10 and on Bonneville Power Administration Sites. September, 1992.

United States Department of Agriculture (USDA), Forest Service. 1997. Pest Management for Chico Genetic Resources Center, Draft Environmental Impact Statement (DEIS). August 1997.

United States Department of Agriculture (USDA), Forest Service. 2001. A Review and assessment of the Results of Water Monitoring for Herbicide Residues For the Years 1991 to 1999, USFS Region Five. Unpublished report. February, 2001, 27 pages

United States Department of Agriculture (USDA), Forest Service. 2002. Analysis of issues surrounding the use of spray adjuvants with herbicides. Unpublished report, written by David Bakke, Pacific Southwest Regional Pesticide-Use Specialist. September 2002. 43 pages.

United States Department of Agriculture (USDA), Forest Service. 2003a. Human and ecological risk assessment of nonylphenol polyethoxylate-based (NPE) surfactants in Forest Service herbicide applications. Unpublished report, written by David Bakke, Pacific Southwest Regional Pesticide-Use Specialist. May 2003. 182 pages.

USDA Forest Service. 2003b. Herger Feinstein Quincy Library Group Forest Recovery Act Final SEIS. USDA Forest Service, Pacific Southwest Region, Vallejo, CA. July 2003. 406 pages.

United States Environmental Protection Agency. 1986. Guidelines for the health risk assessment of chemical mixtures. Federal Register 51 (1850:3414-34025). September 24, 1986.

United States Environmental Protection Agency. 1993. Reregistration Eligibility Decision (RED) – Glyphosate. U.S. EPA 738-R-93-014. September 1993. 291 pages.

United States Environmental Protection Agency. 1998. Reregistration Eligibility Decision (RED) – Triclopyr. U.S. EPA 738-R-98-011. October 1998. 285 pages.

United States Environmental Protection Agency. 1999a. Dicamba (3,6-dichloro-o-anisic acid); Pesticide Tolerance. January 6, 1999. Federal Register. 64(3):759-769.

United States Environmental Protection Agency. 1999b. Notice of Filing of Pesticide [clopyralid] Petitions. February 9, 1999. Federal Register. 64(26):6351-6357.

United States Environmental Protection Agency. 1999c. Clopyralid; Pesticide Tolerances for Emergency Exemptions. November 17, 1999. Federal Register. 64(221):62588-62594.

United States Environmental Protection Agency. 2000a. Notice of Filing of Pesticide [glyphosate] Petition. July 25, 2000. Federal Register. 65(143):45769-45773.

United States Environmental Protection Agency. 2000b. Glyphosate; Pesticide Tolerance. September 27, 2000. Federal Register. 65(188):57957-57966.

United States Environmental Protection Agency. 2000c. [2,4-D] Toxicology Disciplinary Chapter for the Reregistration Eligibility Decision Document. Prepared by: Linda L. Taylor, Ph.D. June 21, 2000. 71 pages.

United States Environmental Protection Agency. 2000d. Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures. Office of Research and Development, US EPA,

Washington, D.C. EPA/630/R-00/002. August 2000. 209 pages. On-line (accessed May 26, 2005) at http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=20533.

United States Environmental Protection Agency. 2001. Clopyralid; Pesticide Tolerance. January 11, 2001. Federal Register. 66(8):2308-2316.

United States Environmental Protection Agency. 2002a. Triclopyr; Pesticide Tolerance. September 18, 2002. Federal Register. 67(181):58712-58725.

United States Environmental Protection Agency. 2002b. Notice of Filing a Pesticide [clopyralid] Petition to Establish a Tolerance for a Certain Pesticide Chemical in or on Food. August 14, 2002. Federal Register. 67(157):52990-52996.

United States Environmental Protection Agency. 2002e. Chlorsulfuron, Pesticide Tolerance. August 14, 2002. Federal Register 67(157):52866-52873.

United States Environmental Protection Agency. 2002f. Notice of Filing a Pesticide Petition to Establish a Tolerance for a Certain Pesticide Chemical in or on Food. March 8, 2002. Federal Register 67(46):10722-10727.

United States Environmental Protection Agency. 2004a. 2,4-D. HED's Human Health Risk Assessment for the Reregistration EligibilityDecision (RED) Revised to Reflect Error-only Comments from Registrants. June 2, 2004. 100 pages.

United States Environmental Protection Agency. 2004b. 2004 edition of the drinking water standards and health advisories. EPA 822-R-04-005. Winter 2004. Office of Water. 20 pages. Accessed on-line at http://www.epa.gov/waterscience/drinking/standards/dwstandards.pdf on December 1, 2004.

United States Environmental Protection Agency. 2005. Reregistration Eligibility Decision for 2,4-D. EPA 738-R-05-002. June 2005. Office of Pesticide Policy. 320 pages. Accessed on-line at http://www.epa.gov/pesticdes on August 12, 2005.

Williams, Gary, R. Kroes, I. Munro. 2000. Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans. *Regulatory Toxicology and Pharmacology* 31, pages 117-165.

Yousef, M., M. Salem, H. Ibrahim, S. Helmi, M. Seehy, K. Bertheussen. 1995. Toxic effects of carbofuran and glyphosate on semen characteristics in rabbits. *Journal of Environmental Science and Health.* B30(4): 513-534.

Zeise, Lauren, R. Wilson, and E. Crouch. 1984. Use of acute toxicity to estimate carcinogenic risk. *Risk Analysis* 4(3):187-199.