Appendix E
Human Health Risk Assessment

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E.1.1 Introduction

The chemicals and application rates proposed under the Diamond Project are identical to or lower than those analyzed under the *Herger-Feinstein Quincy Library Group Forest Recovery Act Final Supplemental Environmental Impact Statement* (HFQLG Act final supplemental EIS) and the Syracuse Environmental Research Associates, Inc. (SERA) Human Health and Ecological Risk Assessment for Borax (2006) (see table-1; therefore, a separate human health risk assessment is not required. Consequently, this appendix includes those portions of the Human Health Risk Assessment included in appendix G of the HFQLG Act final supplemental EIS and the SERA Human Health and Ecological Risk Assessment for Borax (2006) that pertain to the proposed use of clopyralid, glyphosate, and Borax formulations within the Diamond Project Area. It also presents project-specific results from an analysis conducted for the Diamond Project to further characterize risk of herbicide and fungicide exposure to workers and members of the general public. The tables included in this appendix are a summary of the calculations contained in worksheets in the project file and are based on the most recent and relevant SERA risk assessments (SERA 2004, 2003, 2006).

Table E-1. Comparison of the chemicals and application rates proposed under the Diamond Project with those analyzed under the HFQLG Act final supplemental EIS (2003).

	Diamond Analysis			HFQLG FSEIS		
	Typical Application Rate	Lower Application Rate	Upper Application Rate	Typical Application Rate	Lower Application Rate	Upper Application Rate
Chemical	acid equivalent pounds per acre (ae lb/ac)					
Clopyralid	0.25	0.09	0.25	0.25	0.1	0.25
Glyphosate	2.25	1.5	2.25	2.55	0.75	5.6
Borax	1	0.01	1.92	N/A	N/A	N/A

The application of the herbicides glyphosate and clopyralid, as proposed by the Diamond Project, is expected to present a low risk to human health and safety. In addition, based on the available information, the addition of the proposed surfactant and dye, would also pose a low risk to human health and safety. The application of the fungicide, Borax, as proposed by the Diamond Project, is also expected to present a low risk to human health and safety. The incorporation of the Best Management Practices (included in appendix C of this document) would also reduce the level of exposure and associated risk to the health and safety of workers and members of the general public. This is based on the analysis included in appendix G of the HFQLG final supplemental EIS (2003) and the SERA Human Health and Ecological Risk Assessment for Borax (2006), as well as the project-level risk characterization conducted using the specific chemicals, application rates, and volumes proposed under the Diamond Project.

E.1.2 Summary of Project Proposal

Two herbicide treatments are proposed under alternatives B, D, and F for control of Canada thistle in the Diamond Project Area. Approximately 103 gross acres (12 estimated acres of treatment) are proposed for treatment with clopyralid (for example, Transline® or an equivalent formulation) using a backpack sprayer. Approximately 25 gross acres (10 estimated acres of treatment) are proposed for treatment with the aquatic formulation of glyphosate (such as Rodeo® or an equivalent formulation) using a wick applicator. A vegetable

oil and silicone-based surfactant (such as Syl-tac® or an equivalent formulation) and marker dye (such as Hi-Light® Blue or an equivalent formulation) may also be used to increase the efficiency of the treatment. Herbicide treatments would occur in late summer and early fall for two to five years.

Borax treatments are proposed under alternatives B, C, D, and F for control of *annosum* root disease within the Diamond Project Area. Borax would be applied in granular form to all harvested conifer stumps 14 inches and greater in diameter.

Table E-2 provides a summary of the application rates, volumes, and concentrations proposed under the Diamond Project. For purposes of this risk assessment, in instances where a range of values is provided, the upper application rates were used to assess risk.

Table E-2. Chemicals, application rates, and application volumes proposed for Canada thistle control within the Diamond Project Area.

Chemical	Application Rate (ounces per acre)	Acid equivalents (pounds per acre)	Application Volume (gallons/acre)	Concentration in field solution (mg/ml)
Clopyralid (Transline)	4 to 10.6	0.09 to 0.25	10 to 30	1 to 3
Glyphosate (Rodeo)	218	2.25	1.7	160
Vegetable oil-silicone surfactant (Syl-tac)	5-15 (clopyralid) 0.85 (glyphosate)	NA	NA	1.25–3.74
Dye (Hi-light Blue)	5-15 (clopyralid) 0.85 (glyphosate)	NA	NA	0.004
Borax	0.16 to 32	0.01 to 2.0	10 to 25	0.08 to 0.2

E.1.3 Hazard Analysis

A considerable body of information describing the hazards associated with using each of the proposed herbicides and the proposed fungicide is contained in the risk assessments completed by SERA (SERA 2003, 2004, 2006) under contract to the Forest Service, and in the HFQLG Act final supplemental EIS (USDA Forest Service 2003). All of these documents are incorporated by reference into this risk assessment. The following section includes relevant portions of the hazard analysis provided in the HFQLG Act final supplemental EIS (2003), as well as some additional information from the most recent SERA risk assessments (SERA 2003, 2004, 2006).

A note specific to impurities and metabolites: virtually no chemical synthesis yields a totally pure product. Technical grade herbicides and fungicides, as with other technical grade products, undoubtedly contain some impurities. The U.S. Environmental Protection Agency (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 and fungicides is reduced by the fact that the existing toxicity studies on these herbicides and fungicides 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 nonthreshold mechanisms. Because of the nonthreshold assumption, any amount of a carcinogen in an otherwise noncarcinogenic 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 reference dose (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 and fungicide heading.

E.1.3.1 Clopyralid

(*Sources: SERA 1999 in HFQLG Act final supplemental EIS 2003; SERA 2004; Bakke 2006*)

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 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 3,000 milligrams per kilogram [mg/kg]) than the penta process [LD_{50} > 5,000 mg/kg]). These differences, however, are not substantial and may be due to random variability.

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.

Available data do not suggest that Transline® would be more or less toxic than clopyralid following acute oral exposure (SERA 2004). Carreon and New (1981, as referenced in SERA 2004) reported an LD_{50} >5,000 mg/kg for a formulation with no deaths at a dose level of 5000 mg/kg; lethargy was the only treatment-related effect.

Up until 2001, 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 2004) that showed decreases in body weight in females at the next highest dose tested (150 mg/kg/day). In 2001, EPA changed the chronic NOAEL to 15 mg/kg/day (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, 2004). 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 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 2,000 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 2,000 mg/kg clopyralid for 24 hours.

The systemic effects from dermal exposure to the formulation may be influenced by the presence of other adjuvants (additives) 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 (that is, 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. The EPA has established a reproductive NOAEL of >1,500 mg/kg/day (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. 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 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. A neurotoxicant is a chemical that disrupts the function of nerves, either by interacting directly on the nervous system (direct neurotoxicants) or by producing neurologic effects that are secondary to other forms of toxicity (indirect neurotoxicants). Using these definitions, 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 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 immunosuppressive 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 (for example, 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 EPA in support of registration of clopyralid. At nominal concentrations of 1 milligram per liter (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 (1,000 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 parts per million (ppm). The 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 percent 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. The EPA does not consider any clopyralid metabolites to be of toxic significance (EPA 1999b).

Inerts. The commercial formulation of clopyralid used by the Forest Service is Transline®, which is formulated as the monoethanolamine salt (that is, monoethanolamine is considered part of the active ingredient). Transline® also contains isopropyl alcohol and polyglycol as additives. Both monoethanolamine and isopropyl alcohol are approved food additives, and there is no evidence to assert that these compounds will materially impact the risks associated with the use of clopyralid.

No studies specifically mentioning Transline® were located in the search of the studies submitted to the EPA for product registration. Dow AgroSciences (2003, as referenced in SERA 2004) provided clarification of this issue and identified the studies submitted to 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 EPA as a List 3 inert. In other words, there is insufficient information to categorize this compound as either hazardous (Lists 1 or 2) or non-toxic (List 4). Notwithstanding this classification, surfactants such as Polyglycol 26-2 are surface active agents that can disrupt cellular membranes and lead to a number of different adverse effects. In an *in vitro* study on energy production in sub-mitochondrial particles derived from a marine alga, Oakes and Pollak (1999, as referenced in SERA 2004) noted that Polyglycol 26-2 inhibited oxidative function in the submitochondrial preparations at a concentration of about 0.01 percent. 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.

E.1.3.2 Glyphosate

(*Sources: SERA 2003; HFQLG Act final supplemental EIS 2003; Bakke 2006*)

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 nonspecific. 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 2003), 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 EPA as part of the registration process, the EPA

classifies glyphosate as mildly irritating to the eyes and slightly irritating to the skin. 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 non-irritating 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. 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 (that is, the highest dose used was not the maximum tolerated dose). A recent epidemiology study in Sweden (Hardell and Erikkson 1999, as referenced in SERA 2003) 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 EPA, which concluded that the study does not change their risk assessment for the current uses of glyphosate.

According to the 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 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 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 and Vigfusson and Vyse 1980, as referenced in SERA 2003) 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, 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 (such as 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 (EPA 1993), 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 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 that 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 percent 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 2003) 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, as referenced in SERA 2003) study and all other studies that have assessed the reproductive effects of glyphosate cannot be identified unequivocally. As discussed in Williams, et al, (2000, as referenced in SERA 2003) in 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. EPA has determined that there is no evidence of neurotoxicity in any of the exposure studies conducted (EPA 2000). 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 2003). 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.

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 2003). 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 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 2003). 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 2003).

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 percent 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 EPA has assessed the potential consequences of exposures to AMPA as an environmental metabolite. Based on this review, the 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 EPA is supported by reviews that are more extensive. The position taken by 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. Since the late 1990s, 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. The only listed inert ingredient in Rodeo® is water (46 percent), although it is likely that small amounts of isopropylamine and related organic acids of glyphosate also are present.

E.1.3.3 Borax

(*Source: SERA 2006*)

Acute and Chronic Exposures. Boric acid and borate compounds have a low-to-moderate order of acute oral toxicity (ATSDR 1992; ECETOC 1995; Hubbard 1998; WHO 1998, as referenced in SERA 2006). Based on the acute oral LD_{50} of 4.5 grams (g) of Borax/kg in rats, Borax is classified as moderately toxic (Category III), with an oral LD_{50} value between 500 and 5,000 mg/kg (U.S. EPA 2003 as referenced in SERA 2006). Sublethal but serious signs of toxicity, including vomiting, have also been noted in adults at doses of 241 mg/kg/day to 895 mg/kg/day after unsuccessful suicide attempts (Linden et al. 1986, as referenced in SERA 2006).

Several studies have been conducted on the subchronic and chronic toxicity of boric acid and borate compounds, with most of the available data on boric acid and Borax (ATSDR 1992; Hubbard 1998; WHO 1998,

as referenced in SERA 2006). The effects of short-term gestational exposure to boric acid have been investigated in rats, mice, and rabbits (Heindel et al. 1992, 1994; Price et al. 1996a, b, as referenced in SERA 2006). Longer-term toxicity studies (60-90 days) have assessed the subchronic and chronic toxicity of Borax in rats and dogs (Weir and Fisher 1972; Dixon et al. 1976, 1979; Lee et al. 1978, as referenced in SERA 2006). Details for all studies are provided in appendix 1 (of SERA 2006). Results of developmental, subchronic, and chronic toxicity studies show that the developing fetus and the male reproductive system are the primary targets for borate-induced toxicity.

Effects on the Skin and Eyes. Boric acid is rated as a Category III skin irritant (moderate irritant) and anhydrous Borax is rated as a Category IV skin irritant (mild irritant) (U.S. EPA 1993a as referenced in SERA 2006). Application of Borax to skin of rabbits and guinea pigs show that Borax does not cause skin sensitization effects, with no skin irritation. Borax is rated as a Category I (severe) eye irritant (U.S. EPA 1993a, as referenced in SERA 2006). Ocular application of Borax in rabbits resulted in severe eye irritation including irritation of the iris and corneal opacity (Reagan 1985c, as referenced in SERA 2006).

Carcinogenicity and Mutagenicity. The potential carcinogenicity of Borax was assessed in a 2-year feeding study in rats and dogs. In both species, Borax was negative for carcinogenic activity. Furthermore, no borate compound has been shown to produce cancer in any long-term exposure study in any species (ATSDR 1992; Beyer et al. 1983; Dieter et al. 1991; Fail et al. 1998; Hubbard 1998; WHO 1998, as referenced in SERA 2006). Based on the available data, boron (and borate compounds) is classified by the EPA as Group E chemical—that is, evidence of non-carcinogenicity in humans (EPA 1993a, as referenced in SERA 2006).

The mutagenic potential of Borax has been tested, and no mutagenic activity of Borax was observed (Benson et al. 1984; Landolph 1985, as referenced in SERA 2006). It is generally accepted that boron and borate compounds are not mutagenic (ATSDR 1992; Beyer et al. 1983; ECETOC 1995; Fail et al. 1998; Hubbard 1998; WHO 1998, as referenced in SERA 2006).

Reproductive and Teratogenic Effects. The effects on the male reproductive system and the developing fetus appear to be the most sensitive endpoints in borate toxicity, with the developing fetus more sensitive than the male reproductive system. Although no studies investigating the developmental effects of Borax were identified in the available literature, given the similar toxicological profiles for borate compounds, it is likely that gestational exposure to Borax would produce similar effects to those produced by boric acid in the developing fetus. As summarized in appendix 1 (of SERA 2006), gestational exposure of rats, mice, and rabbits to boric acid resulted in increased fetal deaths, decreased in fetal weight, and increased fetal malformations. The most sensitive effect observed from gestational exposure to boric acid is decreased body weight, with a NOAEL (no-adverse-effect-level) of 43.3 mbB/kg/day in mice and NOAELs ranging from 9.6 to <13.6 mg B/kg/day in rats.

Regarding the effects of boarate compounds on the reproductive system of adult animals, since the testes is a primary target organ for boron-induced toxicity, adverse effects on male fertility are expected outcomes of Borax exposure. Exposure of male rats to single doses of Borax up to 450 mg B/kg did not result in decreased fertility. However, dietary exposure of rats to 50 and 100 mg B/kg/day for 60 to 90 days resulted in testicular toxicity and decreased fertility in male rats (Dixon et al. 1979, Lee et al 1978, Weir and Fisher 1972 as referenced in SERA 2006); no signs of systemic toxicity were observed at these exposure levels. At the highest dose level assessed, male rats were completely sterile, with no litters produced, and rats remained sterile up to eight months after Borax treatment was discontinued (Lee et al. 1978, as referenced in SERA 2006). At the

lower dose level, sterility was reversed within five weeks of discontinuing Borax treatment (Dixon et al. 1979, as referenced in SERA 2006).

The reproductive effects of Borax do not appear restricted to males. Results of a single study show that dietary exposure to Borax decreased ovulation in female rates (Weir and Fisher 1972, as referenced in SERA 2006). In female rats exposed to dietary Borax at a concentration of 58.5 mg B/kg/day for 14 weeks, no litters were produced when females were mated with unexposed males. Decreased ovarian weight was also observed. No effects on female reproduction were observed at exposure levels of 5.9 and 17.5 mg B/kg/day.

Other Toxic Endpoints. Borax may be classified as an indirect neurotoxicant. As reviewed in section 3.1.4 (of SERA 2006), acute exposure of rats to lethal doses of Borax causes depression, ataxia, and convulsion (Weir and Fisher 1972, as referenced in SERA 2006). These findings, however, do not implicate Borax as a direct neurotoxicant. No studies designed specifically to detect impairments in motor, sensory, or cognitive functions in animals or humans exposed Borax were identified. No evidence for Borax producing direct effects on the nervous system was found.

There is very little direct information on which to assess the immunotoxic potential of Borax or other borate compounds. Nonetheless, the toxicity of Borax has been examined in several acute, subchronic, and chronic bioassays. Although many of these studies did not focus on the immune system, evidence of changes in immune function was not observed in any of the available long-term animal studies.

As discussed in sections 3.1.5 and 3.1.9 (of SERA 2006), subchronic exposure to Borax results in spermatogenic arrest and sterility in male rats and decreased ovulation in female rats (Weir and Fisher 1972, as referenced in SERA 2006). It is most likely that the adverse effects of Borax on reproductive function are due to a direct testicular effect, rather than an effect on the hypothalamic-pituitary axis (ECETOC 1995; Fail et al. 1998, as referenced in SERA 2006). It is generally accepted that borate compounds are not endocrine disrupters and that the reduction in plasma FSH (follicle stimulating hormone) and LH (plasma luteinizing hormone) levels are secondary to testicular toxicity (Fail et al. 1998, as referenced in SERA 2006).

Inhalation Exposures. Inhalation exposure of rats for 4 hours to 2.0 mg Borax/L did not result in any mortality, placing the 4-hour LC_{50} value at greater than 2.0 mg Borax/L (Wnorowski 1994a, as referenced in SERA 2006). Clinical signs of toxicity noted during the exposure period included ocular and nasal discharge, hunched posture, and hypoactivity. All symptoms resolved within 7 days of exposure.

These extremely limited data suggest that Borax can induce irritant effects and perhaps systemic toxic effects in laboratory mammals following inhalation exposure. In addition, several studies of occupational exposure in workers show that inhalation of dust containing boron causes irritation to the nasal mucosa and respiratory tract (Garabrant et al 1985; Heederik et al. 1994; Woskie et al. 1994, 1998; Hu et al. 1992, as referenced in SERA 2006). As discussed in section 3.2.2 (of SERA 2006), this finding is not directly relevant to this risk assessment because of the implausibility of inhalation exposure to the high concentrations of boron reported for these confined industrial facilities.

Impurities. No information on the impurities of Borax was identified in the available literature. The toxicity studies reviewed in this report were conducted with technical-grade Borax. Thus, if toxic impurities are present, they are likely to be encompassed by the available toxicity studies using technical-grade Borax.

Metabolites. As discussed in section 3.1.3.1 (of SERA 2006), due to the excessive energy required to break the boron-oxygen bond, borates are not metabolized by humans or animals (ECETOC 1995; Hubbard 1998, as referenced in SERA 2006). However, at physiological pH borate salts convert to boric acid (ECETOC 1995; Hubbard 1998; WHO 1998, as referenced in SERA 2006). Therefore, it is likely that most of the administered dose of Borax is converted to boric acid following absorption. Thus, the toxicity of boric acid is encompassed in the available toxicity studies on Borax.

Inerts. As discussed in section 2.2 (of SERA 2006), the Borax formulation Sporax contains 100 percent sodium tetraborate decahydrate (Borax) and has no other active or inert ingredients.

E.1.4 Dose Response Assessment

The purpose of this section is to describe the degree or severity of risk as a function of dose (SERA 2001). In general, dose-response assessments use reference doses (RfD), or dose levels associated with a negligible or defined level of risk, as indices of "acceptable exposure" (SERA 2001). Table E-3 provides a summary of the established reference doses (RfD) for clopyralid, glyphosate, the impurity hexachlorobenzene, and Borax. In this table, RfD values are derived for both acute exposure(s) (occurring within a short time frame), as well as chronic exposure (long-term exposure).

Table E-3. Summary of the Reference Doses established for the two proposed herbicides, the impurity hexachlorobenzene, and Borax.

Pesticide	Reference Dose (RfD)	
	Acute (mg/kg bw)[a]	Chronic (mg/kg bw/day)
Clopyralid	0.75	0.15
Glyphosate	2	2
Hexachlorobenzene	0.008	0.0008
Borax	0.2	0.2

Note:

a. mg/kg/day = milligrams of agent per kilogram of body weight per day.

The following provides relevant portions of the dose response assessment for clopyralid and glyphosate in appendix G of the HFQLG Act final supplemental EIS (USDA Forest Service 2003) as well as pertinent information from the most recent SERA risk assessments (SERA 2003, 2004, 2006).

E.1.4.1 Clopyralid

(*Sources: SERA 1999 in HFQLG Act final supplemental EIS 2003; SERA 2004; Bakke 2006*)

Up until 2001, 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 two 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 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, the 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 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 (that is, 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 a toxic response. Changes in epithelial tissue are less commonly observed and the toxicological significance of this effect is unclear.

The 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 (EPA 2001). This value can be used as an indicator of short-term risk.

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

E.1.4.2 Glyphosate

(*Sources: SERA 2003 in HFQLG Act final supplemental EIS 2003; Bakke 2006*)

The EPA Office of Pesticide Programs has established a provisional RfD of 2 mg/kg/day for glyphosate (EPA 2000). 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 EPA has also derived an RfD for glyphosate of 0.1 mg/kg/day (EPA/IRIS 1990, as referenced in SERA 2003). This RfD was originally derived in 1990 by the EPA Integrated Risk Information System (IRIS) workgroup and is the current RfD posted on IRIS. This RfD is based on a dietary three-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 EPA, the ADI proposed by WHO (1994, as referenced in SERA 2003) 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 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 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 EPA/ODW (1992, as referenced in SERA 2003) 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 EPA Office of Water has established a lifetime health advisory level (HA) of 0.7 mg/L (700 parts per billion [ppb]) and a 10-day HA of 20 mg/L (20 ppm) for glyphosate in drinking water (EPA 2004). 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, the 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 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

E.1.4.3 Hexachlorobenzene

(*Sources: SERA 1999 in HFQLG Act final supplemental EIS 2003; SERA 2004; Bakke 2006*)

Hexachlorobenzene is a contaminant found in technical grade clopyralid. Based on the amount of hexachlorobenzene in clopyralid, it is unlikely that the use of clopyralid proposed under the Diamond Project will substantially contribute to a widespread increase in ambient levels of hexachlorobenzene (SERA 2004). Nevertheless, the potential impact of local contamination was considered in appendix G of the HFQLG Act final supplemental EIS (2003) as well as in the SERA risk assessment for clopyralid (2004). The following provides relevant portions from these documents summarizing the dose response assessment for hexachlorobenzene.

The 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 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 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 EPA. The 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 (EPA 2004).

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 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 nonthreshold phenomenon; that is, 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 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 EPA and reflects the fact 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.

E.1.4.4 Borax

(*Source: SERA 2006*)

The U.S. EPA (2004) has recently derived a chronic RfD of 0.2 mg/kg/day for boron (from boric acid and borates), using the combined data of two developmental toxicity studies in rats using decreased fetal weight as the most sensitive endpoint (Price et al. 1996a; Heindel et al. 1992, as referenced in SERA 2006). The RfD is based on a benchmark dose analysis identifying a 5 percent decrease in mean fetal body weight compared to control as the benchmark response (BMR) level (Allen et al. 1996, as referenced in SERA 2006). The 95 percent lower bound on the dose corresponding to the BMR; that is, the BMDL05, of 10.3 mg B/kg/day is used as the critical dose value to calculate the RfD. The uncertainty factor of 66, which considers both the toxicokinetic and toxicodynamic aspects associated with interspecies and interindividual variability, was applied to the critical dose to derive the chronic RfD of 0.2 mg Borax/kg/day. The U.S. EPA has not derived an acute RfD for boron. Therefore, the chronic RfD of 0.2 mg Borax/kg/day will also be used to characterize risks associated with incidents or accidents that involve an exposure period of 1 day.

E.1.5 Exposure Assessment and Risk Characterization

This section presents a quantitative summary of the risk characterization for workers and the general public associated with exposure to clopyralid, glyphosate, and Borax. Risk characterization is a process that compares the exposure assessment with the dose-response assessment to express the level of concern associated with a specific exposure scenario or set of scenarios (SERA 2001). Risk characterization is expressed as a hazard

quotient, which is the estimated level of exposure divided by an index of acceptable exposure or "reference dose" (SERA 2001).

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 chemicals.

The following includes relevant portions of appendix G of the HFQLG Act final supplemental EIS (2003), as well as the results of a project-level risk characterization using the specific chemicals, application rates, and volumes proposed for noxious weed and annosus root disease control treatments under the Diamond Project. Some of the values presented in the tables below are displayed in scientific notation (for example, 1×10^{-5} is used to represent 0.00001).

E.1.5.1 Workers

Pesticide applicators are likely to be the individuals who are most exposed to a pesticide during the application process. For purposes of this analysis, two different types of worker exposure assessments are considered: general and accidental/incidental. General exposure scenarios are used to analyze exposure resulting from normal use (such as handling and application) of the chemicals (SERA 2001). Accidental and incidental exposure scenarios are used to analyze specific types of exposures associated with mischance or mishandling of a chemical (SERA 2001).

The 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 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 (such as in 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 two chemicals of concern.

Initially, risk assessments for the 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* USDA Forest Service 2003). In 1998, SERA conducted a detailed review and re-evaluation of the available worker exposure studies that can be used to relate absorbed dose to the amount of chemical handled per day (SERA 1998). This review noted that there was no empirical support for a dermal absorption rate correction. Two factors appear to be involved in this unexpected lack of association: (1) algorithms for estimating dermal absorption rates have large margins of error; and (2) actual levels of worker exposure are likely to be far more dependent on individual work practices or other unidentified factors than on differences in dermal absorption rates. 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. Both of the methods proposed for noxious weed control in the Diamond Project (backpack spraying and wick application) fall under the category for directed foliar applications; therefore, only the exposure rates associated with this job activity will be presented in this risk analysis. For control of *annosum* root disease, Borax in granular form would be applied to the surface of freshly cut stumps (directed application) with a "salt-shaker." The only exposure rates associated with this method will be presented in the risk analysis for Borax.

E.1.5.2 General Exposures

As described in SERA (2001), 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 rate for workers is calculated using the proposed application rate, dilution rate, and an estimate of the number of acres treated per day. In this analysis, risk characterization is displayed for three different exposure scenarios, typical, lower, and upper. These rates, which are based on experience within the Forest Service Pacific Southwest Region, are calculated using the lower and upper ranges of the amount handled, acres treated per day, and worker exposure rate. Therefore, the upper level represents a conservative estimate of a worst-case scenario resulting from the highest application rate, lowest dilution rate, and largest number of acres treated per day. This approach is used to encompass as broadly as possible the range of potential exposures. The chemicals and application rates proposed for noxious weed control and *annosum* root disease control in the Diamond Project were presented above in tables ES-1 and ES-2.

Table E-4 displays the hazard quotients calculated for a scenario involving general exposure to clopyralid, glyphosate, and the impurity hexachlorobenzene. This table illustrates that none of the exposure scenarios approach a level of concern; therefore, the risk characterization for workers is considered negligible. Under all of the application rates, workers utilizing backpack sprayers can apply the proposed herbicides without experiencing an unacceptable level of risk.

Table E-4. Hazard quotients (non-cancer) for backpack applicators – general (non-accidental) exposures to herbicides and the impurity hexachlorobenzene.

Chemical	Hazard Quotient[a]		
	Typical Application Rate	Lower Application Rate	Upper Application Rate
Clopyralid	0.01	6×10^{-4}	0.07
Glyphosate	0.007	4×10^{-4}	0.05
Hexachlorobenzene	1×10^{-5}	5×10^{-7}	9×10^{-5}

Note:

a. Hazard Quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

Borax is applied in granular form to the surfaces of cut tree stumps using a "salt-shaker" style. Although the Forest Service uses a standard set of exposure assessments in most risk assessment documents, the typical general exposures considered for directed foliar (backpack), boom (hydraulic ground spray), and aerial spray, as well as typical accidental exposures to a liquid, are not applicable for this risk assessment since Borax is not applied as a liquid. Additionally, although there are several reports detailing local irritant effects resulting from

occupational exposures to borate dust, inhalation exposures are not considered in this risk assessment due to the implausibility of inhalation exposures in the field reaching the high concentrations of boron reported in confined industrial facilities (Garabrant et al. 1985; Heederik et al. 1994; Woskie et al. 1994, 1998; Hu et al. 1992, as referenced in SERA 2006). Thus, the only exposure scenario that is considered plausible for workers is accidental dermal exposure to the hands and lower legs of granular Borax during application.

E.1.5.3 Accidental/Incidental Exposures

Typical occupational exposures may involve multiple routes of exposure (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 in general exposures. Accidental exposures, on the other hand, are most likely to involve splashing a solution of herbicides or fungicide 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 or fungicide 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.

Exposure scenarios involving direct contact with solutions of the chemical are characterized by immersion of the hands for one minute or wearing contaminated gloves for one 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.

Exposure scenarios involving chemical spills on to the skin are characterized by a spill on to the lower legs as well as a spill on to the hands. In these scenarios, it is assumed that a solution of the chemical is spilled on to a given surface area of skin and that a certain amount of the chemical adheres to the skin. The absorbed dose is then calculated as the product of the amount of the chemical on the surface of the skin (that is, 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 one 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, 2006).

The risk characterization associated with accidental exposure to workers is presented in table E-5. Given that all of the values are well below the level of concern (hazard quotient of one), it can be determined that under typical application conditions, the accidental exposure risk to backpack applicators is negligible. Additionally, accidents would be infrequent events, therefore the use of hazard quotients for accident scenarios are inherently conservative. Simply stated, even under the most conservative set of exposure assumptions, workers would not be exposed to levels of clopyralid, glyphosate, the impurity hexachlorobenzene, or Borax that are regarded as unacceptable.

Table E-5. Hazard quotient (non-cancer) for herbicides (backpack applicators) and fungicide (granular application), and accidental/incidental exposures for typical and upper application rates of chemicals (includes the impurity hexachlorobenzene).

	Hazard Quotient[a]							
	Immersion of Hands (1 minute)		Contaminated Gloves (1 hour)		Spill on Hands (1 hour)		Spill on Lower Legs (1 hour)	
	Typical	Upper	Typical	Upper	Typical	Upper	Typical	Upper
Chemical	Application Rate							
Clopyralid	7×10^{-7}	5×10^{-6}	4×10^{-5}	3×10^{-4}	1×10^{-4}	0.001	3×10^{-4}	0.003
Glyphosate	2×10^{-5}	1×10^{-4}	0.001	0.006	0.003	0.008	0.008	0.02
Hexachloro-benzene	2×10^{-4}	0.004	0.01	0.3	3×10^{-6}	8×10^{-5}	7×10^{-6}	2×10^{-4}
Borax[b]	N/A	N/A	0.004	0.005	N/A	N/A	N/A	N/A

Note:

a. Hazard Quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

b. Immersion of hands, spill on hands, and spill on lower legs scenarios not applicable to granular formulations of Borax.

Irritation and damage to the skin and eyes can result from relatively high levels of clopyralid exposure (i.e., placement of clopyralid directly onto eye or skin). In addition, glyphosate is considered a skin and eye irritant and the irritation level of glyphosate (with a POEA surfactant, not included in Rodeo®) has been shown to be equivalent to standard dishwashing detergents, all purpose cleaners, and baby shampoos. Boric acid is rated as a Category III skin irritant (moderate irritant) and anhydrous Borax is rated as a Category IV skin irritant (mild irritant) (EPA 1993a, as referenced in SERA 2006). Borax is rated as a Category I (severe) eye irritant (EPA 1993a, as referenced in SERA 2006). Effects to the eyes and skin from both of these chemicals can be minimized or avoided by safe handling practices.

E.1.5.4 General Public

Under normal conditions, members of the general public should not be exposed to substantial levels of clopyralid or glyphosate. Nonetheless, 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 utilized to characterize this risk.

The two types of exposure scenarios developed for the general public include 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.

Under normal conditions of applications, members of the general public should not be exposed to substantial levels of Borax as a result of Forest Service activities. Nonetheless, any number of exposure scenarios can be constructed for the general public. As discussed in the exposure assessment for workers (Section 3.2.2 of SERA 2006), the atypical application method for Borax limits the number of exposure scenarios for the general public that can be reasonably expected to occur. Therefore, typical exposures involving spray of a chemical to vegetation, such as dermal contact with contaminated vegetation and the consumption of contaminated fruit, are not applicable to this assessment. Exposure scenarios based on oral exposures from consumption of contaminated fish are not considered since borate compounds do no bioaccumulate in fish (Ohlendorf et al. 1986; Klasing and Pilch 1988, as referenced in SERA 2006).

Two types of exposure scenarios, ingestion of Borax from a tree stump by a child and ingestion of contaminated water, are considered the most likely exposure for the general public. For ingestion of Borax from a tree stump, only acute exposure is considered. Exposure scenarios developed for the general public for contaminated water include acute exposure and longer-term or chronic exposure. The scenarios developed for this risk assessment should tend to over-estimate exposures in general.

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 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 2001).

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 percent 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.

Table E-6 presents the risk characterization for the two scenarios discussed above. All of the hazard quotients are well below one; therefore, it can be determined that based on the available information and under the foreseeable conditions of application, there is no route of exposure or scenario that suggests that the general public will be at any substantial risk from general exposure.

Table E-6. Hazard Quotient (non-cancer) for the public—direct spray scenario.

Chemical	Hazard Quotient[a]			
	Child		Woman	
	Typical Application Rate	Upper Application Rate	Typical Application Rate	Upper Application Rate
Clopyralid	0.005	0.04	5×10^{-4}	0.005
Glyphosate	0.1	0.3	0.01	0.03
Hexachlorobenzene	1×10^{-4}	0.003	1×10^{-5}	3×10^{-4}

Note: a. Hazard Quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

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 2001) are used. Other estimates used in this exposure scenario involve estimates of body weight, skin surface area, and first-order dermal absorption rates. Table E-7 demonstrates that, for members of the general public that may contact vegetation sprayed with clopyralid or glyphosate, there is a negligible level of exposure risk.

Table E-7. Hazard quotient (non-cancer) for the public—contact with vegetation sprayed with herbicides.

Chemical	Hazard Quotient[a]	
	Typical Application Rate	Upper Application Rate
Clopyralid	5×10^{-4}	0.002
Glyphosate	0.001	0.003
Hexachlorobenzene	1×10^{-6}	3×10^{-6}

Note:

a. Hazard Quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

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 these compounds to a 100-acre treatment area.

The acute exposure scenario assumes that a young child (2- to 3-years old) consumes one liter (L) of contaminated water (a range of 0.6 to 1.5 L) shortly after an accidental spill of 200 gallons of a field solution into a pond that has an average depth of 1 meter (m), and a surface area of 1,000 m^2 or about 0.25 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.

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 these herbicides (such as glyphosate) that allow for an estimation of expected concentrations in ambient water associated with ground applications of the compound over a wide area. However, for others (such as clopyralid), such monitoring data does not exist. For those herbicides without monitoring data, for this

component of the exposure assessment, estimates of levels in ambient water were made based on the GLEAMS (Groundwater Loading Effects of Agricultural Management Systems) model.

GLEAMS is a root-zone model that can be used to examine the fate of chemicals in various types of soils under different meteorological and hydro-geological conditions (Knisel et al. 1992, as referenced in SERA 2001). SERA (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. It is important to note that water monitoring conducted in the Pacific Southwest Region since 1991 involving glyphosate (USDA Forest Service 2001) has shown that the assumptions in this risk assessment (in terms of water contamination) provide for a conservative (that is, protective) assessment of risk.

For the accidental scenarios, the only exposure level that exceeds the level of concern (hazard quotient greater than one) is in the scenario involving a child that consumes water contaminated with glyphosate (see table E-8). When interpreting this scenario, it is important to take into consideration that this is an arbitrary exposure scenario. In other words, scenarios that are more or less severe (all of which may be equally probable or improbable) could easily be constructed. All of the specific assumptions used to develop this scenario have a simple linear relationship to the resulting hazard quotient. Therefore, 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. Another 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. In the contaminated stream scenario, which presents a more realistic scenario for potential operational contamination of a stream, the hazard quotient values are substantially below one. Nonetheless, this and other acute scenarios help to identify the types of scenarios that are of greatest concern and those that may warrant the greatest steps to mitigate. For glyphosate, such scenarios involve oral (contaminated water) rather than dermal (spills or accidental spray) exposure.

Table E-8. Hazard quotient (non-cancer) for the public—drinking water contaminated by herbicides and fungicide.

Chemical	Hazard Quotient[a]					
	Acute-Spill Scenario (child)		Acute-Stream Scenario (child)		Chronic-Spill Scenario (adult male)	
	Typical Application Rate	Upper Application Rate	Typical Application Rate	Upper Application Rate	Typical Application Rate	Upper Application Rate
Clopyralid	0.1	0.3	5×10^{-4}	0.003	3×10^{-4}	7×10^{-4}
Glyphosate	5	7	0.002	0.05	3×10^{-5}	3×10^{-4}
Hexachlorobenzene	8×10^{-5}	7×10^{-4}	7×10^{-7}	4×10^{-6}	2×10^{-8}	4×10^{-8}
Borax	N/A	N/A	0.2	0.7	0.004	0.02

Note:

a. Hazard Quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

The Borax application method considered in this risk assessment (application to tree stumps) has a limited potential to contaminate water. Nonetheless, after application of tree stumps, rainfall, and consequent runoff could lead to contamination of standing water or streams. In addition, accidental spills of the Borax formulation into a small body of water are possible. Exposure assessments for both of these scenarios are presented.

The accidental spill scenario assumes that a young child consumes contaminated water shortly after an accidental spill into a small pond. Because this scenario is based on the assumption that exposure occurs shortly after the spill, no dissipation of Borax is considered. This scenario is dominated by variability and uncertainty and the specific assumptions used may overestimate or underestimate exposure. The actual concentrations in the water would depend on the actual amount of compound spilled, the size of the body of water 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. This is intended to be an extreme accidental exposure scenario. The purpose of this scenario is simply to suggest the intensity of measures that would be appropriate in response to a relatively large spill of Borax into a relatively small body of water.

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 2001).

Both of the herbicides in this risk assessment have BCF values for fish of 1 or less. However, hexachlorobenzene, an impurity found in clopyralid, has a BCF value for fish that is greater than 1. 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 1,000 m^2 or about 0.25 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 (EPA 1996, as referenced in SERA 2001), separate exposure estimates are made for these two groups. The chronic exposure scenario is constructed in a similar way.

Table E-9 demonstrates that for all of these scenarios, there is no unacceptable level of risk associated with consumption of fish captured from water contaminated with glyphosate, clopyralid, or the impurity hexachlorobenzene.

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 basket weaving 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.

Table E-9. Hazard Quotient (noncancer) for the public—consumption of fish caught from water contaminated by clopyralid and glyphosate. Upper limits are presented representing worst-case scenario.

	Hazard Quotient[a]			
	Fish Consumption (accidental spill)		Chronic Fish Consumption	
Chemical	Adult Male	Subsistence Population	Adult Male	Subsistence Population
Clopyralid	0.007	0.03	3×10^{-6}	3×10^{-5}
Glyphosate	0.05	0.3	5×10^{-7}	4×10^{-6}
Hexachlorobenzene	0.03	0.1	3×10^{-6}	3×10^{-5}

Note:

a. Hazard Quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

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 2001), as modified by Fletcher et al. (1994, as referenced in SERA 2003). 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.

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 pound (0.4536 kg) of contaminated fruit. Based on statistics summarized in EPA (1996, as referenced in SERA 2001), this consumption rate is approximately the mid-range between the mean and upper 95 percent 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 (EPA 1996, as referenced in SERA 2001), as well as the range of concentrations on vegetation and the range of application rates for the herbicides.

Table E-10 displays the hazard quotient values for scenarios involving a woman eating contaminated berries shortly after spraying and eating berries for 90 days after they were sprayed. Under the typical rates of application, the hazard quotients were well below one for both the chronic and acute scenarios. However, at the upper application rate, the hazard quotient is slightly above one in the case of acute exposure to glyphosate and chronic exposure to clopyralid as a result of consuming contaminated vegetation.

These hazard quotients illustrate that there is some uncertainty regarding the potential effects of consuming contaminated vegetation; however the fact that these hazard quotients are very close to one (the acceptable level of risk), it is unlikely that adverse health effects would result in either of these scenarios. It is also important to take into account the fact that these scenarios do not include the mitigative effects of washing contaminated vegetation. In addition, after treatment vegetation would show obvious signs of herbicide effects and would likely be undesirable for consumption.

Table E-10. Hazard Quotient (noncancer) for the public—ingesting fruit contaminated by herbicides

Chemical	Hazard Quotient[a]			
	Acute Exposure		Chronic Exposure	
	Typical Application Rate	Upper Application Rate	Typical Application Rate	Upper Application Rate
Clopyralid				
Fruit	0.004	0.06	0.008	0.2
Vegetation	0.05	0.5	0.1	1.2
Glyphosate				
Fruit	0.01	0.2	0.007	0.1
Vegetation	0.2	1.5	0.1	0.8
Hexachlorobenzene				
Fruit	2×10^{-6}	2×10^{-5}	9×10^{-7}	8×10^{-6}

Note:

a. Hazard Quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

Oral Exposure of Borax Applied to Tree Stumps. For Borax, the acute exposure scenario is used in which a child ingests Borax applied to tree stumps (see table E-11). There is no information in the available literature to estimate the amount of Borax that a child could be predicted to consume in one day. The estimated amount of Borax that a child may consume in one day is based on the amount of soil that an average child may ingest per day. According to the EPA Exposure Factors Handbook (EPA 1996, as referenced in SERA 2006), the mean amount of soil that a child consumes per day is estimated to be 100 mg soil/day, with an upper bound estimate of 400 mg soil/day. For this risk assessment, the amount of Borax consumed from tree stumps in a single day is taken as the range of 50 (an estimated lower bound) to 400 mg Borax/day. A central estimate for Borax consumption is taken as 100 mg Borax/day. It should be emphasized that this exposure estimate is highly uncertain and not based on empirical data for consumption of any borate compound; thus, exposures via this scenario may be under- or overestimated.

Table E-11. Hazard Quotient (noncancer) for the public—ingestion of Borax by a child.

Chemical	Hazard Quotient[a]	
	Acute-Oral Exposure Ingestion Scenario (child)	
	Typical Application Rate	Upper Application Rate
Borax	4	16

Note:

a. Hazard Quotient is the level of exposure divided by the RfD, then rounded to one significant digit.

E.1.6 Cumulative Effects

The proposed use of herbicides or fungicide could result in cumulative doses to workers or the general public. Cumulative doses to the same chemical result from (1) additive doses via various routes of exposure resulting from the management scenarios presented in alternatives B, C, D, and F; and (2) additive doses if an individual is exposed to other herbicide or fungicide treatments.

Additional sources of exposure include use of herbicides and fungicides on adjacent private timberlands or home use by a worker or member of the general public. The Forest Service and state of California pesticide-use records (from 2001 to 2004) indicate that the only pesticide use reported within the Diamond Project Area was the application of clopyralid and Borax. Table E-12 displays the total use of these chemicals on public and private timberlands, rangelands, and road rights-of-ways (the latter assumed to be primarily for noxious weed work) within the four watersheds that make up the Diamond Project Area.

Table E-12. Total pounds of chemical applied and acres treated within the Diamond Project Area between 2001 and 2004.

Chemicals Applied	Total Pounds of Chemical Applied	Acres Treated
Clopyralid	21.6	89
Borax	1260	780
Total	**1281.6**	**869**

Source: California Department of Pesticide Regulation, 2006.

The average amount of glyphosate applied in Plumas and Lassen Counties between 2001 and 2003 was 2,149.3 pounds of active ingredient per year (lbs ai/year) and 1,544 lbs ai/year, respectively, for Lassen and Plumas Counties (California Department of Pesticide Regulation [CDPR] 2006). The average amount of clopyralid applied in Plumas and Lassen Counties between 2001 and 2003 was 160.6 lbs ai/year and 90.5 lbs ai/year, respectively (CDPR 2006). Based on Forest Service annual pesticide-use reports and the California Department of Pesticide Regulation, all of the clopyralid and glyphosate use on timberlands within the Diamond Project Area in the past five years has occurred on private land.

Other foreseeable future Plumas National Forest projects that potentially could involve herbicides within the Diamond Project Area are expected to be small and scattered and would involve the treatment of isolated noxious and invasive plant occurrences. At present, the only known future herbicide project designed to treat noxious weeds, proposes to treat a small number of noxious weed occurrences (four locations and approximately 0.02 acre) within 50 feet of existing roads within the Diamond Project Area.

Under alternatives B, D, and F, it is estimated that approximately 128 acres of Canada thistle would be treated for two to five years. It is assumed that alternatives A and C would not involve any herbicide use. Based on the values included in table E-12 above, total pesticide use within the Diamond Project Area between 2001 and 2004 was 1,281.6 pounds of chemical (primarily Borax and clopyralid) applied over approximately 869 acres. The average number of acres treated with these pesticides over a four-year period was 217 acres. Therefore, alternatives B, D, and F would result in 59 percent increase in forest and rangeland acreage treated with pesticides within the Diamond Project Area.

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. 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. Using glyphosate as an example, the typical levels of exposure for a woman being directly sprayed on the lower legs (0.01), staying in contact with contaminated vegetation (0.001), eating contaminated fruit (0.01), and consuming contaminated vegetation (0.2) leads to a combined hazard quotient of 0.208. With the exception of a child drinking pond water contaminated with glyphosate or Borax and a child ingesting

Borax (discussed in the section above), the addition of all possible exposure scenarios, under a typical rate of application, for both herbicides, leads to hazard quotients that are substantially less than one. 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 glyphosate residues up to 66 weeks after treatment, however, these levels were less than 1 part per million (Segawa et al. 2001). Based on the re-treatment schedule in alternatives B, D, and F (2 to 5 years), it is possible that residues from the initial herbicide application could still be detectable during subsequent re-treatments the following year, 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.

Borax is unusual for a pesticide in that the toxicologic agent of concern –i.e., boron – is a naturally occurring compound. Boron is a normal consistent of the earths crust, all environmental media, as well as all forms of life including humans. Based on estimates of normal background exposures, typical exposures to boron are about 0.14 to 0.36 mg/kg/day. Based on central estimates of exposures to boron associated with the application of Borax in Forest Service Programs, non-accidental exposures are below normal background concentrations. Considering the variability of the estimates of both normal background exposures and estimates of exposure associated with the application of Borax, Borax applications lead to exposures that are below those associated with normal background exposures by factors of 13 to 9000 (Section 3.2.3.4 of SERA 2006). Thus, under foreseeable and typical conditions, applications of Borax in Forest Service programs will not lead to any substantial increase in exposure.

"Borax as used in forestry is identical to the material sold throughout North America as a household cleaning agent and also used for control of household insects" (Dost et al. 1996). Borax has even been recommended as an "environmentally friendly" household cleaning solution and a "safe alternative to common household products" (Wilmington College 2003; AEHA 1998). These household applications are in much closer proximity to humans than tree stump applications.

All Borax applications would follow safety and resource protection measures. The proposed Borax application would comply with all applicable state and federal regulations for the safe use of pesticides (including the Sporax® label requirements). For example, applicators would be adequately trained, medical aid would be available, wash water and eye wash water would be on site or nearby, and personal protective equipment would be used (eye protection, gloves, long-sleeved shirt, and long pants). Best Management Practices for pesticide application, including a spill contingency plan, would be implemented. Borax applications would not occur within 25 feet of stream courses and would not be applied during sustained rainfall.

The SERA risk assessment final report (USDA 2006) concludes, "the use of Sporax® in Forest Service programs will not substantially contribute to boron exposures in humans" and "will not typically or substantially contribute to concentrations of boron in water or soil." In addition, the SERA report concludes, "the use of Sporax® in the control of *annosum* root disease does not present a significant risk to humans or wildlife species under most conditions of normal use, even under the highest application rate. For workers and

the general public, none of the other exposure scenarios considered yield hazard quotients that exceed the level of concern" (USDA 2006).

This project-specific risk assessment analyzed twice the typical application than the SERA risk assessment (2 pounds per acre versus 1 pound per acre) in order to account for the highest application rate in the group selection units. For workers and the general public, the only scenario that yielded a Hazard Quotient above the level of concern (Hazard Quotient equal to 1.0) was the scenario in which a child ingests Borax straight from the tree stump. "While this exposure scenario raises concern in that the RfD could be substantially exceeded in a child directly consuming Borax from a treated stump, the most likely adverse effects would probably be vomiting and diarrhea" (SERA 2006). This scenario may be extreme and highly unlikely as (1) group selection units would be placed away from recreation areas, and (2) Borax would be applied during or immediately after active logging operations where unsupervised visitor use is highly discouraged for safety reasons.

In order to consider the cumulative effects of associated with uses of these herbicides outside of the Diamond Project Area, the 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 (see table E-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 does not change the risk conclusions based on the project-related Hazard Quotient values.

Table E-13. TMRC values for United States population as a whole.

Herbicide	TMRC (mg/kg/day)	Percent of RfD
Clopyralid	0.00903	6.0
Glyphosate	0.02996	1.5

Cumulative effects can also be caused by the interaction of different chemicals with a common metabolite or a common toxic action. However, neither of the herbicides or fungicide in this analysis has been demonstrated to share a common metabolite.

E.1.6.1 Inert Ingredients

The issue concerning inert ingredients and the toxicity of formulations is discussed in USDA (1989, as referenced in USDA Forest Service 2003). 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 the 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, as referenced in USDA Forest Service 2003). The court in NCAP v. Lyng, 844 F.2d 598 (9th Cir 1988) decided that this method of analysis provided sufficient information for a decisionmaker to make a reasoned decision. In SRCC v. Robertson, Civ.No. S-91-217 (E.D. Cal., June 12, 1992) and again in CATs v. Dombeck, Civ. S-00-2016 (E.D. Cal., Aug 31, 2001), the district court upheld the adequacy of the methodology used in USDA (1989) for disclosure of inert ingredients and additives.

The EPA has categorized approximately 1,200 inert ingredients into four lists. Lists 1 and 2 contain inert ingredients of toxicological concern. List 3 includes substances for which the EPA has insufficient information to classify as either hazardous (Lists 1 and 2) or nontoxic (List 4). List 4 contains nontoxic substances such as corn oil, honey, and water. Use of formulations containing inert ingredients on Lists 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 the EPA to review the 13 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 Lists 1 or 2) (USDA 1989, as referenced in USDA Forest Service 2003). The EPA determined that there were no inerts on Lists 1 or 2. 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.

Comparison of acute toxicity (LD_{50} 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, 1984, as referenced in USDA Forest Service 2003, SERA risk assessments).

While these formulated products have not undergone chronic toxicity testing like their active ingredients, the acute toxicity comparisons, the EPA review, and our examination of toxicity information on the inert ingredients in each product leads us to conclude that the inert ingredients in these formulations do not significantly increase the risk to human health and safety over the risks identified for the active ingredients.

As discussed in section 2.2 (of SERA 2006), the Borax formulation of Borax contains 100 percent sodium tetraborate decahydrate (Borax) and has no other active or inert ingredients.

E.1.6.2 Additives

Additives (also known as adjuvants) are mixed with an herbicide solution to improve the performance of the spray mixture by either enhancing the activity of the herbicide's active ingredient or by offsetting problems associated with application, such as water or wind factors (Bakke 2003). Borax is not applied in combination with other products or additives. Two additives are proposed for use in the Diamond Project: a vegetable oil and silicone-based surfactant (such as Syl-tac® or an equivalent formulation) to facilitate and enhance the spreading and penetrating properties of the herbicides and a marker dye (such as Hi-light® Blue or an equivalent formulation) to allow for the identification of plants that have been treated. These two additives were not considered in detail in appendix G of the HFQLG final supplemental EIS.

Additives are not under the same registration guidelines as are pesticides; therefore, much of the information that describes the active ingredients in additives is considered confidential business information. The EPA does not register or approve the labeling of spray additives, although the California Department of Pesticide Regulation does require the registration of those that are considered to increase the action of the pesticide with which it is used. All additives are generally field tested by the manufacturer in combination with several different herbicides and weed species and under a number of different environmental conditions (Bakke 2003).

The most common risk factor associated with the use of the proposed additives is skin or eye exposure. This risk can be minimized through good industrial hygiene practices (that is, personal protective eyewear and gloves) while using these products. Overall, the additives proposed for use in the Diamond Project are not expected to pose an adverse risk to the health and safety of workers or the members of the general public. This is based on information provided on the product labels, as well as on the discussion provided by Bakke (2003), in which the two additives proposed for use under this project are discussed and some acute toxicity data presented. The following provides further discussion of the additives analyzed for the Diamond Project.

Syl-tac® (or an equivalent formulation). Vegetable oil and silicon-based surfactants are gaining in popularity due to their superior spreading ability and their capability to increase herbicide absorption and spray retention (Bakke 2003). The surfactant proposed for use in the Diamond Project is Syl-tac® (or an equivalent formulation), which is a blend of two additional products: Syl-gard 309® (the silicone-component) and Hasten® (the vegetable oil component).

The labels for Syl-tac®, Syl-gard 309®, and Hasten® contain "signal words" (caution, warning, danger, and poison) that indicate the product's relative toxicity to humans. The signal word is assigned using a combination of acute toxicity studies and the toxicity of each of the product's components (Tu et al. 2001). Syl-tac® and Hasten® both contain the "caution" signal word on the label whereas Syl-gard 309® has a "warning" signal word on the label. All three products may cause irritation to the skin and eyes, with Syl-gard 309® considered to cause the most severe irritation to the eyes.

The main ingredient in Hasten® (identified in the Syl-tac® product information) is esterified canola seed oil. 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). However, because of the lack of exact ingredient statements on these surfactants, it is not always clear whether the oils used meet the FDA standard. Hasten® contains a list 4B (nontoxic) non-ionic surfactant known as polyoxyethylene dioleate. The MSDS for Hasten® lists isopropylamine as a hazardous ingredient at levels of 2 percent in the formulation. Isopropylamine is a severe eye and skin irritant, is considered more acutely toxic than the Hasten® formulation, and is not considered a mutagen (Bakke 2003).

The acute toxicity testing results for mammalian and aquatic species summarized in Bakke (2003) indicate that Syl-tac® is no more than slightly toxic when ingested, inhaled, or absorbed through the skin. Syl-tac® is a non-ionic surfactant, which means that it has no electrical charge and is compatible with most pesticides. In general, non-ionic surfactants have less of an effect on the skin, and hence absorption, than their anionic or cationic counterparts (Bakke 2003). None of the ingredients in Syl-Tac® are on the EPA's Inerts List 1 or 2, which identify ingredients of toxicological concern (Bakke 2003). The product label includes precautionary statements that advise users to avoid contact with eyes and to thoroughly wash with soap and water after handling.

Hi-light® Blue (or an equivalent formulation). Hi-Light® Blue dye is not required to be registered as a pesticide; therefore there is no signal word included on the label. However, according to Bakke (2003), this product would likely have a "caution" signal word if required to identify one. The label does indicate that this product is mildly irritating to the skin and eyes. Hi-Light® Blue is commonly used in toilet bowl cleaners and as a colorant for lakes and ponds (SERA 1997). This dye is water soluble, contains no listed hazardous substances, and is considered virtually nontoxic to humans (Bakke 2003; SERA 1997).The effect of use on nontarget terrestrial and aquatic species is unknown; however, the use of this dye use has not resulted in any known problems (Bakke 2003).

The use of Hi-Light® Blue in the proposed herbicide formulations would result in almost no increased risk to the health and safety of the workers or members of the general public. In fact, the use of dye in herbicide application can reduce likelihood and risk of exposure by facilitating avoidance of treated vegetation.

E.1.6.3 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, as referenced in USDA Forest Service 2003) for a detailed discussion on synergistic effects.

It is not anticipated that synergistic effects would be seen with the additives proposed for the Diamond Project. 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 on the skin, there will be no change in absorption as compared to the other compound alone. The studies indicate that, in general, non-ionic surfactants have less of an effect on the skin, and hence absorption, than anionic or cationic surfactants. Compound-specific studies indicate that the alkylphenol ethoxylates generally have little or no effect on absorption of other compounds. In several studies, the addition of a surfactant actually decreased the absorption through the skin. It would appear that there is little support for the contention that the addition of surfactants to herbicide mixtures would increase the absorption through the skin of these herbicides.

Borax is not applied in combination with other products or additives. In addition, no data are available regarding the effects of boron compounds applied in conjunction with other chemicals. Thus, an assessment of toxicological effects of Borax mixed with other chemicals cannot be made.

E.1.6.4 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, as referenced in USDA Forest Service 2003), 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 who 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 Hazard Quotient is equal to or less than 1.

Further information concerning risks to sensitive individuals can be found in USDA (1989, as referenced in USDA Forest Service 2003).

The 1996 *Food Quality Protection Act* requires the EPA to evaluate an additional 10X safety factor, based on data uncertainty or risks to certain age/sex groupings. The 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 RfDs of this risk assessment as it applies to chlorsulfuron.

The likely critical effect of clopyralid in humans cannot be identified clearly (SERA 2004). 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.).

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 2003).

The primary targets for boron toxicity are the developing fetus and the testes. Thus, exposure of pregnant women to borate compounds places the developing fetus at risk. Since the oral (chronic) RfD for boron and borates is based on the effects in the developing fetus, risk to this subgroup is assessed throughout (SERA 2006). Regarding other sensitive subgroups, males with underlying testicular dysfunction could be at increased risk for boron-induced testicular toxicity. However, no data are available to quantify this risk.

E.1.6.5 Worksheets

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

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