

United States
Department of
Agriculture

Forest Service

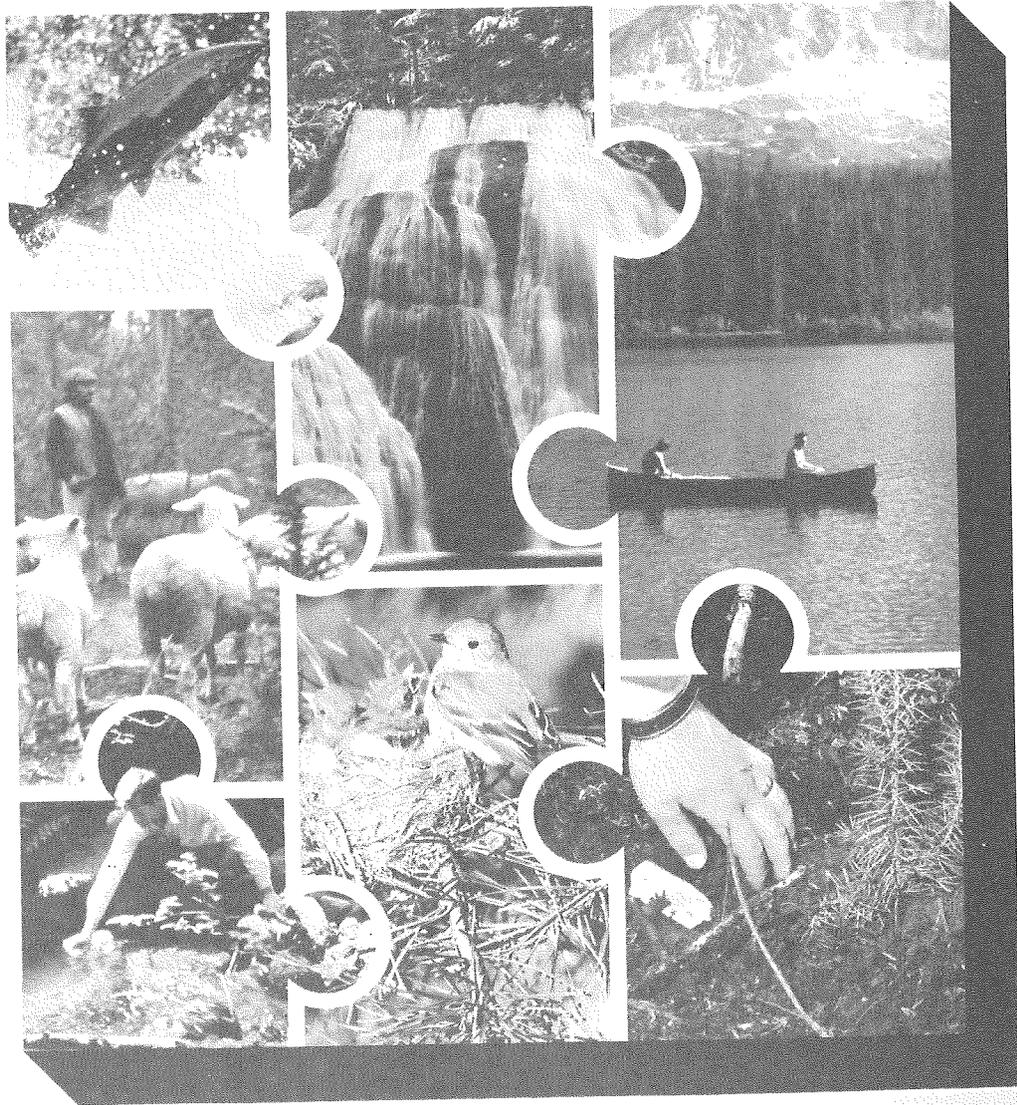
Pacific
Northwest
Region

November 1988



Managing Competing and Unwanted Vegetation

Final Environmental Impact Statement
Appendices D & H



Appendix D

Human Health Risk

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Appendix D
Human Health
Risk Assessment
(Quantitative)



Section 1

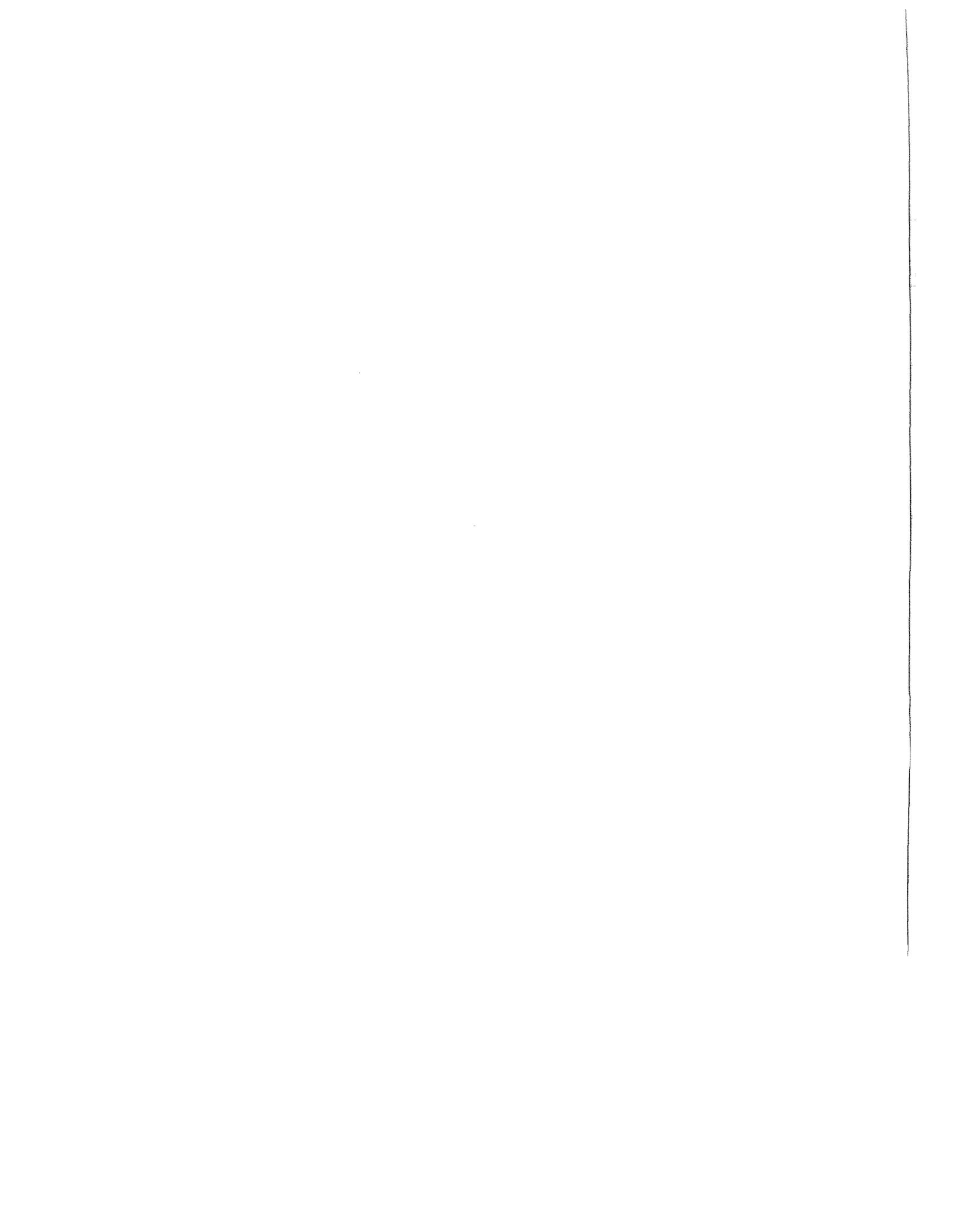


HUMAN HEALTH RISK ASSESSMENT
FOR THE USE OF HERBICIDES IN THE
VEGETATION MANAGEMENT PROGRAMS
OF THE U.S. FOREST SERVICE IN
WASHINGTON AND OREGON AND
THE BUREAU OF LAND MANAGEMENT
IN WESTERN OREGON

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Section 1

INTRODUCTION

PURPOSE

The purpose of this analysis is to assess the risk to human health of using 16 different herbicides for vegetation management on Forest Service lands in Washington and Oregon and on Bureau of Land Management (BLM) lands in Western Oregon. This risk assessment is a supplement to the Forest Service Environmental Impact Statement (EIS) entitled Methods of Managing Competing Vegetation: A Programmatic Environmental Impact Statement (USDA, 1981) and the BLM EIS entitled Western Oregon Program: Management of Competing Vegetation (BLM 1983). The EIS's analyzed the environmental impacts of using various alternatives for managing competing vegetation in the Pacific Northwest.

OVERVIEW OF THE RISK ASSESSMENT

This risk assessment examines the potential health effects on all persons who might be exposed to any of the 16 herbicides as a result of activities related to the vegetation management program. People potentially at risk are considered to belong to two groups. The first group--workers--includes applicators, supervisors, and other personnel who may be exposed to herbicides. The second group--the public--includes forest visitors or nearby residents who could be exposed through the drift of herbicide spray droplets, through contact with sprayed vegetation, or by eating food items such as berries growing in or near forests, by eating game or fish containing herbicide residues, or by drinking water that contains such residues.

The analysis of the potential human health effects of the use of chemical herbicides for vegetation management was accomplished using the methodology of risk assessment generally accepted by the scientific community. In

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essence, pesticide risk assessment consists of comparing doses people may get from applying the pesticides (worker doses) or from being near an application site (public doses) with appropriate dose levels from tests in laboratory animals for general health effects, reproductive effects, and cancer.

A number of factors contribute to the uncertainty in this process of judging risks to human health from laboratory animal studies. For assessment of general health or reproductive/developmental effects, a reference value for comparison to human subjects is the dose at which no adverse effects are observed. To allow for the uncertainty in extrapolating from these no-observed-effect levels (NOEL's) in laboratory animals to safe levels for humans, safety factors are used. The generally accepted factors (NRC, 1986) are 10 for moving from animals to humans (between species variation) and another 10 to account for possible variation in human responses (within species variation). This 10 times 10 or 100-fold safety factor means the laboratory NOEL dose reduced 100-fold would normally be considered a safe dose. In this risk assessment, a margin of safety (MOS) or hazard level:exposure level ratio has been calculated for each estimated dose by dividing the animal NOEL by the estimated dose. The computed MOS is then compared to the 100-fold safety factor to judge the risks of toxic effects.

A second area of uncertainty is in evaluating the risk to humans of exposures that may occur once or perhaps a few times in a person's lifetime (accidental worker doses and all doses to the public fall in this category) by comparing those human doses to levels of the chemical that produced no ill effects in laboratory animals even though the animals are exposed every day of their lives. This risk assessment uses the MOS approach discussed above in comparing one-time human doses to lifetime animal doses in all of these cases even though this leads to an exaggeration of the risks.

A different approach is used to assess the risks for humans of potential carcinogens. Because it is uncertain that a threshold exists (that cancer is caused only above a certain dose level), and because it is biologically plausible that there is no threshold, it is assumed that no threshold

exists. In the case of potential carcinogens, a cancer potency value is used to assess risk. Cancer potency values express the probability that a carcinogenic response will occur at a standard dose rate (typically 1 mg/kg/day). Cancer potency values are derived from laboratory animal studies and adjusted for the differences in metabolism between the laboratory animals and humans. Cancer potency values are multiplied by an estimated human lifetime dose to calculate human cancer risk.

A third area of uncertainty involves the estimation of the human doses likely to occur in herbicide use. This risk assessment has been designed to overestimate doses to err on the side of safety. In reality, workers are likely to experience low level exposures because they work with the chemicals routinely. However, standard safety practices and the use of protective clothing will normally reduce their actual dose levels far below those estimated in this analysis. The same is true of the doses from any spraying or spill accidents that might occur, because the normal procedure would be to wash immediately. In addition, no member of the public is likely to receive as high a dose as estimated in this risk assessment, again because normal safety practice and the remoteness of most treated areas limit the possibility of the public's receiving any dose at all. Furthermore, the public doses estimated here exaggerate the amount they could receive. No herbicide degradation is assumed to occur, the public is not assumed to wash themselves or their food items after a spraying, and they are assumed to consume water that has received herbicide from drift or a spill immediately after the event.

The risk assessment includes analyses of a range of possible exposures--from realistic to worst case--resulting from herbicide application by using three types of scenarios. (1) Typical application scenarios (routine-realistic) are used to estimate the doses to workers and to members of the public who may be nearby that may reasonably be expected to occur during routine operations. (2) Extreme application scenarios (routine-worst case) are used to give very high dose estimates that are not likely to be exceeded except in the case of an accident. (3) Accident scenarios (accidental-worst case) are used to estimate doses to workers and the public that may result from direct exposure to the herbicide spray mix

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or concentrate or from drinking water into which a truckload of herbicide mixture or a drum of herbicide concentrate has been spilled.

Structure of the Risk Assessment

This risk assessment employs the three principal analytical elements described by the National Research Council (1983) as necessary to characterize the potential adverse health effects of human exposures to existing or introduced hazards in the environment: hazard analysis, exposure analysis, and risk analysis.

1. **Hazard Analysis** requires gathering information that is used to determine the toxic properties of each herbicide. Human hazard levels are derived primarily from the results of laboratory experiments on animal models, such as rats, mice, and rabbits, supplemented where appropriate with information on epidemiology studies, human poisoning incidents, field studies of other organisms, and data on chemical structure. (A fourth analytical element--dose-response analysis--is considered in the hazard analysis.)
2. **Exposure Analysis** involves estimating single and multiple exposures to persons potentially exposed to the herbicides, determining the doses likely to result from those estimated exposures, and determining the number and characteristics of persons in the exposed populations.
3. **Risk Analysis** requires comparing the hazard information with the dose estimates and considering the probability that they could occur to predict the health effects to individuals under the given conditions of exposure.

The relationships among these three components are illustrated in figure 1-1. This risk assessment identifies uncertainties, such as areas where scientific studies are unavailable, and presents the results of all

HAZARD ANALYSIS

- o Identify what kinds of health effects have been observed under experimental laboratory conditions and at what levels of exposure
- o Identify any health effects that have been observed in humans
- o Determine median lethal dose (LD₅₀) for acute effects from laboratory rat study
- o Determine lowest no-observed-effect levels (NOEL's), if possible, for general chronic toxic effects, reproductive effects, and birth defects
- o Determine whether the herbicide has the potential to induce cancer or mutations
- o Identify information data gaps in toxicity information

EXPOSURE ANALYSIS

- o Identify people exposed
- o Identify routes of exposure
- o Estimate how much each person would receive by each exposure route using both realistic and worst case scenarios
- o Estimate frequency and duration of exposure
- o Calculate doses

RISK ANALYSIS

- o Compare doses to NOEL's and LD₅₀'s and discuss probability of acute and chronic effects (including birth defects) for routine through worst case scenarios
- o Conduct worst case analysis for cancer risk
- o Conduct worst case analysis for risk of heritable mutations

Figure 1-1 Components of the Risk Assessment Process

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worst case analyses. The discussion that follows describes briefly how each component in the structure was addressed in this risk assessment.

Hazard Analysis

The 16 herbicides being considered by the Forest Service and BLM in their vegetation management programs are amitrole, asulam, atrazine, bromacil, 2,4-D, 2,4-DP (dichlorprop), dalapon, dicamba, diuron, fosamine, glyphosate, hexazinone, picloram, simazine, tebuthiuron, and triclopyr. The hazard involved in the use of each of the herbicides was determined in a thorough review of available toxicological studies. Where no studies have been conducted for a particular toxicity end point, for example, mutagenicity, these data gaps are identified and a worst case analysis for this endpoint is conducted in Section 5. Scientific uncertainty regarding the results of particular studies, for example, concerning the results of the cancer studies on glyphosate and 2,4-D, also is discussed. The hazard analysis is presented in Section 3.

The toxicological data base for each herbicide was reviewed for acute and chronic effects on test animals. Toxicity information is summarized for 12 of the 16 herbicides in the background statements of Forest Service Agricultural Handbook No. 633 (USDA, 1984). Tebuthiuron toxicity is reviewed in a background statement prepared for the Forest Service as a supplement to Handbook No. 633. Toxicity information is summarized for the herbicides asulam, diuron, and bromacil in background statements written in conjunction with this risk assessment. These documents are incorporated by reference into this Supplement in accordance with 40 CFR 1502.21 and are available for review at all Forest Service and BLM District Offices in Oregon and Washington as well as at the address shown on the cover page.

Exposure Analysis

To estimate the potential human exposures to the 16 herbicides, the various aspects of the vegetation management programs of the Forest Service and Bureau of Land Management in Washington and Oregon that employs herbicides to control vegetation were examined. The major aspects of the vegetation

management programs that determine the potential levels of herbicide exposure were identified, including human activities associated with or in proximity to treatment areas, application methods, application rate, size and configuration of spray areas, project design features, and mitigation measures.

Herbicide Spraying Operations

The 16 herbicides examined in this risk assessment are applied aerially, using fixed-wing or helicopter aircraft, or on the ground, using trucks or tractors, backpack sprayers, or handheld application devices. Table 1-1 shows the types of operations where the herbicides are used and the approximate number of acres affected per year in Region 6 for the Forest Service and in western Oregon for BLM. The cumulative analysis makes the worst case assumption that 100,000 acres are treated each year as a result of the combined programs. The size of the program and the mix of activities may vary in any given year as described in each parent EIS.

These annual programs would involve a limited number of large projects and many small projects, ranging from one to many separate treatment units. Individual silviculture treatment units within a project typically range from 15 to 60 acres. A number of individual sites are normally treated at one time, with 120 to 150 acres treated per day. Occasionally the treatment areas are much smaller (less than 1 acre) or much larger (up to 200 acres), especially on wildlife rehabilitation projects. Treatment units for range management projects are generally larger, with 200 to 400 acres normally treated each day.

More than 100 projects, with treatment units ranging in size from less than 1 acre (for facility maintenance) to 400 acres for range management, occur annually on BLM lands in western Oregon and Forest Service lands within Region 6. The area treated with various herbicides in 1982 was less than 1 percent of the possible 21,746,000 acres of National Forest land in Region 6. Slightly more than 1 percent of the 2,383,000 acres of land administered by BLM in western Oregon was treated with herbicides in 1982.

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Table 1-1

Herbicide Spraying Operations for Forest Service and BLM Lands

Treatment Operations	Forest Service Acres	BLM Acres
Silviculture: Site Preparation and Conifer Release	27,000 - 35,000	38,800 - 44,100
Right-of-Way Management	3,000 - 6,000	1,900
Noxious Weed Control	1,400 - 1,600	300 ^a
Range Improvement	2,000 - 5,000	---- ^b
Facilities and Recreation Site Maintenance	100 - 150	---- ^b

^aBLM has prepared a separate EIS on noxious weed control. U.S. Department of the Interior, BLM. Northwest Area Noxious Weed Control Program, Draft EIS, May 1985.

^bIncluded in BLM's noxious weed control program.

The parent EIS's and Section 2 of this risk assessment contain further details about these operations.

Affected Populations

In calculating the potential doses to persons at risk from herbicide applications, two populations were considered: workers and the general public. The workers included personnel directly involved in the spray operations: the mixers and loaders, the truck-sprayer applicators and drivers, the backpack sprayers, the hand applicators, the pilots, the observers, and the supervisors. The public included forest visitors and nearby residents who may be directly exposed to herbicide as a result of drift, by contact with vegetation that has received herbicide drift, or by being accidentally sprayed. The public may be indirectly exposed by eating food items or drinking water containing herbicide residues.

Routine Exposure Scenarios

This risk assessment examines the health effects of exposure to an individual herbicide treatment as well as the cumulative effects of exposure over a number of years. To represent the range of doses under normal operating procedures, eight application scenarios were used. Four application scenarios termed routine-realistic assumed that four types of application (aerial, truck, backpack, and hand application) methods were used, employing normal herbicide application rates and typical treatment unit sizes, to calculate realistic doses to workers. Doses to members of the public who may be in the area or who may live nearby were calculated for aerial, truck, and backpack scenarios. No public exposures were expected from hand-application treatments because drift or other public contact should be negligible with these methods.

Four additional scenarios, using the same application methods as routine-realistic but employing the highest application rates likely to be used and the largest treatment unit sizes under weather conditions conducive to offsite herbicide drift, were used to estimate routine-worst

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case doses to workers and the public. These dose estimates purposely overestimate doses expected from routine applications.

Cumulative lifetime doses were estimated for the analysis of lifetime cancer risk by using information on average and maximum treatment days per year and on average and maximum number of years exposed for workers and for the public.

Accident Exposure Scenarios

Because all human activities involve the possibility of error, the use of herbicides in vegetation management involves the possibility that humans may inadvertently receive unusually high exposures to the herbicides because of accidents.

To examine what potential health effects could occur in an accidental situation, a number of accidental-worst case scenarios were analyzed. Exposures analyzed include direct aerial application of herbicide on a person, spills of concentrate or herbicide mix on workers in mixing and loading, and spills of herbicide into drinking water supplies. One accidental scenario assumes that a person enters a treated area (ignoring warning signs) before any herbicide has dried or degraded.

The probabilities of the accidents depicted in the scenarios actually happening range from unlikely to extremely unlikely. Wherever possible, historical records of accidents were used to indicate the probabilities of accident occurrence.

Dose Estimation

Estimates of routine doses to workers were derived from field studies on the five herbicides (2,4-D, 2-4-DP, dicamba, amitrole, and picloram) for which that information is available (see table 4-3 in section 4). For the other herbicides, doses were extrapolated from a 2,4-D worker exposure study that used the same application method.

Worker exposures to each herbicide were based on the worker's task, for example, backpack sprayer, pilot, mixer-loader, and so forth, rather than the type of vegetation management project, because the same equipment and procedures are often used in these operations. The exposures between operation types are weighted by application rate and number of hours worked per day. Where the exposure of a worker in a particular task, such as mixer-loader, is significantly different from one project type to another, that exposure is determined separately for each representative operation.

Exposures and doses to members of the general public were derived by using data on herbicide drift from field studies and by applying various assumptions about dermal penetration, amount of skin exposed, and diet. Details of the exposure analysis are presented in Section 4.

Risk Analysis

Human health risks of the vegetation management program were evaluated by comparing the doses of workers and the general public calculated for routine operational and accidental exposure scenarios to the laboratory-determined toxicity levels described in the hazard analysis.

Risk of threshold effects (chronic general health and reproductive/development effects) are evaluated by comparing estimated doses to NOEL's (no-observed-effect levels) from laboratory animal studies, using a derived margin of safety (MOS). Risk increases as the estimated dose approaches the laboratory toxicity level, that is, as the MOS decreases. Estimated doses are also compared to LD₅₀'s (median lethal dose) to judge the risk of acute effects.

Nonthreshold risk, that is, the potential for these herbicides to cause cancer and mutations, was evaluated differently. The analysis showed that eight of the herbicides--amitrole, asulam, atrazine, bromacil, picloram, 2,4-D, 2,4-DP, and glyphosate--are known or suspected of causing cancer in laboratory animals and thus could possibly cause cancer in humans. Therefore, this risk analysis uses the worst case assumption that these eight herbicides would cause cancer in exposed persons. The risk of cancer

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at a given level of exposure is based on single or multiple exposures that are averaged over a 70-year lifetime. The cancer potency value used to calculate this cancer risk derived for the herbicide in question from laboratory animal data on tumor incidence at increasing dose levels. The risk of cancer was calculated by multiplying the cancer potency value by the average lifetime dose for the various categories of people that may be exposed to the herbicides.

The risks of heritable mutations are discussed based on the weight of evidence from available test data on bacteria, yeasts, plants, mammalian cells in culture, and whole animals. Where no test data are available, a worst case assumption is made that the herbicide is mutagenic, and the risk of heritable mutations is then based on the herbicide's estimated cancer risk.

Cumulative risk for individuals is discussed (where data were available) in terms of lifetime exposures to a given herbicide for workers and for members of the public. Risk of synergistic effects is discussed in terms of the available evidence of enhanced toxicity in mixtures of two or more herbicides. Risk to more highly sensitive individuals who may be affected at extremely low exposure levels is discussed qualitatively in terms of the likelihood of a sensitive individual being exposed.

WORST CASE ANALYSIS REQUIREMENTS

As indicated earlier, this document is a supplement to the Forest Service and BLM Environmental Impact Statements named on page 1-1 and has been prepared pursuant to the requirements of the National Environmental Policy Act (NEPA) and the Council on Environmental Quality (CEQ) regulations for implementing NEPA.

This risk assessment identifies a number of information data gaps, including the following:

Worst Case Analysis Requirements

1. Field studies on exposure to workers for all of the herbicides except 2,4-D, 2,4-DP, dicamba, amitrole, and picloram.
2. Information on exposure of the public to the 16 herbicides.
3. Field data on residue levels in plants and animals most likely to be found in and around treatment areas for some of the herbicides.
4. Mutagenicity studies for asulam, 2,4-D, 2,4-DP, diuron, fosamine, and picloram.
5. The potential for dalapon, dicamba, diuron, fosamine, simazine, picloram, and glyphosate to cause cancer in laboratory animals.
6. Toxicity information on the synergistic effects from exposure to more than one herbicide.

These information gaps are important in deciding what is the best alternative for action; however, the cost of obtaining this information is an important consideration. From discussions with the Environmental Protection Agency, the Department of Agriculture, the Department of the Interior, and chemical manufacturers, it is estimated that the costs per chemical of conducting some of the standard laboratory toxicity tests would be \$350,000 for a chronic toxicity study with rats and dogs; \$350,000 for an oncogenicity test with rats and mice; and \$50,000 to \$100,000 for each mutagenicity and chromosomal study.

The following are the estimated costs to fill the specific data gaps listed above:

1. Worker exposure studies would cost approximately \$200,000 per chemical.
2. No acceptable protocol is available for measuring all of the various routes of exposure of the public, but these studies would be more expensive than the worker exposure studies.

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3. The cost of measuring residues in plants and animals would be between \$50,000 and \$100,000 per chemical per plant or animal.
4. The mutagenicity and chromosomal studies for bromacil, dalapon, and diuron would cost approximately \$450,000.
5. The five oncogenicity studies for amitrole, asulam, bromacil, 2,4-D, 2,4-DP, picloram, and glyphosate would cost approximately \$1.75 million.
6. Although there are methodologies available that incorporate several chemicals, the feasibility of testing all of the possible combinations of chemicals is questionable. The optimal testing strategy would include 2 chemicals for each study; therefore, 120 separate studies would be necessary. Testing several chemicals simultaneously requires a knowledge of suspected reactions and/or toxic components.

The overall cost of conducting the studies to fill the data gaps is considered exorbitant with respect to the limited funds available to the Forest Service and BLM. In addition, the time necessary to perform and evaluate most of these tests is more than 2 years and would seriously delay the implementation of the vegetation management programs. Many of the desired toxicological studies have already been requested by EPA, and the results of these studies will be considered when they become available. In addition, both agencies have ongoing research and monitoring programs to examine the various aspects of herbicide treatment, and these results will be considered as they become available.

Because the cost of filling the data gaps is considered exorbitant, a worst case analysis was conducted for those areas where information is unavailable or where there is uncertainty. The worst case scenarios involving routine herbicide application operations consist of those combinations of parameters, such as treatment unit size, duration of exposure, application rate, application equipment, and meteorological conditions, that give the highest reasonable exposure value. Worst case

accidents include direct spills of concentrate on workers' skin, the direct spraying of an individual, and public exposure through drinking water contaminated by a spill.

The worst case analysis for the mutagenicity of a herbicide for which there are no data or where there are some positive short term tests for mutagenicity assumed that the herbicide could cause heritable mutations. In establishing genetic risk for these compounds using a worst-case scenario, the risk of heritable mutations was assumed to be no greater than the risk of cancer for a given herbicide. This assumption is based on analysis of existing data for chemicals with both cancer and heritable mutation biassays (see Attachment A).

The worst case analysis for herbicides that had either positive cancer studies or for which there is scientific uncertainty assumed that these chemicals could cause cancer. A conservative cancer potency value for a chemical was computed by using the highest rates of tumor formation found in the available animal studies. A conservative model for estimating human cancer rates from tumor rates in laboratory animals also was used. The worst case analysis for synergistic effects assumed that these effects could occur. The probability of these effects occurring was considered low.

EPA has identified the data gaps shown in section 3, table 3-5, in accordance with the registration guidelines under the Federal Insecticide, Fungicide, and Rodenticide Act. Although there are data gaps or areas of uncertainty for some of the herbicides in this risk assessment, there is a large body of existing data useful for predicting the behavior and toxicity of these herbicides. These studies include the following:

1. Worker exposure studies with 2,4-D, 2,4-DP, dicamba, amitrole, and picloram.
2. Studies on drift of 2,4-D and glyphosate.
3. Residue information for a number of the herbicides in plant and animal tissues.

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4. Cancer studies for those herbicides without mutagenicity studies (since cancer appears to be the more sensitive toxicity endpoint).
5. Chronic feeding studies that show tumor growth or preneoplastic lesions and thus provide some evidence of cancer.
6. Studies either not reviewed by EPA, or validated studies reviewed by EPA, but determined not to be adequate to meet current registration standards, which nonetheless provide some information on toxic effects.

ORGANIZATION OF THIS SUPPLEMENT

Section 1 presents the purpose, describes the structure, and outlines the methodology of the risk assessment. Section 2 outlines the vegetation management programs that use herbicides and the mitigation measures practiced in each. Section 3, the hazard analysis, summarizes and discusses the toxic properties of each herbicide, including the cancer potency of the known or suspected carcinogenic herbicides. Section 4, the exposure analysis, describes the methods used to estimate levels of exposure and resultant doses to workers and the public and presents summary tables and discussions of estimated acute and long-term doses. Section 5, the risk analysis, presents the comparison of the results of the exposure analysis with the toxic effect levels set forth in Section 3. Section 5 also discusses cancer risk, given estimated lifetime doses to workers and the public. Attachment A presents a discussion written by Dr. David Brusick of the use of mutagenicity data in assessing the risks of heritable mutations. Attachment B provides the complete dose estimates for workers and the public derived from the methods described in the exposure analysis. Attachment C presents the complete margin-of-safety tables used in the risk analysis.

Appendix D
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Section 2

Section 2

VEGETATION MANAGEMENT PROGRAMS

This section describes the vegetation management programs that the Forest Service and BLM conduct in Washington and Oregon involving the use of herbicides. The first subsection briefly describes the different types of vegetation management programs that use herbicides. The second subsection identifies the application methods and the principal herbicides used in those programs. The final subsection discusses mitigation measures used to minimize the possible adverse effects of the herbicides on human health and the environment. Complete descriptions of the Forest Service and BLM vegetation management programs are found in the environmental impact statements that this document supplements.

PROGRAM DESCRIPTIONS

The Forest Service and BLM conduct vegetation management programs on Federal lands in Washington and Oregon to sustain and improve the ability of those lands to produce timber, livestock forage, and wildlife; to ensure public safety on roads, other rights-of-way, and recreation sites; and to protect facilities and capital improvements. Herbicides are proposed for use in these programs as described in the Forest Service and BLM environmental impact statements cited in Section 1.

Silviculture operations, designed to ensure the establishment and healthy growth of timber crop species, are the largest proposed program for herbicide treatment by both the Forest Service and BLM (table 2-1). These operations include site preparation, plantation maintenance, conifer release, precommercial thinning, and noncommercial tree removal. Site preparation treatments are used to prepare newly harvested or inadequately stocked areas for planting a new crop of trees. Use of herbicides in sitepreparation reduces vegetation that would compete with the conifers. In the brown and burn method of site preparation, herbicides are used to

D Human Health Risk Assessment (Quantitative) Table 2-1

Typical Annual Acres Treated by Vegetation Management Programs

Application Method	Silviculture	Noxious Weeds	Rights-of-Way	Facility Maintenance	Range Management	Total
<u>Forest Service, Region 6</u>						
Aerial Treatments	16,500	100	300	0	1,750	18,650
Ground Treatments	<u>14,500</u>	<u>1,400</u>	<u>4,200</u>	<u>125</u>	<u>1,750</u>	<u>21,975</u>
All Treatments	31,000	1,500	4,500	125	3,500	40,625
<u>Bureau of Land Management, Western Oregon</u>						
Aerial Treatments	34,500	0	400	0	-	34,900
Ground Treatments	<u>7,000</u>	<u>275</u>	<u>1,500</u>	<u>25</u>	<u>-</u>	<u>8,800</u>
All Treatments	41,500	275	1,900	25	-	43,700

dry the vegetation, which several months later is burned. Herbicides are used in plantations some time after planting to promote the survival and establishment of conifers (maintenance) or to promote the dominance and growth of already established conifers (release). Precommercial thinning reduces competition among conifers, thereby improving the growth rate of the crop trees. Noncommercial tree removal is used to eliminate dwarf mistletoe-infected host trees. These latter two silvicultural practices primarily use manual methods, although the use of herbicides constitutes about 2 to 5 percent of the operations. On the basis of total acreage managed, the Forest Service has historically used herbicides in about 12 percent of its site preparation work, BLM in about 30 percent. The Forest Service has used herbicides in approximately 80 percent of its maintenance and release projects, BLM in more than 90 percent.

Right-of-way management operations include roadside maintenance and maintenance of power transmission lines, waterways, and railroad corridors. In roadside maintenance, vegetation is removed from ditches and the shoulders of roads to prevent brush encroachment into driving lanes, to maintain visibility on curves for the safety of vehicle operators, to permit drainage structures to function as intended, and to facilitate maintenance operations. Herbicides have been used in 16 percent of the Forest Service's roadside maintenance in Region 6. In western Oregon, 30 percent of BLM's roadside maintenance has historically used herbicides.

Noxious weed control programs control noxious and poisonous plants harmful to humans or domestic livestock. Plants most often treated are poison oak, tansy-ragwort, St. Johnswort, skeleton weed, and thistle. BLM's noxious weed control program is analyzed in a separate EIS, "Northwest Area Noxious Weed Control Program" (BLM, 1985).

The Forest Service and BLM have used herbicides extensively in their noxious weed program. The Forest Service has historically used herbicides on almost all acres of noxious weed treated.

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Range improvement operations provide forage for domestic livestock grazing by removing undesirable competing plant species and preparing seedbeds for desirable plants. The Forest Service uses herbicides on about 12 percent of its range improvement acreage in Region 6. BLM's range improvement program is evaluated in a separate EIS (BLM, 1985).

Facilities and recreation site maintenance operations provide for the safe and efficient use of Forest Service and BLM facilities and recreation sites and for permittee/grantee use of such public amenities as ski runs, waterways, and utility terminals. BLM includes its facility maintenance in its roadside maintenance and weed control program. The Forest Service uses herbicides on less than 11 percent of the total acreage maintained by its facility and recreation site maintenance operations.

APPLICATION METHODS AND HERBICIDE USAGE

Herbicides are applied either from the air or on the ground. Aerial methods employ boom-mounted nozzles carried by helicopters or fixed-wing aircraft. Ground application methods include vehicle-mounted, backpack, and hand application techniques. Vehicle-mounted application systems use fixed-boom or hand-held spray nozzles mounted on trucks or tractors. Backpack systems use either a pressurized sprayer or a powered mist blower to apply herbicides as a broadcast spray directly to one or a group of individual plants.

The principal hand application techniques are injection and stump treatment. Injection involves the application of herbicide in hand-held containers or injectors through slits cut into the stems of target plants. Individual stem treatment by the injection method also is used for crop tree thinning or removal of weed trees. Hack-and-squirt and injection bar equipment are most often used in injection treatments. Stump treatment entails directly applying liquid herbicide to the cut stump of the target plant. The herbicide can be applied by dabbing or painting the stump, or using a squeeze bottle on a freshly cut surface to inhibit sprouting. Herbicides may also be applied by hand in solid form as granules spread on the ground

surface. Although all of the application methods have been used in every type of management operation (except aerial methods on facility or recreation sites), only one or two methods are routinely used. Table 2-2 lists the application methods used in each type of management program with an indication of which methods are commonly used and which are only rarely used. Table 2-1 lists Forest Service and BLM acres treated in each management program by aerial and ground methods in a typical year. Actual historical data were used in determining these typical acreages.

The principal herbicides used by both agencies in terms of total acres treated in all programs are 2,4-D, glyphosate, and triclopyr. Figures 2-1 and 2-2 illustrate the historical proportion of total treated acreage for each of the 16 herbicides used by the Forest Service and BLM.

Aerial Methods

The Forest Service treats more than half of its herbicide-treated silviculture and range management sites by air, as indicated in table 2-1. BLM treats more than 80 percent of its silviculture sites by air. In general, helicopters are used on silviculture projects because the many treatment units are far apart, small and irregularly shaped, and in steep terrain. Herbicides are normally released 30 to 90 feet above vegetation as medium-sized droplets in an 80- to 90-foot swath. On an average day, several treatment units totaling 150 acres can be sprayed.

Fixed-wing aircraft commonly are used on range management and noxious weed projects in which large contiguous areas are treated. Herbicides are generally released at the same height and swath width as in helicopter treatments. For a large treatment unit, 400 acres can be treated each day.

Batch trucks are an integral part of any aerial operation. They serve as mixing tanks for preparing the correct proportions of herbicide and carrier, and they move with the operation when different landing areas are required.

The number of workers involved in a typical aerial spray project varies according to the type of activity. A small operation may require only

Table 2-2

Herbicide Application Methods Used in Forest Service
and Bureau of Land Management Vegetation Management Programs

Application Method	Project Type					
	Silviculture Site Preparation	Conifer Release	Range Improvement	Noxious Weeds	Right-of-Way Maintenance	Facilities and Recreation Site Maintenance
<u>Aerial</u>						
Fixed Wing	R	R	0	0	R	
Helicopter	C	C	0	0	C	
<u>Mechanical</u>						
(Truck-mounted or towed sprayer)	R	R	0	0	C	0
Backpack	C	C	0	0	0	C
Hand	0	0	R	R	0	0

Legend

C = Commonly Used
 0 = Occasionally Used
 R = Rarely Used
 Blank = never used

Application Methods
and Herbicide Usage

Aerial Methods

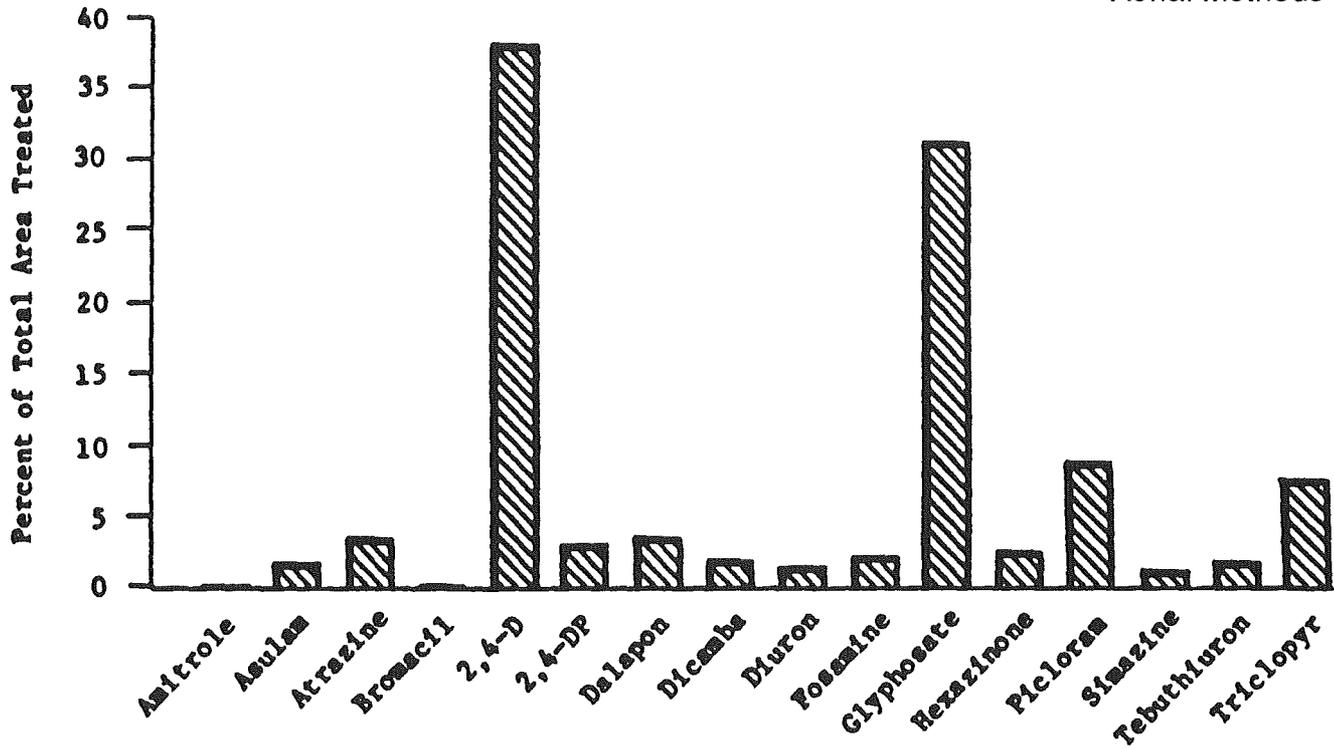


Figure 2-1 Historical Herbicide Use in Region 6 National Forests

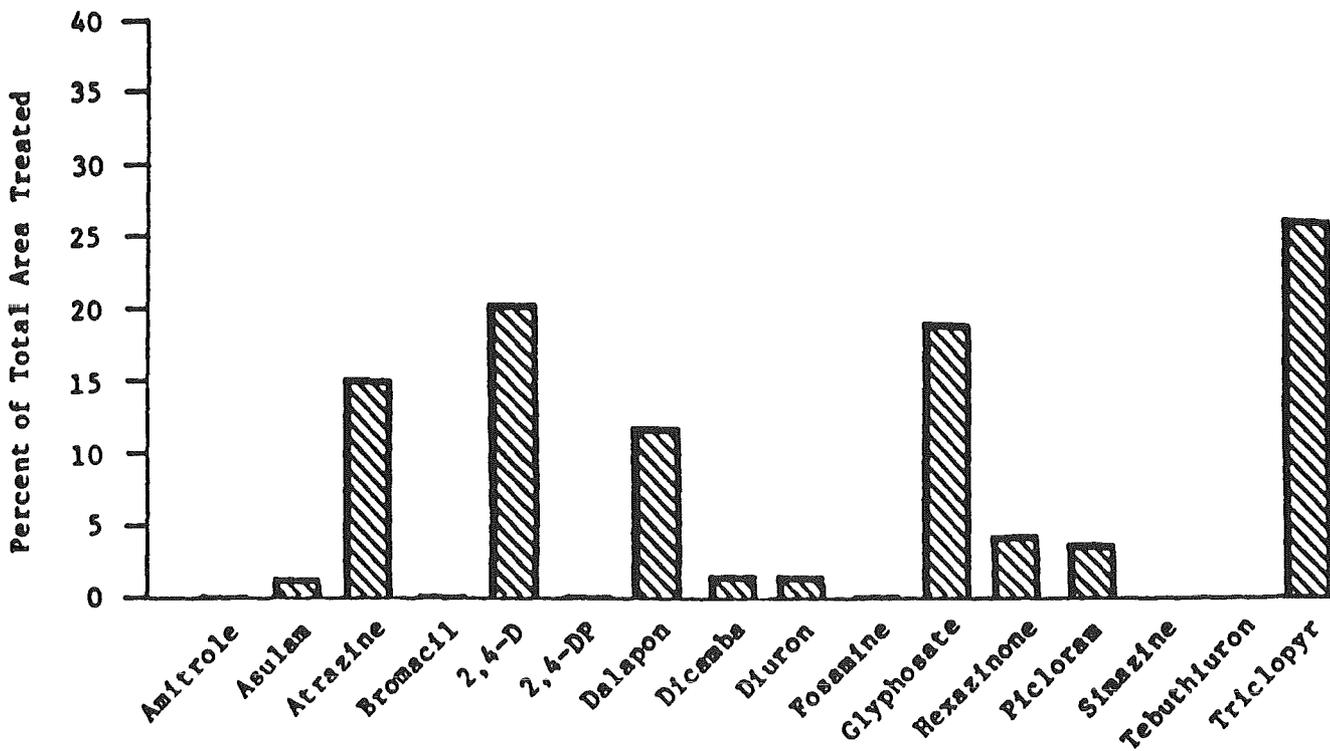


Figure 2-2 Historical Herbicide Use by BLM in Western Oregon

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6 individuals, while a complex spray operation may need as many as 20 to 25 workers. The aerial operations crew for range management, noxious weed control, and right-of-way maintenance normally consists of five to eight individuals. Typical personnel on a large project include a pilot, a mixer-loader, a contracting officer's representative (COR), an observer-inspector, a one to six-member card crew, one or two law enforcement officers, one or two water monitors, and one or two laborers. Optional personnel include an air operations officer, a radio technician, a weather monitor, and a recorder.

The following discussions are based on historical data on actual acres treated from the Forest Service Region 6 and BLM in western Oregon.

Forest Service Aerial Projects

In terms of total annual Forest Service herbicide use, the aerial application of herbicides in silviculture and range management programs normally constitutes about one-third of the herbicide applied.

2,4-D, glyphosate, and triclopyr have historically been the principal herbicides used for the Forest Service's aerial silviculture operations. The main herbicides used in aerial range management have been atrazine, dalapon, and 2,4-D. Picloram and 2,4-D have been the principal herbicides used on the small number of acres treated aerially for noxious weed control and right-of-way maintenance by the Forest Service. In some years, there has been no aerial spraying of rights-of-way.

Aerial silviculture treatment units vary in size from 2 acres to 60 acres. Normally, aerial treatment units are no more than 40 acres. Based on a 150-acre-per-day application schedule, there were roughly 100 total treatment days. Region 6 Forest Service personnel estimate that aerial silviculture programs require 200 to 250 total workers and 2,500 to 3,500 total worker days of labor each year. Range improvement operations may include two or three large aerial projects per year, with treatment units ranging up to 400 acres. The annual work force for range projects was estimated at 25 to 30 workers and 300 to 350 total worker days.

BLM Aerial Projects

Historically, more than 80 percent of the total acres treated by BLM was for aerial silviculture projects. Five principal herbicides have historically been used by BLM aerial silviculture programs: 2,4-D, glyphosate, triclopyr, atrazine, and dalapon. Aerial treatments for right-of-way maintenance using primarily 2,4-D and triclopyr normally accounted for less than 1 percent of the total acreage treated.

Silviculture projects make up the bulk of BLM's aerial operations. BLM generally applies herbicides on about 150 acres/day in aerial treatments. An average of six individuals are normally involved in each of BLM's aerial spray operations.

Ground-Based Methods

Forest Service Ground-Based Treatment Projects

Silviculture and Range Management Projects. Ground treatment in silviculture and range management programs accounted for nearly half of the total acreage treated with herbicides by the Forest Service in 1982 and 1983. Glyphosate, 2,4-D, picloram, and triclopyr were the major herbicides used during ground-based silvicultural treatment in those years. Rangeland was treated predominantly with atrazine, dalapon, and 2,4-D.

Backpack treatment is the predominant ground-based method used for silviculture, although stump treatment and injection also are used. Herbicides may also be applied in granular form. Backpack treatment is also the predominant ground-based method used in range management.

Pressurized backpack treatment operations typically involve a supervisor (who may also function as a mixer-loader), an inspector, a monitor, and 2 to 12 crew members. Backpack sprayers can typically treat one-half of an acre per hour in silviculture operations. Four laborers and one inspector generally make up the work force for stump treatment or injection.

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Major ground-based silviculture programs of the Forest Service in 1982 involved treatment of 300 or more acres in eight of the National Forests within Region 6. A total of 100 to 150 workers and 3,800 to 4,300 total worker days was estimated as a yearly labor allotment.

Right-of-Way Projects. In Region 6, areas treated with herbicides during right-of-way and road maintenance projects historically account for about one-fifth of the total acres treated. Treatments are normally done by permittees of the Forest Service (State highway departments, county road crews, utility companies, and the like). Fosamine, 2,4-D, 2,4-DP, picloram, tebuthiuron, and diuron were the most heavily used herbicides in this program.

Right-of-way maintenance projects frequently use vehicle-mounted application techniques. A truck with a mixing/holding tank uses a front-mounted spray boom or a hand-held pressurized nozzle to treat roadside vegetation on varying slopes. Use of this equipment for off-road right-of-way projects is limited to gentle slopes (less than 20 percent) and open terrain. Contractors spray an average of 30 to 50 acres per day with vehicle-mounted applicators. A driver/mixer-loader and applicator constitute the typical crew for truck spraying. A total of 3,000 to 3,500 worker days and 100 to 125 workers was estimated as a yearly quota for right-of-way maintenance projects.

Noxious Weed Control Projects. Forest Service use of ground-applied herbicides for noxious weed control normally accounted for less than 5 percent of the total acreage treated in both 1982 and 1983. Nearly half of the noxious weeds affected were on rangelands. 2,4-D, picloram, and dicamba are the principal herbicides used for noxious weed control. Backpacks, spray bottles, and trucks or tractors with spray booms or tractor-mounted attachments are used in ground-based noxious weed programs. Backpack sprayers can typically treat only 1 acre every 3 to 4 hours in noxious weed control programs because target plants are normally found as scattered individuals or in small groups. About one-fourth of the total acres treated in noxious weed control projects was hand-treated with herbicides in granular form. Noxious weed control programs, using both

Aerial Methods
Ground-Based Methods

aerial and ground methods, account for 1,500 to 2,200 total worker days and 140 to 150 workers per year.

Facility Maintenance Projects. Facility maintenance by the Forest Service resulted in treatment of about 1 percent of the total acreage controlled by herbicides in 1982 and 1983. Amitrole, glyphosate, 2,4-D, and 2,4-DP were the major herbicides used in 1982, while glyphosate and 2,4-D were the predominant herbicides applied in 1983. All methods of ground application may be used and would typically involve only one or two applicators and one supervisor who would check on the work after the task was completed. Many small short-term projects throughout the Region have resulted in a total treatment of 100 to 125 acres annually.

BLM Ground Application Projects

Ground-based methods of herbicide application are not used as extensively by BLM as they are by the Forest Service. Manual methods are often used in silviculture projects, and controlled burning is commonly used for site preparation. In silviculture projects, ground applications normally constitute less than 20 percent of the total area treated by BLM.

Methods of herbicide application in BLM ground-based operations are similar to those of the Forest Service. Ground application in BLM projects is accomplished through backpack spraying, vehicle-mounted spraying, injection, stump treatment, and other hand application methods.

Triclopyr, glyphosate, atrazine, and dalapon accounted for more than 95 percent of the total herbicides chosen for site preparation operations under the proposed alternative of the EIS for the Western Oregon Program-- Management of Competing Vegetation (BLM, 1983). These four herbicides and 2,4-D accounted for nearly 90 percent of the herbicides selected for use in the maintenance and release projects under the proposed alternative for BLM's silviculture program. BLM's right-of-way maintenance projects used triclopyr, 2,4-D, dicamba, and diuron for almost all of the acres treated. BLM's ground spraying projects are about the same size as the Forest Service's.

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Mitigation measures are intended to ensure the proper and safe application of herbicides on Forest Service and BLM lands in Washington and Oregon and are required by Federal, State, and regional procedures. Federal and State laws and regulations set minimum standards to be followed during herbicide application on forests and rangelands owned by the Federal Government. Each regional and district office also may develop additional restrictions and precautions. The Federal Insecticide, Fungicide, and Rodenticide Act requires that pesticide manufacturers register their chemicals with the U.S. Government and list the allowable uses, application rates, and special restrictions on the herbicide's label. All of the herbicides considered in this risk assessment are registered with the Environmental Protection Agency; and their label rates, uses, and handling instructions must be complied with according to Federal law.

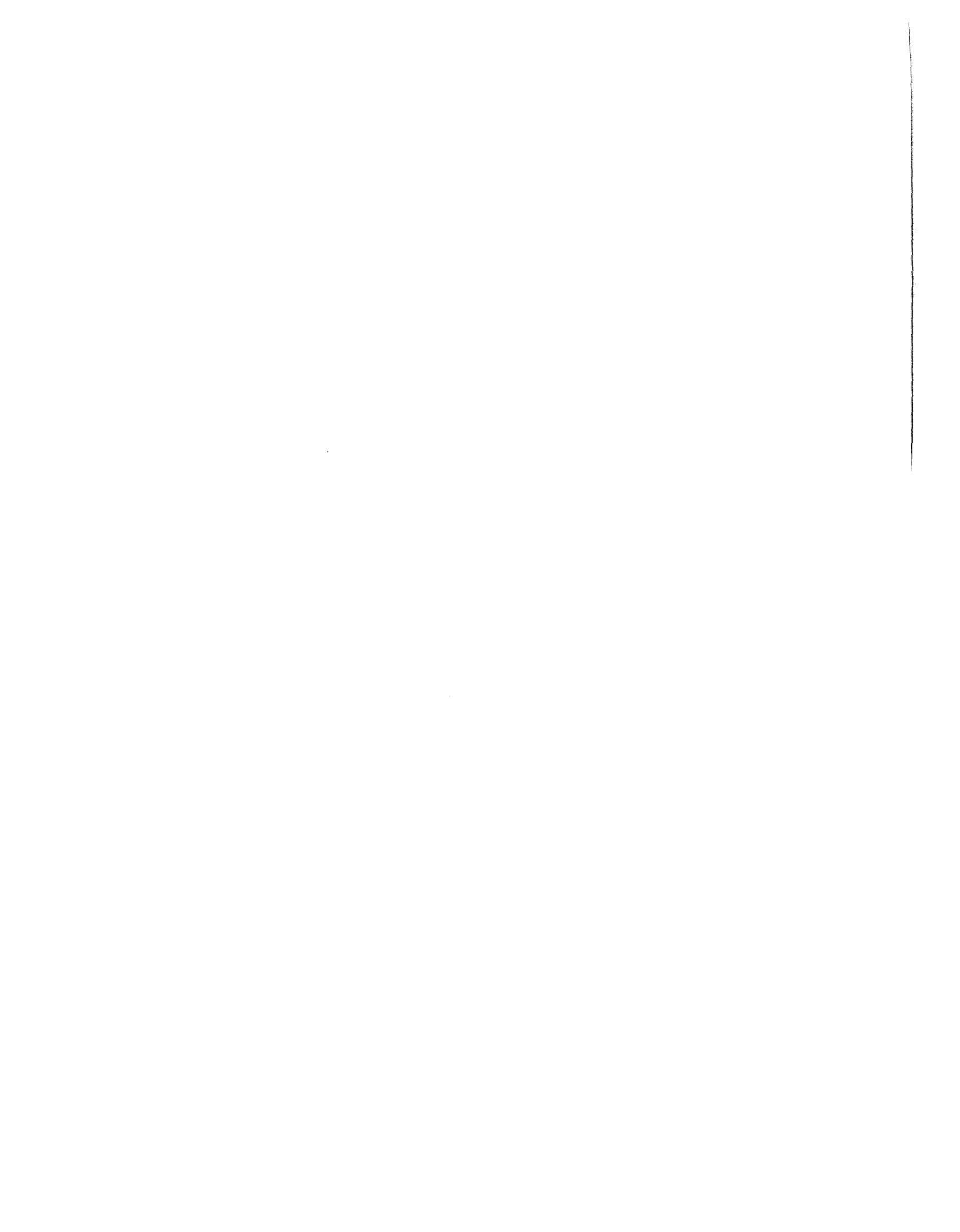
The Department of the Interior (Bureau of Land Management) and the Department of Agriculture (Forest Service) have handbooks that prescribe guidelines for aerial and ground application operations. Regional publications, such as BLM's Western Oregon Program--Management of Competing Vegetation Environmental Impact Statement and the Forest Service's Region 6 Vegetation Management Program Environmental Impact Statement, serve to further refine herbicide application guidelines. The Siskiyou National Forest Aerial Applicator's Handbook (USDA, 1982) is an example of a forest level operational guideline that specifies detailed herbicide application procedures.

Aerial and ground application procedures undergo detailed planning weeks or even months in advance. Mitigation measures, such as not spraying in sensitive areas, notifying the public, posting warning signs, and conducting water monitoring, are specified in site-specific annual vegetation management plans.

Many mitigation measures developed for herbicide operations in Washington and Oregon are described in each agency's environmental impact statements,

which this document supplements. Some specific examples of project mitigation measures include the following:

1. Application operations will be suspended when any of the following conditions exist:
 - a. Wind velocity exceeds 5 miles per hour or air is stagnant
 - b. Air temperature exceeds 70 °F
 - c. Relative humidity is less than 50 percent
 - d. It is raining or misting or there is a 40-percent chance of rain within several hours
 - e. Foggy weather
2. During air operations, a radio network will be maintained to link all parts of the project.
3. Equipment is designed to deliver a median droplet diameter of 200 to 800 microns. This droplet size is large enough to avoid excessive drift while providing adequate coverage of target vegetation.
4. Individuals involved in the herbicide handling or application will be instructed on the safety plan and spill procedures.



Appendix D

**Human Health
Risk Assessment
(Quantitative)**



Section 3



Section 3
HAZARD ANALYSIS

INTRODUCTION

This section presents the results of the hazard analysis: a review of available information on the toxicity of the 16 herbicides--amitrole, asulam, atrazine, bromacil, 2,4-D, 2,4-DP, dalapon, dicamba, diuron, fosamine, glyphosate, hexazinone, picloram, simazine, tebuthiuron, and triclopyr--that are to be used in the Forest Service and BLM vegetation management programs in the Pacific Northwest. The first subsection describes the sources of the toxicity information. The second subsection explains the terminology concerning laboratory toxicity testing used later in describing the toxic properties of the 16 herbicides. The third subsection presents summaries of the threshold toxicity of each herbicide and the potential for each of the 16 herbicides to cause the nonthreshold effects of cancer and genetic mutations. A discussion of the derivation of cancer potency from tumor data is presented for those herbicides suspected of being carcinogenic. The fourth subsection summarizes the data gaps in the toxicity information reviewed by EPA for the 16 herbicides. The final subsection reviews the toxicity information on inert ingredients and herbicide carriers considered to be of toxicological concern (Inerts List 2) by EPA. Inerts of toxicological concern in this assessment include petroleum of distillates (contained in formulations of 2,4-D, triclopyr, and picloram and formaldehyde (contained in diuron, simazine, and picloram formulations)).

SOURCES OF TOXICITY INFORMATION

The toxicity of 12 of the herbicides (amitrole, atrazine, 2,4-D, 2,4-DP, dalapon, dicamba, fosamine, glyphosate, hexazinone, picloram, simazine, and triclopyr) to both laboratory animals and humans is described in detail in the background statements of the Forest Service Agricultural Handbook No. 633 (USDA, 1984). Tebuthiuron toxicity is described in a background statement prepared for the Forest Service as a supplement to Handbook

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No. 633. The toxicity of the herbicides asulam, diuron, and bromacil is described in background statements written in conjunction with this risk assessment. These documents are incorporated by reference into this Supplement to the Final Forest Service and BLM EIS's identified in Section 1 in accordance with 40 CFR 1502.16 and are available for review at all Forest Service and BLM District Offices in Oregon and Washington, as well as at the address shown on the cover page.

Much of the data on pesticide toxicity have been generated to comply with the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended (7 U.S.C. 136 et seq), which establishes procedures for the registration, classification, and regulation of all pesticides, including herbicides. EPA is responsible for implementing FIFRA. EPA registration standards are thorough reviews of all data submitted for registration or re-registration of a chemical and are available through EPA's Freedom of Information Office. EPA has compiled "science chapters" that include discussions of toxicity on many of the herbicides (amitrole, bromacil, dicamba, diuron, hexazinone, picloram, and simazine) and these are also available from EPA. Toxicity levels and related information from the series of studies submitted for registration are compiled by EPA in summary tables called "tox one-liners" that are available on request from EPA's Freedom of Information Office. A large body of additional toxicity information exists in the open literature, particularly for chemicals such as 2,4-D that have been used for many years.

An extensive literature search was funded by the U.S. Department of Agriculture, Forest Service, to ensure that all of the relevant available information was used in this risk analysis. The National Library of Medicine's RTECS and HSDB data bases, as well as Medline, Chem Abstracts Embase (Excerpta Medica), and International Pharmaceutical Abstract data bases were searched in 1986 to locate current literature pertaining to the carcinogenicity and mutagenicity of the herbicides. That search was updated to make the document current for information available as of June 1, 1988.

The data from the U.S. Department of Agriculture, Forest Service, Pesticide Background Statements (USDA, 1984) and the California Department of Food and Agriculture Summaries of Toxicological Data were reviewed and compared to summaries of studies submitted to the Environmental Protection Agency for the registration of the 16 herbicides. Whenever possible, studies that have been reviewed and validated by EPA were used to set toxicity reference levels. In no cases were studies used that have been invalidated by EPA.

HAZARD ANALYSIS TERMINOLOGY

Because of obvious limitations on the testing of chemicals on humans, judgments about the potential hazards of pesticides to humans are necessarily based on the results of toxicity tests on laboratory animals. These toxicity test results are supplemented by information on actual human poisoning incidents and effects on human populations when they are available. The discussion of laboratory toxicity testing that follows is drawn from Hayes (1982), Doull et al. (1980), and Loomis (1978).

Laboratory Toxicity Testing

Test Animal Species

Laboratory test animals function as models of the likely effects of a pesticide in humans. Ideally, the test animal should metabolize the compound the same as a human would and should have the same susceptible organ systems. Results of such tests can be directly extrapolated to humans with some adjustment made for differences in body weight and body surface area. Although no test animal has proven ideal, a number of species have proven to be consistent indicators for certain types of toxicity tests, routes of administration, and types of chemicals; in particular, rats, mice, rabbits, hamsters, guinea pigs, dogs, and monkeys.

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Toxicity Endpoints and Toxicity Reference Levels

Toxicity is the ability of a substance to produce an adverse effect on an organism. In general, adverse effects progress relative to duration of exposure. Toxicity tests are designed to identify specific toxicity endpoints, such as death or cancer, and toxicity reference levels, such as an LD₅₀ or no-observed-effect level (NOEL). In addition to the test animal used (previously discussed), toxicity tests vary according to test duration, route of administration, dose levels, dosing schedule, number of test groups, and number of animals per group. Toxicity tests also vary on the basis of whether it is assumed that the effect in question is a threshold effect or a nonthreshold effect.

Threshold and Nonthreshold Effects

Most chemicals are assumed to have a threshold level of toxic effects on a local basis (at the site of administration) or systemic basis (acting throughout the body), below which no adverse effects occur to the test organism. Chemicals are generally thought to possess no such threshold level for cancer and mutations, thus these toxic endpoints may occur (with a certain level of probability) even in the presence of extremely small quantities of the substance. In the discussion of each herbicide in this hazard analysis, threshold effects are discussed first; nonthreshold effects (cancer and mutagenicity) are discussed second. The term "greater than", which is used frequently to describe threshold effect, indicates that no adverse effects have been observed at the highest dosage level.

Duration of Toxicity Tests

The duration of toxicity tests ranges from very short-term acute tests to longer subchronic studies to chronic studies that may last the lifetime of an animal. Acute toxicity studies involve administration of a single dose to each member of a test group (either at one time or in a cumulative series over a short period of less than 24 hours) or several daily doses

over a short duration (with a maximum duration of two weeks). Subchronic toxicity studies, used to analyze the effects of multiple doses, usually last from 3 weeks to 3 months but generally last less than one-half the lifetime of the test animal. Chronic studies, also used to analyze the effects of multiple or continuous doses, normally last 2 years or more but generally more than one-half the test species' lifetime.

Routes of Administration

Routes of administration include oral via gavage (forced into the stomach with a syringe through plastic tubing) or fed in the diet, dermal (applied to the skin), inhalation (through exposure to vapors or aerosol particles), and parenteral (injection other than into the intestine). Parenteral routes include subcutaneous (injected under the skin), intraperitoneal (injected into the abdominal cavity), and intravenous (injected into a vein). Oral, dermal, and inhalation doses most nearly duplicate the likely routes of exposure to humans; therefore, these administration routes are used most frequently in toxicity testing. In addition, ingestion and inhalation are considered the most important routes of exposure for pesticides in humans. Doses are expressed in several ways. They can be expressed as milligrams (mg, which is 1/1,000 of a gram) of the chemical per kilogram (kg, which is 1,000 grams) of body weight of the test animal, or in parts per million (ppm) in the animal's diet, or in milligrams per liter (mg/L) in the air the animal breathes.

Dosing Levels

A dose is expressed as milligrams of the chemical per kilogram of body weight of the test animal, in parts per million in the animal's diet, or in milligrams per liter in the air that the animal breathes or in the water that the animal drinks. In long-term studies, the test substance is generally administered in the diet with specified amounts in parts per million. The body weight and food consumption of the test animal over the test period is used to convert parts per million in the diet to milligrams of chemical per kilogram of body weight per day (mg/kg/day) for extrapolation to humans. In the majority of chronic toxicity studies, at

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least three dosing levels are used in addition to a zero-dose or control group. In general, the control group animals are administered the vehicle (for example, water or saline) used in administering the test material. In a dietary study, the basal feed would serve as the vehicle.

Types of Laboratory Toxicity Studies Used in the Risk Assessment

Acute Toxicity Studies

Acute toxicity studies are used to determine a number of toxicity endpoints based on a single or several large doses of a substance. An important endpoint in acute testing is the toxicity reference level known as the median lethal dose (LD_{50}), which is the dose usually administered orally, that kills 50 percent of the test animals. The lower the LD_{50} , the greater the toxicity of the chemical. The LD_{50} ranges for the acute oral toxicity categories used in this risk assessment are those of the EPA classification system using rat oral LD_{50} 's, as shown in table 3-1 (adapted from Walstad and Dost, 1984). Acute toxicity studies are also used to estimate dose levels to be used in longer term studies. In addition to the acute oral LD_{50} test in rats, in its battery of laboratory toxicity studies considered as acute tests, EPA (40 CFR Part 158) includes acute dermal, acute inhalation (rat), eye irritation (rabbit), dermal irritation (rabbit), dermal sensitization (guinea pig), and acute delayed neurotoxicity (hen). The last test is required for chemicals, such as organophosphates, that are known to cause cholinesterase depression or other nervous system effects. Because lethality is the intended toxic endpoint in the acute oral, dermal, and inhalation studies, dose levels usually are set relatively high in those studies. Toxic symptoms displayed by the animals may be recorded throughout the study, and tissues and organs are examined for abnormalities at the end of the test. The animal most commonly used for oral LD_{50} 's is the rat. Rabbits are used most often to determine dermal LD_{50} 's.

Figure 3-1 illustrates the relationship between the LD_{50} and the dose level at which no adverse effects were observed (NOEL). For longer term tests the adverse effects may occur on a continuum and progress in intensity.

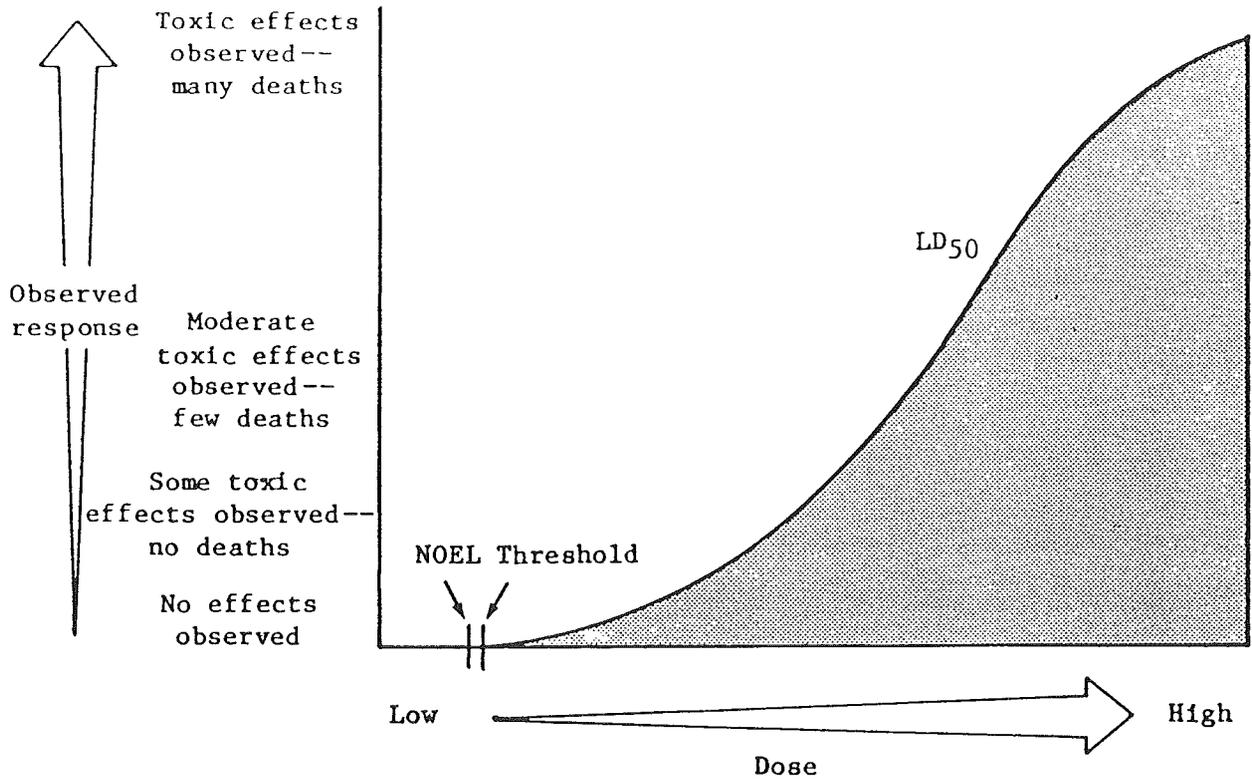
Table 3-1
Categories of Acute Toxicity^a

Toxicity Category ^b	Signal Word	Oral LD ₅₀ (mg/kg)	Dermal LD ₅₀ (mg/kg)	Inhalation LC ₅₀		Eye Effect	Skin Irritation
				Dust or Mist (mg/liter)	Gas or Vapor (ppm)		
I-	Severe	50 or less	200 or less	2 or less	200 or less	Irreversible corneal opacity at 7 days.	Severe irritation or damage at 72 hours.
II-	Moderate	50 through 500	200 through 2,000	2 through 20	200 through 2,000	Corneal opacity reversible within 7 days, or irritation persisting for 7 days.	Moderate irritation at 72 hours.
III-	Slight	500 through 5,000	2,000 through 20,000	20 through 200	2,000 through 20,000	No corneal opacity, irritation reversible within 7 days.	Mild or slight irritation at 72 hours.
IV-	Very slight	5,000 or greater	20,000 or greater	200 or greater	20,000 or greater	No irritation.	No irritation at 72 hours.

^aAdapted from U.S. Environmental Protection Agency toxicology guidelines, summarized in Ashton 1982 in USDA, 1984.

^bAdapted from EPA by Maxwell 1982, as cited in Walstad and Dost, 1984.

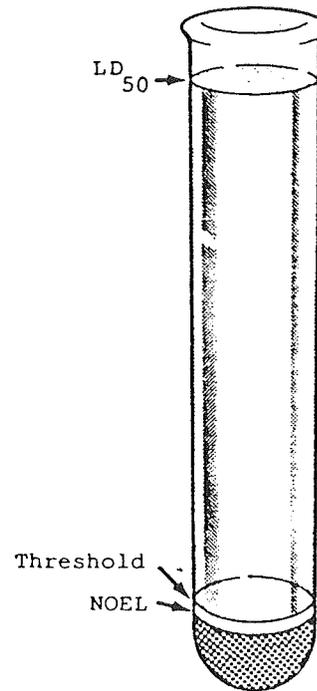
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LD₅₀ - Acute lethal dose. One-time or short-term dose that is lethal to 50 percent of treated animals.

Threshold - Dose level at which toxic effects are first observed in test animals.

NOEL - No-observed-effect level. Long-term dose that does not result in apparent adverse effects in test animals.



(Not To Scale)

Figure 3-1.--Relationships Among Toxicity Reference Levels

Subchronic Toxicity Studies

Subchronic studies are designed to determine the effects of repeated exposure, and in particular, the toxicity reference level called the no-observed-effect level (NOEL), which is the highest dose level at which no toxic effects are observed. If a chemical produces effects at the lowest dose tested (LDT) in a study, the NOEL must be at some lower dose. If the chemical produces no effects, even at the highest dose tested (HDT), the NOEL is equal to or greater than the HDT. Another toxic endpoint of interest is the lowest dose showing toxic effects, the lowest effect level (LEL). For local and systemic effects, the chemical's effect threshold lies between the NOEL and LEL for the tested species (figure 3-1). EPA (40 CFR part 158) includes 90-day feeding tests (rodent and nonrodent), 21-day dermal, 90-day dermal, 90-day inhalation, and 90-day neurotoxicity studies in its battery of subchronic testing requirements under FIFRA.

Subchronic studies, normally employing lower dose levels than acute studies, provide information on systemic effects, cumulative toxicity, the latency period (the time between exposure and the manifestation of a toxic effect), the reversibility of toxic effects, and appropriate dose ranges to be used in chronic tests. Adverse effects may range from death in the extreme case to minor debilitating, often reversible, effects such as decreased rate of food consumption; changes in body weight; decreased enzyme levels; changes in blood constituents, such as red blood cells (RBC's) or white blood cells (WBC's); undesirable constituents in the urine; or microscopic changes in tissues.

Chronic Toxicity Studies

Chronic studies, like subchronic studies, are used to determine systemic NOEL's. All other things being equal, the longer the study from which a NOEL is derived, the more reliable the resulting value. Chronic studies, however, are even more important in determining doses that are hazardous to reproductive success or in determining whether the chemical causes cancer. EPA (40 CFR part 158) includes chronic toxicity (feeding) studies (rodent and nonrodent), oncogenicity (cancer) studies (rat and mouse),

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teratogenicity studies (rat and rabbit), and reproduction studies in its battery of chronic testing requirements under FIFRA.

Teratogenicity tests. Teratogenicity tests (teratology studies) are conducted to determine the potential of a chemical to cause malformations in an embryo or a developing fetus between the time of conception and birth. These studies generally use pregnant female rats or rabbits dosed during the middle period of gestation while the organs of the fetus are developing. The animals are monitored for functional as well as structural deformities.

Reproduction studies. Reproduction studies are conducted to determine the effect of the chemical on reproductive success as indicated by fertility, direct toxicity to the developing fetus, and survival and weight of offspring for low-level, long-term exposure. These tests are usually performed at lower doses than those used in teratogenicity studies and they normally use rats. Both male and female rats are exposed to the chemical for a number of weeks before mating. The number of resulting pregnancies, stillbirths, and live births are recorded. Tests may be conducted over two or three generations.

Carcinogenicity tests. Carcinogenicity is defined as the ability to induce tumors. Benign, as well as malignant tumors, are considered as evidence of carcinogenicity. Carcinogenicity tests (cancer studies or oncogenicity studies) are conducted to determine the potential for a chemical to cause tumors when fed in the diet over the animal's lifetime. Testing is normally conducted with rats or mice for a 2-year period.

The cancer potency of a chemical is defined as the increase in likelihood of getting cancer from a unit increase in the dose of the chemical. It should be noted that the potency is derived from data at high dose levels; therefore, to apply the formula to low doses, one must assume the applicability of the formula. An example of this relationship is illustrated by the graph in figure 3-2. The slope of the line specifies what the increase in cancer probability is for each unit increase in dose

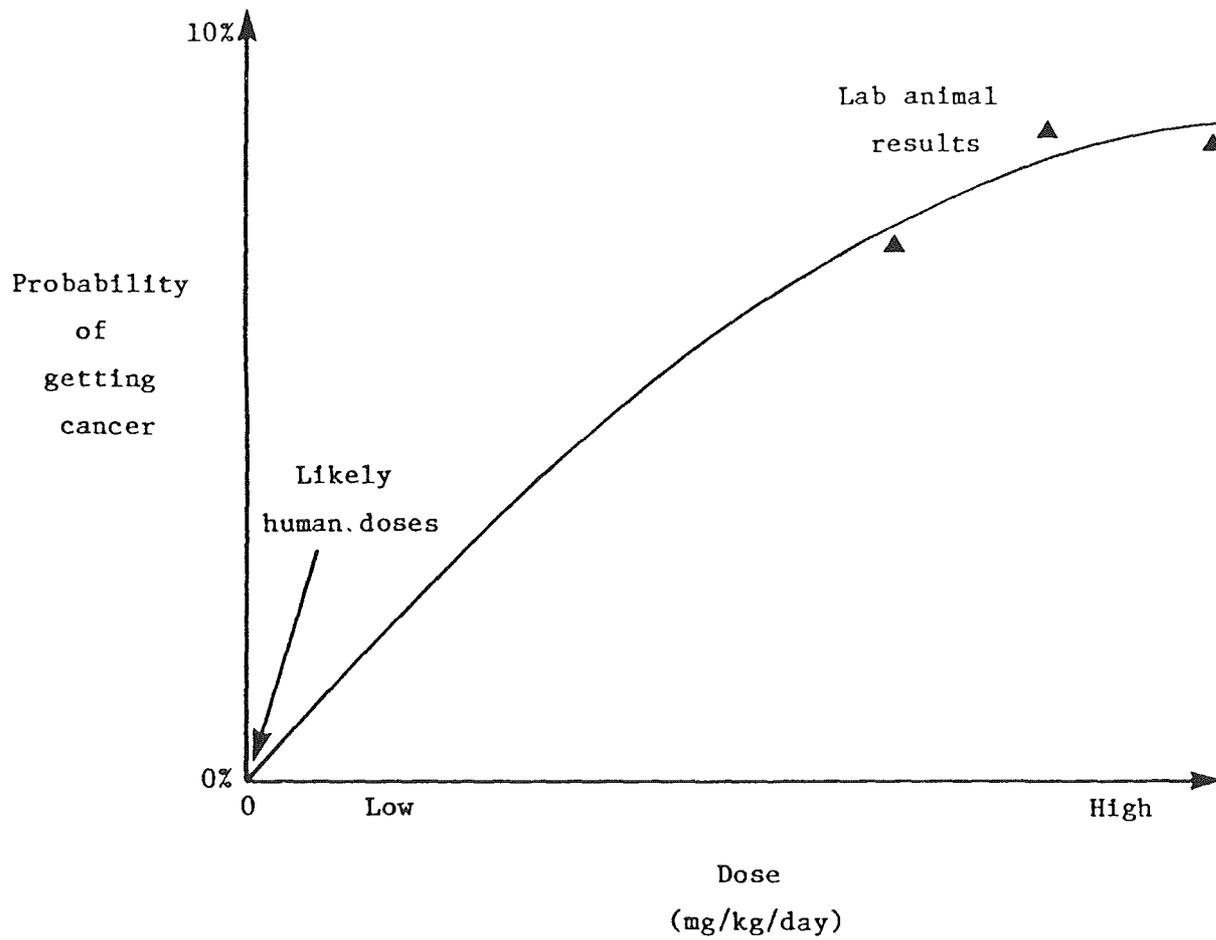


Figure 3-2.--Relationship of increasing tumor incidence with increasing dose.

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in mg/kg/day. The cancer potency value reflects the probability of getting cancer sometime in a person's lifetime for each mg/kg/day.

The cancer potency is derived from tumor data generated in laboratory animal studies. Note in figure 3-2 that the dose levels used in the laboratory cancer studies are high, but those that humans are likely to experience from exposure to the environment are low. The figure also shows that the potency, in general, is a function of the applied dose. Note also that the line relating dose to cancer probability approximates a straight line in the low dose region.

Several assumptions have been made in estimating cancer potencies. First, it is assumed that any dose, no matter how small, has some probability of causing cancer. This is an assumption based on the nonthreshold hypothesis, discussed previously, which postulates that even a single, extremely small dose may be enough to trigger cancer. Second, one of the principal areas of scientific controversy in cancer risk assessment is extrapolating the cancer potency line from the high doses used in animal studies to the far lower doses humans may get. Models other than the linearized multistage model, which assumes a straight line at low doses, as illustrated in figure 3-2, have been used for the extrapolation of cancer data to assess human risk. However, this model is believed to be reasonably conservative (not underestimating risk), and it is the model currently used by EPA. Third, the cancer potency used in the calculation of human risk in this analysis is not the maximum likelihood potency value, but the upper limit value of the 95-percent statistical confidence interval.

Mutagenicity Assays

This section describes the use of the results of mutagenicity assays to draw conclusions about the risk of a chemical causing genetic effects. Mutagenicity assays are used to determine the ability of a chemical to cause structural changes (mutations) in the basic genetic material (DNA) of germ cells or somatic cells. Germ cell genetic defects could possibly lead to the passing of defective genetic instructions to offspring. The offspring may develop diseases or malformations or be predisposed to

diseases because of those inherited defects. Somatic cell genetic defects are believed to play a role in the development of certain diseases, in particular cancer.

Heritable Genetic Disease. Genetic diseases and abnormal phenotypes (e.g. congenital anomalies) are produced in humans as a consequence of genetic errors occurring at the gene or chromosome levels (McKusick, 1983, Denniston, 1983). The vast majority of humans affected by genetic disease inherited their disease or predisposition for the disease as a pre-existing genetic error (Matsunaga 1982, Carter 1977). The same is true for congenital anomalies. A small percentage of affected individuals represent "new" mutations that were not pre-existing in the germ lines of their parents. The specific causes of these "new" mutations are not known, but could arise spontaneously, or could be induced by natural mutagens (i.e. aflatoxins, background radiation), therapeutic regimens (cancer treatment with agents such as cytoxan or Adriamycin) or from environmental or occupational exposures to mutagenic chemicals (Brusick, 1987).

To date, epidemiological studies of human populations have revealed the existence of over two dozen human carcinogens but have failed to confirm epidemiologically an agent that could be legitimately classified as a human germ cell mutagen. Consequently, assessments of human genetic risk must be built upon evidence from nonhuman sources and extrapolated to human populations.

According to EPA's guidelines for germ cell mutagenicity risk assessment (Fed. Reg. 51(185):34006-34012, Sept. 24, 1986), mutagenic endpoints of concern include point mutations (submicroscopic changes in the base sequence of DNA) and structural or numerical chromosome aberrations. Structural aberrations include deficiencies, duplications, insertions, inversions, and translocations. Numerical aberrations are gains or losses of whole chromosomes. Other relevant test endpoints include DNA damage, unscheduled DNA synthesis (UDS), recombination and gene conversion, and sister chromatid exchange (SCE).

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The species used in mutagenicity assays range from primitive organisms, such as the bacteria Salmonella, Escherichia, and Streptomyces; the mold Aspergillus; the yeast Saccharomyces; and the fruit fly Drosophila, to more advanced organisms including mammalian species. Tests may be conducted in vivo (within the body of the living organism) or in vitro (on cells cultured outside the body in a petri dish or test tube).

According to Dr. David Brusick of Hazelton Laboratories, data that might be used in germ cell mutagenicity risk assessments come from mutagenicity studies that can be categorized as follows:

Mammalian germ cell tests:

Mammalian model studies for germ cell alterations consist predominantly of tests on rodent models (typically the mouse) for transmissible effects (specific locus, heritable translocation, and selected dominant genes) and nontransmissible effects (dominant lethal, chromosomal aberrations, gonadal DNA damage and repair).

Short-term tests:

1. Mammalian model studies for somatic cell alterations include many of the tests commonly used in genetic toxicology such as chromosome analysis, micronucleus tests, tests for unscheduled DNA synthesis (UDS), and measurements of DNA adducts.
2. Submammalian model studies for germ cell or somatic cell alterations - typical tests in this group are the Drosophila sex-linked Recessive Lethal assay and the Salmonella reverse mutation assay (Ames test).
3. Mammalian cell in vitro tests - cultured mammalian cells can be screened for all classes of genetic alterations (i.e. chromosome damage, gene mutation, UDS).

Genotoxic Carcinogens. NRC (1987) states that there are two broad mechanisms by which chemicals cause cancer; by some direct chemical interaction with the DNA structures of the cell or by indirect effects on the cellular environment which increase the tumor yield without direct chemical alteration of DNA. The former are termed genotoxic carcinogens and the latter, epigenetic carcinogens.

EPA describes the use of mutagenicity tests as evidence in judging the likelihood that a chemical is a genotoxic carcinogen. According to EPA's guidelines for carcinogen risk assessment (Fed. Reg. 51(185):33992-34003, Sept. 24, 1986):

Tests for point mutations, numerical and structural chromosome aberrations, DNA damage/repair, and in vitro transformation provide supportive evidence of carcinogenicity and may give information on potential carcinogenic mechanisms. A range of tests from each of the above end points helps to characterize an agent's response spectrum.

Short-term in vivo and in vitro tests that can give indication of initiation and promotion activity may also provide supportive evidence for carcinogenicity. Lack of positive results in short-term tests for genetic toxicity does not provide a basis for discounting positive results in long-term animal studies.

The methods for cancer risk analysis using animal data have been reasonably well formulated. However, in the absence of rodent cancer data or with negative rodent cancer data, positive results from short-term tests for genotoxicity have been used as justification for questioning the adequacy of the rodent cancer studies. The rationale for such a use of short-term assays rests with the close mechanistic and correlative association between carcinogens and mutagens (Brusick, 1987; Shelby, 1988).

Estimates of cancer potency which are used to assess cancer risk are based on the results of long term feeding studies indicating tumor induction

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rather than on the results of short-term mutagenicity assays. An approach that has been suggested by some experts is to develop worst-case estimates of cancer risk from cancer studies regardless of whether the studies show significant evidence of increasing tumor incidence with increasing dose. This risk assessment does not adopt this approach because the accepted practice in EPA and the scientific community is to consider only those chemicals with positive tumor evidence as potential human carcinogens.

It is assumed in regard to heritable mutagenicity risk that the cancer tests are the more sensitive toxic endpoint (that is, that no chemical that has been shown to be a germ cell mutagen has not been shown to be carcinogenic at lower doses) and this would constitute the worst-case estimator of risk. This argument is developed in detail in Attachment A of this risk assessment.

Use of Short-term Tests to Evaluate Germ Cell Risk

Background. The published EPA guidelines cited above for using short term test data in assessing mutagenic risk fail to provide recommendations for establishing quantitative risk estimates. Although the EPA guidelines do provide broad qualitatively descriptive risk classifications, the guidelines are not sufficient to formulate a quantitative comparison of two different chemicals which may fall into the same general class. Therefore, Government agencies such as BLM and the USDA Forest Service have no guidelines as to how to conduct quantitative risk assessments to reach worst-case risk estimates which should be at least semiquantitative.

Each type of test described above has its particular advantages and limitations. Knowledge of their advantages and disadvantages is important in extrapolating test responses to humans. There may be a tendency to use a positive response from an in vitro assay, for example, to operationally define a tested chemical as a mutagen even when the chemical is not shown to be mutagenic in any other test. This approach to hazard identification is an inappropriate use of such in vitro tests. Further extension of these limited positive findings into a presumption of genetic risk is not

supported by the available scientific evidence. Attachment A provides a detailed discussion of this topic.

Correlation of Rodent Germ Cell Tests with Short Term Test Results.

Although no chemical has been conclusively established as a human germ cell mutagen, evidence from studies showing chemical-induced mutations in human somatic cells as well as the identification of rodent germ cell mutagens argue that at least some "new" human mutations and their resultant pathologies are the consequence of environmental exposures to mutagenic chemicals. However, without human data, mammalian germ cell models (i.e. mouse assays) will have to serve as the experimental standard upon which human risk estimates are based (Ehling 1988). If the logic of inferring human germ cell risk from the results of rodent germ cell tests is accepted, then one can determine the relative predictive accuracy of any of the nongerm cell test identified in the previous section for identification of germ cell mutagens.

Three review articles have summarized the results of such an exercise (ICPEMC Committee 1, 1983; Russell et al., 1984; Bridges and Mendelsohn, 1986). The scientific evidence indicates, however, that no nongerm cell test is sufficiently accurate to predict the effects that would be obtained from animal germ cell tests. Therefore, positive responses from such tests cannot be considered evidence supporting a presumption of mutagenic risk.

A Weight-of-Evidence Approach to Germ Cell Mutagenicity Risk. The next approach to the use of the abundance of nongerm cell test (i.e. short-term test) results is to establish a weight-of-evidence approach for collectively evaluating the composite response from all tests conducted on a given agent.

Several qualitative (EPA, 1986) and quantitative (Pet-Edwards et. at. 1985, Brusick et. al. 1986) weight-of-evidence schemes for mutagenicity data have been proposed. At the present time none of these weight-of-evidence schemes has been examined in detail for its concordance with the rodent germ cell data base. However, it is probably wise to use some type of weight-of-evidence scheme to evaluate short-term studies.

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The only scientifically sound method to establish human germ cell mutagenic risk is the use of validated rodent models for the assessment of heritable gene or chromosomal mutations. The use of isolated positive responses from short term tests (nongerm cell tests in mammals, submammalian assays or mammalian cell in vitro tests) to establish genetic risks is not supported by available data and is inappropriate use of such data. In the absence of rodent germ cell data, a weight-of-evidence approach should be applied when using short-term test results to identify potential genetic hazard.

The weight-of-evidence discussion of the results of mutagenicity assays for the 16 herbicides in this risk assessment deals with those assays on the basis of 3 broad groups of mutagenicity endpoints: (1) tests for detecting gene mutations, (2) tests for detecting chromosomal aberrations, and (3) tests for detecting primary DNA damage.

Group 1 tests include microbial assays, involving prokaryotic (bacteria) and eukaryotic microorganisms (yeasts, fungus) developed to detect reverse mutations and to a limited extent, forward mutations. Because many mutagens are inactive before bioactivation (by metabolic activity), bacterial tests may include a bioactivation system, such as an S9-fraction, consisting of microsomal enzymes of rats' or other animals' livers to activate the mutagen. A host-mediated assay is conducted to detect mutagenic effects in a microorganism, such as bacteria, by injecting it into the peritoneal cavity of the host (usually mice) to allow for bioactivation of the mutagen in vivo. Other tests useful for predicting gene mutations are the fruitfly sex-linked recessive lethal test, which measures the frequency of lethal mutations, the mouse specific locus test, which detects mutagenicity in germ cells in vivo, and mammalian somatic cell assays in vitro using mouse lymphoma cells, human lymphoblasts, and Chinese hamster ovary cells to detect forward and reverse mutation.

Group 2 tests for detecting chromosomal effects include mammalian cytogenetic assays in Chinese hamster ovary cells in vitro and mice bone marrow micronucleus in vivo. The dominant lethal test in rodents, which determines lethal mutation in germ cells, and the heritable translocation test in mice, which detects the heritability of chromosomal damages, are

both important tests performed with live animals. Fruitflies and other insects also are used to detect heritable chromosomal effects in vivo.

Group 3 tests for the existence of DNA damage caused by mutagens are based on detection of the damage by biologic processes, such as DNA repair and recombination, which occur after DNA damage. Tests to determine such processes use bacteria, yeast, and mammalian cells in vitro, with or without metabolic activation. Unscheduled DNA synthesis, for example, is often used to indicate DNA repair in human cells in vitro. Mitotic recombination and gene conversion indicate DNA damage in yeast, and sister chromatid exchange indicates DNA damage in mouse lymphoma cells, Chinese hamster ovary cells, and human lymphocytes.

The weight-of-evidence approach used in this risk assessment is similar to that of EPA (1986j). It places greater emphasis on assays conducted in germ cells than in somatic cells (for detecting heritable mutations), in vivo rather than in vitro, in eukaryotes rather than prokaryotes, and in mammalian species rather than submammalian species. In vivo mammalian systems are considered to be of greater value because of their similarity to human physiology and metabolism. EPA (1986j) classifies the evidence for potential human germ-cell mutagenicity as sufficient, suggestive, or limited, depending on the results of various tests performed. For instance, positive results in even one in vivo mammalian germ-cell mutation test are considered sufficient evidence for potential human mutagenicity of a specific chemical.

Epidemiology Studies

The effects on humans of exposure to chemicals in the environment can be derived from in vivo or in vitro laboratory studies (as described above), reports of clinical observations of isolated exposed individuals (human poisoning incidents), experimental studies in humans, or from direct observations of exposed human populations. The data on humans generally fall into two categories: clinical data on individuals and epidemiological data revealing patterns of disease or death in groups of humans exposed to single agents or to a variety of substances (NRC, 1986). Thus,

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epidemiology studies are done to investigate the causes of disease in specified human populations by examining relationships between the incidence of particular disease types and factors associated with the disease, such as the use of particular substances in the workplace. One such association is the use of various pesticides by agricultural workers and the incidence of several types of cancer.

Studies conducted by the National Cancer Institute have found that fewer farmers die from cancer than would be expected based on the cancer death rate in the general population in the United States. However, farmers have a higher risk of developing lymphatic and blood-related cancer, including leukemia and cancer of the prostate, skin, and stomach (Blair, 1982; Blair et al., 1985; Blair and Thomas, 1979; Blair and White, 1981, 1985; Cantor, 1982; Cantor and Blair, 1984; Weininger et al., 1987).

Although no single agricultural factor has been consistently associated with increased rates of specific cancer, correlations with insecticide and herbicide use were noted in a number of studies (Blair and White, 1985; Cantor, 1982; Cantor and Blair, 1984; Cantor et al., 1985). In the United States, farmers have a much lower rate of lung cancer than the general population, primarily because of their lower smoking rate (Blair, 1982). However, a cohort study of pesticide-exposed male agricultural workers in the German Democratic Republic (Barthel, 1981) found that they had a significantly higher mortality rate from lung cancer than the general population.

In a cohort study of licensed pesticide applicators in Florida, excess deaths were observed for leukemia and cancers of the brain and lung (Blair et al., 1983). The risk of lung cancer rose with the number of years licensed (Blair et al., 1983). Other studies have found little or no correlation between cancer incidence and pesticide use (Blair and Thomas, 1979; Blair and White, 1981), although factors such as exposure to oncogenic animal viruses have been related to increases in certain types of cancer (Blair, 1982; Blair et al., 1985).

Animal Metabolic Elimination Studies

The herbicides evaluated in this risk assessment are rapidly excreted when administered to animals. Elimination of 90 percent or more, within 2 hours to 5 days, was reported for most of the 10 herbicides. For example, 93-percent of 2,4-D was excreted in rats within 2 hours (Grissom et al., 1985), and 100 percent was excreted within 5 days (Fisher et al., 1985). Dicamba studies revealed up to 100-percent excretion within 48 hours in the rat and 99-percent excretion within 4 days in the mouse (EPA, 1984a). Ninety-nine- to 100-percent of fosamine was excreted in rats within 72 hours (USDA, 1984). For glyphosate, approximately 92 percent of the dose was excreted from rabbits within 5 days (USDA, 1984). Ninety-three-percent of hexazinone was excreted from rats within 24 hours, and 94.2 to 100 percent was excreted within 72 hours (USDA, 1984). Picloram excretion was 90 percent within 48 hours for dogs (USDA, 1984) and 96 percent within 24 hours for an unspecified animal (Nolan et al., 1984, as cited in Lavy and Mattice, 1986). Eighty-three- to 91-percent of triclopyr was excreted from rats within an unspecified time (USDA, 1984). Seventy-four to 82 percent of 2,4-DP was excreted in rats within 4 days (EPA, 1984b). In addition to the rapid elimination of the herbicides, tissue retention studies showed low residue concentrations in animal tissues (USDA, 1984).

Based on the high elimination rates and low tissue retention, the 16 herbicides used for vegetation management present a low risk for bioaccumulation. Bioaccumulation analyses were therefore not conducted for this risk assessment.

TOXICITY OF THE 16 HERBICIDES

Overview of Toxicity

The toxicity reference levels used in this risk assessment to describe both acute and chronic threshold effects of the 16 herbicides are presented in table 3-2. The LD₅₀'s in this table are from rat oral studies. Two types of NOEL's are given in table 3-2. The first NOEL is for general systemic effects, such as growth retardation, decreased red blood cell

Table 3-2
 Laboratory-Determined Toxicity
 Levels Used in the Risk Analysis^a

Herbicide	Acute Oral LD ₅₀ in Rats	Lowest Systemic NOEL	Lowest Reproductive and/or Teratogenic NOEL
Amitrole	Greater than 4,080 mg/kg (EPA, 1984k)	0.5 ppm (0.025 mg/kg/day), subchronic rat feeding study (EPA, 1985a)	100 ppm (5 mg/kg/day), 2-generation rat repro- duction study (EPA, 1985a) Maternal NOEL = 4 mg/kg/day, rabbit teratology study (CDFA, 1986e) Developmental NOEL = 4 mg/kg/day, rabbit teratology study (CDFA, 1986e)
Asulam	Greater than 4,000 mg/kg (EPA, 1985b)	50 mg/kg/day, 107-week rat feeding study (EPA, 1985c)	1,000 ppm (50 mg/kg/day) 2- generation rat reproduction study (EPA, 1985b) Maternal NOEL = 300 mg/kg, rabbit teratology study (EPA, 1985b) No birth defects observed in any studies

^aThe lowest available toxicity levels were used in this analysis.

Table 3-2 (Cont.)

Herbicide	Acute Oral LD ₅₀ in Rats	Lowest Systemic NOEL	Lowest Reproductive and/or Teratogenic NOEL
Atrazine	672 mg/kg (EPA, 1987f)	15 ppm (0.48 mg/kg/day) 2-year dog feeding study (EPA, 1987f)	No birth defects in four studies Three-generation reproduc- tive NOEL of greater than 100 ppm (5 mg/kg/day), rat (EPA, 1984d) Maternal toxic NOEL = 1 mg/kg/day, rabbit teratology study (EPA, 1987f)
Bromacil	3,998 mg/kg (EPA, 1986b)	250 ppm (6.25 mg/kg/ day), 2-year dog feeding study (EPA, 1986b)	No teratogenic effects in two studies Greater than 250 ppm (12.5 mg/kg/day), 3-generation rat repro- duction study (EPA, 1986b)
2,4-D	375 mg/kg (EPA, 1986c)	1.0 mg/kg/day, first year results from 2-year rat feeding study (EPA, 1985e)	No teratogenic effects in 3 studies

Table 3-2 (Cont.)

Herbicide	Acute Oral LD ₅₀ in Rats	Lowest Systemic NOEL	Lowest Reproductive and/or Teratogenic NOEL
2,4-D (con't)			Fetotoxic and maternal toxic NOELS = 5 mg/kg/day, rat reproduction study (EPA, 1986d)
2,4-DP	532 mg/kg (EPA, 1984b)	5 mg/kg/day, 2-year rat feeding study (EPA, 1984b)	Three-generation rat reproduction study, NOEL = 125 ppm (6.25 mg/kg/day) (EPA, 1984b)
		5 mg/kg/day 90-day rat feeding study (EPA, 1984b)	Teratogenic effects at 25 mg/kg/day (LDT). Maternal and fetotoxic NOEL = 25 mg/kg/day, rabbit teratology (EPA, 1984b)
Dalapon	7,577 mg/kg (EPA, 1984f)	8 mg/kg/day, 2-year rat feeding study (EPA, 1987f)	500 ppm (12.5 mg/kg/day), one-generation dog reproduc- tion study (EPA, 1984e)
			Teratogenic NOEL greater than 1,500 mg/kg/day; fetotoxic NOEL = 500 mg/kg/day, rat teratology study (EPA, 1984f)

Table 3-2 (Cont.)

Herbicide	Acute Oral LD ₅₀ in Rats	Lowest Systemic NOEL	Lowest Reproductive and/or Teratogenic NOEL
Dicamba	757 mg/kg (EPA, 1983e)	500 ppm (25 mg/kg/day) 90-day subchronic feeding study (EPA, 1984a; EPA, 1986n) 15.8 mg/kg/day 15-week rat feeding study (EPA, 1987h)	No teratogenic effects reported in 4 studies Fetotoxic and maternal NOEL = 3.0 mg/kg/day, rabbit teratology study (EPA, 1983e)
Diuron	3,750 mg/kg (EPA, 1984g)	25 ppm (0.625 mg/kg/day) 2-year dog feeding study (EPA, 1984g)	No birth defects. NOEL greater than 125 ppm (6.25 mg/kg/day), 3-generation rat reproduc- tion study (Hodge et al., 1967; EPA, 1984g) Teratogenic NOEL greater than 500 mg/kg/day, rat teratology study (EPA, 1986e)
Fosamine	24,400 mg/kg (EPA, 1987c)	1,000 ppm (25 mg/kg/day) 6-month dog feeding study (Schneider and Kaplan, 1983 in USDA, 1984)	No birth defects. Fetotoxic NOEL = 1,000 ppm (50 mg/kg/day), rat teratology study (CDFA, 1986c)

Table 3-2 (Cont.)

Herbicide	Acute Oral LD ₅₀ in Rats	Lowest Systemic NOEL	Lowest Reproductive and/or Teratogenic NOEL
Fosamine (con't)			Reproductive NOEL greater than 5,000/10,000 ppm (250/500 mg/kg/day), rat reproduction study (CDFA, 1986c)
Glyphosate	4,320 mg/kg (EPA, 1986f)	Greater than 31 mg/kg/day, 26-month rat feeding study (EPA, 1986f)	Fetotoxic NOEL = 10 mg/kg/day, 3-generation rat reproduction study (EPA, 1986f) Maternal NOEL = 175 mg/kg/day; fetotoxic and teratogenic NOEL greater than 350 mg/kg/day, rabbit teratology study (EPA, 1986f)
Hexazinone	1,690 mg/kg (EPA, 1986a)	200 ppm (10 mg/kg/day) 2-year rat feeding/ oncogenic study (EPA, 1986a)	Fetotoxic NOEL = 1,000 ppm (50 mg/kg/day); reproductive NOEL greater than 2,500 ppm (125 mg/kg/day), 3-generation rat reproduction study (EPA, 1982c) No teratogenic effects in 2 teratology studies

Table 3-2 (Cont.)

Herbicide	Acute Oral LD ₅₀ in Rats	Lowest Systemic NOEL	Lowest Reproductive and/or Teratogenic NOEL
Picloram	8,200 mg/kg, rat	7 mg/kg/day, 6-month dog feeding study (EPA, 1985i)	No teratogenic effects in 3 studies 3-generation rat study NOEL 50 mg/kg/day (EPA, 1987L) Reproductive NOEL greater than 3,000 ppm (150 mg/kg/day), 3-generation rat repro- duction study (EPA, 1984i)
Simazine	Greater than 5,000 mg/kg (EPA, 1983b)	200 ppm (5 mg/kg/day) 3-week dog feeding study (EPA, 1987k)	Reproductive NOEL greater than 100 ppm (5.0 mg/kg/day) 3-generation rat repro- duction study (EPA, 1983b) Maternal NOEL = 5 mg/kg/day; fetotoxic NOEL = 75 mg/kg/day; teratogenic NOEL greater than 200 mg/kg/day (HDT), rabbit teratology study (EPA, 1987k)
Tebuthiuron	644 mg/kg (EPA, 1987e)	500 ppm (12.5 mg/kg/day), 90-day dog feeding study (EPA, 1987e)	No birth defects. Maternal toxic NOEL = 500 mg/kg/day, rat teratology study (EPA, 1984i)

Table 3-2 (Cont.)

Herbicide	Acute Oral LD ₅₀ in Rats	Lowest Systemic NOEL	Lowest Reproductive and/or Teratogenic NOEL
Tebuthiuron (con't)			<p>Reproductive NOEL less than 400 ppm (20 mg/kg/day) (HDT), 3-generation reproduction study with rats (EPA, 1987k)</p> <p>NOEL of 5.0 mg/kg/day based on a 2-generation rat reproduction study (EPA, 1987d)</p>
Triclopyr	630 mg/kg (EPA, 1986h)	2.5 mg/kg/day (HDT), 6-month dog feeding study (40 CFR Part 180, 50 (84):184-85, May 1, 1985)	<p>No teratogenic effects in 3 studies.</p> <p>Fetotoxic NOEL less than 10 mg/kg, rabbit teratology study (EPA, 1986h)</p> <p>Reproductive NOEL greater than 30 mg/kg (HDT), 3-generation rat reproduction study (EPA, 1986h)</p>

Conversion Factors:

mouse 1 ppm = 0.150 mg/kg/day
 rat (lifetime) 1 ppm = 0.05 mg/kg/day
 rabbit 1 ppm = 0.030 mg/kg/day
 dog 1 ppm = 0.025 mg/kg/day

Source: USDA, 1984

counts, and increased thyroid weight. For amitrole, asulam, fosamine, picloram, tebuthiuron, and triclopyr, subchronic study NOEL's were used because they are the lowest NOEL's found in the literature. The second NOEL is for reproductive and developmental effects, including infertility, miscarriage, general fetal toxicity, and birth defects (teratogenicity). Where information is available, NOEL's are given for both reproductive and teratogenic effects. All the NOEL's used are the lowest found in EPA-validated studies.

The following subsections summarize the most relevant acute, subchronic, and chronic toxicity tests conducted on the 16 herbicides. These studies are included under the "Threshold Effects" subsection of each herbicide. Areas where no validated studies exist or for which EPA has requested additional studies are noted.

The results of cancer and mutagenicity tests are discussed for each herbicide under the "Nonthreshold Effects" subsection. Table 3-3 summarizes the EPA reviewed mutagenicity tests on each of the 16 herbicides for each category of testing recommended by EPA in their guidance documents on mutagenicity (EPA, 1978; EPA, 1984c). Table 3-3 also presents the relevance of the recommended tests to a determination of human mutagenic potential according to Dr. David Brusick of Hazelton Laboratories America, Inc., author of Principles of Genetic Toxicology (Second Edition, Plenum Press, 1987). The weight-of-evidence approach described previously is used to assess mutagenicity risk. In general, mutagenic assays most relevant for determining heritable mutations are in vivo cell studies and germ cell or gonadal studies (for example, the mouse specific locus test). A germ cell study may be considered relevant to evaluating the germ-cell mutagenicity of a chemical even if the test organism is not mammalian (Drosophila Sex-linked Recessive Lethal Assay). In vitro studies using mammalian cells are of lesser reliability because of the high percentage of false positive findings due to nonphysiologic treatment conditions and other phenomena. Tests used to detect primary DNA damage (Group 3 in table 3-3) are not generally reliable for determining the mutagenic potential of a chemical to affect human germ cells. The majority of tests reviewed in the present evaluations were derived from those reviewed by EPA in tox

Table 3-3--Mutagenicity Testing on the 16 Herbicides

Mutagenicity Test Type ^a	Value in Determining Human Mutagenicity ^b	Herbicide							
		Amitrole	Asulam	Atrazine	Bromacil	2,4-D	2-4-DP	Dalapon	Dicamba
Group 1--Tests for detecting gene mutations									
A. Bacteria with and without metabolic activation	+	2(+) 56(-)	1(-)	2(+) 8(-)	1(+) 3(-)	15(-)	1(-)	1(-)	3(-)
B. Eukaryotic microorganisms with and without metabolic activation	+			4(+)	2(-)	1(+) 1(-)	1(+)	1(-)	
C. Insects (e.g., sex-linked recessive lethal test)	++	3(-)		1(+) 1(-)	1(+) 1(-)	2(+) 1(-)			
D. Mammalian somatic cells in culture with and without metabolic activation	++		1(-)	1(+)					
E. Mouse specific locus test <u>in vivo</u>	++								
Group 2--Tests for detecting chromosomal aberrations									
A. Cytogenetic tests in mammals <u>in vivo</u>	++	2(-)		2(+)	1(-)	2(+) 1(-)			
B. Insect tests for heritable chromosomal effects <u>in vivo</u>	++								
C. Dominant-lethal effects in rodents, heritable translocation tests in rodents, and <u>in vitro</u> cytogenetic assays in mammals	++	4(+)	1(-)	1(+) 3(-)	1(-)	2(+) 3(-)		1(-)	1(-)
Group 3--Tests for detecting primary DNA damage									
A. DNA repair in bacteria (including differential killing of DNA repair defective strains) with and without metabolic activation	NA				2(-)	2(+) 1(-)	1(+)		2(+)
B. Unscheduled DNA repair synthesis in mammalian somatic cells in culture, with and without metabolic activation	NA			1(+)	1(-)	1(+) 3(-)			1(-)
C. Mitotic recombination and gene conversion in yeast, with and without metabolic activation	NA			3(+) 6(-)	1(-)	2(+) 3(-)	1(+)		1(-)
D. Sister-chromatid exchange in mammalian cells in culture, with and without metabolic activation	NA	2(-)		1(-)		1(+)			

^aSource: FIFRA, Environmental Protection Agency: Proposed Guidelines for registering pesticides in the U.S. Hazard Evaluation: humans and domestic animals. Fed. Reg. 43:37335-37403, August 22, 1978.

^bSource: USDA, 1985a.

NA = Not Applicable

+ = Applicable

++ = Greater applicability

Sources for mutagenicity data are given in the text discussions of nonthreshold effects.

Table 3-3 (continued)--Mutagenicity Testing on the 16 Herbicides

Mutagenicity Test Type ^a	Value in Determining Human Mutagenicity ^b	Herbicide							
		Diuron	Fosamine	Glyphosate	Hexazinone	Picloram	Simazine	Tebuthiuron	Triclopyr
Group 1--Tests for detecting gene mutations									
A. Bacteria with and without metabolic activation	+		2(-)	3(-)	1(-)	1(+) 5(-)	9(-)	1(-)	3(-)
B. Eukaryotic microorganisms with and without metabolic activation	+			1(-)		3(-)			1(-)
C. Insects (e.g., sex-linked recessive lethal test)	++						2(+)		
D. Mammalian somatic cells in culture with and without metabolic activation	++	1(-) ^d	1(-)	1(-)				1(+)	
E. Mouse specific locus test <u>in vivo</u>	++								
Group 2--Tests for detecting chromosomal aberrations									
A. Cytogenetic tests in mammals <u>in vivo</u>	++		1(-)	1(-)	1(-)	1(-)			1(-)
B. Insect tests for heritable chromosomal effects <u>in vivo</u>	++								
C. Dominant-lethal effects in rodents, heritable translocation tests in rodents, and <u>in vitro</u> cytogenetic assays in mammals	++	1(+)	1(+)	1(-)	1(+)		(-)	1(-)	1(+) 1(-)
Group 3--Tests for detecting primary DNA damage									
A. DNA repair in bacteria (including differential killing of DNA repair defective strains) with and without metabolic activation	NA						1(-)		1(-)
B. Unscheduled DNA repair synthesis in mammalian somatic cells in culture, with and without metabolic activation	NA	1(-)	1(-)	1(-)	1(-)		1(-)		
C. Mitotic recombination and gene conversion in yeast, with and without metabolic activation	NA		1(-)					2(-)	
D. Sister-chromatid exchange in mammalian cells in culture, with and without metabolic activation	NA								

^aSource: FIFRA, Environmental Protection Agency: Proposed Guidelines for registering pesticides in the U.S. Hazard Evaluation: humans and domestic animals. Fed. Reg. 43:37335-37403, August 22, 1978.

^bSource: USDA, 1985a

NA = Not Applicable

+ = Applicable

++ = Greater applicability

Sources for mutagenicity data are given in the text discussions of nonthreshold effects.

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one-liners or EPA science chapters. If tox one-liners or science chapters were not available, studies of mutagenicity were obtained from USDA pesticide background statements, which reported studies from the open literature. Results reported within the same study for different test species or different test types were counted as individual tests. Therefore, a single study reported in EPA tox one-liners may be represented more than once in table 3-3. For instance, one study that reported positive results in the Ames reverse mutation test for bacteria Salmonella spp. and E. coli, both activated and inactivated, would represent four positive results in category 1A. Males and females, as well as different strains of the same species, were counted as one test only, unless different results were reported for each.

Overall results of mutagenicity testing not subclassified into nongerm cell or germ cell assays (numbers of positive and negative assays) for each herbicide are listed in table 3-4. The use of short-term mutagenicity testing to assess germ-cell mutagenic risk is presented in Attachment A. For some of the herbicides, no validated mutagenicity tests exist or the mutagenicity tests conducted are insufficient to conclude whether the chemical is mutagenic. For these herbicides, the worst case analysis presented in Section 5 assumed that these herbicides are mutagenic to somatic cells. In such cases, the results of carcinogenicity tests (see table 3-4) were used to estimate mutagenic risk, based on a high correlation between mutagenic and carcinogenic activity reported in several studies (Blackburn et al., 1984; Pogodina et al., 1984; Parodi et al., 1981, 1982, 1983a,b; Sisak et al, 1988).

The results of studies examining the ability of these herbicides to cause cancer are also discussed below and are summarized in table 3-4. Data gaps and areas of uncertainty of all chemicals are presented following the 16 herbicide discussions. In addition, data gaps are presented in Table 3-5. For those herbicides for which a cancer risk analysis is done, the value used for cancer potency and the study from which it was derived are presented.

Table 3-4

Summary of Mutagenicity and Carcinogenicity of Pesticides

Herbicide	Mutagenicity	Oncogenic Results from Chronic Studies
Amitrole	Nonmutagenic in 63/69 assays (USDA, 1984). Does not present potential for heritable genetic effects (EPA, 1985a)	A probable human carcinogen (EPA, 1985a). EPA Classification: B2.
Asulam	Nonmutagenic in 3/3 assays (EPA, 1985b)	Oncogenic in 2 studies; nononcogenic at HDT in 1 study (EPA, 1985d, 1985b). EPA Classification: C.
Atrazine	Mutagenic in 15/34 assays (USDA, 1984). Mutagenic only in presence of plant cell extracts.	Oncogenic in 1/3 studies (EPA, 1984d; CDFA, 1986a). A possible human carcinogen. EPA Classification: C.
Bromacil	Not considered mutagenic by EPA. Existing studies adequate (EPA, 1982a). Nonmutagenic in 12/14 assays (EPA, 1987a)	Oncogenic in 1/2 studies (EPA, 1986b; EPA, 1985d). Not classified.
2,4-D	Nonmutagenic in 28/41 assays (USDA, 1984)	Oncogenic in 1/3 studies (EPA, 1986d; EPA 1986e). EPA classification: D
2,4-DP	Mutagenic in 3/5 assays (EPA, 1984b)	Oncogenic in 1/3 studies (EPA, 1984b). Not classified.
Dalapon	Nonmutagenic in 3/3 assays (CDFA, 1986b)	Nononcogenic in 3 studies (USDA, 1984; CDFA, 1986b). EPA classification: D.
Dicamba	Nonmutagenic in 6/8 assays (USDA, 1984)	Nononcogenic in two 2-year feeding studies judged inadequate by EPA (1984a); nononcogenic in 1 study accepted by EPA (1986e). Not classified.

Table 3-4 (Cont.)

Herbicide	Mutagenicity	Oncogenic Results from Chronic Studies
Diuron	Nonmutagenic in 2/3 studies judged acceptable by EPA (1987b). Nonmutagenic in 10/11 assays judged unacceptable by EPA (1987b and 1983f).	Nononcogenic in 3 studies (EPA, 1983a); Studies not adequate according to EPA (EPA, 1983a). EPA classification: D.
Fosamine	Nonmutagenic in 5/6 assays (CDFA, 1986c; EPA, 1987c)	Nononcogenic after 1-year interim review of a mouse oncogenic study (EPA, 1987c) and in a 6-month dog feeding study (USDA, 1984). EPA classification: D.
Glyphosate	Nonmutagenic in 8/8 assays (EPA, 1986f)	Evidence of oncogenicity in mice not sufficient. No evidence of cancer in several other chronic studies judged to be unacceptable by EPA (1986g). EPA classification: D.
Hexazinone	Nonmutagenic in 3/4 test systems (EPA, 1986a)	Nononcogenic in 2 studies (EPA, 1986a). Not classified.
Picloram	Nonmutagenic in 9/10 assays (USDA, 1984)	Oncogenic in 1/3 studies (EPA, 1985g; DOW, 1987). EPA classification: D.
Simazine	Nonmutagenic in 15/17 studies, (USDA, 1984; CDFA, 1986d)	Nononcogenic in 1 study judged inadequate to determine carcinogenic potential (EPA, 1983b). EPA classification: D.
Tebuthiuron	Nonmutagenic in 2/3 studies (EPA, 1987d)	Nononcogenic in 2 studies (EPA, 1987e). Additional studies required (EPA, 1987d). Not classified.
Triclopyr	Nonmutagenic in 7/8 bacterial and cytogenetic assays (EPA, 1986h)	Oncogenic in 1/3 studies (EPA, 1986h; Dow, 1987; 40 CFR Part 180 50(84):18485-86, May 1, 1985). Not classified.

Table 3-5--EPA herbicide data gaps

According to FIFRA Guidelines, EPA has Requested the Following Additional Toxicology Information on BLM/Region 6 Forest Service Herbicides¹

Data Gaps	Amitrole	Asulam	Atrazine	Bromacil	2,4-D	2,4-DP	Dalapon	Dicamba
<u>Acute Testing</u>								
Acute oral - rat						X		
Acute dermal						X		
Acute inhalation - rat						X		
Eye irritation - rabbit						X		
Dermal irritatn - rabbit	X					X		
Dermal sensitiz - gn.pig	X							
<u>Subchronic testing</u>								
90-day feeding - rodent								
90-day feeding - nonrodt						X		
21-day dermal						X		X
90-day dermal	P							
90-day inhalation	P							
90-day neurotoxicity								
<u>Chronic testing</u>								
Chronic-dog		X			X		X	
Chronic-rodent							X	
Oncogenicity-rat					R	W	X	
Oncogenicity-mouse						W	X	X
Teratogenicity-rat	P	X				X	X	
Teratogenicity-rabbit	P				X	X	X	
Reproduction-rat							X	
Mutagenicity		X			X	X		

X = Data gap, R = under review by EPA, P = partially fulfilled, W = requirement waived.

Table 3-5 (continued)--EPA herbicide data gaps

According to FIFRA Guidelines, EPA has Requested the Following Additional Toxicology Information on BLM/Region 6 Forest Service Herbicides¹

Data Gaps	Diuron	Fosamine	Glyphosate	Hexazinone	Picloram	Simazine	Tebuthiuron	Triclopyr
<u>Acute Testing</u>								
Acute oral - rat								X
Acute dermal								X
Acute inhalation - rat	X		R		X	R		
Eye irritation - rabbit								X
Dermal irritatn - rabbit								X
Dermal sensitiz - gn.pig	X							X
<u>Subchronic testing</u>								
90-day feeding - rodent							R	
90-day feeding - nonrodt							R	
21-day dermal								
90-day dermal								
90-day inhalation								
90-day neurotoxicity								
<u>Chronic testing</u>								
Chronic-dog		X		X	X	X		
Chronic-rodent		X						X
Oncogenicity-rat	X	X	X		X	X		
Oncogenicity-mouse	X	R	X			X		
Teratogenicity-rat	X	X			X	R		X
Teratogenicity-rabbit	X	X						X
Reproduction-rat	X	X			X	X		
Mutagenicity	X	X			X			

¹No data gaps exist for hexazinone (EPA, 1982e). X = Data gap, R = under review by EPA, P = partially fulfilled.

Amitrole

Threshold Effects

Amitrole is considered to be slightly to very slightly toxic for acute effects (See Table 3-1) based on LD₅₀ values in the rat which range from 1100 to 25,000 mg/kg. Data also suggest that amitrole has a low acute dermal and inhalation toxicity to rodents and is slightly irritating to the eyes of rabbits (Toxicity Category III) (EPA, 1985a). Symptoms of acute toxicity include intestinal paralysis, pulmonary edema, and hemorrhages in various organs (Hayes, 1982).

Subchronic studies indicate that technical amitrole in the diet has an antithyroid effect in laboratory rats. Enlarged thyroid glands and reduced uptake of iodine were observed at the lowest effect level of 2 ppm (0.1 mg/kg/day) in a subchronic rat feeding study. The NOEL for this study was 0.5 ppm (0.025 mg/kg/day) (EPA, 1983c; 1985a).

In another subchronic feeding study, male rats were fed 0, 30, 100, and 300 ppm for 4 weeks followed by 4 weeks on the control diet. The study was designed to demonstrate the reversibility of the antithyroid effects of amitrole. At 100 ppm (5 mg/kg/day), rats showed decreased body weight and decreased thyroid function at test T₃ and T₄ levels. However, T₃ and T₄ values returned to control levels 3 weeks after removing amitrole from the diet. The NOEL for this study was 30 ppm (1.5 mg/kg/day) (EPA, 1985a; EPA, 1986i).

In a two-generation reproduction study, groups of male and female rats (F₀) were fed 500 ppm (25 mg/kg/day) and 1,000 ppm (50 mg/kg/day) amitrole for 107 to 110 days. Two other groups were fed 25 (1.25 mg/kg/day) and 100 ppm (5 mg/kg/day) for 240 to 247 days, and their progeny (F₁) were fed 25 (1.25 mg/kg/day) and 100 ppm (5 mg/kg/day) amitrole for 141 days. Pups born to parents fed 500 and 1,000 ppm amitrole were small and had atropic thymuses and spleens indicative of runting; no signs of runting were observed in the 25 and 100 ppm pups. Hyperplasia of the thyroid was observed in all animals fed 25 ppm and higher. EPA (1985a)

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concluded that, although amitrole is a potent antithyroid agent, it does not pose a significant reproductive hazard.

EPA (1984) lists two teratology studies in mice that showed no teratogenic effects at the highest doses tested.

A rat teratology study reported in CDFA (1986e) reported no indication of adverse effects in offspring when amitrole was given to pregnant rats by gavage on days 6 through 15 of gestation at dose levels of 0, 100, 500, and 1,000 mg/kg/day. A developmental NOEL of 500 mg/kg/day was set based on decreased fetal weight gain at the high dose.

A rabbit teratology study reviewed by CDFA (1986e) administered amitrole to does by gavage during days 6 through 18 of gestation. Dose levels were 0, 4, 40, and 400 mg/kg/day. Abortions and decreased weight gain of does were observed at 40 mg/kg/day. Increased incidence of structural changes at 40 mg/kg/day resulted in a developmental NOEL of 4 mg/kg/day.

In a lifetime feeding/oncogenicity study with hamsters, a systemic NOEL of 10 ppm (1.0 mg/kg/day) was established. Reduced survival time was observed at 100 ppm (10 mg/kg/day) (EPA, 1986i).

Nonthreshold Effects

EPA (1985a) has classified amitrole as a probable human carcinogen. Therefore, a cancer risk analysis for amitrole was done in this risk assessment. Chronic exposure to amitrole through dietary and inhalation routes has resulted in the formation of benign and malignant thyroid tumors in laboratory animals (EPA, 1985a).

Three epidemiology studies have been published linking amitrole to human cancer deaths. The international cancer research group, IARC, stated in 1982 that the evidence is insufficient to establish an association between amitrole and human cancers. The epidemiology studies on humans do not qualify as "at least limited evidence of carcinogenicity to humans" because no conclusive results were found (EPA, 1985a).

The following animal studies were reviewed by EPA (1985a) in their Amitrole Risk Assessment.

Rats given 0, 10, 50, and 500 ppm amitrole in the diet for 2 years showed a significant increase in thyroid adenomas (not classified as to type, follicular or interstitial) in the 50, 100, and 500 ppm treatment groups when compared to concurrent controls. There was no reported increased incidence of liver tumors in any treatment group. No thyroid function tests were reported. Survival was similar for all groups (Hazelton, 1959, as cited in EPA, 1985a).

In another study, rats given 0, 1, 10, and 100 ppm amitrole in the diet for 2 years also showed a significant increase in thyroid adenomas and carcinomas (not classified as to type, follicular or interstitial) in the 100 ppm male and female treatment groups when compared to concurrent controls. In addition, a significant increase in pituitary adenomas and carcinomas was observed in the 100 ppm females. The percentage accumulation of radioiodine in the thyroid and thyroid weights was increased in the 100 ppm males and females. No increase in liver tumors was observed and survivability was similar for all groups (Bayer AG, 1979, as cited in EPA, 1985a).

In another chronic study, rats were pulse fed amitrole in the diet for 2 years in the following manner:

<u>Test Group</u>	<u>Dosing Regimen</u>
A	Control
B	5 ppm (week 1 thru 39)/ 100 ppm (week 40 thru 118)
C	1 ppm (week 1 thru 39)/ 20 ppm intermittent ^a
D	3 ppm (week 1 thru 39)/ 60 ppm intermittent ^a
E	10 ppm (week 1 thru 39)/ 100 ppm intermittent ^a

^a Amitrole diet for 1 month followed by control diet for 1 month, alternating until sacrifice.

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A significant increase in thyroid tumors, mainly classified as follicular type tumors, was observed in male groups "B", "D", "E", and in female groups "B" and "E". In addition, a significant increase in pituitary tumors was observed in the "B" and "E" female groups. Thyroid function tests were performed (T_3 and T_4); however, the values were extremely variable and did not correlate with the observed histopathology. No increase in liver tumors was observed and survivability was similar for all groups (Food and Drug Research, 1981, as cited in EPA, 1985a).

In a chronic inhalation study, rats were exposed to an unverified amount of amitrole (Food and Drug Research, 1983, as cited in EPA, 1985a). There was an increased incidence in thyroid tumors at the unverified dose. Thyroid function tests (T_3 and T_4) were highly variable and did not permit analysis (EPA, 1985a).

Lifetime feeding studies were conducted in hamsters, mice, and rats using 0, 1, 10, and 100 ppm of amitrole (Steinhoff et al., 1983, as cited in EPA, 1985a). The results of these studies further confirm the relationship of the disturbance of thyroid function and tumor formation, as well as interspecies variation. The rat showed the most significant changes, as both thyroid and pituitary tumors were observed at 100 ppm. The mouse study showed changes in thyroid organ weights and percent iodine accumulation at 100 ppm; however, no increased incidence in tumor production was observed. The thyroid changes seen in the mouse are^a considered by EPA to be a less profound indicator of thyroid disruption. In the hamster study, neither thyroid function changes nor tumors were observed, thereby indicating that the hamster was the least sensitive species (EPA, 1985a).

Two additional studies reviewed by EPA (1985a) were reported to have serious experimental design and/or reporting flaws, but they did demonstrate amitrole's oncogenic potential in two animal species. Thyroid tumors were reported in mice given 2,192 ppm amitrole for 18 months after the mice were weaned (Innes, 1969, as cited in EPA, 1985a). Benign and malignant thyroid and liver tumors were also found in rats given 20 and 25

mg/kg/day amitrole in drinking water or 250 and 500 mg/kg/day amitrole in the diet for 10 to 32 months (Napalkov, 1969, as cited in EPA, 1985a).

In a study conducted by Tsuda (1975, as cited in EPA, 1984e) female rats were given 2,500 ppm amitrole in the drinking water for 30 weeks. Weakened peroxidase activity in follicular cells was followed by the development of goiter. Goiter tissue often proliferated to show malignant adenoma breaking through the capsule, infiltrating into surrounding tissues, and invading blood vessels. An atypical nodular type adenoma was also noted.

As indicated from this rather extensive body of data, amitrole has consistently demonstrated an oncogenic potential in feeding studies using rats, with the thyroid and pituitary as the primary target organs at doses as low as 0.05 ppm amitrole. The oncogenic potential in mice is not as clearly demonstrated, as liver and thyroid tumors occurred only after feeding amitrole at doses in excess of 2,000 ppm. In a comparative species study, doses of 100 ppm amitrole in the diet for 2 years produced an increased incidence of thyroid tumors in rats only, not in mice or hamsters (EPA 1985a).

An epidemiology study found a slightly dose-dependent, significantly increased tumor incidence and mortality among Swedish railway workers exposed to amitrole while applying the pesticide (Axelson and Sundell, 1974). No specific type of tumor predominated in the study. However, the study was deemed inconclusive by EPA (1985a) because the workers were also exposed to phenoxy acids during the same time period. A followup study concluded that the causal relationship of increased cancer incidence with pesticide application could not be confined to specific pesticides (Axelson et al., 1980).

Amitrole's cancer potency was estimated by calculating three separate cancer potencies using tumor data from three studies. The highest calculated potency was then used in the calculation of cancer risk. The three studies were:

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1. The 2-year rat feeding study conducted by Hazleton Laboratories, Inc.
2. The study by Tsuda et al. (1976) in which rats were given 2,500 ppm in their drinking water.
3. The study by Food and Drug Research (1981, as cited in EPA, 1985a) in which rats alternately were fed food with and without amitrole.

The cancer potency for amitrole estimated from the Hazleton Laboratories, Inc. rat study data was 0.15 per (mg/kg/day). The data of Tsuda et al. (1976) gave a potency of 0.011 per (mg/kg/day) for all invasive thyroid lesions and 0.00098 per (mg/kg/day) for papillary adenoma. The Food and Drug Research 1981 study (as cited in EPA, 1985a) indicated a cancer potency for thyroid tumors of 0.61 (considering only the intermittently dosed groups). In this risk assessment, the highest of these potencies is used to estimate human cancer risk. The 95-percent upper confidence limit for the potency of 0.61 per (mg/kg/day) based on the Food and Drug Research data is 1.4 per (mg/kg/day).

Amitrole did not produce mutagenic effects in 56 bacterial assays, 3 assays with insects, 2 mammalian in vivo assays, and 2 mammalian sister chromatid exchange assays (USDA, 1984) and is not viewed as genotoxic. Positive results were observed in two tests in an unvalidated forward mutation system with bacteria (USDA, 1984). The chemical also induced in vitro cell transformations in four mammalian cell assays (EPA, 1985a). Cell transformation assays are capable of detecting some classes of nongenotoxic carcinogens. EPA (1985a) concluded and this risk assessment concurs that the extensive genotoxic data base indicates that amitrole is not mutagenic (that is, it does not cause heritable genetic damage) but that amitrole does have oncogenic potential (possibly epigenetic) as demonstrated in the positive in vivo cell transformation studies.

The mutagenic potential of amitrole is summarized in EPA (1985a) as follows:

Amitrole has been evaluated in a variety of mutagenicity test systems. Although positive results were reported by Braun et al., 1977, (using added nitrite) in Salmonella and by Venitt and Crofton-Sleigh (1981) in Salmonella and E. coli, 49 other Salmonella gene mutation tests and 9 other E. coli tests were negative. The validity of the two positive studies is questionable. The weakly positive results by Carere et al. (1976, 1978, and 1981) were in an unvalidated system using unusual bacteria. The mechanisms for these positive results reported for the DNA repair assays cannot be determined without positive gene mutation or chromosome aberration assays. The negative results in the sister chromatid exchange assay in mammalian cells in culture (which is a very sensitive assay) and the chromosome aberration assays in cultured human lymphocytes or in vivo mouse bone marrow cells cast doubt on the significance of the DNA repair assays. Amitrole does not present a potential for heritable genetic effects.

Amitrole is able to induce transformation of cultured cells. It was positive in four in vitro transformation studies using rat and hamster cells (Pienta, 1977; Inoue, 1981; Dunkel, 1981; Styles, 1981) following treatment of 0.1 to 100 ug/ml. This test is used to establish the malignant activities of test compounds on mammalian cells in vitro. Cells treated in vitro with chemical carcinogens give rise to foci of cellular growth superimposed on the cell monolayer. If these foci are picked from the cultures, grown to larger numbers, and injected into animals, a malignant tumor will be obtained, in most cases. Therefore, the appearance of piled-up colonies in treated cell cultures is correlated with malignant transformation. In addition, weak cellular transformation capacity was observed in EUE cells (no data presented, only summary) (Benigni, 1980).

These transformation assays are not able to determine a mechanism for tumor formation and do not necessarily show that a transformation inducer is genotoxic. These results support oncogenicity potential but not necessarily mutagenicity potential.

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Asulam

Threshold Effects

Based on the acute oral LD₅₀ value in rats of greater than 4,000 mg/kg asulam can be classified as very slightly toxic. Technical asulam was not a primary skin or eye irritant in laboratory animals and was not a dermal sensitizer in humans (EPA, 1985b).

In a 5-day feeding study, dogs exhibited occasional vomiting, anorexia, slight decrease in activity, slight gastritis, and slight inflammation of the duodenum at 2,000 mg/kg/day, the only level tested. In a 90-day feeding study, no treatment-related effects were observed in dogs at 500 mg/kg/day. Dogs fed asulam for 6 months exhibited increased thyroid and body weights at 300 mg/kg/day. The NOEL for this study was 60 mg/kg/day (EPA, 1985b).

In a 90-day rat feeding study, a NOEL of 2,000 ppm (100 mg/kg/day) was established based on fatty deposits observed in the liver at 10,000 ppm (500 mg/kg/day). In a 30-day inhalation study, rats exhibited a significantly increased organ/body weight ratio in the adrenal and pituitary at 15.3 mg/L, the highest dose tested (EPA, 1985j).

Increased liver weights were observed in rats at 2,200 ppm (110 mg/kg/day) after the first year of a 2-year feeding study. In a 2-year dog feeding study, no effects were observed at the highest dose level, 6,000 ppm (150 mg/kg/day), after the first year. Mice exhibited decreased thyroid weights, increased kidney and heart weights, and hyperkeratosis of skin and subcutis at 1,500 ppm (225 mg/kg/day), the lowest dose tested, in an 18-month feeding/oncogenicity study (EPA, 1985b). EPA (1985b) has determined the lowest systemic NOEL to be 1,000 ppm (50 mg/kg/day) based on a 107-week rat feeding study.

Teratology and reproduction studies indicate that asulam does not cause teratogenic or fetotoxic effects in test animals. A two-generation rat reproduction study resulted in possible systemic effects indicated by

reduced body weight at 25,000 ppm (1,250 mg/kg/day); reproductive effects characterized by a decrease in the number of live births were reported at 5,000 ppm (250 mg/kg/day) and 25,000 ppm (1,250 mg/kg/day) (EPA, 1985b). The reproductive NOEL for this study was established at 1,000 ppm (50 mg/kg/day). In a rabbit teratology study, no teratogenic effects were noted; however, a possible maternal toxic effect of decreased weight gain was noted at the 750 mg/kg/dose. In another rabbit teratology study, no effects were observed at the highest dose tested, 40 mg/kg/day. A third teratology study also found no teratogenic or maternal toxic effects in rats at the highest dose tested (1,500 mg/kg/day) (EPA, 1985b).

Nonthreshold Effects

A cancer risk analysis was done for asulam in this risk assessment because of positive cancer effects seen in two studies. An 18-month oncogenicity study in mice resulted in undifferentiated sarcoma of the skin/subcutis at 5,000 ppm (750 mg/kg/day) (EPA, 1985b). Findings in this study are considered inconclusive for oncogenic potential (EPA 1988).

A statistically significant increase in thyroid cell carcinomas was also observed in rats at 1,000 ppm (50 mg/kg/day) in a 107-week feeding study (EPA, 1985c). Asulam's cancer potency of 0.02 per (mg/kg/day) is based on the rate of tumor formation in thyroid cells in female rats in the 107-week feeding study.

A five strain Ames assay bacterial assay, a cell transformation assay, and a dominant lethal mouse assay on asulam were all negative for mutagenic activity (EPA, 1985b). Positive results in the oncogenicity studies indicate that asulam may have mutagenic potential if it is assumed that it is a genotoxic carcinogen. However, it is not likely to produce heritable mutations at the expected exposures described in this risk assessment.

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Atrazine

Threshold Effects

Atrazine has a low toxicity from acute exposure based on the lowest rat oral LD₅₀ of 672 mg/kg (Gaines and Linder, 1986, as cited in EPA, 1987f). EPA (1983d) classified atrazine as (slightly toxic for acute oral exposure (see Table 3-1). Acute toxicity symptoms in rats include reduced respiratory rate, motor incoordination, muscle spasms, and hypothermia (Hayes, 1982). Dermal exposure to rats did not produce toxicity, and a dermal LD₅₀ of greater than 2,000 mg/kg was established. The dermal LD₅₀ in rabbits was 7,550 mg/kg. Rabbits exposed to technical atrazine failed to show dermal irritation after 24 hours. The dermal toxicity studies are sufficient to classify the chemical as slightly toxic for dermal effects. There has been one reported case by a farmer of skin allergy contracted after application of atrazine (Hayes, 1982). A case of severe contact dermatitis was reported by Schlichter and Beat (1972, as cited in EPA, 1987f) in a 40-year-old farm worker exposed to atrazine formulation. The clinical signs were red, swollen, and blistered hands with hemorrhagic bullae between the fingers. An aqueous suspension of technical atrazine has been tested for eye irritation properties in white rabbits. Corneal opacity of minimal severity was present at 1 hour through 72 hours after exposure. Complete reversibility occurred before 7 days. The study is adequate to place the chemical as moderately toxic for eye irritation (EPA, 1983d).

Acute exposure (1 hour) of rats to atrazine by inhalation revealed that the LC₅₀ was greater than a nominal value of 167 mg/L. The data indicate that atrazine does not possess a high toxicity via inhalation. When considered with the oral LD₅₀, EPA concludes that the data are sufficient to classify the chemical as very slightly toxic for inhalation (EPA, 1983d).

In a subacute study with rats, test animals received 100, 200, 400, or 600 mg/kg atrazine for 14 days. Renal effects observed included increased elimination of sodium, potassium, and chloride, decreased levels of creatinine clearance, increased urine protein levels, and increased lactate

dehydrogenase activity. These results suggest that the nephrotoxic properties of atrazine may affect not only its excretion but also increase its toxicity in the kidney (Santa Maria et al., 1986).

In a 2-year feeding study in which beagle dogs were fed up to 1,500 ppm (375 mg/kg/day) of the 80W formulation, body weights were lowered at the HDT, but not at the mid-dose level. Reduced food intake, increased adrenal weights, occasional tremors and stiffness in the limbs, and reduced hematocrit values were also noted at the high dose. Liver and heart weights were increased, and food intake was reduced in the mid-dose females. The systemic NOEL for this study was reported as 15 ppm (0.48 mg/kg/day as converted by EPA) (EPA, 1987f, 1986j).

A 2-year feeding study with rats resulted in a systemic NOEL of 70 ppm (3.5 mg/kg/day) based on reduced body weights, reduced clinical blood parameters, and decreased glucose levels at the next higher dose (CDFA, 1986). A chronic rat feeding study that used atrazine 50W was reported. After 65 weeks the lowest dose (1 ppm) was elevated to 1,000 ppm for the remainder of the study. Body weights and food intake of females were reduced at 1,000 ppm. Other changes included indications of severely infected animals with numerous animals dying, however, this effect was unrelated to compound dosage. The study does not delineate the oncogenic potential of the compound because of the small number of animals surviving to the end of the study. The feed was not analyzed. EPA considers the study to be supplementary as a chronic or oncogenic study in rodents (EPA, 1983d).

A 22-month chronic feeding/oncogenicity study in mice established a systemic NOEL of 300 ppm (15 mg/kg/day) with decreased male and female body weights and increased cardiac thrombi (small nucleated cells).

The National Cancer Institute testing program included atrazine exposure to three strains of mice to determine teratogenic effects. Subcutaneous injections of 46.4 mg/kg of atrazine in DMSO on days 6 to 14 of pregnancy

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resulted in increased fetal mortality in two strains. Due to the confounding effects of DMSO and insufficient litter data, the study is considered supplementary, does not fulfill registration needs, and is considered to be a data gap (EPA, 1983d).

In more recently reported studies conducted by Ciba-Geigy (1984a,b, as cited in EPA, 1987f), developmental effects were noted at lower doses. In a rat study, atrazine was given at dose levels of 0, 10, 70, and 700 mg/kg/day during days 6 to 15 of gestation. Excessive mortality was observed at 700 mg/kg/day but not at lower doses. Reduced weight gain and food consumption were noted at 70 and 700 mg/kg/day. Fetal weights were severely reduced at 700 mg/kg/day, delays in skeletal development occurred at 70 mg/kg/day, and dose-related runting was noted at 10 mg/kg/day and above. The maternal NOEL was 10 mg/kg/day, and the fetotoxic NOEL was less than 10 mg/kg/day (LDT) (Ciba-Geigy, 1984a, as cited in EPA, 1987f).

In a second teratology study with rats, treatment at 100, 500, and 1,000 mg/kg on days 6 to 15 of gestation caused an increase in embryonic and fetal resorptions at 500 mg/kg. Ossification centers were delayed in formation at the highest dosage. A NOEL for maternal toxicity and fetotoxicity (embryonic resorptions) was reported as 100 mg/kg. Teratogenic effects were not observed at any dosage up to and including 1,000 mg/kg (HDT) (EPA, 1983d).

In a rabbit teratology study reported by Ciba-Geigy, dose levels of 0, 1, 5, or 75 mg/kg/day were given by gavage during gestation days 7 through 19. Decreased body weight gain and food consumption occurred in does in the mid- and high-dose groups. At 75 mg/kg/day, increased resorption rate, reduced fetal weights, and delays in ossification were observed. No teratogenic effects were indicated. The NOEL was established as 1 mg/kg/day for maternal toxicity in this study (Ciba-Geigy, 1984b, as cited in EPA, 1987f).

The effect of atrazine as an 80-percent wettable powder on the reproductive performance of rats was examined in a three-generation study where the HDT was 100 ppm (5 mg/kg/day) in the diet. No adverse reproductive effects

were noted. The study is considered supplementary by EPA because of alteration in the diets at an important maturation period of neonates. The study also used only two dosage levels that EPA considered to be too low and that did not elicit observable toxicity. Considering the fact that a 2-year rat feeding study and the rat teratology study used up to 50 mg/kg/day and 1,000 mg/kg/day, respectively, EPA believed this reproduction study, tested at 5 mg/kg/day, may not adequately assess atrazine's reproductive toxicity (EPA, 1983d).

A 2-generation reproduction study in rats established a NOEL of 10 ppm (0.5 mg/kg/day) based on decreased pup weights at the lowest effect level of 50 ppm (2.5 mg/kg/day) (EPA, 1988a).

Nonthreshold Effects

Available data suggest that atrazine may be carcinogenic; therefore, a cancer risk analysis was done for atrazine in this risk assessment. In a 2-year feeding/oncogenicity study, rats were fed technical atrazine at doses of 0, 10, 70, 500, and 1,000 ppm in the diet. Dose-related increases in adenocarcinomas and fibroadenomas were observed in female mammary glands. Results were statistically significant at 70 ppm (3.5 mg/kg/day) and above for carcinomas and at 1,000 ppm (50 mg/kg/day) and above for adenomas and fibroadenomas. No oncogenic effects were observed in males. A 22-month chronic feeding/oncogenicity study revealed no oncogenic findings in mice (EPA 1988a).

An 18-month mouse feeding study showed no tumor induction when mice were given 21.5 mg/kg by gavage from days 7 to 28 of age, then given 82 ppm (12.3 mg/kg/day) for the remainder of the experiment (Innes et al. 1969, as cited in USDA, 1984).

Cantor et al. (1985) indicated that elevated risks of small cell lymphocytic lymphoma were associated with the use of atrazine (among a number of agricultural chemicals) in a case-control study of farmers in Iowa and Minnesota. Although they did not include an analysis of atrazine-exposed workers, other studies sponsored by the National Cancer

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Institute have found no link between specific pesticides and cancer incidence (Blair and White, 1981; Blair and Thomas, 1979).

Based on the information available, EPA (1987f) has classified atrazine as a possible human carcinogen (Group C). Atrazine cancer potency for this risk assessment was calculated based on the rate of mammary tumor formation in female rats in the 2-year chronic feeding oncogenicity study (CDFA, 1986a). The cancer potency in rats estimated using the one-hit cancer model is 0.03 per (mg/kg/day) (USDA, 1986). The cancer potency adjusted for humans is 0.18 per (mg/kg/day).

Atrazine did not induce mutations in microbial assay systems validated by EPA which included a recombination and conversion assay in strains of B. Subtilis, E. coli, and S. typhymurium; an Ames assay with/without metabolic activation in 4 strains of bacteria; and a DNA repair assay using rat hepatocytes (EPA 1988a).

All of the following positive results were reported in USDA (1984). Atrazine represents an unusual situation because many of the positive genotoxicity studies were conducted using a metabolic activation system of plant origin. Atrazine alone or when tested in vitro in tests using animal metabolic systems was not genotoxic in most cases. Because plant metabolism is not generally considered important in developing a human hazard assessment, the relevance of the "plant-activated" tests in a risk analysis is doubtful.

Atrazine is not genotoxic in bacteria or yeast directly or with the typical rodent S9 activation. Yeast tests for mitotic crossing over and mutation do show positive responses, but only when tested with atrazine incubated with plant cell extracts. Bacteriophage T4 mutation and a B. subtilis test for repairable DNA damage were negative with atrazine alone. A Streptomyces coelicolor mutation assay was positive, but this assay appears to have very little reliability to discriminate true positives and false positives.

In vitro tests with mammalian cells also fail to respond to atrazine directly or with mammalian metabolism (aberrations and sister chromatid

exchange tests in hamster cells were negative), but when hamster V79 cells were exposed to atrazine in the presence of plant cell extracts, the chemical was reported to be mutagenic. Positive unscheduled DNA synthesis (UDS) effects in EUE cells were also reported with atrazine plus plant cell extracts.

Atrazine was reported to be genotoxic directly in plants (mutations at the waxy locus in corn; chromosome aberrations in plant cells) and the mold Aspergillus nidulans (crossing over). Mutation studies in Aspergillus were conducted with plant cell extracts. In the presence of plant cell extracts, a mutation to 8 azaguanine resistance was reported for Aspergillus.

Atrazine was reported to induce sex-linked recessive lethal mutations in the fruit fly (Drosophila melanogaster) in one of two studies.

In vivo studies measuring chromosome aberrations in rodent bone marrow and dominant lethal mutations in the mouse were reported positive at dose levels of 2,000 and 1,500 mg/kg, respectively.

Yoder et al. (1973, as cited in EPA, 1987f) examined chromosomes in lymphocyte cultures taken from agricultural workers exposed to herbicides, including atrazine. There were more chromosomal aberrations in the workers during mid-season exposure to herbicides than during the off-season (no spraying). These aberrations included a four-fold increase in chromatid gaps and a 25-fold increase in chromatid breaks. During the off-season, the mean number of gaps and breaks was lower in this group than in controls who were in occupations unlikely to involve herbicide exposure. This observation led the authors to speculate that there is enhanced chromosomal repair during this period of time resulting in compensatory protection.

Atrazine was positive for mutagenicity in eight gene mutation studies and negative in nine others. Three of these positive responses were in tests with the fruit fly that measured gene mutations in germ cells. Positive results were also obtained in tests with mice that measured chromosome alterations in germ cells. Positive responses in these types of assays indicate a potential for mutagenic hazard. Chromosome aberrations in bone

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marrow cells in vivo support this conclusion. However, these in vivo responses were observed only at very high levels of atrazine equal to or exceeding 1,500 mg/kg (USDA, 1984).

Although all mutagenicity assays that have been validated by EPA are negative, there are many studies in the open literature which are indicative of a possible human germ cell mutagen. For the purpose of this analysis, it is conservatively assumed that atrazine is a human germ cell mutagen at high levels of exposure. The degree of hazard to humans from low levels of exposure is likely to be minimal.

N-Nitrosoatrazine

N-Nitroso derivatives of some herbicides are carcinogenic and mutagenic (Young and Khan, 1978; Braun et al., 1977). Little information is available on the formation of these compounds under normal conditions of herbicide application or on their metabolism in soil and water (Greenhalgh, 1978). Concerns have been raised over the potential for the nitrosation of atrazine to N-Nitrosoatrazine (NNA) under field conditions and the potential toxicity of this compound. No information is available on the toxicity, mutagenicity, or carcinogenicity of N-nitrosoatrazine.

Kearney et al. (1977) have examined the formation and degradation of NNA in soils and aquatic environments. Their results indicate that the formation of NNA is highly unlikely under normal application rates of atrazine (2 ppm) in agricultural soils of pH 5 to 7. They used elevated levels of nitrogen fertilizer (approximately 100 ppm), and these rates are much higher than those used in forestry. In an examination of its persistence, most of the NNA added to soil was converted relatively quickly to atrazine by denitrosation.

The degradation of NNA in aquatic environments is very rapid primarily because of photolysis. However, the formation of NNA in ground water contaminated with atrazine is unknown (Wolfe et al., 1976).

Bromacil

Threshold Effects

Based on the lowest acute oral LD₅₀ of 3,998 mg/kg in rats, bromacil can be classified as slightly toxic. The acute dermal LD₅₀ for rabbits is 2,000 mg/kg, and the acute inhalation LC₅₀ in rats is greater than 57.6 mg/L. Bromacil is a mild eye irritant and is very slightly irritating to the skin of rabbits (EPA, 1986b).

In a 90-day feeding study using an 80-percent wettable powder formulation, rats were given bromacil doses of 0, 50, 500, or 2,500 ppm. The high dose was raised to 5,000 ppm the sixth week. At 5,000 ppm, lower growth rates, decreased erythrocyte count, increased in thyroid activity, and enlargement of centrolobular cells of the liver were observed. The NOEL for this study was 500 ppm (25 mg/kg/day). In a 2-week feeding study, rats exhibited gastrointestinal disturbance and CNS incoordination after receiving 10 doses of 1,035 mg/kg each (EPA, 1986b).

In a 2-year dog feeding study, beagles were given 0, 50, 250, or 1,250 ppm bromacil (82 to 83.4 percent) in the diet. At 1,250 ppm, some decline in body weights was observed. The NOEL was 250 ppm (6.25 mg/kg/day) (EPA, 1986b; CDFA, 1986f).

In a 2-year rat feeding/oncogenicity study, dose levels were 0, 50, 250, and 1,250 ppm. Weight retardation was observed at the 1,250 ppm level. Thus the NOEL for this study is 250 ppm (12.5 mg/kg/day) (EPA, 1986b).

In a 2-year mouse feeding/oncogenicity study, mice were given 0, 250, 1,250, or 5,000 ppm. At the lowest dose, testicular abnormalities in the form of focal atrophy of seminiferous tubules were found. In addition, carcinomas and hepatocellular adenomas were observed in males at all dosage levels (EPA 1988b).

In rat and rabbit teratology studies, no teratogenic, fetotoxic, or maternal toxic effects were observed at the highest dose tested (165

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mg/m³ converted to 7.92 mg/kg in a rat inhalation study and 250 ppm converted to 7.5 mg/kg in a rabbit dietary study). No reproductive effects were observed in a three-generation rat reproduction study at 250 ppm (12.5 mg/kg/day)--the only dose tested (EPA, 1986b).

Nonthreshold Effects

Based on positive results in a mouse oncogenicity study, a cancer risk analysis was done for bromacil in this risk assessment. In a 2-year feeding/oncogenicity study in rats, no oncogenic effects were observed at dietary levels of up to 1,250 ppm (HDT). The 2-year mouse feeding/oncogenicity study, discussed previously, showed an increased incidence of hepatocellular adenomas and carcinomas at the 5,000 ppm (750 mg/kg/day) dose level (EPA, 1986b). Bromacil is classified as a possible human carcinogen (Group C) based on the available data (EPA, 1987a).

Bromacil cancer potency for this risk assessment was based on the rate of liver tumor formation in male mice in the 2-year feeding study. The estimated cancer potency is 0.0038 per (mg/kg/day) (EPA, 1985d).

Because of the potent mutagenicity of 5-bromouracil, which is a structurally related chemical, the metabolic fate of bromacil has been examined to determine whether the formation of 5-bromouracil occurs in vivo. Metabolic fate studies indicate that 5-bromouracil was not isolated from the urine and feces of rats exposed to bromacil or from the urine of bromacil production plant workers (DOE, 1983).

The mutagenicity studies submitted to EPA for the registration of bromacil were deemed unacceptable (EPA, 1984d); however, a letter was written to the manufacturer of bromacil regarding the mutagenic potential of the chemical.

According to EPA (1982) in a letter to E.I. DuPont De Nemours Co., Inc. dated September 30, 1982, EPA has sufficient data to characterize bromacil as nonmutagenic. Bromacil showed negative results in microbial assays for gene mutation, a mammalian in vivo assay, a mouse dominant lethal assay, and mammalian and microbial assays for DNA damage (EPA, 1987a). In one

Ames assay, bromacil did induce reverse mutation (EPA, 1987e). Bromacil caused weakly positive results in one Drosophila recessive lethal assay and negative results in another (EPA, 1987a). Thus, the weight of evidence reviewed for this risk assessment indicates that bromacil does not present a risk of heritable mutations.

2,4-D

Threshold Effects

2,4-D can be classified as moderately toxic in rats with an LD₅₀ of 375 mg/kg (EPA, 1986c). The acute dermal LD₅₀ of 2,4-D (21.1 percent active ingredient) in the rabbit is greater than 3,980 mg/kg (EPA, 1986c). Skin absorption of 2,4-D is limited. Feldman and Maibach (1974) found that approximately 5 to 6 percent of the 2,4-D dermally applied to humans was recovered in the urine. When dermal contact continues, nausea, vomiting, muscular weakness, and diarrhea have been reported, indicating absorption (Poland et al., 1971). Acute eye irritation can result from occupational exposures (WHO, 1984).

2,4-D ingestion or skin exposure in humans can cause irritation to the gastrointestinal tract, chest pain, and muscle twitching. Ingestion of large doses of 2,4-D causes gastroenteritis, skeletal and cardiac myotonia, and central nervous system depression in humans. A human dose of 80 mg/kg of the dimethylamine salt of 2,4-D caused congestion of all organs, degenerative nerve cells, and death. Accidental swallowing of 110 mg/kg of isooctyl ester of 2,4-D caused muscle twitching and paralysis, although the individual recovered in 24 hours (Mullison, 1981, as cited in USDA, 1984).

Peripheral neuropathy has been reported to result in humans from dermal exposure to 2,4-D. In one study, Goldstein et al. (1959) reported three cases in agricultural workers following dermal exposure to 2,4-D. The neuropathy was characterized by progressive numbness, aching of the extremities, muscular fasciculations, denervation of muscles, and decreased conduction velocity in the ulnar nerve. The condition may be partially or totally reversible, depending on the dose level and the individual exposed

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(Goldstein and Brown, 1960; Todd, 1962; Berkley and Magee, 1963; and Wallis et al., 1970). In one patient, only partial recovery was reported, even after 3 years of treatment (Goldstein et al., 1959). His estimated exposure was 60 cc of a 10-percent ester solution, approximately 60 mg/kg.

Peripheral neuropathy has not been seen in laboratory animals dermally exposed to 2,4-D. Four groups of male and female Fischer CDF 344 rats (15 rats/group) were used in a study to determine whether repeated dermal exposure of rats to 2,4-D would result in pharmacological or toxicological effects on the peripheral nervous system. The skin of the animals in the three treatment groups was painted with a 12-percent 2,4-D amine solution for 2 hours per day, 5 days per week, for 3 weeks. Control animals were treated with tap water. Dermal exposure to 2,4-D resulted in two systemic effects: (1) treated rats weighed less than control rats, and (2) the kidneys of treated rats weighed more than those of the control rats. Even though the rats had clear systemic effects of exposure to 2,4-D, there were no treatment-related changes in the function or structure of the nervous system (EPA, 1986d).

In a 90-Day rat subchronic feeding study, histopathological abnormalities were observed at the lowest dose tested of 1.0 mg/kg/day.

Results from the first year of a chronic feeding study on rats have been reviewed by EPA (1985e). Based on renal effects, a NOEL of 1 mg/kg/day was established; the lowest effect level was 5 mg/kg/day. Based on this study and using a hundredfold safety factor, EPA has established a provisional ADI of 0.01 mg/kg/day.

Schwetz et al. (1971) examined the effects of 2,4-D and two esters of 2,4-D on fetal development and neonatal growth and survival in rats. Dose levels up to the maximum tolerated dose of 87.5 mg/kg/day were administered to the laboratory animals on days 6 through 15 of gestation. The fetuses then were delivered by cesarean section on day 20 of gestation and examined for anomalies. The anomalies observed include decreased fetal body weight, subcutaneous edema, delayed ossification of bone, lumbar ribs, and wavy ribs. Since none of these anomalies interferes with fetal or neonatal

development and survival, they were classified in this study as neither embryotoxic nor fetotoxic. There were no treatment-related teratogenic responses observed. At the highest dose level, decreased viability and lactation indices were observed. Therefore, a reproductive NOEL of 5 mg/kg/day was established.

EPA has recently reviewed a teratology study on rats that used an acid form of 2,4-D (EPA, 1985e). Based on fetotoxicity and delayed ossification, a NOEL of 25 mg/kg/day was established; the lowest effect level was found to be 75 mg/kg/day.

A recent multigeneration rat study was conducted at dose levels of 0, 5, 20, and 80 mg/kg/day. During gestation and lactation of the original parents, the female high-dose group was actually receiving about 120 mg/kg/day. Adverse effects on the original parents in this dose group and their offspring were excessive, and the 80 mg/kg/day dosage level was terminated (Mullison, 1986). According to EPA, the results showed no effects at 5 mg/kg/day. At the next higher dose tested (20 mg/kg/day), however, maternal body weights and pup weights decreased (EPA, 1986d).

The n-butylester of 2,4-D was analyzed for immunotoxicity in an acute and subacute oral study, an acute and subacute dermal study, and a teratology study with mice. In the acute dermal study, mice exhibited suppressed antibody production against sheep red blood cells at high exposure levels (500 mg/kg). This response was believed to be a secondary manifestation of clinical signs observed rather than a direct immunological effect. In the subacute dermal study, antibody production was not suppressed, but it did enhance lymphocyte proliferative responses. The authors concluded that the results of this study suggest that 2,4-D esters are unlikely to have any major immunotoxicological significance (Blakley and Schiefer, 1986).

In the acute and subacute oral studies, immunostimulatory effects were observed at relatively high exposures to 2,4-D (100 to 200 mg/kg/day). It was also concluded that these immune alterations would not have any major toxicological significance (Blakley, 1986). Likewise in the teratology study, no net suppressive effect was observed and although subtle effects

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were noted in lymphocyte blastogenesis, the authors concluded that the 2,4-D ester was unlikely to be of any immunotoxicological or teratological significance (Blakley and Blakley, 1986).

Nonthreshold Effects

There is much controversy and little definitive evidence from laboratory studies and epidemiology studies to indicate that 2,4-D may be carcinogenic. Nevertheless, a cancer risk analysis was done for 2,4-D in this risk assessment. Several chronic toxicity/oncogenicity studies have been reported in the literature using various esters of 2,4-D. Innes et al. (1969) reported that the maximum tolerated dose of butyl, isopropyl, or isocetyl esters of 2,4-D was fed to two strains of mice for up to 78 weeks with no significant increase in the tumor incidences observed at a 95-percent confidence level. A study was reported by Hansen et al. (1971) in which, over a period of more than 2 years, rats were fed 2,4-D at 0, 5, 25, 125, 625, and 1,250 ppm, and dogs were fed 2,4-D at 0, 10, 50, 100, and 500 ppm. In the dogs, no increased tumor incidence was observed, and no other lesions were attributed to 2,4-D. The rats showed a high incidence of tumors (30 percent) in both the treated and untreated (control) groups. The male rats had a significantly higher incidence of malignant tumors in the high-dose group (1,250 ppm), and the female rats showed a trend toward increased tumor formation with the logarithm of dose. However, Hansen et al. (1971) concluded that, because the tumors were not target organ types but were randomly distributed types normally found in aging Osborne-Mendel rats and because survival rates were not affected, the data "support the pathological interpretation that a carcinogenic effect of 2,4-D has not been shown."

A later review of this study by the National Cancer Institute (as cited in USDA, 1984) agreed that a carcinogenic effect was not demonstrated for 2,4-D. However, one expert, Dr. M. Reuber, has reexamined the data and challenged the conclusion that no carcinogenic effect was demonstrated (Reuber, 1979).

In a study of adult female sheep that were examined at slaughter, exposure to phenoxy herbicides was associated with significant increases in the rate of small intestinal adenocarcinoma (Newell et al., 1984). Tumor rates rose significantly with the total number of phenoxy sprays used on the farm.

According to the World Health Organization (WHO) (1984), "the carcinogenic potential of 2,4-D and its derivatives such as the amine salts and esters has not been adequately tested. The reports on animal bioassays carried out so far are either too brief for proper evaluation or have been the subject of scientific controversy."

EPA has recently received and reviewed a long-term study on the oncogenic potential of 2,4-D. Preliminary findings indicate an increased incidence of brain tumors in rats. It must be emphasized that EPA's review of the recent cancer study is not complete at this time. EPA has requested an independent expert to review the brain tissue slides from this study. EPA may also request a review of this study by the Scientific Advisory Panel. Thus, a thorough review of this study may take months to complete. Therefore, EPA does not believe it is appropriate at this time to derive a specific numerical estimate of cancer potency based on the new data. However, EPA has stated that, based on their preliminary review, the level of cancer potency indicated by the reported results would be of about the same order of magnitude as the potency value based on the Hansen study (EPA, 1986k).

At 106 weeks, a preliminary pathology report from a recent mouse study found that 2,4-D was not oncogenic at dosages of 1, 15, and 45 mg/kg/day (Hazelton Laboratories, 1986).

Several epidemiological investigations have been conducted to examine the link between human phenoxyacid herbicide exposure and cancer. In the mid and late 1970's, Hardell and colleagues (Hardell and Sandstrom, 1979; Eriksson et al., 1981; Hardell et al., 1981) conducted a series of case-control studies in rural Sweden. These studies found a significant increase of five- to sixfold in the relative risk of soft-tissue carcinomas, Hodgkin's disease, and non-Hodgkin's lymphoma among farmers

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using various herbicides. However, because of selection bias, observation bias, and uncontrolled confounding variables, many experts have questioned the validity of the results of these studies (Colton, 1986).

In a Danish cohort study of workers involved in the manufacture of phenoxy herbicides, a significant increase in risk of soft-tissue sarcoma (STS) was found, but no similar increase in malignant lymphoma (Lynge, 1985). The cancer risk among persons employed in the manufacture and packaging of phenoxy herbicides was equivalent to the cancer risk in the Danish population (Lynge, 1985). A recent Swedish cohort study found no significantly increased relative risk (0.9) of STS in Swedish agricultural and forestry workers exposed to phenoxy acid herbicides (Wiklund and Holm, 1986). In addition, a case-control study conducted in New Zealand by Smith et al. (1984) was negative for soft-tissue carcinomas showing an estimated relative risk of 1.3.

Recently, Hoar et al. (1986) completed a case control study in Kansas examining the risk of lymphoma and STS in men from agricultural herbicide exposure. The study found no association between exposure and soft-tissue carcinoma or Hodgkin's disease, but a significant association was observed for non-Hodgkin's lymphoma (NHL) and phenoxyacetic acid herbicide exposure, especially 2,4-dichlorophenoxyacetic acid exposure. In addition, individuals exposed to herbicides for more than 20 days per year had a sixfold increase in NHL. Nonetheless, this study suffers from the same inherent limitations as other case-control studies, mainly that it relies on the recall of the subject or their next of kin to determine their exposure status. If their recall is faulty, then misclassification occurs. It is especially difficult to assess exposure-disease relationships in these types of epidemiological studies (NRC, 1986). For example, it is possible to have common exposures to other carcinogenic agents or other factors that result in disease but are not discovered in the interview and confound the results. Thus, uncontrolled confounding factors in observational epidemiological studies can be particularly troublesome in interpreting the results. However, the apparent dose-response relationship observed in the Hoar et al. (1986) study for NHL is of public health concern and needs further examination. It should be

noted that at least two additional studies are now under way that should be helpful in assessing risk to humans from the use of 2,4-D and other phenoxy herbicides (Colton, 1986).

In a recent review of the Hoar et al. (1986) study conducted for EPA, Brian MacMahon, M.D., Ph.D., of the Harvard School of Public Health, concluded:

In my opinion the weight of evidence does not support the conclusion that there is an association between exposure to 2,4-D and NHL. It is axiomatic that, except when relative risks are very high--and sometimes even then--no single study will establish an association between an exposure and an outcome. The acceptance of an association depends on a number of studies showing consistent results across populations and across different epidemiologic methods. The study of Hoar et al. is a strong study--strong enough on its own to establish a hypothesis of relationship of exposure to 2,4-D with some small proportion of cases of NHL--a hypothesis that clearly deserves attempts at refutation or support in other populations. When one attempts to place the results of this study among the results of those published previously, the picture becomes very confusing--much more than if Hoar et al. had been the only study published. Taken as a whole, I believe that the weight of evidence indicates that an association between 2,4-D and NHL remains a hypothesis that is still to be tested. I am unwilling to speculate as to whether 2,4-D causes NHL (or some cases of NHL) until the evidence is clear that there is an association between them.

A recent case-control study conducted by Pearce et al. (1986) in New Zealand found no significant differences between cases and controls for NHL regarding exposure to phenoxy herbicides.

Other recent case-control studies of phenoxy herbicides have been reviewed by the Canadian Centre for Toxicology (1987). A study conducted in western

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Washington State reported no overall increased risk associated with past occupational exposure to phenoxy herbicides for STS or NHL (Woods et al., 1987). There was an elevated risk of NHL for men who had been farmers, forestry herbicide applicators, and those potentially exposed to phenoxy herbicides for 15 years or more during the period prior to 15 years before cancer diagnosis. However, exposure to 2,4-D was not singled out.

Another study reviewed by the Canadian Centre for Toxicology (1987) is being conducted by the National Cancer Institute in Iowa and Minnesota. Preliminary results indicate no overall increased risk for NHL associated with living or working on a farm, and a slightly elevated (but not significant) risk in persons using 2,4-D (Cantor and Blair, 1986). The investigators have decided to recontact subjects to gather more information on the number of days per year of pesticide use.

Two recent case-control studies conducted in New Zealand were negative for soft-tissue carcinoma (Smith et al., 1984) and NHL (Pearce et al., 1986) in association with phenoxy herbicide exposure.

In a recent cohort study of forestry workers in Ontario, no evidence of increased mortality risk or cancer risk was observed in forestry workers after 15 or more years of employment associated with phenoxy herbicide use (Green, 1986). The forestry workers had been employed by Ontario Hydro during the period 1950 through 1982.

Following the review of 2,4-D epidemiology studies, the Canadian Centre for Toxicology (1987) concluded that there is limited evidence of carcinogenicity in man from exposure to phenoxy herbicides, and there is inadequate evidence to classify 2,4-D as a carcinogen. At least two more studies are now under way that should be helpful in assessing risks to humans from the use of 2,4-D and other phenoxy herbicides (Colton, 1986).

Because of the uncertainty about the carcinogenicity of 2,4-D, a cancer risk analysis was conducted for 2,4-D in this risk assessment. 2,4-D cancer potency was calculated based on the rate of tumor formation in the female Osborne-Mendel rats studied by Hansen et al. (1971). This is the

species and sex that have exhibited the highest increase in tumor formation after 2,4-D administration. All tumors were considered, although many of them were benign. The 95-percent upper confidence limit of the cancer potency, calculated by Crump (1983) using the GLOBAL 82 computer program, was 0.00503 per (mg/kg/day). The potency adjusted for humans is 0.029. A preliminary review of an additional long-term oncogenicity study submitted to EPA in 1986 indicates that the cancer potency level would be of about the same magnitude as the cancer potency calculated by Crump (EPA, 1986e).

Several studies have been performed to examine the mutagenic potential of 2,4-D. These studies have been reviewed by Newton and Dost (1981) and have shown negative, weakly positive, and positive results, depending upon the test systems used and the purity of the test substances. Eight strains of histidine-requiring mutants of bacteria (Salmonella typhimurium) exposed to 2,4-D failed to show point mutations (Anderson et al., 1972). Styles (1973) failed to show increases in mutations with serum from rats treated with 2,4-D in a host-mediated assay with histidine-requiring S. typhimurium mutants. The sex-linked lethality assay of 2,4-D using Drosophila was negative (Vogel and Chandler, 1974), weakly positive (Magnusson et al., 1977), and positive (Rasmussen and Svahlin, 1978) in three different studies. 2,4-D caused a highly significant increase in rates of sister chromatid exchange in cultured human lymphocytes at a 50 ug/mL dosage, but not at dosages of 100 and 250 ug/mL (Turkula and Jalal, 1985). Bovine fetal muscle cells exposed to a culture media containing 2 and 20 mg/L of 2,4-D exhibited an initial drop in mitotic index, an increase in differentiating and degenerating cells, unipolar and tripolar spindles, and a variety of other abnormalities (Basrur et al., 1976). In a recent study, 2,4-D induced clastogenicity in white rats (Turkula and Jalal, 1987). According to WHO (1984), "studies available at present are not adequate for the quantitative evaluation of the mutagenic effects of 2,4-D and evidence does not suggest that 2,4-D derivatives are potent mutagens." Newton and Dost (1981), in their review, concluded that 2,4-D may be a weak mutagen "but is without significance as an environmental mutagenic hazard." Thus, the review of the evidence of 2,4-D mutagenicity in this risk assessment indicates that 2,4-D cannot be ruled out as a weak mutagen, but that it is not likely to present a risk of human heritable mutations at the exposure

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levels that might occur in the Forest Service or BLM's vegetation management program.

2,4-D Contaminants

In the case of 2,4-D, special attention must be paid to two contaminants, one of which is also a metabolic product in microorganisms. The issue arises not because of data indicating hazard but because of allegations based on incorrect evaluation of the data.

In the manufacture of 2,4-D, 2,4-dichlorophenol (2,4-DCP) is an intermediate, a minute fraction of which may remain in the final product. It is also an environmental metabolite of 2,4-D. Because of its relatively low toxicity (the LD₅₀ is approximately 1,300 mg/kg), 2,4-DCP has not been judged sufficiently toxic to be eliminated from 2,4-D formulations.

The effects of 2,4-DCP on human health have not been well studied. Boutwell and Bosch (1959) examined the carcinogenicity of 2,4-DCP and found it to be a weak tumor promoter. It was also found to inhibit oxidative phosphorylation in rat liver and brain mitochondria (Mitsuda et al., 1963). Somani and Khalique (1982) found that after intravenous administration of 2,4-DCP in rats, the chemical was rapidly metabolized to glucuronide and other conjugates and was eliminated from the body. They showed that half-lives in the kidney and liver are longer than in other tissues, indicating that the liver is a major organ for metabolism, and that the higher levels in the kidneys correlate with that being the route of elimination. Seyler et al. (1984) performed some preliminary reproductive screening procedures and found that 2,4-DCP did not depress sperm penetration of ova and sperm motility in vitro when compared with controls. A 2,4-DCP teratology study recently reviewed by EPA found a NOEL of 350 mg/kg/day; the lowest effect level was found to be 750 mg/kg/day with the effect being delayed ossification (EPA, 1985f). In conclusion, 2,4-DCP appears to be less toxic than the parent herbicide 2,4-D. 2,4-DCP is the immediate microbial breakdown product of 2,4-D and is in turn further oxidized by the same organisms. The rate function for each of the steps in this long series of oxidations is higher than the preceding step.

Breakdown thus becomes easier with each step. The products are mostly not liberated but remain captive in the microorganisms.

2,4-DCP is so volatile that if it were to escape it would immediately dissipate. It also has an exceedingly low olfactory threshold; extremely small amounts are detectable by smell. Because of these factors, only applicators or others working directly with the material before it is applied have any significant opportunity for contact.

The eight manufacturers of 2,4-D in the United States have subjected their products to analysis for 2,4-DCP. Total chlorophenols, of which 2,4-DCP is predominant, were about 0.3 percent in the most contaminated sample. Therefore, at worst, such immediate contact is something less than 0.3 percent of the corresponding exposure to 2,4-D. Many contained no detectable chlorophenols. Other chlorophenols include 2,6-DCP and the 2-chloro- and 4-chlorophenols, all of which are minor contributors (Warren, 1983).

Environmental exposures will not correspond to the amount of 2,4-D applied, either as a fixed fraction of impurity or as a fraction of applied and degraded 2,4-D. As an impurity, 2,4-DCP has a high vapor pressure, so it evaporates and disappears quickly. As a metabolite of soil organisms, 2,4-DCP is almost entirely entrained in those organisms, although at high levels of 2,4-D in water some DCP can be found. Environmental exposure to 2,4-DCP is so low that it cannot be measured.

The other impurity of concern in 2,4-D formulations is 2,7-dichloro dibenzo-p-dioxin (DCDD), which differs only slightly in structure from the well-known 2,3,7,8 TCDD, but differs by about a millionfold in toxicity. Two concerns of biological danger have been expressed: DCDD is alleged to be a teratogen and is alleged to be carcinogenic.

DCDD has been found in 3 of 30 samples of U.S.-produced 2,4-D, along with traces of other relatively nontoxic chlorodioxins with three and four chlorines. The concentrations in the three positive samples ranged from 25 to 60 ppb. If the maximum expected human dose of 2,4-D is 0.1 mg/kg, and

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for convenience all 2,4-D is assumed to contain 100 ppb of DCDD, the dose of DCDD to the exposed human would be 0.00000001 mg/kg.

The toxicologic studies from which these concerns arise are reported by Khera and Ruddick (1973), who discussed fetotoxic effects of DCDD, and the National Cancer Institute (1979), which conducted carcinogenesis studies in two species. Khera and Ruddick fed DCDD at dosages of 1 and 2 mg/kg daily to determine whether DCDD could cause birth defects. The observed effect at 1 mg/kg was a modest degeneration of heart muscle fibers and some fluid accumulation around the heart in a few of the animals. A somewhat greater number of animals were affected at 2 mg/kg. Both effects are in the category of general fetal toxicity. No teratogenic effect was found.

The National Cancer Institute (1979) work was carried out by feeding DCDD as 0.5 and 1 percent of the total diet for 2 years. The data indicated a "suggested" carcinogenic effect in male mice that was not strong enough to support a conclusion that DCDD is a carcinogen. Male mice and rats of both sexes did not significantly respond.

The conclusion, therefore, is that neither 2,4-DCP nor 2,7-DCDD, at maximum occupational or environmental exposures to 2,4-D, represents a human hazard.

2,4-DP

Threshold Effects

2,4-DP can be classified as slightly toxic based on the acute oral LD₅₀ of 532 mg/kg in rats. The acute dermal LD₅₀ is greater than 2,000 mg/kg in rabbits. 2,4-DP caused very slight eye irritation and slight dermal irritation (EPA, 1984b).

In a 90-day rat feeding study, doses of 0, 100, 500, or 2,500 ppm were given in the diet. At 500 ppm (25 mg/kg/day), rats exhibited increased kidney and liver weights and decreased packed cell volume and blood sodium. The NOEL was established at 100 ppm (5 mg/kg/day). In another 90-day rat feeding study, test animals were given doses of 100, 300, 1,000,

and 3,000 ppm in the diet. At 1,000 ppm, rats exhibited hematological changes (EPA, 1984b).

2,4-DP appears to cause fetotoxic, maternal toxic, and teratogenic effects in laboratory animals. In a three-generation rat reproduction study, test animals were given 0, 125, 500, 1,000, and 2,000 ppm in the diet. At 500 ppm, increased mortality was observed in fetuses. Increased pup mortality during the lactation period, reduced body weight in dams, and increased number of small litters were observed at 2,000 ppm. The maternal and reproductive NOEL's for this study were both 1,000 ppm (50 mg/kg/day). The fetotoxic NOEL was 125 ppm (6.25 mg/kg/day) (EPA, 1984b).

In two teratology studies in rats, no teratogenic effects were noted at the highest dose tested of 100 mg/kg/day. However, in a rabbit teratology range-finding study, teratogenic effects in the form of omphalocele (navel hernia), displaced kidneys, and distorted ribs occurred at the lowest dose tested of 25 mg/kg/day. At 100 mg/kg/day (HDT), reduced fetal weight and reduced crown to rump distance were noted in fetuses, and unsteadiness in gait, reduced food intake, and increased mortality were noted in does (EPA, 1984b).

In a 2-year feeding/oncogenicity study in rats, systemic toxic effects occurred at 300 ppm (15 mg/kg/day). Effects were decreases in urinary specific gravity and protein in males. Dose levels tested were 0, 100, 300, 1,000, and 3,000 ppm. The systemic NOEL was 100 ppm (5 mg/kg/day) (EPA, 1984b).

In another 2-year feeding/oncogenic study in rats, systemic effects reported were decreased weight gain, decreased hematocrit and RBC, renal degeneration, chronic prostatitis, testicular tubular atrophy, edema, and leydig cell hyperplasia. These were observed at 150 mg/kg/day. The NOEL was therefore 50 mg/kg/day (EPA, 1984b).

In an 18-month mouse feeding/oncogenicity study, increases in liver weight, bile retention, regeneration, and degeneration were observed at 300

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mg/kg/day. Doses tested were 0, 25, 100, and 300 mg/kg/day. The NOEL was established at 100 mg/kg/day (EPA, 1984b).

Nonthreshold Effects

A cancer risk analysis was done for 2,4-DP in this risk assessment because 2,4-DP was found to be carcinogenic in one of three oncogenicity studies. In a 2-year feeding/oncogenicity study in rats, males exhibited increased frequency of malignant tumors of all types at 25, 50, and 150 mg/kg/day. Pituitary and thyroid medulary tumors increased with dose in males. In males and females, a significant increase of rare malignant brain tumors occurred at the low dose only (25 mg/kg/day) (EPA, 1984b).

An 18-month mouse oncogenicity study and another 2-year feeding/oncogenicity study with rats both found no oncogenic effects at the highest dose tested (300 mg/kg/day in mice and 150 mg/kg/day in rats) (EPA, 1984b).

A cancer study involving rats fed up to 200 mg/kg (EPA, 1982b) was used to derive 2,4-DP cancer potency. In this study, the highest dose group showed signs of general toxicity because they were fed more than the maximum tolerated dose of 2,4-DP. Many of the females at all dose levels had tumors but tumor incidence did not show a dose-related response. Males showed a significant increase in the rate of incidence of malignant tumors, with a corresponding decrease in the rate of benign tumors. The tumors were primarily in the thyroid and pituitary glands.

The 95-percent upper confidence limit for the cancer potency of 2,4-DP was estimated from the male rat data as 0.012 per (mg/kg/day). The cancer potency adjusted for humans is 0.059 per (mg/kg/day). Only malignant tumors were considered in this case, and the high dose group showing signs of general toxicity was not considered in order to give the highest cancer potency indicated by the data. The high dose group actually had fewer malignant tumors than the intermediate dose group.

2,4-DP was negative for gene mutation in the Ames assay both with and without activation at up to 1,000 mg/plate (HDT). Negative results were also reported for a mitotic crossing over assay with Saccharomyces cerevisiae at the highest dose tested (10 mg/mL). In an unscheduled DNA synthesis assay with E. coli, doses tested were 0.0008 to 8 mg/mL. 2,4-DP tested positive only with activation at the highest dose. All other results for this assay were negative, both with and without activation. In a mitotic gene conversion assay and a reverse mutation assay with Saccharomyces cerevisiae, positive results were obtained without activation (EPA, 1984b). Based on the inconsistent genotoxic responses in these short-term tests and the positive oncogenic effects observed in a chronic/oncogenicity study of rats, 2,4-DP is considered to be possibly mutagenic in this risk assessment, but does not present a significant risk of causing human heritable mutations.

Dalapon

Threshold Effects

Based on the lowest acute oral LD₅₀ of 7,577 mg/kg in the rat, dalapon can be classified as very slightly toxic. In a primary eye irritation study with rabbits, a 26.8-percent formulation of dalapon caused slight eye irritation, which subsided within 24 hours. Based on this study, dalapon was categorized by EPA as slightly toxic for eye irritation. The acute dermal LD₅₀ for the 26.8-percent formulation in rabbits was greater than 4 mg/kg (HDT). Based on the slight local erythema observed in this study, dalapon was also classified as slightly toxic for dermal toxicity (EPA, 1984f).

In a 2-year feeding study, rats were given 100, 300, and 1,000 ppm dalapon sodium salt in the diet. The only adverse effect noted was increased average kidney weights at the highest dose level. Microscopic examination of tissues revealed no abnormal pathology (Paynter et al., 1960, as cited in USDA, 1984). The NOEL for this study was therefore established at 300 ppm (15 mg/kg/day) (EPA, 1984f). Because the test substance was only 65

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percent dalapon, EPA has converted the NOEL to 8 mg/kg/day for 100 percent dalapon in the drinking water health advisory (EPA, 1987g).

In another chronic toxicity study, dogs were administered dalapon sodium salt by capsule (15, 50, or 100 mg/kg/day) 5 days a week for 52 weeks. At the high dose level, adverse effects were limited to an increase in average kidney weights. Histopathological examination revealed no significant difference in tissues of treated and untreated animals (Paynter et al., 1960, as cited in USDA, 1984). The NOEL for this study was therefore determined to be 100 mg/kg/day (EPA, 1984f).

In a 2-year mouse feeding/oncogenicity study, test animals exhibited increased liver weight at 200 mg/kg/day, the highest dose tested (CDFA, 1986b). A systemic NOEL of 60 mg/kg/day was therefore established.

No teratogenic effects were noted in two rat teratology studies. In one study, rats were administered 500, 1,000, or 1,500 mg/kg/day by gavage during days 6 to 15 of gestation. Fetal weight was significantly decreased at 1,000 and 1,500 mg/kg (CDFA, 1986b). The fetotoxic NOEL was therefore established as 500 mg/kg/day, and the teratogenic NOEL was greater than 1,500 mg/kg/day (EPA, 1984f).

In another teratology study, pregnant rats were given 250, 500, 1,000, 1,500, or 2,000 mg/kg/day during the sixth through fifteenth day of gestation. Pup weights were significantly lower at the 1,000 mg/kg/day dosage level, and weight gains of pregnant dams were reduced at 1,500 mg/kg/day. No adverse effects were observed at the 250 and 500 mg/kg/day dose levels (USDA, 1984).

In a three-generation reproduction study, rats were fed 0.03, 0.1, or 0.3 percent dalapon sodium salt in the diet. No adverse effects on fertility, gestation, viability, or growth and maturation were observed (Paynter et al., 1960, as cited in USDA, 1984). The NOEL was reported as 0.3 percent (approximately 300 mg/kg/day) (EPA, 1984f). In another three-generation rat reproduction study, the NOEL was determined to be

3,000 ppm (150 mg/kg/day) (EPA, 1984f). A one-generation reproduction study in dogs established a NOEL of 500 ppm (12.5 mg/kg/day) (EPA, 1984f).

Nonthreshold Effects

In a 2-year feeding/oncogenicity study, rats were fed diets containing 100, 300, or 1,000 ppm dalapon sodium salt. At 104 weeks, histological examination of tissues revealed no differences between treated and control animals. However, findings specifically related to tumor formation were not reported (Paynter et al., 1960, as cited in USDA, 1984).

In a mouse oncogenicity study reported by the California Department of Food and Agriculture (CDFA, 1986b), animals were fed 0, 2, 60, or 200 mg/kg/day over 2 years. Although this study was judged incomplete, CDFA (1986b) concluded that dalapon was not oncogenic in this study.

No abnormal pathology or evidence of tumor formation was found of histology sections of test animal tissues in a 52-week dog feeding study (Paynter et al., 1960, as cited in USDA, 1984). Available data do not indicate that dalapon is carcinogenic. EPA (1987g) has placed dalapon in Group D: not classifiable as to human carcinogenicity due to lack of sufficient study data.

Mutagenicity studies also were reported by the California Department of Food and Agriculture (CDFA, 1986b). Dalapon tested negative for gene mutation in Salmonella with and without activation and in Aspergillus nidulans. Dalapon was also negative for chromosomal aberrations in the Chinese hamster ovary cell. The weight of evidence reviewed in this risk assessment therefore indicates that dalapon does not present a risk of heritable mutations.

Dicamba

Threshold Effects

Based on its acute oral LD₅₀ of 757 mg/kg in the rat, dicamba can be

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classified as slightly toxic. However, dicamba is classified as a severe eye irritant.

The Pesticide Incident Monitoring System data base revealed 10 incident reports involving humans from 1966 to March 1981 for dicamba (EPA, 1981, as cited in EPA, 1987h). Six of the ten reported incidents involved spraying operations. No concentrations were specified. Exposed workers developed symptoms that included muscle cramps, dyspnea, nausea, vomiting, skin rashes, loss of voice, and swelling of cervical glands. Coughing and dizziness resulted in one child involved in an undescribed agricultural incident. Three children who sucked mint leaves from a ditch bank previously sprayed with dicamba were asymptomatic.

The NOEL from a 90-day rat study is given as 500 ppm (25 mg/kg/day) based on slight liver cell alterations at the 800-ppm dose (EPA (1986n). A 15-week rat feeding study in which male Wistar rats (20/dose) were fed diets containing technical dicamba at 0, 31.6, 100, 316, 1,000, or 3,162 ppm (0, 1.6, 5, 15.8, 50 or 158 mg/kg/day) showed liver-to-body weight ratio increases at the 2 highest doses (EPA, 1987h). The NOEL for this study was determined to be 15.8 mg/kg/day.

A 2-year oral toxicity study on rats established a NOEL of 125 mg/kg/day, which was the highest dose tested (EPA 1988c). In addition, a 1-year oral toxicity study in dogs established a NOEL of 52 mg/kg/day, which was the highest dose tested.

A 90-day subchronic feeding study with male and female rats was performed with dosages of 1,000, 5,000, 10,000 and 0 ppm. There were no compound related changes in general behavior and appearance. The high dose groups showed a slight decrease in comparative body weight gains and food consumption. There were no gross lesions or organ weight gain variations in treated groups. There was an absence or reduction of cytoplasmic vacuolation of hepatocytes indicating reduced glycogen storage in high-dose groups. The no-observed effect level was 250 mg/kg/day (systemic).

The following discussion of dicamba's toxicity is taken from the 1983 EPA Reregistration Standard (EPA, 1983e):

The available data indicate that technical dicamba is a severe eye irritant but has low oral and primary skin irritation toxicities. Available supplementary data indicate low dermal and inhalation toxicities. Technical dicamba is classified as severely toxic based on eye irritation. Additional subchronic dermal testing is required.

Data to support the establishment of reentry protection standards are not required because the Agency has determined, based on the use patterns and available toxicity data for dicamba, that the criteria in 158.14 are not met.

A three-generation reproduction study in rats showed no evidence of toxicity among the rats from any of the generations utilized in the study. No test-article related effects were evident for any of the reproduction indices examined during the course of the study. The findings of this study indicate a no-observable effect level of 25 mg/kg/day.

A teratology study in female rabbits was performed with levels of 0, 1.0, 3.0, and 10.0 mg/kg/day. The 10 mg/kg/day dose caused slightly reduced fetal body weights and increased post-implantation loss. No teratogenicity was observed in this study. The no-observed effect level was 3.0 mg/kg/day for maternal toxicity.

Nonthreshold Effects

Dicamba is considered to be not carcinogenic in this risk assessment. Although the above chronic feeding studies do not meet the current FIFRA registration guidelines, they do provide information on the chronic effects of dicamba. Likewise, although none of these studies was conducted as a

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cancer study (and they would not meet today's strict guidelines for cancer studies), the histopathology screening conducted does provide some information on the ability of dicamba to cause cancer.

A recent 2-year rat study, accepted by EPA, showed no oncogenic or systemic effects at the highest dose tested (125 mg/kg/day) (EPA, 1986e). Although these are valid data to determine that dicamba is not a carcinogen, the FIFRA guidelines require negative data on two species. Data to complete the guidelines package have been requested by EPA. Dicamba is presently included in Group D: not classifiable as to human carcinogenicity risk (EPA, 1987h).

Dicamba has been tested for mutagenicity and for its effect on unscheduled DNA synthesis. The following studies are cited in USDA (1984) and most have been reviewed by EPA (1985g). The results were negative for gene mutation in Salmonella typhimurium (Poole et al., 1977; Eisenbeis et al., 1981; and Anderson et al., 1972), Escherichia coli (Poole et al., 1977), and Saccharomyces cerevisiae (Poole et al., 1977). Unscheduled DNA synthesis, assayed in human fibroblast line WI-38, was negative for dicamba (Poole et al., 1977). Dicamba was positive in relative toxicity assays in E. coli (Poole et al., 1977). The weight of evidence indicates that dicamba is not mutagenic and thus does not present a risk of heritable mutations.

Dicamba Contaminants

The manufacturing process for dicamba has the potential of resulting in traces of 2,7-dichlorodibenzo-p-dioxin as a contaminant.

2,7-dichlorodibenzo-p-dioxin is present at levels to 50 parts per billion (ppb). The more toxic dioxin isomer 2,3,7,8-tetrachlorodibenzo-p-dioxin has not been found at the limit of detection (2 ppb) of the method and is not expected as an impurity in dicamba. Dicamba products formulated with dimethylamine have the potential of adding dimethylnitrosoamine (DMNA) contaminant. Nitrosoamine levels in the diethylamine formulations are expected to be less than 1 ppm. The risk levels for the dicamba products with the nitrosoamine contaminant are in the range of 1×10^{-7} to $1 \times$

10^{-8} . EPA considers the benefits to outweigh the risks associated with the nitrosoamines (EPA, 1983e).

Diuron

Threshold Effects

Based on the acute oral LD₅₀ of 3,750 mg/kg in rats, diuron can be classified as slightly toxic (EPA, 1984g). Signs of toxicity were related to nervous depression and included slowed respiration and heart rate, weakness, and lethargy (EPA, 1983a). The LD₅₀ for dermal exposure was found to be more than 10,000 mg/kg in rats; therefore, diuron is classified as very slightly toxic for dermal effects (1983a). Acute primary dermal irritation studies in rabbits found slight erythema or edema at 24 hours (EPA, 1983a). All test data from acute primary dermal irritation studies that applied diuron to animal skin, abraded and unabraded, resulted in normal findings at 72 hours. Diuron is classified as very slightly toxic for acute primary eye irritation because no primary eye irritation was found in the unwashed eyes of rabbits (EPA, 1983a).

Two 2-year feeding studies, one using rats and one using dogs, were evaluated by EPA (1983a). In both of these studies, the sample fed was a wettable powder formulation containing 80 percent diuron. The dietary levels were based on diuron.

In the 2-year rat study, rats were given diets containing 0, 25, 125, 250, or 2,500 ppm diuron. High mortality was attributed by the investigators to an epidemic of pneumonitis-peritonitis. The highest dose depressed growth. Increased mortality was observed at the 2,500 and 250 ppm level in males given diuron. During pathology examinations, the authors noted slight anemia, enlarged spleens, increased erythrogenic activity in bone marrow, and abnormal blood pigments in the blood of groups fed 125 ppm or more. The NOEL was 25 ppm (1.25 mg/kg/day) in rats. No evidence of tumorigenicity was found. However, although this study is accepted as a chronic toxicity study, it is of only supplemental value as an oncogenicity test because limited pathology did not include all rats that died during the study or all rats sacrificed at the end of the study (EPA, 1983a).

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A 2-year feeding study in dogs was done at levels of 0, 25, 125, 250, and 1,250 ppm in the diet. The highest dose caused weight loss, depressed red blood cell counts, erythrocytic activity in bone marrow, elevated liver weight, and increased pigment disposition in liver cells. Also, abnormal pigments were found in the blood of males at levels higher than 25 ppm and females at levels higher than 125 ppm. Slightly decreased hematological values were seen in the 125 ppm group, but they were statistically significant only in the red blood cell count in male dogs. No other abnormal effects were noted with respect to hematology, urine biochemistry, or histology. No evidence of tumorigenicity was found (EPA, 1983a). Therefore, the NOEL in dogs is 25 ppm (0.625 mg/kg/day) (EPA, 1983a).

EPA (1986, as cited in EPA, 1987b) has established an acceptable daily intake (ADI) of 0.002 mg/kg/day based on the NOEL of 0.625 mg/kg/day in the dog study and an uncertainty factor of 300.

In a teratology study, rats were administered 80-percent diuron by gavage from the 6th through the 15th day of pregnancy. The dose levels were 0, 125, 250, and 500 mg/kg/day. Some abnormalities were observed at all treatment levels. Included among these were wavy ribs, sternoschisis, and delayed calvarium ossification, all of which could result from fetal toxicity. Delayed ossification of the calvarium found in one rat at the lowest dose level, 125 mg/kg/day, was of borderline significance (EPA, 1983a). No teratogenic effects were observed, and the teratogenic NOEL was reported as greater than 500 mg/kg (EPA, 1986e).

A three-generation rat reproduction study of the 80 percent wettable powder formulation of diuron resulted in body weight depression in the F₂b and F₃a litters but this was not considered a fetotoxic, reproductive, or teratogenic effect (EPA, 1984g). A reproductive NOEL of greater than 125 ppm active ingredient (6.25 mg/kg/day) (only dose tested) was established (EPA, 1984g).

Nonthreshold Effects

Diuron is considered to be not carcinogenic in this risk assessment because

studies relating to diuron's oncogenicity, reviewed in EPA (1983a) and EPA (1987b), show no clear evidence that diuron causes tumor growth.

In a mouse oncogenicity study, 7-day-old mice were given doses of 464 mg/kg diuron by intubation for 4 weeks. After weaning, they were given diets containing 1,400 ppm diuron for 18 months. The study showed no positive evidence that diuron was tumorigenic. However, because this study was a screening study, it was judged by EPA to be of limited value for making final decisions (EPA, 1983a).

EPA, (1983a) indicated the following concerning a Russian study that showed positive oncogenic effects for diuron:

The following comments are offered on an invalid study because it purported to be positive. Rubenchick, B.L. et al., *Onkologiya* (Kiev) 4:10-16, 1973, reported carcinogenic activity of several urea derivatives including diuron. However, this study cannot be considered valid for several important reasons. The identity and purity of the material tested are unknown. Mortality data are lacking. Detail data relating tumors to time and kind are lacking. Dosage levels are uncertain.

EPA (1983a) indicated that the above rat and dog 2-year feeding studies, which tested levels up to 2,500 ppm, have value as supplemental information but do not meet the needs of EPA for evaluation of oncogenicity because of the limited pathology provided. Therefore, EPA stated, while there is no valid evidence that diuron is oncogenic, there is insufficient evidence that it is not. Further testing in the rat and another species for oncogenicity has been requested by EPA (1983a). Diuron is presently placed in Group D: not classifiable as to human carcinogenicity (EPA, 1987b).

Diuron showed negative results in microbial assays for gene mutation and DNA damage in a Chinese hamster ovary cell forward mutation assay and in an unscheduled DNA synthesis assay in rat hepatocytes (EPA, 1987b). In an in vivo cytogenetic assay with rats, diuron caused clastogenic effects (EPA, 1987b); however, negative results were reported in a mouse micronucleus

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assay in vivo (that was deemed inadequate) (EPA, 1983a). An Ames assay using five strains of bacteria resulted in positive findings for mutagenicity. Positive results also were reported in a reverse mutation bacterial assay and a testicular DNA synthesis inhibition assay, which were judged unacceptable (EPA, 1983a). EPA (1983a) believed the results of the latter test to be cause for concern because it suggests that diuron can enter the testes, and, if shown to be mutagenic, diuron may produce heritable mutagenic effects. EPA (1983a) has therefore requested additional studies for chromosomal aberrations, and other genotoxic effects (such as DNA damage and repair). Because of the uncertainty in the studies and EPA's conclusion about possible entry to the testes, this risk assessment concludes that diuron may present some risk of human heritable mutations.

Fosamine

Threshold Effects

Based on the acute oral LD₅₀ of 24,400 mg/kg in the rat, fosamine can be classified as very slightly toxic. Acute effects observed in the rat included respiratory distress, diarrhea, and weight loss. The acute oral LD₅₀ for guinea pigs is 7,380 mg/kg, and effects included tremors, pallor, and convulsions. The acute dermal LD₅₀ for rabbits is greater than 1,683 mg/kg, which classifies fosamine as slightly toxic for dermal effects. Transient, mild skin irritation was observed. Fosamine was negative for dermal sensitization and irritation in guinea pigs using a 50-percent dilution material or less. In a 10-day oral study, no toxic signs were observed in rats at the highest dose, 2,200 mg/kg/day (EPA, 1987c).

In a reproduction study reviewed by the California Department of Food and Agriculture (CDFA, 1986c) and judged unacceptable, no adverse reproductive effects in rats were reported at the high dose level of 5,000/10,000 ppm (250/500 mg/kg/day). In a rat teratology study also judged unacceptable by CDFA (1986c), an adverse effect was noted at the high dose (10,000 ppm) as

hydronephrosis (urine in the kidney) in pups. One female in each of the mid- and high-dose groups (1,000 and 10,000 ppm) had complete resorptions.

In a 1-year interim review of a mouse oncogenicity study, systemic effects such as changes in BUN, SGOT, SGPT, brain weight, and kidney weight were reported as possible systemic toxic effects (EPA, 1987c). Neither the dosage levels administered nor the dosage levels at which toxic effects occurred were reported. A systemic NOEL of 1,000 ppm (25 mg/kg/day) was reported for a 6-month dog feeding study. Increased stomach weight was the only toxic effect noted (Schneider and Kaplan, 1983, as cited in USDA, 1984). A systemic NOEL of 5,000/10,000 ppm (250/500 mg/kg/day) was established for a 90-day rat feeding study with no toxic effects observed (Schneider and Kaplan, 1983, as cited in USDA 1984).

Nonthreshold Effects

Although there are no data available from chronic studies to evaluate the oncogenic potential of fosamine, available evidence from other studies does not indicate that fosamine is carcinogenic. No oncogenic effects were observed in a 1-year interim review of a mouse oncogenicity study (EPA, 1987c) or in a 6-month dog feeding study (USDA, 1984).

Fosamine tested negative for point mutation in two studies with Salmonella typhimurium with and without activation. However, these two studies were deemed unacceptable by the California Department of Food and Agriculture (CDFA, 1986c). An additional test for gene mutation using mammalian cells was considered acceptable. In this study, Chinese hamster ovary cells exhibited no mutagenic effect upon exposure to fosamine with and without rat liver activation (CDFA, 1986c).

In an in vivo cytogenicity assay, rats were orally administered doses of 0, 1,000, 3,000, or 10,000 mg/kg. Fosamine was negative for chromosome breakage at all doses. In an in vitro test with Chinese hamster ovary cells, fosamine was positive for chromosome aberration both with and without activation. Fosamine tested negative for induction of unscheduled DNA synthesis using rat hepatocytes (EPA, 1987c; CDFA, 1986c). The weight

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of evidence reviewed in this risk assessment indicates, particularly because in vivo mammalian assays generally carry more weight than in vitro assays, that fosamine is nonmutagenic.

Glyphosate

Threshold Effects

Based on the acute oral LD₅₀ of 4,320 mg/kg in the rat, glyphosate can be classified as slightly toxic (EPA, 1986f). The dermal LD₅₀ in rabbits for both the Roundup formulation and pure glyphosate is greater than 5,000 mg/kg body weight (Monsanto, 1982). Primary eye and skin irritation data show that technical glyphosate is not a primary skin irritant and is only minimally irritating to the eye (EPA, 1986f).

Glyphosate was less irritating than a standard liquid dishwashing detergent and a general all-purpose cleaner when tested for dermal irritation on 346 human volunteers (Maibach, 1986). In the same study, there was no evidence of the induction of photoirritation and allergic or photoallergic contact dermatitis.

EPA's Pesticide Incident Monitoring System, which is a voluntary reporting system, contains 91 reports of incidents in which humans were exposed to glyphosate. Of those, 49 reports involved humans who had a history of exposure and 39 reports documented some kind of diagnosis being made by a physician or through a poison control center. The primary and most frequent diagnosis was contact dermatitis and conjunctivitis. No fatal cases of human poisoning have been reported (WSSA, 1983).

A 26-month rat feeding study using technical glyphosate reports no oncogenicity at the highest dose tested and a systemic NOEL greater than 31 mg/kg/day (EPA, 1986f). Based on these study results, EPA has established a systemic NOEL of greater than 31 mg/kg/day.

A 2-year chronic/oncogenicity mouse feeding study noted effects on the liver and kidneys in the females at 30,000 ppm. The NOEL for nonneoplastic chronic effects was 5,000 ppm (750 mg/kg/day) (EPA, 1986g).

A 1-year chronic feeding study in dogs tested doses of 0, 20, 100, and 500 mg/kg/day, administered by capsule (EPA 1988d). A NOEL of 500 mg/kg/day was established.

A three-generation reproduction study of glyphosate in rats established a NOEL of 10 mg/kg/day (EPA, 1986f). This NOEL was based on renal tubular dilation in the kidneys of the pups. No effects on fertility or reproductive parameters were noted. In rat and rabbit teratology studies, no evidence of teratogenicity was observed (EPA, 1986f). In the rat study, evidence of developmental toxicity in the form of unossified sternebrae was observed in fetuses at 3,500 mg/kg/day (EPA, 1986f). This dose was also toxic to dams as evidenced by weight gain deficits, altered physical appearance, and mortality. The rat fetotoxic and maternal toxic NOEL's were therefore established at 1,000 mg/kg/day for this study.

In the rabbit teratology study, the highest dose (350 mg/kg/day) was toxic to does as evidenced by altered appearance and mortality (EPA, 1986f). No treatment-related fetal effects were observed. The maternal toxic NOEL for this study was 175 mg/kg/day and the fetotoxic NOEL was greater than 350 mg/kg/day (HDT).

Nonthreshold Effects

Although the available evidence for glyphosate carcinogenicity is equivocal and additional test results are pending, a cancer risk analysis was conducted for glyphosate in this risk assessment. The chronic feeding/oncogenicity study in mice tested dosages of 1,000, 5,000, and 30,000 ppm. Glyphosate produced an equivocal oncogenic response in the mouse causing a slight increase in the incidence of renal tubular adenomas (benign kidney tumors) in males at the highest dose tested of 30,000 ppm. The EPA Toxicology Branch Ad Hoc Oncogenicity Committee tentatively classified glyphosate as a "Class C" oncogen. The studies were reexamined by a consulting pathologist, and data were submitted showing that another kidney tumor had been found in control group males. No renal tumors were found in controls in the original examination (EPA, 1986g).

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EPA then requested that more kidney sections from the mouse study be prepared and examined. The resultant microslides were examined by several pathologists, who found no more tumors but confirmed the presence of the tumors found in the original study. The apparent lesion in the control kidney was not present in any of the additional sections. After examination of the slides, EPA (1986g) concluded that this lesion did not "represent a pathophysiologically significant change."

The apparent oncogenic response, however, was a marginal response at best. The doses tested were high--3 percent of the diet--and the target tissue had no corresponding increase in the incidence of preneoplastic changes, such as hyperplasia or dysplasia. Moreover, because glyphosate was found to be negative in acceptable mutagenicity studies, the compound is not known to be genotoxic (EPA, 1986g).

Because of the equivocal nature of the findings, the EPA Toxicology Branch Ad Hoc Oncogenicity Committee asked the expert assistance of the FIFRA Science Advisory Panel (SAP) in determining the proper weight-of-the-evidence classification for the study. After reviewing all the existing evidence, the SAP proposed that glyphosate be classified as "Class D," or having "inadequate animal evidence of oncogenicity." The principal reason for the panel's assessment was their determination that, after adjusting for the greater survival in the high-dose mice compared to concurrent controls, no statistically significant difference existed. The panel further noted that, although comparison of these findings to historical control incidences yielded a statistically significant result, this finding did not override the lack of significance of comparisons to concurrent controls. The panel determined that the oncogenic potential of glyphosate could not be determined from existing data and proposed that the study be repeated to clarify these equivocal findings (EPA, 1986g).

After considering the expert opinion of the panel and reconsidering all relevant data for this compound, in particular the statistical assessment provided by the panel, EPA agreed that not enough data exist to adequately address the question of whether the apparent effects noted in the mouse study are biologically relevant. Therefore, to fully address this

question, EPA is requiring that this study be repeated with more animals in each test group to increase the statistical power of the study (EPA, 1986g).

Other nonneoplastic changes noted in high-dose male mice included centrilobular hypertrophy and necrosis of hepatocytes, chronic interstitial nephritis, and proximal tubule epithelial cell basophilia and hypertrophy in females. The NOEL for nonneoplastic chronic effects was the mid-dose level of 5,000 ppm. This study is acceptable as a chronic feeding study (EPA, 1986g).

The lifetime feeding study in rats tested dietary concentrations of glyphosate of 0, 30, 100, and 300 ppm. These concentrations were adjusted during the study to maintain actual doses of 0, 3, 10, and 31 mg/kg/day in males and 0, 3, 11, and 34 mg/kg/day in female rats. Thus, the doses tested in the rat chronic study were about 1/100 of those tested in the mouse study. Although no effect of treatment on the incidence of nonneoplastic lesions was noted, a marginal apparent increase in the incidence of interstitial cell tumors of the testes was observed in rats (EPA, 1986g).

Historical controls were used in the weight-of-evidence analysis to show the range of variability in the background spontaneous incidence of any lesion. Historical controls were also used to supplement the data provided by a concurrent control group. Because of the absence of a dose-dependent effect, the lack of preneoplastic changes, the wide variability in the spontaneous incidence of this tumor, the similarity in incidence between the high-dose group and the historical controls, and lack of any evidence of genotoxicity, the analysis concluded that the observed incidence did not show an oncogenic response (EPA, 1986g).

An independent review of the data raised a question of possible thyroid carcinoma in high-dose females. After a review of the slides by a consulting pathologist and a reassessment of all relevant data, including the fact that no effect of treatment on tumor latency or the combined incidences of adenoma and carcinoma was apparent, EPA (1986g) concluded that the data did not show a carcinogenic response in the thyroid.

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In view of the large difference in doses between the rat and mouse studies, the EPA Toxicology Branch Oncogenicity Review Committee speculated that "a toxic, or MTD (Maximally Tolerated Dose), was not reached in [the rat] study," and that at doses "close to an MTD, tumors might have been induced." The rat study was re-reviewed for evidence that the highest dose tested was an MTD. Because no effects of treatment on survival, body weight gain, clinical pathology, or findings of necropsy were noted, no evidence exists that the highest dose tested is an MTD. A repeat rat study is required in which the highest dose tested is an MTD. This study is acceptable as a chronic feeding study because an MTD is not required to satisfy EPA guidelines for chronic toxicity studies. Because an MTD was apparently not reached in this study, it does not fulfill the EPA Guidelines for a rat oncogenicity study (EPA, 1986g).

Glyphosate cancer potency was based on the rate of kidney tumor formation in male mice in the feeding study reported in EPA (1985h). The upper 95-percent limit of the cancer potency of glyphosate calculated from the kidney tumor data was 0.000026 per (mg/kg/day).

The weight of evidence reviewed in this risk assessment indicates that glyphosate does not have mutagenic potential. Glyphosate was nonmutagenic in the CHO gene mutation assay, DNA repair assay with rat hepatocytes, mouse dominant lethal assay, rat and mice host-mediated assay, Ames microbial assay, rec-assay with yeast, reverse mutation assay with bacteria, and in vivo mammalian bone marrow assay (EPA, 1986f).

N-Nitrosoglyphosate

N-Nitroso derivatives of some herbicides are carcinogenic and mutagenic (Young and Khan, 1978; Braun et al., 1977). Little information is available on the formation of these compounds under normal conditions of herbicide application or on their metabolism in soil and water (Greenhalgh, 1978). It has been suggested that the herbicide glyphosate may include N-nitrosoglyphosate (NNG) as a trace contaminant or that the compound may be formed in the environment after herbicidal application (Dost, 1983; Newton et al., 1984). However, EPA has determined that NNG does not occur

as a contaminant in significant enough amounts in the herbicide glyphosate to pose a hazard to human health (Dost, 1983). Newton et al. (1984) found traces of NNG (approximately 0.02 ppm) in one foliage sample and one forest litter sample after aerial application of glyphosate; however, they concluded that this may have been the result of the evaporation procedure used in the analysis.

Nitrosation in soil generally requires elevated nitrite levels and a pH of 3 to 4. Nitrite levels in forest area soils are generally much less than those in agricultural soils. Several studies have been conducted to measure the extent of nitrosation of glyphosate in soil with respect to temperature, pH, and organic matter content (Khan and Young, 1977; Young and Khan, 1978). NNG formed in several types of soil that were treated with glyphosate and nitrite. Levels of 5 ppm of NNG were reached when glyphosate was applied at approximately 185 ppm. This application rate is 90 to 100 times greater than normal rates. No NNG formed at glyphosate concentrations of 5 ppm and nitrite concentrations of 2 ppm. It was concluded that NNG is not likely to form in soils at the recommended application rates of 2.24 kg/ha.

In some herbicides, N-nitrosation has been observed to increase with increased organic matter (OM) content of the soil; however, this has not been found for glyphosate. In fact, NNG formation may be inversely related to OM content. A soil with a 1.1 percent OM content had a much greater degree of nitrosation than a soil with an 18 percent OM content (Khan, 1981).

NNG is persistent in soils. A Fox soil treated with 740 ppm glyphosate had NNG levels of 7 ppm up to 140 days after herbicidal application. The persistence of NNG is dependent on the soil type, organic matter content, clay content, pH, microflora, moisture content, and temperature (Khan, 1981).

Little information is available on the uptake of NNG by plants. It can be absorbed by oat roots when levels of 5 ppm are reached in soils. At levels of 5, 10, and 25 ppm in soil, the following levels were detected in oat

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roots: 4.7, 9.1, and 21.3 ppm, respectively. NNG was detected in the shoots of the plant at concentrations of 4.4 ppm at only the highest soil concentration tested (Khan, 1981).

Glyphosate is readily nitrosated in water. The herbicide is relatively persistent in irrigation waters where nitrite levels may also be elevated due to surface runoff from agricultural lands (Khan, 1981). More information is needed on NNG formation in water with respect to required glyphosate concentrations and pH.

EPA (1986g) has classified NNG as slightly toxic and has concluded that because the amount of NNG in glyphosate is less than 1.0 mg/kg, no additional toxicology data are required. Monsanto (1986) has conducted a number of studies on NNG and has concluded that it is not teratogenic, mutagenic, or oncogenic.

Hexazinone

Threshold Effects

Hexazinone can be classified as slightly toxic based on the acute oral LD₅₀ of 1,690 mg/kg in rats. The dermal LD₅₀ in rabbits is greater than 5,278 mg/kg with slight skin irritation, and the inhalation LC₅₀ in rats is greater than 7.48 mg/L. Data on primary eye irritation indicate that hexazinone is an eye irritant, but primary skin irritation and dermal sensitization studies demonstrate that it is not a skin irritant. The EPA has categorized hexazinone as slightly toxic for acute oral, dermal, and inhalation exposure and for dermal irritation and sensitization. Primary eye irritation for hexazinone is classified as moderate (EPA, 1982c).

The Pesticide Incident Monitoring System data base (EPA, 1981, as cited in EPA, 1987i) indicated that 3 of 43,729 incident reports involved hexazinone. Only one report cited exposure to hexazinone alone, without other compounds involved. A 26-year-old woman inhaled hexazinone dust (concentration not specified). Vomiting occurred within 24 hours. No other effects were reported and no treatment was administered.

Hexazinone

Subchronic 90-day feeding studies with hexazinone have been conducted on both rats and dogs. Hexazinone was fed to 30-day-old male and female rats for 3 months at levels of 0, 200, 1,000, and 5,000 ppm in the diet. The NOEL was set at 1,000 ppm (50 mg/kg/day) (EPA, 1982c). Animals receiving 5,000 ppm hexazinone exhibited body weight gains that were slightly less than those of the control rats and had lower food efficiency values. However, none of the test groups showed other nutritional, clinical, hematological, urinary, or biochemical evidence of toxicity. Histopathological examination of tissues from animals in the 5,000 ppm group showed no evidence of toxicity.

In a subchronic feeding study with dogs, young adult male and female beagles were fed dietary levels of 0, 200, 1,000, and 5,000 ppm of hexazinone (97.5-percent active ingredient) for 3 months. The only clinical sign of toxicity observed was slightly reduced weight gain at 5,000 ppm. At this dietary concentration, the dogs also exhibited significantly elevated alkaline phosphatase activities and lower albumin:globulin ratios; this suggests some injury to the liver. Both male and female dogs at the highest concentration (5,000 ppm) had slightly heavier livers and increased liver-to-body weight ratios than the controls. No histopathological change was observed in the liver or other organs of animals from both the 5,000 ppm and control groups. The NOEL is 1,000 ppm (25 mg/kg/day) (EPA, 1982c).

In a chronic feeding study, male and female rats were fed hexazinone for 2 years at levels of 0, 200, 1,000, and 2,500 ppm. The average body weight gains of males and females receiving dietary levels of 2,500 ppm and of females receiving 1,000 ppm were lower than those of the controls and other test groups. Slightly lower food efficiency values were seen for these groups as was a decreased food consumption for high level male rats (2,500 ppm). There were no clinical signs of toxicity that could be attributed to hexazinone and no meaningful differences among mortality rates for control and test rats. Male rats fed 2,500 ppm hexazinone had significantly higher total leucocyte counts and relative eosinophil counts; male and female rats fed 2,500 ppm hexazinone excreted a more alkaline urine than the controls and other test groups. No significant gross or histopathologic changes

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were observed in any of the test rats that could be attributed to the feeding of hexazinone. The systemic NOEL for this study was 200 ppm (10 mg/kg/day) (EPA, 1982c).

In a 2-year feeding/oncogenicity study with mice, test animals were given hexazinone doses of 200, 2,500, or 10,000 ppm. Liver hypertrophy, liver hyperplastic nodules, and focal necrosis were observed at the 2,500 ppm level. The systemic NOEL for this study was therefore 200 ppm (30 mg/kg/day) (EPA, 1986a).

In a teratology study, pregnant albino rats were fed technical hexazinone from days 6 through 15 of gestation at levels of 0, 200, 1,000, and 5,000 ppm in the diet. All animals were sacrificed on the 21st day of gestation. In the 5,000 ppm group, slightly decreased food consumption and body weight gains of pregnant rats were observed. No adverse effects on the number of implantations, resorptions, live fetuses per litter, and mean weight and crown-rump length of the fetuses were found. No malformation or major abnormalities were noticed in fetuses exposed to the test material. The material was neither embryotoxic nor teratogenic at 5,000 ppm (250 mg/kg/day), the highest level tested (EPA, 1982c).

In another teratology study, female rabbits were artificially inseminated and later dosed with either 0, 20, 50, or 125 mg/kg/day of hexazinone on days 6 through 19 of gestation. The test material, dissolved in 0.5 percent methocel, was administered by gavage. On day 29, the pups were delivered by Cesarean section. The dams and pups were subsequently examined for abnormalities. Only minor differences were noted in the controls and high-dose-group dams with respect to clinical signs and body weight. No dose-dependent gross pathological lesions were noted in dams. No consistent statistical differences between controls and test animals in pregnancy rate, uterine weight, corpora lutea, implantations, fetal viability, or size were reported (EPA, 1982c). There were four incidences of pups with remarkable soft tissue and skeletal abnormalities but the pattern of occurrence did not demonstrate a dose-dependent response. However, the highest dose level showed a higher percentage of fetuses showing abnormality in skeletal development than did controls. Notable

differences included delayed ossification in extremities and also extra ribs. Hexazinone is not considered to be teratogenic at 125 mg/kg/day. The teratogenic NOEL is therefore greater than 125 mg/kg/day (EPA, 1982c). The fetotoxic NOEL for this study was also established as 125 mg/kg/day (EPA, 1986a).

Summary data from a three-generation reproduction study with rats that received 0, 200, 1,000, 2,500 ppm hexazinone in the diet showed no meaningful differences among control and test groups with respect to reproduction and lactation performance. However, the average body weight of the pups at weaning in the group receiving the highest dietary level of hexazinone (2,500 ppm) was slightly lower than those of the controls and other test groups in the F2A and F3A litters. The reproductive NOEL for this study is greater than 2,500 ppm (125 mg/kg/day), and the fetotoxic NOEL is 1,000 ppm (50 mg/kg/day) (EPA, 1982e).

Nonthreshold Effects

Because there is no evidence from animal studies that hexazinone causes cancer, hexazinone is considered to be not carcinogenic in this risk assessment. In the chronic rat feeding study discussed above, no oncogenic effects were observed at the highest dose (EPA, 1986a). In the 2-year feeding/oncogenicity study with mice, no oncogenic effects were observed at the highest dose (EPA, 1986a). EPA has placed hexazinone in Group D: not classifiable as to human carcinogenicity (EPA, 1987i).

Hexazinone was nonmutagenic in the Ames bacterial assays testing five strains of Salmonella typhimurium under activated and nonactivated conditions. In an in vivo rat bone marrow assay, negative responses for chromosomal aberrations were observed at 100, 300, and 1,000 mg/kg. Hexazinone was also negative for unscheduled DNA synthesis in rat hepatocytes. Positive results were obtained both with and without activation in an in vitro Chinese hamster ovary cell assay (EPA, 1986a). This positive effect was observed only at very high levels and could be caused by a secondary effect, such as high ionic concentrations or pH. On

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the weight of this evidence, hexazinone is considered in this risk assessment not to present a mutagenic hazard to humans.

Picloram

Threshold Effects

Based on the acute oral LD₅₀ of 8,200 mg/kg in rats, picloram can be classified as very slightly toxic. Based on the acute dermal LD₅₀ of greater than 4,000 mg/kg in rabbits, picloram is classified as slightly toxic is for acute dermal effects (EPA, 1984h). Human skin sensitization studies have shown that the combination of 2,4-D and picloram is capable of producing sensitizing reactions (USDA, 1984).

In a 14-day study of potassium picloram in rats, no compound-related effects were observed at the highest dose tested of 600 mg/kg/day (Hayes et al., 1986). In a 90-day study, rats were given 60, 190, 600, or 1,070 mg/kg/day of potassium picloram in the drinking water (Hayes et al., 1986). Mild lesions in the kidney were noted at levels up to 1,070 mg/kg/day, and at 190 and 600 mg/kg/day, increased incidence of mononuclear liver foci was noted.

A 6-month dog feeding study, during which test animals were exposed to picloram at the dietary levels of 0, 7, 35, and 175 mg/kg/day, resulted in a chronic NOEL of 7 mg/kg/day. Increased liver weights for males were reported at 35 mg/kg/day. In addition to increased liver weights, decreased levels of liver enzymes were observed at the highest dose tested of 175 mg/kg/day (EPA 1985). In a recent 2-year chronic feeding/oncogenicity study reported by Dow (1987), rats fed 20 mg/kg/day showed no treatment-related effects. Rats given 60 and 200 mg/kg/day exhibited increased size and altered properties of liver cells. No other chronic feeding studies have been reported. EPA has requested a chronic nonrodent feeding study for picloram.

In a 3-generation reproduction study, a NOEL of 50 mg/kg/day was established based on reduced fertility at the highest dose tested of 150

mg/kg/day (1988). In a rat teratology study, maternal toxicity was observed at 1,000 mg/kg/day and fetal toxicity (delayed bone ossification) was observed at all levels which included 500, 750 and 1,000 mg/kg/day (EPA, 1984i). Therefore, the fetotoxic NOEL was less than 500 mg/kg/day in this study. A rabbit teratology study found no dose-related teratogenic or embryotoxic effects at the highest dose of 400 mg/kg/day (John-Greene et al., 1985).

In a 3-generation rat reproduction study reported in EPA (1987L), in which rats were maintained on diets of 0, 7.5, 25, or 75 mg/kg/day, picloram caused reduced fertility at the high dose level. The study NOEL was set at 25 mg/kg/day.

Nonthreshold Effects

Although there is disagreement among experts on the interpretation of studies regarding the potential of picloram to cause cancer and only benign tumors have been definitively associated with increasing picloram doses, a cancer risk analysis was done on picloram for this risk assessment. The early studies were not designed as carcinogenicity assays but rather were lifetime general toxicity evaluations in which observation of tumor formation was incidental. In a study sponsored by the National Cancer Institute, rats were maintained at average dietary concentrations of about 7,437 and 14,875 ppm (approximately 372 and 744 mg/kg/day) picloram in the diet for 80 weeks. The rats were then observed for 33 weeks and sacrificed. Mice were given a diet containing 2,531 ppm and 5,062 ppm (approximately 380 and 759 mg/kg/day) for 80 weeks and observed for 10 weeks. The lifespan is somewhat over 2 years for both species. These studies showed a nonsignificant increase in thyroid tumors in rats but not in mice and a significant increase in benign liver tumors in female rats. EPA has judged the mouse study to be negative and the rat study to be weakly positive. An additional feeding/oncogenicity rat study (Dow 1986) revealed no oncogenic effects at the highest dose of 200 mg/kg/day.

In the study discussed for 2,4-D in which adult female sheep were examined at slaughter, exposure to picolinic acid herbicides (including picloram)

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was also evaluated (Newell et al., 1984). Results showed that exposure to picolinic acids was associated with significantly increased tumor rates of small-intestinal adenocarcinoma. Tumor rate also increased with the total number of picolinic acid sprays used on the farm.

Picloram is currently included with the Group D carcinogens: not classifiable as to human carcinogenicity. The data do not support a contention of carcinogenicity, but an open and valid scientific question exists about the meaning of the nodules or benign tumors of the liver. Therefore, a worst case assumption is made that picloram is carcinogenic (EPA, 1987j).

A 95-percent upper confidence limit on picloram carcinogenicity, calculated by Crump (1983) using the GLOBAL 82 computer program, was 0.00057 per (mg/kg/day). This potency value is used in this risk assessment.

Picloram was nonmutagenic in microbial assay systems and in the rat in vivo cytogenetic assay (USDA, 1984; EPA, 1984h). Picloram was mutagenic in one assay on a previously untested system (USDA, 1984). The test has not been validated for use in the standard battery of tests for mutagenicity. EPA has determined that the positive study was insensitive (i.e. the study design did not permit accurate evaluation for mutagenic potential) (EPA, 1984i). Thus, the weight of evidence indicates that it does not present a mutagenic risk to humans. EPA has requested additional picloram mutagenicity studies.

Picloram Contaminants

Studies have shown that hexachlorobenzene (HCB), a contaminant of picloram, is a carcinogen in several species of rodents. Based on this information, EPA conducted a risk assessment and has estimated the dietary cancer risk to the general public of HCB in the fat and milk of cattle fed picloram-treated grass to be 4.6×10^{-8} to a 70-kg adult and 1.4×10^{-7} to a 10-kg child. These risk estimates are based on 200 ppm of HCB in currently registered technical picloram. EPA has concluded that this risk is acceptable. EPA will impose a maximum limitation of 200 ppm of HCB in

technical picloram and is requiring the registrant to submit a revised confidential statement of formula to reflect this required limit (EPA, 1985i).

Nitrosamine may be a potential contaminant of the various amines used to produce the amine salts of picloram. This chemical is regulated under the rule (45 FR 42854) that requires testing to show that a level of 1 ppm of nitrosamine contamination is not exceeded.

Simazine

Threshold Effects

Based on the acute oral LD₅₀ of greater than 5,000 mg/kg/day in the rat, simazine is classified as very slightly toxic. Based on available data, EPA has classified simazine as very slightly toxic for acute oral and dermal toxicity and as moderately toxic for acute inhalation toxicity and for eye and dermal irritation (EPA, 1983b; EPA, 1987k). A 21-day subacute dermal toxicity study in rabbits at doses of up to 1,000 mg/kg/day produced no systemic toxicity and no dose-related alterations of the skin. The findings of this study indicate a NOEL of more than 1,000 mg/kg/day (EPA, 1983b).

There were 124 cases of contact dermatitis noted by Yelizarov (1977, as cited in EPA, 1987i) in the Soviet Union among workers manufacturing simazine and propazine. Mild cases lasting 3 or 4 days involved pale pink erythema and slight edema. Serious cases lasting 7 to 10 days involved greater erythema and edema and also a vesiculopapular reaction that sometimes progressed to the formation of bullae.

In a 3-week rat feeding study, test animals were given dose levels of 200, 2,000, or 4,000 ppm of technical simazine. At the lowest dose tested, rats exhibited reduced erythrocyte and leucocyte counts and elevated cholesterol and inorganic phosphate levels. The maximum tolerated dose (MTD) was determined to be less than 2,000 ppm (100 mg/kg/day) because this dose seriously affected the nutrition of treated rats. The NOEL was established as less than 200 ppm (10 mg/kg/day) (EPA, 1987k).

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In a 3-week dog feeding study, beagles were also given simazine doses of 200, 2,000, or 4,000 ppm. At the 2,000 ppm (50 mg/kg/day) level, reduced albumin levels, increased globulin levels, and elevated urinary specific gravity and ketone levels were observed. The MTD was also reported as less than 2,000 ppm based on the seriously affected nutrition of treated dogs. The NOEL for this study was set at 200 ppm (5 mg/kg/day) (EPA, 1987k).

In a 22-week feeding study with sheep, adverse effects were observed at the lowest dose tested, 1.4 mg/kg/day (EPA, 1987i). However, because of deficiencies in the study, this NOEL was not used as the lowest NOEL to determine the reference dose. A 2-year chronic rat feeding study showed no dose-related pathological changes at 1, 10, and 100 ppm dose levels (EPA, 1983b, 1987k). Mortality was primarily the result of respiratory infections, with very few males in test and control groups surviving (EPA, 1983b). Histopathologic evaluation was not provided for animals that died during the study (EPA, 1983b). The systemic NOEL for simazine in this study was greater than 100 ppm (5 mg/kg/day) (EPA, 1987k).

A 2-year chronic dog feeding study showed no signs of toxicity from simazine dosages of 15, 150, and 1,500 ppm, except net weight loss at 1,500 ppm and lower weight gain at 150 ppm. Weight gain differences did not occur during the second half of the study. The ages of individual dogs used in the study and individual observation records were lacking. Chronic toxicity could not be determined from this study (EPA, 1983b).

In a rabbit teratology study, New Zealand white rabbits were administered 5, 75, or 200 mg/kg/day simazine by gavage. Doses at the 75 mg/kg/day level exhibited tremors, abortions, and decreased body weight gain and food consumption. At the 200 mg/kg/day level, reduced mean fetal weight and increased skeletal variations were observed. No teratogenic effects were noted at the highest dose tested (200 mg/kg/day). The NOEL's reported for this study were as follows: 5 mg/kg/day for maternal effects, and 75 mg/kg/day for fetotoxic effects, and greater than 200 mg/kg/day for teratogenic effects, (EPA, 1987k).

In a three-generation reproduction study, simazine had no adverse effects on reproductive performance in rats at a dietary level of 100 ppm. The findings of this study indicate a NOEL of greater than 100 ppm (5 mg/kg/day) (EPA, 1983b).

Nonthreshold Effects

Simazine is considered to be not carcinogenic in this risk assessment. The chronic rat and dog feeding studies were not adequate to evaluate the carcinogenic potential of simazine (EPA, 1983b). In an 18-month mouse oncogenicity study, no treatment-related tumor induction was noted at 603 ppm (90.4 mg/kg/day), the highest dose tested (Innes et al., 1969, as cited in USDA, 1984). Another mouse oncogenicity study conducted by IBT was judged invalid (EPA, 1987k). Simazine is therefore placed in Group D: not classifiable as to human carcinogenicity (EPA, 1987i).

Mutagenicity studies for simazine have been reviewed by the California Department of Food and Agriculture (CDFA, 1986d). One study judged acceptable by CDFA reported no adverse effects in an unscheduled DNA synthesis assay with rat hepatocytes. Other studies deemed unacceptable by CDFA indicated negative results for gene mutation in a Salmonella host-mediated assay in mice and an in vitro mouse lymphoma assay, and negative results for chromosome aberration in an in vivo Chinese hamster micronucleus assay. In additional studies reviewed by USDA (1984), simazine was also negative for mutagenicity in microbial assays with E. coli, B. subtilis, Saccharomyces cerevisiae, and Serratia marcescens. A weakly mutagenic response and an increase in dominant lethals resulted from fruit fly (Drosophila melanogaster) feeding studies (USDA, 1984). Simazine was also positive in a sister chromatid exchange assay in human lymphocytes (CDFA, 1986). Thus, the weight of evidence indicates that simazine at worst may present only a slight mutagenic risk to humans.

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Tebuthiuron

Threshold Effects

Based on an acute oral LD₅₀ of 644 mg/kg/day in rats, tebuthiuron can be classified as slightly toxic. The acute dermal LD₅₀ in rabbits is greater than 200 mg/kg/day. Tebuthiuron is not a dermal sensitizer or irritant and causes only slight eye irritation in laboratory animals. Based on available data, tebuthiuron was categorized as very slightly toxic for eye and skin irritation (EPA, 1987e).

In 90-day feeding studies, rats exhibited growth suppression and pancreatic lesions at doses of 2,500 ppm (125 mg/kg/day), and dogs exhibited increased thyroid and spleen weights at 25 mg/kg/day. The NOEL's for these studies were therefore 1,000 ppm (50 mg/kg/day) for rats and 12.5 mg/kg/day for dogs (EPA, 1987e).

In a subchronic dermal toxicity study, rabbits were exposed dermally to 0 or 1,000 mg/kg/day of dry-form technical tebuthiuron, applied to 10 percent of the total body surface area for 21 days, 6 hours per day. No signs of dermal toxicity or deaths were reported. Of the 10 treated animals, 2 showed slight erythema, which cleared by day 7. No systemic effects that could be attributed to dermal exposure were reported (EPA, 1987d).

A teratology study was submitted to EPA but was found to be inadequate to support registration of tebuthiuron. Rats were offered diets containing 0, 600, 1,200, or 1,800 ppm technical tebuthiuron on days 6 to 15 of gestation. No teratogenic effects were reported at the highest dose. However, no detailed analytical data, such as individual dam body weights or individual litter data, were supplied. In addition, the test material was offered in the diet rather than being given by gavage as recommended (EPA, 1987d).

A rabbit teratology study reported a teratogenic NOEL of greater than 25 mg/kg/day (HDT) for technical tebuthiuron (EPA, 1987d). However, this study has not been graded by EPA. Teratology studies for two mammalian species are still required for registration of tebuthiuron (EPA, 1987e).

Sufficient data are available to EPA to satisfy the requirement for a multigeneration reproduction study. Rats were offered diets containing 0, 100, 200, or 400 ppm (0, 5, 10, or 20 mg/kg/day) technical tebuthiuron through two generations of offspring. No adverse effects were reported except that F1 females, in the pre-mating phase, showed a lower rate of body weight gain in the 200 and 400 ppm groups. No adverse effects were reported on reproductive performance at any level. The NOEL for reproductive effects is greater than 400 ppm (20 mg/kg/day). The NOEL for maternal effects is 100 ppm (5.0 mg/kg/day) (EPA, 1987d).

In a three-generation reproduction study that was not reviewed for the registration of tebuthiuron, a reproductive NOEL of less than 400 ppm (20 mg/kg/day) (LDT) was reported for rats. The NOEL was based on decreased body weight of weanling pups (EPA 1987e).

In a chronic toxicity study with dogs, beagles were given technical tebuthiuron by capsule for 1 year at levels of 0, 12.5, 25, or 50 mg/kg/day. Effects included increased liver to body weight ratios in high dose males and females, increased kidney to body weight ratios in high dose females, and increased thyroid to body weight ratios in high dose males. Although there were no adverse histopathological findings for these organs, alanine transaminase and alkaline phosphatase values were significantly increased in the high dose males, as was alanine transaminase in the high dose females. This indicates a significant hepatotoxic effect at this level in both sexes. Increased thrombocyte counts in the high dose males throughout the study appear to be an isolated finding. The NOEL based on these effects is 25 mg/kg/day (EPA, 1987d).

In a 2-year feeding oncogenicity study, rats exhibited growth suppression at 800 ppm (40 mg/kg/day). The systemic NOEL was therefore 400 ppm (20 mg/kg/day). No oncogenic effects were reported at 1,600 ppm (80 mg/kg/day), the highest dose tested (EPA, 1987e). A 2-year feeding/oncogenicity study with mice reported no adverse effects at the highest dose tested, 1,600 ppm (240 mg/kg/day) (EPA, 1987L).

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Nonthreshold Effects

Tebuthiuron is not considered carcinogenic in this risk assessment. A chronic rat and a chronic mouse study were negative for oncogenicity up to 1,000 ppm, the highest tested (EPA, 1987e).

An Ames assay was performed using Salmonella typhimurium at doses of 5 to 5,000 ug/plate with and without activation. None of the tests showed evidence of induction of point mutation in 8 testor strains of S. typhimurium. Technical tebuthiuron was not mutagenic in these assays either with or without metabolic activation (EPA, 1987d). In an in vitro mouse lymphoma assay for the induction of forward mutations, which was sensitive to direct-acting and activation-dependent mutagens, technical tebuthiuron was slightly mutagenic without metabolic activation. Technical tebuthiuron was not mutagenic in activated assays (EPA, 1987d). Tebuthiuron tested negative for mutagenicity in a dominant lethal assay with rats after a single injection of 75 mg/kg/day (EPA, 1987e). The weight of evidence, therefore, indicates that tebuthiuron does not present a risk of heritable mutations.

Triclopyr

Threshold Effects

With an acute oral LD₅₀ ranging from 630 to 729 mg/kg/day in rats, triclopyr can be classified as slightly toxic. In an acute dermal study, no mortalities were observed in rabbits at 2,000 mg/kg, the only dose tested. This classified triclopyr as slightly toxic for acute dermal exposure. Triclopyr caused slight redness in a primary dermal irritation study with rabbits. In a primary eye irritation study, rabbits exhibited slight corneal injury lasting less than 48 hours and slight to moderate conjunctival redness lasting more than 7 days classified triclopyr as moderately toxic for eye irritation (EPA, 1986h).

In a 14-day feeding study, rats were given 30, 100, 200, or 300 mg/kg/day of triclopyr in their diet. Decreased weight gains were observed at 100

Triclopyr

mg/kg/day; thus, the NOEL is 30 mg/kg/day. In a 90-day feeding study, rats were given doses of 0, 3, 10, 30, and 100 mg/kg/day in the diet. At 100 mg/kg/day, rats exhibited decreases in body weight, food consumption, and absolute liver weights. The NOEL for this study was also set at 30 mg/kg/day (EPA, 1986h).

Beagle dogs were given 5, 10, or 20 mg/kg/day of triclopyr in the diet for 228 days. Decreased body weight gain and food consumption, and liver and kidney effects were noted at the lowest dose level (5 mg/kg/day) (EPA, 1986h; USDA, 1984).

In a 6-month feeding study, dogs were administered 0.1, 0.5, or 2.5 mg/kg/day. A slight reduction in kidney excretion, determined by means of PSP dye excretion tests, was observed at 2.5 mg/kg/day. However, because PSP excretion has been deemed inappropriate for establishing a NOEL, EPA has established the NOEL for this study as 2.5 mg/kg/day (DOW, 1985; 40 CFR Part 180 50(84):18485-86, May 1985).

In a 2-year feeding/oncogenicity study, rats were given doses of 3, 10, and 30 mg/kg/day. No effects on hematology, clinical chemistry, or urinalysis were observed at the highest dose tested (EPA, 1986h). In a recent 2-year chronic toxicity/oncogenicity study reported by DOW (1987), no toxicological effects were observed at 3 mg/kg/day. Male rats fed 12 and 36 mg/kg/day had increased relative and absolute kidney weights (Dow, 1987). Because data from this study are inadequate to establish a NOEL, additional data have been requested by EPA (1988f).

In a rat teratology study, test animals were given doses of 0, 50, 100, or 200 mg/kg/day by gavage during days 6 through 15 of gestation. No teratogenic effects were noted at the highest dose tested. Retarded ossification of skull bones was observed at 200 mg/kg/day, and decreased body weight gains and food consumption were found at 50 mg/kg/day in dams. The fetotoxic NOEL was 50 mg/kg/day, and the maternal toxic NOEL was less than 50 mg/kg/day (EPA, 1986h; CDFA 1986g).

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In a three-generation reproduction study, rats were given doses of 0, 3, 10, or 30 mg/kg/day in the diet. No effects were noted at the highest dose tested (EPA, 1986h).

Two rabbit teratology studies were conducted with triclopyr. In one study, rabbits were given 0, 10, or 25 mg/kg/day by gavage during days 6 through 18 of gestation. Reduced body weight values were observed at the 25 mg/kg/day level. The NOEL for this study was established at 10 mg/kg/day. In an additional rabbit teratology study, test animals were given 0, 25, 50, or 100 mg/kg/day by gavage during days 6 through 18 of gestation. Teratogenic effects were not observed in survivors at up to 100 mg/kg/day (HDT). However, because of the high mortality of animals and because no data on teratogenic parameters were reported for animals that died, this study was judged supplementary by EPA and unacceptable by CDFA (EPA, 1986h; CDFA, 1986g).

Nonthreshold Effects

Laboratory evidence is equivocal on triclopyr's carcinogenicity; in this risk assessment, triclopyr is considered to be possibly carcinogenic. No oncogenic effects were observed at all levels tested (24, 80, or 240 ppm) in a mouse oncogenicity study on triclopyr (40 CFR Part 180 50(84):18485-86, May 1, 1985). No oncogenic effects were observed in rats in a feeding/oncogenicity study with doses of up to 30 mg/kg/day (EPA, 1986h). A recent 2-year chronic toxicity-oncogenicity study in rats, submitted in response to EPA's request for a repeat rat oncogenicity study (Dow, 1987), showed a statistically significant increase in mammary tumors when the number of adenomas (1) and adenocarcinomas (4) were combined for high dose females (36 mg/kg/day) (Dow, 1987). However, the researchers reported that the incidence was within a range of historical controls and the statistical result was partially because of the low incidence (0) in control rats. Because tumor data were not available, no quantitative cancer risk analysis was performed on triclopyr.

Triclopyr was negative for gene mutation in two Ames assays, with and without activation, using several strains of Salmonella typhimurium and in

a host-mediated assay in mice using Salmonella and Saccharomyces. Negative results were reported for a dominant lethal assay in mice at dietary levels of 0, 3, 15, and 70 mg/kg/day. However, in a dominant lethal assay with rats, weak positive effects were observed. Dosage levels were 0.7, 7, and 70 mg/kg/day by gavage. A trend toward increase in resorptions was found at the 7 and 70 mg/kg/day dose levels. In an in vivo cytogenic assay in rats, negative results were obtained. Doses administered were 0.7, 7, and 70 mg/kg/day either as a single dose or daily for 5 days. Triclopyr was also negative in a recombination repair assay with B. subtilis using concentrations of 20 to 2,000 ug/disk (EPA, 1986h). Based on the weight of evidence, triclopyr may be mutagenic in some test systems, but it presents only a slight mutagenic risk to humans.

TOXICITY DATA GAPS

The registration process for herbicides, conducted by EPA under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), requires pesticide manufacturers to submit toxicology studies in support of registration of their product. Table 3-5 indicates what EPA considers to be toxicity data gaps for the 16 herbicides, either because a particular study has not been submitted, because submitted studies are not considered adequate according to current EPA guidelines, or because a study is still undergoing review. Although registration or reregistration of a herbicide under FIFRA requires these gaps to be filled, in most instances data are available in studies already reviewed by EPA or from other sources to characterize the toxic endpoints of concern for these herbicides so that their risks can be assessed for the purposes of this document. Data gaps identified by the California Department of Food and Agriculture for toxicity information on the selected herbicides are summarized in table 3-6.

In addition, for studies still undergoing review (table 3-5), preliminary findings were often available for use in this risk assessment. Where EPA requires two or more studies for a specified toxic endpoint (such as chronic toxicity, oncogenicity, and teratogenicity), the existing data base may be sufficient to use in the risk assessment based on the studies that have been completed. For example, EPA requires cancer (oncogenicity)

Table 3-6--CDFA Herbicide Data Gaps

Data Gaps	Amitrole	Asulam	Atrazine	Bromacil	2,4-D	Dalapon	Dicamba
Chronic							
Rat	X ^a	X ^a		X ^a		X	X
Dog	X	X	X	X	X	X	X
Oncogenic							
Rat	X ^a	X ^a		X ^a		X	X
Mouse	X	X	X	X	X	X	X
Reproduction							
Rat	X	X	X	X		X	X
Dog						X	
Teratogenic							
Rat		X	X	X	X	X	
Rabbit		X	X	X	X	X	X
Mouse							
Gene mutation	X	X	X	X		X	
Chromosome	X	X	X	X	X	X	X
DNA damage	X	X	X	X	X	X	
Neurotox	NR		NR	NR	NR	NR	NR

^aCombined chronic and oncogenic study

NR = Study not required.

Table 3-6 (continued)--CDFA Herbicide Data Gaps

Data Gaps	Diuron	Fosamine	Glyphosate	Picloram	Simazine	Triclopyr
Chronic						
Rat	X ^a	X	X		X	X ^a
Dog	X	X		X	X	X
Oncogenic						
Rat	X ^a	X	X		X	X ^a
Mouse	X	X		X	X	X
Reproduction						
Rat	X	X	X	X	X	X
Dog						
Teratogenic						
Rat	X	X		X	X	
Rabbit	X	X		X		X
Mouse	X					
Gene mutation				X	X	
Chromosome				X	X	
DNA damage	X	X	X	X		
Neurotox	NR	NR	NR	NR	NR	NR

^aCombined chronic and oncogenic study

NR = Study not required.

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studies on two rodents--the rat and mouse--although data on just one of these species are sufficient to determine a cancer potency. The following discussion describes how the existing data were used in the risk assessment.

Amitrole

According to the amitrole registration standard (EPA, 1983c), EPA has identified primary skin irritation and dermal sensitization studies as amitrole toxicity data gaps. EPA considers 90-day dermal, 90-day inhalation, and teratogenicity study requirements to be only partially satisfied with the current studies. There is no acute delayed neurotoxicity study on amitrole, however, EPA indicates that this study is not required because amitrole "is not structurally related to a known neurotoxin nor does it inhibit cholinesterase" (EPA, 1983c).

Amitrole did show transitory skin irritation in the acute dermal toxicity study on rabbits (EPA, 1983c). It is assumed in this risk assessment that amitrole may cause skin irritation and dermal sensitization in exposed humans not wearing protective clothing. Data requirements for 90-day inhalation and 90-day dermal studies were waived according to the EPA tox one-liner on amitrole (EPA, 1986i).

A subchronic inhalation study (21 days) showed enlarged thyroids in rats at 0.1 mg/L (LDT). The 90-day inhalation study is not considered a data gap for this risk assessment. No separate inhalation risk analysis is conducted because amitrole is not considered a lung toxicant (effects on thyroid were the same as in oral exposures).

The amitrole NOEL for teratogenicity (4 mg/kg/day) is based on the rabbit teratology study reviewed in CDFA (1986e).

The 90-day dermal study is not considered a data gap because EPA appears to have waived that requirement, dermal penetration of amitrole is low (0.1 percent), and human doses by all routes (dermal, inhalation, oral) are added in the risk assessment for comparison with doses from chronic studies.

Asulam

The chronic systemic NOEL of 50 mg/kg/day used in this risk assessment was based on a 107-week rat study (EPA, 1985c), and asulam's cancer potency was based on increased thyroid cell carcinomas in a rat study (EPA, 1985c). EPA considers mutagenicity studies a data gap for asulam; however, no indication of mutagenic effects was found in bacteria and mouse assays on asulam according to EPA (1985b). Thus, asulam is not considered to pose a risk of germ cell mutagenicity in this risk assessment. In addition, a teratology study in rats and a chronic feeding study in dogs have been listed by EPA (1988g) as data gaps.

Atrazine

The risk assessment bases the systemic NOEL for atrazine of 15 ppm (0.48 mg/kg/day) on a 2-year dog-feeding study reviewed by EPA (1986j). The reproductive NOEL of 1 mg/kg/day is based on a rabbit teratology study (EPA, 1987f). The cancer potency of atrazine is based on interim results of a 2-year study on rats. Atrazine is considered mutagenic in this risk assessment based on positive test results in assays on microbial systems, mouse bone marrow cells, and human cells.

Bromacil

According to EPA (1988h), there are no existing data gaps for bromacil. This risk assessment bases the chronic NOEL on a dog feeding study reported in EPA (1986b) and in CDFA (1986h). Bromacil's cancer potency is based on a 2-year mouse feeding study reported in EPA (1986b). The reproductive NOEL (12.5 mg/kg) was based on a 3-generation reproduction study in rats.

2,4-D

According to EPA (1988i), existing data gaps include a chronic feeding study in dogs, and a teratology study in rabbits. In addition, EPA considers mutagenicity studies to be a data gap for 2,4-D. The mutagenic potential of 2,4-D is judged in this risk assessment based on studies

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reported by Anderson et al. (1972), styles (1973), Vogel and Chandler (1974), Magnusson et al. (1977), Rassmussen and Svalilin (1978) and reviews by WHO (1984) and Newton and Dost (1981). This risk assessment bases 2,4-D's cancer potency on the rate of tumor formation in rats reported by Hansen et al. (1971). The systemic NOEL (1.0 mg/kg/day) from a 2-year rat study was used in this analysis. A reproductive NOEL of 5.0 mg/kg/day from a multigeneration rat study was used in this analysis.

2,4-DP

EPA has indicated that data gaps exist for 2,4-DP studies on acute dermal toxicity, primary eye irritation, skin irritation, skin sensitization, and acute inhalation toxicity (Whang Phang, Toxicology Branch, personal communication, January 7, 1988). Data gaps also exist for a subchronic 90-day nonrodent feeding study, a 21-day subchronic dermal toxicity study, teratogenicity studies and mutagenicity studies. None of the studies is considered necessary to evaluate general health or reproductive effects in this risk assessment. Requirements for oncogenicity testing have been waived.

Dalapon

EPA (1988j) reports that data gaps for dalapon include a chronic feeding study in rats, a chronic feeding study in dogs, a reproduction study in rats, and teratology studies in rats and rabbits. CDFA (1986b) reported negative mutagenicity assays for dalapon, so it was considered not mutagenic in this risk assessment. Dalapon is considered to pose a risk of skin irritation, eye irritation, and skin sensitization in this risk assessment because of those data gaps. Acute toxicity in the risk assessment is based on oral studies so the acute dermal study is not considered a data gap. There is no indication that dalapon is a specific lung toxicant or that it poses a risk of high doses via inhalation; therefore, the inhalation study is not considered a data gap for this risk assessment. The systemic NOEL for dalapon used in this risk assessment (8 mg/kg/day) was established in a chronic rat feeding study as cited by EPA (1984f); however, an additional chronic feeding study in rats must be

completed to fulfill EPA requirements. The teratogenic NOEL of 12.5 used in this risk assessment was established in a dog teratology study. To meet EPA requirements a rabbit teratology study must be performed, and teratology and reproduction studies in rats must be performed in addition to the previously existing studies. Dalapon was not considered oncogenic in this risk assessment based on negative findings in a 2-year rat feeding study and a 52-week dog feeding study reported in USDA (1984) and a 2-year mouse oncogenicity study reported in CDFA (1986b). No oncogenicity studies have fulfilled requirements of EPA; therefore, oncogenicity study in rats and mice must be completed.

Dicamba

EPA has indicated that a 21-day dermal study and a mouse oncogenicity study are data gaps for dicamba (table 3-5). Results of the 21-day dermal study are not considered necessary for the human health risk assessment because a more conservative approach is used by relying on chronic feeding studies. Benchmark toxicity levels (NOEL's) for risk comparison are normally set from these chronic studies at much lower doses than those tested in the dermal studies. Dicamba is considered not oncogenic for this risk assessment because of negative results in a recent 2-year rat study reported by EPA (1986e) and in older 2-year rat and 2-year dog feeding studies that were negative (EPA, 1986f), although these latter studies are considered inadequate by EPA (1986f).

Diuron

EPA (1983a) indicates that acute inhalation (LC_{50}), dermal sensitization, oncogenicity, mutagenicity, and teratogenicity studies are data gaps for diuron. An additional reproduction study in rats must also be performed due to an undetermined NOEL in the existing reproduction study. The risk assessment assumes that diuron may be a skin sensitizer but that dermal effects should not be severe based on only slight erythema and edema seen in acute dermal irritation studies and a dermal LD_{50} of greater than 10,000 mg/kg. EPA's Office of Drinking Water Health Advisory on Diuron (August 1987) indicates that diuron is in Group D: not classified

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(substances with inadequate animal evidence of carcinogenicity). Diuron therefore was not considered carcinogenic in the risk assessment and no cancer risk analysis was done.

The risk assessment assumes that diuron may be mutagenic because of the mutagenicity data gaps. The lowest NOEL for reproductive/developmental effects used in the risk assessment was 6.25 mg/kg/day from a 3-generation rat reproduction study; however, because this dosage level was the only dose tested, EPA has requested that an additional study be performed.

Fosamine

EPA (1987n) has indicated that no chronic data base exists for fosamine, although a chronic mouse study is currently under review. The risk assessment bases fosamine's systemic NOEL on a 6-month study in dogs reported in USDA (1984). The reproductive NOEL is based on a rat teratology study reported by CDFA (1986c). Fosamine is considered noncarcinogenic based on negative results in the 6-month dog study and negative interim results from a 2-year mouse study. Fosamine is considered nonmutagenic based on negative assays reviewed in CDFA (1986c) and EPA (1987c).

Glyphosate

According to EPA (1988K), oncogenicity studies are required with rats and mice. Although both studies have been submitted, EPA has requested additional studies due to equivocal evidence of oncogenicity in the mouse study and a supplementary rating in the rat study.

Hexazinone

According to EPA (1981L), a chronic dog study is the only existing data gap for hexazinone.

Picloram

An acute inhalation study and mutagenicity studies are considered data gaps for picloram. The systemic NOEL for picloram of 7 mg/kg/day was based on a 6-month dog feeding study reported by Mullison (1985) and EPA (1985i), while a recent rat study reported by Dow (1987) gave a systemic NOEL of 20 mg/kg/day. The reproductive NOEL of 50 mg/kg/day was based on a three-generation rat reproduction study (EPA, 1984i): however, due to the supplemental rating of this study, it must be repeated. A rabbit teratology study is considered a data gap by EPA (1988m) for picloram. Picloram is considered carcinogenic in this risk assessment because of liver tumors produced in female rats (NCI, 1978). Although an oncogenicity study in rats has been previously submitted, EPA has requested that an additional study be performed due to a supplementary rating of the previous study (EPA 1988m). Picloram is considered nonmutagenic based on negative results in microbial and rat bone marrow assays (USDA, 1984).

Simazine

EPA considers the rat and dog chronic studies, rat and mouse oncogenicity studies, and a rabbit teratology study to be data gaps for simazine. The systemic NOEL for simazine (5 mg/kg/day) was based on a 21-day rat and dog feeding study reported by EPA (1987k). The reproductive NOEL of 5 mg/kg/day was based on a rabbit teratology study (EPA, 1987k); however, EPA has requested that this study be repeated due to a supplemental rating. The inhalation study is not considered necessary for the risk assessment. Simazine is not considered oncogenic in this risk assessment based on negative results in an oncogenicity study reported in EPA (1984j). Additional oncogenicity studies have been requested by EPA (1980).

Tebuthiuron

According to the tebuthiuron registration standard (EPA, 1987n), EPA considers acute oral (rate), acute dermal, eye irritation (rabbit), dermal irritation (rabbit), dermal sensitization (guinea pig), chronic toxicity (rodent), and teratology (rat) studies to be data gaps for tebuthiuron.

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The chronic rat and rat teratology studies, previously submitted to EPA, must be repeated due to supplemental ratings. The NOEL of 12.5 mg/kg/day for systemic effects is based on a 90-day dog feeding study. The reproductive NOEL of 5 mg/kg/day is based on a 2-generation study in rats.

Triclopyr

EPA (1987n) indicates that data gaps for triclopyr have not yet been identified. EPA reported a triclopyr systemic NOEL of 2.5 mg/kg/day (40 CFR Part 180 50(84):18485-86, May 1, 1985). A reproductive NOEL of 10 mg/kg/day used in this risk assessment was based on a rabbit teratology study (EPA, 1986h). Triclopyr is assumed to be possibly carcinogenic in the risk assessment but tumor data from the rat study that showed benign tumors (DOW, 1987) were not available to evaluate cancer risk. Triclopyr is also assumed to present a slight mutagenic risk to humans based on positive results in a dominant lethal assay.

Neurotoxicity and Immunotoxicity

Tests of neurotoxicity and immunotoxicity were not considered significant data gaps for the assessment of human health risks in this risk assessment. Because of the difficulty in extrapolating data from cellular or animal models to humans, neurotoxicological and immunotoxicological studies are not normally used by toxicologists to establish NOEL's for regulatory purposes (NRC, 1986). EPA does not require these tests in routine registration testing unless other toxicity tests or information on exposed humans indicates that these tests are warranted.

Except for 2,4-D, none of the herbicides has been suspected of causing neurotoxic effects. Dicamba has been tested for neurotoxic effects with negative results. Peripheral neuropathy has been reported as a result of 2,4-D exposure, but studies in rats showed no neuropathology. None of the 16 herbicides has been shown to cause immunotoxic effects.

TOXICITY OF INERT INGREDIENTS AND HERBICIDE CARRIERS

Petroleum Distillates (Diesel Oil and Kerosene)

Threshold Effects

Using an acute oral LD₅₀ of 9.0 mL/kg (7,380 mg/kg) (1 milliliter of diesel oil weighs 820 milligrams), diesel oil is classified as a very slightly toxic compound (Beck et al., 1982). The most marked acute toxic effect observed after the administration of diesel oil to test animals occurred during primary dermal irritation studies (Beck et al., 1982). In these studies, a single exposure of rabbits to diesel oil resulted in a rating of "extremely irritating," based on a score of 6.82 (on a scale of 1 to 10). The irritation may have been caused by additives for internal combustion in diesel oil. Diesel oil was nonirritating in primary eye irritation studies (Beck et al., 1982). A subacute 3-week dermal study of eight rabbits reported an average weight loss of 0.38 kg at the dose level of 4.0 mL/kg (3,280 mg/kg) and an average weight loss of 0.55 kg with a 67-percent mortality rate at the dose level of 8.0 mL/kg (6,560 mg/kg) (Beck et al., 1982). An inhalation teratology study in which rats were exposed to 5.09 or 20.075 uL/kg of diesel fuel on days 6 through 15 of gestation did not result in any significant teratogenic effects (Mecler and Beliles, 1979).

Kerosene is classified as very slightly toxic, based on the lowest oral lethal dose of 28,000 mg/kg/day in rats (HSDB, 1987a). Kerosene and all other hydrocarbons represent an acute ingestion hazard to humans. They can lead to chemical pneumonia and should never be swallowed (HSDB, 1987a). Chemical pneumonitis from hydrocarbons, such as kerosene, is described in Doull et al. (1980) as follows:

An important toxicologic problem associated with the hydrocarbon solvents is the inadvertent or intentional ingestion of gasoline, kerosene, or paint thinners. Although in most instances the acute toxicity of these compounds is quite low, small amounts may be aspirated into the lungs

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during ingestion, during attempts to induce vomiting, or while pumping the stomach. The response of the lung to small quantities of hydrocarbon solvents is rapid and severe. Relatively small amounts will spread a thin layer over the large moist surfaces of the lung resulting in pneumonitis, pulmonary edema, and hemorrhage.

Kerosene causes moderate local irritation, central nervous system depression, and sometimes mild lesions in the kidneys, liver, bone marrow, and spleen (Gosselin, 1976, as cited in HSDB, 1987a). In a 28-day dermal toxicity study with rabbits, kerosene was moderately irritating at the 200 and 1,000 mg/kg/day dose levels and was severely irritating at the 2,000 mg/kg/day dose level (American Petroleum Institute, 1983a). Treatment-related skin lesions (acanthotic dermatitis, hyperkeratosis, and dermal microabscesses) and liver lesions (acute multifocal necrosis) occurred at the highest dose (2,000 mg/kg/day). Jet fuel A (a type of kerosene) was mildly irritating to the skin and eyes of rabbits in primary skin and eye studies. No reactions were observed for guinea pigs used in the same studies (Beck et al., 1982). Rats exposed to 300 mg/m³ for 14 to 75 weeks exhibited morphologic changes (such as thickening, congestion, and presence of infiltrates) and cytoenzymatic changes (increased/decreased enzyme activity) in the lungs and kidneys and showed disorders of their acid-base equilibrium (Starek and Kaminski, 1981 and 1982).

In a study in which baboons were administered kerosene by various routes, the primate brain appears to be resistant to direct toxic effects of kerosene (Wolfsdorf and Paed, 1976). The authors believe this shows that the lung and liver are able to filter out sufficient amounts of large doses to protect the brain. Jet fuel A was not reported to be teratogenic in a rat inhalation study at the highest dose tested (400 ppm) (Beliles and Mecler, 1982).

Nonthreshold Effects

Diesel oil was nonmutagenic when tested with and without metabolic activation in the Ames assay and the mouse lymphoma assay. However, it was

found to be clastogenic (causing chromosomal breaks) in rat bone marrow cells (Conaway et al., 1982). Kerosene was nonmutagenic when tested with and without metabolic activation in the Ames assay, the mouse lymphoma assay, and the rat bone marrow cell assay (Conaway et. al., 1982). However, because diesel oil and kerosene contain polycyclic aromatic hydrocarbons (PAH's) and other constituents that are known or suspected mutagens, they are considered to be mutagens for this risk assessment.

The oncogenic potential of petroleum fuels is directly related to refinery processing methods used to obtain the petroleum product and the crude oil composition from which the fuel was derived. An evaluation of the composition of petroleum fuels has revealed that a positive correlation exists between PAH content and carcinogenicity in human epidemiology studies or experimental laboratory studies (Bingham et al., 1979).

Diesel fuel is usually a straight-run distillation product composed of a complex variable mixture of hydrocarbons with a boiling point range of 175 to 370 °C (DOE, 1983). Although the aromatic content ranges up to 35 percent, few of them are polycyclic compounds. Diesel fuel has not been shown to be carcinogenic. In a 2-year oncogenic skin painting study, which was terminated after 62 weeks because of the presence of extensive skin lesions, Swiss Epley mice were exposed to 0.05 mL (41 mg) of diesel fuel products. Skin carcinomas were found in 2 of 50 animals, which was not statistically significant by chi-square analysis (American Petroleum Institute, 1983b).

Kerosene is a straight-run distillation product with a boiling point range of 175 to 325 °C (HSDB, 1987a) and an aromatic content of 18 percent (Conaway et al., 1982). Higher boiling point (greater than 370 °C) petroleum products that are subjected to additional refinement processes, such as cracking or hydrogenation, and that contain polycyclic aromatics may be carcinogenic to experimental animals (Bingham et al., 1979).

Specific substances that are known or suspected of being carcinogenic, which are contained in diesel oil and kerosene in small amounts, include benzo(a)pyrene and benzene (Bingham et al., 1979). Benzo(a)pyrene (BaP), a

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potent carcinogen, is a PAH that also occurs at low levels in foods and in products of combustion, including cigarette smoke (Bingham et al., 1979). Bioassays indicate that the concentration of this single carcinogen can often serve as a guide in predicting carcinogenic potency, although other substances are also known to be involved (Bingham et al., 1979). There is sufficient evidence to conclude that BaP is carcinogenic in experimental animals: BaP has incited tumors in all of the nine species for which data have been reported, despite the use of different methods of administration (U.S. Department of Health and Human Services (DHHS), 1985). These studies reported both local and systemic carcinogenic effects.

For benzene, another aromatic hydrocarbon known to be present in petroleum fuels, there is sufficient evidence to indicate that it is carcinogenic in experimental animals and in humans (DHHS, 1985). Benzene has been shown to cause leukemia in chronically exposed workers (DHHS, 1985).

Because of the carcinogenicity of the aromatic hydrocarbons found in diesel fuel and kerosene, these light fuel oils are considered carcinogenic for this risk assessment.

The carcinogenic potencies of diesel oil and kerosene have been estimated for this risk assessment based on the potencies of both benzene and BaP. EPA (1986p) has estimated the carcinogenic potency of BaP as 11.5 per (mg/kg/day).

The carcinogenic potency of benzene, however, is much less than that of BaP. EPA has estimated the carcinogenic potency of benzene as 0.0445 per (mg/kg/day) (EPA, 1986).

Samples of diesel oil and fuel oil have been found to have a BaP content of only 0.026 ppm, but No. 2 heating oil (which may be subjected to cracking, rather than being a straight-run distillation product) can contain 600 ppb (Bingham et al., 1979). The midpoint of this concentration range (313 ppb) has been used to calculate the carcinogenic potency of diesel oil, although most diesel fuels can be expected to have a lower BaP content. The content of benzene in diesel fuel was assumed to be 28.5 ppm, based on analysis of

water extracts of No. 2 fuel oil by Anderson (1975), with corrections for solubility relationships. The resulting estimate of carcinogenic potencies of diesel oil and kerosene are both 0.0000049 per (mg/kg/day). Seventy-four percent of this potency is a result of the BaP component.

Formaldehyde

Threshold Effects

Based on an acute oral LD₅₀ for rats of 800 mg/kg, formaldehyde can be classified as a slightly toxic pesticide (RTECS, 1987). Other reported LD₅₀'s are 270 mg/kg/day for guinea pigs; 42 and 660 mg/kg/day for mice (RTECS, 1987; HSDB, 1987b).

Occupational exposure limits have been set for formaldehyde by several authorities. Exposure to formaldehyde used as an indoor fumigant, for example, in egg handling facilities and hospitals, is currently limited by EPA to 3 ppm (EPA, 1986o). The Occupational Safety and Health Administration (OSHA) has also set a limit of 3 ppm as an 8-hour time-weighted average, but a level of 1.0 or 1.5 ppm was proposed December 10, 1985, in 50 FR 50412. The exposure limit (TLV) currently specified by the American Conference of Governmental Industrial Hygienists is 1 ppm, as a time-weighted average.

Studies of the toxic effects of formaldehyde have been reviewed by the International Agency for Cancer Research (IARC, 1982) and by EPA during the preparation of the "Draft Guidance for the Reregistration of Products Containing Formaldehyde and Paraformaldehyde" (EPA, 1986o). The following paragraphs summarize some of the information and conclusions presented in those reviews.

The acute toxic effects of formaldehyde for humans include irritation of the eyes, nose, and throat leading to lachrymation (tearing), sneezing, shortness of breath, sleeplessness, tight chest, nausea, and excess phlegm. At a concentration of 0.1 to 3 ppm, most people experience irritation of the eyes, nose, and throat. (For comparison, the maximum

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concentration of formaldehyde in air in an area treated for grasshopper control will be less than 0.024 ppm.) Many people cannot tolerate exposure to 4 to 5 ppm over an extended period of time. More severe symptoms, including difficulty in breathing, are encountered if concentrations are 10 to 20 ppm. Serious injury to the respiratory tract may occur at concentrations greater than 50 ppm. However, at concentrations comparable to those that could occur as a result of grasshopper control (0.03 ppm), no irritation or other effects were observed (Weber-Tschopp et al., 1977).

Formaldehyde has been shown experimentally to be a potent allergen in humans. About 8 percent of male subjects exhibited skin sensitization after repeated occlusive applications of 1.8 or 3.7 percent formaldehyde for 3.5 weeks, and then an application of 1 percent 2 weeks later (Marzulli and Maibach, 1973). About 4 percent of the subjects in another study had allergic reactions to 0.8 percent formaldehyde applied under an occlusive patch (Rudner et al., 1973). Experiments indicate that most sensitized subjects can tolerate 0.003 percent formaldehyde solution applied to the armpit, but tests using occlusive patches indicate a greater sensitivity: one out of five sensitized subjects reacted to concentrations as low as 0.004 percent (Jordan et al., 1979; Marzulli and Maibach, 1973).

Inhalation studies in animals and epidemiological studies in workers have not demonstrated teratogenic effects. However, these studies were not considered adequate by EPA, and additional studies have been requested (EPA, 1986o). A reproductive study showed prolonged diestrus but no impairment of reproductive function. The reproductive study also was considered inadequate by EPA, and a two generation rat reproduction study has been requested.

The effects of chronic exposure to formaldehyde include respiratory impairment and dermatitis.

Nonthreshold Effects

EPA has classified formaldehyde as a probable human carcinogen (EPA, 1986o). It has been placed in Group B₁, which indicates sufficient

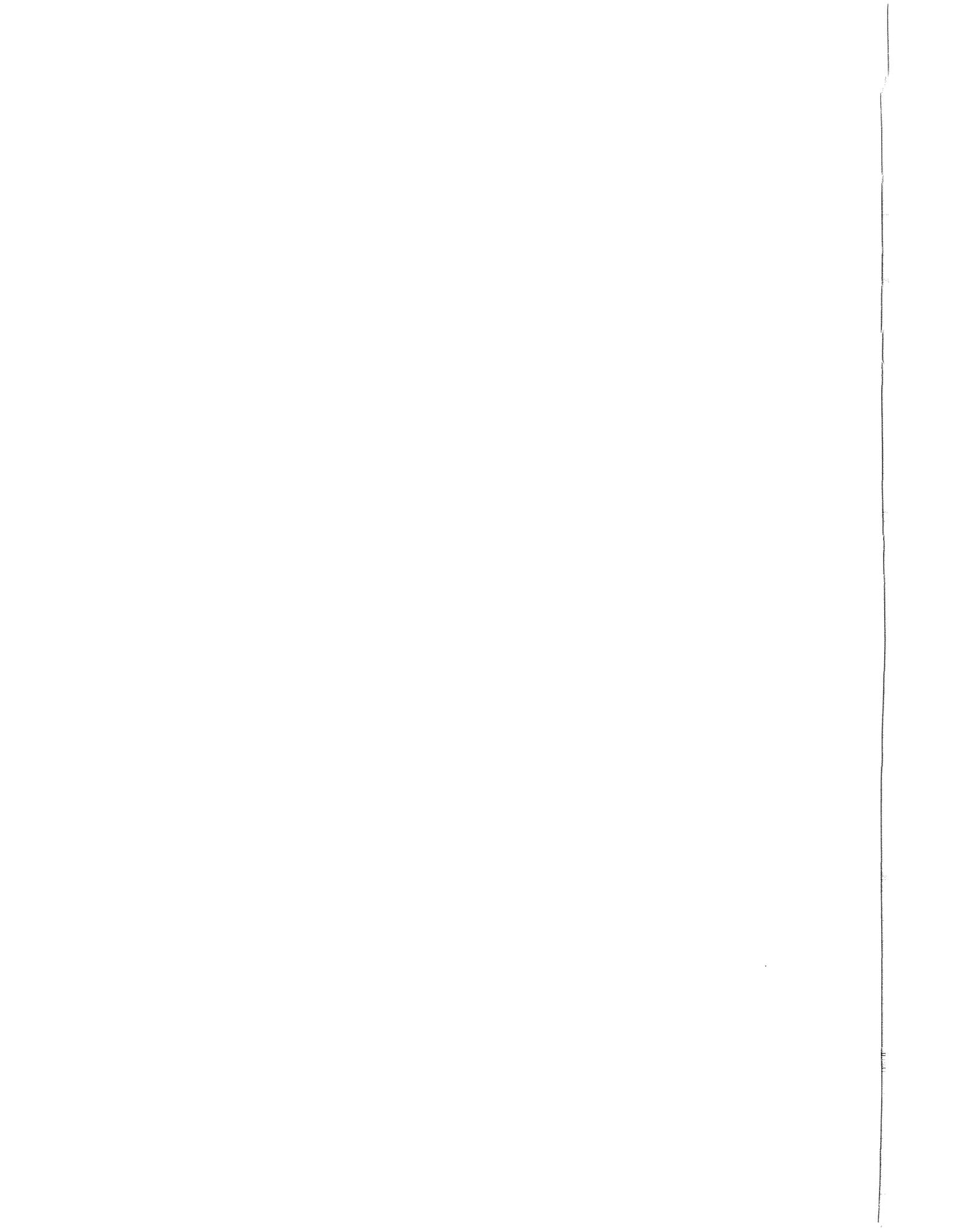
Formaldehyde

evidence of carcinogenicity of a substance in experimental animals and limited evidence of carcinogenicity in humans. Formaldehyde has been found to be carcinogenic by inhalation in two strains of rats, and there is evidence of potential carcinogenicity in mice (EPA, 1986o). There is also evidence that formaldehyde may promote tumor formation when administered in drinking water to rats (EPA, 1986o).

EPA (1986o) has reviewed 28 epidemiological studies of formaldehyde exposure and found that formaldehyde may be a human carcinogen, but the evidence was classified as limited because exposures to multiple chemicals may confound the findings of excess cancers.

EPA (1986o) calculated a unit cancer risk of 1.3×10^{-5} corresponding to an exposure of 1 ug/m^3 of formaldehyde over a 70-year period. EPA (1986o) also calculated the corresponding cancer risk for agricultural workers subject to high exposure levels of formaldehyde used as a preservative in agricultural pesticides. Assuming 0.3 percent formaldehyde in the formulation, a 40 year worklife, and exposure from mixing, loading, one boom sprayer application, and 4 airblast sprayer applications per year, the cancer risk was estimated not to exceed 1 in 1 million (1×10^{-6}). The risk is primarily because of dermal exposure. The risk from the inhalation component was estimated to be in the range of 1 chance in 10^{-7} to 10^{-8} .

Data from mutagenicity tests of formaldehyde were reviewed by the Consensus Workshop on Formaldehyde. They concluded that formaldehyde acts as a weak mutagen. However, none of these data are acceptable to EPA for regulatory purposes (EPA, 1986o). EPA has requested gene mutation, structural chromosomal aberration, and other genotoxicity tests.

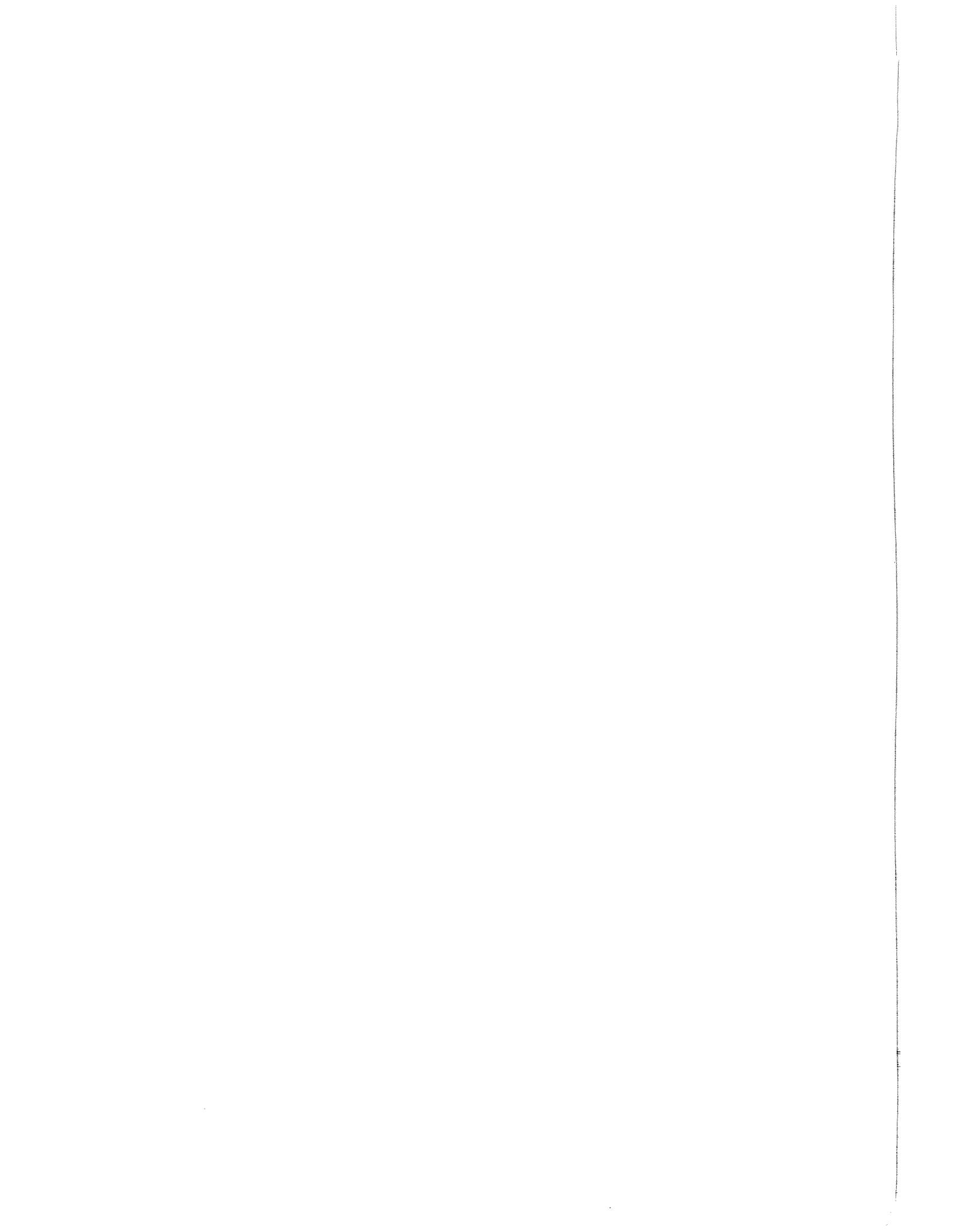


Appendix D

**Human Health
Risk Assessment
(Quantitative)**



Section 4



Section 4

EXPOSURE ANALYSIS

INTRODUCTION

This section presents the methods and results of the herbicide exposure analysis. The first subsection contains the basic background information used in defining the exposure analysis methods. The terminology of herbicide use and the potential human exposure from that use are discussed.

The second subsection presents the methods used to estimate herbicide doses to workers and members of the general public. The methods used for determining lifetime doses to workers and the public to evaluate the risk of cancer are described. The second subsection also discusses the populations at risk in the vegetation management programs.

The third subsection gives the results of the routine and accidental dose calculations for workers and the public for each herbicide and the results of the lifetime dose estimation.

Some Helpful Terms

This subsection defines some of the terms used in the discussion of the exposure analysis methods and explains the relationship between the doses estimated in the analysis and the doses that might actually occur in future herbicide treatment operations. Other terms may be found in the Glossary.

Herbicide Characteristics

Most herbicides are packaged and sold by the manufacturer in liquid form as a concentrate with a specified number of pounds of active ingredient, usually between 1 and 10, per gallon of concentrate and with inert ingredients forming the remaining portion. Many of the herbicides also are marketed in the form of wettable powder and granular formulations.

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Before herbicides are applied, they are mixed with a carrier, usually water, according to the manufacturer's label instructions for the particular treatment purpose and the desired application rate in pounds of active ingredient per acre. The amount of concentrate that produces the desired amount of active ingredient per acre treated normally is mixed with 10 to 15 gallons of carrier for every acre to be treated in aerial applications and with 50 to 100 gallons of carrier for every acre to be treated in ground applications. Herbicide concentrate, stored in 30- to 55-gallon drums, is prepared for application and then is transferred to application equipment by a mixer-loader, who uses a batch truck that has separate storage tanks for the carrier and for the herbicide mixture.

Herbicide application equipment is designed to cover the target plants with a minimum of off-target spray movement, called drift. Spray equipment nozzles are designed to produce medium to large droplets because smaller droplets tend to remain airborne and may drift with air currents away from the target vegetation. Despite the effectiveness of the application equipment used, some small fraction of the droplets may break up into smaller droplets that the wind could blow offsite. Hand application techniques, such as injection and hack and squirt, do not use sprays; thus, these techniques do not produce herbicide drift (see the description of hand applications in Section 2).

Exposure and Dose

Two primary conditions are necessary for a human to receive an herbicide dose that may result in a toxic effect. First, the herbicide must be present in the person's immediate environment so that it is available for intake. It must be in the air the person breathes, on the person's skin, or in the person's food or water. The amount of herbicide present in the person's immediate environment is the exposure level.

Second, the herbicide must get into the person's body by some route. If it is in the air, it may be inhaled into the air passages and lungs. If it is

Some Helpful Terms

Human Exposure

on the clothing that is in contact with the skin or the skin itself, it may penetrate the skin. The amount that moves into the body by any of these routes constitutes the dose.

Thus, although two people may be subjected to the same level of exposure--for example, two workers applying herbicide with backpack sprayers--one may get a much lower dose than the other by wearing protective clothing, using a respirator, or washing immediately after spraying. Exposure, then, is the amount of herbicide available to be taken in; dose is the amount that actually enters the body.

Worker dose levels were extrapolated from actual field studies which analyzed urine samples from exposed workers. By determining the amount of an herbicide in the urine of a worker, it is possible to estimate the exposure (or dose) that the worker has received.

Potential Routes of Human Exposure

The potential routes of exposure to humans from herbicide treatment operations are illustrated in figure 4-1. The routes of exposure considered in this risk assessment in estimating doses to workers and the public that might occur during routine operations or in the event of an accident are listed in table 4-1 and are described below. Food items and drinking water sources that may lead to ingestion (dietary) exposures are listed in table 4-2.

Potential Human Exposures From Routine Operations

The greatest doses to humans in routine herbicide applications are to workers who may be exposed while (1) mixing and loading herbicide into application equipment, (2) applying herbicide to vegetation using ground-based equipment, or (3) supervising or monitoring aerial or ground-based herbicide applications. Use of protective clothing and equipment and adherence to proper cleanup procedures and label precautions in general lead to significant reductions in the doses of workers.

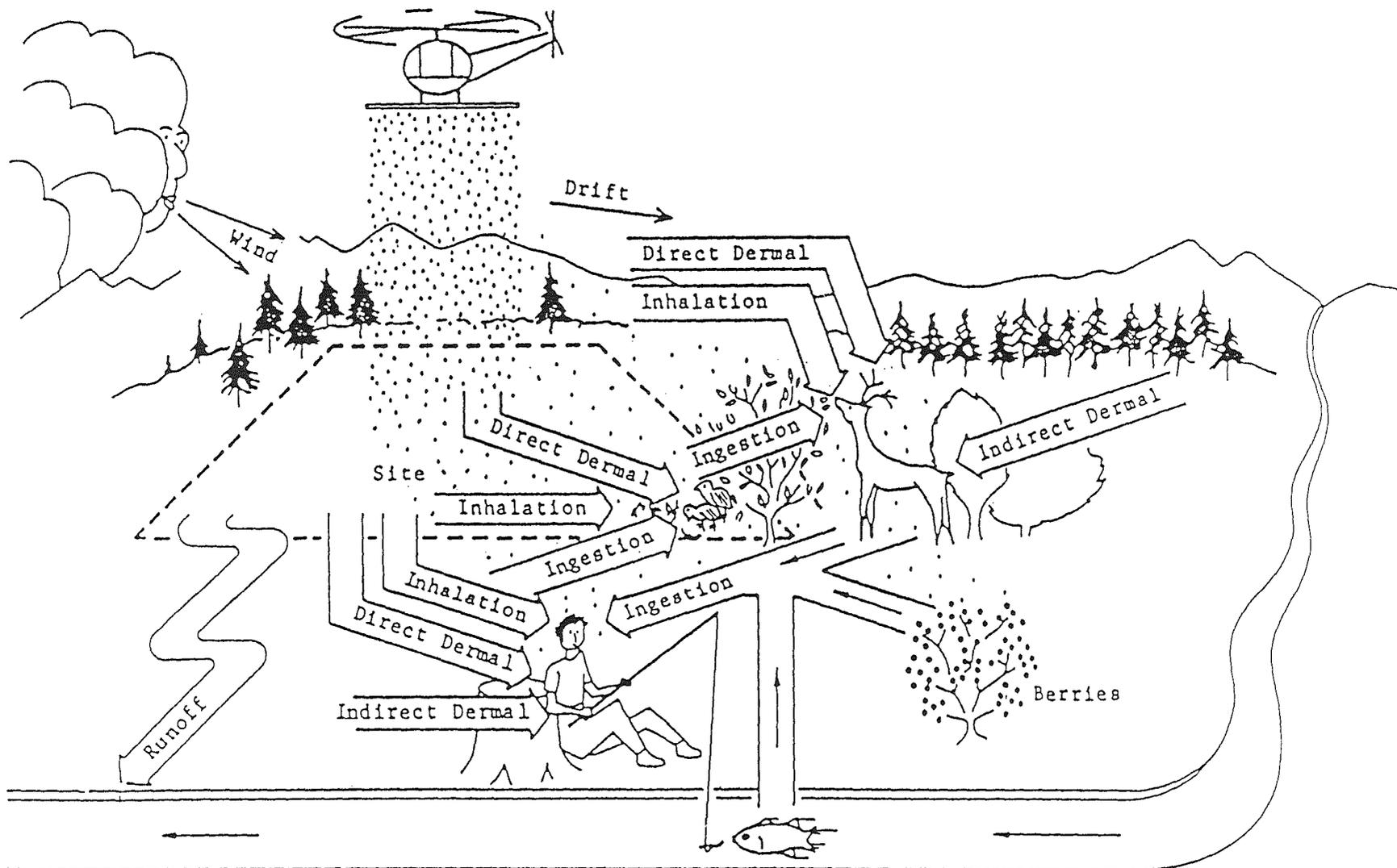


Figure 4-1 Routes of Exposure to Herbicides in Spraying Operations

Table 4-1

Routes of Exposure Considered in This Risk Assessment

Scenario	Doses from Direct Exposure	Doses from Indirect Exposure
<u>Routine</u>		
Workers	Total dose (based on field studies)	Dermal dose from reentry to treated area based on field data
General Public	Dermal dose ^a from drift (based on modeling)	Dermal dose from vegetation contact in drift area and from consuming food with residues ^b
<u>Accidental</u>		
Spraying	Dermal dose ^a to member of public directly sprayed	Worker vegetation contact dose from reentry to treated area immediately after spraying; dose to member of public who walks through treated area and who eats directly sprayed food items ^b
Spills	Worker dermal dose from spill of concentrate or mixture on skin	Dose to member of public from drinking water contaminated by an herbicide spill

^aInhalation is negligible based on field study data.

^bSee table 4-2 for diet items used in dose estimates.

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Table 4-2

Dietary Exposures Estimated in This Risk Analysis

Scenario	Water	Food Items
<u>Routine</u>		
Realistic	Drift onto pond	Garden vegetables offsite Berries offsite Meat from a deer feeding offsite Meat from a game bird feeding offsite Fish caught in a pond receiving drift
Worst Case	Drift onto pond that is closer than realistic	Food items same as in realistic but closer to treatment unit
<u>Accidental</u>		
Spraying	Pond directly sprayed	Garden vegetables onsite Berries onsite Deer feeding in treated area Fish caught in pond directly sprayed Game bird directly sprayed
Spills	100- or 2,000-gal spill of mix in drinking water supply	Drinking water

The single most important source of exposure to persons who do not handle the herbicide containers or spray equipment in routine operations is from the drift off target of airborne herbicide spray droplets. Spraying only under favorable weather conditions and the use of spray equipment that limits the number of smaller spray droplets reduces the amount and extent of drift.

During routine operations, workers may be dermally exposed to an herbicide if the herbicide concentrate, mixture, or drifting spray droplets contact their skin or if the herbicide is brushed off of sprayed vegetation. Inhalation exposure may result from breathing without protective devices in the area of the drifting spray droplets or where there are vapors from a volatile herbicide. However, a variety of studies have shown that inhalation exposure is very small compared with dermal exposure. In this analysis, inhalation doses have not been estimated separately for workers; they are included with dermal doses in the estimated total worker doses based on herbicide levels in the urine of workers in field experiments.

Members of the general public who are within the area of drift of the smaller spray droplets may also receive dermal and inhalation exposure, but their exposures are relatively low compared to the exposures of workers directly involved in the spraying operations. Field studies of workers have consistently shown that inhalation exposure represents only a small part of the total exposure. Total 2,4-D exposure to truck applicators via inhalation assuming an 8-hour day and a breathing rate of 29 L/min would be a maximum 0.03 mg versus a maximum 18 mg via dermal exposure according to data of Draper and Street (1982). Inhalation, therefore, constituted 0.17 percent of dermal exposure. Nigg and Stamper (1983) calculated inhalation exposure to be 0.03 percent of total body exposure for Florida airboat sprayers. In their study of right-of-way applicators using 2,4-D, 2,4-DP, and picloram, Libich et al. (1984) found dermal exposure to be up to 50 times greater than exposure from inhalation. Therefore, doses to the general public in this analysis have been calculated only for dermal and dietary routes (see the description of worker studies later in this section).

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Herbicide may be ingested by members of the general public from food containing herbicide residues. Food items such as garden vegetables, wild berries, or game animals may have received some level of herbicide from spray drift. Game animals may have fed on plants from the drift area. Ingestion exposure could also result from drinking water that has received herbicide drift or from eating fish from a body of water that has received herbicide drift.

Potential Human Exposures From Accidents

In the event of an accident, workers and members of the public may be exposed to much greater amounts of herbicide than they would under normal circumstances. Workers who spill the concentrate or some of the prepared spray mixture on their skin during mixing, loading, or spraying operations or who are doused when a transfer hose breaks would be dermally exposed. Workers or members of the public who are accidentally sprayed with herbicide because they are beneath a spray aircraft or are too close to a truck or backpack applicator would receive a dermal dose.

The dermal dose would depend on the concentration of herbicide in the spray mix, the area of the sprayed person's exposed skin, the extent to which the person's clothing absorbed herbicide (some clothing is water repellent, but other material would permit penetration of the herbicide to the skin), and the time that elapses before the person can wash. Indirect dermal (reentry) exposure may occur if workers or members of the public brush up against wet vegetation in the sprayed area.

Members of the public may accidentally be exposed to the herbicide by eating food or drinking water that has been directly sprayed. For example, members of the public may eat berries that have been directly sprayed, or they may eat meat from deer that have recently foraged on a sprayed site. Exposure to even higher levels of herbicide is possible if a container of herbicide concentrate were to break open and spill into a drinking water supply.

EXPOSURE ANALYSIS METHODS

Application Scenarios

To make reasonable estimates of the possible herbicide doses to workers and the public, a number of application scenarios are used that represent an array of likely treatment situations. Routine application scenarios were designed to provide a range of human dose estimates, from realistic to worst case, for normal operating conditions. Accidental-worst case scenarios--direct application, spills on the skin, and large spills into bodies of water--are used to estimate the highest doses that could ever be reasonably expected to occur. Actual exposures from all vegetation management projects conducted in the Pacific Northwest are within or below the range of doses predicted in these scenarios.

The scenarios specify those characteristics of each kind of herbicide application operation that determine human doses. For example, for workers involved in backpack operations, the number of work hours and the herbicide application rate are used to determine their doses. For aerial applications, the number and size of the sites treated in a day's operation are used. To calculate doses to nearby residents who may eat a garden vegetable containing herbicide residue, it was necessary to estimate how much residue was on the vegetable and to specify how much of the vegetable was eaten.

The application scenarios were not intended to show what necessarily will happen as a result of a given treatment operation, but what could happen if all of the conditions specified in the scenario were met in the actual operations. For example, worker doses are based on actual dose levels found in field exposure studies in which no protective clothing or equipment was worn. If workers were to wear protective clothing and equipment during actual operations, their doses could be significantly lower than those estimated here. However, despite all precautions, workers present during treatment operations will be exposed to some extent.

Additional factors must be recognized when evaluating the likelihood of a member of the public receiving an herbicide dose. A forest user would

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receive a dose only in the immediate vicinity of the treatment area and only at the time of the herbicide application. However, because of the limited area of forest being treated and the public's restricted access and use, the possibility of this occurrence is slight. Likewise, a nearby resident would receive a dose as high as the one estimated in this analysis from eating garden vegetables with herbicide residue only if all of the following conditions were met:

1. The resident's garden was close enough to a particular treatment area to receive some level of herbicide drift.
2. The weather conditions on the day of treatment were such that the herbicide happened to drift offsite in the direction of the garden.
3. The resident ate the vegetable immediately after the herbicide residue landed on it.

A combination of factors makes the possibility of the resident receiving such a dose highly unlikely. First, most treatment areas are located considerably further from any residence than the distance assumed in this analysis--600 feet. Second, mitigation measures described in Section 2 reduce the likelihood of drift onto a garden, even if one happened to be nearby. Third, there is only a remote possibility that the resident would immediately pick and eat a garden vegetable that had herbicide residue from that operation.

Workers Doses from Routine Operations

Herbicide doses to workers involved in routine operations were estimated using eight herbicide application scenarios: four routine-realistic and four routine-worst case scenarios. For each application scenario, worker categories were chosen to represent the normal range of work activities in terms of potential herbicide exposure. Other categories of workers may experience less exposure, but no category of workers in the field is expected to experience greater exposure than the types of workers considered in this analysis.

Doses to members of the public as a result of routine operations were estimated using three of the routine-realistic and three of the routine-worst case scenarios used to derive the worker doses. Again, other categories of the public may receive less exposure, but no one should receive more under normal operating conditions.

Worker Categories and Calculations in Routine Operations

Worker dose levels were extrapolated directly from worker doses determined by urine analysis in field studies of actual herbicide treatment operations. Because the field studies showed what dose levels are experienced in actual operations, they were considered the most appropriate basis for estimating the doses of Forest Service Region 6 and BLM herbicide applicators involved in the same or similar vegetation management practices. Those studies are discussed in the next subsection.

Dose estimates were scaled to the anticipated work hours and herbicide application rates specified in each of eight application scenarios.

Routine-realistic. To estimate routine-realistic worker doses, average dose levels found by urine analysis in field studies of workers exposed in spraying 2,4-D using the same application method were used. Nominal dose levels in mg/kg for workers in each category (see below) were derived from these average dose levels by dividing by the field study acreage and application rate.

Application rates for the routine-realistic dose scenarios are listed in table 4-3.

The worker categories and scenarios used for estimating the routine-realistic worker doses included the following:

1. Doses to pilots, mixer-loaders, supervisors, and observers in a helicopter broadcast treatment of four 40-acre silviculture sites.

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Table 4-3

Application Rates Used for
Routine-Realistic and Routine-Worst Case Scenarios
(1b active ingredient/acre)

Chemical	Aerial		Backpack		Right-of-Way	
	Realistic	Worst Case	Realistic	Worst Case	Realistic	Worst Case
Amitrole	2.00	4.00	2.00	5.00	2.00	8.00
Asulam	2.40	3.34	1.20	3.34	2.40	5.00
Atrazine	3.75	4.00	3.00	4.00	3.00	8.50
Bromacil	0.00	0.00	4.00	10.00	4.00	10.00
2,4-D	2.50	4.00	2.00	4.00	2.50	4.10
2,4-DP	2.00	2.50	2.00	4.30	2.50	5.00
Dalapon	4.00	10.00	4.00	12.00	4.00	10.00
Dicamba	1.00	4.00	0.50	4.00	1.00	3.60
Diuron	0.00	0.00	4.00	6.00	4.00	16.00
Fosamine	3.00	12.00	3.00	11.50	4.00	10.70
Glyphosate	2.00	5.00	1.50	5.00	2.00	5.00
Hexazinone	2.50	3.00	1.12	3.00	2.50	6.00
Picloram	1.00	5.00	1.00	4.00	1.00	2.00
Simazine	4.00	5.00	2.00	4.60	2.00	4.60
Tebuthiuron	1.00	6.00	1.50	6.00	2.20	4.60
Triclopyr	2.00	8.00	2.00	8.00	2.00	8.00

2. Doses to applicators, mixer-loaders, and applicator/mixer-loaders in truck broadcast spraying of 12 acres (33 feet wide by 3 miles long) of vegetated roadway right-of-way.
3. Backpack applicator doses in backpack spraying of a 6-acre facilities maintenance site by two applicators for 6 hours.
4. Doses to applicators using hack-and-squirt and injection-bar methods in hand treatment of 3 acres by two applicators for 6 hours.

Worker doses for each worker category were estimated by extrapolating from the average dose levels found in field studies of workers exposed to 2,4-D using the same application method. The following steps were involved:

1. The average dose observed in the 2,4-D field study was expressed in terms of dose per pound of active ingredient applied.
2. The acreage figure was used to determine the number of pounds of active ingredient used in the scenario by multiplying by the herbicide's typical application rate (listed in table 4-3).
3. The herbicide-specific dose was determined by multiplying the pounds of herbicide applied by the dose of 2,4-D per pound of 2,4-D applied for that worker category in the field studies and then adjusting for the herbicide's dermal penetration rate. The dermal penetration rates used in the analysis were 6 percent for 2,4-D (Feldman and Maibach, 1974), 6.4 percent for 2,4-DP, 0.48 percent for picloram (Lavy et al., 1984), 5 percent for dicamba (Draper and Street, 1982), 0.1 percent for amitrole, and 10 percent for the other 11 herbicides (USDA, 1984).

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The worker doses given in tables B-1 through B-6 (in Attachment B) were calculated for each herbicide and each scenario using the following equation:

$$\text{DOSE} = \text{STDOSE} \times \text{RATE} \times \text{ACRES} \times \text{DPRCF}$$

where:

DOSE = dose to worker in mg/kg

STDOSE = dose from field study with 2,4-D reported in table 4-4

RATE = application rate for the herbicide used in the scenario from table 4-3

ACRES = the number of acres treated in 1 day for the scenario as described in the text

DPRCF = the dermal penetration rate correction factor derived from the ratio of the dermal penetration rate of the herbicide given in Chapter 4 to the dermal penetration rate of 2,4-D (6 percent)

An example calculation using this equation follows for a pilot's dose of amitrole under the routine-realistic aerial scenario (table B-1):

$$7.55 \times 10^{-5} \text{ mg/kg/lb applied} \times 2.0 \text{ lb/acre} \times 40 \text{ acres/site} \times 4 \text{ sites/day} \times (0.1/6) = 0.0004 \text{ mg/kg/day}$$

The doses given in the example calculations may differ very slightly from the values reported in the tables because of differences in rounding. The values in the tables were generated by a computer program; the example calculations were performed with a desk-top calculator.

Table 4-4

Doses from Worker Exposure Studies Used to Calculate
Doses for Each Scenario

Scenario/Worker	Study ^a	Dose (mg/kg)
Small Aerial - Pilot	1, 2, 3	0.0000755 (Weighted Aver.)
Small Aerial - Batchman	1, 2, 3	0.000108 (Weighted Aver.)
Small Aerial - Supervisor	2	0.00231
Small Aerial - Observer	2	0.00049
Large Aerial - Pilot	1, 2, 3	0.0002511 (Weighed aver., upper 97.5 percentile)
Large Aerial - Batchman	1, 2, 3	0.0003201 (Weighted aver., upper 97.5 percentile)
Large Aerial - Supervisor	2	0.0087 (Upper 97.5 percentile)
Large Aerial - Observer	2	0.00155 (Upper 97.5 percentile)
Small Backpack - Sprayer	4	0.075639
Large Backpack - Sprayer	4	0.1895 (95th percentile)
Small R-O-W - Applicator	3	0.012
Small R-O-W - Mixer Loader	3	0.00681
Small R-O-W - A/M/L	3	0.02
Large R-O-W - Applicator	3	0.0557 (95th percentile)
Large R-O-W - M/L	3	0.0179 (95th percentile)
Large R-O-W - A/M/L	3	0.0445 (95th percentile)
Small Hack and Squirt	4	0.0156
Small Hypohatchet	4	0.0456
Small Injection	4	0.0061
Large Hack and Squirt	4	0.1262 (95th percentile)
Large Hypohatchet	4	0.4070 (95th percentile)
Large Injection	4	0.0347 (95th percentile)

^a1 = Franklin et al. 1982; 2 = Lavy et al. 1982; 3 = Nash et al. 1982;
4 = Lavy et al. 1984.

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Worker doses for hand application methods reported in tables B-7 and B-8 were calculated using the following equation:

$$\text{DOSE} = (\text{STDOSE}/\text{STHRS}) \times \text{LBGAL} \times \text{HRS} \times \text{DPRCF}$$

DOSE = same as previous equation

STDOSE = same as previous equation

STHRS = number of hours worker in study applied 2,4-D

LBGAL = pounds of active ingredient per gallon of herbicide (table 4-5)

HRS = number of hours worker applies herbicide in scenario

DPRCF = same as previous equation

An example calculation using the equation for a worker applying amitrole by the hack and squirt method in the routine realistic scenario is as follows:

$$\begin{aligned} \text{DOSE} &= (0.015657 \text{ mg/kg (lb/gal)}/6 \text{ hours}) \times 2 \text{ lbs/gallon} \times 6.4 \text{ hours/day} \\ &\times (0.1/6) = 0.00056 \text{ mg/kg/day} \end{aligned}$$

Routine-Worst Case. Routine-worst case worker doses were estimated for the same worker categories used in the routine-realistic scenarios. However, the site size, application rate, equipment type, meteorological conditions, and duration of exposure were set to those that would lead to the highest levels of exposure in herbicide treatment operations in the Region.

Herbicide-specific dose levels in the routine-worst case scenarios were again derived from the worker field studies and weighted for application rate and hours exposed, but here the 95-percent upper confidence level of the field study doses was used for extrapolating to the nominal dose in mg/kg/hr for a 1 lb/acre application rate. Application rates used in the routine-worst case scenarios are listed in table 4-3.

The worker categories and scenarios used for estimating routine-worst case worker doses included the following:

Table 4-5

Maximum Herbicide Concentrations in Drums and Batch Trucks

Herbicide	Pounds (a.i.) per Gallon Concentrate	Pounds (a.i.) per 50-Gallon Drum	Pounds (a.i.) per 2,000-Gallon Batch Tank
Amitrole	2	100	800
Asulam	4	200	668
Atrazine	4	200	800
Bromacil	4	200	400
2,4-D	4	200	800
2,4-DP	6	300	500
Dalapon	-- ^a	--	2,000
Dicamba	4	200	800
Diuron	4	200	640
Fosamine	4	200	2,400
Glyphosate	3	150	1000
Hexazinone	2	100	600
Picloram	2	100	1000
Simazine	4	200	1000
Tebuthiuron	--	--	1200
Triclopyr	4	200	1600

^aNot purchased in liquid formulation by the Forest Service or BLM.

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1. Doses to pilots, mixer-loaders, supervisors, and observers in fixed-wing broadcast spraying of a 400-acre site for range improvement.
2. Doses to applicators, mixer-loaders, and applicator/mixer-loaders in truck broadcast spraying of 40 acres of transmission line right-of-way.
3. Backpack applicator doses in backpack spraying of a 60-acre conifer release site by 14 applicators for 9 hours.
4. Doses to applicators using hack-and-squirt and injection-bar methods in hand treatment of 9 acres by four applicators for 9 hours.

Field Studies of Worker Exposure to 2,4-D

Field studies of the exposures and resultant doses of workers using a variety of application equipment have been conducted on 2,4-D by Lavy et al. (1982), Lavy et al. (1984), Nash et al. (1982), and Franklin et al. (1982). Doses for each worker category found in the studies are listed in table 4-6. Lavy et al. (1982) monitored three helicopter spray crews for worker exposure to 2,4-D, using portable air filters, denim patches, and urine analysis on two separate spraying dates; the first observing normal precautions, the second using special protective clothing and procedures. Nash et al. (1982) monitored exposure of workers to 2,4-D during aerial spraying in Washington and ground spraying in North Dakota under normal spray conditions (that is, without special precautions).

Lavy et al. (1984) investigated herbicide exposure to four spraying crews of 20 workers each, monitoring urine levels over two 5-day periods.

Table 4-6

Doses of 2,4-D Measured in Exposure Studies for Each Worker Category

Investigator	Application Type and Rate	Equipment Used	Worker Category	Number of Workers	Method of Analysis	Doses	
						Average	Range
Smy et al., 1982	Aerial, 2.2 Kg a.i./ha	Helicopter	Flagman	2		--	0.00119-0.00177 mg/kg/day
			Pilot	3	Denim	0.00057 mg/kg	n.d.-0.0010 mg/kg
			Mechanic	3	Patches	0.0233	0.0233-0.0617
			Batchman	3		0.0448	0.0233-0.0911
			Supervisor	3		0.0167	n.d.-0.0005
			Observer	6		8×10^{-5}	n.d.-0.0005
			Pilot	3	Urine	0.00248 mg/kg	0.00179-0.0557 mg/kg
			Mechanic	3		0.00068	0.00044-0.0136
			Batchman	3		0.00245	0.00215-0.0377
			Supervisor	3		0.00029	n.d.-0.0069
			Observer	6		0.00006	n.d.-0.0013
			Aerial	Helicopter, Special Precautions: Protective Coveralls, Gloves, Boots, Hats, Goggles	Pilot	3	Denim
	Mechanic	3			Patches	0.00577	0.0005-0.0162
	Batchman	3				0.01055	0.00016-0.0216
	Supervisor	3				0.0009	n.d.-0.0027
	Observer	6				0.0014	n.d.-0.0045
	Pilot	3			Urine	0.00854 mg/kg	n.d.-0.0237 mg/kg
			Mechanic	3		0.00301	n.d.-0.00516
Batchman			3		0.01401	0.00053-0.0219	
Supervisor			3		0.00013	n.d.-0.00038	
Observer			6		9×10^{-5}	n.d.-0.00056	

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Workers Doses from
Routine Operations

Table 4-6 (Cont.)

Investigator	Application Type and Rate	Equipment Used	Worker Category	Number of Workers	Method of Analysis	Doses	
						Average	Range
Lash et al., 1982	Aerial, 585 kg a.i. applied in 20 hrs.	4 Thrush Commanders	Mixer- loader	6	Urine	0.0199 mg/kg	0.0008-0.0545 mg/kg
		4 Grumman Ag-Cats	Mixer/ loader-pilot	1		0.0180	
	360 kg a.i. applied in 14 hrs.	4 Pipers					
		1 Snow					
		1 Cessna	Pilot	10		0.006 mg/kg	0.0013-0.0202 mg/kg
Ground, 34 kg a.i. applied in 3.5 hrs.	Sprayers: 4 Pull-type 21 Self- propelled 10 cab	Sprayers	9	Urine	0.012 mg/kg	n.d.-0.0760 mg/kg	
18 kg a.i. applies in 2.4 hrs.	16 no cab	Mixer- loader	7		0.0068	0.00165-0.0164	
38 kg a.i. applied in 7.9 hrs.		Mixer/ loader-sprayer	8		0.020	0.0037-0.0442	

Investigator	Application Type and Rate	Equipment Used	Worker Category	Number of Workers	Method of Analysis	Average	Range
Avy et al., 1984 as cited in USDA, 1984)	Ground, Weedone 170 (50% 2,4-D, 50% 2,4-DP), 1 gal. herbi- cide/24 gal. water	Backpack	Operator	20	Urine	0.01752 mg/kg/day	n.d.-0.0903 mg/kg/day
	Tordon 101-R (80% 2,4-D, 20% Picloram)	Injection bar	Operator	20	Urine	0.0019	n.d.-0.0095
	Tordon 101-R	Hypohatchet	Operator	20	Urine	0.01696	n.d.-0.0866
	Tordon 101-R	Hack and squirt	Operator	20	Urine	0.00576	n.d.-0.0451
Wearing protective overalls, gloves, boots, goggles, and a hard hat	Weedone 170	Backpack	Operator	20	Urine	0.0196 mg/kg/day	0.0004-0.1175 mg/kg/day
	Tordon 101-R	Injection bar	Operator	20		0.00086	n.d.-0.0035
	Tordon 101-R	Hypohatchet	Operator	20		0.0079	n.d.-0.0439
	Tordon 101-R	Hack and squirt	Operator	20		0.00244	n.d.-0.0148

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Franklin et al. (1982) estimated worker exposure in pasture brush clearing operations in Saskatchewan using techniques similar to Lavy et al. Urine samples were collected from personnel who conducted operations on 3 of 4 consecutive days.

All of the doses extrapolated from the worker studies above are based on work crews wearing ordinary work clothes and taking no special precautions against exposure. Doses from the worker studies that were used to calculate exposures are in table 4-4.

Why the Worker Dose Estimates Are Higher than Would Occur in Actual Operations

As described above, this risk assessment estimates two separate dose levels for each category of worker in routine operations--a realistic dose and a worst case dose. The realistic dose is an estimate of the average dose a worker should receive on a typical day during normal treatment operations. The realistic dose is based on combining average nominal doses from field studies with scenario conditions that are typical for Forest Service and BLM operations in the Pacific Northwest.

However, the realistic dose estimates are higher than those that would occur in actual operations for two reasons. First, the doses are based on field study doses of applicators who wore no special protective clothing or devices. Many of the field studies measured doses to workers both with and without protective gear, and the applicators in many of the proposed Forest Service and BLM operations will wear protective gear, but the lower doses of protected workers were not used in extrapolating to the doses estimated in this analysis. Second, during the field exposure studies, many of the less severe types of accidents occurred that could be termed operational errors. For example, pilots handled the transfer hoses and helped with the mixing and loading operations and, in one instance when a pump broke down, transferred spray mix by bucket to the spray tank. In both of these cases, these individuals received higher doses during that day's work than they would have otherwise. Nevertheless, their doses were used in deriving the average worker doses for that field study.

The worst case estimates of worker doses in routine operations are extremely high for two reasons. First, the nominal dose levels from the field studies used for extrapolation are not the average doses seen but the dose at the upper limit of the 95-percent confidence interval. This means that there is only 1 chance in 40 that a worker in the same field operation under the same conditions of terrain, weather, and equipment should receive a dose higher than the specified dose. Second, when this upper limit dose is combined with the assumptions of largest site size and highest application rate for dose extrapolation, extremely high doses are estimated that are unlikely to occur under true operational conditions. The probability of all of these events occurring at the same time, as discussed in Section 5, is less than 1 in 10,000. No workers are likely to receive a higher dose under routine operational conditions unless they are involved in one of the accidents described later in Section 4.

Because of the large number of actual field measurements, these extreme or routine-worst case estimates of doses to workers also take into account normal operational errors such as the following:

1. Errors of measurement during manufacturing and formulation.
2. Errors of measurement during field mixing.
3. Excessive swath overlap during application.

Public Exposures and Doses from Routine Operations

Public Exposure Categories and Calculations for Doses From Routine Operations

Herbicide doses to the public potentially exposed to routine herbicide applications were estimated using six application scenarios. They are the same as the worker scenarios except that hack-and-squirt and injection-bar methods were not included. The hand application scenario was excluded because no drift is involved and the chance that any other type of public

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contact with the herbicides might occur in these operations is negligible. In the remaining six scenarios, inhalation exposure was not estimated because none of the herbicides in question is a specific lung toxicant and because the worker field studies have consistently shown inhalation exposure to be an insignificant fraction of the total herbicide dose received (USDA, 1984). Only dermal and dietary routes of exposure were considered in this analysis.

The scenarios used for deriving routine-realistic public exposures and doses were as follows:

1. Helicopter spraying of a single 40-acre silviculture site.
2. Truck spraying of a 12-acre roadway right-of-way.
3. Backpack spraying of a 6-acre facilities maintenance site by two applicators for 6 hours.

The scenarios used for deriving routine-worst case public exposures and doses were as follows:

1. Fixed-wing spraying of a 400-acre site for range improvement.
2. Truck spraying of 40 acres of transmission line right-of-way.
3. Backpack spraying of a 60-acre conifer release site by 14 applicators for 9 hours.

Single Routes of Exposure. The following categories of exposure were estimated for each scenario: doses due to drift, vegetation contact by a hiker or berrypicker, and the dietary exposures shown in table 4-2.

Dermal dose estimates were derived from the estimated dermal exposure levels by assuming that 2 square feet of a person's skin was exposed and by

adjusting for the dermal penetration rate of each herbicide. Ingestion dose estimates were made for the five specific food items and drinking water that receive herbicide residues shown in table 4-2.

Multiple Routes of Exposure. In addition to estimating doses to the public from routine operations through the specific exposure routes described above, five categories of persons were assumed to receive doses simultaneously through a number of exposure routes: (1) a hiker, (2) a person who picks berries, (3) a hunter, (4) a fisherman, and (5) a nearby resident. Each of these persons was assumed to receive an herbicide dose that is the sum of the doses from several routes of exposure as shown in table 4-7.

It is extremely unlikely that a member of the public will receive simultaneous herbicide doses through more than two of the exposure routes described above. However, to ensure that no possible dose was omitted from the analysis, it was assumed that the hiker receives dermal exposure from drift as well as vegetation contact exposure from brushing against offsite plants that have received drift. The hiker also drinks water that has received herbicide drift. The berrypicker receives the same dermal and drinking water exposure from drift as the hiker, but the berrypicker is exposed to a higher level of vegetation contact exposure from brushing against plants that have received drift because of continuous contact with the berry plants. The berrypicker also receives exposure from feeding on berries that have herbicide residues from drift.

The hunter is assumed to get the same dermal exposure, vegetation contact, and drinking water exposure as the hiker. In addition, the hunter is assumed to kill and eat a deer and a game bird that have been exposed and have fed on items in the area of herbicide drift. The fisherman receives the same doses as the hunter, except the fisherman eats fish taken from a pond that has received drift rather than eating a deer and a game bird. The nearby resident receives the same dermal exposure, vegetation contact, and drinking water exposure as the hunter, but the resident eats vegetables from a garden that has received herbicide drift.

Table 4-7
Multiple Routes of Exposure for Example People

Example People	Direct Dermal	Reentry Hiker	Reentry Berrypicker	Drinking Water	Eating				
					Berries	Vegetables	Deer	Bird	Fish
Hiker	X	X		X					
Berrypicker	X		X	X	X				
Hunter	X	X		X			X	X	
Fisherman	X	X		X					X
Nearby Resident	X	X		X		X			

X = Member of the public is exposed by this route.

Public Dose Estimation

Because no field studies existed on actual doses to the public comparable to those used for estimating worker doses, it was necessary to estimate public doses by modeling the transport and fate of the applied herbicides. Details of the transport and fate modeling are in the next subsection.

Surface herbicide residue levels were estimated using data from field studies of the drift and surface deposition of herbicides in aerial and ground-based spray operations. These empirical studies were used to calculate how much was deposited on people's skin and how much was deposited on food and vegetation and in bodies of water.

The exposure models required input of expected distances to various sources of human exposure. Figures 4-2 through 4-7 illustrate the distances to sources of public exposure in each scenario. The distances were derived from an examination of currently used mitigation measures.

Why the Public Dose Estimates Are Higher than Would Occur From Actual Operations

The doses estimated for members of the general public are overestimates for a number of reasons. First, downwind concentrations on surfaces used to compute dermal exposure were those found on flat mylar deposition sheets.

The smaller spray particles in offsite drift tend to move around rather than impact on curved surfaces and therefore would be less likely to adhere to a human body. Second, no degradation of the herbicide is assumed to occur, and it is assumed that the herbicide does not bind with any material, such as vegetation, to become biologically unavailable to humans. This would be an important factor in diminishing doses that may occur from any activity involving contact with treated vegetation.

The routine-worst case dose levels to the public can be considered the highest possible doses for routine spray operations because the doses are

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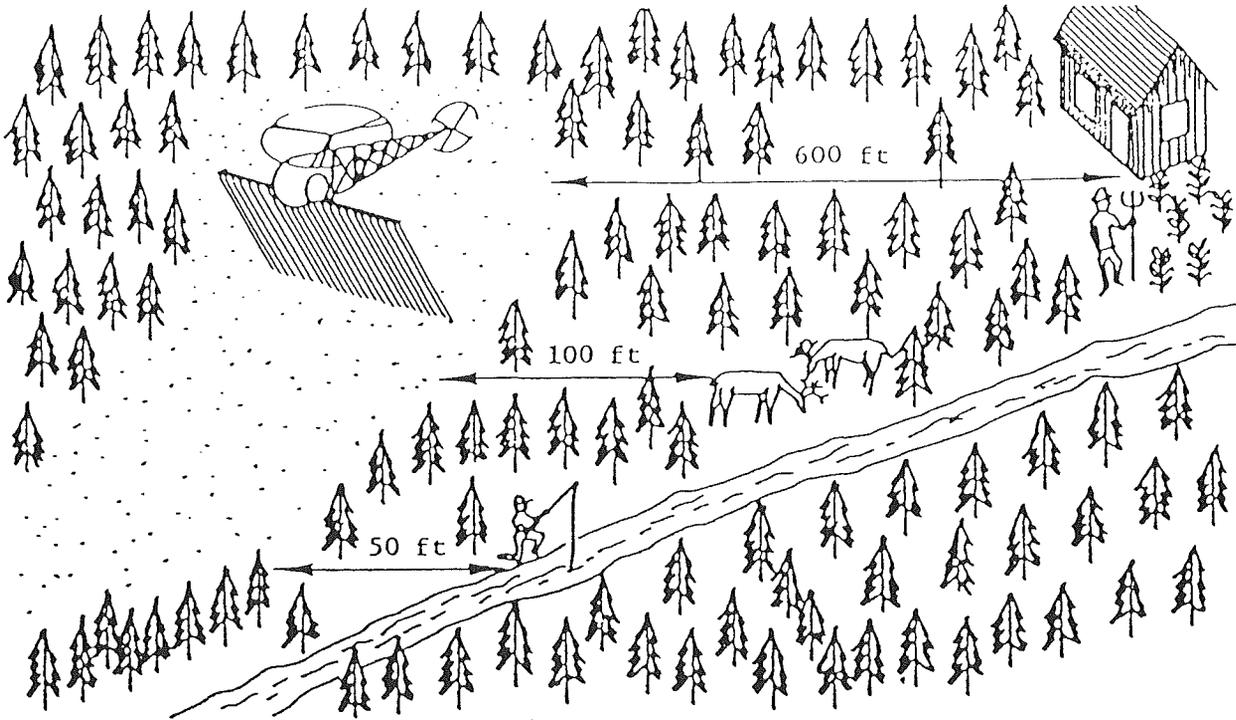


Figure 4-2 Routine-Realistic Aerial Scenario:
Helicopter Spraying of a 40-Acre Silviculture Site

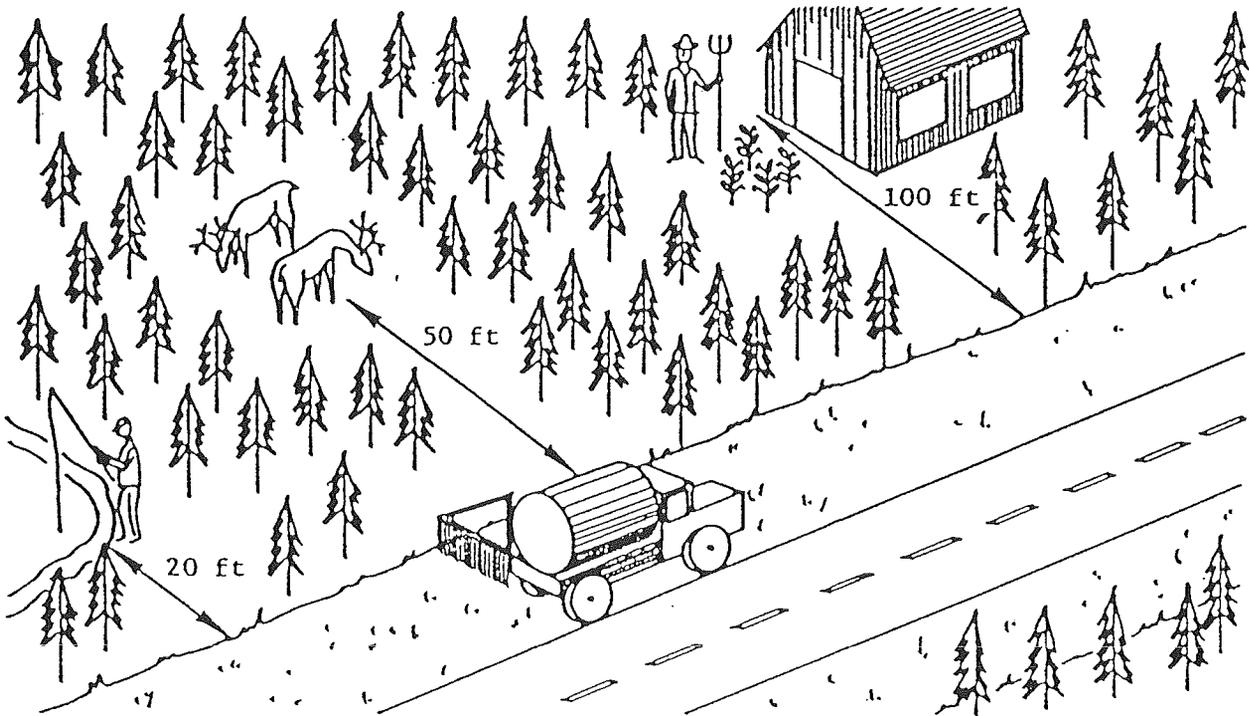


Figure 4-3 Routine-Realistic Right-of-Way Scenario:
Truck Spraying of a 4-Acre Roadway Right-of-Way

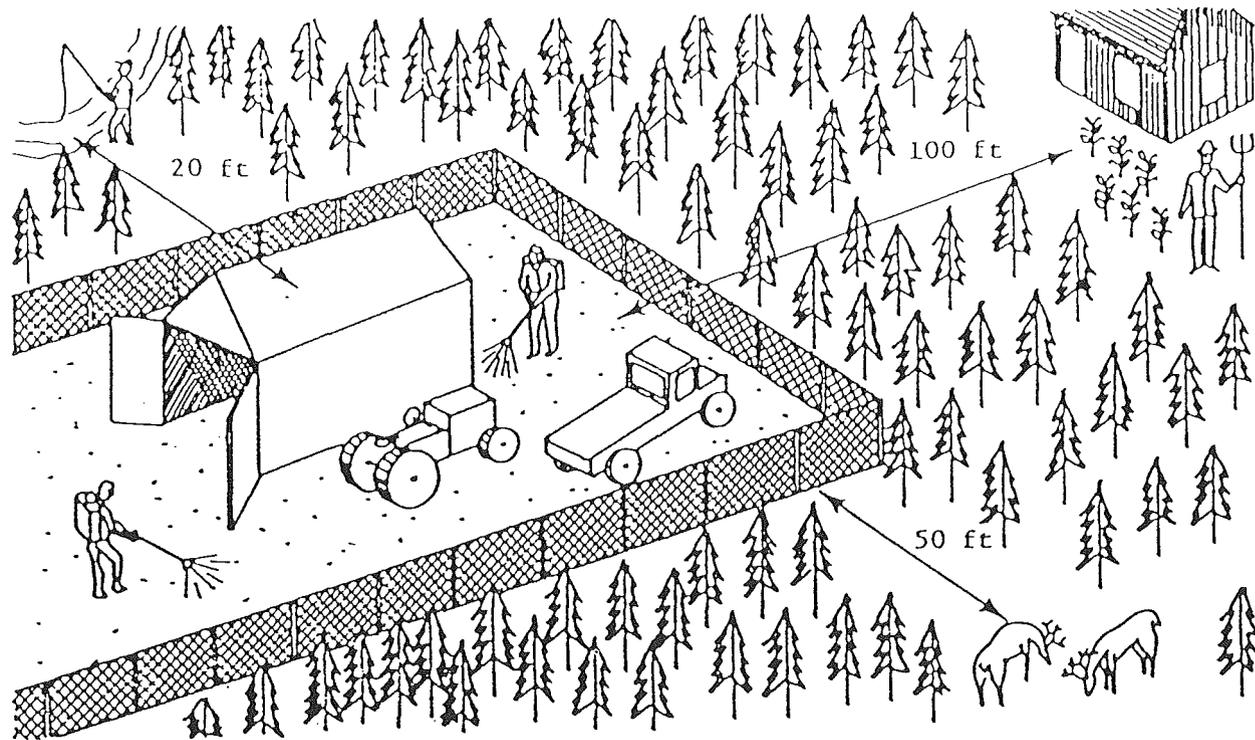


Figure 4-4 Routine-Realistic Backpack Scenario:
Treatment of a 6-Acre Facilities Maintenance Site

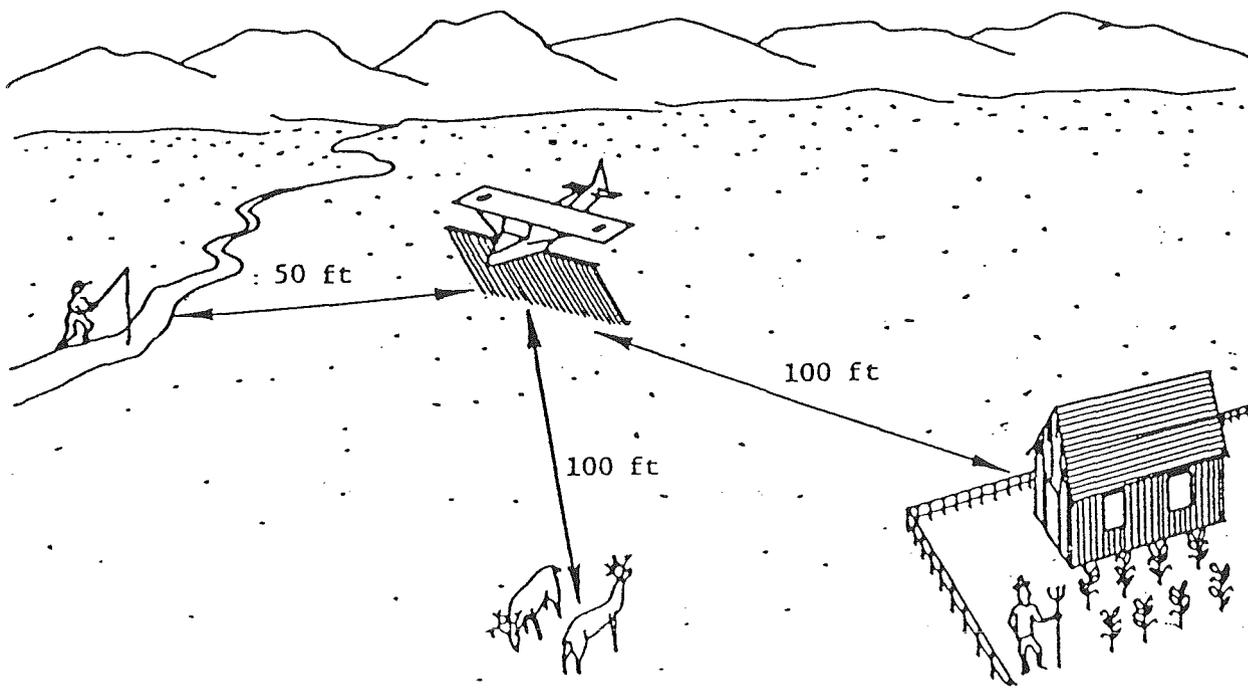


Figure 4-5 Routine-Worst Case Aerial Scenario
Fixed Wing Spraying of a 400-Acre Range Improvement Site

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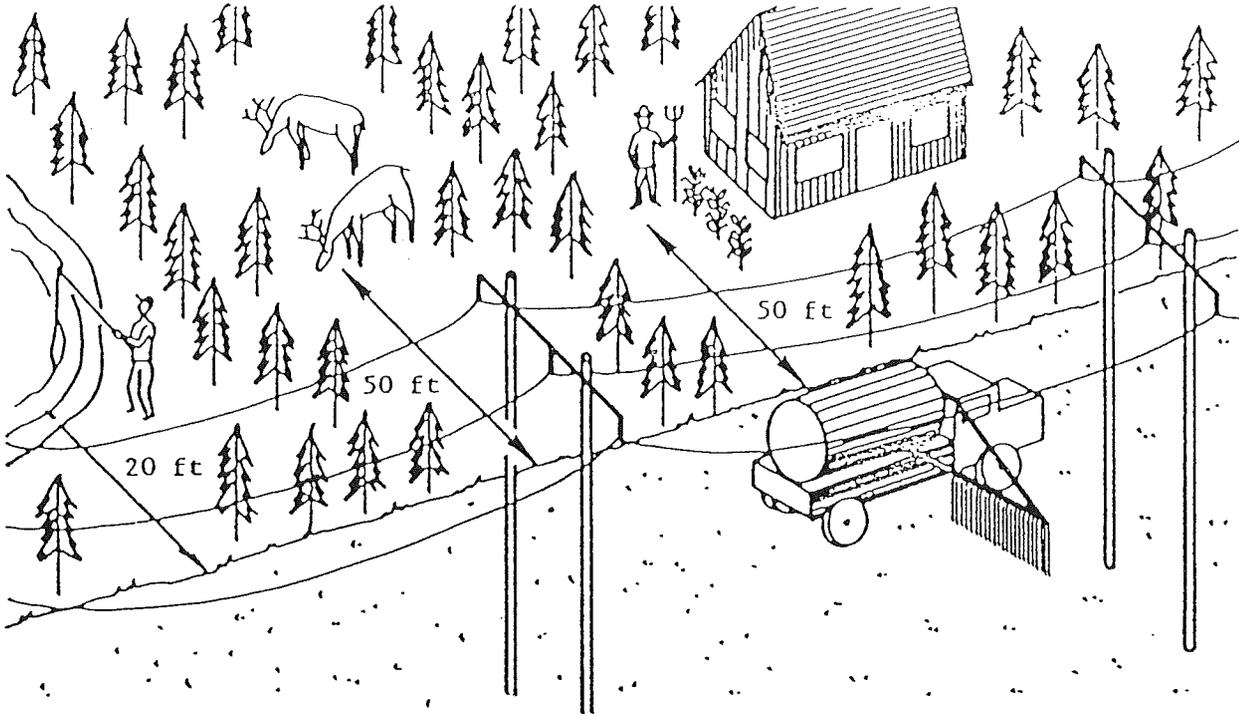


Figure 4-6 Routine-Worst Case Right-of-Way Scenario:
Truck Spraying of 40 Acres of Transmission
Line Right-of-Way

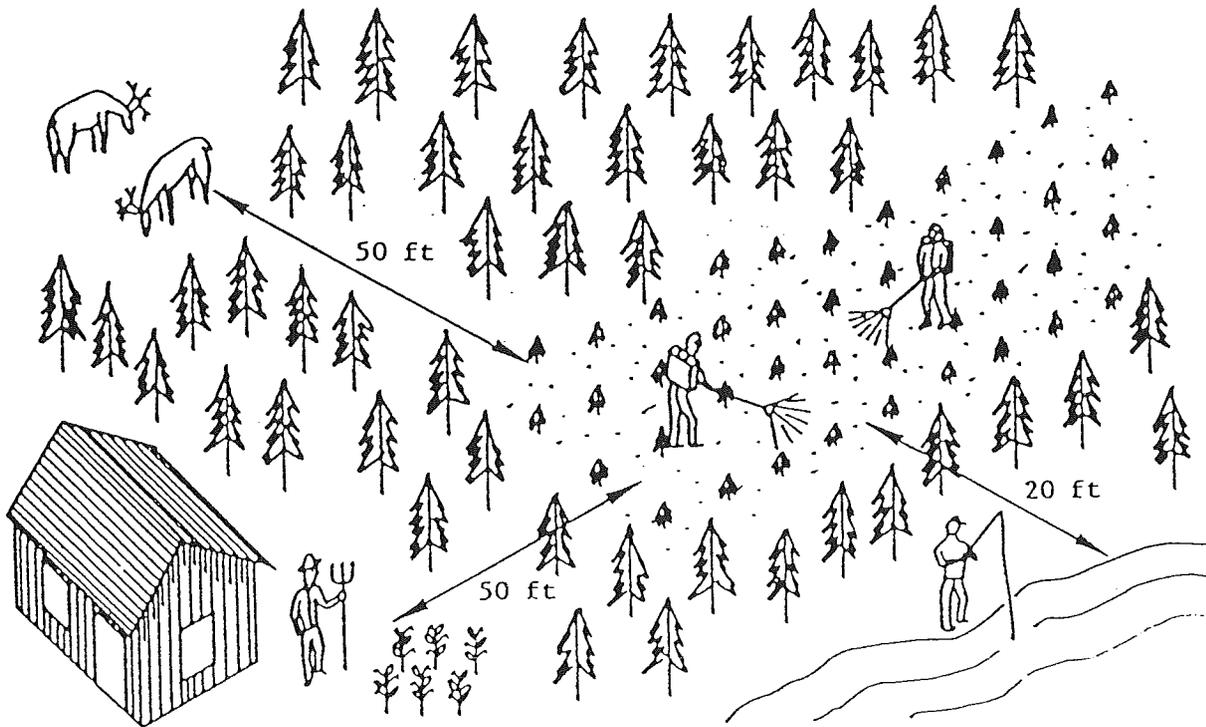


Figure 4-7 Routine-Worst Case Backpack Scenario:
Treatment of a 60-Acre Conifer Release Site

Modeling Public Exposures

calculated in scenarios that combine many unlikely factors and events, including largest site size, highest application rate, least favorable weather conditions, and spray equipment most susceptible to offsite drift. No member of the public should get a dose that is any higher than the doses estimated in the routine-worst case scenarios except in the case of an accident.

Modeling Public Exposures and Doses

The following subsection presents a detailed discussion of the transport and fate modeling used in estimating herbicide doses to the public. Various sources for assumptions and methods of calculation were consulted (Dost, 1983; Crump, 1983; Simmons, 1983; USDA, 1984).

Spray Drift

The potential for herbicide sprays to drift onto adjacent lands or into nearby bodies of water was assessed based entirely on the results of empirical studies reported in the scientific literature. The analysis considered deposition on surfaces, including exposed skin, water, game animals, and various classes of plants that may contribute directly or indirectly to the human diet.

Specific field studies were chosen to best represent the equipment and conditions appropriate for each scenario. Unfavorable conditions were chosen to show the degree of drift that could occur under the routine-worst case scenarios. Drift estimates for sprays applied in large range improvement projects were made based on the drift of 2,4-D from a fixed-wing aircraft (Miller, 1980). This test was conducted when winds averaged 9.5 mph. Mitigation measures specify no spraying if winds exceed 5 mph. Drift estimates for sprays applied in silvicultural projects were made based on drift of a dye tracer solution sprayed over a coniferous seed orchard by helicopter (Parry et al., 1983). The winds ranged from 4.5 to 9 mph. Drift of sprays applied by ground equipment was estimated based on a field test reported in Yates et al. (1978). In that test, glyphosate was sprayed by a ground sprayer in winds of 8.5 mph.

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To facilitate use of the data from the various published field tests discussed above, a computer program was written to show how residues accumulate from multiple swaths (the long, narrow pattern of herbicide laid down by a broadcast sprayer such as an aircraft) and to correct for various application rates and swath widths. The program was then run to calculate deposition at selected representative distances for a nominal application rate of 1 pound per acre. The results are given in table 4-8 for each of the six broadcast spray scenarios. The drift calculated for water bodies is intended to represent deposition at the edge of a minimum buffer strip (50 feet for aerial spraying and 20 feet for ground spraying).

Residues on Plants

Herbicide residues on plants on treated sites were estimated based on factors reported by Hoerger and Kenaga (1972). These factors were derived from a large number of studies, and they allow prediction of residues in parts per million (ppm) based on the application rate in pounds per acre. These residue estimates were calculated assuming no herbicide degradation, so they apply to conditions immediately after application. Following Hoerger and Kenaga (1972), the plants were classified into broad groups based on vegetative yield, surface-to-mass ratio, and plant interception factors. The residues estimated for each type of plant are intended to represent realistic yet relatively high estimates.

Offsite plant residues were calculated first for grasses based on the spray drift data discussed in the previous section and by using a regression equation given in Yates et al. (1978) to relate spray deposition on young wheat plants to that on sampling devices. The deposition was then estimated for other plant groups, including berries and leafy vegetables, by using the same relative factors given by Hoerger and Kenaga (1972), assuming that deposition on young wheat was approximately the same as deposition on range grass.

Herbicide doses to individuals were calculated assuming that they eat 400 grams (0.9 pounds) of contaminated berries or peas.

Table 4-8

Herbicide Drift for Routine Scenarios
(1 lb active ingredient/acre)

Scenario	Realistic (mg/m ²) ^a	Worst Case (mg/m ²) ^a
<u>Aerial</u>		
To Public and Crops	0.0215 (0.0020)	11.39 (1.0595)
To Berries and Animals	1.689 (0.1571)	11.39 (1.0595)
To Water	7.183 (0.6682)	24.18 (2.2491)
<u>Right-of-Way</u>		
To Public and Crops	0.0462 (0.0043)	0.1613 (0.0150)
To Berries and Animals	0.0968 (0.0090)	0.1613 (0.0150)
To Water	0.0284 (0.0264)	0.3795 (0.0353)
<u>Backpack</u>		
To Public and Crops	0.0239 (0.0222)	0.4601 (0.0428)
To Berries and Animals	0.3666 (0.0341)	0.4601 (0.0428)
To Water	0.0632 (0.0588)	0.7289 (0.0678)

^amg/ft² in parentheses.

D Human Health Risk Assessment (Quantitative)

Calculations for the public dietary doses given in tables B-9, B-11, B-13, B-15, B-17, and B-19 are based on the following equation:

$$\text{DOSE} = \text{RESIDUE} \times \text{AMT} \times (1/\text{BWT})$$

where:

DOSE = ug/kg

RESIDUE = herbicide residue in diet item based on discussions in this section (see table 4-9 for examples)

AMT = amount of diet item consumed based on scenario

BWT = body weight of person assumed to be 50 kg

Residues for amitrole are given in table 4-9 as an example. The dose to a human consuming berries contaminated with amitrole from the realistic aerial scenario is as follows:

$$0.135 \text{ mg/kg (from table 4-9)} \times 0.4 \text{ kg} \times 1/50 \text{ kg} = 1.08 \times 10^{-3} \text{ mg/kg}$$

(see table B-9)

Residues in Water

Residues in water were calculated assuming that the water is only 6 inches deep, and that the herbicide spray drifts directly downwind to the water body over a minimum buffer distance. The buffer strips were assumed to be only 50 feet for aerial spraying and 20 feet for ground spraying. The actual residues in water would be less under more favorable spray conditions, at greater distances, or with deeper water bodies. For example, if the water were 2 feet deep then the residues would be only one-fourth of those calculated for this analysis. Dilution or degradation would also decrease residues. Herbicide doses to individuals were calculated assuming that they drink 1 liter of the maximally contaminated water.

Table 4-9

Residues of Amitrole in Diet Items Used to Calculate
Doses for Each Scenario
(ppm)^a

Scenario	Diet Item					
	Water	Berries	Legumes	Deer	Quail	Fish
Realistic Aerial	94.189	0.135	0.270	0.018	0.061	94.189
Large Aerial	634.040	1.303	2.606	0.190	0.784	634.040
Small Backpack	8.292	0.038	0.076	0.005	0.014	8.292
Large Backpack	23.875	0.115	0.230	0.014	0.042	23.875
Small Right of Way	3.720	0.013	0.026	0.002	0.004	3.720
Large Right of Way	19.912	0.078	0.155	0.009	0.025	19.912
Accidental Spraying	5.87	11.65	24.19	2.34	14.51	5.87

^appm is the same as mg/L in water, or mg/kg in plant or animal tissue.

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Residues in Game Animals

A series of reasonable simplifying assumptions were used to calculate residues for two representative game animals: a 150-pound deer and a 0.25-pound game bird, such as a quail. The entire body surface area of the animal was assumed to be exposed to spray drift as shown in table 4-8. Forty percent of the body surface was assumed to contact vegetation and thereby gain an additional average dermal residue level equal to that on the vegetation. Penetration of the herbicides through animal skin was assumed to be the same as through human skin.

The game animals were assumed to get an oral dose both by grooming and in their diet. The dose from grooming was assumed to amount to 29 percent of the nonabsorbed dermal dose for deer and 40 percent for quail. The deer diet was assumed to consist of 2.45 kg of forage plants and 4 liters of water per day, both containing the herbicide. The quail diet was assumed to consist of 33 g of seed (grain) per day and 15 mL of water, both containing herbicide.

The concentration of herbicide in game meat was calculated by summing the animal's doses from both the dermal and oral routes of exposure and by assuming that 10 percent of that total dose was retained in the meat of the animal. Inhalation exposure was considered insignificant compared to dermal and oral exposures. This is similar to the method used in the exposure analysis of USDA (1984). Herbicide doses to humans were calculated by assuming that they eat 400 g of deer meat or 400 g of bird meat per day. Assumptions of meat consumption were based on what was considered to be a reasonably conservative figure.

To illustrate the method used to determine human dietary exposures from consumption of game animals, the following is the formula used to calculate the amount of herbicide in deer meat:

Variables used in the calculations:

WT = Weight, 150 lbs (68 kg); Dress wt, 120 lbs (54.4 kg)

BSA = Body surface area, 1.6666 m²

DFI = Daily food intake, 2.45 kg

BSCV = Fraction of body surface contacting vegetation, 0.39

BSG = Fraction of body surface groomed, 0.20

WC = Water consumption, 4 L/day

DPR = Dermal penetration rate (chemical specific)

Dermal Dose:

1. Direct dermal exposure (DDE)(mg) = Deposition rate on surface
(mg/m²) x BSA (m²)
2. Indirect dermal exposure (IDE)(mg) = Deposition rate on vegetation
x BSCV x BSA
3. Total dermal exposure (TDE)(mg) = DDE + IDE
4. Dose absorbed through skin (DAS)(mg) = TDE x DPR

Ingestion Dose:

5. Ingestion via grooming (IVG)(mg) = (TDE - DAS) x BSG
6. Ingestion via diet (IVD)(mg) = Forage level x DFI
7. Ingestion via drinking (IVDR)(mg) = Concentration x WC
in water
8. Total ingestion dose (TID)(mg) = IVG + IVD + IVDR

D Human Health Risk Assessment (Quantitative)

Total Dose:

9. Total dose (TDOSE)(mg) = DAS + TID
10. Amount retained in meat (RMEAT)(mg) = TDOSE x Dose to tissue concentration ratio 0.10
11. mg/kg in meat (PPMDEER) = RMEAT/dress wt

An example calculation for amitrole in deer meat for the routine realistic aerial scenario follows. The amounts deposited on vegetation, animals, and water were taken from table 4-8 as mg/m² per lb/acre applied and adjusted for an application rate of 2 lb/acre.

1. DDE = 3.38 mg/m² x 1.667 m² = 5.63 mg
2. IDE = 3.38 mg/m² x 0.39 x 1.667 m² = 2.197 mg
3. TDE = 5.63 mg + 2.197 mg = 7.83 mg
4. DAS = 7.83 mg x 0.001 = 0.00783 mg
5. IVG = (7.83 - 0.00783) x 0.29 = 2.27 mg
6. IVD = 2.96 mg/kg x 2.45 kg = 7.25 mg
7. IVDR = 0.094 mg/liter x 4 liters = 0.376 mg
8. TID = 2.27 mg + 7.25 mg + 0.376 mg = 9.90 mg
9. TDOSE = 0.00783 mg + 9.90 mg = 9.91 mg
10. RMEAT = 9.91 mg x 0.1 = 0.991 mg
11. PPMDEER = 0.991 mg/54.4 kg = 0.018 mg/kg or ppm

Residues in Fish

Residues in fish were calculated assuming that the fish lived in and were caught from waters 6 inches deep, directly downwind of a treated site, with a minimum buffer strip of 20 feet for ground-based applications and 50 feet for aerial applications. For most of the herbicides considered in this analysis, which do not appreciably bioaccumulate, the concentrations in fish were taken to be equal to the particular herbicide's concentrations in

water. For the herbicides for which bioconcentration is likely to be greater--atrazine, diuron, and tebuthiuron--a bioconcentration factor was used. A bioconcentration factor of 10 was used for tebuthiuron, a value of 5 was used for atrazine, and a bioconcentration factor of 20 was used for diuron (Koeman et al., 1969). Doses to humans from eating fish containing herbicide were calculated assuming that 400 g are eaten daily.

To illustrate the method used to determine human dietary exposures from consuming fish contaminated with herbicides, the following example is provided for a routine-realistic right-of-way operation using atrazine:

The first step is to calculate the herbicide concentration per pound applied in a water body 6 inches deep. According to table 4-8, the value of drift to water for the scenario is 0.0264 mg/ft². The concentration in a 6-inch deep body of water per pound applied per acre is:

$$\frac{0.0264 \text{ mg}}{\text{ft}^2} \times \frac{1}{0.5 \text{ ft}} \times \frac{0.0353 \text{ ft}^3}{\text{liter}} = \frac{1.86 \times 10^{-3} \text{ mg/liter}}{1.86 \text{ ug/liter}}$$

The concentration of atrazine is adjusted for the 1b/acre applied for the scenario in table 4-3:

$$1.86 \text{ ug/liter} \times 3.00 = 5.58 \text{ ug/liter}$$

The concentration in the fish is based on the bioconcentration factor of atrazine. This assumes that a fish accumulates 5 ug of atrazine into its body for every 1 ug in water and is calculated as follows:

$$5.58 \text{ ug/liter} \times 5 = 27.9 \text{ ug/kg}$$

The dose to a 50-kg human based on consumption of 0.4 kg of fish is:

$$\frac{(27.9 \text{ ug/kg} \times 0.4 \text{ kg})}{50 \text{ kg}} = 0.223 \text{ ug/kg}$$

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This value is given in table B-17.

Dermal Exposure

Dermal exposure from drift was estimated by assuming that 2 square feet of skin were exposed (Dost, 1983) and the level of deposition on skin is the same as that found on the sampling sheets used in the drift monitoring studies. The dose was calculated as the deposited amount times the dermal penetration rate.

Indirect dermal exposure resulting from contact with foliage with surface residues of drifted herbicide was calculated by using the "unified field model" of Pependorf and Leffingwell (1982) and Pependorf (1985). This model was developed to estimate the possible doses and effects of insecticides on agricultural workers; however, it was only used to estimate exposure for this analysis. The model was applied to estimate the relatively heavy exposures that could result from extensive foliage contact, such as that which would be experienced in berry picking. The model takes into account the following:

1. The residue on foliage at any point in time after application (this analysis assumes no decay after initial application).
2. A crop-specific residue transfer coefficient (cm^2/hr).
3. The exposure period in hours.
4. The dermal penetration rate for each herbicide and the body mass of a human (50 kg).

The residue transfer coefficient has been determined for a few agricultural situations. The value of $1,600 \text{ cm}^2/\text{hour}$ for this coefficient was used in this analysis to estimate doses to berry pickers. This value, derived from data collected for grape harvesting (Pependorf, 1985), represents a relatively high exposure situation. People engaged in activities involving less foliage contact, for example, tree planting, can be expected to

Estimation of Doses

receive doses that are considerably less. People who contacted foliage after the initial application also receive reduced doses because of degradation of the herbicides (see table 4-10).

Dermal doses due to incidental contact with foliage, represented in the scenarios by vegetation contact for the hiker, were estimated by another method. Lavy et al. (1980) measured the level of 2,4,5-T on cloth patch samplers attached to a person who walked through a treated forest area. The residues were less than the detection limit of 0.01 mg per 100 cm² patch, but in this analysis a conservative assumption was made that the residues were at the detection limit. The area of clothing contacting foliage was assumed to be 40 percent of the total human surface area, and 10 percent of the total area was assumed to be bare skin contacting foliage. The same dermal penetration rates discussed previously were applied to bare skin, but the penetration through clothing was assumed to be 30 percent over a 6-hour period, based on work by Newton and Norris (1981).

Estimation of Doses to Workers and the Public From Accidents

The following scenarios were used to estimate the worst case doses that would result from the exposure to high amounts of herbicide that could occur in accidents.

1. Accidental Spraying. Members of the public are accidentally sprayed with herbicide because they are beneath a spray aircraft or too close to a truck or backpack applicator. (This dose would also apply to workers.) Indirect exposures to the same categories of people examined in the routine scenario are also estimated here. However, in the accidental-worst case spraying scenario, all items that they eat, drink, or brush against are sprayed at the full application rate, not just through drift.
2. Spills. Members of the public receive herbicide exposure via drinking water when a load of herbicide mixture is spilled or when a container of herbicide concentrate breaks open and spills into a

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Table 4-10

Doses Resulting From Vegetation Contact on a Treated Site
(micrograms/kg)

Herbicide	Degradation Rate per Day	Hiker			Berrypicker		
		Day 1	Day 30	Day 90	Day 1	Day 30	Day 90
Amitrole	0.0866	12.0	0.9	0.0	7168.0	533.5	3.0
Asulam	0.0110	4.2	3.0	1.6	2508.8	1803.6	932.2
Atrazine	0.0621	15.0	2.3	0.1	8960.0	1390.6	33.5
Bromacil	0.0116	18.0	12.7	6.3	10752.0	7592.0	3785.2
2,4-D	0.0431	2.0	0.6	0.0	1225.7	336.4	25.3
2,4-DP	0.0431	3.0	0.8	0.1	1792.0	491.8	37.0
Dalapon	0.0542	18.0	3.5	0.1	10752.0	2115.1	81.8
Dicamba	0.0578	4.8	0.8	0.0	2867.2	506.3	15.8
Diuron	0.2740	35.9	0.0	0.0	21504.0	5.8	0.0
Fosamine	0.0990	7.2	0.4	0.0	4300.8	220.5	0.6
Glyphosate	0.0495	3.0	0.7	0.0	1792.0	405.9	20.8
Hexazinone	0.0584	7.2	1.2	0.0	4300.8	745.9	22.4
Picloram	0.0693	0.0	0.0	0.0	18.6	2.3	0.0
Simazine	0.0455	2.8	0.7	0.0	1648.6	421.0	27.5
Tebuthiuron	0.0834	4.8	0.4	0.0	2867.2	234.9	1.6
Triclopyr	0.3120	4.8	0.0	0.0	2867.2	0.2	0.0

drinking water supply. Workers spill concentrate or prepared spray mixture on their skin during mixing, loading, or spraying operations; or are doused when a transfer hose breaks.

Accidental dermal doses were derived from modeling the dermal penetration of herbicide concentrate or mixture for direct exposures. Accidental ingestion doses were estimated by modeling the dilution of herbicide concentrate or mixture in a body of water of a given size.

To calculate the dose to a person directly sprayed at the full per-acre application rate, the worst case application rates shown in table 4-3 were converted to mg/ft^2 . It is assumed that 2 square feet of human skin is exposed (Dost, 1983).

For example, the application rate of amitrole in the routine-worst case aerial application scenario is 8.0 lb a.i./acre (table 4-3). This can be converted to kg/ha through a conversion factor:

$$8.0 \text{ lb a.i./acre} \times 1.12 \frac{\text{kg/ha}}{\text{lb/acre}} = 8.96 \text{ kg a.i./ha}$$
$$8.96 \text{ kg/ha} \times 1,000,000 \frac{\text{mg}}{\text{kg}} \times 0.0001 \text{ ha}/\text{m}^2 \times 0.093 \frac{\text{m}^2}{\text{ft}^2} = 83.3 \text{ mg}/\text{ft}^2$$

If 2 square feet of skin were exposed on a 50 kg person, then the surface deposit would be $166.7 \text{ mg}/\text{ft}^2$.

The absorbed dose must consider the dermal penetration rate: $166.7 \text{ mg} \times 0.001$ (dermal penetration rate) = 0.167 mg absorbed. This is equivalent to a dose of 0.003 mg/kg or 3 ug/kg, as given in table 4-11.

Reentry exposure to the general public is estimated assuming an individual walks through a treated area after an operation has been completed, even though the area is posted. Reentry exposure is also calculated for an individual who picks berries for 4 hours in a treated area, even though the area is posted. Accidental dietary exposure is derived by assuming an individual eats food items that have been directly sprayed rather than food items receiving only spray drift or eats meat from animals that have fed

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Table 4-11

Doses to the Public from Items Receiving the Full per-Acre
Application Rate by Exposure Type,
Accidental-Worst Case
(micrograms/kg)

Herbicide	Direct Dermal	Reentry Hiker	Reentry Picker	Drink Water	Eating Berries	Eating Vegs.	Eating Deer	Eating Bird	Eating Fish
Amitrole	3	0	9	117	93	194	19	116	47
Asulam	209	3	538	73	58	121	13	83	29
Atrazine	355	5	914	125	99	206	22	141	249
Bromacil	417	6	1,075	147	116	242	26	165	59
2,4-D	103	1	264	60	48	99	10	64	24
2,4-DP	2	0	5	73	58	121	12	73	29
Dalapon	417	6	1,075	147	116	242	26	165	59
Dicamba	116	2	299	59	47	97	10	64	23
Diuron	667	10	1,720	235	186	387	42	265	1,878
Fosamine	501	7	1,290	176	140	290	31	199	70
Glyphosate	209	3	538	73	58	121	13	83	29
Hexazinone	250	4	645	88	70	145	16	99	35
Picloram	4	0	10	73	58	121	12	73	29
Simazine	209	3	538	73	58	121	13	83	29
Tebuthiuron	250	4	645	88	70	145	16	99	352
Triclopyr	55	1	142	117	93	194	19	119	47

Estimation/Lifetime Doses

directly on sprayed vegetation or fish taken from directly sprayed water bodies or drinks water from those water bodies.

An individual receives an accidental ingestion exposure resulting from a major spill by drinking water from a pond or a reservoir that has been contaminated by a dump of 100 gallons of herbicide mix as from a helicopter, or 2,000 gallons of spray mix from a batch truck. Two thousand gallons is approximately the largest amount of spray mix that might be carried by a tank truck supplying a large aerial spraying operation. One hundred gallons is approximately the largest load that can be carried by the types of helicopters currently used in the Pacific Northwest. The maximum herbicide concentrations in drums and batch trucks are shown in table 4-15. The pond is assumed to be 1 acre in area and 4 feet deep and to have no inflow or outflow. The reservoir is assumed to be 16 acres in area and 8 feet deep. A person is assumed to drink 1 liter of water after complete mixing has occurred.

Direct dermal exposures were calculated for spills of 0.5 liter of herbicide concentrate (if liquid concentrates are used) or 0.5 liter of the most concentrated spray mixture. The person exposed during the spill is assumed to weigh 50 kg, and most of his surface area (0.8 m^2 or 8.6 ft^2) is thoroughly wetted by the solution. Denim fabric commonly used in clothing retains about 57.5 mL of solution per square foot (Weeks, 1985), and absorption of herbicide through the cloth was calculated as before, based on Newton and Norris (1981). However, 20 percent of the solution was assumed to wet bare skin. A spill resulting in this exposure could result from broken hoses, spilled containers, or emergency and accidental dumps by helicopters.

Estimation of Lifetime Doses to Workers and the Public

Doses used in the cancer risk analysis for 2,4-D, 2,4-DP, picloram, amitrole, asulam, bromacil, and glyphosate (discussed in Section 5) were derived by combining available information on the number of days per year an individual worker may spray an herbicide using a particular application method and estimates of the expected daily dose and the number of years of

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employment. Expected daily doses were calculated assuming that the worst case dose is experienced 5 percent of the time and the realistic dose 95 percent of the time, in all routine scenarios. The realistic cases assume that workers are employed in pesticide application for 5 years, and the worst cases assume 20 years employment in herbicide applications.

Average numbers of exposures per lifetime were used with expected daily doses for each scenario to derive realistic lifetime doses. Extreme lifetime doses were derived by multiplying expected daily dose levels estimated in worker scenarios by estimates of the highest number of days a worker is likely to be engaged in the particular type of application method. Exposures per lifetime in the realistic scenarios were estimated to be the following: aerial, 30; right-of-way, 45; backpack, 50; and hand application, 70. For the routine-worst case scenario doses, the number of exposures per lifetime were as follows: aerial, 288; right-of-way, 416; backpack, 440; and hand application, 480.

Lifetime exposures to the public for the five herbicides were derived by assuming a realistic estimate would be a single exposure per lifetime in each of the public exposure scenarios, and a high estimate would be one exposure per year for 30 years. The exposure levels derived in the realistic and extreme public scenarios and in accidental spraying and spills were multiplied by 1 for realistic lifetime and 30 for extreme lifetime doses.

Effect of Body Size on Exposure

All doses estimated in the exposure analysis were calculated for a representative 50-kg person. This weight was chosen to represent an adult of less than average weight, so that doses to adults would be calculated in a conservative manner. Doses for a larger person would be less in terms of mg per kg body weight. For example, a 70-kg person would receive approximately 25 percent more herbicide than a 50-kg person by dermal exposure because of his greater surface area. A 70-kg person would also receive on average about 25 percent more herbicide by dietary exposure

routes because both metabolic rate and dietary intake are related to body surface area which is approximately proportional to body weight raised to the 2/3 power:

$$\frac{(70)^{2/3}}{(50)^{2/3}} = 1.25$$

However, a 70-kg person also has a body weight greater than a 50-kg person, by a greater factor:

$$\frac{70}{50} = 1.4$$

The combined effect of these two factors is that a 70-kg person will receive a dose in mg/kg that is only 89 percent as great as for a 50-kg person.

Conversely, smaller people can be expected to receive greater doses in terms of mg per kg body weight. A 20-kg child will receive only about 54 percent as much herbicide as a 50-kg person, but his weight is only 40 percent as great. The net effect is that a 20-kg child will receive a dose that is 36 percent greater in terms of mg/kg than it would be for a 50-kg person.

It should be noted that small children may, in some cases, be among the more sensitive individuals.

Table 4-12 illustrates the effect of body size on expected dose. The table shows doses for a 20-kg child and 50- and 70-kg adults for each route of exposure in the routine-worst case aerial scenario.

Time Dependence of Dermal Exposure Due to Vegetation Contact

Herbicide residues on plant surfaces decline over time as a result of absorption by the plant, degradation, volatilization, and washing by rainfall. After herbicide sprays dry on plant surfaces they cannot be completely rubbed off because of binding to the plant surface materials.

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Table 4-12

Effect of Body Size on Dose:
2,4-D Aerial Routine-Worst Case Scenario
(doses in micrograms/kg)

Exposure Route	20-kg Child	50-kg Adult	70-kg Adult
Drift, Dermal	13.86	10.19	9.07
Veg. Contact, Hiker	0.20	0.15	0.13
Veg. Contact, Picker	35.72	26.27	23.38
Drinking Water	17.25	12.68	11.29
Eating Berries	14.18	10.42	9.28
Eating Vegetables	28.35	20.85	18.55
Eating Deer Meat	2.16	1.59	1.41
Eating Game Bird	9.20	6.77	6.02
Eating Fish	6.90	5.07	4.51

Consequently, persons entering a treated area a short time after spraying are likely to receive dermal doses much smaller than the conservative doses calculated in this analysis. However, specific data were not available for most of the 16 herbicides regarding persistence on plant surfaces. The most appropriate data would be measurements of dislodgeable residues, but such data were not available for the herbicides. In most cases, measurements of total plant residues over time were available, so these data have been used to calculate degradation rates in those cases where surface measurements were unavailable. Degradation rates calculated in this way should be considered minimum degradation rates for dislodgeable residues because the residues that were measured in deriving the data may have been largely or entirely unavailable for dermal exposure through vegetation contact. Degradation rates for the 16 herbicides were determined using the following references:

1. amitrole	Ghassemi et al. (1981)
2. asulam	Gortz and Van Oorschot (1984)
3. atrazine	Montgomery and Freed (1961)
4. bromacil	WSSA (1983)
5. 2,4-D	USDA (1984)
6. 2,4-DP	USDA (1984)
7. dalapon	USDA (1984)
8. dicamba	USDA (1984)
9. diuron	Leonard et al. (1975)
10. fosamine	Ghassemi et al. (1981)
11. glyphosate	Newton and Dost (1981)
12. hexazinone	USDA (1984)
13. picloram	Bovey et al. (1967)
14. simazine	Ghassemi et al. (1981)
15. tebuthiuron	Bovey et al. (1978)
16. triclopyr	USDA (1984)

Table 4-10 shows the dermal exposures calculated for a hiker and a person picking berries for 4 hours on a treated site. The table shows the doses at the first day and also after 30 and 90 days. The doses decline dramatically even with these minimum rates of degradation. In the case of

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bromacil, no degradation rate was found in the available literature, so a minimal degradation rate corresponding to a half life of 60 days was used. The actual rate of degradation is likely to be greater.

Even the 90-day time period is considerably less than the minimum period between treatment for site preparation and reentry for tree planting. Vegetation contact for tree planters is also much less than for berrypickers, so the maximum dose for planters will be significantly less.

EXPOSURE ANALYSIS RESULTS

This subsection presents the results of the exposure analysis. Doses to workers and the public estimated for routine operations and for accidents are summarized and discussed. Complete dose estimates are presented in Attachment B.

Doses to Workers

Realistic Worker Doses in Routine Operations

Routine-realistic worker doses are summarized in table 4-13. No worker in any of the realistic scenarios receives a dose of any herbicide greater than 1.0 mg/kg. All backpack workers receive doses greater than 0.1 mg/kg except those using amitrole, dicamba, and picloram. Helicopter mixer-loaders receive atrazine, dalapon, and simazine doses greater than 0.1 mg/kg, but all other doses in the realistic aerial scenario for mixer-loaders, pilots, supervisors, and observers are less than 0.1 mg/kg. Bromacil, 2,4-DP, diuron, fosamine, and triclopyr doses to hack-and-squirt applicators are greater than 0.1 mg/kg. All other hand application doses are less than 0.1 mg/kg.

Worst Case Worker Doses in Routine Operations

In the routine-worst case worker application scenarios (summarized in table 4-14), doses to aerial supervisors and observers, right-of-way applicators, and injection-bar applicators are all less than 1.0 mg/kg.

Table 4-13

Worker^a Doses for Routine-Realistic Scenarios

Herbicide	Aerial ^b				Backpack ^b	Truck ^b			Hand Application ^b	
	Pilot	M/L	Sup	Obs		App	M/L	App M/L	Hack/ Squirt	Inj Bar
Amitrole	0	0	-1	-1	1	-1	-1	-1	0	0
Asulam	2	2	1	1	3	1	1	2	--	--
Atrazine	2	3	2	1	3	2	2	2	--	--
Bromacil	--	--	--	--	3	2	2	2	3	2
2,4-D	2	2	1	0	3	1	1	1	2	2
2,4-DP	2	2	1	0	3	1	1	1	3	2
Dalapon	2	3	2	1	3	2	2	2	--	--
Dicamba	2	2	1	0	2	1	1	1	2	2
Diuron	--	--	--	--	3	2	2	2	3	2
Fosamine	2	2	1	1	3	2	2	2	3	2
Glyphosate	2	2	1	1	3	1	1	1	--	--
Hexazinone	2	2	1	1	3	1	1	2	--	--
Picloram	0	0	-1	-1	1	-1	-1	-1	1	0
Simazine	2	3	2	1	3	1	1	1	--	--
Tebuthiuron	2	2	1	0	3	1	1	2	--	--
Triclopyr	1	1	1	0	2	1	1	1	2	1

^aM = Mixer, L = Loader, App = Applicator, Sup = Supervisor, Obs = Observer.

^bNumbers represent the following doses:

- 4 10.0 mg/kg
- 3 1.0 mg/kg (less than 1 milligram/kg)
- 2 0.1 mg/kg
- 1 0.01 mg/kg
- 0 0.001 mg/kg (less than 1 microgram/kg)
- 1 0.0001 mg/kg
- 2 0.00001 mg/kg
- herbicide not used in this scenario

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Table 4-14

Worker^a Doses for Routine-Worst Case Scenarios

Herbicide	Aerial ^b				Backpack ^b	Truck ^b			Hand Application ^b	
	Pilot	M/L	Sup	Obs		App	M/L	App M/L	Hack/ Squirt	Inj Bar
Amitrole	1	1	1	0	2	1	1	1	2	1
Asulam	3	3	2	2	4	3	3	3	--	--
Atrazine	3	3	3	2	4	3	3	3	--	--
Bromacil	--	--	--	--	4	3	3	3	4	3
2,4-D	3	3	2	2	4	3	2	2	4	3
2,4-DP	3	3	2	1	4	3	2	3	4	3
Dalapon	4	4	3	2	4	3	3	3	--	--
Dicamba	3	3	2	2	4	3	2	2	3	3
Diuron	--	--	--	--	4	3	3	3	4	3
Fosamine	4	4	3	2	4	3	3	3	4	3
Glyphosate	3	4	3	2	4	3	3	3	--	--
Hexazinone	3	3	2	2	4	3	3	3	--	--
Picloram	2	2	1	0	2	1	1	1	2	1
Simazine	3	4	3	2	4	3	3	3	--	--
Tebuthiuron	4	4	3	2	4	3	3	3	--	--
Triclopyr	3	3	2	1	3	2	2	2	3	2

^aM = Mixer, L = Loader, App = Applicator, Sup = Supervisor, Obs = Observer.

^bNumbers represent the following doses:

- 4 10.0 mg/kg
- 3 1.0 mg/kg (less than 1 milligram/kg)
- 2 0.1 mg/kg
- 1 0.01 mg/kg
- 0 0.001 mg/kg (less than 1 microgram/kg)
- 1 0.0001 mg/kg
- 2 0.00001 mg/kg
- herbicide not used in this scenario

Doses to Workers

Doses to the Public

Doses of dalapon, fosamine, tebuthiuron, and triclopyr exceed 1.0 mg/kg for pilots and mixer-loaders in the aerial scenario. Doses of simazine and glyphosate to mixer-loaders also exceed 1.0 mg/kg. All herbicide doses to backpack workers exceed 1.0 mg/kg except for amitrole and picloram. Hack-and-squirt applicator doses of bromacil, 2,4-DP, diuron, fosamine, and triclopyr all exceed 1.0 mg/kg. All other doses are less than 1.0 mg/kg.

Doses to the Public

Doses via Individual Exposure Routes

Doses to the public via specific exposure routes in the three routine-realistic scenarios are shown in Attachment B. In none of the routine-realistic scenarios does the public receive a dose greater than 0.01 mg/kg (10 micrograms/kg) for any of the 16 herbicides through any single exposure route. Doses are lowest (less than 0.006 micrograms/kg) to the hiker who contacts vegetation with herbicide residues. Doses are highest for the ingestion routes of exposure, particularly drinking water and eating berries or garden vegetables.

Doses to the public via individual exposure routes in the routine-worst case scenarios also are shown in Attachment B. No dose to the public is greater than 0.01 mg/kg for any chemical through any exposure route in either the truck (right-of-way) or backpack scenarios. Highest public doses occur in the routine-worst case aerial scenario--in particular, for the berrypicker contacting vegetation, where the berrypicker dose is slightly higher than 0.1 mg/kg (100 micrograms/kg) for dalapon and fosamine. It is less than 0.1 mg/kg for all the other herbicides.

Doses via Multiple Exposure Routes

Doses for people who receive combined herbicide doses of each of the 16 herbicides through the various exposure routes outlined in table 4-7 are listed for the three routine-realistic scenarios in table 4-15, and for the three routine-worst case scenarios in table 4-16.

Table 4-15
Doses to Example People in
Routine-Realistic Exposure Scenarios

Herbicide	Aerial					Truck (row)					Backpack				
	Hiker	Berry- picker	Hunter	Fisher- man	Nearby Resident	Hiker	Berry- picker	Hunter	Fisher- man	Nearby Resident	Hiker	Berry- picker	Hunter	Fisher- man	Nearby Resident
Amitrole	1	1	1	1	1	-1	0	0	0	0	0	0	0	0	0
Asulam	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0
Atrazine	1	2	1	2	1	0	0	0	0	0	0	1	0	1	1
Bromacil	-	-	-	-	-	1	1	1	1	1	1	1	1	1	1
2,4-D	1	1	1	1	1	0	0	0	0	0	0	1	0	0	0
2,4-DP	1	1	1	1	1	-1	0	0	0	0	0	0	0	0	0
Dalapon	1	2	1	1	1	0	0	0	0	0	0	1	1	0	1
Dicamba	0	1	1	1	1	-1	0	-1	-1	0	-1	0	0	-1	0
Diuron	-	-	-	-	-	0	0	0	1	0	0	1	1	1	1
Fosamine	1	1	1	1	1	0	0	0	0	0	0	1	0	0	1
Glyphosate	1	1	1	1	1	0	0	0	0	0	0	1	0	0	0
Hexazinone	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0
Picloram	0	1	1	1	1	-1	-1	-1	-1	0	-1	0	0	0	0
Simazine	1	2	1	1	1	0	0	0	0	0	0	1	0	0	0
Tebuthiuron	0	1	1	1	1	0	0	0	0	0	0	1	0	0	0
Triclopyr	1	1	1	1	1	-1	0	0	0	0	0	0	0	0	0

DOSE LEVELS

- not used
- 2 0.1 mg/kg
- 1 0.01 mg/kg
- 0 0.001 mg/kg
- 1 0.0001 mg/kg

Doses to Representative Members of the Public in
Routine-Worst Case Exposure Scenarios

Herbicide	Aerial					Truck (row)					Backpack				
	Hiker	Berry- picker	Hunter	Fisher- man	Nearby Resident	Hiker	Berry- picker	Hunter	Fisher- man	Nearby Resident	Hiker	Berry- picker	Hunter	Fisher- man	Nearby Resident
Amitrole	2	2	2	2	2	0	1	0	0	1	0	1	0	0	1
Asulam	2	2	2	2	2	0	1	0	0	1	0	1	1	1	1
Atrazine	2	2	2	2	2	0	1	1	1	1	1	1	1	1	1
Bromacil	-	-	-	-	-	0	0	0	0	0	0	1	1	0	1
2,4-D	2	2	2	2	2	0	1	0	0	0	0	1	1	0	1
2,4-DP	1	2	2	2	2	0	1	0	0	1	0	1	0	0	1
Dalapon	2	3	2	2	3	1	1	1	1	1	1	2	1	1	1
Dicamba	2	2	2	2	2	0	0	0	0	1	0	1	1	1	1
Diuron	-	-	-	-	-	1	1	1	1	1	1	1	1	1	1
Fosamine	2	3	3	3	3	1	1	1	1	1	1	2	1	1	1
Glyphosate	2	3	2	2	2	0	1	0	0	1	1	1	1	1	1
Hexazinone	2	2	2	2	2	0	1	0	0	1	0	1	1	0	1
Picloram	2	2	2	2	2	0	0	0	0	0	0	1	0	0	1
Simazine	2	3	2	2	2	0	1	0	0	1	1	1	1	1	1
Tebuthiuron	2	3	2	3	2	0	1	0	1	1	1	1	1	1	1
Triclopyr	2	2	2	2	2	0	1	0	0	1	0	1	1	1	1

DOSE LEVELS

3	1.0 mg/kg
2	0.1 mg/kg
1	0.01 mg/kg
0	0.001 mg/kg
-1	0.0001 mg/kg

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In no instance do any of the combined doses of any of the herbicides in the routine-realistic scenarios exceed 0.1 mg/kg. Those that exceed 0.01 mg/kg (berrypickers for atrazine, dalapon, and simazine; fishermen for atrazine) are all lower than 0.015 mg/kg (see Attachment B).

No representative member of the public receives a dose of any herbicide higher than 0.01 mg/kg in the routine-worst case right-of-way scenario. Dalapon and fosamine doses to berrypickers exceed 0.01 mg/kg in the routine-worst case backpack scenario. Highest public doses range from greater than 0.01 mg/kg to less than 0.3 mg/kg for combined public doses in the routine-worst case aerial scenario for all 16 herbicides. Highest public doses are from dalapon and fosamine.

Accidental Doses to Workers and the Public

Doses from Accidental Spraying

Doses to members of the public from accidental spraying are listed for the 16 herbicides in table 4-11. The table lists doses in micrograms/kg rather than mg/kg (1 mg = 1,000 micrograms). Doses exceed 1 mg/kg for berrypicker dermal exposure (reentry) for bromacil, dalapon, diuron, and fosamine. Doses of diuron from eating fish exceed 1 mg/kg. All other doses are less than 1 mg/kg.

Doses to representative members of the public from accidental spraying, listed in table 4-17, exceed 1 mg/kg for the berrypicker for atrazine, bromacil, dalapon, hexazinone, tebuthiuron, and triclopyr. Doses of fosamine to the berrypicker exceed 2 mg/kg. Doses of diuron to the hunter and nearby resident exceed 1 mg/kg; for the berrypicker and fisherman, doses exceed 2 mg/kg. All doses of all other herbicides are less than 1 mg/kg for representative members of the public in spraying accidents.

Doses from Spills

Doses from spill accidents, both direct dermal and via drinking water, are listed in table 4-18. The spill doses are listed in mg/kg (not

Table 4-17

Doses for Example People^a for
Accidental-Worst Case Spraying
(micrograms/kg)

Herbicide	Hiker	Berry- picker	Hunter	Fisherman	Nearby Resident
Amitrole	121	222	256	168	314
Asulam	285	878	381	314	406
Atrazine	484	1,492	647	734	690
Bromacil	570	1,755	761	628	812
2,4-D	164	475	239	188	263
2,4-DP	75	139	160	105	196
Dalapon	570	1,755	761	628	812
Dicamba	176	521	250	200	273
Diuron	912	2,809	1,218	2,790	1,299
Fosamine	684	2,107	914	754	974
Glyphosate	285	878	381	314	406
Hexazinone	342	1,053	457	377	487
Picloram	77	145	162	107	198
Simazine	285	878	381	314	406
Tebuthiuron	342	1,053	457	694	487
Triclopyr	173	408	311	220	367

^aAll of these people receive multiple exposures as shown in table 4-7.

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Table 4-18

Doses from Herbicide Spills
(mg/kg)

Herbicide	Spill of One Pint Concentrate on Skin	Spill of One Pint Tank Mix on Skin	Helicopter ^a Dump into Pond	Helicopter ^a Dump into Reservoir	Truck ^a Spill into Pond	Truck ^a Spill into Reservoir
Amitrole	1.20	0.24	0.0737	0.0023	0.7365	0.0230
Asulam	240.00	20.04	0.0615	0.0019	0.6150	0.0192
Atrazine	240.00	24.00	0.0737	0.0023	0.7365	0.0230
Bromacil	240.00	12.00	-- ^b	--	0.3683	0.0115
2,4-D	144.00	14.40	0.0737	0.0023	0.7365	0.0230
2,4-DP	3.60	0.15	0.0460	0.0014	0.9206	0.0288
Dalapon	--	60.00	0.1841	0.0058	1.8413	0.0575
Dicamba	167.04	16.70	0.0737	0.0023	1.4730	0.0460
Diuron	240.00	19.20	--	--	0.5892	0.0184
Fosamine	240.00	72.00	0.2210	0.0069	2.2095	0.0690
Glyphosate	180.00	30.00	0.0921	0.0029	0.9206	0.0288
Hexazinone	120.00	18.00	0.0552	0.0017	0.5524	0.0173
Picloram	2.16	0.54	0.0921	0.0029	1.8413	0.0575
Simazine	240.00	30.00	0.0921	0.0029	0.9206	0.0288
Tebuthiuron	--	36.00	0.1105	0.0035	1.1048	0.0345
Triclopyr	39.60	7.92	0.1473	0.0046	2.9460	0.0921

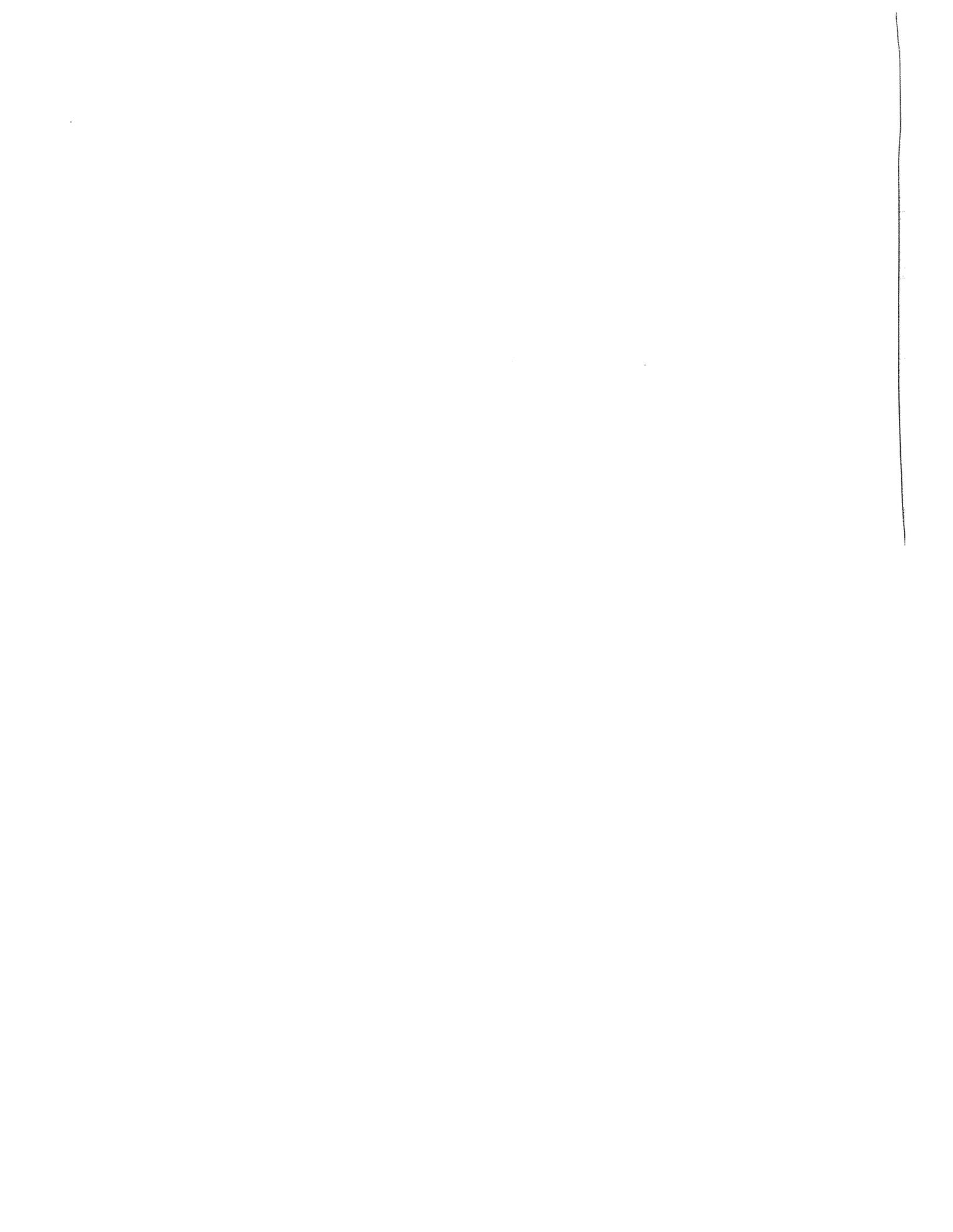
^aAssuming 1 liter of water drunk per day.

^b-- indicates herbicide not used in a form that could cause this kind of spill.

micrograms/kg as in the spraying accidents). By far, the highest doses are received in worker spill accidents where workers receive doses exceeding 100 mg/kg for all the herbicides except amitrole, dalapon, picloram, and tebuthiuron. Spills of mixture on workers' skin lead to estimated doses that exceed 10 mg/kg for all herbicides except amitrole, 2,4-DP, and picloram. Doses to the public from truck spills rarely exceed 1 mg/kg. Those from helicopter dumps into a reservoir never exceed 0.01 mg/kg.

Lifetime Doses

Lifetime doses to workers and the public from herbicide spraying for a specified number of exposures over a 70-year lifetime are listed in the final set of tables in Attachment B. Cancer risk based on the specified number of exposures is discussed in Section 5.

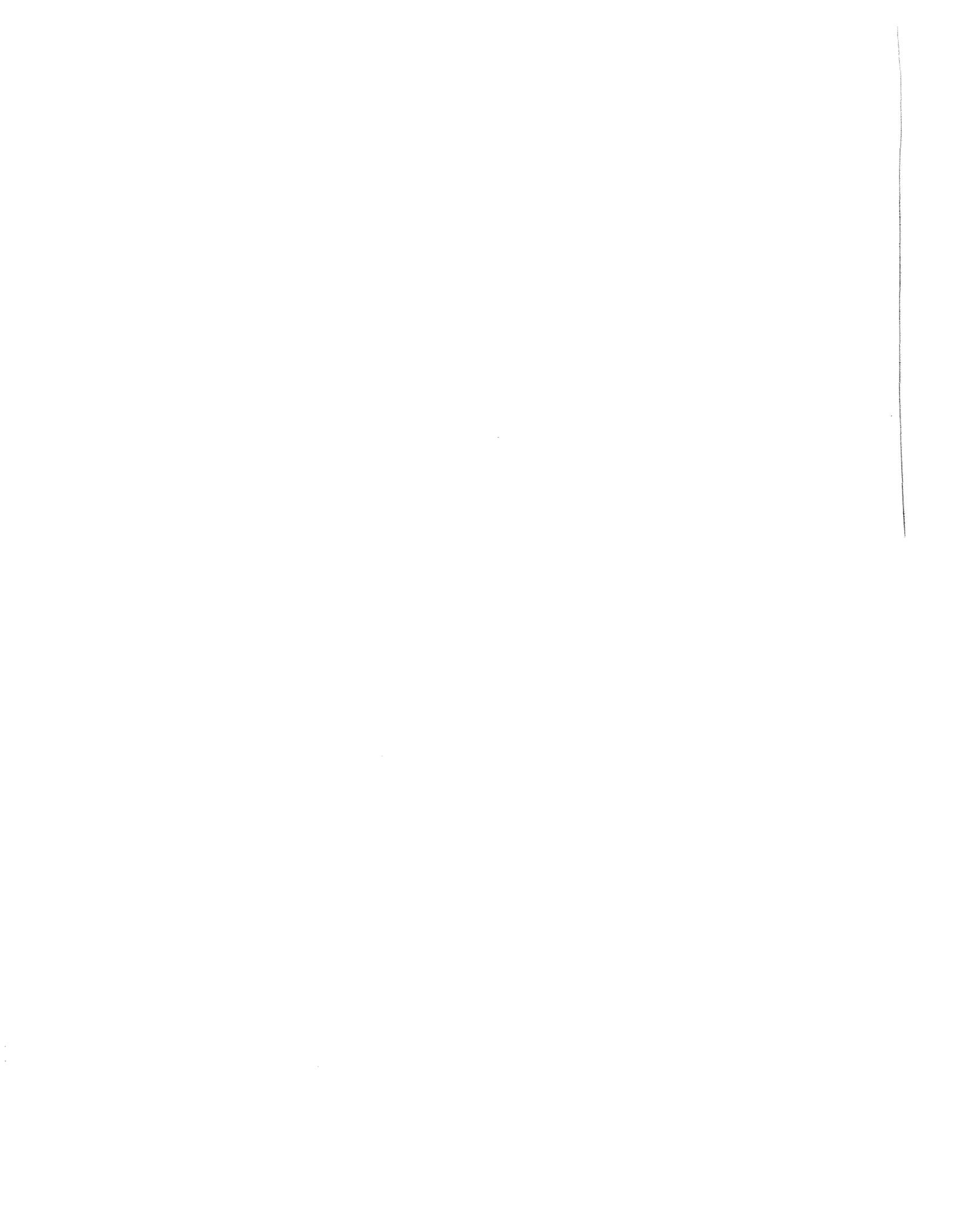


Appendix D

**Human Health
Risk Assessment
(Quantitative)**



Section 5



Section 5

HUMAN HEALTH RISK ANALYSIS

This section presents information on potential risks to the health of workers and members of the public from the proposed herbicide applications by comparing the exposure levels estimated in Section 4 with the toxic effect levels described in Section 3. The first subsection describes the methods used to evaluate risks. The second subsection evaluates the risks of threshold effects that include acute toxic effects, chronic systemic effects, and reproductive (fetotoxic and maternal toxic) and teratogenic effects. The last subsection evaluates the risks of the herbicides causing cancer or mutagenic effects in the population at risk. All judgments about risk are discussed in light of the probabilities of the estimated exposures actually occurring.

HOW THE RISKS TO WORKERS AND THE PUBLIC WERE DETERMINED

In this risk analysis, the risks to humans exposed to the 16 herbicides were quantified by comparing the doses estimated in the range of exposure scenarios presented in Section 4 with the results of toxicity tests on laboratory animals described in Section 3. There are two basic approaches for extrapolating from laboratory animal NOEL's to the general human population: the reference dose approach and the margin-of-safety (MOS) approach. Under the reference dose (RFD) approach, uncertainty factors based on the quality of the data are applied to the lowest (EPA) NOEL dose found in animal studies. These factors have been used for estimating acceptable human exposures based on experimental human and animal studies where systemic effects were observed following exposure to a toxic chemical substance (NRC, 1986). An uncertainty factor of 10 has normally been used in the estimation of safe levels in humans from experimental studies when there are valid human studies available and no indication of carcinogenicity. An uncertainty factor of 100 is used when there are few or no human studies available but there are valid long-term

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animal studies; when there are very limited toxicological data, 1,000 or greater could be used as an uncertainty factor.

Uncertainty factors and the "RFD approach" are used by Federal regulatory agencies, such as the FDA and EPA, to set RFD's for chemicals that a broad segment of the general public are likely to be exposed to for an indeterminate period of time. Thus, the RFD is a lifetime safe dose for threshold toxic effects based on the best available toxicity information on a particular chemical. Cancer and mutation effects are not dealt with in this way because they are not assumed to have a predictable threshold of reversible toxic effects.

The margin-of-safety (MOS) approach used in this risk assessment is based on the same concepts of a threshold of toxicity (approximated by animal no-observed-effect levels (NOEL's) in long-term studies) and of the safety of a dose. However, it differs from the RFD approach in that the actual difference between the field dose and the NOEL can be determined. First, the MOS approach is not being used here to establish a regulatory standard safe level for the general public against which samples of possibly contaminated products, for example, marketed vegetables or drinking water, would be tested. The margins-of-safety computed here are dose ratios that are direct comparisons of the doses estimated in this risk assessment with the NOEL's from animal studies. For example, an MOS of 100 means the laboratory-determined level is 100 times higher than the estimated dose. The lower the margin of safety, the greater the risk of toxic effects. Based on current accepted practice by EPA and the National Academy of Sciences, the standard margin of safety is 100. Thus, a margin of safety greater than 100 is considered to represent negligible risk, and a margin of less than 100 is considered to represent a risk of toxic effects. Although these MOS's correspond with the uncertainty factors used to determine the RFD's, they are applicable only in this risk assessment. Also, a margin of safety does not always mean that the dose is safe. An MOS of three, for example, could represent a high risk of toxic effects for repeated exposures.

How Risks to Workers and Public Were Determine

Second, the RFD as a standard level for comparison of tested samples should remain relatively stable over the years, modified only when the results of new toxicity tests produce a new NOEL or make a change in the RFD uncertainty factor appropriate. The margins of safety in this risk assessment, however, vary with the estimated doses in a particular exposure scenario and are thus used to indicate the potential toxic effects of a proposed chemical under differing conditions or routes of exposure or in comparison with alternative chemicals that may be used for the same purpose.

For doses that are not likely to occur more than once, such as those received by workers spilling a quart of spray mix over their entire upper body, a dose estimate that exceeds the laboratory test animal NOEL does not necessarily lead to the conclusion that there will be toxic effects. All the NOEL's in this risk analysis are based on (or take into account) long-term exposure. Estimated doses that exceed the NOEL are compared to the herbicide's acute oral LD₅₀ so that a judgment can be made on the risk of immediate, severe effects including fatalities. For convenience in this analysis, the ratio between the herbicide's LD₅₀ and the estimated human dose also is expressed as an MOS; however, it should not be interpreted in the same way as the MOS based on a NOEL in terms of the expectation of no effects in humans.

The larger the margin of safety (the smaller the estimated human dose compared to the animal NOEL), the lower the risk to human health. As the estimated dose to humans approaches the animal NOEL (as the MOS approaches one), the risk to humans increases. When an estimated dose exceeds a NOEL (giving an MOS of less than one), the ratio is reversed (the dose is divided by the NOEL) to indicate how high the estimated dose is above the laboratory toxicity level; a minus sign is attached to indicate that the dose exceeded the NOEL; and the result is no longer termed a margin of safety but is called simply a negative ratio.

A ratio of -3, for example, means that the estimated dose is 3 times the laboratory-determined level. A negative ratio implies that the estimated dose (given all the assumptions of the scenario) represents a clear risk of

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possible acute effects if the ratio is based on the LD₅₀, or of possible chronic effects if the ratio is based on the systemic or reproductive NOEL.

In general, when repeated doses to humans approach the animal NOEL (the MOS is less than 10), there is some possibility of harmful effects. In general, when the MOS is less than 100, sensitive individuals may be at risk. Conversely, when the human dose is small compared with the animal NOEL (giving an MOS greater than 100), the risk to humans can be judged negligible. Comparing one-time or once-per-year doses (such as those experienced by the public) to NOEL's derived from lifetime studies tends to greatly overestimate the risk from those rare events.

Systemic effects are evaluated based on the lowest systemic NOEL found in a 2-year feeding study of dogs, rats, or mice. (When subchronic studies reported effects at lower levels than chronic studies, the subchronic NOEL's were used.) Reproductive effects are evaluated based on the lowest maternal, fetotoxic, or teratogenic NOEL found in a 3-generation reproductive study or in a teratology study.

A worst case analysis of cancer risk is conducted for the herbicides for which there are cancer studies indicative of possible carcinogenic response--amitrole, asulam, atrazine, bromacil, picloram, 2,4-D and 2,4-DP--and for herbicides for which there is scientific controversy about their ability to cause cancer, such as and glyphosate. The risk of cancer is calculated for an individual by comparing estimates of lifetime dose over a 70-year period (computed in Section 4) with cancer potency estimates derived in the Hazard Analysis section. A worst case analysis also is conducted for those herbicides that have positive mutagenicity tests or those for which no data are available. The risk of these herbicides causing mutations is qualitative rather than quantitative, with a statement of the probable risk based on the available evidence of mutagenicity and carcinogenicity.

RISK OF GENERAL SYSTEMIC AND REPRODUCTIVE EFFECTS

For each application scenario, routine-realistic, routine-worst case, and accidental worst case assumptions were used to compute margins of safety for workers and the public for all 16 herbicides. Complete tables for each herbicide are in Attachment C. The margins of safety were computed by comparing the laboratory-determined NOEL's and LD₅₀'s in table 5-1 with the doses shown in Attachment B.

Risk to the Public Under Routine Operations

Table 5-2 summarizes the margin-of-safety results for the public for the 16 herbicides under the routine-realistic and the routine-worst case exposure scenarios.

Risk to the Public Under Routine-Realistic Scenarios

Margins of Safety for the Public Under Routine-Realistic Scenarios.

Table 5-2 shows that there are very large margins of safety (greater than 1,000) for every category of exposure--even cumulative exposures--under the routine-realistic scenario for asulam, bromacil, 2,4-DP, fosamine, glyphosate, hexazinone, picloram, and tebuthiuron. Margins of safety are all greater than 150 for the herbicides 2,4-D, dalapon, dicamba, diuron, simazine, and triclopyr. Although the public should not be chronically exposed to these herbicides (indeed, because of the remote location of most spray areas, it is unlikely that any member of the public will be exposed at all), these large margins of safety mean that they could be repeatedly exposed to these levels, or cumulatively exposed to these levels, and suffer no adverse effects. This is true for all individuals, including pregnant women and the most sensitive individuals.

MOS's for atrazine are less than 100 for several routes of exposure and for combined exposures in the routine-realistic scenarios for aerial applications. MOS's for truck and backpack applications are all greater than 100 for atrazine. Sensitive members of the general public could experience some ill effects from these exposures, but the kinds of effects

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Table 5-1

Toxicity and Cancer Potency of Herbicides

Herbicide	Rat LD50 mg/kg	Systemic NOEL mg/kg/day	Reproductive/ Terat. NOEL mg/kg/day	Cancer Potency per mg/kg/day
Amitrole	4,080.00	0.025	4.0	1.4
Asulam	4,000.00	50.0	50.0	0.02
Atrazine	672.00	0.48	0.5	0.03
Bromacil	3,998.00	6.25	12.5	0.0038
2,4-D	375.00	1.0	5.0	0.00503
2,4-DP	532.00	5.0	6.25	0.012
Dalapon	7,577.00	8.0	12.5	*
Dicamba	757.00	15.8	3.0	*
Diuron	3,750.00	0.625	6.25	*
Fosamine	24,400.00	25.0	50.0	*
Glyphosate	4,320.00	31.0	10.0	0.000026
Hexazinone	1,690.00	10.0	50.0	*
Picloram	8,200.00	7.0	50.0	0.00057
Simazine	5,000.00	5.0	5.0	*
Tebuthiuron	644.00	12.5	5.0	*
Triclopyr	630.00	2.5	10.0	*

*No oncogenic potential was indicated from laboratory studies, therefore a cancer potency analysis was not conducted.

Herbicide	Routine-Realistic Scenarios	Routine-Worst Case ^a Scenarios
Amitrole	All right-of-way MOS's at least 50. Most backpack MOS's are greater than 50: exceptions are eating vegetables (41) and resident (32). Most aerial MOS's are below 50, including several below 10: the berrypicker (8.3), hunter (9.9), fisherman (9.5), and resident (6.2).	Several backpack and several right-of-way MOS's are between 10 and 50. Most aerial MOS's are below 10. The aerial exposure to the resident exceeds the NOEL.
Asulam	All situations 6,700 or greater.	All situations at least 710.
Atrazine	All situations greater than 50 except for aerial application combined route exposure to the berrypicker (41) and the fisherman (45).	All backpack and right-of-way scenarios have MOS's at least 130. Most aerial MOS's are less than 10: berrypicker combined routes (5.7), fisherman (8.7), and resident (9.5).
Bromacil	All situations are at least 2,300.	All situations are 700 or greater.
2,4-D	All situations at least than 160.	All right-of-way and backpack MOS's are at least 390. All aerial MOS's are greater than 10 with the following situations having MOS's of 10 to 50: vegetation contact by picker (38), eating vegetables (48), hiker (43), berrypicker (17), hunter (32), fisherman (36) and resident (23).
2,4-DP	All situations 1,200 or greater.	All situations at least 240.
Dalapon	At least 640 in all situations.	Only aerial scenarios had MOS's less than 100; MOS was less than 50 only for the berrypicker (38).

^aA margin of safety of 50 was chosen as the cutoff to report values in this table for ease of comparison. It was not intended to indicate what would be considered low or high risk.

Table 5-2 (Cont.)

Herbicide	Routine-Realistic Scenarios	Routine-Worst Case ^a Scenarios
Dicamba	Greater than 1000 for all situations.	All situations greater than 100 except for vegetation contact by the berry picker (98), and cumulative exposures for berrypickers (46), hunters (91), and residents (66) for 400-acre aerial application.
Diuron	At least 190 in all situations.	All MOS's 77 or greater in all situations.
Fosamine	All at least 2,700.	All 99 or greater.
Glyphosate	All at least 1,600.	All 95 or greater.
Hexazinone	All greater than 1,200.	All greater than 150.
Picloram	All at least 4,600.	All at least 170.
Simazine	All at least 400.	All greater than 50 except for berrypickers (48) in 400-acre aerial application.
Tebuthiuron	All at least 2,600.	All MOS's 40 or greater.
Triclopyr	All at least 710.	All situations greater than 50 except for the multiple routes for berrypicker (38), and resident (34) in the 400-acre aerial application.

^aA margin of safety of 50 was chosen as the cutoff to report values in this table for ease of comparison. It was not intended to indicate what would be considered low or high risk.

seen in long term animal studies (reduced heart and liver weights, reduced food intake) would likely occur only if they received these doses repeatedly; this is extremely unlikely to occur.

Amitrole margins of safety are less than 20 for systemic effects in a number of exposure situations. (The margin of safety for reproductive effects is 990 or greater, indicating negligible risk for reproductive effects.) The greatest risk under the aerial application scenario is for individuals who drink a liter of water from a shallow stream 50 feet from the treatment area immediately after application, or eat vegetables from within 600 feet of the treatment area immediately after application. For this reason, all of the amitrole cumulative exposures for the berrypicker, hunter, fisherman, and residents are less than 10. This indicates that people chronically exposed to these levels of amitrole could experience thyroid problems. The large ratios compared to the LD₅₀ indicate very little chance of acute effects.

The greatest risk by exposure route occurs in contacting vegetation that has just been sprayed with one of the herbicides while picking berries and in eating vegetables that have received spray drift. Because of this, the representative members of the public at greatest risk from any of the herbicides are the nearby resident and the berrypicker. Exposure routes leading to least risk are direct dermal exposure to spray drift, drinking water with drift residues, and eating animals or fish that have drift residues. Persons at least risk are the hunter, hiker, and fisherman. These relationships hold for all 16 herbicides.

MOS's for all herbicides estimated in the three routine-realistic public exposure scenarios are in Attachment C. MOS's for the three most heavily used herbicides, 2,4-D, glyphosate, and triclopyr begin in tables C-57, C-93, and C-123, respectively.

Probability of Occurrence of Estimated Routine-Realistic Public Doses.

Although these three scenarios represent what can happen under routine operations, the probability of people receiving doses as high as those projected here is quite low.

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There are no residents, hikers, fishermen, or berrypickers in the vicinity of most treatment units. Additional precautions, such as posting the area, are normally used to ensure that no one would be exposed during or immediately after an herbicide application operation.

Moreover, as described in Section 4, these routine-realistic scenarios use a number of conservative assumptions that tend to overestimate rather than underestimate what is expected in the majority of operations. For example, predicted levels in water (which determine doses for drinking water, eating fish, and all of the cumulative exposures) are 100 times higher than levels seen in extensive field testing. Extensive monitoring studies conducted by the Forest Service for phenoxy herbicides from 1974 to 1978 showed negligible levels of herbicides in streams (all were less than 0.04 parts per million). These extremely low levels were found despite the fact that during the 1974-78 period not all herbicide applications were monitored. Only those applications most likely to result in significant residues or cause for public concern were actually monitored (USDA, 1980).

The levels predicted on berries also are higher than those found in similar forest plants (USDA, 1984). In addition, the levels predicted for deer in the routine-realistic scenario are similar to the highest levels found by Newton and Norris (1968, as cited in Dost, 1983), who did not find levels greater than 0.08 parts per million in edible deer tissues.

Risk to the Public Under Routine-Worst Case Scenarios

The routine-worst case scenarios described in Section 4 were intended to indicate the upper bound for public exposure to herbicide applications in the Pacific Northwest. The low probability of occurrence of each event that is assumed to occur that would apply to all of the events that led to the exposures described in table 5-2, must be emphasized. It is extremely unlikely that anyone would receive a dose as high as those estimated here.

Margins of Safety Under Routine-Worst Case Scenarios. Table 5-2 indicates that margins of safety projected under this routine-worst case scenario are greater than 100 for asulam, bromacil, 2,4-DP, hexazinone, and picloram.

The public should experience no ill effects from these herbicides even under these extreme exposure assumptions. MOS's are less than 100 (but greater than 77) for diuron, fosamine, glyphosate, and tebuthiuron so there is some slight chance of ill health effects to sensitive members of the public for these herbicides. MOS's are less than 50 in some instances for amitrole, atrazine, 2,4-D, dalapon, dicamba, and triclopyr. Under these extreme assumptions, risk to individuals is very low except for people who receive multiple exposures from a 400-acre fixed wing application. Amitrole has a number of situations where the margin of safety is less than 10. For amitrole, people repeatedly receiving doses as high as predicted here over a long period could experience thyroid problems. In addition, risks to sensitive individuals (for example, an individual with thyroid disfunction), the risk may be substantially greater. Margins of safety calculated for combined routes of exposure to 2,4-D and triclopyr all ranged from 10 to 50 in the worst case aerial application. Chronic doses of 2,4-D, as predicted by this analysis, could affect the peripheral nervous system which, in most cases, would be a reversible effect. For triclopyr, people who chronically receive doses predicted here could experience kidney problems. Because the margins of safety were computed by comparing acute exposures with chronic no-effect levels, the risk of occurrence of these effects can be considered extremely low, especially considering the extreme unlikelihood of nearby residents receiving repeated doses over the long term. The margin of safety derived for triclopyr also is extremely conservative because the toxic effects observed in dogs that resulted in a systemic NOEL of 2.5 mg/kg/day may have been exacerbated by the decreased renal excretion capacity of dogs, which is not representative of human renal physiology. Feeding studies in other test species did not result in kidney problems or other toxic effects at a higher dose level (30 mg/kg/day) (USDA, 1984). However, a sensitive individual (for example, an individual with renal or hepatic disfunction, may exhibit a toxic response similar to the dog.

Public MOS's for all 16 herbicides are presented in Attachment C. MOS's for the doses estimated in the routine-worst case public exposure scenarios for the three most heavily used herbicides--2,4-D, glyphosate, and triclopyr--begin in tables C-60, C-96, and C-126, respectively.

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Probability of the Routine-Worst Case Doses Occurring. The probability of someone receiving a dose as high as those predicted under the routine-worst case scenario is negligible. The probability is low because this scenario assumes that a number of unlikely events occur simultaneously. For example, using the assumptions that the probability of treating a unit as big as 400 acres is 1 in 100, and the probability of the high drift case is 1 in 100, and the probability of someone being in the vicinity of the treatment area is 1 in 100, then the probability of someone receiving a dose as high as those predicted here is 1 in 1 million ($0.01 \times 0.10 \times 0.01 = 0.000001$). In fact, historical records indicate that the probability of these events occurring simultaneously is less than this.

Risk to the Public Under Accidental Scenarios

Table 5-3 summarizes the risk to the public from direct exposure to aerial applications or from eating food or drinking water that has been directly hit at the highest application rate. The relatively low margins of safety for amitrole, atrazine, bromacil, 2,4-D, dalapon, dicamba, diuron, simazine, and triclopyr indicate that people exposed to a direct aerial application or exposed to items that received the highest application rate could experience some toxic effects. The extent of effects would depend upon their duration of exposure and any precautionary measures that were taken. For example, if people gathered a bushel of berries from a spray area and did not wash them but froze them and then ate them every day for a month, they might feel quite ill. However, if people bathed after being in the forest or washed food items before eating them, the doses would drop (and thus substantially increase the margins of safety).

The risk of a member of the public being directly hit by an aerial spray operation is very small. The probability of a pesticide application in an area not scheduled for treatment is low. According to the Forest Service data on insecticide application (USDA, 1984), the probability, based on empirical data, of some kind of significant error in a pesticide application is 0.0002 (at the 95-percent confidence level). Operational features of herbicide operations make the probability of applying an herbicide in an area not scheduled for treatment less than that of

Table 5-3

Margins of Safety Less Than 10 for the General Public
in the Accidental-Worst Case Scenarios

Herbicide	MOS Less Than 10	
	Items Sprayed at Full Application Rate	Spill
Amitrole	All exposures except vegetation contact by the hiker are less than 10. Doses from all other routes except direct spray, vegetation contact by berry picker, and eating deer meat exceed the NOEL.	Doses from helicopter and truck spill into pond and from truck spill into reservoir exceed the NOEL.
Asulam	None less than 10 for either scenario.	
Atrazine	All scenarios except eating deer and vegetation contact by a hiker. Doses from vegetation contact by a berry picker and from the combined exposures for the hiker, berry picker, hunter, fisherman, and resident exceed the NOEL.	Helicopter spill into pond; truck spill into pond exceeds NOEL.
Bromacil	Vegetation contact by the berrypicker, combined exposures for berrypicker, hunter, fisherman, and resident.	Truck spill into pond.
2,4-D	Direct spray exposure, vegetation contact by berrypicker, combined exposure routes for hiker, berrypicker, hunter, fisherman, and resident.	Truck spill into pond dose exceeds NOEL.

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Table 5-3 (Cont.)

Herbicide	MOS Less Than 10	
	Items Sprayed at Full Application Rate	Spill
2,4-DP	None less than 10.	Truck spill into pond.
Dalapon	Vegetation contact by berrypicker, combined routes for berrypicker and resident.	Truck spill into pond
Dicamba	Vegetation contact by berrypicker, and combined exposure for resident.	Truck spill into pond.
Diuron	All margins of safety, except hiker vegetation contact and person eating deer are less than 10. The direct spray contact, berrypicker vegetation contact, and eating fish exposures and all combined exposures exceed the systemic NOEL.	Truck spill into pond dose exceeds NOEL
Fosamine	None less than 10.	Truck spill into pond.
Glyphosate	None less than 10.	Truck spill into pond.
Hexazinone	Only the combined exposure berrypicker MOS is less than 10.	Truck spill into pond.
Picloram	None less than 10.	Truck spill into pond.
Simazine	Berrypicker vegetation contact and combined routes for berrypicker.	Truck spill into pond.

Table 5-3 (Cont.)

Herbicide	MOS Less Than 10	
	Items Sprayed at Full Application Rate	Spill
Tebuthiuron	None less than 10.	Truck spill into pond.
Triclopyr	Combination exposure for berrypicker, hunter, and resident.	Truck spill into pond dose exceeds NOEL.

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insecticide operations. Using this value as an extremely conservative estimate of the probability of an application directly hitting a human being, there might be three accidents over a period of 8 years if a spraying operation occurred every day for 6 months during each of those years. In addition, the probability that someone will be in the area being sprayed is very low because normally the area is posted before spraying and humans will be kept out of the treated areas during spray operations. Thus, the probability of such accidents can be considered negligible.

Again, it must be noted that these are one-time, rather than repeat or chronic, exposures and that the comparison of these doses with the acute LD₅₀'s shows that no one is at risk of fatal effects. Complete margins of safety computed for each chemical and application under the accidental worst-case scenario are presented in Attachment C.

Risk to the Public From Herbicides Used in Brown and Burn Operations

Brown and burn operations are conducted on approximately 500 to 1,500 acres of Forest Service and BLM land every year. These operations are generally limited to the coast range of Oregon on brushy hardwood vegetation and often steep terrain. 2,4-D accounts for approximately 75 percent of the total herbicide used during this type of operation. Glyphosate and triclopyr are used to a much lesser extent. Typically, the selected herbicide is applied aerially in the fall and the vegetation is not burned until the following spring, approximately 5 to 7 months later. However, in some cases burning may take place as soon as 2 weeks after the herbicide has been applied. The treatment units average approximately 30 acres. Crew size at any given site may vary from 10 to 26 workers during the burning operation.

To estimate worker exposure during these operations, it is necessary to calculate the amount of herbicide that will remain on the vegetation at the time of burning. The half-lives for 2,4-D, glyphosate, and triclopyr are 16, 14, and 18 days, respectively. Therefore, after 2 weeks, residues of the amount of applied herbicides would remain on the vegetation: 54 percent of 2,4-D, 50 percent of glyphosate, and 58 percent of triclopyr.

The following assumptions were used to calculate potential worker exposure to smoke:

1. 32 metric tons (32,000 kg) of fuel is used per acre.
2. 40 percent of the available fuel by weight is burned.
3. Smoke density is 5 mg/m^3 (visibility 100 m).
4. 8.5 g smoke/kg of fuel burned.
5. 30 acres is the average treatment unit.
6. All herbicide residue is released to the atmosphere upon burning.
7. Respiration rate for workers at moderate work is 29 liters per minute or 1.74 m^3 per hour.

$$32,000 \text{ kg/acre} * 0.40 = 13,000 \text{ kg of fuel per acre}$$

$$13,000 \text{ kg} * 8.5 \text{ g/kg} = 110,000 \text{ g of smoke produced per acre}$$

$$110,000 \text{ g} / (5 \text{ mg/m}^3) = 22,000,000 \text{ m}^3 \text{ of smoke per acre}$$

$$22,000,000 \text{ m}^3 * 30 \text{ acres} = 6.6 \times 10^8 \text{ m}^3 \text{ of smoke per treatment unit}$$

2,4-D. The number of kilograms of 2,4-D applied at 5.7 lb/acre is:

$$5.7 \text{ lb} / (2.2 \text{ lb/kg}) = 2.6 \text{ kg}$$

The amount of 2,4-D available after 2 weeks is: $2.6 \text{ kg} * 0.54 = 1.4 \text{ kg}$ of 2,4-D per acre.

$$\text{The atmospheric concentration of 2,4-D is: } 1.4 \times 10^6 \text{ mg} / 2.2 \times 10^7 \text{ m}^3 = 0.0636 \text{ mg/m}^3$$

The expected dose of 2,4-D for an average worker (50 kg body weight) respiring at a rate of 1.74 m^3 /hour is: $(0.0636 \text{ mg/m}^3 * 1.74 \text{ m}^3 / \text{hour}) / 50 \text{ kg} = 2.2 \times 10^3 \text{ mg/kg/hour}$.

This is far below the NOEL of 1.0 mg/kg/day. A 1-hour-per-day exposure to smoke of this density is a reasonable expectation. If a worker were exposed to 3 hours of smoke per day, the dose would be only 3 times greater

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than that calculated and would still be well below the NOEL. A worker is not typically exposed to brown and burn operations more than 12 days per year. Therefore, the overall health risk from this type of operation with 2,4-D is negligible.

Glyphosate. The number of kilograms of glyphosate applied at 5 lb/acre is:

$$5 \text{ lb} / (2.2 \text{ lb/kg}) = 2.3 \text{ kg}$$

The amount of glyphosate available after 2 weeks is: $2.3 \text{ kg} * 0.50 = 1.15$ of glyphosate per acre.

The atmospheric concentration of glyphosate is: $1.15 \times 10^6 \text{ mg} / 2.2 \times 10^7 \text{ m}^3 = 0.0523 \text{ mg/m}^3$.

The expected dose of glyphosate for an average worker (50 kg body weight) respiring at a rate of 1.74 m^3 /hour is: $(0.0523 \text{ mg/m}^3 * 1.74 \text{ m}^3 / \text{hour}) / 50 \text{ kg} = 1.82 \times 10^{-3} \text{ mg/kg/hour}$. This dose is well below the NOEL of greater than 31 mg/kg/day and should pose no risk to health.

Triclopyr. The number of kilograms of triclopyr at a maximum application rate of 8 lb/acre is: $8 / (2.2 \text{ lb/kg}) = 3.6 \text{ kg}$.

The amount of triclopyr available after 2 weeks is: $3.6 \text{ kg} * 0.58 = 2.09 \text{ kg}$ of triclopyr.

The atmospheric concentration of triclopyr is: $2.09 \times 10^6 \text{ mg} / 2.2 \times 10^7 \text{ m}^3 = 0.095 \text{ mg/m}^3$.

The expected dose of triclopyr for an average worker (50 kg body weight) respiring at a rate of 1.74 m^3 / hour is: $(0.095 \text{ mg/m}^3 * 1.74 \text{ m}^3 / \text{hour}) / 50 \text{ kg} = 3.31 \times 10^{-3} \text{ mg/kg/hour}$. This dose is insignificant and is far below the NOEL of 2.5 mg/kg/day. No adverse health effects are expected.

Combustion Project. Bush et al. (1987) measured residues released from burning wood (in wood stoves or fireplaces) from herbicide-injected trees. Residues under rapid combustion were generally much less than under slow combustion. Based on these measurements, Bush et al. estimated indoor air concentrations of herbicides for rapid and slow combustion conditions, respectively, as follows 0.0000036 mg/m³ to 0.000088 mg/m³ for 2,4-D; 0.00012 mg/m³ to 0.001 mg/m³ for 2,4-DP; less than 0.0000001 mg/m³ for picloram; and less than 0.00005 mg/m³ for triclopyr (Bush et al., 1987).

These concentrations are much less than the maximum exposure concentrations estimated for these herbicides in brown-and-burn operations.

Cancer Risk From Burning Vegetation

Dost (1986) has performed a cancer risk assessment of the main carcinogens found in wood smoke, the polynuclear aromatic hydrocarbons (PAH's). This chemical group includes benzo(a)pyrene (BaP), a known human carcinogen with a cancer potency of 0.0033. Other PAH's in wood smoke that are carcinogenic in laboratory animal studies include benzo(c)phenanthrene, benzofluoranthrene, 3-methyl-cholanthrene, and dimethylbenzanthrene. All of these PAH's have potencies less than or equal to BaP. However, PAH's do exhibit a potential for respiratory effects.

Dost used the following assumption in estimating BaP exposure:

1. 2,500 mg BaP is released from every kg of fuel that is burned (EPA finds this number sufficiently conservative).
2. All BaP is incorporated into fine particulate matter that is of respirable size, and 8,500 mg of particulate is produced per kg of fuel that is burned (the Forest Service frequently uses this number).
3. Smoke density is 0.155 mg/m³ based on a visibility of 2 miles.

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4. A person is exposed for 6 hours per day, 20 days per year, for 10 years.

Based on these assumptions, the average lifetime exposure concentration would be $9.1 \times 10^{-5} \text{ ug/m}^3$ of BaP. The increased cancer risk resulting from would be 3×10^{-7} or 3 in 10,000,000.

Dost completed similar calculations for the four other carcinogenic PAH's. The total increased risk of cancer from the PAH's, including BaP, is 1.1×10^{-6} .

Therefore, based on these assumptions, little risk exists of adverse health effects from exposure to weed smoke from BLM burning operations.

Risk to Workers From Routine Operations

Tables 5-4 to 5-7 summarize the margins of safety for workers based on the systemic and reproductive NOEL's for the 16 herbicides. Full tables showing margins of safety computed for the 16 herbicides are presented in Attachment C, tables C-1 through C-160. Because of the assumptions that were made to overestimate risk, the Forest Service and BLM estimate that almost all of the operations that take place will fall within the values predicted for the routine-realistic scenarios. Routine-worst case estimates are presented to show the upper bound or 95-percent confidence level of risk to workers.

It must be emphasized that the routine worker exposures and resultant margins of safety are what could be expected in the majority of vegetation management programs in the Pacific Northwest for workers not wearing protective clothing or equipment. All of the studies from which the routine-realistic exposures were calculated are based on workers wearing no protective clothing. The use of protective clothing can substantially reduce worker doses, as shown in field studies of worker exposure, and thereby increase their margins of safety.

Worker Margins of Safety for Systemic Effects
Routine-Realistic Exposures

Herbicide	Aerial				Back Pack	Truck			Hand Application	
	PILOT	MIX/L	SUP	OBS	BP	APPL	MIX/L	APPL MIX/L	H&S	INJ BAR
Amitrole	62(150)	43(59)	410(970)	++(++)	7.6(24)	360(++)	360(490)	260(500)	45(110)	120(260)
Asulam	++(++)	720(990)	++(++)	++(++)	250(810)	++(++)	++(++)	++(++)	--	--
Atrazine	6.4(15)	4.4(6.1)	42(100)	200(480)	-1.09(3.1)	47(150)	46(63)	33(64)	--	--
Bromacil	--	--	--	--	9.5(30)	460(++)	450(610)	320(620)	56(130)	150(330)
2,4-D	33(79)	23(32)	220(520)	++(++)	5.1(16)	190(620)	190(260)	140(270)	15(35)	39(87)
2,4-DP	++(++)	++(++)	++(++)	++(++)	++(++)	++(++)	++(++)	++(++)	++(++)	++(++)
Dalapon	99(240)	69(95)	650(++)	++(++)	12(39)	580(++)	570(790)	420(800)	--	--
Dicamba	++(++)	790(++)	++(++)	++(++)	280(880)	++(++)	++(++)	++(++)	200(480)	540(++)
Diuron	--	--	--	--	-1.1(3.0)	46(150)	45(61)	32(62)	5.6(13)	15(33)
Fosamine	410(990)	290(400)	++(++)	++(++)	51(160)	++(++)	++(++)	++(++)	220(530)	590(++)
Glyphosate	770(++)	540(740)	++(++)	++(++)	130(400)	++(++)	++(++)	++(++)	--	--
Hexazinone	200(470)	140(190)	++(++)	++(++)	54(170)	++(++)	++(++)	830(++)	--	--
Picloram	++(++)	++(++)	++(++)	++(++)	++(++)	++(++)	++(++)	++(++)	++(++)	++(++)
Simazine	62(150)	43(59)	410(970)	++(++)	15(49)	730(++)	720(980)	520(++)	--	--
Tebuthiuron	620(++)	430(590)	++(++)	++(++)	51(160)	++(++)	++(++)	++(++)	--	--
Triclopyr	380(900)	260(360)	++(++)	++(++)	46(150)	++(++)	++(++)	++(++)	140(320)	360(790)

Numbers in parentheses refer to margins of safety for workers wearing protective clothing.

- MIX/L = Mixer/Loader
- SUP = Supervisor
- OBS = Observer
- BP = Backpack
- APPL = Sprayer
- H&S = Hack and Squirt
- INJ BAR = Injection Bar
- ++ = MOS of 1000 or more
- = Not used in respective operation

Table 5-5

Worker Margins of Safety for Reproductive Effects
Routine-Realistic Scenarios

Herbicide	Aerial				Back Pack	Truck			Hand Application	
	PILOT	MIX/L	SUP	OBS	BP	APPL	MIX/L	APPL MIX/L	H&S	INJ BAR
Amitrole	++(++)	++(++)	++(++)	++(++)	++(++)	++(++)	++(++)	++(++)	++(++)	++(++)
Asulam	++(++)	720(990)	++(++)	++(++)	250(810)	++(++)	++(++)	++(++)	--	--
Atrazine	6.5(16)	4.6(6.5)	43.5(105)	205(485)	1.0(3.3)	48.5(155)	47.5(65)	34.5(65)	--	--
Bromacil	--	--	--	--	19(61)	910(++)	890(++)	650(++)	110(260)	300(650)
2,4-D	170(390)	120(160)	++(++)	++(++)	25(81)	970(++)	950(++)	690(++)	75(180)	200(430)
2,4-DP	++(++)	++(++)	++(++)	++(++)	++(++)	++(++)	++(++)	++(++)	++(++)	++(++)
Dalapon	160(370)	110(150)	++(++)	++(++)	19(61)	910(++)	890(++)	650(++)	--	--
Dicamba	210(430)	150(170)	++(++)	++(++)	52(140)	++(++)	++(++)	890(++)	39(76)	100(190)
Diuron	--	--	--	--	9.5(30)	460(++)	450(610)	320(620)	56(130)	150(330)
Fosamine	830(++)	580(790)	++(++)	++(++)	100(320)	++(++)	++(++)	++(++)	450(++)	++(++)
Glyphosate	250(590)	170(240)	++(++)	++(++)	40(130)	++(++)	++(++)	++(++)	--	--
Hexazinone	990(++)	690(950)	++(++)	++(++)	270(870)	++(++)	++(++)	++(++)	--	--
Picloram	++(++)	++(++)	++(++)	++(++)	++(++)	++(++)	++(++)	++(++)	++(++)	++(++)
Simazine	62(150)	43(59)	410(970)	++(++)	15(49)	730(++)	720(980)	520(++)	--	--
Tebuthiuron	250(++)	170(590)	++(++)	++(++)	20(160)	++(++)	++(++)	++(++)	--	--
Triclopyr	380(900)	260(360)	++(++)	++(++)	46(150)	++(++)	++(++)	++(++)	140(320)	360(790)

Numbers in parentheses refer to margins of safety for workers wearing protective clothing.

MIX/L = Mixer/Loader

SUP = Supervisor

OBS = Observer

BP = Backpack

APPL = Sprayer

H&S = Hack and Squirt

INJ BAR = Injection Bar

++ = MOS of 1000 or more

-- = Not used in respective operation

TABLE 3.0
Worker Margins of Safety for Systemic Effects
Routine-Worst Case Scenarios

Herbicide	Aerial				Back Pack	Truck			Hand Application	
	PILOT	MIX/L	SUP	OBS	BP	APPL	MIX/L	APPL MIX/L	H&S	INJ BAR
Amitrole	3.7(8.9)	2.9(4.0)	22(51)	120(290)	-1.2(2.6)	5.9(19)	10(14)	8.7(17)	4.0(9.3)	15(33)
Asulam	89(210)	70(96)	520(++)	++(++)	24(77)	190(600)	330(450)	280(540)	--	--
Atrazine	-1.4(1.7)	-1.8(-0.8)	4.1(9.9)	23(56)	-5.2(-0.6)	-1.1(3.4)	1.8(2.5)	1.6(3.0)	--	--
Bromacil	--	--	--	--	1.0(3.2)	12(38)	20(28)	17(34)	5.0(12)	19(41)
2,4-D	2.5(5.9)	2.0(2.7)	14(34)	81(190)	-1.5(2.2)	7.7(25)	13(18)	11(22)	1.3(3.1)	4.9(11)
2,4-DP	++(++)	940(++)	++(++)	++(++)	190(600)	++(++)	++(++)	++(++)	260(620)	990(++)
Dalapon	4.8(11)	3.7(5.1)	28(66)	150(370)	1.1(3.4)	15(48)	26(36)	22(43)	--	--
Dicamba	34(81)	27(36)	200(470)	++(++)	9.2(29)	120(380)	210(280)	180(340)	18(42)	67,150)
Diuron	--	--	--	--	-5.9(-1.9)	-1.4(2.4)	1.3(1.8)	1.1(2.1)	-2.0(1.2)	1.9(4.1)
Fosamine	12(30)	9.8(13)	72(170)	400(960)	3.5(11)	44(140)	76(100)	65(130)	20(47)	74(160)
Glyphosate	37(88)	29(40)	210(510)	++(++)	10(32)	120(370)	200(280)	170(330)	--	--
Hexazinone	20(48)	16(21)	110(270)	650(++)	5.4(17)	31(100)	54(75)	47(90)	--	--
Picloram	460(++)	360(500)	++(++)	++(++)	160(500)	++(++)	++(++)	++(++)	620(++)	++(++)
Simazine	6.0(14)	4.7(6.4)	34(82)	190(460)	1.8(5.6)	20(66)	36(49)	30(58)	--	--
Tebuthiuron	12(30)	9.8(13)	72(170)	400(960)	3.4(11)	51(160)	89(120)	76(150)	--	--
Triclopyr	11(27)	8.9(12)	65(160)	370(870)	3.1(9.8)	36(110)	62(85)	53(100)	12(28)	45(99)

Numbers in parentheses refer to margins of safety for workers wearing protective clothing.

- MIX/L = Mixer/Loader
- SUP = Supervisor
- OBS = Observer
- BP = Backpack
- APPL = Sprayer
- H&S = Hack and Squirt
- INJ BAR = Injection Bar
- ++ = MOS of 1000 or more
- = Not used in respective operation

Table 5-7

Worker Margins of Safety for Reproductive Effects
Routine-Worst Case Scenarios

Herbicide	Aerial				Back Pack	Truck			Hand Application	
	PILOT	MIX/L	SUP	OBS	BP	APPL	MIX/L	APPL MIX/L	H&S	INJ BAR
Amitrole	600(++)	470(640)	++(++)	++(++)	130(410)	940(++)	++(++)	++(++)	630(++)	++(++)
Asulam	89(210)	70(96)	520(++)	++(++)	24(77)	190(600)	330(450)	280(540)	--	--
Atrazine	0.8(1.8)	0.6(0.8)	4.3(10.5)	24(60)	-1.3(0.7)	1.1(3.6)	1.9(2.7)	1.7(3.2)	--	--
Bromacil	--	--	--	--	2.0(6.5)	24(76)	41(56)	35(67)	9.9(23)	37(82)
2,4-D	12(30)	9.8(13)	72(170)	400(960)	3.4(11)	38(120)	66(91)	57(110)	6.6(16)	25(55)
2,4-DP	++(++)	++(++)	++(++)	++(++)	230(750)	++(++)	++(++)	++(++)	330(780)	++(++)
Dalapon	7.5(18)	5.9(8.0)	43(100)	240(580)	1.7(5.4)	24(76)	41(56)	35(67)	--	--
Dicamba	6.4(15)	5.0(6.9)	37(89)	210(500)	1.7(5.6)	23(72)	39(54)	33(64)	3.4(8.1)	13(28)
Diuron	--	--	--	--	1.7(5.4)	7.4(24)	13(18)	11(21)	5.0(12)	19(41)
Fosamine	25(59)	20(27)	140(340)	810(++)	7.0(22)	88(280)	150(210)	130(250)	40(93)	150(330)
Glyphosate	12(29)	9.4(13)	69(160)	390(920)	3.2(10)	38(120)	65(90)	56(110)	--	--
Hexazinone	100(240)	78(110)	570(++)	++(++)	27(86)	160(500)	270(370)	230(450)	--	--
Picloram	++(++)	++(++)	++(++)	++(++)	560(++)	++(++)	++(++)	++(++)	++(++)	++(++)
Simazine	6.0(14)	4.7(5.4)	34(82)	190(460)	1.8(5.6)	20(66)	36(49)	30(58)	--	--
Tebuthiuron	5.0(12)	3.9(5.4)	29(69)	160(380)	1.3(4.3)	20(66)	36(49)	30(58)	--	--
Triclopyr	11(27)	8.9(12)	65(160)	370(870)	3.1(9.8)	36(110)	62(85)	53(100)	12(28)	45(99)

Numbers in parentheses refer to margins of safety for workers wearing protective clothing.

MIX/L = Mixer/Loader

SUP = Supervisor

OBS = Observer

BP = Backpack

APPL = Sprayer

H&S = Hack and Squirt

INJ BAR = Injection Bar

++ = MOS of 1000 or more

-- = Not used in respective operation

Effects of the Use of Protective Clothing

Protective clothing can reduce worker exposures by 27 to 99 percent, as shown in a number of relevant field studies. The calculated doses presented below were based on the assumption that workers work with bare hands and wear ordinary work clothing, such as cotton pants and short-sleeve shirts. It is common practice, however, for herbicide applicators to wear clothing that affords more protection. Typical clothing often includes long-sleeve shirts or coveralls, gloves, and hats.

Research has shown that such protective clothing can substantially reduce worker exposure. For example, in right-of-way spraying, doses of spray gun applicators wearing clean coveralls and gloves were reduced by 68 percent compared to doses they received without this protection (Libich et al., 1984). During an aerial spraying operation, mixer-loaders wearing protective clothing reduced their exposure by 27 percent and other crew members reduced their exposure by 58 percent compared to the levels observed without precautions (Lavy et al., 1982).

During insecticide applications to orchards, mixers reduced their exposure by 35 percent and sprayers reduced their exposure by 49 percent by wearing coveralls (Davies et al., 1982). Putnam and coworkers found that nitrofen applicators and mixer-loaders wearing protective clothing reduced their exposure by 94 to 99 percent compared to the doses experienced without protection (Waldron, 1985). Although protective clothing generally does reduce worker exposure and resulting doses, the degree of protection depends on the application system, the work practices, and the specific herbicide. In one extreme case, workers wearing protective clothing did not receive significantly lower doses than workers with less clothing (Lavy et al., 1984). In this case backpack applicators had to treat and move through dense vegetation that was taller than themselves.

Most exposure to herbicide applicators is dermal, not inhalation (Kolmodin-Hedman et al., 1983), so the use of respirators is ineffective and unnecessary. The hands are the site of the greatest potential herbicide exposure, and rubber gloves are generally quite effective in preventing exposure to hands (Putnam et al., 1983).

D Human Health Risk Assessment (Quantitative)

Based on the review of field studies, protective clothing was normally found to reduce worker doses by the following amounts:

<u>Type of Worker</u>	<u>Percent Reduction in Dose</u>
1. Right-of-way applicators	68.1
2. Aerial application crew members	57.1
3. Aerial mixer-loaders	27.1
4. Injection bar applicators	54.7
5. Hack-and-squirt applicators	57.6

Doses to protected backpack applicators were based on doses to right-of-way applicator who used hand-held nozzles. Tables 5-4 and 5-5 list routine-realistic margins of safety computed for workers without protective clothing and, in parentheses, for workers with protective clothing. Tables 5-6 and 5-7 list the same values for routine-worst case doses.

Risk to Workers Under Routine-Realistic Scenarios

In the routine-realistic scenarios, all categories of workers applying asulam or picloram have MOS's greater than 100. This indicates that even workers chronically exposed to these herbicides should suffer no ill effects. For all the other herbicides, as shown in tables 5-4 and 5-5, at least one category of worker (in most cases backpack sprayers) had MOS's less than 100 in the routine-realistic scenario. This means that unprotected sensitive workers that routinely receive doses this high may experience some toxic effects from applying these herbicides.

Based on comparisons of estimated doses with systemic and reproductive NOEL's for all of the herbicides, backpack sprayers are at greatest risk. Hand applicators are next, while pilots and mixer-loaders are at somewhat lower risk. Observers and right-of-way applicators are at least risk.

Except for backpack sprayers using asulam, glyphosate, or picloram, all backpack sprayers have margins of safety less than 100. Amitrole, atrazine, bromacil, and 2,4-D have MOS's less than 10; and in the cases of

atrazine and diuron, the dose exceeds the NOEL. The doses and margins of safety are based on 6 hours per day of exposure. Any reduction in the time of exposure would reduce the dose and increase the margin of safety proportionally.

Atrazine and diuron appear to present the greatest risk from repeated exposures. Backpack sprayers using atrazine and diuron in the routine-realistic scenario receive a dose that is higher than the systemic NOEL. Atrazine MOS's for pilots and mixer-loaders are less than 10. The diuron systemic MOS for hack-and-squirt applicators also is less than 10 in the routine-realistic case.

Amitrol, bromacil, and 2,4-D present the next highest long-term risk. Backpack sprayers using any of these four herbicides in the routine-realistic scenarios receive doses that have systemic margins of safety less than 10. Pilots, mixer-loaders, and hand applicators have MOS's less than 60.

Risk to Workers Under Routine-Worst Case

As shown in tables 5-6 and 5-7, a number of herbicides have margins of safety less than 10 in the routine-worst case scenario.

Backpack sprayers using diuron, amitrole, atrazine, 2,4-D, and diuron in the routine-worst case scenario receive doses that exceed their respective systemic NOEL's. Atrazine doses to pilots, mixer-loaders, and truck applicators exceed the systemic NOEL. In addition, doses calculated for truck applicators and hack-and-squirt applicators using diuron exceed the systemic NOEL. Margins of safety for the reproductive NOEL's are much higher. Only the atrazine dose to the backpack applicator exceeds the reproductive NOEL.

All categories of workers, except the aerial supervisor and observer, have margins of safety less than 10 for at least one of the herbicides. Picloram and asulam are the only herbicides that have margins of safety greater than 20 for all categories of workers.

D Human Health Risk Assessment (Quantitative)

The probability of workers receiving repeated daily doses as high as predicted here is extremely low (less than 1 chance in 1,000). Therefore, even if a worker felt ill for a day or so from an unusually high dose, permanent damage would be unlikely. Most of the time workers will be receiving doses less than those predicted in the routine-realistic scenario. Sensitive individuals would be at greater risk.

The routine-worst case analysis for workers is based on a series of assumptions that, acting together, greatly increase the estimated risk. The analysis uses the upper 2.5 percent of doses received in field studies, the highest application rates used by BLM and the Forest Service, and the longest work hours for each type of project.

If we combine the probability of a dose above the upper 95 percent confidence level of field studies (1 in 40), with a probability of using the highest application rate of 1 in 20, and a probability of someone working the maximum hours of 1 in 20, then the probability of a worker receiving a dose as high as predicted here is 1 in 16,000. ($1/40 \times 1/20 \times 1/20 = 1/16,000$).

Risk to Workers From Spilling Concentrate or Spray Mix on Their Skin

The doses estimated in this analysis are based on dermal penetration levels derived in studies over many days; these chemicals do not penetrate the skin immediately but over a considerable period of time. Thus, workers would have to ignore their own safety and not wash the chemical off to receive doses as high as predicted in these accidents. Workers who spill a pint of concentrate or spray mix on their skin, with the exception of picloram, may experience some acute toxic effects if they do not wash it off. The margins of safety for this accidental-worst case scenario are presented in table 5-8. In the case of a spill of a pint of concentrate, many of the doses approach the LD₅₀. This represents a clear risk of severe toxic effects if the chemical is not washed off. There is some possibility that the damage caused by such a large acute dose could cause long-term damage to vital organs. Also, in rare instances, limited exposure to 2,4-D was reported to cause permanent nerve damage. The dose

Table 5-8

Margins of Safety for
Spills onto the Skin of Workers Compared to Systemic
NOEL's and LD₅₀'s this Table updated

Herbicide	Spray Mix		Concentrate	
	NOEL	LD ₅₀	NOEL	LD ₅₀
Amitrole	-9.6	17,000	-48	3,400
Asulam	2.5	200	-4.8	17
Atrazine	-54	28	-500	2.8
Bromacil	-1.9	330	-38	17
2,4-D	-14	26	-140	2.6
2,4-DP	33	3,500	1.4	150
Dalapon	-7.5	130	--	--
Dicamba	-1.1	45	-11	4.5
Diuron	-31	200	-380	16
Fosamine	-2.9	340	-9.6	100
Glyphosate	1.0	140	-5.8	24
Hexazinone	-1.8	94	-12	14
Picloram	13	15,000	3.2	3,800
Simazine	-6.0	170	-48	21
Tebuthiuron	-2.9	18	--	--
Triclopyr	-3.2	80	-16	16

D Human Health Risk Assessment (Quantitative)

and the risk are much greater for spills of concentrate than for the spray mix but, again, it is highly unlikely a worker would allow a chemical to penetrate his skin for any length of time. Attachment C presents the complete MOS and comparisons to LD₅₀'s for each herbicide.

Risk to Workers and the Public From Accidents Causing Large Spills of Herbicide

Table 5-9 summarizes the margins of safety for people drinking one liter of water contaminated by a large spill of herbicide from a helicopter or truck (see Attachment C, tables C-145 through C-160). Most drinking water reservoirs would dilute the herbicide below no-observable-effect levels in a relatively short period of time. Both BLM and the Forest Service, in addition to EPA and the States, have procedures to minimize the risk to human health of a spill of this magnitude in or near a drinking water reservoir. Therefore, after the spill has been diluted, the risk to the public can be considered very low.

Spills into a small, stagnant pond would result in significantly higher doses, and a truck spill of 2,000 gallons would constitute a risk of chronic effects if people continued to drink from it. Both the Forest Service and BLM have detailed spill prevention and cleanup procedures to ensure that no one is chronically exposed to a spill of this magnitude.

Probability of a Worst Case Accident

Some indication of the likelihood of significant herbicide spill accidents may be derived from historical data. Herbicide spill accidents recorded by BLM and the Forest Service over 11 years were classified by location, date, and quantity spilled. Also included was information specifying the occurrence of accidents on the ground or in the air, and whether the spill was near a waterway. Over an 11-year period, from 1973 through 1983, there were 24 recorded spills averaging 44.4 gallons per accident. Herbicide use rates ranged from 1.5 lb a.i. to 7 lb a.i. per acre for normal use rates. Of the 302,085 acres sprayed during the 11-year period, one accident occurrence for every 12,587 acres and 54 percent of the spills involved 30 gallons or less.

Table 5-9

Margins of Safety for People Drinking One Liter of Water
Contaminated by a Large Spill of Herbicide^a
Compared to the Systemic NOEL

Herbicide	Helicopter		Truck	
	Into a Reservoir	Into a Pond	Into a Reservoir	Into a Pond
Amitrole	11	-2.9	-1.8	-59
Asulam	26,000	810	1,300	41
Atrazine	210	6.5	8.1	-3.9
Bromacil	--	--	270	8.5
2,4-D	430	14	22	-1.5
2,4-DP	3,500	110	170	5.4
Dalapon	1,400	43	70	2.2
Dicamba	6,900	210	340	11
Diuron	--	--	17	-1.9
Fosamine	3,600	110	180	5.7
Glyphosate	11,000	340	540	17
Hexazinone	5,800	180	290	9.1
Picloram	2,400	76	120	3.8
Simazine	1,700	54	87	2.7
Tebuthiuron	3,600	110	180	5.7
Triclopyr	540	17	27	-1.2

^aAssume a helicopter carrying 100 gallons of spray mix jettisons the entire load in a 16-acre by 8-foot-deep reservoir and a 1-acre by 4-foot-deep pond.

D Human Health Risk Assessment (Quantitative)

Table 5-10 shows the acreage sprayed, gallons spilled, and type of spill for the years 1973 to 1983. Figures 5-1 and 5-2 show that as the number of gallons increases, the probability of a spill decreases.

CANCER RISK

A worst case analysis for cancer was conducted for the herbicides that had positive laboratory oncogenic studies (amitrole, asulam, atrazine, bromacil, and 2,4-DP) and for the herbicides (2,4-D, glyphosate, and picloram) for which there is scientific uncertainty. There is no evidence to suggest that any of the other herbicides could cause cancer. All of the other herbicides have negative cancer studies. EPA has requested additional data on the cancer potential of a number of the other 11 herbicides, and BLM and the Forest Service will consider the results of their findings when they become available.

Cancer is generally thought of as a nonthreshold response, which means a very small amount could cause a tumor and there is general agreement that amitrole has the potential to cause cancer in humans. In the case of amitrole, however, EPA has determined that the available evidence indicates a threshold carcinogenic response. A threshold response is consistent with the theory that amitrole is a secondary carcinogen because of its well-established anti-thyroid effects. Nevertheless, because some uncertainty exists about the mechanism of action of amitrole, a conservative approach has been taken in this analysis by assuming that amitrole's carcinogenicity is not a threshold effect. A threshold model would indicate zero or negligible carcinogenicity at low doses. This would be true of the log-probit model suggested by EPA (EPA, 1984s), but instead, the models used here assume that even low doses may cause cancer. The one-hit model used for estimating the risk for most of the herbicides in this analysis predict the maximum rates of cancer that could occur at low doses under any of the models that have been in general use. At high doses, all of the commonly used models would predict nearly the same rate of tumor formation.

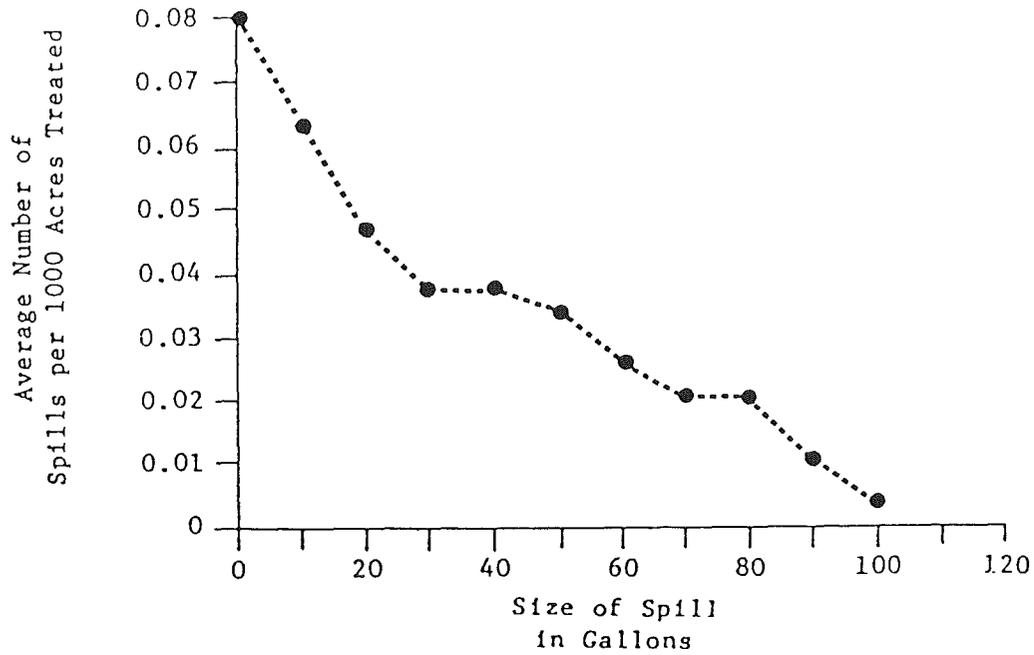


Figure 5-1 Frequency and Size of Spills from Air and Ground Operations

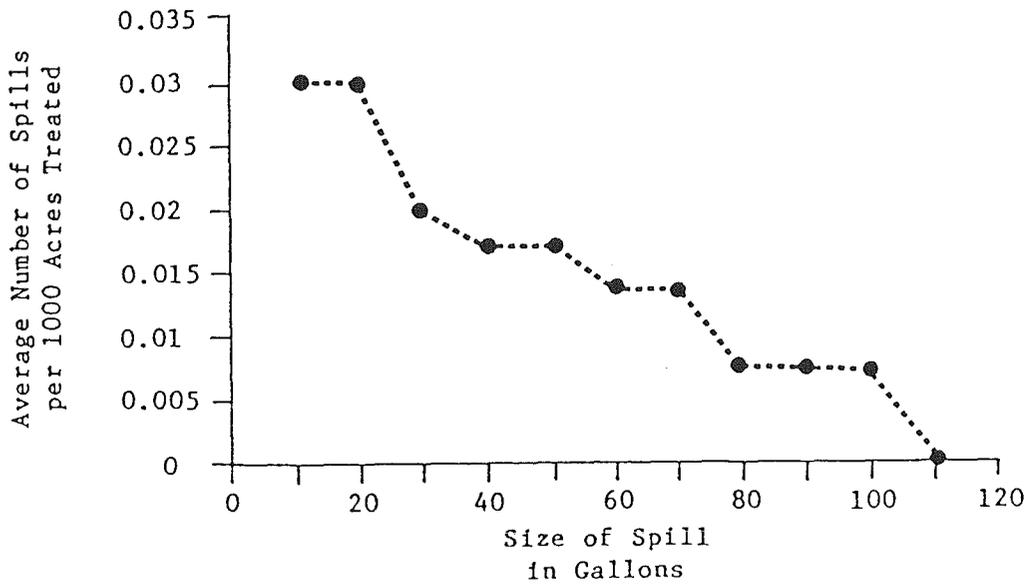


Figure 5-2 Frequency and Size of Spills from Air Operations

D Human Health Risk Assessment (Quantitative)

Table 5-10

Number of Spills on Forest Service Land in Washington and Oregon over the Last 10 Years

Number of Gallons	Number Spills (air and ground)	Avg. No. of Spills/ 1,000 Acres	Number Spills (air)	Avg. No. of Spills/ 1,000 Acres
0	24	0.0795	9	0.0298
10	19	0.0629	9	0.0298
20	14	0.0464	6	0.0199
30	11	0.0364	5	0.0166
40	11	0.0364	5	0.0166
50	10	0.0331	4	0.0132
60	8	0.0265	4	0.0132
70	6	0.0199	2	0.0066
80	6	0.0199	2	0.0066
90	3	0.0099	2	0.0066
100	1	0.0033	0	0.0000

Cancer risks for amitrole, asulam, atrazine, bromacil, 2,4-DP, 2,4-D, glyphosate, and picloram have been calculated based on a variety of conservative assumptions that are likely to overestimate the risks. These assumptions include the following:

1. Amitrole, asulam, bromacil, 2,4-DP, glyphosate, picloram, and 2,4-D are all assumed to be carcinogenic. Picloram and 2,4-D have not been shown conclusively to be carcinogenic in laboratory tests and there are many uncertainties about the glyphosate study, but the evidence also cannot show conclusively that they are not carcinogenic. Consequently, a worst case approach was taken.
2. When more than one data set is available, the data set indicating greater carcinogenic potency has been chosen. Carcinogenic potencies of 2,4-D and 2,4-DP have been calculated based on the rate of tumor formation in the female Osborne-Mendel rats studied by Hansen et al. (1971). This is the species and sex that have exhibited the highest rate of tumor formation after 2,4-D administration. All tumors were considered, although many of them were benign. Similarly for amitrole, the Food and Drug Research Laboratories rat study data (discussed in Section 3) have been used.
3. It is assumed that carcinogenicity in all seven cases is not a threshold phenomenon; i.e., any dose of these chemicals has some probability of causing cancer, no matter how small the dose. This assumption is questionable for amitrole; EPA has determined that the evidence suggests a threshold phenomenon in this case.
4. The one-hit model was used to represent the relationship between dose and rate of tumor formation for most of the herbicides. This is the most conservative of several models that have been proposed because it predicts the highest cancer rates at the relatively low doses predicted for exposed humans. Other models that could have been used include the multistage, multihit, Weibull, logit, and probit models. The multistage model was used for 2,4-DP and

D Human Health Risk Assessment (Quantitative)

glyphosate. The choice of model can affect the predicted cancer rates over several orders of magnitude. The one-hit model was used at one time by EPA, but the less conservative multistage model is now normally used. In the case of amitrole, EPA has suggested use of the even less conservative log-probit model.

5. In each case a 95-percent upper confidence limit was used to estimate cancer potency. For asulam, bromacil, 2,4-D, and picloram, these potencies were estimated using the maximum-likelihood procedure of the GLOBAL 82 computer program (Howe and Crump, 1982).
6. Interspecies extrapolation is a major source of uncertainty in judging cancer risk. The scaling method used in this analysis is the most conservative of the commonly accepted methods. The cancer potency of each chemical for humans was assumed to be the same as the potency for rats when scaled in terms of mg per m² of body surface area (mg/m²). This method is commonly used by EPA and others, but it is not the only acceptable approach. Another equally acceptable (OSTP, 1985) method is to scale doses in terms of mg per kg of body weight (mg/kg), resulting in estimates of cancer risk that are about 16 percent of those calculated here.
7. The range of doses calculated for workers and the public in the basic scenarios covers even extreme exposures that might be encountered with each application method. Unusual exposure situations, represented by accidental spraying and large herbicide spills, also have been considered.

The probability of occurrence of cancer over a lifetime as a result of exposure to each of the chemicals was calculated using the following equations:

$$P(d) = 1 - \exp(-K \times b \times d)$$

$$d = D \times N/L$$

where:

P(d) is a conservative estimate of the probability of cancer during a person's lifetime as the result of dose d.

d is the average daily dose over a lifetime (mg/kg/day)

K is an interspecies extrapolation factor

b is a conservative estimate for cancer potency in the test animal (derived in Section 2).

The following cancer potencies (per mg/kg/day) were used: atrazine, 3.0×10^{-2} ; amitrole, 1.4; 2,4-DP, 1.2×10^{-2} ; asulam, 2×10^{-2} ; 2,4-D, 5×10^{-3} ; bromacil, 3.8×10^{-3} ; picloram, 5.7×10^{-4} ; and glyphosate, 2.6×10^{-5} .

D is the daily dose (mg/kg/day)

N is the number of days during which the dose d occurs during an individual's lifetime

L is the number of days in a lifetime, taken to be 25,550 for a 70-year life span.

The interspecies extrapolation factor, K, can be estimated by assuming that body surface area is proportional to body weight to the 2/3 power (Mantel and Schneiderman, 1975), so that K would be:

$$K = (\text{human weight/test animal weight})^{1/3}$$

For an average human weight of 50 kg and an average rat weight of 350 g, K is estimated to be 5.2.

D Human Health Risk Assessment (Quantitative)

Cancer Risk to the Public

Cancer risk for the general public was calculated for a single occurrence of each type of exposure, and for 30 occurrences of each type of exposure over a lifetime. The approximate cancer risks to the public for the routine-realistic and routine-worst case aerial scenarios are shown in tables 5-11 and 5-12. (See Attachment C for the presentation of cancer risks to the public for the other four routine exposure scenarios). Of the eight chemicals, the greatest risks occur with amitrole. In the highest exposure situation, the large aerial scenario, the maximum risk of cancer for a single exposure is less than 6 in 1 million, for a person eating vegetables from near the spray site. When several routes of exposure are added for the example nearby resident, the resulting risk for a single lifetime exposure is less than 1 in 100 thousand. The cumulative risk resulting from several exposures of this magnitude would be the sum of the risks for each exposure. The risk of cancer from 30 exposures is also given in the tables, but the chance of receiving 30 exposures as large as those in the worst case is negligible. If 30 routine-worst case amitrole exposures were experienced, the cumulative risk would be less than 3 in 10,000. Exposures in the routine-realistic cases lead to much lower risk. The risk of cancer resulting from doses from any of the routes of exposure in the typical aerial spraying scenario is less than 7 in 10,000,000 even for amitrole. Cancer risks for the other chemicals are very much less. The realistic aerial scenario risk for glyphosate is never greater than 3 in 1 billion. For 2,4-D, 2,4-DP, asulam, and picloram, none of the routes of exposure in any scenario results in a cancer risk greater than about 2 in 10 million, for 30 lifetime exposures. The highest risk of cancer to the public from bromacil usage is from backpack spraying of large areas because bromacil is not aerially applied in the forests of Region 6. The risk from any of the routes of exposure is less than 8 in 10 million (table C-162).

Routes of Exposure	Exposures per Lifetime	Risk from Exclusive Use of:							
		Amitrole	Asulam	Atrazine	Bromacil	2,4-D	2,4-DP	Glyphosate	Picloram
For a Single Exposure:									
Dermal, Spray	1	4.52E-11	7.84E-11	1.84E-10	--	1.23E-11	3.92E-13	2.06E-13	1.67E-14
Vegetation Contact									
Hiker	1	6.48E-13	1.12E-12	2.64E-12	--	1.77E-13	5.62E-15	2.95E-15	2.39E-16
Picker	1	9.13E-09	1.58E-08	3.71E-08	--	2.49E-09	7.92E-11	4.16E-11	3.38E-12
Drinking Water	1	5.30E-07	9.20E-09	2.16E-08	--	2.41E-09	4.60E-09	2.42E-11	1.09E-10
Eating Berries	1	3.04E-07	5.27E-09	1.23E-08	--	1.38E-09	2.63E-09	1.38E-11	6.24E-11
Eating Vegets.	1	6.07E-07	1.05E-08	2.47E-08	--	2.76E-09	5.27E-09	2.77E-11	1.25E-10
Eating Deer	1	4.11E-08	7.52E-10	1.76E-09	--	1.93E-10	3.56E-10	1.97E-12	8.44E-12
Eating Fish	1	2.12E-07	3.68E-09	4.31E-08	--	9.64E-10	1.84E-09	9.66E-12	4.36E-11
Combined Routes of Exposure:									
Hiker	1	5.30E-07	9.28E-09	2.18E-08	--	2.42E-09	4.60E-09	2.44E-11	1.09E-10
Berry Picker	1	8.43E-07	3.04E-08	7.12E-08	--	6.29E-09	7.31E-09	7.98E-11	1.75E-10
Hunter	1	7.09E-07	1.27E-08	2.98E-08	--	3.29E-09	6.15E-09	3.34E-11	1.46E-10
Fisherman	1	7.42E-07	1.30E-08	6.49E-08	--	3.39E-09	6.44E-09	3.40E-11	1.52E-10
Resident	1	1.14E-06	1.98E-08	4.65E-08	--	5.18E-09	9.87E-09	5.20E-11	2.34E-10
For 30 Exposures:									
Dermal, Spray	30	1.35E-09	2.35E-09	5.51E-09	--	3.70E-10	1.18E-11	6.17E-12	5.01E-13
Vegetation Contact									
Hiker	30	1.94E-11	3.37E-11	7.91E-11	--	5.30E-12	1.69E-13	8.85E-14	7.18E-15
Picker	30	2.74E-07	4.75E-07	1.11E-06	--	7.47E-08	2.38E-09	1.25E-09	1.01E-10
Drinking Water	30	1.59E-05	2.76E-07	6.47E-07	--	7.23E-08	1.38E-07	7.25E-10	3.27E-09
Eating Berries	30	9.11E-06	1.58E-07	3.70E-07	--	4.14E-08	7.90E-08	4.15E-10	1.87E-09
Eating Vegets.	30	1.82E-05	3.16E-07	7.41E-07	--	8.28E-08	1.58E-07	8.30E-10	3.74E-09
Eating Deer	30	1.23E-06	2.26E-08	5.29E-08	--	5.79E-09	1.07E-08	5.92E-11	2.53E-10
Eating Fish	30	6.36E-06	1.10E-07	1.29E-06	--	2.89E-08	5.52E-08	2.90E-10	1.31E-09
Combined Routes of Exposure:									
Hiker	30	1.59E-05	2.78E-07	6.53E-07	--	7.27E-08	1.38E-07	7.31E-10	3.27E-09
Berry Picker	30	2.53E-05	9.12E-07	2.14E-06	--	1.89E-07	2.19E-07	2.39E-09	5.24E-09
Hunter	30	2.13E-05	3.82E-07	8.94E-07	--	9.86E-08	1.85E-07	1.00E-10	4.37E-09
Fisherman	30	2.23E-05	3.89E-07	1.95E-06	--	1.02E-07	1.93E-07	1.02E-09	4.57E-09
Resident	30	3.41E-05	5.95E-07	1.39E-06	--	1.56E-07	2.96E-07	1.56E-09	7.01E-09

^aCancer risks shown in this Table were calculated based on a variety of assumptions that tend to overestimate risks as explained in Section 5.

^cNot used in aerial application.

^bAll of these numbers shown exponentially are to be interpreted as follows:

^cNot used in aerial application.

10⁻⁷ means 1 out of 10 million individuals exposed to a given herbicide via a given exposure scenario.

10⁻⁸ means 1 out of 100 million individuals,

10⁻⁹ means 1 out of 1 billion individuals, etc.

Table 5-12
 Lifetime Cancer Risk^a--Exposed Public
 Large Aerial, 400 Acres by Fixed Wing, Worst Case

Routes of Exposure	Exposures per Lifetime	Risk from Exclusive Use of:							
		Amitrole	Asulam	Atrazine	Bromacil	2,4-D	2,4-DP	Glyphosate	Picloram
For a Single Exposure:									
Dermal, Spray	1	4.78E-08	5.77E-08	1.04E-07	----	1.04E-08	2.59E-10	2.72E-10	4.42E-11
Vegetation Contact									
Hiker	1	6.86E-10	8.28E-10	1.49E-09	----	1.50E-10	3.72E-12	3.90E-12	6.34E-13
Picker	1	1.23E-07	1.49E-07	2.67E-07	----	2.69E-08	6.68E-10	7.02E-10	1.14E-10
Drinking Water	1	3.57E-06	4.31E-08	7.74E-08	----	1.30E-08	1.94E-08	2.03E-10	1.83E-09
Eating Berries	1	2.93E-06	3.54E-08	6.36E-08	----	1.07E-08	1.59E-08	1.67E-10	1.51E-09
Eating Vegets.	1	5.87E-06	7.09E-08	1.27E-07	----	2.13E-08	3.18E-08	3.34E-10	3.01E-09
Eating Deer	1	4.28E-07	5.54E-09	9.96E-09	----	1.62E-09	2.32E-09	2.61E-11	2.20E-10
Eating Fish	1	1.43E-06	1.72E-08	1.55E-07	----	5.19E-09	7.74E-09	8.13E-11	7.33E-10
Combined Routes of Exposure:									
Hiker	1	3.62E-06	1.02E-07	1.83E-07	----	2.36E-08	1.96E-08	4.79E-10	1.88E-09
Berry Picker	1	6.67E-06	2.85E-07	5.12E-07	----	6.10E-08	3.62E-08	1.34E-09	3.50E-09
Hunter	1	5.81E-06	1.31E-07	2.36E-07	----	3.21E-08	3.15E-08	6.19E-10	3.00E-09
Fisherman	1	5.05E-06	1.19E-07	3.37E-07	----	2.88E-08	2.74E-08	5.61E-10	2.61E-09
Resident	1	9.49E-06	1.72E-07	3.10E-07	----	4.49E-08	5.14E-08	8.13E-10	4.89E-09
For 30 Exposures:									
Dermal, Spray	30	1.43E-06	1.73E-06	3.11E-06	----	3.13E-07	7.78E-09	8.17E-09	1.33E-09
Vegetation Contact									
Hiker	30	2.06E-08	2.48E-08	4.46E-08	----	4.49E-09	1.12E-10	1.17E-10	1.90E-11
Picker	30	3.70E-06	4.46E-06	8.02E-06	----	8.07E-07	2.00E-08	2.10E-08	3.42E-09
Drinking Water	30	1.07E-04	1.29E-07	2.32E-06	----	3.89E-07	5.81E-07	6.10E-09	5.50E-08
Eating Berries	30	8.80E-05	1.06E-06	1.91E-06	----	3.20E-07	4.77E-07	5.01E-09	4.52E-08
Eating Vegets.	30	1.76E-04	2.13E-06	3.82E-06	----	6.40E-07	9.55E-07	1.00E-08	9.04E-08
Eating Deer	30	1.28E-05	1.66E-07	2.99E-07	----	4.87E-08	6.97E-08	7.84E-10	6.60E-09
Eating Fish	30	4.28E-05	5.17E-07	4.65E-06	----	1.56E-07	2.32E-07	2.44E-09	2.20E-08
Combined Routes of Exposure:									
Hiker	30	1.09E-04	3.05E-06	5.48E-06	----	7.07E-07	5.89E-07	1.44E-08	5.63E-08
Berry Picker	30	2.00E-04	8.55E-06	1.54E-05	----	1.83E-06	1.09E-06	4.03E-08	1.05E-07
Hunter	30	1.74E-04	3.94E-06	7.08E-06	----	9.63E-07	9.46E-07	1.86E-08	9.01E-08
Fisherman	30	1.51E-04	3.57E-06	1.01E-05	----	8.63E-07	8.21E-07	1.68E-08	7.83E-08
Resident	30	2.85E-04	5.17E-06	9.30E-06	----	1.35E-06	1.54E-06	2.44E-08	1.47E-07

^aCancer risks shown in this Table were calculated based on a variety of assumptions that tend to overestimate risks as explained in Section 5.

^bAll of these numbers shown exponentially are to be interpreted as follows:

10⁻⁷ means 1 out of 10 million individuals exposed to a given herbicide via a given exposure scenario.

10⁻⁸ means 1 out of 100 million individuals,

10⁻⁹ means 1 out of 1 billion individuals, etc.

^cNot used in aerial application.

Cancer Risk to Workers

Cancer risk to workers has been calculated for an expected case assuming 5 years of employment in herbicide application, and an average number of days of spraying per year. The average number of exposures per lifetime was estimated to range from 30 to 70. The risk has been calculated in the extreme cases assuming 30 years of employment and a total of 288 to 480 exposures. It is very unlikely that a worker would apply herbicides on the number of days assumed in the worst case. The lifetime cancer risks for workers are shown in table 5-13. (Cancer risks to workers for the accidental-worst case scenario are shown in Attachment C.) The risks for each herbicide were calculated assuming that only that herbicide was used. The highest risks for workers involve atrazine use. The lifetime cancer risk to a backpack sprayer using only atrazine is about 6 in 100,000 in the expected case. In the worst case the risk is greater than 5 in 10,000. The risk is less for the other chemicals. The highest risk for 2,4-D is about 1 in 100,000 for backpack spraying in the expected case, and in the extreme case, the greatest risk is about 1 in 10,000. The risk is somewhat greater for amitrole: as high as 7 in 100,000 for the realistic backpack exposure. Workers using asulam in the extreme case have a lifetime cancer risk of less than 6 in 10,000 in all worker categories. Workers using bromacil have a risk of less than 8 in 10,000 in the worst case. The cancer risk from picloram or glyphosate use is even less for all worker categories. The risk in the expected case never exceeds 3 in 10 million for glyphosate and never exceeds 2 in 100 million for picloram.

EPA (1985a) has also conducted a carcinogenic risk assessment for workers using amitrole (see table 5-14). EPA assumed that workers wore no protective clothing, and the estimated exposures were only 1.5×10^{-3} mg/kg/day for the highest exposures. EPA estimated cancer potency for liver and thyroid tumors, using the log-probit and multistage models. Estimated cancer risks for the anti-thyroid action of amitrole were all less than 1 in 10 billion based on the log-probit model. The multistage model gave much higher risk estimates, especially for liver tumors.

Table 5-13
Lifetime Cancer Risk^a--Exposed Workers

Routes of Exposure	Exposures per Lifetime	Risk from Exclusive Use of:							
		Amitrole	Asulam	Atrazine	Bromacil	2,4-D	2,4-DP	GLYPHOSATE	PICLORAM
For Realistic Number of Exposures:									
Pilot	30	6.06E-06	9.02E-06	1.93E-05	--	1.50E-06	4.34E-08	3.08E-08	3.81E-09
Mixer/Loader	30	8.24E-06	1.24E-05	2.67E-05	--	2.05E-06	5.98E-08	4.16E-08	5.04E-09
Supervisor	30	9.84E-07	1.45E-06	3.07E-06	--	2.42E-07	6.94E-09	5.04E-09	6.35E-10
Observer	30	1.92E-07	2.87E-07	6.16E-07	--	4.76E-08	1.38E-09	9.74E-10	1.19E-10
Backpack	50	6.59E-05	5.93E-05	1.81E-04	8.77E-05	1.34E-05	5.45E-07	2.50E-07	2.92E-08
R-O-W Sprayer	45	3.51E-06	3.86E-06	8.88E-06	3.34E-06	5.26E-07	2.35E-08	1.14E-08	8.02E-10
R-O-W Mix/L	45	2.39E-06	2.86E-06	6.31E-06	2.41E-06	4.03E-07	1.75E-08	8.24E-09	5.97E-10
R-O-W AP/M/L	45	2.97E-06	3.65E-06	7.95E-06	3.05E-06	5.19E-07	2.24E-08	1.04E-08	7.63E-10
Hack & Squirt	70	1.66E-05	--	--	2.22E-05	7.26E-06	4.33E-07	--	1.23E-08
Injection Bar	70	5.63E-06	--	--	7.49E-06	2.46E-06	1.46E-07	--	4.16E-09
Worst Case Number of Exposures:									
Pilot	288	5.82E-05	1.66E-05	1.85E-04	--	1.44E-05	4.16E-07	2.96E-07	3.65E-08
Mixer/Loader	288	7.91E-05	1.19E-04	2.56E-04	--	1.97E-05	5.74E-07	4.00E-07	4.84E-08
Supervisor	288	9.45E-06	1.39E-05	2.95E-05	--	2.32E-06	6.67E-08	4.84E-08	6.10E-09
Observer	288	1.84E-06	2.76E-06	5.91E-06	--	4.57E-07	1.33E-08	9.35E-09	1.15E-09
Backpack	440	5.80E-04	5.22E-04	1.59E-03	7.72E-04	1.18E-04	4.80E-06	2.20E-06	2.57E-07
R-O-W Sprayer	416	3.25E-05	3.57E-05	8.21E-05	3.08E-05	4.86E-06	2.17E-07	1.05E-07	7.41E-09
R-O-W Mix/L	416	2.21E-05	2.64E-05	5.83E-05	2.23E-05	3.72E-06	1.62E-07	7.62E-08	5.52E-09
R-O-W AP/M/L	416	2.75E-05	3.37E-05	7.35E-05	2.82E-05	4.80E-06	2.07E-07	9.65E-08	7.06E-09
Hack & Squirt	480	1.14E-04	--	--	1.52E-04	4.98E-05	2.97E-06	--	8.43E-08
Injection Bar	480	3.86E-05	--	--	5.14E-05	1.68E-05	1.00E-06	--	2.85E-08

^aCancer risks shown in this Table were calculated based on a variety of assumptions that tend to overestimate risks as explained in Section 5.

^bAll of these numbers shown exponentially are to be interpreted as follows:

10⁻⁷ means 1 out of 10 million individuals exposed to a given herbicide via a given exposure scenario.

10⁻⁸ means 1 out of 100 million individuals,

10⁻⁹ means 1 out of 1 billion individuals, etc.

^cNot used in hand application.

^dNot used in aerial application.

Table 5-14

Amitrole Worker Exposure Estimates
and Related Estimates of Cancer Risk

Exposure Situation ^a	Exposure (mg/kg/day)	Log-Probit ^b	Upper 95% Bound on Risk	
			Q _{1e} * = .20 ^c	Q _{1u} * = .076 ^d
<u>Utility Power Wagon Mixer-Loader/Applicator</u>				
Minimum	1.1x10 ^{-4e}	10 ⁻¹⁰	10 ⁻⁵	10 ⁻⁵
Average	4.6x10 ⁻⁴	10 ⁻¹⁰	10 ⁻⁴	10 ⁻⁵ - 10 ⁻⁴
Maximum	1.2x10 ⁻³	10 ⁻¹⁰	10 ⁻⁴	10 ⁻⁴
<u>Industry Power Wagon Mixer-Loader/Applicator</u>				
Minimum	6.3x10 ⁻⁵	10 ⁻¹⁰	10 ⁻⁵¹	10 ⁻⁶ - 10 ⁻⁵
Average	4.3x10 ⁻⁴	10 ⁻¹⁰	10 ⁻⁴	10 ⁻⁵ - 10 ⁻⁴
Maximum	1.1x10 ⁻³	10 ⁻¹⁰	10 ⁻⁴	10 ⁻⁴
<u>Industry Knapsack/Hand Carry Applicator</u>				
Minimum	4.9x10 ⁻⁶	10 ⁻¹⁰	10 ⁻⁶	10 ⁻⁷ - 10 ⁻⁶
Average	3.7x10 ⁻⁴	10 ⁻¹⁰	10 ⁻⁵ - 10 ⁻⁴	10 ⁻⁵
Maximum	1.5x10 ⁻³	10 ⁻¹⁰	10 ⁻⁴ - 10 ⁻³	10 ⁻⁴
<u>Industry Knapsack/Hand Carry/Mixer-Loader</u>				
Minimum	5.3x10 ⁻⁷	10 ⁻¹⁰	10 ⁻⁷	10 ⁻⁸ - 10 ⁻⁷
Average	2.7x10 ⁻⁵	10 ⁻¹⁰	10 ⁻⁶ - 10 ⁻⁵	10 ⁻⁶
Maximum	1.3x10 ⁻⁴	10 ⁻¹⁰	10 ⁻⁵	10 ⁻⁵

^aExposure estimates of dermal exposure and inhalation exposure were taken from Hitch memo of 12/15/83 adjusted for a maximum of 0.1 percent dermal penetration. Zendzian memo of 6/26/85, annual exposure estimate is divided by 70 kg to obtain exposure in mg/kg and by 365 and 2 to obtain average daily dose for one-half of a 70-year lifetime.

^bLog-Probit: This column represents the risks bounds under the assumption of the anti-thyroid action of amitrole.

^cQ_{1e}* : This column represents the risk bounds under the assumption of the interspecies surface area correction; and based on liver tumors in female mice.

^dQ_{1u}* : This column represents the risk bounds without the interspecies surface area correction; and based on thyroid tumors in male rats.

^eCancer risk shown in this Table were calculated based on a variety of assumptions that tend to overestimate risks as explained in Section 5.

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Calculated risks for average worker exposures were not greater than 1 in 10,000, and for maximum exposures the risks were not greater than 1 in 1,000. Amitrole carcinogenicity risks calculated in this risk assessment are consistent with EPA's independently derived results.

Cancer Risks in Accidental Situations

Cancer risks calculated for exposures resulting from accidental spraying are shown in Attachment C (table C-165). The greatest risks among the eight chemicals are for amitrole. A single incident of accidental spraying of amitrole gives calculated risks of 6 in 100,000 for a person eating sprayed vegetables and 3 in 100,000 for a person drinking sprayed water. Among the other chemicals, the greatest risks are about 6 in 1 million for exposures to atrazine, and 3 in 10 million for 2,4-D. Multiple incidents result in greater risks. Cancer risks calculated for spill situations are shown in table C-166. The greatest risks are for spills of herbicide concentrate directly onto worker clothing and skin. The tabled values assume that most of a person's skin has been contacted by the solution and cleanup does not occur for several hours. This is contrary to standard practice. A spill of atrazine concentrate onto a person gives a risk of about 1.5 in 1,000, and a spill of spray mixture gives a lesser risk of about 1.5 in 10,000. The corresponding risks for 2,4-D and amitrole are about a factor of 10 less. The risks of cancer resulting from spills of asulam and bromacil are less than 5 in 10,000 for the concentrate and about 2 in 100 thousand for the spray mixture. A spill of picloram or glyphosate concentrate gives a risk of 2 in 1 million or less.

Cancer risks to the public arising from even major spills into drinking water supplies are significantly less. A 100-gallon helicopter load of amitrole spray mixture dumped into a 1-acre pond would lead to a risk of cancer of no more than 2 in 100,000 for a person drinking a liter of the water. The corresponding risks for the other chemicals are much less. If a 1,000-gallon tank truck of spray mixture were spilled into a small pond, the risk for amitrole would be about 4 in 10,000. For 2,4-D the corresponding cancer risk is less than 2 in 1 million.

Comparison of Cancer Risks with Other Common Risks

To put the cancer risks calculated here in perspective, table 5-15 lists risks resulting from some more familiar hazards and occupational risks. Motor vehicle accidents have a risk of fatality that averages 2 in 10,000 per person each year. Over a 30-year period, the cumulative risk would be 6 in 1,000. A variety of hazards are listed in the table that have a risk of about 1 in 1 million. They include smoking 2 cigarettes, eating 6 pounds of peanut butter, drinking 40 sodas sweetened with saccharin, or taking 1 transcontinental round trip by air. The cancer risk for a single x-ray is 7 in 1 million. Many occupational risks are greater. Working for 30 years in agriculture or construction has a risk of about 1.8 in 100, and in mining and quarrying, the risk is even greater: 3 in 100 over 30 years.

RISK OF HERITABLE MUTATIONS

No human studies are available that associate any of the herbicides with heritable mutations. No risk assessments that quantify the probability of mutations from the herbicides are available in the literature or from EPA. Laboratory studies constitute the best available information on mutagenic potential. Results of the mutagenicity assays conducted on the 16 herbicides are summarized in table 3-3.

For some of the herbicides, no acceptable mutagenicity tests exist. For these herbicides, a worst case assumption is made that these herbicides have the potential to cause mutations in humans. In these cases the results of carcinogenicity tests (see table 3-3) or cancer risk assessments can be used to estimate the worst case risk for nonthreshold toxicity. The rationale for this assumption is summarized by the USDA (1985) as follows: "Since mutagenicity and carcinogenicity both follow similar mechanistic steps (at least those that involve genetic toxicity), the calculated risk of cancer can be used as a worst case approximation of somatic cell mutation risk. The basis for this assumption is that both mutagenicity and at least primary carcinogens react with DNA to form a mutation or DNA lesion affecting a particular gene or set of genes. The genetic lesions

Table 5-15

Lifetime Risk of Death or Cancer Resulting from Everyday Activities^a

Activity	Need to Accumulate a One in a Million Risk of Death	Average Annual Risk ^b per Capita
Based on living in the United States		
Motor vehicle accident	1.5 days	2×10^{-4} ^c
Falls	6 days	6×10^{-5}
Drowning	10 days	4×10^{-5}
Fires	13 days	3×10^{-5}
Firearms	36 days	1×10^{-5}
Electrocution	2 months	5×10^{-6}
Tornados	20 months	6×10^{-7}
Floods	20 months	6×10^{-7}
Lightning	2 years	5×10^{-7}
Animal bite or sting	4 years	2×10^{-7}
Occupational Risks		
General		
manufacturing	4.5 days	8×10^{-5}
trade	7 days	5×10^{-5}
service and government	3.5 days	1×10^{-4}
transport and public utilities	1 day	4×10^{-4}
agriculture	15 hours	6×10^{-4}
construction	14 hours	6×10^{-4}
mining and quarrying	9 hours	1×10^{-3}
Specific		
coal mining (accidents)	14 hours	6×10^{-4}
police duty	1.5 days	2×10^{-4}
railroad employment	1.5 days	2×10^{-4}
fire fighting	11 days	8×10^{-4}

Table 5-15 (Cont.)

Activity	Need to Accumulate a One in a Million Risk of Death	Average Annual Risk ^a per Capita
Everyday Risks		
Eating and drinking	40 diet sodas (saccharin)	
	6 pounds of peanut butter (aflatoxin B1)	
	180 pints of milk (aflatoxin G)	
	200 gallons of drinking water from Miami or New Orleans	
	90 pounds of broiled steak (cancer risk only)	
Smoking	2 cigarettes	

^aThese risks are not directly comparable to risk values for the 16 herbicides due to the many conservative assumptions that the herbicide risks were based on.

^bNote to calculate the risk over a lifetime multiply this column by 70. From Crouch and Wilson (1982).

^cCancer risk shown in this Table were calculated based on a variety of assumptions that tend to overestimate risk as explained in Section 5.

Note: All of these numbers shown exponentially are to be interpreted as follows: 10^{-7} means 1 out of 10 million individuals exposed to a given herbicide via a given exposure scenario.

10^{-8} means 1 out of 100 million individuals,

10^{-9} means 1 out of 1 billion individuals.

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then require specific metabolic processes to occur, or the cells must divide to insert the lesion into the genetic code of the cell.

We believe the cancer risk provides a worst case approximation to heritable mutations because:

1. There are no germ cell mutagenic noncarcinogens. All chemicals known to induce heritable germ cell mutation in mammals also produce cancer in mammals and almost always at a lower total dose.
2. Many chemicals that are carcinogens in rodents fail to induce heritable germ cell mutations even at the MTD.
3. Mammalian meiotic processes in gonadal tissue appear to be much more efficient in eliminating DNA lesions than somatic cells.
4. Human epidemiology studies of populations exposed to genotoxic carcinogens (radiation exposures in Nagasaki and Hiroshima) have demonstrated significant induction of cancer but no evidence of mutations at specific dose levels.

Asulam and glyphosate tested negative for mutagenicity in all assays conducted, and thus can be considered to pose no mutagenic risk. Fosamine, hexazinone, and simazine were nonmutagenic in most assays conducted and were nononcogenic in all of the carcinogenicity tests performed; therefore, it can be assumed that their germ cell mutagenic risk is slight to negligible. Dicamba was nonmutagenic in most of the assays performed, and no oncogenicity was found in several long-term studies. EPA (1985d) has classified the chronic studies as "inadequate to evaluate the oncogenic potential of dicamba." Because of the bulk of negative results, dicamba can be considered a mutagen in the worst case analysis, but the germ cell mutagenic hazard would be extremely limited.

No acceptable mutagenicity studies are available for dalapon or diuron. The worst case assumption is that all of these chemicals are mutagenic. The probability of dalapon or diuron causing heritable mutations is negligible because they have not been shown to cause cancer in any long-term studies.

The negative oncogenicity studies for diuron were classified by EPA (1985d) as inadequate to determine carcinogenic potential to mammalian organisms. The lack of positive results in mutagenicity or oncogenicity tests with diuron suggests that diuron would present a very low risk to human germ cells as a mutagen.

Bromacil tested positive in one of two oncogenic studies. The risk of heritable mutations from the chemical should be no greater than the estimates of cancer risk.

Atrazine tested positive for mutagenicity in 15 of 33 assays. The worst case assumption is that atrazine is mutagenic. However, many of the positive results were achieved through tests that may not be relevant to evaluating mutagenic risk in humans. Some positive results in rodents were also achieved, but these in vivo responses were only observed at levels greater than 1,500 mg/kg body weight. These are exceptionally high levels and suggest that the degree of germ cell risk would be lower than the risk for cancer and DNA change from low levels of atrazine would be minimal. The worst case estimate for atrazine mutagenic effects would be no greater than the risk of cancer as shown in tables 5-11 through 5-13.

Amitrole was nonmutagenic in 56 microbial gene mutation tests. The results of two tests that were positive are considered of questionable validity by EPA (1985a), and overall it is considered to pose no potential for heritable mutations (EPA, 1985a). The worst case estimate for amitrole mutagenic effects would be the risk of cancer, as shown in tables 5-11 and 5-12.

For picloram and 2,4-D, only a few studies have been performed and these have indicated positive and negative mutagenic potential. EPA has requested more mutagenicity-test information for these compounds. A number of comprehensive reviews of the 2,4-D mutagenic data have indicated that it does not pose significant risk of human gene mutations (USDA, 1984). 2,4-D has been shown to be nononcogenic in the two carcinogenicity studies that have been conducted. Based on a worst case estimate, the risk of heritable mutations from these chemicals would be no greater than the estimates of cancer risk.

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Mutagenic tests with 2,4-DP have shown mixed results. 2,4-DP was negative in four microbial assays and positive in four other assays; therefore, it may have limited genotoxic potential. Based on the limited test data presented in Section 3, one cannot presume mutagenic hazard, because no in vivo or mammalian assays have been conducted. However, the worst case assumption is that 2,4-DP is mutagenic and the mutagenic risk in the worst case would be no greater than the risk of cancer.

OTHER POSSIBLE EFFECTS OF THE 16 HERBICIDES

Synergistic Effects

Synergism occurs when the combined effects of the two chemicals cannot be predicted based on the known toxic effects of the individual chemicals or when their combined effect is much greater than the sum of the effects of each agent given alone. Synergistic effects of chemicals that occur or more chemicals either simultaneously or within a relatively short period of time. For example, forestry workers exposed to the fungicide thiram have experienced skin blotching and nausea from drinking alcoholic beverages within 10 days of their thiram exposure. For example, a mixture of the herbicides 2,4-D and picloram has produced skin irritation in test animals while neither herbicide alone has been found to be a skin irritant. Cigarette smoke and asbestos are both known carcinogens. When inhaled in combination, they have been found to increase cancer risk eight-fold above the risk of persons exposed to asbestos who do not smoke.

Evidence of Synergistic Effects From Pesticides

Instances of chemical combinations that cause synergistic effects are relatively rare. Kociba and Mullison (1985) in describing toxicological interactions with agricultural chemicals state the following:

Our present scientific knowledge in toxicology indicates that an exposure to a mixture of pesticides is more likely to lead to additivity or antagonism rather than synergism when considering the

toxicological effects of such a combination. To be conservative and for reasons of safety, an additive type of toxicological response is generally assumed rather than an antagonistic type of response.

In the case of registered pesticides, much toxicological information is developed during the research and development of each individual pesticide. In addition to this information on individual pesticides, short-term toxicity studies are always done prior to the selling of a pesticide mixture. Should synergism unexpectedly be present in a proposed commercial mixture of two pesticides, it would be identified in such cases and would then be dealt with accordingly. In toxicological tests involving a combination of commercial pesticides, synergism has generally not been observed.

The herbicide mixtures that may be used in the Forest Service's program have not shown synergistic effects in humans who have used them in other applications, although, as noted above, there is some evidence that mixtures of 2,4-D and picloram may cause skin irritation.

The toxic effects of the possible herbicide combinations other than the EPA-registered commercial mixtures have not been studied. Time and money normally limit toxicity testing to the first priority--the effects of the herbicides individually--and this type of information is not yet sufficient in some cases. Moreover, the combinations that could be tested are too numerous to make that testing feasible. The combinations of interest in this risk assessment include not only combinations of two or more of the 13 herbicides, but also combinations of the herbicides with other chemicals, such as insecticides, that exist in the environment. Based on the limited amount of data available on pesticide combinations, it is possible but very unlikely that synergistic effects could occur as a result of exposure to two or more of the herbicides considered in this analysis.

Likelihood of Exposure to Two Herbicides

For several reasons, it is highly unlikely that synergistic adverse effects could result from exposure to more than one herbicide applied in separate

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projects. First, unlike the situation in conventional agriculture, herbicide residues in plants and soil are not expected to persist from one application to another, even for the more persistent herbicides.

Second, the 13 herbicides are known to be rapidly excreted from the body. None of the herbicides has been found to accumulate in test animal body tissues, so exposure of an individual to two herbicides at different times would be unlikely to cause simultaneous residues within the body.

Third, public exposures to the herbicides should be low (except for accidents) and should occur only very infrequently. The probability of a larger accidental exposure to any single herbicide is extremely low. Because the probability of a member of the public receiving a large exposure is so low for one herbicide, the probability of simultaneous large exposures to two herbicides is negligible. This is because the probability of two independent events occurring simultaneously is the product of the probabilities of the individual events. For example, if the probability of a person receiving a given exposure is 1 in 1,000 for each of two herbicides, then the probability of receiving that exposure to both herbicides would be 1 in 1 million.

Risks From Herbicide Mixtures

Simultaneous exposure to more than one chemical is likely in cases where those chemicals are combined in a single spray mixture. Although most vegetation control projects in the Region would involve only a single herbicide, some areas would be treated with a mixture of herbicides, but only mixtures that have been approved for use by the Environmental Protection Agency.

The EPA guidelines for assessing the risk from exposures to chemical mixtures (EPA, 1986) recommend using additivity models when little information exists on the toxicity of the mixture and when components of the mixture appear to induce the same toxic effect by the same mode of action. They suggest in their discussion of interactions (synergistic or antagonistic effects) of chemical mixtures that "there seems to be a

Synergistic Effects

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

The EPA guidelines suggest using a hazard index (HI) as the model of additivity based on the dose and toxicity reference level (NOEL) for each chemical as follows:

$$HI = D_1/L_1 + D_2/L_2$$

where:

D_i is the dose of the i^{th} component and

L_i is the level of safety (NOEL)

As HI approaches 1, the risk from the mixture becomes greater and greater.

Although the herbicides used for vegetation control are unlikely to have synergistic toxic effects, other substances occurring in the diets of exposed people may have some influence on the toxicity of the herbicides. This is one of several factors that may influence the sensitivity of individuals.

Effects on Sensitive Individuals

If the response of a population of test animals to varying doses of a chemical follows a normal distribution (bell-shaped curve), the hypersensitive individuals are those on the left hand side of the curve that respond at much lower doses than the average. A safety factor of 10 has traditionally been used by regulatory agencies (NAS, 1977) to account for this intraspecies (that is, interindividual) variation. Not all sensitive individuals will be covered by an MOS of 100, as human susceptibility to toxic substances can vary two to three orders of magnitude (Calabrese, 1985). (These individuals could correspond to the very tail of the bell-shaped curve.)

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Factors Affecting the Sensitivity of Individuals

Factors that may affect individual susceptibility to toxic substances include diet, age, heredity, preexisting diseases, and life style (Calabrese, 1978). These factors have been studied in detail for very few cases, and their significance in controlling the toxicity of the proposed herbicides is not known. However, enough data have been collected on other chemicals to show that these factors can be important.

Elements of the diet known to affect toxicity include vitamins and minerals (Calabrese and Dorsey, 1984). For example, the mineral selenium can prevent the destruction of blood-forming tissues by chronic heavy exposure to benzene. Large doses of vitamin C have also been shown to protect animals and humans from toxic effects of chronic benzene exposure. Vitamin A seems to have a preventative effect on cancer induced by chemicals such as benzo(a)pyrene (found in cigarette and wood smoke) and DMBA. This effect has been seen in laboratory animals and human epidemiological studies. The food additives BHT and BHA may also be active in preventing the carcinogenicity of benzo(a)pyrene. Various levels of the B vitamin riboflavin have also been tested with mixed results. Vitamin C has been shown to prevent nitrites from combining with amines to form nitrosamines, and vitamin E seems to be at least as effective. These vitamins would be likely to prevent the formation of N-nitrosoatrazine and N-nitrosoglyphosate if conditions were otherwise favorable for their formation in the human stomach (Calabrese and Dorsey, 1984).

Genetic factors are also known in some cases to be important determinants of susceptibility to toxic environmental agents (Calabrese, 1984). Susceptibility to irritants and allergic sensitivity vary widely among individuals and are known to be largely dependent on genetic factors. Race has been shown to be a significant factor influencing sensitivity to irritants, and some investigations have indicated that women may be more sensitive than men (Calabrese, 1984).

A variety of human genetic conditions have been identified as possibly enhancing susceptibility to environmental agents. For example, persons with beta thalassaemia may be at increased risk when exposed chronically to benzene. However, only one condition, G-6-PD deficiency, has been conclusively demonstrated to cause enhanced susceptibility to industrial pollutants. Several other genetic conditions have been shown to involve defects in the cellular mechanisms for repair of damage to DNA. Persons with these diseases share an increased sensitivity to the effects of ultraviolet light, which can cause cancer. Cells from individuals with at least one of these diseases, xeroderma pigmentosum, are also sensitive to a variety of chemical substances implicated as causative agents of human cancers (Calabrese, 1984).

Persons with other types of preexisting medical conditions may also be at increased risk of toxic effects. For example, sensitivity to chemical skin irritants can be expected to be greater for people with a variety of chronic skin ailments. Patients with these conditions may be advised to avoid occupational exposure to irritating chemicals (Shmunis, 1980, as cited in Calabrese, 1984).

Allergic Hypersensitivity

A particular form of sensitivity reaction to a foreign substance is allergic hypersensitivity. Except for contact dermatitis in delayed allergic reactions, these are responses to high molecular weight organic molecules or whole cells. None of the herbicides in the Forest Service vegetation management program is of high molecular weight so the immediate allergic reactions and the delayed allergic reactions except for contact dermatitis can be ruled out as possible toxic effects. Contact dermatitis may be induced by lower molecular weight substances such as the catechols of poison ivy, cosmetics, drugs, or antibiotics (Volk and Wheeler, 1983). Benzocaine, neomycin, formaldehyde, nickel, chromium, and thiram are all known to produce these reactions (Marzulli and Maibach, 1983).

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Likelihood of Effects in Sensitive Individuals

Based on the current state of knowledge, individual susceptibility to the toxic effects of the 16 herbicides cannot be specifically predicted. As discussed above, safety factors have traditionally been used to account for variations in susceptibility among people. The margin-of-safety approach used in this risk assessment takes into account much of the variation in human response as discussed earlier by Calabrese (1985). As described in the introduction to this risk assessment, a safety factor of 10 is used for interspecies variation, an additional safety factor of 10 is used for within-species variation.

Thus, the normal margin-of-safety of 100 for both types of variation is sufficient to ensure that most people will experience no toxic effects. However, unusually sensitive individuals may experience effects even when the margin-of-safety is equal to or greater than 100. For example, there have been a few cases of peripheral neuropathy among the thousands of people exposed over the years to 2,4-D. In particular, in instances in the risk assessment where margins-of-safety are less than 100 for an exposure to a particular herbicide, it is possible that an exposed sensitive individual would experience toxic effects, whereas the average person would not. It must be noted, however, that sensitive individuals comprise only a fraction of the population at large and that it is not likely that a sensitive individual would be among those few people who might be exposed in any of the Forest Service's applications. It must also be noted that the great majority of public exposures that have been estimated to occur in this risk assessment are very low, and in most applications that will actually occur when the program is implemented, no member of the public is liable to be exposed.

There may be some people who develop contact dermatitis from herbicide exposure. The Roundup formulation of glyphosate, for example, has been reported to produce contact dermatitis although a controlled study in human volunteers did not show this effect (Maibach, 1986). This type of reaction would most likely be limited to workers who handle the herbicides regularly

and are exposed to relatively large amounts on a number of occasions. The small, infrequent exposures of the public should limit the possibility of their experiencing this type of reaction.

Effects from Inert Ingredients in Herbicide Formulations

Inert ingredients are chemicals that are added to the active ingredient to prepare a pesticide formulation. Inert ingredients provide a carrier for the active ingredient that facilitates the effective application of the pesticide but that is not intended to supplement the pesticide's toxic properties.

This risk assessment characterizes human health risks by comparing estimated herbicide doses with toxicity levels found in laboratory animal studies. The estimated doses and laboratory hazard levels are based on the active ingredients of the proposed herbicides, not on the formulated products. This is reasonable because the active ingredients possess the intended pesticidal properties. However, consideration of the possible toxic properties of the remaining portion of the formulations, the inert ingredients, is also warranted as is the possibility of synergism from the combination of active and inert ingredients in the formulations.

Toxicity of the Inert Ingredients

With respect to the toxicity of the inert ingredients alone, EPA's Office of Pesticide Programs (EPA, 1986h) has identified about 1,200 inert ingredients that are now used in approved pesticides and has reviewed the available evidence concerning their toxicity. The data included laboratory toxicity tests, epidemiological data, and structure/activity relationships. A particular concern in reviewing the inerts was their potential for causing chronic human health effects. On completion of its review, EPA categorized the 1,200 inerts into four lists.

List 1 contains about 55 inerts that have been shown to be carcinogens, developmental toxicants, neurotoxins, or potential ecological hazards that merit the highest priority for regulatory action. EPA is

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requesting manufacturers to replace these inerts in their formulations with less toxic chemicals.

List 2 contains approximately 50 chemicals that have been given high priority for testing because of available toxicity data that are suggestive, but not conclusive, of possible chronic health effects or because they have structures similar to chemicals on List 1.

List 3 contains approximately 800 chemicals that are of lower priority for testing because there is no evidence from available toxicity data or from a review of their chemical structure that would place them in Lists 1 or 2.

List 4 of about 300 chemicals contains those inerts generally recognized as safe. It includes substances such as corn oil, honey, peanut oil, and water.

Because EPA normally classifies inert ingredients as "Confidential Business Information," information on them does not have to be released to the public under the Freedom of Information Act (see also 40 CFR 1506.(a)). Nonetheless, the Forest Service requested that EPA review each of the formulations of the 16 herbicides proposed for use and disclose whether any of them contained inert ingredients of, or suggestive of, toxicological concern.

EPA has reviewed the formulations and has determined none contain inerts on List 1, but that several contain inerts on List 2. The Esteron-99 formulation of 2,4-D and triclopyr formulations contain a petroleum distillate (kerosene) of high priority for testing. Accordingly, a risk analysis was conducted on the petroleum distillate kerosene. Atrazine, diuron, and simazine formulations contain formaldehyde. Otherwise, formulations of the herbicides proposed for use contain inerts that EPA has determined do not support a specific concern for toxicity or risk.

Toxicity of the Formulations

With respect to the possibility of synergism in the formulated combination of active and inert ingredients, EPA generally requires only acute toxicity data on formulated products. These data also allow EPA to address concerns about the acute toxicity of the pesticide formulations' inert ingredients. A comparison of their acute LD₅₀'s provides an indication of the toxicity of the formulated product (including inerts) versus the active ingredient alone. As shown in table 5-16, the formulations proposed for use by the Forest Service are less acutely toxic than their active ingredient.

However, none of the herbicide formulations proposed for use by the Forest Service have undergone chronic toxicity testing, including cancer testing, or any reproductive, developmental, or mutagenicity testing. The inert ingredients in the proposed formulated products might cause cancer or other long-term health effects. Given the little information that is available on each herbicide's formulation, the possibility that the formulated product is more toxic than the active ingredient cannot be discounted entirely. Neither can it be assumed to be true. The possibility that the herbicides' formulations may pose greater risk than their components is largely an untested hypothesis, and as to the herbicides' formulations acute toxicity, as table 5-16 shows, the possibility should not follow.

Turning to the competing viewpoint, and the one adopted in this FEIS, the data gaps about the herbicides as formulated products are largely beside the point because the risks posed by the herbicide's active ingredient are over stated. Any risk posed by the herbicides as formulated products is considered to be subsumed by the analysis of the active ingredients. Moreover, it is important to remember that each herbicide as a formulated product contains two types of ingredients: active and inert. Each type of ingredient has known and suspected properties. The herbicides' active ingredients have undergone cancer, reproductive, developmental, and mutagenicity tests of varying degrees. The herbicides' inerts have undergone categorization according to their toxicity and risks, if any. With only one lone exception, no specific concern exists with the

Table 5-16
Acute LD₅₀'s of Herbicide Mixtures Compared to Acute LD₅₀'s of Mixtures

Combination	Test	Level in Comp. 1	Level in Comp. 2	Level in Comp. 3	Level in Comp. 4
Banvel 4 Atrazine 80 WP Princip. WP Paraquat 2EC	Acute Dermal LD ₅₀ rabbit (level not given) LD ₅₀ 20,000 mg/kg	Banvel 4 (Dicamba) rabbit (level not given) LD ₅₀ 2,000 mg/kg Tech., DMA Salt	Atrazine 80 WP (level not given) LD ₅₀ 7,000 kg/mg Tech., rabbit	Princip WP Simazine (level not given) BOW formulation rabbit	Paraquat 2EC (level not given) LD ₅₀ 24 mg/kg (W.S.S.A)
Banvel 4 Atrazine 80 WP Princip. WP Paraquat 2EC	Acute Oral rat (level not given) LD ₅₀ 5,000 mg/kg	Banvel 4 LD ₅₀ 757 mg/kg	Atrazine 80 WP LD ₅₀ 1,869 kg/mg	Princip. WP (Simazine) LD ₅₀ 5,000 kg/mg	Paraquat 2EC LD ₅₀ 120 mg/kg (W.S.S.A)
2,4-D MCPA Dicamba	Acute Oral rat LD ₅₀ 5,000 mg/kg	2,4-D 71.42% 532 mg/kg	MCPA .71% 800 kg/mg	Dicamba .04% 757 kg/mg rat	
2,4-D MCPA Dicamba	Acute Dermal rabbit LD ₅₀ 2,000 mg/kg	2,4-D 1,400 mg/kg (DOE 1983)	MCPA	Dicamba LD ₅₀ 2,000 mg/kg	
2,4-D and Banvel 45 (Dicamba) Levels not given	Acute Oral rat LD ₅₀ 1,847 mg/kg	2,4-D LD ₅₀ 532 mg/kg	Banvel 45 LD ₅₀ 757 mg/kg		
2,4-D and Banvel 45 (Dicamba) Levels not given	Acute Dermal rabbit LD ₅₀ 11,892 mg/kg	2,4-D LD ₅₀ 400 mg/kg (DOE 1983)	Banvel 45 LD ₅₀ 2,000 mg/kg		
2,4-D 1.15% Dicamba 1.60% MCPP 1.06%	Acute Oral 10 LD ₅₀ 20 gm slight erytherae edema	2,4-D 1.15% LD ₅₀ 532 mg/kg 532 mg/kg	Dicamba 1.60% LD ₅₀ 757 mg/kg 800 kg/mg	MCPP 1.06% (mecoprop) 1,060 mg/kg W.S.S.A.	
2,4-D .99% MCPP .99%	Acute Dermal LD ₅₀ 2,000 mg/kg	2,4-D .99% LD ₅₀ 1,400 mg/kg (DOE 1983)	MCPP .99% LD ₅₀ 900 mg/kg (W.S.S.A.)		

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Table 5-16 (continued).

Combination		Test	Level in Comp. 1	Level in Comp. 2	Level in Comp. 3	Level in Comp. 4
2,4-D	.5820%	Acute Oral	2,4-D .582%	MCPP .2448%	Dicamba .0516%	
MCPP	.2448%	LD ₅₀ 5,050 mg/kg	LD ₅₀ 532 mg/kg	LD ₅₀ 1,060 mg/kg	LD ₅₀ 757 mg/kg	
Dicamba	.0516%			(W.S.S.A.)		
Banvel 45		Acute Oral	Banvel 45	Lasso 4EC		
+ Lasso 4EC		LD ₅₀ 5,000 mg/kg	LD ₅₀ 757 mg/kg	(Alachlor)		
(Alachlor)				1,000 mg/kg		
% comp. not given				(W.S.S.A.)		
Banvel 45		Acute Dermal	Banvel 45	Lasso 4EC		
+ Lasso 4EC		LD ₅₀ 20,000 mg/kg	(Dicamba)	(Alachlor)		
(Alachlor)			LD ₅₀ 2,000 mg/kg	13,300 mg/kg		
% comp. not given				(W.S.S.A.)		
2,4-D	1.455%	Acute Dermal,	2,4-D 1.455%	MCPA .612%	Dicamba .129%	
MCPA	.612%	rabbit	LD ₅₀ 1,400 mg/kg		LD ₅₀ 2,000 mg/kg	
Dicamba	.129%	LD ₅₀ 2,005 mg/kg	(DOE 1983)			
2,4-D	.680%	Acute Oral	2,4-D .680%	MCPP .680%	Dicamba .027%	
MCPP	.680%	LD ₅₀ 5,000 mg/kg	LD ₅₀ 532 mg/kg	LD ₅₀ 1,060 mg/kg	LD ₅₀ 757 mg/kg	
Dicamba	.027%			(WSSA 1983)		
2,4-D	.680%	Acute Dermal	2,4-D .680%	MCPP .680%	Dicamba .027%	
MCPP	.680%	LD ₅₀ 2,000 mg/kg	LD ₅₀ 1,400 mg/kg	LD ₅₀ 900 mg/kg	LD ₅₀ 2,000 mg/kg	
Dicamba	.027%		(DOE 1983)	(WSSA 1983)		
2,4-D	1.37%	Acute Oral	2,4-D 1.37%	MCPP 1.37%	Dicamba .055%	
MCPP	1.37%	LD ₅₀ 5,000 mg/kg	LD ₅₀ 532 mg/kg	LD ₅₀ 1,060 mg/kg	LD ₅₀ 2,000 mg/kg	
Dicamba	.055%			(WSSA 1983)		
2,4-D	1.370%	Acute Dermal,	2,4-D 1.37%	MCPP 1.37%	Dicamba .055%	
MCPP	1.37%	rabbit	LD ₅₀ 1,400 mg/kg	LD ₅₀ 900 mg/kg	LD ₅₀ 2,000 mg/kg	
Dicamba	.055%	LD ₅₀ 2,000 mg/kg	(DOE 1983)	(WSSA 1983)		
2,4-D	.58%	Acute Oral,	2,4-D .58%	MCPP .58%		
MCPP	.58%	rat	LD ₅₀ 532 mg/kg	LD ₅₀ 1,060 mg/kg		
		LD ₅₀ 5,000 mg/kg		(WSSA 1983)		
2,4-D	.58%	Acute Dermal,	2,4-D .58%	MCPP .58%		
MCPP	.58%	rabbit	LD ₅₀ 1,400 mg/kg	LD ₅₀ 900 mg/kg		
		LD ₅₀ 2,000 mg/kg	(DOE 1983)	(WSSA 1983)		
2,4-D	.99%	Acute Oral	2,4-D .99%	MCPP .99%		
MCPP	.99%	LD ₅₀ 5,000 mg/kg	LD ₅₀ 532 mg/kg	LD ₅₀ 1,060 mg/kg		
				(WSSA 1983)		

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Effects on Sensitive
Individuals

Table 5-16 (continued).

Combination	Test	Level in Comp. 1	Level in Comp. 2	Level in Comp. 3	Level in Comp. 4
2,4-D 46.7%	Acute Oral	2,4-D 46.7%	2,4-DP 45.9%		
2,4-DP 45.9%	LD ₅₀ 887 mg/kg	LD ₅₀ 532 mg/kg	LD ₅₀ 532 mg/kg		
2,4-D 46.7%	Acute Dermal	2,4-D 46.7%	2,4-DP 45.9%		
2,4-DP 45.9%	LD ₅₀ 2,405 mg/kg	LD ₅₀ 1,400 mg/kg (DOE 1983)	LD ₅₀ 2,000 mg/kg		
Dicloram 17.1%	Acute Oral	Dicloram 17.1%	Triclopyr 32.5%		
Triclopyr 32.5%	LD ₅₀ 2,991 mg/kg ^(m) 3,011 mg/kg ^(f)	LD ₅₀ 8,200 mg/kg	LD ₅₀ 630-739 mg/kg		
Dicloram 17.1%	Acute Dermal	Dicloram 17.1%	Triclopyr 32.5%		
Triclopyr 32.5T	LD ₅₀ 1,485 mg/kg	LD ₅₀ 4,000 mg/kg	LD ₅₀ 2,000 mg/kg		
Simazine, same status listed under dicamba princep WP. acute dermal and acute oral					

herbicides' inerts. The Forest Service will continue to monitor the status of inert ingredients in these formulations and conduct further analysis if they are recategorized.

Therefore, based on EPA's classification of the inerts, it is assumed that the risk analysis on the active ingredients sufficiently characterizes the risks of the formulated products with the exception of the petroleum distillates whose risk is discussed below.

Risk From Petroleum Distillates

A 2,4-D formulation and a triclopyr formulation proposed for use contain kerosene, a petroleum distillate. Diesel oil, a similar petroleum distillate, is used as an herbicide carrier. The oncogenic potential of petroleum distillates is directly related to refinery processing methods used to obtain the petroleum product and the crude oil composition from which the fuel was derived. An evaluation of the composition of petroleum fuels has revealed that a positive correlation exists between polycyclic aromatic hydrocarbon (PAH) content and carcinogenicity in human epidemiology studies or experimental laboratory studies (Bingham et al., 1979).

Although kerosene and diesel oil have not been shown to cause cancer, they are likely to have a slight carcinogenic potency because they contain small amounts of chemicals known or suspected to cause cancer. Among these are benzene and benzo(a)pyrene. The cancer potencies of kerosene and diesel oil are about 6,000 times lower than the 2,4-D cancer potency; therefore, it would not add significantly to the potency of the 2,4-D formulation or mixtures. Their systemic toxicities should not appreciably increase the toxicities of 2,4-D or triclopyr nor is there any indication that they would increase reproductive toxicity for either chemical.

Formaldehyde is both a strong irritant and a carcinogen. Sufficient information on the amount in the atrazine, diuron, and simazine formulations is not available to accurately quantify the risk of their use due to formaldehyde toxicity. The Forest Service will therefore suspend use of those formulations until a risk assessment can be done.

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Cumulative Effects

The total area of U.S. Forest Service land in Washington and Oregon and BLM land in western Oregon is 38,000 square miles. This area makes up about one-fourth of the total land area (165,000 mi²) of those two States. In a given year, the Forest Service and BLM may treat up to 156 mi² (100,000 acres) with herbicides for vegetation management. The treated area would thus comprise less than one-thousandth (less than 0.1 percent) of the total land area of the two States. Moreover, the treatments would occur for the most part in the remote areas of either these densely forested or range lands. In general, treatment units are sprayed only once in a given year, then not treated again until a number of years later. The later treatment also may be with a different herbicide.

No individual member of the public is likely to receive repeated exposures to any of the herbicides because of the remoteness of most treatment units, the widely spaced timing of repeated treatments, and the use of a variety of herbicides for different purposes. In addition, the precautions taken by the Forest Service and BLM in their treatment operations make any dose at all to the public quite unlikely. This risk assessment used the lowest NOEL's found in chronic animal laboratory studies for comparison with estimated human doses. The risk analysis results showed that, except for amitrole and atrazine, margins of safety for the public from realistic treatment scenarios are greater than 100. Thus, members of the public could receive doses of these herbicides repeatedly over the years, even though the chance of receiving multiple doses is negligible, and still not suffer toxic effects. Some individuals who may be particularly sensitive to amitrole or atrazine may experience ill effects but, again, this should occur only in the unusual circumstance of repeated doses. The public can be exposed to a wide variety of other chemical compounds through voluntary and involuntary routes of exposure. The Forest Service and BLM acknowledge that the potentially exposed public from proposed vegetation management program does not live in a chemical free environment. However, because of the reasons stated above additional risk to humans from Forest Service and BLM operations from year to year would be insignificant.

Cumulative Effects
Populations at Risk

Cumulative effects on workers have been considered throughout this analysis. The risk of workers experiencing toxic effects, including cancer, assumes that they are chronically exposed to these herbicides. Backpack applicators are at greatest risk from cumulative effects. Contract employees are not expected to be at any greater risk than government employees.

Populations at Risk

The populations at potential risk in herbicide spraying operations in the Pacific Northwest fall into three categories: (1) workers involved in the spray operations, (2) forest users such as hikers, hunters, and fishermen, and (3) residents of dwellings in and near the forest.

The number of workers involved in spraying operations for a typical spray year for the Forest Service and BLM is discussed in Section 2. The number of forest visitors to Forest Service and BLM land is recorded as visitor days by the agencies. The Forest Service in Region 6 averages approximately 30 million total visitor days annually. Total visitor days for BLM averages about 2 million annually in western Oregon. The number of residents living within a specified distance of Forest Service and BLM land is as follows:

<u>Distance</u>	<u>Number of Residents</u>	
	<u>Forest Service Land</u>	<u>BLM Land</u>
1/4 mile	29,831	30,357
1/2 mile	50,919	53,395

Again, because of the remote locations of most herbicide application sites, no member of the public should be exposed during most operations. Silvicultural operations present the least probability of exposure, while right-of-way and facilities maintenance operations present the greatest probability of exposure.

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The only possibility for exposure beyond one-half mile distance is in the extremely unlikely event of an accidental worst case spill. BLM estimates that the number of people living within a mile of its land in western Oregon is approximately 130,000. The Forest Service estimates that the number of residents with a mile of its land is approximately 100,000.

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Appendix D

**Human Health
Risk Assessment
(Quantitative)**



Attachment A

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Attachment A

PROCEDURES FOR THE SELECTION OF DATA SETS FOR WORST CASE RISK ANALYSIS:
MUTAGENICITY/CARCINOGENICITY

BACKGROUND

The methods for cancer risk analysis using animal data have been reasonably well formulated. However, in the absence of rodent cancer data or with negative rodent cancer data, positive results from short-term tests for genotoxicity have been used as justification for either (a) questioning the adequacy of the rodent cancer studies or (b) recommending risk assessments for heritable mutations by way of germ cell damage in rodents.

The rationale for such a use of short-term assays rests with the close mechanistic and correlative association between carcinogens and mutagens (Brusick, 1987). It also assumes that agents defined by short-term tests as mutagens have the potential to induce similar damage in mammalian germ cells and that such damage could be transmitted to successive generations in the form of genetic disease or congenital malformations (Brusick et al., 1981).

DEFINITIONS

Often the meaning of technical terms are not universally consistent and without general agreement as to what they mean, arbitrary use of some terms or phrases may tend to increase confusion surrounding the analysis of a scientific issue. The five terms or phrases underlined in the above statement may be defined in several ways. Their meanings in this discussion are as follows:

Short-term tests--submammalian, mammalian in vitro cell culture or mammalian somatic cell tests measuring DNA alterations.

Genotoxicity--the process of chemical-induced damage to the DNA of an organism that will produce cell death, mutation, DNA alterations and repair, or cell transformation.

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Heritable mutations--mutations that are induced at any germ cell stage in mammalian gametogenesis and that can be transmitted to and expressed in subsequent generations.

Germ cell damage--in rodents, this is measured by very specific types of assays. Germ cell damage may produce lethal or heritable effects; in this discussion, only those effects that are heritable are considered relevant to risk assessment. The two standard tests for assessment of germ cell damage in this context are the mouse specific locus test (SLT) and the mouse heritable translocation test (HTT).

Mutagens--chemicals capable of inducing gene or chromosome damage that is stable and survives cell division. Effects may be in somatic cells or germ cells.

NATURE OF THE DATA ENCOUNTERED IN DEVELOPING RISK ASSESSMENTS

The mutation and cancer data configurations of interest are summarized in table A-1. The selection of a data set for use in making a risk analysis is based on the data most likely to provide the worst case estimate.

ISSUES AND RECOMMENDATIONS

The issues have been formulated as follows:

1. From the data sets shown in table A-1, how does one support selection of data for the worst case risk?
2. For chemicals with no germ cell mutagenicity studies and inconclusive or negative cancer studies, should positive short-term test results for genotoxicity assays be used as evidence in a worst case analysis that a heritable mutation risk may exist at exposures lower than the MTD used to test for cancer?

Table A-1

Bioassay Results and Data Selection for Risk Analysis

Rodent Cancer Studies	Rodent Germ Cell Mutation Studies	Selection of Data for Risk Analysis
Positive	Positive	Cancer data
Positive	Negative or no data	Cancer data
Negative or no data	Positive	Mutation data
Negative or inconclusive	Negative or no data ^a	Estimated from upper bound of high dose cancer data

^aShort-term tests for genotoxicity show some positive effects.

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Recommendations: Issue #1

In the cases where rodent cancer studies have been performed, these data should be used to set the human risk levels unless it can be shown from corresponding rodent germ cell data that statistically significant specific locus mutation or heritable translocation responses occur at comparable or lower exposures.

Rationale

The existing data base for chemicals that have been tested in rodents for carcinogenic as well as heritable mutation effects supports the judgment that carcinogenesis is the more sensitive of the two endpoints. Human cancer and mutational epidemiology information accumulated from atomic bomb survivors in Japan shows clear associations between dose and cancer but no mutations have been found. Radiation is mutagenic in rodents. The data in table A-2 are used to support the sensitivity argument by comparing the results and effective dose levels for virtually all chemicals that have been tested for heritable germ cell mutation and have corresponding rodent cancer studies. Data from chemicals negative in both bioassay types are not included. Although all compounds listed were found to be carcinogenic, seven were clearly nonmutagenic at the highest dose tested and three were evaluated as inconclusive (no significant effect in the sample size examined). It is important to note that no compounds have been shown to induce heritable germ cell responses in rodents without concomitant carcinogenicity.

Potency comparisons (lowest effective daily dose for mutagenicity vs. tumor dose 50 [TD_{50}] daily dose for carcinogenicity, which is the dose estimated to result in 50 percent tumor-free animals at the end of the study) with chemicals that produced both effects showed that risk to cancer was found at lower average daily dose levels than risk to heritable mutation in all cases and for total cumulative dose for most chemicals. For some nonmutagens, the total applied dose was lower than the cumulative dose needed to achieve a TD_{50} . This is explained by the fact that mutation studies are conducted with single acute exposures and the total

Table A-2

Comparison of the Carcinogenic and Germ Cell
Mutagenicity Activities of 20 Chemicals

Chemical	Rodent ^a		Total Dose Applied (mg/kg)		Most Sensitive Endpoint	
	Carcinogen	Mutagen	Cancer (ADD) ^b	Mutation ^c	Avg. Daily Dose	Total Dose
Benzo(a)pyrene	+	-	1000 (2)	5000	C	C
Cyclophosphamide	+	+	3500 (7)	350	C	M
Diethylnitrosamine	+	-	10 (.02)	119	C	C
7,12 Dimethylbenzanthracene	+	inc.	40 (.08)	10	C	C
Ethylmethane sulfonate	+	+	-	300	?	?
Ethlnitrosourea	+	+	-	250	?	?
Methylmethane sulfonate	+	+	17,500 (35)	20	M	M
Methylnitrosoguanidine	+	inc.	1,000 (2)	50	C	C
Mitomycin C	+	+	.05 (.001)	5	C	C
Procarbazine	+	+	250 (.5)	400	C	C
Propylmethane sulfonate	+	+	-	800	?	?
Triethylene melanine	+	+	-	0.2	?	?
Trenimon	+	+	250 (.5)	0.13	M	M
Nitrogen mustard	+	+	5 (.01)	-	?	?
Captan	(+)	-	50,000 (100)	3000	C	C
Ethylcarbamate (urethane)	+	-	25,000 (50)	1750	C	C
Hexamethylphosphamide	+	-	-	1989	C	C
Ethylene Dibromide	+	inc.	1500 (3)	167	C	C
1,2-Dibromo-3-chloropropane	+	-	2000 (4)	384	C	C
Nitriolotriacetic acid	+	-	112,500 (225)	3000	C	C

^aMouse or rat.

^b(ADD) average daily dose required to produce TD₅₀.

^cIn mutation studies exposures are generally acute and thus Total Dose = ADD.

^dC = cancer, M = mutation, ? = data gap.

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amount of material applied acutely will be less than that which could be applied by repeated exposures of lower doses.

There are many possible explanations for the observations that cancer is the more sensitive endpoint; for example, mammalian gonads are generally more protective from the systemic exposures by the blood-gonad barriers than somatic tissues preventing compound exposure. It also appears that the meiotic process associated with germ cell production is extremely effective in eliminating damaged DNA before it becomes part of mature spermatozoa or ova. This is probably accomplished by DNA repair or by selective elimination of damaged cells from the gene pool.

When cumulative exposures from chronic cancer studies (approximately 500 days) are compared to single total doses from mutation studies, a few of the chemicals (cyclophosphamide, methylmethane sulfonate, trenimon) appear to show greater activity for mutation than cancer. These examples are probably not exceptions but represent the bias encountered toward the mutation data. The following points illustrate three aspects of comparisons that would tend to enhance the apparent sensitivity of mutation assays:

Fractionation of Doses. Cancer studies are conducted with low daily doses given chronically while mutation studies are conducted generally with a single acute high dose. Occasionally, multiple dose studies for mutation are performed. When chemicals are tested for mutation using both single acute and subchronic applications, the results are often different.

Fractionated doses for mutation appear to result in a significant drop in mutation. Russell et al. (1982) have shown that 10 x 10 mg/kg doses of ethyl nitrosourea given over 10 weeks gives a much lower mutation frequency than a single dose of 100 mg/kg. Other findings indicate that, for some agents, the results for fractionated doses appear to be additive (Ehling, 1980; Ehling and Neuhauser-Klaus, 1984). In order to make the most conservative comparisons, the cumulative TD_{50} average (mg/kg) daily dose (roughly 500 days for a chronic study) from the rodent cancer studies was compared with either the lowest effective dose for mutagens or the highest

dose tested for nonmutagens. Dose rate differences would tend to bias sensitivity toward the mutation data.

Route of Administration. Most of the mutation assays were performed using intraperitoneal (IP) injection of the test agent. This route of administration is believed to over-estimate risk because chemicals that are not readily absorbed from the GI tract following ingestion will be active by this route. Chemicals that would readily hydrolyze to nonmutagenic forms under ingestion or gavage routes are also known to produce positive effects by the IP route. None of the cancer studies were conducted using intraperitoneal injection exposure. Chemicals such as nitrosoguanidine, ethylmethane sulfonate and methylmethane sulfonate would probably not be mutagenic in mice if administered via oral ingestion. The routes of exposure used would tend to bias sensitivity toward the mutation data.

Response Parameters. The dose levels used from the cancer studies represent the TD_{50} . The TD_{50} is not necessarily the lowest effective carcinogenic dose; it is used as a means of normalizing responses from different species and study designs. The doses used from positive mutation studies represent the lowest tested dose producing a statistically significant increase in either specific locus mutation or heritable translocation in mice. Studies defined as negative were of sufficient power to declare a noneffect. Studies defined as inconclusive showed no increase in mutation but the sample size examined was insufficient to declare the chemical a clear negative. In either of the latter two cases, the dose shown was the highest dose tested. Comparing the cancer bioassay TD_{50} dose to the lowest effective mutagenic dose would probably tend to bias the sensitivity toward the mutagenicity data.

Thus, it is not surprising that for a few selected chemicals mutation risks may appear greater than cancer risks; however, if these compounds could be compared at the same dose rate and by a relevant route of exposure (oral ingestion or inhalation), it is very likely that the apparent sensitivity of the mutation endpoint would disappear.

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Recommendations: Issue #2

Germ cell mutation data can be used for worst case risk analysis only when (1) no rodent cancer studies have been conducted and positive germ cell data (heritable translocation assay or specific locus mutation assay) are available, or (2) rodent cancer studies have been conducted producing negative results and positive germ cell data are available. Positive short-term test results are insufficient evidence for presumption of germ cell risk.

Rationale

As argued under Issue #1, genotoxins have a higher probability of expressing biological activity as carcinogens rather than inducers of heritable germ cell effects in rodents (table A-2). All available data also support the fact that carcinogenic potential in rodents will be exhibited at lower (average daily or cumulative) doses than heritable mutagenicity for mutagenic carcinogens. Consequently, agents tested in rodents at the MTD that fail to elicit an effect as a somatic cell tumorigen are not going to produce heritable effects under similar exposure conditions in the intrinsically more resistant germ cells.

Occasionally, the toxicity data available to calculate worst case risk may consist of chemicals with negative or inconclusive rodent cancer data and positive short-term test results for genotoxicity (excluding positive germ cell responses). The tendency might be to generate a worst case by "assuming" that the short-term studies are adequate evidence that the chemical would induce heritable germ cell effects and therefore should be treated as a mutagen. This is not a supportable assumption based on the rationale supporting the recommendations for Issue #1 and an analysis of how well positive short-term test results predict germ cell mutagenesis in rodents.

Evidence that argues against the presumption that "a chemical that is not carcinogenic in rodents but is positive in short-term tests should be treated as a germ cell mutagen" comes from analyses of the predictivity of

short-term genotoxicity assays for concomitant responses in rodent germ cells. Three independent analyses of the concordance values clearly demonstrate that one cannot accurately predict heritable genetic damage in vivo from single short-term assays (ICPEMC Committee 1, 1983; Russell et al., 1984; Bridges and Mendelsohn, 1986). Tables A-3 and A-4 give results from the EPA GeneTox data base in which the concordance between individual short-term tests and responses in either the mouse specific locus or the mouse heritable translocation assays are calculated. When the concordance values for any individual comparison are corrected for random assortment, none of the short-term test observed concordance values is statistically significant (Russell et al., 1984). This finding precludes general extrapolation from a positive short-term test response to a presumption of effects in rodent germ cells.

Thus, a hope that one can develop a worst case risk analysis for heritable mutation with a compound that is not carcinogenic in rodents but has some positive short-term test results is not supported by the available data. Semianalytical weight-of-evidence approaches considering data from extensive batteries of short-term tests are available and may prove valuable in performing this type of hazard assessment. A better approach to establish a worst case would be to establish the estimated risk from the cancer study assuming an effect at the upper bound of the 95 percent confidence limits. This would provide a suitable conservative worst case assessment for nonthreshold effects. It would also prevent short-term test data from being inappropriately used in risk analysis.

CONCLUSIONS

The available data generated from rodent risk assessment assays on chemicals tested for cancer and mutation support the general practice of setting worst case human risks for nonthreshold toxicity on the basis of estimated tumor induction. This practice is not only supported quantitatively by comparing lowest effective doses where both biological endpoints have been induced but is also supported qualitatively in that:

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Table A-3

Performance of Various Assays Relative to Specific-Locus-Test (SLT) Results

Assay Compared with SLT ^a	Concordance	
	Observed	Calculated for Random Assortment ^b
Mouse spot test	91.7	77.8
Unscheduled DNA synthesis in testis	83.3	55.6
Micronucleus test	71.4	50.0
Plant gene mutations	61.5	60.4
Saccharomyces mutation	69.2	69.2
Dominant lethal	66.7	53.3
Drosophila sex-linked recessive lethals	62.5	55.5
Salmonella mutation	64.3	54.1
Sperm anomalies in treated males	66.7	61.1
Neurospora mutation	63.6	63.6
Plant chromosome anomalies	63.6	63.6

^aOnly assays that gave results for at least 20 of the chemicals tests by the assays.

^bOn the null hypothesis.

Table A-4

Performance of Various Assays Relative to
Heritable-Translocation-Test (HTT) Results

Assay Compared with HTT ^a	Concordance	
	Observed	Calculated for Random Assortment ^b
Unscheduled DNA synthesis in testis	90.9 ^c	64.5
Dominant lethal	76.5	64.0
SCE, animal cells, in vitro	91.7	77.8
Sperm anomalies in treated males	91.7	77.8
Drosophila heritable translocations	83.3	70.8
Micronucleus test	80.0	72.0
Salmonella mutation	71.4	65.3
Plant chromosome anomalies	92.3	92.3
Neurospora mutation	90.9	90.9
Drosophila sex-linked recessive lethals	83.3	83.3
Saccharomyces mutation	78.6	78.6
Male germ-cell cytogenetics	50.0	50.0
Host-mediated assay	78.6	80.6
Plant gene mutation	66.7	72.2

^aOnly assays that gave results for at least 20 of the chemicals tests by the assays.

^bOn the null hypothesis.

^cBorderline of significance, $P = 0.055$.

Adapted by Russell et al., 1984.

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1. Chemicals that are effective carcinogens in rodent models have not been found to be mutagenic to the germ cells at comparable or even higher exposures.
2. No chemical has produced unequivocal heritable mutation in rodents that is not also carcinogenic and generally at lower exposures.
3. Humans exposed to a genotoxic carcinogen (radiation) showed significant increases in cancer but no evidence of induced germ cell mutation.

Extrapolation of positive responses from short-term nongerm cell mutagenicity studies to a presumption of effect or risk to germ cells is not supported by the available data. Positive short-term tests results should be used to support a presumption of carcinogenic potential.

Short-term assay data sets should be evaluated using a weight-of-evidence approach.

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Appendix D
Human Health
Risk Assessment
(Quantitative)



Attachment B

Table B-1
Doses to workers (mg/kg)
ROUTINE REALISTIC AERIAL, 40 ACRES BY HELICOPTER

HERBICIDE	PILOT	MIXER/LOADER	SUPERVISOR	OBSERVER
Amitrole	0.0004	0.0006	0.0001	0.0000
Asulam	0.0483	0.0693	0.0074	0.0016
Atrazine	0.0755	0.1083	0.0115	0.0025
Bromacil	---	---	---	---
2,4-D	0.0302	0.0433	0.0046	0.0010
2,4-DP	0.0004	0.0006	0.0001	0.0000
Dalapon	0.0806	0.1156	0.0123	0.0026
Dicamba	0.0140	0.0201	0.0021	0.0005
Diuron	---	---	---	---
Fosamine	0.0604	0.0867	0.0092	0.0020
Glyphosate	0.0403	0.0578	0.0062	0.0013
Hexazinone	0.0504	0.0722	0.0077	0.0016
Picloram	0.0004	0.0005	0.0001	0.0000
Simazine	0.0806	0.1156	0.0123	0.0026
Tebuthiuron	0.0201	0.0289	0.0031	0.0007
Triclopyr	0.0066	0.0095	0.0010	0.0002

---: not used by this application method

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Table B-2

Doses to workers (mg/kg)

LARGE AERIAL, 400 ACRES BY FIXED WING, ROUTINE WORST CASE

<u>HERBICIDE</u>	<u>PILOT</u>	<u>MIXER/LOADER</u>	<u>SUPERVISOR</u>	<u>OBSERVER</u>
Amitrole	0.0067	0.0085	0.0012	0.0002
Asulam	0.5591	0.7128	0.0969	0.0173
Atrazine	0.6696	0.8536	0.1160	0.0207
Bromacil	---	---	---	---
2,4-D	0.4018	0.5122	0.0696	0.0124
2,4-DP	0.0042	0.0053	0.0007	0.0001
Dalapon	1.6740	2.1340	0.2900	0.0517
Dicamba	0.4660	0.5941	0.0807	0.0144
Diuron	---	---	---	---
Fosamine	2.0088	2.5608	0.3480	0.0620
Glyphosate	0.8370	1.0670	0.1450	0.0258
Hexazinone	0.5022	0.6402	0.0870	0.0155
Picloram	0.0151	0.0192	0.0026	0.0005
Simazine	0.8370	1.0670	0.1450	0.0258
Tebuthiuron	1.0044	1.2804	0.1740	0.0310
Triclopyr	0.2210	0.2817	0.0383	0.0068

Table B-3
Doses to workers (mg/kg)
SMALL BACKPACK, 6.0 ACRES, ROUTINE REALISTIC CASE

<u>HERBICIDE</u>	<u>DOSE</u>
Amitrole	0.0033
Asulam	0.1978
Atrazine	0.4946
Bromacil	0.6595
2,4-D	0.1978
2,4-DP	0.0033
Dalapon	0.6595
Dicamba	0.0574
Diuron	0.6595
Fosamine	0.4946
Glyphosate	0.2473
Hexazinone	0.1846
Picloram	0.0030
Simazine	0.3297
Tebuthiuron	0.2473
Triclopyr	0.0544

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Table B-4
Doses to workers (mg/kg)
LARGE BACKPACK, 60 ACRES, ROUTINE WORST CASE

<u>HERBICIDE</u>	<u>DOSE</u>
Amitrole	0.0310
Asulam	2.0693
Atrazine	2.4782
Bromacil	6.1955
2,4-D	1.4869
2,4-DP	0.0266
Dalapon	7.4346
Dicamba	1.7248
Diuron	3.7173
Fosamine	7.1248
Glyphosate	3.0978
Hexazinone	1.8587
Picloram	0.0446
Simazine	2.8499
Tebuthiuron	3.7173
Triclopyr	0.8178

Table B-5
Doses to workers (mg/kg)
SMALL RIGHT OF WAY, ROUTINE REALISTIC CASE

HERBICIDE	APPLICATOR	MIX/LOADER	APPL/MIX/LOADER
Amitrole	0.0001	0.0001	0.0001
Asulam	0.0082	0.0084	0.0116
Atrazine	0.0103	0.0105	0.0145
Bromacil	0.0137	0.0140	0.0193
2,4-D	0.0051	0.0052	0.0072
2,4-DP	0.0001	0.0001	0.0001
Dalapon	0.0137	0.0140	0.0193
Dicamba	0.0024	0.0024	0.0034
Diuron	0.0137	0.0140	0.0193
Fosamine	0.0137	0.0140	0.0193
Glyphosate	0.0069	0.0070	0.0096
Hexazinone	0.0086	0.0087	0.0120
Picloram	0.0001	0.0001	0.0001
Simazine	0.0069	0.0070	0.0096
Tebuthiuron	0.0075	0.0077	0.0106
Triclopyr	0.0011	0.0012	0.0016

D Human Health Risk Assessment (Quantitative)

Table B-6
Doses to workers (mg/kg)
LARGE RIGHT OF WAY, ROUTINE WORST CASE

<u>HERBICIDE</u>	<u>APPLICATOR</u>	<u>MIX/LOADER</u>	<u>APPL/MIX/LOADER</u>
Amitrole	0.0042	0.0024	0.0029
Asulam	0.2652	0.1530	0.1787
Atrazine	0.4509	0.2601	0.3038
Bromacil	0.5305	0.3060	0.3574
2,4-D	0.1305	0.0753	0.0879
2,4-DP	0.0027	0.0015	0.0018
Dalapon	0.5305	0.3060	0.3574
Dicamba	0.1329	0.0767	0.0896
Diuron	0.8488	0.4896	0.5719
Fosamine	0.5676	0.3274	0.3824
Glyphosate	0.2652	0.1530	0.1787
Hexazinone	0.3183	0.1836	0.2145
Picloram	0.0019	0.0011	0.0013
Simazine	0.2440	0.1408	0.1644
Tebuthiuron	0.2440	0.1408	0.1644
Triclopyr	0.0700	0.0404	0.0472

Table B-7
Doses to workers (mg/kg)
HAND APPLICATION TO SMALL SITE, ROUTINE REALISTIC

<u>HERBICIDE</u>	<u>HACK & SQUIRT</u>	<u>INJECTION BAR</u>
Amitrole	0.00056	0.00021
Bromacil	0.11134	0.04235
2,4-D	0.06680	0.02541
2,4-DP	0.00167	0.00064
Dicamba	0.07749	0.02948
Diuron	0.11134	0.04235
Fosamine	0.11134	0.04235
Picloram	0.00100	0.00038
Triclopyr	0.01837	0.00699

D Human Health Risk Assessment (Quantitative)

Table B-8
Doses to workers (mg/kg)
HAND APPLICATION TO LARGE SITE, ROUTINE WORST CASE

<u>HERBICIDE</u>	<u>HACK & SQUIRT</u>	<u>INJECTION BAR</u>
Amitrole	0.00631	0.00169
Bromacil	1.26170	0.33728
2,4-D	0.75702	0.20237
2,4-DP	0.01893	0.00506
Dicamba	0.87814	0.23475
Diuron	1.26170	0.33728
Fosamine	1.26170	0.33728
Picloram	0.01136	0.00304
Triclopyr	0.20818	0.05565

Table B-9

Dose in micrograms/kg by exposure type:

ROUTINE REALISTIC AERIAL, 40 ACRES BY HELICOPTER

HERBICIDE	SPRAY DRIFT DERMAL	VEGETATION CONTACT HIKER	VEGETATION CONTACT PICKER	DRINK WATER	EATING BERRIES	EATING VEGS.	EATING DEER	EATING BIRD	EATING FISH
Amitrole	0.000	0.000	0.032	1.884	1.079	2.158	0.146	0.489	0.754
Asulam	0.019	0.000	3.894	2.261	1.295	2.589	0.185	0.660	0.904
Atrazine	0.030	0.000	6.084	3.532	2.023	4.045	0.289	1.031	7.064
2,4-D	0.012	0.000	2.434	2.355	1.348	2.697	0.188	0.656	0.942
2,4-DP	0.000	0.000	0.032	1.884	1.079	2.158	0.146	0.489	0.754
Dalapon	0.032	0.000	6.490	3.768	2.158	4.315	0.308	1.100	1.507
Dicamba	0.006	0.000	1.129	0.942	0.539	1.079	0.076	0.266	0.377
Fosamine	0.024	0.000	4.867	2.826	1.618	3.236	0.231	0.825	1.130
Glyphosate	0.016	0.000	3.245	1.884	1.079	2.158	0.154	0.550	0.754
Hexazinone	0.020	0.000	4.056	2.355	1.348	2.697	0.192	0.687	0.942
Picloram	0.000	0.000	0.029	0.942	0.539	1.079	0.073	0.245	0.377
Simazine	0.032	0.000	6.490	3.768	2.158	4.315	0.308	1.100	1.507
Tebuthiuron	0.008	0.000	1.622	0.942	0.539	1.079	0.077	0.275	3.768
Triclopyr	0.003	0.000	0.535	1.884	1.079	2.158	0.147	0.498	0.754

D Human Health Risk Assessment (Quantitative)

Table B-10

Doses in micrograms/kg for example people:
ROUTINE REALISTIC AERIAL, 40 ACRES BY HELICOPTER

HERBICIDE	HIKER	BERRY PICKER	HUNTER	FISHERMAN	NEARBY RESIDENT
Amitrole	1.884	2.995	2.518	2.637	4.041
Asulam	2.280	7.468	3.125	3.184	4.869
Atrazine	3.563	11.669	4.882	10.627	7.608
2,4-D	2.367	6.149	3.212	3.309	5.064
2,4-DP	1.884	2.995	2.518	2.637	4.041
Dalapon	3.800	12.447	5.208	5.307	8.115
Dicamba	0.948	2.616	1.289	1.324	2.026
Fosamine	2.850	9.335	3.906	3.980	6.086
Glyphosate	1.900	6.223	2.604	2.654	4.058
Hexazinone	2.375	7.779	3.255	3.317	5.072
Picloram	0.942	1.511	1.260	1.319	2.021
Simazine	3.800	12.447	5.208	5.307	8.115
Tebuthiuron	0.950	3.112	1.302	4.718	2.029
Triclopyr	1.886	3.501	2.532	2.640	4.044

Table B-11

Dose in micrograms/kg by exposure type:
 LARGE AERIAL, 400 ACRES BY FIXED WING, ROUTINE WORST CASE

HERBICIDE	SPRAY DRIFT DERMAL	VEGETATION CONTACT HIKER	VEGETATION CONTACT PICKER	DRINK WATER	EATING BERRIES	EATING VEGS.	EATING DEER	EATING BIRD	EATING FISH
Amitrole	0.170	0.002	0.438	12.681	10.423	20.846	1.522	6.274	5.072
Asulam	14.180	0.203	36.553	10.588	8.703	17.406	1.362	5.930	4.235
Atrazine	16.981	0.244	43.776	12.681	10.423	20.846	1.631	7.102	25.362
2,4-D	10.189	0.146	26.266	12.681	10.423	20.846	1.587	6.767	5.072
2,4-DP	0.106	0.002	0.274	7.926	6.514	13.028	0.951	3.921	3.170
Dalapon	42.454	0.609	109.440	31.702	26.057	52.114	4.077	17.754	12.681
Dicamba	11.819	0.170	30.468	12.681	10.423	20.846	1.597	6.848	5.072
Fosamine	50.944	0.731	131.328	38.042	31.268	62.537	4.892	21.305	15.217
Glyphosate	21.227	0.305	54.720	15.851	13.028	26.057	2.039	8.877	6.340
Hexazinone	12.736	0.183	32.832	9.511	7.817	15.634	1.223	5.326	3.804
Picloram	0.382	0.005	0.985	15.851	13.028	26.057	1.903	7.851	6.340
Simazine	21.227	0.305	54.720	15.851	13.028	26.057	2.039	8.877	6.340
Tebuthiuron	25.472	0.365	65.664	19.021	15.634	31.268	2.446	10.653	76.085
Triclopyr	5.604	0.080	14.446	25.362	20.846	41.691	3.077	12.808	10.145

D Human Health Risk Assessment (Quantitative)

Table B-12

Doses in micrograms/kg for example people:

LARGE AERIAL, 400 ACRES BY FIXED WING, ROUTINE WORST CASE

HERBICIDE	HIKER	BERRY PICKER	HUNTER	FISHERMAN	NEARBY RESIDENT
Amitrole	12.853	23.711	20.649	17.925	33.699
Asulam	24.971	70.024	32.263	29.207	42.377
Atrazine	29.906	83.861	38.638	55.267	50.751
2,4-D	23.016	59.558	31.370	28.088	43.861
2,4-DP	8.033	14.819	12.906	11.203	21.062
Dalapon	74.765	209.653	96.596	87.445	126.879
Dicamba	24.669	65.391	33.114	29.742	45.515
Fosamine	89.718	251.583	115.915	104.935	152.254
Glyphosate	37.382	104.826	48.298	43.723	63.439
Hexazinone	22.429	62.896	28.979	26.234	38.064
Picloram	16.239	30.247	25.993	22.579	42.296
Simazine	37.382	104.826	48.298	43.723	63.439
Tebuthiuron	44.859	125.792	57.958	120.944	76.127
Triclopyr	31.046	66.257	46.931	41.191	72.737

Table B-13

Dose in micrograms/kg by exposure type:
 SMALL BACKPACK, 6.0 ACRES, ROUTINE REALISTIC CASE

HERBICIDE	SPRAY DRIFT DERMAL	VEGETATION CONTACT HIKER	VEGETATION CONTACT PICKER	DRINK WATER	EATING BERRIES	EATING VEGS.	EATING DEER	EATING BIRD	EATING FISH
Amitrole	0.002	0.000	0.007	0.166	0.306	0.612	0.038	0.109	0.066
Asulam	0.107	0.002	0.423	0.100	0.184	0.367	0.024	0.073	0.040
Atrazine	0.267	0.004	1.057	0.249	0.459	0.918	0.060	0.184	0.498
Bromacil	0.356	0.005	1.409	0.332	0.612	1.224	0.080	0.245	0.133
2,4-D	0.107	0.002	0.423	0.166	0.306	0.612	0.039	0.117	0.066
2,4-DP	0.002	0.000	0.007	0.166	0.306	0.612	0.038	0.109	0.066
Dalapon	0.356	0.005	1.409	0.332	0.612	1.224	0.080	0.245	0.133
Dicamba	0.031	0.000	0.123	0.041	0.076	0.153	0.010	0.030	0.017
Diuron	0.356	0.005	1.409	0.332	0.612	1.224	0.080	0.245	2.654
Fosamine	0.267	0.004	1.057	0.249	0.459	0.918	0.060	0.184	0.100
Glyphosate	0.134	0.002	0.528	0.124	0.229	0.459	0.030	0.092	0.050
Hexazinone	0.100	0.001	0.395	0.093	0.171	0.343	0.022	0.069	0.037
Picloram	0.002	0.000	0.006	0.083	0.153	0.306	0.019	0.055	0.033
Simazine	0.178	0.003	0.705	0.166	0.306	0.612	0.040	0.122	0.066
Tebuthiuron	0.134	0.002	0.528	0.124	0.229	0.459	0.030	0.092	0.498
Triclopyr	0.029	0.000	0.116	0.166	0.306	0.612	0.038	0.111	0.066

D Human Health Risk Assessment (Quantitative)

Table B-14

Doses in micrograms/kg for example people:
SMALL BACKPACK, 6.0 ACRES, ROUTINE REALISTIC CASE

HERBICIDE	HIKER	BERRY PICKER	HUNTER	FISHERMAN	NEARBY RESIDENT
Amitrole	0.168	0.481	0.315	0.234	0.780
Asulam	0.208	0.813	0.305	0.248	0.575
Atrazine	0.520	2.032	0.763	1.017	1.438
Bromacil	0.693	2.709	1.017	0.825	1.917
2,4-D	0.274	1.001	0.430	0.341	0.886
2,4-DP	0.168	0.481	0.315	0.234	0.780
Dalapon	0.693	2.709	1.017	0.825	1.917
Dicamba	0.073	0.272	0.112	0.089	0.226
Diuron	0.693	2.709	1.017	3.346	1.917
Fosamine	0.520	2.032	0.763	0.619	1.438
Glyphosate	0.260	1.016	0.381	0.310	0.719
Hexazinone	0.194	0.759	0.285	0.231	0.537
Picloram	0.085	0.244	0.158	0.118	0.391
Simazine	0.346	1.354	0.509	0.413	0.958
Tebuthiuron	0.260	1.016	0.381	0.757	0.719
Triclopyr	0.196	0.617	0.345	0.262	0.808

Table B-15

Dose in micrograms/kg by exposure type:
LARGE BACKPACK, 60 ACRES, ROUTINE WORST CASE

HERBICIDE	SPRAY DRIFT DERMAL	VEGETATION CONTACT HIKER	VEGETATION CONTACT PICKER	DRINK WATER	EATING BERRIES	EATING VEGS.	EATING DEER	EATING BIRD	EATING FISH
Amitrole	0.009	0.000	0.022	0.477	0.922	1.843	0.116	0.339	0.191
Asulam	0.572	0.008	1.475	0.319	0.616	1.231	0.081	0.255	0.128
Atrazine	0.685	0.010	1.766	0.382	0.737	1.475	0.097	0.305	0.764
Bromacil	1.713	0.025	4.416	0.955	1.843	3.687	0.242	0.762	0.382
2,4-D	0.411	0.006	1.060	0.382	0.737	1.475	0.095	0.291	0.153
2,4-DP	0.007	0.000	0.019	0.411	0.793	1.585	0.099	0.292	0.164
Dalapon	2.056	0.029	5.299	1.146	2.212	4.424	0.290	0.915	0.458
Dicamba	0.477	0.007	1.229	0.382	0.737	1.475	0.095	0.295	0.153
Diuron	1.028	0.015	2.650	0.573	1.106	2.212	0.145	0.457	4.584
Fosamine	1.970	0.028	5.078	1.098	2.120	4.240	0.278	0.876	0.439
Glyphosate	0.857	0.012	2.208	0.477	0.922	1.843	0.121	0.381	0.191
Hexazinone	0.514	0.007	1.325	0.286	0.553	1.106	0.073	0.229	0.115
Picloram	0.012	0.000	0.032	0.382	0.737	1.475	0.092	0.272	0.153
Simazine	0.788	0.011	2.031	0.439	0.848	1.696	0.111	0.351	0.176
Tebuthiuron	1.028	0.015	2.650	0.573	1.106	2.212	0.145	0.457	2.292
Triclopyr	0.226	0.003	0.583	0.764	1.475	2.949	0.186	0.553	0.306

D Human Health Risk Assessment (Quantitative)

Table B-16

Doses in micrograms/kg for example people:

LARGE BACKPACK, 60 ACRES, ROUTINE WORST CASE

HERBICIDE	HIKER	BERRY PICKER	HUNTER	FISHERMAN	NEARBY RESIDENT
Amitrole	0.486	1.430	0.941	0.677	2.330
Asulam	0.899	2.982	1.235	1.027	2.131
Atrazine	1.077	3.571	1.479	1.841	2.552
Bromacil	2.693	8.927	3.697	3.075	6.379
2,4-D	0.799	2.590	1.185	0.952	2.274
2,4-DP	0.418	1.230	0.809	0.582	2.003
Dalapon	3.231	10.713	4.436	3.690	7.655
Dicamba	0.866	2.826	1.256	1.019	2.340
Diuron	1.616	5.356	2.218	6.200	3.828
Fosamine	3.096	10.267	4.251	3.536	7.336
Glyphosate	1.346	4.464	1.848	1.537	3.190
Hexazinone	0.808	2.678	1.109	0.922	1.914
Picloram	0.395	1.163	0.759	0.547	1.869
Simazine	1.239	4.107	1.701	1.414	2.935
Tebuthiuron	1.616	5.356	2.218	3.908	3.828
Triclopyr	0.993	3.048	1.733	1.299	3.943

Table B-17

Dose in micrograms/kg by exposure type:
SMALL RIGHT OF WAY, ROUTINE REALISTIC CASE

HERBICIDE	SPRAY DRIFT DERMAL	VEGETATION CONTACT HIKER	VEGETATION CONTACT PICKER	DRINK WATER	EATING BERRIES	EATING VEGS.	EATING DEER	EATING BIRD	EATING FISH
Amitrole	0.000	0.000	0.002	0.074	0.102	0.204	0.012	0.030	0.030
Asulam	0.041	0.001	0.224	0.089	0.123	0.245	0.015	0.041	0.036
Atrazine	0.052	0.001	0.280	0.112	0.153	0.307	0.019	0.051	0.223
Bromacil	0.069	0.001	0.373	0.149	0.204	0.409	0.025	0.068	0.060
2,4-D	0.026	0.000	0.140	0.093	0.128	0.256	0.016	0.041	0.037
2,4-DP	0.000	0.000	0.002	0.093	0.128	0.256	0.015	0.038	0.037
Dalapon	0.069	0.001	0.373	0.149	0.204	0.409	0.025	0.068	0.060
Dicamba	0.012	0.000	0.065	0.037	0.051	0.102	0.006	0.016	0.015
Diuron	0.069	0.001	0.373	0.149	0.204	0.409	0.025	0.068	1.191
Fosamine	0.069	0.001	0.373	0.149	0.204	0.409	0.025	0.068	0.060
Glyphosate	0.034	0.000	0.187	0.074	0.102	0.204	0.013	0.034	0.030
Hexazinone	0.043	0.001	0.233	0.093	0.128	0.256	0.016	0.042	0.037
Picloram	0.000	0.000	0.002	0.037	0.051	0.102	0.006	0.015	0.015
Simazine	0.034	0.000	0.187	0.074	0.102	0.204	0.013	0.034	0.030
Tebuthiuron	0.038	0.001	0.205	0.082	0.112	0.225	0.014	0.037	0.327
Triclopyr	0.006	0.000	0.031	0.074	0.102	0.204	0.012	0.031	0.030

D Human Health Risk Assessment (Quantitative)

Table B-18
Doses in micrograms/kg for example people:
SMALL RIGHT OF WAY, ROUTINE REALISTIC CASE

HERBICIDE	HIKER	BERRY PICKER	HUNTER	FISHERMAN	NEARBY RESIDENT
Amitrole	0.075	0.179	0.117	0.105	0.279
Asulam	0.131	0.477	0.187	0.167	0.377
Atrazine	0.164	0.597	0.234	0.387	0.471
Bromacil	0.219	0.796	0.312	0.278	0.628
2,4-D	0.119	0.387	0.175	0.156	0.375
2,4-DP	0.093	0.224	0.147	0.131	0.349
Dalapon	0.219	0.796	0.312	0.278	0.628
Dicamba	0.049	0.165	0.072	0.064	0.152
Diuron	0.219	0.796	0.312	1.409	0.628
Fosamine	0.219	0.796	0.312	0.278	0.628
Glyphosate	0.109	0.398	0.156	0.139	0.314
Hexazinone	0.137	0.497	0.195	0.174	0.392
Picloram	0.038	0.090	0.059	0.052	0.140
Simazine	0.109	0.398	0.156	0.139	0.314
Tebuthiuron	0.120	0.438	0.172	0.448	0.345
Triclopyr	0.080	0.213	0.123	0.110	0.285

Table B-19
Dose in micrograms/kg by exposure type:
LARGE RIGHT OF WAY, ROUTINE WORST CASE

HERBICIDE	SPRAY DRIFT DERMAL	VEGETATION CONTACT HIKER	VEGETATION CONTACT PICKER	DRINK WATER	EATING BERRIES	EATING VEGS.	EATING DEER	EATING BIRD	EATING FISH
Amitrole	0.005	0.000	0.012	0.398	0.620	1.240	0.075	0.197	0.159
Asulam	0.300	0.004	0.773	0.249	0.388	0.775	0.049	0.138	0.100
Atrazine	0.510	0.007	1.314	0.423	0.659	1.318	0.083	0.234	0.846
Bromacil	0.600	0.009	1.546	0.498	0.775	1.550	0.098	0.275	0.199
2,4-D	0.147	0.002	0.380	0.204	0.318	0.636	0.040	0.108	0.082
2,4-DP	0.003	0.000	0.008	0.249	0.388	0.775	0.047	0.123	0.100
Dalapon	0.600	0.009	1.546	0.498	0.775	1.550	0.098	0.275	0.199
Dicamba	0.150	0.002	0.387	0.179	0.279	0.558	0.035	0.096	0.072
Diuron	0.959	0.014	2.473	0.796	1.240	2.481	0.157	0.441	6.372
Fosamine	0.642	0.009	1.654	0.533	0.829	1.659	0.105	0.295	0.213
Glyphosate	0.300	0.004	0.773	0.249	0.388	0.775	0.049	0.138	0.100
Hexazinone	0.360	0.005	0.927	0.299	0.465	0.930	0.059	0.165	0.119
Picloram	0.002	0.000	0.006	0.100	0.155	0.310	0.019	0.049	0.040
Simazine	0.276	0.004	0.711	0.229	0.357	0.713	0.045	0.127	0.092
Tebuthiuron	0.276	0.004	0.711	0.229	0.357	0.713	0.045	0.127	0.916
Triclopyr	0.079	0.001	0.204	0.398	0.620	1.240	0.076	0.201	0.159

D Human Health Risk Assessment (Quantitative)

Table B-20
 Doses in micrograms/kg for example people:
 LARGE RIGHT OF WAY, WORST CASE

HERBICIDE	HIKER	BERRY PICKER	HUNTER	FISHERMAN	NEARBY RESIDENT
Amitrole	0.403	1.036	0.675	0.562	1.643
Asulam	0.553	1.709	0.740	0.653	1.328
Atrazine	0.940	2.905	1.258	1.786	2.258
Bromacil	1.106	3.418	1.479	1.305	2.656
2,4-D	0.354	1.050	0.501	0.435	0.989
2,4-DP	0.252	0.647	0.422	0.352	1.027
Dalapon	1.106	3.418	1.479	1.305	2.656
Dicamba	0.332	0.996	0.462	0.403	0.890
Diuron	1.770	5.469	2.367	8.141	4.250
Fosamine	1.183	3.657	1.583	1.396	2.842
Glyphosate	0.553	1.709	0.740	0.653	1.328
Hexazinone	0.664	2.051	0.888	0.783	1.594
Picloram	0.102	0.262	0.170	0.142	0.412
Simazine	0.509	1.572	0.681	0.600	1.222
Tebuthiuron	0.509	1.572	0.681	1.425	1.222
Triclopyr	0.479	1.302	0.755	0.638	1.719

Table B-21

Dose in micrograms/kg from items receiving the full per acre application rate by exposure type:
 ACCIDENTAL WORST CASE SPRAYING

HERBICIDE	DIRECT DERMAL	REENTRY HIKER	REENTRY PICKER	DRINK WATER	EATING BERRIES	EATING VEGS.	EATING DEER	EATING BIRD	EATING FISH
Amitrole	3.	0.	9.	117.	93.	194.	19.	116.	47.
Asulam	209.	3.	538.	73.	58.	121.	13.	83.	29.
Atrazine	355.	5.	914.	125.	99.	206.	22.	141.	249.
Bromacil	417.	6.	1075.	147.	116.	242.	26.	165.	59.
2,4-D	103.	1.	264.	60.	48.	99.	10.	64.	24.
2,4-DP	2.	0.	5.	73.	58.	121.	12.	73.	29.
Dalapon	417.	6.	1075.	147.	116.	242.	26.	165.	59.
Dicamba	116.	2.	299.	59.	47.	97.	10.	64.	23.
Diuron	667.	10.	1720.	235.	186.	387.	42.	265.	1878.
Fosamine	501.	7.	1290.	176.	140.	290.	31.	199.	70.
Glyphosate	209.	3.	538.	73.	58.	121.	13.	83.	29.
Hexazinone	250.	4.	645.	88.	70.	145.	16.	99.	35.
Picloram	4.	0.	10.	73.	58.	121.	12.	73.	29.
Simazine	209.	3.	538.	73.	58.	121.	13.	83.	29.
Tebuthiuron	250.	4.	645.	88.	70.	145.	16.	99.	352.
Triclopyr	55.	1.	142.	117.	93.	194.	19.	119.	47.

D Human Health Risk Assessment (Quantitative)

Table B-22
Doses in micrograms/kg for example people:
ACCIDENTAL WORST CASE SPRAYING

HERBICIDE	HIKER	BERRY PICKER	HUNTER	FISHERMAN	NEARBY RESIDENT
Amitrole	121.	222.	256.	168.	314.
Asulam	285.	878.	381.	314.	406.
Atrazine	484.	1492.	647.	734.	690.
Bromacil	570.	1755.	761.	628.	812.
2,4-D	164.	475.	239.	188.	263.
2,4-DP	75.	139.	160.	105.	196.
Dalapon	570.	1755.	761.	628.	812.
Dicamba	176.	521.	250.	200.	273.
Diuron	912.	2809.	1218.	2790.	1299.
Fosamine	684.	2107.	914.	754.	974.
Glyphosate	285.	878.	381.	314.	406.
Hexazinone	342.	1053.	457.	377.	487.
Picloram	77.	145.	162.	107.	198.
Simazine	285.	878.	381.	314.	406.
Tebuthiuron	342.	1053.	457.	694.	487.
Triclopyr	173.	408.	311.	220.	367.

Table B-23

DOSES FROM HERBICIDE SPILLS (mg/kg) assuming 1 liter of water drunk per day

HERBICIDE	SPILL OF CONCENTRATE ON SKIN	SPILL OF TANK MIX ON SKIN	HELICOPTER DUMP INTO POND	HELICOPTER DUMP INTO RESERVOIR	TRUCK SPILL INTO POND	TRUCK SPILL INTO RESERVOIR
Amitrole	1.20	0.24	0.0737	0.0023	1.4730	0.0460
Asulam	240.00	20.04	0.0615	0.0019	1.2300	0.0384
Atrazine	240.00	24.00	0.0737	0.0023	1.4730	0.0460
Bromacil	240.00	12.00	-----	-----	0.7365	0.0230
2,4-D	144.00	14.40	0.0737	0.0023	1.4730	0.0460
2,4-DP	3.60	0.15	0.0460	0.0014	0.9206	0.0288
Dalapon	---	60.00	0.1841	0.0058	3.6825	0.1151
Dicamba	167.04	16.70	0.0737	0.0023	1.4730	0.0460
Diuron	240.00	19.20	-----	-----	1.1784	0.0368
Fosamine	240.00	72.00	0.2210	0.0069	4.4191	0.1381
Glyphosate	180.00	30.00	0.0921	0.0029	1.8413	0.0575
Hexazinone	120.00	18.00	0.0552	0.0017	1.1048	0.0345
Picloram	2.16	0.54	0.0921	0.0029	1.8413	0.0575
Simazine	240.00	30.00	0.0921	0.0029	1.8413	0.0575
Tebuthiuron	---	36.00	0.1105	0.0035	2.2095	0.0690
Triclopyr	39.60	7.92	0.1473	0.0046	2.9460	0.0921



Appendix D

**Human Health
Risk Assessment
(Quantitative)**



Attachment C



Table C-1
Margins of Safety For Workers Using Amitrole

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (4080.0)	SYSTEMIC NOEL (0.025)	REPRODUCTIVE NOEL (4.00)
<hr/>				
Routine-Realistic Exposures				
PILOT	0.0004	1000000+	62	9900
MIXER/LOADER	0.0006	1000000+	43	6900
SUPERVISOR	0.0001	1000000+	410	65000
OBSERVER	0.0000	1000000+	1900	310000
BACKPACK	0.0033	1000000+	7.6	1200
R-O-W SPRAYER	0.0001	1000000+	360	58000
R-O-W MIX/L	0.0001	1000000+	360	57000
R-O-W AP/M/L	0.0001	1000000+	260	41000
HACK & SQUIRT	0.0006	1000000+	45	7200
INJECTION BAR	0.0002	1000000+	120	19000
Routine-Worst Case Exposures				
PILOT	0.0067	610000	3.7	600
MIXER/LOADER	0.0085	480000	2.9	470
SUPERVISOR	0.0012	1000000+	22	3400
OBSERVER	0.0002	1000000+	120	19000
BACKPACK	0.0310	130000	-1.2	130
R-O-W SPRAYER	0.0042	960000	5.9	940
R-O-W MIX/L	0.0024	1000000+	10	1600
R-O-W AP/M/L	0.0029	1000000+	8.7	1400
HACK & SQUIRT	0.0063	650000	4.0	630
INJECTION BAR	0.0017	1000000+	15	2400

D Human Health Risk Assessment (Quantitative)

Table C-2
Margins of Safety For Workers Using Asulam

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (4000.0)	SYSTEMIC NOEL (50.00)	REPRODUCTIVE NOEL (50.00)
Routine-Realistic Exposures				
PILOT	0.0483	83000	1000	1000
MIXER/LOADER	0.0693	58000	720	720
SUPERVISOR	0.0074	540000	6800	6800
OBSERVER	0.0016	1000000+	32000	32000
BACKPACK	0.1978	20000	250	250
R-O-W SPRAYER	0.0082	490000	6100	6100
R-O-W MIX/L	0.0084	480000	6000	6000
R-O-W AP/M/L	0.0116	350000	4300	4300
HACK & SQUIRT	---	---	---	---
INJECTION BAR	---	---	---	---
Routine-Worst Case Exposures				
PILOT	0.5591	7200	89	89
MIXER/LOADER	0.7128	5600	70	70
SUPERVISOR	0.0969	41000	520	520
OBSERVER	0.0173	230000	2900	2900
BACKPACK	2.0693	1900	24	24
R-O-W SPRAYER	0.2652	15000	190	190
R-O-W MIX/L	0.1530	26000	330	330
R-O-W AP/M/L	0.1787	22000	280	280
HACK & SQUIRT	---	---	---	---
INJECTION BAR	---	---	---	---

Table C-3
Margins of Safety For Workers Using Atrazine

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (672.0)	SYSTEMIC NOEL (0.48)	REPRODUCTIVE NOEL (0.5)
Routine-Realistic Exposures				
PILOT	0.0755	8900	6.4	6.5
MIXER/LOADER	0.1083	6200	4.4	4.6
SUPERVISOR	0.0115	58000	42	43.5
OBSERVER	0.0025	270000	200	205
BACKPACK	0.4946	1400	-1.0	1.0
R-O-W SPRAYER	0.0103	65000	47	48.5
R-O-W MIX/L	0.0105	64000	46	47.5
R-O-W AP/M/L	0.0145	46000	33	34.5
HACK & SQUIRT	---	---	---	---
INJECTION BAR	---	---	---	---
Routine-Worst Case Exposures				
PILOT	0.6696	1000	-1.4	0.8
MIXER/LOADER	0.8536	790	-1.8	0.6
SUPERVISOR	0.1160	5800	4.1	4.3
OBSERVER	0.0207	33000	23	24
BACKPACK	2.4782	270	-5.2	-1.3
R-O-W SPRAYER	0.4509	1500	1.1	1.1
R-O-W MIX/L	0.2601	2600	1.8	1.9
R-O-W AP/M/L	0.3038	2200	1.6	1.7
HACK & SQUIRT	---	---	---	---
INJECTION BAR	---	---	---	---

D Human Health Risk Assessment (Quantitative)

Table C-4
Margins of Safety For Workers Using Bromacil

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (3998.0)	SYSTEMIC NOEL (6.25)	REPRODUCTIVE NOEL (12.50)
Routine-Realistic Exposures				
PILOT	---	---	---	---
MIXER/LOADER	---	---	---	---
SUPERVISOR	---	---	---	---
OBSERVER	---	---	---	---
BACKPACK	0.6595	6100	9.5	19
R-O-W SPRAYER	0.0137	290000	460	910
R-O-W MIX/L	0.0140	290000	450	890
R-O-W AP/M/L	0.0193	210000	320	650
HACK & SQUIRT	0.1113	36000	56	110
INJECTION BAR	0.0424	94000	150	300
Routine-Worst Case Exposures				
PILOT	---	---	---	---
MIXER/LOADER	---	---	---	---
SUPERVISOR	---	---	---	---
OBSERVER	---	---	---	---
BACKPACK	6.1955	650	1.0	2.0
R-O-W SPRAYER	0.5305	7500	12	24
R-O-W MIX/L	0.3060	13000	20	41
R-O-W AP/M/L	0.3574	11000	17	35
HACK & SQUIRT	1.2617	3200	5.0	9.9
INJECTION BAR	0.3373	12000	19	37

Table C-5
Margins of Safety For Workers Using 2,4-D

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (375.0)	SYSTEMIC NOEL (1.00)	REPRODUCTIVE NOEL (5.00)
Routine-Realistic Exposures				
PILOT	0.0302	12000	33	170
MIXER/LOADER	0.0433	8700	23	120
SUPERVISOR	0.0046	81000	220	1100
OBSERVER	0.0010	380000	1000	5100
BACKPACK	0.1978	1900	5.1	25
R-O-W SPRAYER	0.0051	73000	190	970
R-O-W MIX/L	0.0052	72000	190	950
R-O-W AP/M/L	0.0072	52000	140	690
HACK & SQUIRT	0.0668	5600	15	75
INJECTION BAR	0.0254	15000	39	200
Routine-Worst Case Exposures				
PILOT	0.4018	930	2.5	12
MIXER/LOADER	0.5122	730	2.0	9.8
SUPERVISOR	0.0696	5400	14	72
OBSERVER	0.0124	30000	81	400
BACKPACK	1.4869	250	-1.5	3.4
R-O-W SPRAYER	0.1305	2900	7.7	38
R-O-W MIX/L	0.0753	5000	13	66
R-O-W AP/M/L	0.0879	4300	11	57
HACK & SQUIRT	0.7570	500	1.3	6.6
INJECTION BAR	0.2024	1900	4.9	25

D Human Health Risk Assessment (Quantitative)

Table C-6
Margins of Safety For Workers Using 2,4-DP

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (532.0)	SYSTEMIC NOEL (5.00)	REPRODUCTIVE NOEL (6.25)
Routine-Realistic Exposures				
PILOT	0.0004	1000000+	12000	16000
MIXER/LOADER	0.0006	920000	8700	11000
SUPERVISOR	0.0001	1000000+	81000	100000
OBSERVER	0.0000	1000000+	380000	480000
BACKPACK	0.0033	160000	1500	1900
R-O-W SPRAYER	0.0001	1000000+	58000	73000
R-O-W MIX/L	0.0001	1000000+	57000	72000
R-O-W AP/M/L	0.0001	1000000+	41000	52000
HACK & SQUIRT	0.0017	320000	3000	3700
INJECTION BAR	0.0006	840000	7900	9800
Routine-Worst Case Exposures				
PILOT	0.0042	130000	1200	1500
MIXER/LOADER	0.0053	100000	940	1200
SUPERVISOR	0.0007	730000	6900	8600
OBSERVER	0.0001	1000000+	39000	48000
BACKPACK	0.0266	20000	190	230
R-O-W SPRAYER	0.0027	200000	1900	2400
R-O-W MIX/L	0.0015	350000	3300	4100
R-O-W AP/M/L	0.0018	300000	2800	3500
HACK & SQUIRT	0.0189	28000	260	330
INJECTION BAR	0.0051	110000	990	1200

Table C-7
Margins of Safety For Workers Using Dalapon

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (7577.0)	SYSTEMIC NOEL (8.00)	REPRODUCTIVE NOEL (12.50)
Routine-Realistic Exposures				
PILOT	0.0806	94000	99	160
MIXER/LOADER	0.1156	66000	69	110
SUPERVISOR	0.0123	620000	650	1000
OBSERVER	0.0026	1000000+	3100	4800
BACKPACK	0.6595	11000	12	19
R-O-W SPRAYER	0.0137	550000	580	910
R-O-W MIX/L	0.0140	540000	570	890
R-O-W AP/M/L	0.0193	390000	420	650
HACK & SQUIRT	---	---	---	---
INJECTION BAR	---	---	---	---
Routine-Worst Case Exposures				
PILOT	1.6740	4500	4.8	7.5
MIXER/LOADER	2.1340	3600	3.7	5.9
SUPERVISOR	0.2900	26000	28	43
OBSERVER	0.0517	150000	150	240
BACKPACK	7.4346	1000	1.1	1.7
R-O-W SPRAYER	0.5305	14000	15	24
R-O-W MIX/L	0.3060	25000	26	41
R-O-W AP/M/L	0.3574	21000	22	35
HACK & SQUIRT	---	---	---	---
INJECTION BAR	---	---	---	---

D Human Health Risk Assessment (Quantitative)

Table C-8
Margins of Safety For Workers Using Dicamba

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (757.0)	SYSTEMIC NOEL (15.80)	REPRODUCTIVE NOEL (3.00)
Routine-Realistic Exposures				
PILOT	0.0140	54000	1100	210
MIXER/LOADER	0.0201	38000	790	150
SUPERVISOR	0.0021	350000	7400	1400
OBSERVER	0.0005	1000000+	35000	6600
BACKPACK	0.0574	13000	280	52
R-O-W SPRAYER	0.0024	320000	6600	1300
R-O-W MIX/L	0.0024	310000	6500	1200
R-O-W AP/M/L	0.0034	230000	4700	890
HACK & SQUIRT	0.0775	9800	200	39
INJECTION BAR	0.0295	26000	540	100
Routine-Worst Case Exposures				
PILOT	0.4660	1600	34	6.4
MIXER/LOADER	0.5941	1300	27	5.0
SUPERVISOR	0.0807	9400	200	37
OBSERVER	0.0144	53000	1100	210
BACKPACK	1.7248	440	9.2	1.7
R-O-W SPRAYER	0.1329	5700	120	23
R-O-W MIX/L	0.0767	9900	210	39
R-O-W AP/M/L	0.0896	8500	180	33
HACK & SQUIRT	0.8781	860	18	3.4
INJECTION BAR	0.2347	3200	67	13

Table C-9
Margins of Safety For Workers Using Diuron

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (3750.0)	SYSTEMIC NOEL (0.63)	REPRODUCTIVE NOEL (6.25)
Routine-Realistic Exposures				
PILOT	---	---	---	---
MIXER/LOADER	---	---	---	---
SUPERVISOR	---	---	---	---
OBSERVER	---	---	---	---
BACKPACK	0.6595	5700	-1.1	9.5
R-O-W SPRAYER	0.0137	270000	46	460
R-O-W MIX/L	0.0140	270000	45	450
R-O-W AP/M/L	0.0193	190000	32	320
HACK & SQUIRT	0.1113	34000	5.6	56
INJECTION BAR	0.0424	89000	15	150
Routine-Worst Case Exposures				
PILOT	---	---	---	---
MIXER/LOADER	---	---	---	---
SUPERVISOR	---	---	---	---
OBSERVER	---	---	---	---
BACKPACK	3.7173	1000	-5.9	1.7
R-O-W SPRAYER	0.8488	4400	-1.4	7.4
R-O-W MIX/L	0.4896	7700	1.3	13
R-O-W AP/M/L	0.5719	6600	1.1	11
HACK & SQUIRT	1.2617	3000	-2.0	5.0
INJECTION BAR	0.3373	11000	1.9	19

D Human Health Risk Assessment (Quantitative)

Table C-10
Margins of Safety For Workers Using Fosamine

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (24400.0)	SYSTEMIC NOEL (25.00)	REPRODUCTIVE NOEL (50.00)
Routine-Realistic Exposures				
PILOT	0.0604	400000	410	830
MIXER/LOADER	0.0867	280000	290	580
SUPERVISOR	0.0092	1000000+	2700	5400
OBSERVER	0.0020	1000000+	13000	26000
BACKPACK	0.4946	49000	51	100
R-O-W SPRAYER	0.0137	1000000+	1800	3600
R-O-W MIX/L	0.0140	1000000+	1800	3600
R-O-W AP/M/L	0.0193	1000000+	1300	2600
HACK & SQUIRT	0.1113	220000	220	450
INJECTION BAR	0.0424	580000	590	1200
Routine-Worst Case Exposures				
PILOT	2.0088	12000	12	25
MIXER/LOADER	2.5608	9500	9.8	20
SUPERVISOR	0.3480	70000	72	140
OBSERVER	0.0620	390000	400	810
BACKPACK	7.1248	3400	3.5	7.0
R-O-W SPRAYER	0.5676	43000	44	88
R-O-W MIX/L	0.3274	75000	76	150
R-O-W AP/M/L	0.3824	64000	65	130
HACK & SQUIRT	1.2617	19000	20	40
INJECTION BAR	0.3373	72000	74	150

Table C-11
Margins of Safety For Workers Using Glyphosate

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (4320.0)	SYSTEMIC NOEL (31.00)	REPRODUCTIVE NOEL (10.00)
Routine-Realistic Exposures				
PILOT	0.0403	110000	770	250
MIXER/LOADER	0.0578	75000	540	170
SUPERVISOR	0.0062	700000	5000	1600
OBSERVER	0.0013	1000000+	24000	7700
BACKPACK	0.2473	17000	130	40
R-O-W SPRAYER	0.0069	630000	4500	1500
R-O-W MIX/L	0.0070	620000	4400	1400
R-O-W AP/M/L	0.0096	450000	3200	1000
HACK & SQUIRT	---	---	---	---
INJECTION BAR	---	---	---	---
Routine-Worst Case Exposures				
PILOT	0.8370	5200	37	12
MIXER/LOADER	1.0670	4000	29	9.4
SUPERVISOR	0.1450	30000	210	69
OBSERVER	0.0258	170000	1200	390
BACKPACK	3.0978	1400	10	3.2
R-O-W SPRAYER	0.2652	16000	120	38
R-O-W MIX/L	0.1530	28000	200	65
R-O-W AP/M/L	0.1787	24000	170	56
HACK & SQUIRT	---	---	---	---
INJECTION BAR	---	---	---	---

D Human Health Risk Assessment (Quantitative)

Table C-12
Margins of Safety For Workers Using Hexazinone

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (1690.0)	SYSTEMIC NOEL (10.00)	REPRODUCTIVE NOEL (50.00)
Routine-Realistic Exposures				
PILOT	0.0504	34000	200	990
MIXER/LOADER	0.0722	23000	140	690
SUPERVISOR	0.0077	220000	1300	6500
OBSERVER	0.0016	1000000	6100	31000
BACKPACK	0.1846	9200	54	270
R-O-W SPRAYER	0.0086	200000	1200	5800
R-O-W MIX/L	0.0087	190000	1100	5700
R-O-W AP/M/L	0.0120	140000	830	4200
HACK & SQUIRT	---	---	---	---
INJECTION BAR	---	---	---	---
Routine-Worst Case Exposures				
PILOT	0.5022	3400	20	100
MIXER/LOADER	0.6402	2600	16	78
SUPERVISOR	0.0870	19000	110	570
OBSERVER	0.0155	110000	650	3200
BACKPACK	1.8587	910	5.4	27
R-O-W SPRAYER	0.3183	5300	31	160
R-O-W MIX/L	0.1836	9200	54	270
R-O-W AP/M/L	0.2145	7900	47	230
HACK & SQUIRT	---	---	---	---
INJECTION BAR	---	---	---	---

Table C-13
Margins of Safety For Workers Using Picloram

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (8200.0)	SYSTEMIC NOEL (7.00)	REPRODUCTIVE NOEL (50.00)
Routine-Realistic Exposures				
PILOT	0.0004	1000000+	19000	140000
MIXER/LOADER	0.0005	1000000+	13000	96000
SUPERVISOR	0.0001	1000000+	130000	900000
OBSERVER	0.0000	1000000+	600000	1000000+
BACKPACK	0.0030	1000000+	2400	17000
R-O-W SPRAYER	0.0001	1000000+	110000	810000
R-O-W MIX/L	0.0001	1000000+	110000	800000
R-O-W AP/M/L	0.0001	1000000+	81000	580000
HACK & SQUIRT	0.0010	1000000+	7000	50000
INJECTION BAR	0.0004	1000000+	18000	130000
Routine-Worst Case Exposures				
PILOT	0.0151	540000	460	3300
MIXER/LOADER	0.0192	430000	360	2600
SUPERVISOR	0.0026	1000000+	2700	19000
OBSERVER	0.0005	1000000+	15000	110000
BACKPACK	0.0446	180000	160	1100
R-O-W SPRAYER	0.0019	1000000+	3700	26000
R-O-W MIX/L	0.0011	1000000+	6400	45000
R-O-W AP/M/L	0.0013	1000000+	5400	39000
HACK & SQUIRT	0.0114	720000	620	4400
INJECTION BAR	0.0030	1000000+	2300	16000

D Human Health Risk Assessment (Quantitative)

Table C-14
Margins of Safety For Workers Using Simazine

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:			
	LD50 (5000.0)	SYSTEMIC NOEL (5.00)	REPRODUCTIVE NOEL (5.00)	
Routine-Realistic Exposures				
PILOT	0.0806	62000	62	62
MIXER/LOADER	0.1156	43000	43	43
SUPERVISOR	0.0123	410000	410	410
OBSERVER	0.0026	1000000+	1900	1900
BACKPACK	0.3297	15000	15	15
R-O-W SPRAYER	0.0069	730000	730	730
R-O-W MIX/L	0.0070	720000	720	720
R-O-W AP/M/L	0.0096	520000	520	520
HACK & SQUIRT	---	---	---	---
INJECTION BAR	---	---	---	---
Routine-Worst Case Exposures				
PILOT	0.8370	6000	6.0	6.0
MIXER/LOADER	1.0670	4700	4.7	4.7
SUPERVISOR	0.1450	34000	34	34
OBSERVER	0.0258	190000	190	190
BACKPACK	2.8499	1800	1.8	1.8
R-O-W SPRAYER	0.2440	20000	20	20
R-O-W MIX/L	0.1408	36000	36	36
R-O-W AP/M/L	0.1644	30000	30	30
HACK & SQUIRT	---	---	---	---
INJECTION BAR	---	---	---	---

Table C-15
Margins of Safety For Workers Using Tebuthiuron

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (644.0)	SYSTEMIC NOEL (12.50)	REPRODUCTIVE NOEL (5.00)
Routine-Realistic Exposures				
PILOT	0.0201	32000	620	250
MIXER/LOADER	0.0289	22000	430	170
SUPERVISOR	0.0031	210000	4100	1600
OBSERVER	0.0007	990000	19000	7700
BACKPACK	0.2473	2600	51	20
R-O-W SPRAYER	0.0075	85000	1700	660
R-O-W MIX/L	0.0077	84000	1600	650
R-O-W AP/M/L	0.0106	61000	1200	470
HACK & SQUIRT	----	----	----	----
INJECTION BAR	----	----	----	----
Routine-Worst Case Exposures				
PILOT	1.0044	640	12	5.0
MIXER/LOADER	1.2804	500	9.8	3.9
SUPERVISOR	0.1740	3700	72	29
OBSERVER	0.0310	21000	400	160
BACKPACK	3.7173	170	3.4	1.3
R-O-W SPRAYER	0.2440	2600	51	20
R-O-W MIX/L	0.1408	4600	89	36
R-O-W AP/M/L	0.1644	3900	76	30
HACK & SQUIRT	----	----	----	----
INJECTION BAR	----	----	----	----

D Human Health Risk Assessment (Quantitative)

Table C-16
Margins of Safety For Workers Using Triclopyr

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:			
	LD50 (630.0)	SYSTEMIC NOEL (2.50)	REPRODUCTIVE NOEL (2.50)	
Routine-Realistic Exposures				
PILOT	0.0066	95000	380	380
MIXER/LOADER	0.0095	66000	260	260
SUPERVISOR	0.0010	620000	2500	2500
OBSERVER	0.0002	1000000+	12000	12000
BACKPACK	0.0544	12000	46	46
R-O-W SPRAYER	0.0011	560000	2200	2200
R-O-W MIX/L	0.0012	550000	2200	2200
R-O-W AP/M/L	0.0016	400000	1600	1600
HACK & SQUIRT	0.0184	34000	140	140
INJECTION BAR	0.0070	90000	360	360
Routine-Worst Case Exposures				
PILOT	0.2210	2900	11	11
MIXER/LOADER	0.2817	2200	8.9	8.9
SUPERVISOR	0.0383	16000	65	65
OBSERVER	0.0068	92000	370	370
BACKPACK	0.8178	770	3.1	3.1
R-O-W SPRAYER	0.0700	9000	36	36
R-O-W MIX/L	0.0404	16000	62	62
R-O-W AP/M/L	0.0472	13000	53	53
HACK & SQUIRT	0.2082	3000	12	12
INJECTION BAR	0.0557	11000	45	45

Table C-17
Margins of Safety For Workers Wearing Protective Clothing and Using Amitrole

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (4080.0)	SYSTEMIC NOEL (0.03)	REPRODUCTIVE NOEL (4.00)
<hr/>				
Routine-Realistic Exposures				
PILOT	0.0002	1000000+	150	24000
MIXER/LOADER	0.0004	1000000+	59	9500
SUPERVISOR	0.0000	1000000+	970	150000
OBSERVER	0.0000	1000000+	4600	730000
BACKPACK	0.0010	1000000+	24	3900
R-O-W SPRAYER	0.0000	1000000+	1200	190000
R-O-W MIX/L	0.0001	1000000+	490	79000
R-O-W AP/M/L	0.0001	1000000+	500	80000
HACK & SQUIRT	0.0002	1000000+	110	17000
INJECTION BAR	0.0001	1000000+	260	42000
<hr/>				
Routine-Worst Case Exposures				
PILOT	0.0028	1000000+	8.9	1400
MIXER/LOADER	0.0062	660000	4.0	640
SUPERVISOR	0.0005	1000000+	51	8200
OBSERVER	0.0001	1000000+	290	46000
BACKPACK	0.0097	420000	2.6	410
R-O-W SPRAYER	0.0013	1000000+	19	3000
R-O-W MIX/L	0.0018	1000000+	14	2200
R-O-W AP/M/L	0.0015	1000000+	17	2700
HACK & SQUIRT	0.0027	1000000+	9.3	1500
INJECTION BAR	0.0008	1000000+	33	5200

D Human Health Risk Assessment (Quantitative)

Table C-18
 Margins of Safety For Workers Wearing Protective Clothing and Using Asulam

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (4000.0)	SYSTEMIC NOEL (50.00)	REPRODUCTIVE NOEL (50.00)
<hr/>			
Routine-Realistic Exposures			
PILOT	0.0203	200000	2500
MIXER/LOADER	0.0505	79000	990
SUPERVISOR	0.0031	1000000+	16000
OBSERVER	0.0007	1000000+	76000
BACKPACK	0.0617	65000	810
R-O-W SPRAYER	0.0026	1000000+	19000
R-O-W MIX/L	0.0061	650000	8200
R-O-W AP/M/L	0.0060	660000	8300
HACK & SQUIRT	---	---	---
INJECTION BAR	---	---	---
<hr/>			
Routine-Worst Case Exposures			
PILOT	0.2343	17000	210
MIXER/LOADER	0.5196	7700	96
SUPERVISOR	0.0406	99000	1200
OBSERVER	0.0072	550000	6900
BACKPACK	0.6456	6200	77
R-O-W SPRAYER	0.0828	48000	600
R-O-W MIX/L	0.1115	36000	450
R-O-W AP/M/L	0.0930	43000	540
HACK & SQUIRT	---	---	---
INJECTION BAR	---	---	---

Table C-19
Margins of Safety For Workers Wearing Protective Clothing and Using Atrazine

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:			
	LD50 (672.0)	SYSTEMIC NOEL (0.48)	REPRODUCTIVE NOEL (0.5)	
Routine-Realistic Exposures				
PILOT	0.0317	21000	15	16
MIXER/LOADER	0.0790	8500	6.1	6.5
SUPERVISOR	0.0048	140000	100	105
OBSERVER	0.0010	650000	480	485
BACKPACK	0.1543	4400	3.1	3.3
R-O-W SPRAYER	0.0032	210000	150	155
R-O-W MIX/L	0.0076	88000	63	65
R-O-W AP/M/L	0.0075	89000	64	65
HACK & SQUIRT	---	---	---	---
INJECTION BAR	---	---	---	---
Routine-Worst Case Exposures				
PILOT	0.2806	2400	1.7	1.8
MIXER/LOADER	0.6223	1100	-0.8	0.8
SUPERVISOR	0.0486	14000	9.9	10.5
OBSERVER	0.0087	78000	56	60
BACKPACK	0.7732	870	-0.6	0.7
R-O-W SPRAYER	0.1407	4800	3.4	3.6
R-O-W MIX/L	0.1896	3500	2.5	2.7
R-O-W AP/M/L	0.1581	4200	3.0	3.2
HACK & SQUIRT	---	---	---	---
INJECTION BAR	---	---	---	---

D Human Health Risk Assessment (Quantitative)

Table C-20
Margins of Safety For Workers Wearing Protective Clothing and Using Bromacil

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (3998.0)	SYSTEMIC NOEL (6.25)	REPRODUCTIVE NOEL (12.50)
<hr/>				
Routine-Realistic Exposures				
PILOT	---	---	---	---
MIXER/LOADER	---	---	---	---
SUPERVISOR	---	---	---	---
OBSERVER	---	---	---	---
BACKPACK	0.2057	19000	30	61
R-O-W SPRAYER	0.0043	930000	1500	2900
R-O-W MIX/L	0.0102	390000	610	1200
R-O-W AP/M/L	0.0100	400000	620	1200
HACK & SQUIRT	0.0472	85000	130	260
INJECTION BAR	0.0192	210000	330	650
Routine-Worst Case Exposures				
PILOT	---	---	---	---
MIXER/LOADER	---	---	---	---
SUPERVISOR	---	---	---	---
OBSERVER	---	---	---	---
BACKPACK	1.9330	2100	3.2	6.5
R-O-W SPRAYER	0.1655	24000	38	76
R-O-W MIX/L	0.2231	18000	28	56
R-O-W AP/M/L	0.1860	21000	34	67
HACK & SQUIRT	0.5350	7500	12	23
INJECTION BAR	0.1528	26000	41	82
<hr/>				

Table C-21
Margins of Safety For Workers Wearing Protective Clothing and Using 2,4-D

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (375.0)	SYSTEMIC NOEL (1.00)	REPRODUCTIVE NOEL (5.00)
<hr/>				
Routine-Realistic Exposures				
PILOT	0.0127	30000	79	390
MIXER/LOADER	0.0316	12000	32	160
SUPERVISOR	0.0019	190000	520	2600
OBSERVER	0.0004	910000	2400	12000
BACKPACK	0.0617	6100	16	81
R-O-W SPRAYER	0.0016	230000	620	3100
R-O-W MIX/L	0.0038	98000	260	1300
R-O-W AP/M/L	0.0038	100000	270	1300
HACK & SQUIRT	0.0283	13000	35	180
INJECTION BAR	0.0115	33000	87	430
<hr/>				
Routine-Worst Case Exposures				
PILOT	0.1683	2200	5.9	30
MIXER/LOADER	0.3734	1000	2.7	13
SUPERVISOR	0.0292	13000	34	170
OBSERVER	0.0052	72000	190	960
BACKPACK	0.4639	810	2.2	11
R-O-W SPRAYER	0.0407	9200	25	120
R-O-W MIX/L	0.0549	6800	18	91
R-O-W AP/M/L	0.0458	8200	22	110
HACK & SQUIRT	0.3210	1200	3.1	16
INJECTION BAR	0.0917	4100	11	55

D Human Health Risk Assessment (Quantitative)

Table C-22

Margins of Safety For Workers Wearing Protective Clothing and Using 2,4-DP

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (532.0)	SYSTEMIC NOEL (5.00)	REPRODUCTIVE NOEL (6.25)

Routine-Realistic Exposures

PILOT	0.0002	1000000+	30000	37000
MIXER/LOADER	0.0004	1000000+	12000	15000
SUPERVISOR	0.0000	1000000+	190000	240000
OBSERVER	0.0000	1000000+	910000	1000000+
BACKPACK	0.0010	520000	4900	6100
R-O-W SPRAYER	0.0000	1000000+	190000	230000
R-O-W MIX/L	0.0001	1000000+	79000	98000
R-O-W AP/M/L	0.0001	1000000+	80000	100000
HACK & SQUIRT	0.0007	750000	7100	8800
INJECTION BAR	0.0003	1000000+	17000	22000

Routine-Worst Case Exposures

PILOT	0.0018	300000	2900	3600
MIXER/LOADER	0.0039	140000	1300	1600
SUPERVISOR	0.0003	1000000+	16000	21000
OBSERVER	0.0001	1000000+	92000	120000
BACKPACK	0.0083	64000	600	750
R-O-W SPRAYER	0.0008	640000	6000	7600
R-O-W MIX/L	0.0011	480000	4500	5600
R-O-W AP/M/L	0.0009	570000	5400	6700
HACK & SQUIRT	0.0080	66000	620	780
INJECTION BAR	0.0023	230000	2200	2700

Table C-23

Margins of Safety For Workers Wearing Protective Clothing and Using Dalapon

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (7577.0)	SYSTEMIC NOEL (8.00)	REPRODUCTIVE NOEL (12.50)
<hr/>				
Routine-Realistic Exposures				
PILOT	0.0338	220000	240	370
MIXER/LOADER	0.0842	90000	95	150
SUPERVISOR	0.0052	1000000+	1500	2400
OBSERVER	0.0011	1000000+	7300	11000
BACKPACK	0.2057	37000	39	61
R-O-W SPRAYER	0.0043	1000000+	1900	2900
R-O-W MIX/L	0.0102	740000	790	1200
R-O-W AP/M/L	0.0100	760000	800	1200
HACK & SQUIRT	---	---	---	---
INJECTION BAR	---	---	---	---
Routine-Worst Case Exposures				
PILOT	0.7014	11000	11	18
MIXER/LOADER	1.5557	4900	5.1	8.0
SUPERVISOR	0.1215	62000	66	100
OBSERVER	0.0216	350000	370	580
BACKPACK	2.3196	3300	3.4	5.4
R-O-W SPRAYER	0.1655	46000	48	76
R-O-W MIX/L	0.2231	34000	36	56
R-O-W AP/M/L	0.1860	41000	43	67
HACK & SQUIRT	---	---	---	---
INJECTION BAR	---	---	---	---

D Human Health Risk Assessment (Quantitative)

Table C-24

Margins of Safety For Workers Wearing Protective Clothing and Using Dicamba

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (757.0)	SYSTEMIC NOEL (15.80)	REPRODUCTIVE NOEL (2.50)

Routine-Realistic Exposures

PILOT	0.0059	130000	2700	430
MIXER/LOADER	0.0147	52000	1100	170
SUPERVISOR	0.0009	840000	18000	2800
OBSERVER	0.0002	1000000+	83000	13000
BACKPACK	0.0179	42000	880	140
R-O-W SPRAYER	0.0007	1000000	21000	3400
R-O-W MIX/L	0.0018	430000	8900	1400
R-O-W AP/M/L	0.0017	430000	9000	1400
HACK & SQUIRT	0.0329	23000	480	76
INJECTION BAR	0.0134	57000	1200	190

Routine-Worst Case Exposures

PILOT	0.1953	3900	81	13
MIXER/LOADER	0.4331	1700	36	5.8
SUPERVISOR	0.0338	22000	470	74
OBSERVER	0.0060	130000	2600	410
BACKPACK	0.5381	1400	29	4.6
R-O-W SPRAYER	0.0415	18000	380	60
R-O-W MIX/L	0.0559	14000	280	45
R-O-W AP/M/L	0.0466	16000	340	54
HACK & SQUIRT	0.3723	2000	42	6.7
INJECTION BAR	0.1063	7100	150	24

Table C-25
Margins of Safety For Workers Wearing Protective Clothing and Using Diuron

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (3750.0)	SYSTEMIC NOEL (0.63)	REPRODUCTIVE NOEL (6.25)
Routine-Realistic Exposures			
PILOT	---	---	---
MIXER/LOADER	---	---	---
SUPERVISOR	---	---	---
OBSERVER	---	---	---
BACKPACK	0.2057	18000	3.0
R-O-W SPRAYER	0.0043	880000	150
R-O-W MIX/L	0.0102	370000	61
R-O-W AP/M/L	0.0100	370000	62
HACK & SQUIRT	0.0472	79000	13
INJECTION BAR	0.0192	200000	33
Routine-Worst Case Exposures			
PILOT	---	---	---
MIXER/LOADER	---	---	---
SUPERVISOR	---	---	---
OBSERVER	---	---	---
BACKPACK	1.1598	3200	-1.9
R-O-W SPRAYER	0.2648	14000	2.4
R-O-W MIX/L	0.3569	11000	1.8
R-O-W AP/M/L	0.2977	13000	2.1
HACK & SQUIRT	0.5350	7000	1.2
INJECTION BAR	0.1528	25000	4.1

D Human Health Risk Assessment (Quantitative)

Table C-26
 Margins of Safety For Workers Wearing Protective Clothing and Using Fosamine

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:			
	LD50 (24400.0)	SYSTEMIC NOEL (25.00)	REPRODUCTIVE NOEL (50.00)	
Routine-Realistic Exposures				
PILOT	0.0253	960000	990	2000
MIXER/LOADER	0.0632	390000	400	790
SUPERVISOR	0.0039	1000000+	6500	13000
OBSERVER	0.0008	1000000+	30000	61000
BACKPACK	0.1543	160000	160	320
R-O-W SPRAYER	0.0043	1000000+	5800	12000
R-O-W MIX/L	0.0102	1000000+	2500	4900
R-O-W AP/M/L	0.0100	1000000+	2500	5000
HACK & SQUIRT	0.0472	520000	530	1100
INJECTION BAR	0.0192	1000000+	1300	2600
Routine-Worst Case Exposures				
PILOT	0.8417	29000	30	59
MIXER/LOADER	1.8668	13000	13	27
SUPERVISOR	0.1458	170000	170	340
OBSERVER	0.0260	940000	960	1900
BACKPACK	2.2229	11000	11	22
R-O-W SPRAYER	0.1771	140000	140	280
R-O-W MIX/L	0.2387	100000	100	210
R-O-W AP/M/L	0.1991	120000	130	250
ACK & SQUIRT	0.5350	46000	47	93
INJECTION BAR	0.1528	160000	160	330

Table C-27
Margins of Safety For Workers Wearing Protective Clothing and Using
Glyphosate

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:			
	LD50 (4320.0)	SYSTEMIC NOEL (31.00)	REPRODUCTIVE NOEL (10.00)	
<hr/>				
Routine-Realistic Exposures				
PILOT	0.0169	260000	1800	590
MIXER/LOADER	0.0421	100000	740	240
SUPERVISOR	0.0026	1000000+	12000	3900
OBSERVER	0.0005	1000000+	57000	18000
BACKPACK	0.0772	56000	400	130
R-O-W SPRAYER	0.0021	1000000+	14000	4700
R-O-W MIX/L	0.0051	850000	6100	2000
R-O-W AP/M/L	0.0050	860000	6200	2000
HACK & SQUIRT	---	---	---	---
INJECTION BAR	---	---	---	---
Routine-Worst Case Exposures				
PILOT	0.3507	12000	88	29
MIXER/LOADER	0.7778	5600	40	13
SUPERVISOR	0.0608	71000	510	160
OBSERVER	0.0108	400000	2900	920
BACKPACK	0.9665	4500	32	10
R-O-W SPRAYER	0.0828	52000	370	120
R-O-W MIX/L	0.1115	39000	280	90
R-O-W AP/M/L	0.0930	46000	330	110
HACK & SQUIRT	---	---	---	---
INJECTION BAR	---	---	---	---

D Human Health Risk Assessment (Quantitative)

Table C-28
 Margins of Safety For Workers Wearing Protective Clothing and Using Hexazinone

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (1690.0)	SYSTEMIC NOEL (10.00)	REPRODUCTIVE NOEL (50.00)
<hr/>				
Routine-Realistic Exposures				
PILOT	0.0211	80000	470	2400
MIXER/LOADER	0.0526	32000	190	950
SUPERVISOR	0.0032	520000	3100	15000
OBSERVER	0.0007	1000000+	15000	73000
BACKPACK	0.0576	29000	170	870
R-O-W SPRAYER	0.0027	630000	3700	19000
R-O-W MIX/L	0.0064	270000	1600	7900
R-O-W AP/M/L	0.0063	270000	1600	8000
HACK & SQUIRT	---	---	---	---
INJECTION BAR	---	---	---	---
Routine-Worst Case Exposures				
PILOT	0.2104	8000	48	240
MIXER/LOADER	0.4667	3600	21	110
SUPERVISOR	0.0365	46000	270	1400
OBSERVER	0.0065	260000	1500	7700
BACKPACK	0.5799	2900	17	86
R-O-W SPRAYER	0.0993	17000	100	500
R-O-W MIX/L	0.1338	13000	75	370
R-O-W AP/M/L	0.1116	15000	90	450
HACK & SQUIRT	---	---	---	---
INJECTION BAR	---	---	---	---

Table C-29
Margins of Safety For Workers Wearing Protective Clothing and Using Picloram

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (8200.0)	SYSTEMIC NOEL (7.00)	REPRODUCTIVE NOEL (50.00)
<hr/> Routine-Realistic Exposures				
PILOT	0.0002	1000000+	46000	330000
MIXER/LOADER	0.0004	1000000+	18000	130000
SUPERVISOR	0.0000	1000000+	300000	1000000+
OBSERVER	0.0000	1000000+	1000000+	1000000+
BACKPACK	0.0009	1000000+	7600	54000
R-O-W SPRAYER	0.0000	1000000+	360000	1000000+
R-O-W MIX/L	0.0000	1000000+	150000	1000000+
R-O-W AP/M/L	0.0000	1000000+	160000	1000000+
HACK & SQUIRT	0.0004	1000000+	16000	120000
INJECTION BAR	0.0002	1000000+	41000	290000
<hr/> Routine-Worst Case Exposures				
PILOT	0.0063	1000000+	1100	7900
MIXER/LOADER	0.0140	590000	500	3600
SUPERVISOR	0.0011	1000000+	6400	46000
OBSERVER	0.0002	1000000+	36000	260000
BACKPACK	0.0139	590000	500	3600
R-O-W SPRAYER	0.0006	1000000+	12000	84000
R-O-W MIX/L	0.0008	1000000+	8700	62000
R-O-W AP/M/L	0.0007	1000000+	10000	75000
HACK & SQUIRT	0.0048	1000000+	1500	10000
INJECTION BAR	0.0014	1000000+	5100	36000

D Human Health Risk Assessment (Quantitative)

Table C-30
Margins of Safety For Workers Wearing Protective Clothing and Using Simazine

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (5000.0)	SYSTEMIC NOEL (5.00)	REPRODUCTIVE NOEL (5.00)
<hr/> Routine-Realistic Exposures				
PILOT	0.0338	150000	150	150
MIXER/LOADER	0.0842	59000	59	59
SUPERVISOR	0.0052	970000	970	970
OBSERVER	0.0011	1000000+	4600	4600
BACKPACK	0.1029	49000	49	49
R-O-W SPRAYER	0.0021	1000000+	2300	2300
R-O-W MIX/L	0.0051	980000	980	980
R-O-W AP/M/L	0.0050	1000000	1000	1000
HACK & SQUIRT	---	---	---	---
INJECTION BAR	---	---	---	---
<hr/> Routine-Worst Case Exposures				
PILOT	0.3507	14000	14	14
MIXER/LOADER	0.7778	6400	6.4	6.4
SUPERVISOR	0.0608	82000	82	82
OBSERVER	0.0108	460000	460	460
BACKPACK	0.8892	5600	5.6	5.6
R-O-W SPRAYER	0.0761	66000	66	66
R-O-W MIX/L	0.1026	49000	49	49
R-O-W AP/M/L	0.0856	58000	58	58
HACK & SQUIRT	---	---	---	---
INJECTION BAR	---	---	---	---

Table C-31
Margins of Safety For Workers Wearing Protective Clothing and Using
Tebuthiuron

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (644.0)	SYSTEMIC NOEL (12.50)	REPRODUCTIVE NOEL (5.00)
<hr/> Routine-Realistic Exposures				
PILOT	0.0084	76000	1500	590
MIXER/LOADER	0.0211	31000	590	240
SUPERVISOR	0.0013	500000	9700	3900
OBSERVER	0.0003	1000000+	46000	18000
BACKPACK	0.0772	8300	160	65
R-O-W SPRAYER	0.0024	270000	5300	2100
R-O-W MIX/L	0.0056	110000	2200	890
R-O-W AP/M/L	0.0055	120000	2300	910
HACK & SQUIRT	---	---	---	---
INJECTION BAR	---	---	---	---
<hr/> Routine-Worst Case Exposures				
PILOT	0.4208	1500	30	12
MIXER/LOADER	0.9334	690	13	5.4
SUPERVISOR	0.0729	8800	170	69
OBSERVER	0.0130	50000	960	380
BACKPACK	1.1598	560	11	4.3
R-O-W SPRAYER	0.0761	8500	160	66
R-O-W MIX/L	0.1026	6300	120	49
R-O-W AP/M/L	0.0856	7500	150	58
HACK & SQUIRT	---	---	---	---
INJECTION BAR	---	---	---	---

D Human Health Risk Assessment (Quantitative)

Table C-32
 Margins of Safety For Workers Wearing Protective Clothing and Using Triclopyr

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (630.0)	SYSTEMIC NOEL (2.50)	REPRODUCTIVE NOEL (2.50)
<hr/>				
Routine-Realistic Exposures				
PILOT	0.0028	230000	900	900
MIXER/LOADER	0.0069	91000	360	360
SUPERVISOR	0.0004	1000000+	5900	5900
OBSERVER	0.0001	1000000+	28000	28000
BACKPACK	0.0170	37000	150	150
R-O-W SPRAYER	0.0004	1000000+	7100	7100
R-O-W MIX/L	0.0008	750000	3000	3000
R-O-W AP/M/L	0.0008	760000	3000	3000
HACK & SQUIRT	0.0078	81000	320	320
INJECTION BAR	0.0032	200000	790	790
<hr/>				
Routine-Worst Case Exposures				
PILOT	0.0926	6800	27	27
MIXER/LOADER	0.2054	3100	12	12
SUPERVISOR	0.0160	39000	160	160
OBSERVER	0.0029	220000	870	870
BACKPACK	0.2552	2500	9.8	9.8
R-O-W SPRAYER	0.0218	29000	110	110
R-O-W MIX/L	0.0294	21000	85	85
R-O-W AP/M/L	0.0246	26000	100	100
HACK & SQUIRT	0.0883	7100	28	28
INJECTION BAR	0.0252	25000	99	99

Table C-33
Margins of Safety For Exposed Members of the Public

REALISTIC AERIAL, 40 ACRES BY HELICOPTER
HERBICIDE: Amitrole

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (4080.0)	SYSTEMIC NOEL (0.03)	REPRODUCTIVE NOEL (4.00)

For Single Route of Exposure

DERMAL, SPRAY	0.0000	1000000+	160000	1000000+
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0000	1000000+	770	120000
DRINKING WATER	0.0019	1000000+	13	2100
EATING BERRIES	0.0011	1000000+	23	3700
EATING VEGETS.	0.0022	1000000+	12	1900
EATING DEER	0.0001	1000000+	170	27000
EATING BIRD	0.0005	1000000+	51	8200
EATING FISH	0.0008	1000000+	33	5300

For Combined Routes of Exposure:

HIKER	0.0019	1000000+	13	2100
BERRY PICKER	0.0030	1000000+	8.3	1300
HUNTER	0.0025	1000000+	9.9	1600
FISHERMAN	0.0026	1000000+	9.5	1500
RESIDENT	0.0040	1000000	6.2	990

D Human Health Risk Assessment (Quantitative)

Table C-34

Margins of Safety For Exposed Members of the Public

SMALL BACKPACK, 6.0 ACRES, REALISTIC CASE
HERBICIDE: Amitrole

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (4080.0)	SYSTEMIC NOEL (0.03)	REPRODUCTIVE NOEL (4.00)

For Single Route of Exposure

DERMAL, SPRAY	0.0000	1000000+	14000	1000000+
VEGETATION CONTACT				
HIKER	0.0000	1000000+	980000	1000000+
PICKER	0.0000	1000000+	3500	570000
DRINKING WATER	0.0002	1000000+	150	24000
EATING BERRIES	0.0003	1000000+	82	13000
EATING VEGETS.	0.0006	1000000+	41	6500
EATING DEER	0.0000	1000000+	660	110000
EATING BIRD	0.0001	1000000+	230	37000
EATING FISH	0.0001	1000000+	380	60000

For Combined Routes of Exposure:

HIKER	0.0002	1000000+	150	24000
BERRY PICKER	0.0005	1000000+	52	8300
HUNTER	0.0003	1000000+	79	13000
FISHERMAN	0.0002	1000000+	110	17000
RESIDENT	0.0008	1000000+	32	5100

Table C-35
Margins of Safety For Exposed Members of the Public

SMALL RIGHT OF WAY, REALISTIC CASE
HERBICIDE: Amitrole

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (4080.0)	SYSTEMIC NOEL (0.03)	REPRODUCTIVE NOEL (4.00)

For Single Route of Exposure

DERMAL, SPRAY	0.0000	1000000+	72000	1000000+
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0000	1000000+	13000	1000000+
DRINKING WATER	0.0001	1000000+	340	54000
EATING BERRIES	0.0001	1000000+	240	39000
EATING VEGETS.	0.0002	1000000+	120	20000
EATING DEER	0.0000	1000000+	2000	330000
EATING BIRD	0.0000	1000000+	820	130000
EATING FISH	0.0000	1000000+	840	130000

For Combined Routes of Exposure:

HIKER	0.0001	1000000+	330	54000
BERRY PICKER	0.0002	1000000+	140	22000
HUNTER	0.0001	1000000+	210	34000
FISHERMAN	0.0001	1000000+	240	38000
RESIDENT	0.0003	1000000+	90	14000

D Human Health Risk Assessment (Quantitative)

Table C-36
 Margins of Safety For Exposed Members of the Public

LARGE AERIAL, 400 ACRES BY FIXED WING, WORST CASE
 HERBICIDE: Amitrole

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (4080.0)	SYSTEMIC NOEL (0.03)	REPRODUCTIVE NOEL (4.00)

For Single Route of Exposure

DERMAL, SPRAY	0.0002	1000000+	150	24000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	10000	1000000+
PICKER	0.0004	1000000+	57	9100
DRINKING WATER	0.0127	320000	2.0	320
EATING BERRIES	0.0104	390000	2.4	380
EATING VEGETS.	0.0208	200000	1.2	190
EATING DEER	0.0015	1000000+	16	2600
EATING BIRD	0.0063	650000	4.0	640
EATING FISH	0.0051	800000	4.9	790

For Combined Routes of Exposure:

HIKER	0.0129	320000	1.9	310
BERRY PICKER	0.0237	170000	1.1	170
HUNTER	0.0206	200000	1.2	190
FISHERMAN	0.0179	230000	1.4	220
RESIDENT	0.0337	120000	-1.3	120

Table C-37
Margins of Safety For Exposed Members of the Public

LARGE BACKPACK, 60 ACRES, WORST CASE
HERBICIDE: Amitrole

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (4080.0)	SYSTEMIC NOEL (0.03)	REPRODUCTIVE NOEL (4.00)

For Single Route of Exposure

DERMAL, SPRAY	0.0000	1000000+	2900	470000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	200000	1000000+
PICKER	0.0000	1000000+	1100	180000
DRINKING WATER	0.0005	1000000+	52	8400
EATING BERRIES	0.0009	1000000+	27	4300
EATING VEGETS.	0.0018	1000000+	14	2200
EATING DEER	0.0001	1000000+	220	35000
EATING BIRD	0.0003	1000000+	74	12000
EATING FISH	0.0002	1000000+	130	21000

For Combined Routes of Exposure:

HIKER	0.0005	1000000+	51	8200
BERRY PICKER	0.0014	1000000+	17	2800
HUNTER	0.0009	1000000+	27	4300
FISHERMAN	0.0007	1000000+	37	5900
RESIDENT	0.0023	1000000+	11	1700

D Human Health Risk Assessment (Quantitative)

Table C-38
 Margins of Safety For Exposed Members of the Public

LARGE RIGHT OF WAY, WORST CASE
 HERBICIDE: Amitrole

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (4080.0)	SYSTEMIC NOEL (0.03)	REPRODUCTIVE NOEL (4.00)

For Single Route of Exposure

DERMAL, SPRAY	0.0000	1000000+	5200	830000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	360000	1000000+
PICKER	0.0000	1000000+	2000	320000
DRINKING WATER	0.0004	1000000+	63	10000
EATING BERRIES	0.0006	1000000+	40	6400
EATING VEGETS.	0.0012	1000000+	20	3200
EATING DEER	0.0001	1000000+	330	53000
EATING BIRD	0.0002	1000000+	130	20000
EATING FISH	0.0002	1000000+	160	25000

For Combined Routes of Exposure:

HIKER	0.0004	1000000+	62	9900
BERRY PICKER	0.0010	1000000+	24	3900
HUNTER	0.0007	1000000+	37	5900
FISHERMAN	0.0006	1000000+	44	7100
RESIDENT	0.0016	1000000+	15	2400

Table C-39
Margins of Safety For Exposed Members of the Public

REALISTIC AERIAL, 40 ACRES BY HELICOPTER
HERBICIDE: Asulam

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (4000.0)	SYSTEMIC NOEL (50.00)	REPRODUCTIVE NOEL (50.00)

For Single Route of Exposure

DERMAL, SPRAY	0.0000	1000000+	1000000+	1000000+
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0039	1000000	13000	13000
DRINKING WATER	0.0023	1000000+	22000	22000
EATING BERRIES	0.0013	1000000+	39000	39000
EATING VEGETS.	0.0026	1000000+	19000	19000
EATING DEER	0.0002	1000000+	270000	270000
EATING BIRD	0.0007	1000000+	76000	76000
EATING FISH	0.0009	1000000+	55000	55000

For Combined Routes of Exposure:

HIKER	0.0023	1000000+	22000	22000
BERRY PICKER	0.0075	540000	6700	6700
HUNTER	0.0031	1000000+	16000	16000
FISHERMAN	0.0032	1000000+	16000	16000
RESIDENT	0.0049	820000	10000	10000

D Human Health Risk Assessment (Quantitative)

Table C-40
Margins of Safety For Exposed Members of the Public

SMALL BACKPACK, 6.0 ACRES, REALISTIC CASE
HERBICIDE: Asulam

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (4000.0)	SYSTEMIC NOEL (50.00)	REPRODUCTIVE NOEL (50.00)
<hr/> For Single Route of Exposure				
DERMAL, SPRAY	0.0001	1000000+	470000	470000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0004	1000000+	120000	120000
DRINKING WATER	0.0001	1000000+	500000	500000
EATING BERRIES	0.0002	1000000+	270000	270000
EATING VEGETS.	0.0004	1000000+	140000	140000
EATING DEER	0.0000	1000000+	1000000+	1000000+
EATING BIRD	0.0001	1000000+	680000	680000
EATING FISH	0.0000	1000000+	1000000+	1000000+
 For Combined Routes of Exposure:				
HIKER	0.0002	1000000+	240000	240000
BERRY PICKER	0.0008	1000000+	62000	62000
HUNTER	0.0003	1000000+	160000	160000
FISHERMAN	0.0002	1000000+	200000	200000
RESIDENT	0.0006	1000000+	87000	87000

Table C-41
Margins of Safety For Exposed Members of the Public

SMALL RIGHT OF WAY, REALISTIC CASE
HERBICIDE: Asulam

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (4000.0)	SYSTEMIC NOEL (50.00)	REPRODUCTIVE NOEL (50.00)
<hr/>				
For Single Route of Exposure				
DERMAL, SPRAY	0.0000	1000000+	1000000+	1000000+
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0002	1000000+	220000	220000
DRINKING WATER	0.0001	1000000+	560000	560000
EATING BERRIES	0.0001	1000000+	410000	410000
EATING VEGETS.	0.0002	1000000+	200000	200000
EATING DEER	0.0000	1000000+	1000000+	1000000+
EATING BIRD	0.0000	1000000+	1000000+	1000000+
EATING FISH	0.0000	1000000+	1000000+	1000000+
For Combined Routes of Exposure:				
HIKER	0.0001	1000000+	380000	380000
BERRY PICKER	0.0005	1000000+	100000	100000
HUNTER	0.0002	1000000+	270000	270000
FISHERMAN	0.0002	1000000+	300000	300000
RESIDENT	0.0004	1000000+	130000	130000

D Human Health Risk Assessment (Quantitative)

Table C-42

Margins of Safety For Exposed Members of the Public

LARGE AERIAL, 400 ACRES BY FIXED WING, WORST CASE
HERBICIDE: Asulam

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (4000.0)	SYSTEMIC NOEL (50.00)	REPRODUCTIVE NOEL (50.00)
<hr/> For Single Route of Exposure				
DERMAL, SPRAY	0.0142	280000	3500	3500
VEGETATION CONTACT				
HIKER	0.0002	1000000+	250000	250000
PICKER	0.0366	110000	1400	1400
DRINKING WATER	0.0106	380000	4700	4700
EATING BERRIES	0.0087	460000	5700	5700
EATING VEGETS.	0.0174	230000	2900	2900
EATING DEER	0.0014	1000000+	37000	37000
EATING BIRD	0.0059	670000	8400	8400
EATING FISH	0.0042	940000	12000	12000
 For Combined Routes of Exposure:				
HIKER	0.0250	160000	2000	2000
BERRY PICKER	0.0700	57000	710	710
HUNTER	0.0323	120000	1500	1500
FISHERMAN	0.0292	140000	1700	1700
RESIDENT	0.0424	94000	1200	1200

Table C-43
Margins of Safety For Exposed Members of the Public

LARGE BACKPACK, 60 ACRES, WORST CASE
HERBICIDE: Asulam

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (4000.0)	SYSTEMIC NOEL (50.00)	REPRODUCTIVE NOEL (50.00)

For Single Route of Exposure

DERMAL, SPRAY	0.0006	1000000+	87000	87000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0015	1000000+	34000	34000
DRINKING WATER	0.0003	1000000+	160000	160000
EATING BERRIES	0.0006	1000000+	81000	81000
EATING VEGETS.	0.0012	1000000+	41000	41000
EATING DEER	0.0001	1000000+	620000	620000
EATING BIRD	0.0003	1000000+	200000	200000
EATING FISH	0.0001	1000000+	390000	390000

For Combined Routes of Exposure:

HIKER	0.0009	1000000+	56000	56000
BERRY PICKER	0.0030	1000000+	17000	17000
HUNTER	0.0012	1000000+	40000	40000
FISHERMAN	0.0010	1000000+	49000	49000
RESIDENT	0.0021	1000000+	23000	23000

D Human Health Risk Assessment (Quantitative)

Table C-44
Margins of Safety For Exposed Members of the Public

LARGE RIGHT OF WAY, WORST CASE
HERBICIDE: Asulam

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (4000.0)	SYSTEMIC NOEL (50.00)	REPRODUCTIVE NOEL (50.00)

For Single Route of Exposure

DERMAL, SPRAY	0.0003	1000000+	170000	170000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0008	1000000+	65000	65000
DRINKING WATER	0.0002	1000000+	200000	200000
EATING BERRIES	0.0004	1000000+	130000	130000
EATING VEGETS.	0.0008	1000000+	64000	64000
EATING DEER	0.0000	1000000+	1000000	1000000
EATING BIRD	0.0001	1000000+	360000	360000
EATING FISH	0.0001	1000000+	500000	500000

For Combined Routes of Exposure:

HIKER	0.0006	1000000+	90000	90000
BERRY PICKER	0.0017	1000000+	29000	29000
HUNTER	0.0007	1000000+	68000	68000
FISHERMAN	0.0007	1000000+	77000	77000
RESIDENT	0.0013	1000000+	38000	38000

Table C-45
Margins of Safety For Exposed Members of the Public

REALISTIC AERIAL, 40 ACRES BY HELICOPTER
HERBICIDE: Atrazine

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (672.0)	SYSTEMIC NOEL (0.48)	REPRODUCTIVE NOEL (0.5)

For Single Route of Exposure

DERMAL, SPRAY	0.0000	1000000+	16000	16500
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	500000+
PICKER	0.0061	110000	79	80
DRINKING WATER	0.0035	190000	140	140
EATING BERRIES	0.0020	330000	240	245
EATING VEGETS.	0.0040	170000	120	125
EATING DEER	0.0003	1000000+	1700	1750
EATING BIRD	0.0010	650000	470	485
EATING FISH	0.0071	95000	68	70

For Combined Routes of Exposure:

HIKER	0.0036	190000	130	140
BERRY PICKER	0.0117	58000	41	43
HUNTER	0.0049	140000	98	100
FISHERMAN	0.0106	63000	45	47
RESIDENT	0.0076	88000	63	65

D Human Health Risk Assessment (Quantitative)

Table C-46

Margins of Safety For Exposed Members of the Public

SMALL BACKPACK, 6.0 ACRES, REALISTIC CASE

HERBICIDE: Atrazine

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (672.0)	SYSTEMIC NOEL (0.48)	REPRODUCTIVE NOEL (0.5)
For Single Route of Exposure				
DERMAL, SPRAY	0.0003	1000000+	1800	1850
VEGETATION CONTACT				
HIKER	0.0000	1000000+	130000	130000
PICKER	0.0011	640000	450	475
DRINKING WATER	0.0002	1000000+	1900	2000
EATING BERRIES	0.0005	1000000+	1000	1100
EATING VEGETS.	0.0009	730000	520	550
EATING DEER	0.0001	1000000+	8000	8500
EATING BIRD	0.0002	1000000+	2600	2700
EATING FISH	0.0005	1000000+	960	1000
For Combined Routes of Exposure:				
HIKER	0.0005	1000000+	920	950
BERRY PICKER	0.0020	330000	240	245
HUNTER	0.0008	880000	630	650
FISHERMAN	0.0010	660000	470	490
RESIDENT	0.0014	470000	330	350

Table C-47
Margins of Safety For Exposed Members of the Public

SMALL RIGHT OF WAY, REALISTIC CASE
HERBICIDE: Atrazine

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (672.0)	SYSTEMIC NOEL (0.48)	REPRODUCTIVE NOEL (0.5)
<hr/>				
For Single Route of Exposure				
DERMAL, SPRAY	0.0001	1000000+	9300	9500
VEGETATION CONTACT				
HIKER	0.0000	1000000+	650000	500000+
PICKER	0.0003	1000000+	1700	1800
DRINKING WATER	0.0001	1000000+	4300	4500
EATING BERRIES	0.0002	1000000+	3100	3250
EATING VEGETS.	0.0003	1000000+	1600	1650
EATING DEER	0.0000	1000000+	25000	26000
EATING BIRD	0.0001	1000000+	9500	10000
EATING FISH	0.0002	1000000+	2200	2250
For Combined Routes of Exposure:				
HIKER	0.0002	1000000+	2900	3050
BERRY PICKER	0.0006	1000000+	800	850
HUNTER	0.0002	1000000+	2100	2150
FISHERMAN	0.0004	1000000+	1200	1300
RESIDENT	0.0005	1000000+	1000	1050

D Human Health Risk Assessment (Quantitative)

Table C-48
Margins of Safety For Exposed Members of the Public

LARGE AERIAL, 400 ACRES BY FIXED WING, WORST CASE
HERBICIDE: Atrazine

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (672.0)	SYSTEMIC NOEL (0.48)	REPRODUCTIVE NOEL (0.5)
<hr/>				
For Single Route of Exposure				
DERMAL, SPRAY	0.0170	40000	28	30
VEGETATION CONTACT				
HIKER	0.0002	1000000+	2000	2050
PICKER	0.0438	15000	11	12
DRINKING WATER	0.0127	53000	38	40
EATING BERRIES	0.0104	64000	46	48
EATING VEGETS.	0.0208	32000	23	24
EATING DEER	0.0016	410000	290	305
EATING BIRD	0.0071	95000	68	70
EATING FISH	0.0254	26000	19	20
For Combined Routes of Exposure:				
HIKER	0.0299	22000	16	17
BERRY PICKER	0.0839	8000	5.7	6
HUNTER	0.0386	17000	12	13
FISHERMAN	0.0553	12000	8.7	9
RESIDENT	0.0508	13000	9.5	10

Table C-49
Margins of Safety For Exposed Members of the Public

LARGE BACKPACK, 60 ACRES, WORST CASE
HERBICIDE: Atrazine

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (672.0)	SYSTEMIC NOEL (0.48)	REPRODUCTIVE NOEL (0.5)

For Single Route of Exposure

DERMAL, SPRAY	0.0007	980000	700	750
VEGETATION CONTACT				
HIKER	0.0000	1000000+	49000	50000
PICKER	0.0018	380000	270	285
DRINKING WATER	0.0004	1000000+	1300	1300
EATING BERRIES	0.0007	910000	650	700
EATING VEGETS.	0.0015	460000	330	340
EATING DEER	0.0001	1000000+	5000	5000
EATING BIRD	0.0003	1000000+	1600	1650
EATING FISH	0.0008	880000	630	650

For Combined Routes of Exposure:

HIKER	0.0011	620000	450	465
BERRY PICKER	0.0036	190000	130	140
HUNTER	0.0015	450000	320	340
FISHERMAN	0.0018	370000	260	270
RESIDENT	0.0026	260000	190	195

D Human Health Risk Assessment (Quantitative)

Table C-50

Margins of Safety For Exposed Members of the Public

LARGE RIGHT OF WAY, WORST CASE

HERBICIDE: Atrazine

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (672.0)	SYSTEMIC NOEL (0.48)	REPRODUCTIVE NOEL (0.5)
<hr/>				
For Single Route of Exposure				
DERMAL, SPRAY	0.0005	1000000+	940	1000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	66000	70000
PICKER	0.0013	510000	370	380
DRINKING WATER	0.0004	1000000+	1100	1200
EATING BERRIES	0.0007	1000000	730	750
EATING VEGETS.	0.0013	510000	360	380
EATING DEER	0.0001	1000000+	5800	6000
EATING BIRD	0.0002	1000000+	2100	2150
EATING FISH	0.0008	790000	570	600
For Combined Routes of Exposure:				
HIKER	0.0009	710000	510	550
BERRY PICKER	0.0029	230000	170	170
HUNTER	0.0013	530000	380	400
FISHERMAN	0.0018	380000	270	280
RESIDENT	0.0023	300000	210	220

Table C-51
Margins of Safety For Exposed Members of the Public

REALISTIC AERIAL, 40 ACRES BY HELICOPTER
HERBICIDE: Bromacil

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50	SYSTEMIC NOEL	REPRODUCTIVE NOEL
	(3998.0)	(6.25)	(12.50)

For Single Route of Exposure

DERMAL, SPRAY	----	----	----	----
VEGETATION CONTACT				
HIKER	----	----	----	----
PICKER	----	----	----	----
DRINKING WATER	----	----	----	----
EATING BERRIES	----	----	----	----
EATING VEGETS.	----	----	----	----
EATING DEER	----	----	----	----
EATING BIRD	----	----	----	----
EATING FISH	----	----	----	----

For Combined Routes of Exposure:

HIKER	----	----	----	----
BERRY PICKER	----	----	----	----
HUNTER	----	----	----	----
FISHERMAN	----	----	----	----
RESIDENT	----	----	----	----

D Human Health Risk Assessment (Quantitative)

Table C-52

Margins of Safety For Exposed Members of the Public

SMALL BACKPACK, 6.0 ACRES, REALISTIC CASE

HERBICIDE: Bromacil

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (3998.0)	SYSTEMIC NOEL (6.25)	REPRODUCTIVE NOEL (12.50)

For Single Route of Exposure

DERMAL, SPRAY	0.0004	1000000+	18000	35000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0014	1000000+	4400	8900
DRINKING WATER	0.0003	1000000+	19000	38000
EATING BERRIES	0.0006	1000000+	10000	20000
EATING VEGETS.	0.0012	1000000+	5100	10000
EATING DEER	0.0001	1000000+	78000	160000
EATING BIRD	0.0002	1000000+	26000	51000
EATING FISH	0.0001	1000000+	47000	94000

For Combined Routes of Exposure:

HIKER	0.0007	1000000+	9000	18000
BERRY PICKER	0.0027	1000000+	2300	4600
HUNTER	0.0010	1000000+	6100	12000
FISHERMAN	0.0008	1000000+	7600	15000
RESIDENT	0.0019	1000000+	3300	6500

Table C-53
Margins of Safety For Exposed Members of the Public

SMALL RIGHT OF WAY, REALISTIC CASE
HERBICIDE: Bromacil

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (3998.0)	SYSTEMIC NOEL (6.25)	REPRODUCTIVE NOEL (12.50)

For Single Route of Exposure

DERMAL, SPRAY	0.0001	1000000+	91000	180000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0004	1000000+	17000	33000
DRINKING WATER	0.0001	1000000+	42000	84000
EATING BERRIES	0.0002	1000000+	31000	61000
EATING VEGETS.	0.0004	1000000+	15000	31000
EATING DEER	0.0000	1000000+	250000	490000
EATING BIRD	0.0001	1000000+	92000	180000
EATING FISH	0.0001	1000000+	100000	210000

For Combined Routes of Exposure:

HIKER	0.0002	1000000+	29000	57000
BERRY PICKER	0.0008	1000000+	7900	16000
HUNTER	0.0003	1000000+	20000	40000
FISHERMAN	0.0003	1000000+	22000	45000
RESIDENT	0.0006	1000000+	10000	20000

D Human Health Risk Assessment (Quantitative)

Table C-54
 Margins of Safety For Exposed Members of the Public

LARGE AERIAL, 400 ACRES BY FIXED WING, WORST CASE
 HERBICIDE: Bromacil

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (3998.0)	SYSTEMIC NOEL (6.25)	REPRODUCTIVE NOEL (12.50)

For Single Route of Exposure

ERMAL, SPRAY	---	---	---	---
VEGETATION CONTACT				
HIKER	---	---	---	---
PICKER	---	---	---	---
DRINKING WATER	---	---	---	---
EATING BERRIES	---	---	---	---
EATING VEGETS.	---	---	---	---
EATING DEER	---	---	---	---
EATING BIRD	---	---	---	---
EATING FISH	---	---	---	---

For Combined Routes of Exposure:

HIKER	---	---	---	---
BERRY PICKER	---	---	---	---
HUNTER	---	---	---	---
FISHERMAN	---	---	---	---
RESIDENT	---	---	---	---

Table C-55
Margins of Safety For Exposed Members of the Public

LARGE BACKPACK, 60 ACRES, WORST CASE
HERBICIDE: Bromacil

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (3998.0)	SYSTEMIC NOEL (6.25)	REPRODUCTIVE NOEL (12.50)

For Single Route of Exposure

DERMAL, SPRAY	0.0017	1000000+	3600	7300
VEGETATION CONTACT				
HIKER	0.0000	1000000+	250000	510000
PICKER	0.0044	910000	1400	2800
DRINKING WATER	0.0010	1000000+	6500	13000
EATING BERRIES	0.0018	1000000+	3400	6800
EATING VEGETS.	0.0037	1000000+	1700	3400
EATING DEER	0.0002	1000000+	26000	52000
EATING BIRD	0.0008	1000000+	8200	16000
EATING FISH	0.0004	1000000+	16000	33000

For Combined Routes of Exposure:

HIKER	0.0027	1000000+	2300	4600
BERRY PICKER	0.0089	450000	700	1400
HUNTER	0.0037	1000000+	1700	3400
FISHERMAN	0.0031	1000000+	2000	4100
RESIDENT	0.0064	630000	980	2000

D Human Health Risk Assessment (Quantitative)

Table C-56
Margins of Safety For Exposed Members of the Public

LARGE RIGHT OF WAY, WORST CASE
HERBICIDE: Bromacil

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (3998.0)	SYSTEMIC NOEL (6.25)	REPRODUCTIVE NOEL (12.50)

For Single Route of Exposure

DERMAL, SPRAY	0.0006	1000000+	10000	21000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	730000	1000000+
PICKER	0.0015	1000000+	4000	8100
DRINKING WATER	0.0005	1000000+	13000	25000
EATING BERRIES	0.0008	1000000+	8100	16000
EATING VEGETS.	0.0016	1000000+	4000	8100
EATING DEER	0.0001	1000000+	64000	130000
EATING BIRD	0.0003	1000000+	23000	45000
EATING FISH	0.0002	1000000+	31000	63000

For Combined Routes of Exposure:

HIKER	0.0011	1000000+	5700	11000
BERRY PICKER	0.0034	1000000+	1800	3700
HUNTER	0.0015	1000000+	4200	8400
FISHERMAN	0.0013	1000000+	4800	9600
RESIDENT	0.0027	1000000+	2400	4700

Table C-57
Margins of Safety For Exposed Members of the Public

REALISTIC AERIAL, 40 ACRES BY HELICOPTER
HERBICIDE: 2,4-D

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (375.0)	SYSTEMIC NOEL (1.00)	REPRODUCTIVE NOEL (5.00)
<hr/>				
For Single Route of Exposure				
DERMAL, SPRAY	0.0000	1000000+	83000	420000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0024	150000	410	2100
DRINKING WATER	0.0024	160000	420	2100
EATING BERRIES	0.0013	280000	740	3700
EATING VEGETS.	0.0027	140000	370	1900
EATING DEER	0.0002	1000000+	5300	27000
EATING BIRD	0.0007	570000	1500	7600
EATING FISH	0.0009	400000	1100	5300
For Combined Routes of Exposure:				
HIKER	0.0024	160000	420	2100
BERRY PICKER	0.0061	61000	160	810
HUNTER	0.0032	120000	310	1600
FISHERMAN	0.0033	110000	300	1500
RESIDENT	0.0051	74000	200	990

D Human Health Risk Assessment (Quantitative)

Table C-58
 Margins of Safety For Exposed Members of the Public

SMALL BACKPACK, 6.0 ACRES, REALISTIC CASE
 HERBICIDE: 2,4-D

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (375.0)	SYSTEMIC NOEL (1.00)	REPRODUCTIVE NOEL (5.00)
For Single Route of Exposure				
DERMAL, SPRAY	0.0001	1000000+	9400	47000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	650000	1000000+
PICKER	0.0004	890000	2400	12000
DRINKING WATER	0.0002	1000000+	6000	30000
EATING BERRIES	0.0003	1000000+	3300	16000
EATING VEGETS.	0.0006	610000	1600	8200
EATING DEER	0.0000	1000000+	26000	130000
EATING BIRD	0.0001	1000000+	8500	43000
EATING FISH	0.0001	1000000+	15000	75000
For Combined Routes of Exposure:				
HIKER	0.0003	1000000+	3600	18000
BERRY PICKER	0.0010	370000	1000	5000
HUNTER	0.0004	870000	2300	12000
FISHERMAN	0.0003	1000000+	2900	15000
RESIDENT	0.0009	420000	1100	5600

Table C-59
Margins of Safety For Exposed Members of the Public

SMALL RIGHT OF WAY, REALISTIC CASE
HERBICIDE: 2,4-D

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (375.0)	SYSTEMIC NOEL (1.00)	REPRODUCTIVE NOEL (5.00)
For Single Route of Exposure				
DERMAL, SPRAY	0.0000	1000000+	39000	190000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0001	1000000+	7100	36000
DRINKING WATER	0.0001	1000000+	11000	54000
EATING BERRIES	0.0001	1000000+	7800	39000
EATING VEGETS.	0.0003	1000000+	3900	20000
EATING DEER	0.0000	1000000+	64000	320000
EATING BIRD	0.0000	1000000+	25000	120000
EATING FISH	0.0000	1000000+	27000	130000
For Combined Routes of Exposure:				
HIKER	0.0001	1000000+	8400	42000
BERRY PICKER	0.0004	970000	2600	13000
HUNTER	0.0002	1000000+	5700	28000
FISHERMAN	0.0002	1000000+	6400	32000
RESIDENT	0.0004	1000000	2700	13000

D Human Health Risk Assessment (Quantitative)

Table C-60

Margins of Safety For Exposed Members of the Public

LARGE AERIAL, 400 ACRES BY FIXED WING, WORST CASE
HERBICIDE: 2,4-D

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (375.0)	SYSTEMIC NOEL (1.00)	REPRODUCTIVE NOEL (5.00)
<hr/>				
For Single Route of Exposure				
DERMAL, SPRAY	0.0102	37000	98	490
VEGETATION CONTACT				
HIKER	0.0001	1000000+	6800	34000
PICKER	0.0263	14000	38	190
DRINKING WATER	0.0127	30000	79	390
EATING BERRIES	0.0104	36000	96	480
EATING VEGETS.	0.0208	18000	48	240
EATING DEER	0.0016	240000	630	3200
EATING BIRD	0.0068	55000	150	740
EATING FISH	0.0051	74000	200	990
For Combined Routes of Exposure:				
HIKER	0.0230	16000	43	220
BERRY PICKER	0.0596	6300	17	84
HUNTER	0.0314	12000	32	160
FISHERMAN	0.0281	13000	36	180
RESIDENT	0.0439	8500	23	110

Table C-6J
Margins of Safety For Exposed Members of the Public

LARGE BACKPACK, 60 ACRES, WORST CASE
HERBICIDE: 2,4-D

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (375.0)	SYSTEMIC NOEL (1.00)	REPRODUCTIVE NOEL (5.00)
<hr/>				
For Single Route of Exposure				
DERMAL, SPRAY	0.0004	910000	2400	12000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	170000	850000
PICKER	0.0011	350000	940	4700
DRINKING WATER	0.0004	980000	2600	13000
EATING BERRIES	0.0007	510000	1400	6800
EATING VEGETS.	0.0015	250000	680	3400
EATING DEER	0.0001	1000000+	11000	53000
EATING BIRD	0.0003	1000000+	3400	17000
EATING FISH	0.0002	1000000+	6500	33000
For Combined Routes of Exposure:				
HIKER	0.0008	470000	1300	6300
BERRY PICKER	0.0026	140000	390	1900
HUNTER	0.0012	320000	840	4200
FISHERMAN	0.0010	390000	1100	5300
RESIDENT	0.0023	160000	440	2200

D Human Health Risk Assessment (Quantitative)

Table C-62
Margins of Safety For Exposed Members of the Public

LARGE RIGHT OF WAY, WORST CASE
HERBICIDE: 2,4-D

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (375.0)	SYSTEMIC NOEL (1.00)	REPRODUCTIVE NOEL (5.00)
<hr/>				
For Single Route of Exposure				
DERMAL, SPRAY	0.0001	1000000+	6800	34000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	470000	1000000+
PICKER	0.0004	990000	2600	13000
DRINKING WATER	0.0002	1000000+	4900	24000
EATING BERRIES	0.0003	1000000+	3100	16000
EATING VEGETS.	0.0006	590000	1600	7900
EATING DEER	0.0000	1000000+	25000	130000
EATING BIRD	0.0001	1000000+	9300	46000
EATING FISH	0.0001	1000000+	12000	61000
For Combined Routes of Exposure:				
HIKER	0.0004	1000000+	2800	14000
BERRY PICKER	0.0010	360000	950	4800
HUNTER	0.0005	750000	2000	10000
FISHERMAN	0.0004	860000	2300	11000
RESIDENT	0.0010	380000	1000	5100

Table C-63
Margins of Safety For Exposed Members of the Public

REALISTIC AERIAL, 40 ACRES BY HELICOPTER
HERBICIDE: 2,4-DP

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (532.0)	SYSTEMIC NOEL (5.00)	REPRODUCTIVE NOEL (6.25)
For Single Route of Exposure				
DERMAL, SPRAY	0.0000	1000000+	1000000+	1000000+
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0000	1000000+	150000	190000
DRINKING WATER	0.0019	280000	2700	3300
EATING BERRIES	0.0011	490000	4600	5800
EATING VEGETS.	0.0022	250000	2300	2900
EATING DEER	0.0001	1000000+	34000	43000
EATING BIRD	0.0005	1000000+	10000	13000
EATING FISH	0.0008	710000	6600	8300
For Combined Routes of Exposure:				
HIKER	0.0019	280000	2700	3300
BERRY PICKER	0.0030	180000	1700	2100
HUNTER	0.0025	210000	2000	2500
FISHERMAN	0.0026	200000	1900	2400
RESIDENT	0.0040	130000	1200	1500

D Human Health Risk Assessment (Quantitative)

Table C-64

Margins of Safety For Exposed Members of the Public

SMALL BACKPACK, 6.0 ACRES, REALISTIC CASE
 HERBICIDE: 2,4-DP

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (532.0)	SYSTEMIC NOEL (5.00)	REPRODUCTIVE NOEL (6.25)
<hr/>				
For Single Route of Exposure				
DERMAL, SPRAY	0.0000	1000000+	1000000+	1000000+
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0000	1000000+	710000	890000
DRINKING WATER	0.0002	1000000+	30000	38000
EATING BERRIES	0.0003	1000000+	16000	20000
EATING VEGETS.	0.0006	870000	8200	10000
EATING DEER	0.0000	1000000+	130000	160000
EATING BIRD	0.0001	1000000+	46000	57000
EATING FISH	0.0001	1000000+	75000	94000
For Combined Routes of Exposure:				
HIKER	0.0002	1000000+	30000	37000
BERRY PICKER	0.0005	1000000+	10000	13000
HUNTER	0.0003	1000000+	16000	20000
FISHERMAN	0.0002	1000000+	21000	27000
RESIDENT	0.0008	680000	6400	8000

Table C-65
Margins of Safety For Exposed Members of the Public

SMALL RIGHT OF WAY, REALISTIC CASE
HERBICIDE: 2,4-DP

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (532.0)	SYSTEMIC NOEL (5.00)	REPRODUCTIVE NOEL (6.25)
For Single Route of Exposure				
DERMAL, SPRAY	0.0000	1000000+	1000000+	1000000+
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0000	1000000+	1000000+	1000000+
DRINKING WATER	0.0001	1000000+	54000	67000
EATING BERRIES	0.0001	1000000+	39000	49000
EATING VEGETS.	0.0003	1000000+	20000	24000
EATING DEER	0.0000	1000000+	330000	410000
EATING BIRD	0.0000	1000000+	130000	160000
EATING FISH	0.0000	1000000+	130000	170000
For Combined Routes of Exposure:				
HIKER	0.0001	1000000+	54000	67000
BERRY PICKER	0.0002	1000000+	22000	28000
HUNTER	0.0001	1000000+	34000	43000
FISHERMAN	0.0001	1000000+	38000	48000
RESIDENT	0.0003	1000000+	14000	18000

D Human Health Risk Assessment (Quantitative)

Table C-66
Margins of Safety For Exposed Members of the Public

LARGE AERIAL, 400 ACRES BY FIXED WING, WORST CASE
HERBICIDE: 2,4-DP

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (532.0)	SYSTEMIC NOEL (5.00)	REPRODUCTIVE NOEL (6.25)
<hr/>				
For Single Route of Exposure				
DERMAL, SPRAY	0.0001	1000000+	47000	59000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0003	1000000+	18000	23000
DRINKING WATER	0.0079	67000	630	790
EATING BERRIES	0.0065	82000	770	960
EATING VEGETS.	0.0130	41000	380	480
EATING DEER	0.0010	560000	5300	6600
EATING BIRD	0.0039	140000	1300	1600
EATING FISH	0.0032	170000	1600	2000
For Combined Routes of Exposure:				
HIKER	0.0080	66000	620	780
BERRY PICKER	0.0148	36000	340	420
HUNTER	0.0129	41000	390	480
FISHERMAN	0.0112	47000	450	560
RESIDENT	0.0211	25000	240	300

Table C-67
Margins of Safety For Exposed Members of the Public

LARGE BACKPACK, 60 ACRES, WORST CASE
HERBICIDE: 2,4-DP

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (532.0)	SYSTEMIC NOEL (5.00)	REPRODUCTIVE NOEL (6.25)
For Single Route of Exposure				
DERMAL, SPRAY	0.0000	1000000+	680000	850000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0000	1000000+	260000	330000
DRINKING WATER	0.0004	1000000+	12000	15000
EATING BERRIES	0.0008	670000	6300	7900
EATING VEGETS.	0.0016	340000	3200	3900
EATING DEER	0.0001	1000000+	50000	63000
EATING BIRD	0.0003	1000000+	17000	21000
EATING FISH	0.0002	1000000+	30000	38000
For Combined Routes of Exposure:				
HIKER	0.0004	1000000+	12000	15000
BERRY PICKER	0.0012	430000	4100	5100
HUNTER	0.0008	660000	6200	7700
FISHERMAN	0.0006	910000	8600	11000
RESIDENT	0.0020	270000	2500	3100

D Human Health Risk Assessment (Quantitative)

Table C-68
Margins of Safety For Exposed Members of the Public

LARGE RIGHT OF WAY, WORST CASE
HERBICIDE: 2,4-DP

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (532.0)	SYSTEMIC NOEL (5.00)	REPRODUCTIVE NOEL (6.25)
For Single Route of Exposure				
DERMAL, SPRAY	0.0000	1000000+	1000000+	1000000+
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0000	1000000+	650000	810000
DRINKING WATER	0.0002	1000000+	20000	25000
EATING BERRIES	0.0004	1000000+	13000	16000
EATING VEGETS.	0.0008	690000	6400	8100
	0.0000	1000000+	110000	130000
EATING BIRD	0.0001	1000000+	41000	51000
EATING FISH	0.0001	1000000+	50000	63000
For Combined Routes of Exposure:				
HIKER	0.0003	1000000+	20000	25000
BERRY PICKER	0.0006	820000	7700	9700
HUNTER	0.0004	1000000+	12000	15000
FISHERMAN	0.0004	1000000+	14000	18000
RESIDENT	0.0010	520000	4900	6100

Table C-69
Margins of Safety For Exposed Members of the Public

REALISTIC AERIAL, 40 ACRES BY HELICOPTER
HERBICIDE: Dalapon

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (7577.0)	SYSTEMIC NOEL (8.00)	REPRODUCTIVE NOEL (12.50)
For Single Route of Exposure				
DERMAL, SPRAY	0.0000	1000000+	250000	390000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0065	1000000+	1200	1900
DRINKING WATER	0.0038	1000000+	2100	3300
EATING BERRIES	0.0022	1000000+	3700	5800
EATING VEGETS.	0.0043	1000000+	1900	2900
EATING DEER	0.0003	1000000+	26000	41000
EATING BIRD	0.0011	1000000+	7300	11000
EATING FISH	0.0015	1000000+	5300	8300
For Combined Routes of Exposure:				
HIKER	0.0038	1000000+	2100	3300
BERRY PICKER	0.0124	610000	640	1000
HUNTER	0.0052	1000000+	1500	2400
FISHERMAN	0.0053	1000000+	1500	2400
RESIDENT	0.0081	930000	990	1500

D Human Health Risk Assessment (Quantitative)

Table C-70
Margins of Safety For Exposed Members of the Public

SMALL BACKPACK, 6.0 ACRES, REALISTIC CASE
HERBICIDE: Dalapon

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (7577.0)	SYSTEMIC NOEL (8.00)	REPRODUCTIVE NOEL (12.50)
<hr/>				
For Single Route of Exposure				
DERMAL, SPRAY	0.0004	1000000+	22000	35000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0014	1000000+	5700	8900
DRINKING WATER	0.0003	1000000+	24000	38000
EATING BERRIES	0.0006	1000000+	13000	20000
EATING VEGETS.	0.0012	1000000+	6500	10000
EATING DEER	0.0001	1000000+	100000	160000
EATING BIRD	0.0002	1000000+	33000	51000
EATING FISH	0.0001	1000000+	60000	94000
For Combined Routes of Exposure:				
HIKER	0.0007	1000000+	12000	18000
BERRY PICKER	0.0027	1000000+	3000	4600
HUNTER	0.0010	1000000+	7900	12000
FISHERMAN	0.0008	1000000+	9700	15000
RESIDENT	0.0019	1000000+	4200	6500

Table C-71
Margins of Safety For Exposed Members of the Public

SMALL RIGHT OF WAY, REALISTIC CASE
HERBICIDE: Dalapon

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (7577.0)	SYSTEMIC NOEL (8.00)	REPRODUCTIVE NOEL (12.50)
For Single Route of Exposure				
DERMAL, SPRAY	0.0001	1000000+	120000	180000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0004	1000000+	21000	33000
DRINKING WATER	0.0001	1000000+	54000	84000
EATING BERRIES	0.0002	1000000+	39000	61000
EATING VEGETS.	0.0004	1000000+	20000	31000
EATING DEER	0.0000	1000000+	310000	490000
EATING BIRD	0.0001	1000000+	120000	180000
EATING FISH	0.0001	1000000+	130000	210000
For Combined Routes of Exposure:				
HIKER	0.0002	1000000+	37000	57000
BERRY PICKER	0.0008	1000000+	10000	16000
HUNTER	0.0003	1000000+	26000	40000
FISHERMAN	0.0003	1000000+	29000	45000
RESIDENT	0.0006	1000000+	13000	20000

D Human Health Risk Assessment (Quantitative)

Table C-72

Margins of Safety For Exposed Members of the Public

LARGE AERIAL, 400 ACRES BY FIXED WING, WORST CASE

HERBICIDE: Dalapon

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (7577.0)	SYSTEMIC NOEL (8.00)	REPRODUCTIVE NOEL (12.50)
For Single Route of Exposure				
DERMAL, SPRAY	0.0425	180000	190	290
VEGETATION CONTACT				
HIKER	0.0006	1000000+	13000	21000
PICKER	0.1094	69000	73	110
DRINKING WATER	0.0317	240000	250	390
EATING BERRIES	0.0261	290000	310	480
EATING VEGETS.	0.0521	150000	150	240
EATING DEER	0.0041	1000000+	2000	3100
EATING BIRD	0.0178	430000	450	700
EATING FISH	0.0127	600000	630	990
For Combined Routes of Exposure:				
HIKER	0.0748	100000	110	170
BERRY PICKER	0.2097	36000	38	60
HUNTER	0.0966	78000	83	130
FISHERMAN	0.0874	87000	91	140
RESIDENT	0.1269	60000	63	99

Table C-73
Margins of Safety For Exposed Members of the Public

LARGE BACKPACK, 60 ACRES, WORST CASE
HERBICIDE: Dalapon

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY LD50 (7577.0)	MARGIN OF SAFETY RELATIVE TO:	
		SYSTEMIC NOEL (8.00)	REPRODUCTIVE NOEL (12.50)

For Single Route of Exposure

DERMAL, SPRAY	0.0021	1000000+	3900	6100
VEGETATION CONTACT				
HIKER	0.0000	1000000+	270000	420000
PICKER	0.0053	1000000+	1500	2400
DRINKING WATER	0.0011	1000000+	7000	11000
EATING BERRIES	0.0022	1000000+	3600	5700
EATING VEGETS.	0.0044	1000000+	1800	2800
EATING DEER	0.0003	1000000+	28000	43000
EATING BIRD	0.0009	1000000+	8700	14000
EATING FISH	0.0005	1000000+	17000	27000

For Combined Routes of Exposure:

HIKER	0.0032	1000000+	2500	3900
BERRY PICKER	0.0107	710000	750	1200
HUNTER	0.0044	1000000+	1800	2800
FISHERMAN	0.0037	1000000+	2200	3400
RESIDENT	0.0077	990000	1000	1600

D Human Health Risk Assessment (Quantitative)

Table C-74

Margins of Safety For Exposed Members of the Public

LARGE RIGHT OF WAY, WORST CASE

HERBICIDE: Dalapon

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (7577.0)	SYSTEMIC NOEL (8.00)	REPRODUCTIVE NOEL (12.50)

For Single Route of Exposure

DERMAL, SPRAY	0.0006	1000000+	13000	21000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	930000	1000000+
PICKER	0.0015	1000000+	5200	8100
DRINKING WATER	0.0005	1000000+	16000	25000
EATING BERRIES	0.0008	1000000+	10000	16000
EATING VEGETS.	0.0016	1000000+	5200	8100
EATING DEER	0.0001	1000000+	82000	130000
EATING BIRD	0.0003	1000000+	29000	45000
EATING FISH	0.0002	1000000+	40000	63000

For Combined Routes of Exposure:

HIKER	0.0011	1000000+	7200	11000
BERRY PICKER	0.0034	1000000+	2300	3700
HUNTER	0.0015	1000000+	5400	8400
FISHERMAN	0.0013	1000000+	6100	9600
RESIDENT	0.0027	1000000+	3000	4700

Table C-75
Margins of Safety For Exposed Members of the Public

REALISTIC AERIAL, 40 ACRES BY HELICOPTER
HERBICIDE: Dicamba

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (757.0)	SYSTEMIC NOEL (15.80)	REPRODUCTIVE NOEL (3.00)

For Single Route of Exposure

DERMAL, SPRAY	0.0000	1000000+	1000000+	540000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0011	670000	14000	2700
DRINKING WATER	0.0009	800000	17000	3200
EATING BERRIES	0.0005	1000000+	29000	5600
EATING VEGETS.	0.0011	700000	15000	2800
EATING DEER	0.0001	1000000+	210000	40000
EATING BIRD	0.0003	1000000+	60000	11000
EATING FISH	0.0004	1000000+	42000	8000

For Combined Routes of Exposure:

HIKER	0.0009	800000	17000	3200
BERRY PICKER	0.0026	290000	6000	1100
HUNTER	0.0013	590000	12000	2300
FISHERMAN	0.0013	570000	12000	2300
RESIDENT	0.0020	370000	7800	1500

D Human Health Risk Assessment (Quantitative)

Table C-76
Margins of Safety For Exposed Members of the Public

SMALL BACKPACK, 6.0 ACRES, REALISTIC CASE
HERBICIDE: Dicamba

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (757.0)	SYSTEMIC NOEL (15.80)	REPRODUCTIVE NOEL (3.00)

For Single Route of Exposure

DERMAL, SPRAY	0.0000	1000000+	510000	97000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0001	1000000+	130000	24000
DRINKING WATER	0.0000	1000000+	380000	72000
EATING BERRIES	0.0001	1000000+	210000	39000
EATING VEGETS.	0.0002	1000000+	100000	20000
EATING DEER	0.0000	1000000+	1000000+	310000
EATING BIRD	0.0000	1000000+	530000	100000
EATING FISH	0.0000	1000000+	950000	180000

For Combined Routes of Exposure:

HIKER	0.0001	1000000+	220000	41000
BERRY PICKER	0.0003	1000000+	58000	11000
HUNTER	0.0001	1000000+	140000	27000
FISHERMAN	0.0001	1000000+	180000	34000
RESIDENT	0.0002	1000000+	70000	13000

Table C-77
Margins of Safety For Exposed Members of the Public

SMALL RIGHT OF WAY, REALISTIC CASE
HERBICIDE: Dicamba

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (757.0)	SYSTEMIC NOEL (15.80)	REPRODUCTIVE NOEL (3.00)

For Single Route of Exposure

DERMAL, SPRAY	0.0000	1000000+	1000000+	210000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0001	1000000+	240000	46000
DRINKING WATER	0.0000	1000000+	420000	81000
EATING BERRIES	0.0001	1000000+	310000	59000
EATING VEGETS.	0.0001	1000000+	150000	29000
EATING DEER	0.0000	1000000+	1000000+	480000
EATING BIRD	0.0000	1000000+	960000	180000
EATING FISH	0.0000	1000000+	1000000+	200000

For Combined Routes of Exposure:

HIKER	0.0000	1000000+	320000	61000
BERRY PICKER	0.0002	1000000+	96000	18000
HUNTER	0.0001	1000000+	220000	42000
FISHERMAN	0.0001	1000000+	250000	47000
RESIDENT	0.0002	1000000+	100000	20000

D Human Health Risk Assessment (Quantitative)

Table C-78
Margins of Safety For Exposed Members of the Public

LARGE AERIAL, 400 ACRES BY FIXED WING, WORST CASE
HERBICIDE: Dicamba

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (757.0)	SYSTEMIC NOEL (15.80)	REPRODUCTIVE NOEL (3.00)

For Single Route of Exposure

DERMAL, SPRAY	0.0118	64000	1300	250
VEGETATION CONTACT				
HIKER	0.0002	1000000+	93000	18000
PICKER	0.0305	25000	520	98
DRINKING WATER	0.0127	60000	1200	240
EATING BERRIES	0.0104	73000	1500	290
EATING VEGETS.	0.0208	36000	760	140
EATING DEER	0.0016	470000	9900	1900
EATING BIRD	0.0068	110000	2300	440
EATING FISH	0.0051	150000	3100	590

For Combined Routes of Exposure:

HIKER	0.0247	31000	640	120
BERRY PICKER	0.0654	12000	240	46
HUNTER	0.0331	23000	480	91
FISHERMAN	0.0297	25000	530	100
RESIDENT	0.0455	17000	350	66

Table C-79
Margins of Safety For Exposed Members of the Public

LARGE BACKPACK, 60 ACRES, WORST CASE
HERBICIDE: Dicamba

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (757.0)	SYSTEMIC NOEL (15.80)	REPRODUCTIVE NOEL (3.00)

For Single Route of Exposure

DERMAL, SPRAY	0.0005	1000000+	33000	6300
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	440000
PICKER	0.0012	620000	13000	2400
DRINKING WATER	0.0004	1000000+	41000	7900
EATING BERRIES	0.0007	1000000	21000	4100
EATING VEGETS.	0.0015	510000	11000	2000
EATING DEER	0.0001	1000000+	170000	31000
EATING BIRD	0.0003	1000000+	54000	10000
EATING FISH	0.0002	1000000+	100000	20000

For Combined Routes of Exposure:

HIKER	0.0009	870000	18000	3500
BERRY PICKER	0.0028	270000	5600	1100
HUNTER	0.0013	600000	13000	2400
FISHERMAN	0.0010	740000	16000	2900
RESIDENT	0.0023	320000	6800	1300

D Human Health Risk Assessment (Quantitative)

Table C-80
Margins of Safety For Exposed Members of the Public

LARGE RIGHT OF WAY, WORST CASE
HERBICIDE: Dicamba

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (757.0)	SYSTEMIC NOEL (15.80)	REPRODUCTIVE NOEL (3.00)

For Single Route of Exposure

DERMAL, SPRAY	0.0002	1000000+	110000	20000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0004	1000000+	41000	7700
DRINKING WATER	0.0002	1000000+	88000	17000
EATING BERRIES	0.0003	1000000+	57000	11000
EATING VEGETS.	0.0006	1000000+	28000	5400
EATING DEER	0.0000	1000000+	450000	86000
EATING BIRD	0.0001	1000000+	160000	31000
EATING FISH	0.0001	1000000+	220000	42000

For Combined Routes of Exposure:

HIKER	0.0003	1000000+	48000	9000
BERRY PICKER	0.0010	760000	16000	3000
HUNTER	0.0005	1000000+	34000	6500
FISHERMAN	0.0004	1000000+	39000	7400
RESIDENT	0.0009	850000	18000	3400

Table C-81
Margins of Safety For Exposed Members of the Public

REALISTIC AERIAL, 40 ACRES BY HELICOPTER
HERBICIDE: Diuron

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (3750.0)	SYSTEMIC NOEL (0.63)	REPRODUCTIVE NOEL (6.25)

For Single Route of Exposure

DERMAL, SPRAY	---	---	---	---
VEGETATION CONTACT				
HIKER	---	---	---	---
PICKER	---	---	---	---
DRINKING WATER	---	---	---	---
EATING BERRIES	---	---	---	---
EATING VEGETS.	---	---	---	---
EATING DEER	---	---	---	---
EATING BIRD	---	---	---	---
EATING FISH	---	---	---	---

For Combined Routes of Exposure:

HIKER	---	---	---	---
BERRY PICKER	---	---	---	---
HUNTER	---	---	---	---
FISHERMAN	---	---	---	---
RESIDENT	---	---	---	---

D Human Health Risk Assessment (Quantitative)

Table C-82
Margins of Safety For Exposed Members of the Public

SMALL BACKPACK, 6.0 ACRES, REALISTIC CASE

HERBICIDE: Diuron

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (3750.0)	SYSTEMIC NOEL (0.63)	REPRODUCTIVE NOEL (6.25)

For Single Route of Exposure

DERMAL, SPRAY	0.0004	1000000+	1800	18000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	120000	1000000+
PICKER	0.0014	1000000+	440	4400
DRINKING WATER	0.0003	1000000+	1900	19000
EATING BERRIES	0.0006	1000000+	1000	10000
EATING VEGETS.	0.0012	1000000+	510	5100
EATING DEER	0.0001	1000000+	7800	78000
EATING BIRD	0.0002	1000000+	2600	26000
EATING FISH	0.0027	1000000+	240	2400

For Combined Routes of Exposure:

HIKER	0.0007	1000000+	900	9000
BERRY PICKER	0.0027	1000000+	230	2300
HUNTER	0.0010	1000000+	610	6100
FISHERMAN	0.0033	1000000+	190	1900
RESIDENT	0.0019	1000000+	330	3300

Table C-83
Margins of Safety For Exposed Members of the Public

SMALL RIGHT OF WAY, REALISTIC CASE
HERBICIDE: Diuron

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (3750.0)	SYSTEMIC NOEL (0.63)	REPRODUCTIVE NOEL (6.25)

For Single Route of Exposure

DERMAL, SPRAY	0.0001	1000000+	9100	91000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	630000	1000000+
PICKER	0.0004	1000000+	1700	17000
DRINKING WATER	0.0001	1000000+	4200	42000
EATING BERRIES	0.0002	1000000+	3100	31000
EATING VEGETS.	0.0004	1000000+	1500	15000
EATING DEER	0.0000	1000000+	25000	250000
EATING BIRD	0.0001	1000000+	9200	92000
EATING FISH	0.0012	1000000+	520	5200

For Combined Routes of Exposure:

HIKER	0.0002	1000000+	2900	29000
BERRY PICKER	0.0008	1000000+	790	7900
HUNTER	0.0003	1000000+	2000	20000
FISHERMAN	0.0014	1000000+	440	4400
RESIDENT	0.0006	1000000+	1000	10000

D Human Health Risk Assessment (Quantitative)

Table C-84
 Margins of Safety For Exposed Members of the Public

LARGE AERIAL, 400 ACRES BY FIXED WING, WORST CASE
 HERBICIDE: Diuron

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (3750.0)	SYSTEMIC NOEL (0.63)	REPRODUCTIVE NOEL (6.25)

For Single Route of Exposure

DERMAL, SPRAY	----	----	----	----
VEGETATION CONTACT				
HIKER	----	----	----	----
PICKER	----	----	----	----
DRINKING WATER	----	----	----	----
EATING BERRIES	----	----	----	----
EATING VEGETS.	----	----	----	----
EATING DEER	----	----	----	----
EATING BIRD	----	----	----	----
EATING FISH	----	----	----	----

For Combined Routes of Exposure:

HIKER	----	----	----	----
BERRY PICKER	----	----	----	----
HUNTER	----	----	----	----
FISHERMAN	----	----	----	----
RESIDENT	----	----	----	----

Table C-85
Margins of Safety For Exposed Members of the Public

LARGE BACKPACK, 60 ACRES, WORST CASE
HERBICIDE: Diuron

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (3750.0)	SYSTEMIC NOEL (0.63)	REPRODUCTIVE NOEL (6.25)

For Single Route of Exposure

DERMAL, SPRAY	0.0010	1000000+	610	6100
VEGETATION CONTACT				
HIKER	0.0000	1000000+	42000	420000
PICKER	0.0026	1000000+	240	2400
DRINKING WATER	0.0006	1000000+	1100	11000
EATING BERRIES	0.0011	1000000+	570	5700
EATING VEGETS.	0.0022	1000000+	280	2800
EATING DEER	0.0001	1000000+	4300	43000
EATING BIRD	0.0005	1000000+	1400	14000
EATING FISH	0.0046	820000	140	1400

For Combined Routes of Exposure:

HIKER	0.0016	1000000+	390	3900
BERRY PICKER	0.0054	700000	120	1200
HUNTER	0.0022	1000000+	280	2800
FISHERMAN	0.0062	600000	100	1000
RESIDENT	0.0038	980000	160	1600

D Human Health Risk Assessment (Quantitative)

Table C-86
Margins of Safety For Exposed Members of the Public

LARGE RIGHT OF WAY, WORST CASE
HERBICIDE: Diuron

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (3750.0)	SYSTEMIC NOEL (0.63)	REPRODUCTIVE NOEL (6.25)

For Single Route of Exposure

DERMAL, SPRAY	0.0010	1000000+	650	6500
VEGETATION CONTACT				
HIKER	0.0000	1000000+	45000	450000
PICKER	0.0025	1000000+	250	2500
DRINKING WATER	0.0008	1000000+	780	7800
EATING BERRIES	0.0012	1000000+	500	5000
EATING VEGETS.	0.0025	1000000+	250	2500
EATING DEER	0.0002	1000000+	4000	40000
EATING BIRD	0.0004	1000000+	1400	14000
EATING FISH	0.0064	590000	98	980

For Combined Routes of Exposure:

HIKER	0.0018	1000000+	350	3500
BERRY PICKER	0.0055	690000	110	1100
HUNTER	0.0024	1000000+	260	2600
FISHERMAN	0.0081	460000	77	770
RESIDENT	0.0043	880000	150	1500

Table C-87
Margins of Safety For Exposed Members of the Public

REALISTIC AERIAL, 40 ACRES BY HELICOPTER
HERBICIDE: Fosamine

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (24400.0)	SYSTEMIC NOEL (25.00)	REPRODUCTIVE NOEL (50.00)
For Single Route of Exposure				
DERMAL, SPRAY	0.0000	1000000+	1000000	1000000+
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0049	1000000+	5100	10000
DRINKING WATER	0.0028	1000000+	8800	18000
EATING BERRIES	0.0016	1000000+	15000	31000
EATING VEGETS.	0.0032	1000000+	7700	15000
EATING DEER	0.0002	1000000+	110000	220000
EATING BIRD	0.0008	1000000+	30000	61000
EATING FISH	0.0011	1000000+	22000	44000
For Combined Routes of Exposure:				
HIKER	0.0029	1000000+	8800	18000
BERRY PICKER	0.0093	1000000+	2700	5400
HUNTER	0.0039	1000000+	6400	13000
FISHERMAN	0.0040	1000000+	6300	13000
RESIDENT	0.0061	1000000+	4100	8200

D Human Health Risk Assessment (Quantitative)

Table C-88
 Margins of Safety For Exposed Members of the Public

SMALL BACKPACK, 6.0 ACRES, REALISTIC CASE
 HERBICIDE: Fosamine

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (24400.0)	SYSTEMIC NOEL (25.00)	REPRODUCTIVE NOEL (50.00)
For Single Route of Exposure				
DERMAL, SPRAY	0.0003	1000000+	94000	190000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0011	1000000+	24000	47000
DRINKING WATER	0.0002	1000000+	100000	200000
EATING BERRIES	0.0005	1000000+	54000	110000
EATING VEGETS.	0.0009	1000000+	27000	54000
EATING DEER	0.0001	1000000+	420000	840000
EATING BIRD	0.0002	1000000+	140000	270000
EATING FISH	0.0001	1000000+	250000	500000
For Combined Routes of Exposure:				
HIKER	0.0005	1000000+	48000	96000
BERRY PICKER	0.0020	1000000+	12000	25000
HUNTER	0.0008	1000000+	33000	66000
FISHERMAN	0.0006	1000000+	40000	81000
RESIDENT	0.0014	1000000+	17000	35000

Table C-89
Margins of Safety For Exposed Members of the Public

SMALL RIGHT OF WAY, REALISTIC CASE
HERBICIDE: Fosamine

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (24400.0)	SYSTEMIC NOEL (25.00)	REPRODUCTIVE NOEL (50.00)
<hr/>				
For Single Route of Exposure				
DERMAL, SPRAY	0.0001	1000000+	360000	720000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0004	1000000+	67000	130000
DRINKING WATER	0.0001	1000000+	170000	340000
EATING BERRIES	0.0002	1000000+	120000	240000
EATING VEGETS.	0.0004	1000000+	61000	120000
EATING DEER	0.0000	1000000+	980000	1000000+
EATING BIRD	0.0001	1000000+	370000	740000
EATING FISH	0.0001	1000000+	420000	840000
For Combined Routes of Exposure:				
HIKER	0.0002	1000000+	110000	230000
BERRY PICKER	0.0008	1000000+	31000	63000
HUNTER	0.0003	1000000+	80000	160000
FISHERMAN	0.0003	1000000+	90000	180000
RESIDENT	0.0006	1000000+	40000	80000

D Human Health Risk Assessment (Quantitative)

Table C-90
Margins of Safety For Exposed Members of the Public

LARGE AERIAL, 400 ACRES BY FIXED WING, WORST CASE
HERBICIDE: Fosamjne

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (24400.0)	SYSTEMIC NOEL (25.00)	REPRODUCTIVE NOEL (50.00)
For Single Route of Exposure				
DERMAL, SPRAY	0.0509	480000	490	980
VEGETATION CONTACT				
HIKER	0.0007	1000000+	34000	68000
PICKER	0.1313	190000	190	380
DRINKING WATER	0.0380	640000	660	1300
EATING BERRIES	0.0313	780000	800	1600
EATING VEGETS.	0.0625	390000	400	800
EATING DEER	0.0049	1000000+	5100	10000
EATING BIRD	0.0213	1000000+	1200	2300
EATING FISH	0.0152	1000000+	1600	3300
For Combined Routes of Exposure:				
HIKER	0.0897	270000	280	560
BERRY PICKER	0.2516	97000	99	200
HUNTER	0.1159	210000	220	430
FISHERMAN	0.1049	230000	240	480
RESIDENT	0.1523	160000	160	330

Table C-91
Margins of Safety For Exposed Members of the Public

LARGE BACKPACK, 60 ACRES, WORST CASE
HERBICIDE: Fosamine

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (24400.0)	SYSTEMIC NOEL (25.00)	REPRODUCTIVE NOEL (50.00)
For Single Route of Exposure				
DERMAL, SPRAY	0.0020	1000000+	13000	25000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	880000	1000000+
PICKER	0.0051	1000000+	4900	9800
DRINKING WATER	0.0011	1000000+	23000	46000
EATING BERRIES	0.0021	1000000+	12000	24000
EATING VEGETS.	0.0042	1000000+	5900	12000
EATING DEER	0.0003	1000000+	90000	180000
EATING BIRD	0.0009	1000000+	29000	57000
EATING FISH	0.0004	1000000+	57000	110000
For Combined Routes of Exposure:				
HIKER	0.0031	1000000+	8100	16000
BERRY PICKER	0.0103	1000000+	2400	4900
HUNTER	0.0043	1000000+	5900	12000
FISHERMAN	0.0035	1000000+	7100	14000
RESIDENT	0.0073	1000000+	3400	6800

D Human Health Risk Assessment (Quantitative)

Table C-92
Margins of Safety For Exposed Members of the Public

LARGE RIGHT OF WAY, WORST CASE
HERBICIDE: Fosamine

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (24400.0)	SYSTEMIC NOEL (25.00)	REPRODUCTIVE NOEL (50.00)
For Single Route of Exposure				
DERMAL, SPRAY	0.0006	1000000+	39000	78000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0017	1000000+	15000	30000
DRINKING WATER	0.0005	1000000+	47000	94000
EATING BERRIES	0.0008	1000000+	30000	60000
EATING VEGETS.	0.0017	1000000+	15000	30000
EATING DEER	0.0001	1000000+	240000	480000
EATING BIRD	0.0003	1000000+	85000	170000
EATING FISH	0.0002	1000000+	120000	230000
For Combined Routes of Exposure:				
HIKER	0.0012	1000000+	21000	42000
BERRY PICKER	0.0037	1000000+	6800	14000
HUNTER	0.0016	1000000+	16000	32000
FISHERMAN	0.0014	1000000+	18000	36000
RESIDENT	0.0028	1000000+	8800	18000

Table C-93
Margins of Safety For Exposed Members of the Public

REALISTIC AERIAL, 40 ACRES BY HELICOPTER
HERBICIDE: Glyphosate

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (4320.0)	SYSTEMIC NOEL (31.00)	REPRODUCTIVE NOEL (10.00)

For Single Route of Exposure

DERMAL, SPRAY	0.0000	1000000+	1000000+	620000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0032	1000000+	9600	3100
DRINKING WATER	0.0019	1000000+	16000	5300
EATING BERRIES	0.0011	1000000+	29000	9300
EATING VEGETS.	0.0022	1000000+	14000	4600
EATING DEER	0.0002	1000000+	200000	65000
EATING BIRD	0.0005	1000000+	56000	18000
EATING FISH	0.0008	1000000+	41000	13000

For Combined Routes of Exposure:

HIKER	0.0019	1000000+	16000	5300
BERRY PICKER	0.0062	690000	5000	1600
HUNTER	0.0026	1000000+	12000	3800
FISHERMAN	0.0027	1000000+	12000	3800
RESIDENT	0.0041	1000000+	7600	2500

D Human Health Risk Assessment (Quantitative)

Table C-94
Margins of Safety For Exposed Members of the Public

SMALL BACKPACK, 6.0 ACRES, REALISTIC CASE
HERBICIDE: Glyphosate

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (4320.0)	SYSTEMIC NOEL (31.00)	REPRODUCTIVE NOEL (10.00)
For Single Route of Exposure				
DERMAL, SPRAY	0.0001	1000000+	230000	75000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0005	1000000+	59000	19000
DRINKING WATER	0.0001	1000000+	250000	80000
EATING BERRIES	0.0002	1000000+	140000	44000
EATING VEGETS.	0.0005	1000000+	68000	22000
EATING DEER	0.0000	1000000+	1000000	330000
EATING BIRD	0.0001	1000000+	340000	110000
EATING FISH	0.0000	1000000+	620000	200000
For Combined Routes of Exposure:				
HIKER	0.0003	1000000+	120000	38000
BERRY PICKER	0.0010	1000000+	31000	9800
HUNTER	0.0004	1000000+	81000	26000
FISHERMAN	0.0003	1000000+	100000	32000
RESIDENT	0.0007	1000000+	43000	14000

Table C-95
Margins of Safety For Exposed Members of the Public

SMALL RIGHT OF WAY, REALISTIC CASE

HERBICIDE: Glyphosate

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (4320.0)	SYSTEMIC NOEL (31.00)	REPRODUCTIVE NOEL (10.00)
For Single Route of Exposure				
DERMAL, SPRAY	0.0000	1000000+	900000	290000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0002	1000000+	170000	54000
DRINKING WATER	0.0001	1000000+	420000	130000
EATING BERRIES	0.0001	1000000+	300000	98000
EATING VEGETS.	0.0002	1000000+	150000	49000
EATING DEER	0.0000	1000000+	1000000+	780000
EATING BIRD	0.0000	1000000+	920000	300000
EATING FISH	0.0000	1000000+	1000000	340000
For Combined Routes of Exposure:				
HIKER	0.0001	1000000+	280000	91000
BERRY PICKER	0.0004	1000000+	78000	25000
HUNTER	0.0002	1000000+	200000	64000
FISHERMAN	0.0001	1000000+	220000	72000
RESIDENT	0.0003	1000000+	99000	32000

D Human Health Risk Assessment (Quantitative)

Table C-96
Margins of Safety For Exposed Members of the Public

LARGE AERIAL, 400 ACRES BY FIXED WING, WORST CASE
HERBICIDE: Glyphosate

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (4320.0)	SYSTEMIC NOEL (31.00)	REPRODUCTIVE NOEL (10.00)
<hr/>				
For Single Route of Exposure				
DERMAL, SPRAY	0.0212	200000	1500	470
VEGETATION CONTACT				
HIKER	0.0003	1000000+	100000	33000
PICKER	0.0547	79000	570	180
DRINKING WATER	0.0159	270000	2000	630
EATING BERRIES	0.0130	330000	2400	770
EATING VEGETS.	0.0261	170000	1200	380
EATING DEER	0.0020	1000000+	15000	4900
EATING BIRD	0.0089	490000	3500	1100
EATING FISH	0.0063	680000	4900	1600
For Combined Routes of Exposure:				
HIKER	0.0374	120000	830	270
BERRY PICKER	0.1048	41000	300	95
HUNTER	0.0483	89000	640	210
FISHERMAN	0.0437	99000	710	230
RESIDENT	0.0634	68000	490	160

Table C-97
Margins of Safety For Exposed Members of the Public

LARGE BACKPACK, 60 ACRES, WORST CASE
HERBICIDE: Glyphosate

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (4320.0)	SYSTEMIC NOEL (31.00)	REPRODUCTIVE NOEL (10.00)
<hr/>				
For Single Route of Exposure				
DERMAL, SPRAY	0.0009	1000000+	36000	12000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	810000
PICKER	0.0022	1000000+	14000	4500
DRINKING WATER	0.0005	1000000+	65000	21000
EATING BERRIES	0.0009	1000000+	34000	11000
EATING VEGETS.	0.0018	1000000+	17000	5400
EATING DEER	0.0001	1000000+	260000	83000
EATING BIRD	0.0004	1000000+	81000	26000
EATING FISH	0.0002	1000000+	160000	52000
For Combined Routes of Exposure:				
HIKER	0.0013	1000000+	23000	7400
BERRY PICKER	0.0045	970000	6900	2200
HUNTER	0.0018	1000000+	17000	5400
FISHERMAN	0.0015	1000000+	20000	6500
RESIDENT	0.0032	1000000+	9700	3100

D Human Health Risk Assessment (Quantitative)

Table C-98

Margins of Safety For Exposed Members of the Public

LARGE RIGHT OF WAY, WORST CASE
HERBICIDE: Glyphosate

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (4320.0)	SYSTEMIC NOEL (31.00)	REPRODUCTIVE NOEL (10.00)
For Single Route of Exposure				
DERMAL, SPRAY	0.0003	1000000+	100000	33000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0008	1000000+	40000	13000
DRINKING WATER	0.0002	1000000+	120000	40000
EATING BERRIES	0.0004	1000000+	80000	26000
EATING VEGETS.	0.0008	1000000+	40000	13000
EATING DEER	0.0000	1000000+	630000	200000
EATING BIRD	0.0001	1000000+	230000	73000
EATING FISH	0.0001	1000000+	310000	100000
For Combined Routes of Exposure:				
HIKER	0.0006	1000000+	56000	18000
BERRY PICKER	0.0017	1000000+	18000	5900
HUNTER	0.0007	1000000+	42000	14000
FISHERMAN	0.0007	1000000+	48000	15000
RESIDENT	0.0013	1000000+	23000	7500

Table C-99
Margins of Safety For Exposed Members of the Public

REALISTIC AERIAL, 40 ACRES BY HELICOPTER
HERBICIDE: Hexazinone

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (1690.0)	SYSTEMIC NOEL (10.00)	REPRODUCTIVE NOEL (50.00)

For Single Route of Exposure

DERMAL, SPRAY	0.0000	1000000+	500000	1000000+
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0041	420000	2500	12000
DRINKING WATER	0.0024	720000	4200	21000
EATING BERRIES	0.0013	1000000+	7400	37000
EATING VEGETS.	0.0027	630000	3700	19000
EATING DEER	0.0002	1000000+	52000	260000
EATING BIRD	0.0007	1000000+	15000	73000
EATING FISH	0.0009	1000000+	11000	53000

For Combined Routes of Exposure:

HIKER	0.0024	710000	4200	21000
BERRY PICKER	0.0078	220000	1300	6400
HUNTER	0.0033	520000	3100	15000
FISHERMAN	0.0033	510000	3000	15000
RESIDENT	0.0051	330000	2000	9900

D Human Health Risk Assessment (Quantitative)

Table C-100
Margins of Safety For Exposed Members of the Public

SMALL BACKPACK, 6.0 ACRES, REALISTIC CASE
HERBICIDE: Hexazinone

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (1690.0)	SYSTEMIC NOEL (10.00)	REPRODUCTIVE NOEL (50.00)

For Single Route of Exposure

DERMAL, SPRAY	0.0001	1000000+	100000	500000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0004	1000000+	25000	130000
DRINKING WATER	0.0001	1000000+	110000	540000
EATING BERRIES	0.0002	1000000+	58000	290000
EATING VEGETS.	0.0003	1000000+	29000	150000
EATING DEER	0.0000	1000000+	450000	1000000+
EATING BIRD	0.0001	1000000+	150000	730000
EATING FISH	0.0000	1000000+	270000	1000000+

For Combined Routes of Exposure:

HIKER	0.0002	1000000+	52000	260000
BERRY PICKER	0.0008	1000000+	13000	66000
HUNTER	0.0003	1000000+	35000	180000
FISHERMAN	0.0002	1000000+	43000	220000
RESIDENT	0.0005	1000000+	19000	93000

Table C-101
Margins of Safety For Exposed Members of the Public

SMALL RIGHT OF WAY, REALISTIC CASE
HERBICIDE: Hexazinone

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (1690.0)	SYSTEMIC NOEL (10.00)	REPRODUCTIVE NOEL (50.00)
<hr/> For Single Route of Exposure				
DERMAL, SPRAY	0.0000	1000000+	230000	1000000+
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0002	1000000+	43000	210000
DRINKING WATER	0.0001	1000000+	110000	540000
EATING BERRIES	0.0001	1000000+	78000	390000
EATING VEGETS.	0.0003	1000000+	39000	200000
EATING DEER	0.0000	1000000+	630000	1000000+
EATING BIRD	0.0000	1000000+	240000	1000000+
EATING FISH	0.0000	1000000+	270000	1000000+
<hr/> For Combined Routes of Exposure:				
HIKER	0.0001	1000000+	73000	370000
BERRY PICKER	0.0005	1000000+	20000	100000
HUNTER	0.0002	1000000+	51000	260000
FISHERMAN	0.0002	1000000+	57000	290000
RESIDENT	0.0004	1000000+	25000	130000

D Human Health Risk Assessment (Quantitative)

Table C-102
 Margins of Safety For Exposed Members of the Public

LARGE AERIAL, 400 ACRES BY FIXED WING, WORST CASE
 HERBICIDE: Hexazinone

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (1690.0)	SYSTEMIC NOEL (10.00)	REPRODUCTIVE NOEL (50.00)

For Single Route of Exposure

DERMAL, SPRAY	0.0127	130000	790	3900
VEGETATION CONTACT				
HIKER	0.0002	1000000+	55000	270000
PICKER	0.0328	51000	300	1500
DRINKING WATER	0.0095	180000	1100	5300
EATING BERRIES	0.0078	220000	1300	6400
EATING VEGETS.	0.0156	110000	640	3200
EATING DEER	0.0012	1000000+	8200	41000
EATING BIRD	0.0053	320000	1900	9400
EATING FISH	0.0038	440000	2600	13000

For Combined Routes of Exposure:

HIKER	0.0224	75000	450	2200
BERRY PICKER	0.0629	27000	160	790
HUNTER	0.0290	58000	350	1700
FISHERMAN	0.0262	64000	380	1900
RESIDENT	0.0381	44000	260	1300

Table C-103
Margins of Safety For Exposed Members of the Public

LARGE BACKPACK, 60 ACRES, WORST CASE
HERBICIDE: Hexazinone

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (1690.0)	SYSTEMIC NOEL (10.00)	REPRODUCTIVE NOEL (50.00)

For Single Route of Exposure

DERMAL, SPRAY	0.0005	1000000+	19000	97000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0013	1000000+	7500	38000
DRINKING WATER	0.0003	1000000+	35000	170000
EATING BERRIES	0.0006	1000000+	18000	90000
EATING VEGETS.	0.0011	1000000+	9000	45000
EATING DEER	0.0001	1000000+	140000	690000
EATING BIRD	0.0002	1000000+	44000	220000
EATING FISH	0.0001	1000000+	87000	440000

For Combined Routes of Exposure:

HIKER	0.0008	1000000+	12000	62000
BERRY PICKER	0.0027	630000	3700	19000
HUNTER	0.0011	1000000+	9000	45000
FISHERMAN	0.0009	1000000+	11000	54000
RESIDENT	0.0019	880000	5200	26000

D Human Health Risk Assessment (Quantitative)

Table C-104
Margins of Safety For Exposed Members of the Public

LARGE RIGHT OF WAY, WORST CASE
HERBICIDE: Hexazinone

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (1690.0)	SYSTEMIC NOEL (10.00)	REPRODUCTIVE NOEL (50.00)
<hr/>				
For Single Route of Exposure				
DERMAL, SPRAY	0.0004	1000000+	28000	140000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0009	1000000+	11000	54000
DRINKING WATER	0.0003	1000000+	33000	170000
EATING BERRIES	0.0005	1000000+	21000	110000
EATING VEGETS.	0.0009	1000000+	11000	54000
EATING DEER	0.0001	1000000+	170000	850000
EATING BIRD	0.0002	1000000+	61000	300000
EATING FISH	0.0001	1000000+	84000	420000
<hr/>				
For Combined Routes of Exposure:				
HIKER	0.0007	1000000+	15000	75000
BERRY PICKER	0.0021	820000	4900	24000
HUNTER	0.0009	1000000+	11000	56000
FISHERMAN	0.0008	1000000+	13000	64000
RESIDENT	0.0016	1000000+	6300	31000

Table C-105
Margins of Safety For Exposed Members of the Public

REALISTIC AERIAL, 40 ACRES BY HELICOPTER
HERBICIDE: Picloram

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (8200.0)	SYSTEMIC NOEL (7.00)	REPRODUCTIVE NOEL (50.00)
<hr/>				
For Single Route of Exposure				
DERMAL, SPRAY	0.0000	1000000+	1000000+	1000000+
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0000	1000000+	240000	1000000+
DRINKING WATER	0.0009	1000000+	7400	53000
EATING BERRIES	0.0005	1000000+	13000	93000
EATING VEGETS.	0.0011	1000000+	6500	46000
EATING DEER	0.0001	1000000+	96000	690000
EATING BIRD	0.0002	1000000+	29000	200000
EATING FISH	0.0004	1000000+	19000	130000
For Combined Routes of Exposure:				
HIKER	0.0009	1000000+	7400	53000
BERRY PICKER	0.0015	1000000+	4600	33000
HUNTER	0.0013	1000000+	5600	40000
FISHERMAN	0.0013	1000000+	5300	38000
RESIDENT	0.0020	1000000+	3500	25000

D Human Health Risk Assessment (Quantitative)

Table C-106
 Margins of Safety For Exposed Members of the Public

SMALL BACKPACK, 6.0 ACRES, REALISTIC CASE
 HERBICIDE: Picloram

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (8200.0)	SYSTEMIC NOEL (7.00)	REPRODUCTIVE NOEL (50.00)
For Single Route of Exposure				
DERMAL, SPRAY	0.0000	1000000+	1000000+	1000000+
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0000	1000000+	1000000+	1000000+
DRINKING WATER	0.0001	1000000+	84000	600000
EATING BERRIES	0.0002	1000000+	46000	330000
EATING VEGETS.	0.0003	1000000+	23000	160000
EATING DEER	0.0000	1000000+	370000	1000000+
EATING BIRD	0.0001	1000000+	130000	920000
EATING FISH	0.0000	1000000+	210000	1000000+
For Combined Routes of Exposure:				
HIKER	0.0001	1000000+	83000	590000
BERRY PICKER	0.0002	1000000+	29000	210000
HUNTER	0.0002	1000000+	44000	320000
FISHERMAN	0.0001	1000000+	59000	420000
RESIDENT	0.0004	1000000+	18000	130000

Table C-107
Margins of Safety For Exposed Members of the Public

SMALL RIGHT OF WAY, REALISTIC CASE
HERBICIDE: Picloram

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (8200.0)	SYSTEMIC NOEL (7.00)	REPRODUCTIVE NOEL (50.00)
For Single Route of Exposure				
DERMAL, SPRAY	0.0000	1000000+	1000000+	1000000+
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0000	1000000+	1000000+	1000000+
DRINKING WATER	0.0000	1000000+	190000	1000000+
EATING BERRIES	0.0001	1000000+	140000	980000
EATING VEGETS.	0.0001	1000000+	68000	490000
EATING DEER	0.0000	1000000+	1000000+	1000000+
EATING BIRD	0.0000	1000000+	460000	1000000+
EATING FISH	0.0000	1000000+	470000	1000000+
For Combined Routes of Exposure:				
HIKER	0.0000	1000000+	190000	1000000+
BERRY PICKER	0.0001	1000000+	78000	550000
HUNTER	0.0001	1000000+	120000	850000
FISHERMAN	0.0001	1000000+	130000	950000
RESIDENT	0.0001	1000000+	50000	360000

D Human Health Risk Assessment (Quantitative)

Table C-108
Margins of Safety For Exposed Members of the Public

LARGE AERIAL, 400 ACRES BY FIXED WING, WORST CASE
HERBICIDE: Picloram

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (8200.0)	SYSTEMIC NOEL (7.00)	REPRODUCTIVE NOEL (50.00)

For Single Route of Exposure

DERMAL, SPRAY	0.0004	1000000+	18000	130000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0010	1000000+	7100	51000
DRINKING WATER	0.0159	520000	440	3200
EATING BERRIES	0.0130	630000	540	3800
EATING VEGETS.	0.0261	310000	270	1900
EATING DEER	0.0019	1000000+	3700	26000
EATING BIRD	0.0079	1000000	890	6400
EATING FISH	0.0063	1000000+	1100	7900

For Combined Routes of Exposure:

HIKER	0.0162	500000	430	3100
BERRY PICKER	0.0302	270000	230	1700
HUNTER	0.0260	320000	270	1900
FISHERMAN	0.0226	360000	310	2200
RESIDENT	0.0423	190000	170	1200

Table C-109
Margins of Safety For Exposed Members of the Public

LARGE BACKPACK, 60 ACRES, WORST CASE
HERBICIDE: Picloram

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (8200.0)	SYSTEMIC NOEL (7.00)	REPRODUCTIVE NOEL (50.00)
<hr/>				
For Single Route of Exposure				
DERMAL, SPRAY	0.0000	1000000+	570000	1000000+
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0000	1000000+	220000	1000000+
DRINKING WATER	0.0004	1000000+	18000	130000
EATING BERRIES	0.0007	1000000+	9500	68000
EATING VEGETS.	0.0015	1000000+	4700	34000
EATING DEER	0.0001	1000000+	76000	540000
EATING BIRD	0.0003	1000000+	26000	180000
EATING FISH	0.0002	1000000+	46000	330000
For Combined Routes of Exposure:				
HIKER	0.0004	1000000+	18000	130000
BERRY PICKER	0.0012	1000000+	6000	43000
HUNTER	0.0008	1000000+	9200	66000
FISHERMAN	0.0005	1000000+	13000	91000
RESIDENT	0.0019	1000000+	3700	27000

D Human Health Risk Assessment (Quantitative)

Table C-110
Margins of Safety For Exposed Members of the Public

LARGE RIGHT OF WAY, WORST CASE
HERBICIDE: Picloram

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (8200.0)	SYSTEMIC NOEL (7.00)	REPRODUCTIVE NOEL (50.00)
<hr/>				
For Single Route of Exposure				
DERMAL, SPRAY	0.0000	1000000+	1000000+	1000000+
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0000	1000000+	1000000+	1000000+
DRINKING WATER	0.0001	1000000+	70000	500000
EATING BERRIES	0.0002	1000000+	45000	320000
EATING VEGETS.	0.0003	1000000+	23000	160000
EATING DEER	0.0000	1000000+	370000	1000000+
EATING BIRD	0.0000	1000000+	140000	1000000+
EATING FISH	0.0000	1000000+	180000	1000000+
For Combined Routes of Exposure:				
HIKER	0.0001	1000000+	69000	490000
BERRY PICKER	0.0003	1000000+	27000	190000
HUNTER	0.0002	1000000+	41000	290000
FISHERMAN	0.0001	1000000+	49000	350000
RESIDENT	0.0004	1000000+	17000	120000

Table C-111
Margins of Safety For Exposed Members of the Public

REALISTIC AERIAL, 40 ACRES BY HELICOPTER
HERBICIDE: Simazine

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (5000.0)	SYSTEMIC NOEL (5.00)	REPRODUCTIVE NOEL (5.00)
For Single Route of Exposure				
DERMAL, SPRAY	0.0000	1000000+	160000	160000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0065	770000	770	770
DRINKING WATER	0.0038	1000000+	1300	1300
EATING BERRIES	0.0022	1000000+	2300	2300
EATING VEGETS.	0.0043	1000000+	1200	1200
EATING DEER	0.0003	1000000+	16000	16000
EATING BIRD	0.0011	1000000+	4500	4500
EATING FISH	0.0015	1000000+	3300	3300
For Combined Routes of Exposure:				
HIKER	0.0038	1000000+	1300	1300
BERRY PICKER	0.0124	400000	400	400
HUNTER	0.0052	960000	960	960
FISHERMAN	0.0053	940000	940	940
RESIDENT	0.0081	620000	620	620

D Human Health Risk Assessment (Quantitative)

Table C-112
 Margins of Safety For Exposed Members of the Public

SMALL BACKPACK, 6.0 ACRES, REALISTIC CASE
 HERBICIDE: Simazine

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (5000.0)	SYSTEMIC NOEL (5.00)	REPRODUCTIVE NOEL (5.00)
For Single Route of Exposure				
DERMAL, SPRAY	0.0002	1000000+	28000	28000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0007	1000000+	7100	7100
DRINKING WATER	0.0002	1000000+	30000	30000
EATING BERRIES	0.0003	1000000+	16000	16000
EATING VEGETS.	0.0006	1000000+	8200	8200
EATING DEER	0.0000	1000000+	130000	130000
EATING BIRD	0.0001	1000000+	41000	41000
EATING FISH	0.0001	1000000+	75000	75000
For Combined Routes of Exposure:				
HIKER	0.0003	1000000+	14000	14000
BERRY PICKER	0.0014	1000000+	3700	3700
HUNTER	0.0005	1000000+	9800	9800
FISHERMAN	0.0004	1000000+	12000	12000
RESIDENT	0.0010	1000000+	5200	5200

Table C-113
Margins of Safety For Exposed Members of the Public

SMALL RIGHT OF WAY, REALISTIC CASE
HERBICIDE: Simazine

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (5000.0)	SYSTEMIC NOEL (5.00)	REPRODUCTIVE NOEL (5.00)
<hr/>				
For Single Route of Exposure				
DERMAL, SPRAY	0.0000	1000000+	140000	140000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0002	1000000+	27000	27000
DRINKING WATER	0.0001	1000000+	67000	67000
EATING BERRIES	0.0001	1000000+	49000	49000
EATING VEGETS.	0.0002	1000000+	24000	24000
EATING DEER	0.0000	1000000+	390000	390000
EATING BIRD	0.0000	1000000+	150000	150000
EATING FISH	0.0000	1000000+	170000	170000
For Combined Routes of Exposure:				
HIKER	0.0001	1000000+	46000	46000
BERRY PICKER	0.0004	1000000+	13000	13000
HUNTER	0.0002	1000000+	32000	32000
FISHERMAN	0.0001	1000000+	36000	36000
RESIDENT	0.0003	1000000+	16000	16000

D Human Health Risk Assessment (Quantitative)

Table C-114
Margins of Safety For Exposed Members of the Public

LARGE AERIAL, 400 ACRES BY FIXED WING, WORST CASE
HERBICIDE: Simazine

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (5000.0)	SYSTEMIC NOEL (5.00)	REPRODUCTIVE NOEL (5.00)
For Single Route of Exposure				
DERMAL, SPRAY	0.0212	240000	240	240
VEGETATION CONTACT				
HIKER	0.0003	1000000+	16000	16000
PICKER	0.0547	91000	91	91
DRINKING WATER	0.0159	320000	320	320
EATING BERRIES	0.0130	380000	380	380
EATING VEGETS.	0.0261	190000	190	190
EATING DEER	0.0020	1000000+	2500	2500
EATING BIRD	0.0089	560000	560	560
EATING FISH	0.0063	790000	790	790
For Combined Routes of Exposure:				
HIKER	0.0374	130000	130	130
BERRY PICKER	0.1048	48000	48	48
HUNTER	0.0483	100000	100	100
FISHERMAN	0.0437	110000	110	110
RESIDENT	0.0634	79000	79	79

Table C-115
Margins of Safety For Exposed Members of the Public

LARGE BACKPACK, 60 ACRES, WORST CASE
HERBICIDE: Simazine

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (5000.0)	SYSTEMIC NOEL (5.00)	REPRODUCTIVE NOEL (5.00)
For Single Route of Exposure				
DERMAL, SPRAY	0.0008	1000000+	6300	6300
VEGETATION CONTACT				
HIKER	0.0000	1000000+	440000	440000
PICKER	0.0020	1000000+	2500	2500
DRINKING WATER	0.0004	1000000+	11000	11000
EATING BERRIES	0.0008	1000000+	5900	5900
EATING VEGETS.	0.0017	1000000+	2900	2900
EATING DEER	0.0001	1000000+	45000	45000
EATING BIRD	0.0004	1000000+	14000	14000
EATING FISH	0.0002	1000000+	28000	28000
For Combined Routes of Exposure:				
HIKER	0.0012	1000000+	4000	4000
BERRY PICKER	0.0041	1000000+	1200	1200
HUNTER	0.0017	1000000+	2900	2900
FISHERMAN	0.0014	1000000+	3500	3500
RESIDENT	0.0029	1000000+	1700	1700

D Human Health Risk Assessment (Quantitative)

Table C-116
 Margins of Safety For Exposed Members of the Public

LARGE RIGHT OF WAY, WORST CASE
 HERBICIDE: Simazine

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (5000.0)	SYSTEMIC NOEL (5.00)	REPRODUCTIVE NOEL (5.00)
For Single Route of Exposure				
DERMAL, SPRAY	0.0003	1000000+	18000	18000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0007	1000000+	7000	7000
DRINKING WATER	0.0002	1000000+	22000	22000
EATING BERRIES	0.0004	1000000+	14000	14000
EATING VEGETS.	0.0007	1000000+	7000	7000
EATING DEER	0.0000	1000000+	110000	110000
EATING BIRD	0.0001	1000000+	39000	39000
EATING FISH	0.0001	1000000+	55000	55000
For Combined Routes of Exposure:				
HIKER	0.0005	1000000+	9800	9800
BERRY PICKER	0.0016	1000000+	3200	3200
HUNTER	0.0007	1000000+	7300	7300
FISHERMAN	0.0006	1000000+	8300	8300
RESIDENT	0.0012	1000000+	4100	4100

Table C-117
Margins of Safety For Exposed Members of the Public

REALISTIC AERIAL, 40 ACRES BY HELICOPTER
HERBICIDE: Tebuthiuron

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (644.0)	SYSTEMIC NOEL (12.50)	REPRODUCTIVE NOEL (5.00)

For Single Route of Exposure

DERMAL, SPRAY	0.0000	1000000+	1000000+	620000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0016	400000	7700	3100
DRINKING WATER	0.0009	680000	13000	5300
EATING BERRIES	0.0005	1000000+	23000	9300
EATING VEGETS.	0.0011	600000	12000	4600
EATING DEER	0.0001	1000000+	160000	65000
EATING BIRD	0.0003	1000000+	45000	18000
EATING FISH	0.0038	170000	3300	1300

For Combined Routes of Exposure:

HIKER	0.0010	680000	13000	5300
BERRY PICKER	0.0031	210000	4000	1600
HUNTER	0.0013	490000	9600	3800
FISHERMAN	0.0047	140000	2600	1100
RESIDENT	0.0020	320000	6200	2500

D Human Health Risk Assessment (Quantitative)

Table C-118
Margins of Safety For Exposed Members of the Public

SMALL BACKPACK, 6.0 ACRES, REALISTIC CASE
HERBICIDE: Tebuthiuron

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (644.0)	SYSTEMIC NOEL (12.50)	REPRODUCTIVE NOEL (15.50)

For Single Route of Exposure

DERMAL, SPRAY	0.0001	1000000+	94000	37000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0005	1000000+	24000	9500
DRINKING WATER	0.0001	1000000+	100000	40000
EATING BERRIES	0.0002	1000000+	54000	22000
EATING VEGETS.	0.0005	1000000+	27000	11000
EATING DEER	0.0000	1000000+	420000	170000
EATING BIRD	0.0001	1000000+	140000	54000
EATING FISH	0.0005	1000000+	25000	15000

For Combined Routes of Exposure:

HIKER	0.0003	1000000+	48000	19000
BERRY PICKER	0.0010	630000	12000	4900
HUNTER	0.0004	1000000+	33000	13000
FISHERMAN	0.0008	850000	17000	6600
RESIDENT	0.0007	900000	17000	7000

Table C-119
Margins of Safety For Exposed Members of the Public

SMALL RIGHT OF WAY, REALISTIC CASE
HERBICIDE: Tebuthiuron

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (644.0)	SYSTEMIC NOEL (12.50)	REPRODUCTIVE NOEL (5.00)

For Single Route of Exposure

DERMAL, SPRAY	0.0000	1000000+	330000	130000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0002	1000000+	61000	24000
DRINKING WATER	0.0001	1000000+	150000	61000
EATING BERRIES	0.0001	1000000+	110000	44000
EATING VEGETS.	0.0002	1000000+	56000	22000
EATING DEER	0.0000	1000000+	890000	360000
EATING BIRD	0.0000	1000000+	340000	130000
EATING FISH	0.0003	1000000+	38000	15000

For Combined Routes of Exposure:

HIKER	0.0001	1000000+	100000	42000
BERRY PICKER	0.0004	1000000+	29000	11000
HUNTER	0.0002	1000000+	73000	29000
FISHERMAN	0.0004	1000000+	28000	11000
RESIDENT	0.0003	1000000+	36000	14000

D Human Health Risk Assessment (Quantitative)

Table C-120
Margins of Safety For Exposed Members of the Public

LARGE AERIAL, 400 ACRES BY FIXED WING, WORST CASE
HERBICIDE: Tebuthiuron

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50	SYSTEMIC NOEL	REPRODUCTIVE NOEL
	(644.0)	(12.50)	(5.00)

For Single Route of Exposure

DERMAL, SPRAY	0.0255	25000	490	200
VEGETATION CONTACT				
HIKER	0.0004	1000000+	34000	14000
PICKER	0.0657	9800	190	76
DRINKING WATER	0.0190	34000	660	260
EATING BERRIES	0.0156	41000	800	320
EATING VEGETS.	0.0313	21000	400	160
EATING DEER	0.0024	260000	5100	2000
EATING BIRD	0.0107	60000	1200	470
EATING FISH	0.0761	8500	160	66

For Combined Routes of Exposure:

HIKER	0.0449	14000	280	110
BERRY PICKER	0.1258	5100	99	40
HUNTER	0.0580	11000	220	86
FISHERMAN	0.1209	5300	100	41
RESIDENT	0.0761	8500	160	66

Table C-121
Margins of Safety For Exposed Members of the Public

LARGE BACKPACK, 60 ACRES, WORST CASE
HERBICIDE: Tebuthiuron

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (644.0)	SYSTEMIC NOEL (12.50)	REPRODUCTIVE NOEL (5.00)

For Single Route of Exposure

DERMAL, SPRAY	0.0010	630000	12000	4900
VEGETATION CONTACT				
HIKER	0.0000	1000000+	850000	340000
PICKER	0.0026	240000	4700	1900
DRINKING WATER	0.0006	1000000+	22000	8700
EATING BERRIES	0.0011	580000	11000	4500
EATING VEGETS.	0.0022	290000	5700	2300
EATING DEER	0.0001	1000000+	86000	34000
EATING BIRD	0.0005	1000000+	27000	11000
EATING FISH	0.0023	280000	5500	2200

For Combined Routes of Exposure:

HIKER	0.0016	400000	7700	3100
BERRY PICKER	0.0054	120000	2300	930
HUNTER	0.0022	290000	5600	2300
FISHERMAN	0.0039	160000	3200	1300
RESIDENT	0.0038	170000	3300	1300

D Human Health Risk Assessment (Quantitative)

Table C-122
 Margins of Safety For Exposed Members of the Public

LARGE RIGHT OF WAY, WORST CASE
 HERBICIDE: Tebuthiuron

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (644.0)	SYSTEMIC NOEL (12.50)	REPRODUCTIVE NOEL (5.00)

For Single Route of Exposure

DERMAL, SPRAY	0.0003	1000000+	45000	18000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0007	910000	18000	7000
DRINKING WATER	0.0002	1000000+	55000	22000
EATING BERRIES	0.0004	1000000+	35000	14000
EATING VEGETS.	0.0007	900000	18000	7000
EATING DEER	0.0000	1000000+	280000	110000
EATING BIRD	0.0001	1000000+	99000	39000
EATING FISH	0.0009	700000	14000	5500

For Combined Routes of Exposure:

HIKER	0.0005	1000000+	25000	9800
BERRY PICKER	0.0016	410000	7900	3200
HUNTER	0.0007	950000	18000	7300
FISHERMAN	0.0014	450000	8800	3500
RESIDENT	0.0012	530000	10000	4100

Table C-123
Margins of Safety For Exposed Members of the Public

REALISTIC AERIAL, 40 ACRES BY HELICOPTER
HERBICIDE: Triclopyr

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (630.0)	SYSTEMIC NOEL (2.50)	REPRODUCTIVE NOEL (2.50)

For Single Route of Exposure

DERMAL, SPRAY	0.0000	1000000+	940000	940000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0005	1000000+	4700	4700
DRINKING WATER	0.0019	330000	1300	1300
EATING BERRIES	0.0011	580000	2300	2300
EATING VEGETS.	0.0022	290000	1200	1200
EATING DEER	0.0001	1000000+	17000	17000
EATING BIRD	0.0005	1000000+	5000	5000
EATING FISH	0.0008	840000	3300	3300

For Combined Routes of Exposure:

HIKER	0.0019	330000	1300	1300
BERRY PICKER	0.0035	180000	710	710
HUNTER	0.0025	250000	990	990
FISHERMAN	0.0026	240000	950	950
RESIDENT	0.0040	160000	620	620

D Human Health Risk Assessment (Quantitative)

Table C-124
Margins of Safety For Exposed Members of the Public

SMALL BACKPACK, 6.0 ACRES, REALISTIC CASE
HERBICIDE: Triclopyr

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (630.0)	SYSTEMIC NOEL (2.50)	REPRODUCTIVE NOEL (2.50)

For Single Route of Exposure

DERMAL, SPRAY	0.0000	1000000+	85000	85000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0001	1000000+	22000	22000
DRINKING WATER	0.0002	1000000+	15000	15000
EATING BERRIES	0.0003	1000000+	8200	8200
EATING VEGETS.	0.0006	1000000	4100	4100
EATING DEER	0.0000	1000000+	65000	65000
EATING BIRD	0.0001	1000000+	22000	22000
EATING FISH	0.0001	1000000+	38000	38000

For Combined Routes of Exposure:

HIKER	0.0002	1000000+	13000	13000
BERRY PICKER	0.0006	1000000	4000	4000
HUNTER	0.0003	1000000+	7200	7200
FISHERMAN	0.0003	1000000+	9500	9500
RESIDENT	0.0008	780000	3100	3100

Table C-125
Margins of Safety For Exposed Members of the Public

SMALL RIGHT OF WAY, REALISTIC CASE
HERBICIDE: Triclopyr

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (630.0)	SYSTEMIC NOEL (2.50)	REPRODUCTIVE NOEL (2.50)

For Single Route of Exposure

DERMAL, SPRAY	0.0000	1000000+	440000	440000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0000	1000000+	81000	81000
DRINKING WATER	0.0001	1000000+	34000	34000
EATING BERRIES	0.0001	1000000+	24000	24000
EATING VEGETS.	0.0002	1000000+	12000	12000
EATING DEER	0.0000	1000000+	200000	200000
EATING BIRD	0.0000	1000000+	81000	81000
EATING FISH	0.0000	1000000+	84000	84000

For Combined Routes of Exposure:

HIKER	0.0001	1000000+	31000	31000
BERRY PICKER	0.0002	1000000+	12000	12000
HUNTER	0.0001	1000000+	20000	20000
FISHERMAN	0.0001	1000000+	23000	23000
RESIDENT	0.0003	1000000+	8800	8800

D Human Health Risk Assessment (Quantitative)

Table C-126
Margins of Safety For Exposed Members of the Public

LARGE AERIAL, 400 ACRES BY FIXED WING, WORST CASE
HERBICIDE: Triclopyr

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (630.0)	SYSTEMIC NOEL (2.50)	REPRODUCTIVE NOEL (2.50)

For Single Route of Exposure

DERMAL, SPRAY	0.0056	110000	450	450
VEGETATION CONTACT				
HIKER	0.0001	1000000+	31000	31000
PICKER	0.0144	44000	170	170
DRINKING WATER	0.0254	25000	99	99
EATING BERRIES	0.0208	30000	120	120
EATING VEGETS.	0.0417	15000	60	60
EATING DEER	0.0031	200000	810	810
EATING BIRD	0.0128	49000	200	200
EATING FISH	0.0101	62000	250	250

For Combined Routes of Exposure:

HIKER	0.0310	20000	81	81
BERRY PICKER	0.0663	9500	38	38
HUNTER	0.0469	13000	53	53
FISHERMAN	0.0412	15000	61	61
RESIDENT	0.0727	8700	34	34

Table C-127
Margins of Safety For Exposed Members of the Public

LARGE BACKPACK, 60 ACRES, WORST CASE
HERBICIDE: Triclopyr

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (630.0)	SYSTEMIC NOEL (2.50)	REPRODUCTIVE NOEL (2.50)

For Single Route of Exposure

DERMAL, SPRAY	0.0002	1000000+	11000	11000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	770000	770000
PICKER	0.0006	1000000+	4300	4300
DRINKING WATER	0.0008	820000	3300	3300
EATING BERRIES	0.0015	430000	1700	1700
EATING VEGETS.	0.0029	210000	850	850
EATING DEER	0.0002	1000000+	13000	13000
EATING BIRD	0.0006	1000000+	4500	4500
EATING FISH	0.0003	1000000+	8200	8200

For Combined Routes of Exposure:

HIKER	0.0010	630000	2500	2500
BERRY PICKER	0.0030	210000	820	820
HUNTER	0.0017	360000	1400	1400
FISHERMAN	0.0013	490000	1900	1900
RESIDENT	0.0039	160000	630	630

D Human Health Risk Assessment (Quantitative)

Table C-128
Margins of Safety For Exposed Members of the Public

LARGE RIGHT OF WAY, WORST CASE
HERBICIDE: Triclopyr

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (630.0)	SYSTEMIC NOEL (2.50)	REPRODUCTIVE NOEL (2.50)

For Single Route of Exposure

DERMAL, SPRAY	0.0001	1000000+	32000	32000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	1000000+	1000000+
PICKER	0.0002	1000000+	12000	12000
DRINKING WATER	0.0004	1000000+	6300	6300
EATING BERRIES	0.0006	1000000	4000	4000
EATING VEGETS.	0.0012	510000	2000	2000
EATING DEER	0.0001	1000000+	33000	33000
EATING BIRD	0.0002	1000000+	12000	12000
EATING FISH	0.0002	1000000+	16000	16000

For Combined Routes of Exposure:

HIKER	0.0005	1000000+	5200	5200
BERRY PICKER	0.0013	480000	1900	1900
HUNTER	0.0008	830000	3300	3300
FISHERMAN	0.0006	990000	3900	3900
RESIDENT	0.0017	370000	1500	1500

Table C-129
Margins of Safety For Exposed Members of the Public

ACCIDENTAL SPRAYING
HERBICIDE: Amitrole

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (4080.0)	SYSTEMIC NOEL (0.03)	REPRODUCTIVE NOEL (4.00)

For Single Route of Exposure

DERMAL, SPRAY	0.0033	1000000+	7.5	1200
VEGETATION CONTACT				
HIKER	0.0000	1000000+	520	84000
PICKER	0.0086	470000	2.9	470
DRINKING WATER	0.1174	35000	-4.7	34
EATING BERRIES	0.0932	44000	-3.7	43
EATING VEGETS.	0.1935	21000	-7.7	21
EATING DEER	0.0187	220000	1.3	210
EATING BIRD	0.1161	35000	-4.6	34
EATING FISH	0.0470	87000	-1.9	85

For Combined Routes of Exposure:

HIKER	0.1208	34000	-4.8	33
BERRY PICKER	0.2225	18000	-8.9	18
HUNTER	0.2556	16000	-10	16
FISHERMAN	0.1677	24000	-6.7	24
RESIDENT	0.3143	13000	-13	13

D Human Health Risk Assessment (Quantitative)

Table C-130
Margins of Safety For Exposed Members of the Public

ACCIDENTAL SPRAYING
HERBICIDE: Asulam

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (4000.0)	SYSTEMIC NOEL (50.00)	REPRODUCTIVE NOEL (50.00)
<hr/> For Single Route of Exposure				
DERMAL, SPRAY	0.2085	19000	240	240
VEGETATION CONTACT				
HIKER	0.0030	1000000+	17000	17000
PICKER	0.5376	7400	93	93
DRINKING WATER	0.0734	55000	680	680
EATING BERRIES	0.0582	69000	860	860
EATING VEGETS.	0.1210	33000	410	410
EATING DEER	0.0131	310000	3800	3800
EATING BIRD	0.0827	48000	600	600
EATING FISH	0.0293	140000	1700	1700
<hr/> For Combined Routes of Exposure:				
HIKER	0.2849	14000	180	180
BERRY PICKER	0.8777	4600	57	57
HUNTER	0.3807	11000	130	130
FISHERMAN	0.3142	13000	160	160
RESIDENT	0.4059	9900	120	120

Table C-131
Margins of Safety For Exposed Members of the Public

ACCIDENTAL SPRAYING
HERBICIDE: Atrazine

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (672.0)	SYSTEMIC NOEL (0.48)	REPRODUCTIVE NOEL (0.5)

For Single Route of Exposure

DERMAL, SPRAY	0.3545	1900	1.4	1.4
VEGETATION CONTACT				
HIKER	0.0051	130000	94	100
PICKER	0.9139	740	-1.9	0.6
DRINKING WATER	0.1247	5400	3.8	4
EATING BERRIES	0.0990	6800	4.8	5
EATING VEGETS.	0.2056	3300	2.3	2.5
EATING DEER	0.0222	30000	22	23
EATING BIRD	0.1406	4800	3.4	3.6
EATING FISH	0.2494	2700	1.9	2.0

For Combined Routes of Exposure:

HIKER	0.4843	1400	-1.0	1.1
BERRY PICKER	1.4922	450	-3.1	-0.8
HUNTER	0.6471	1000	-1.3	0.8
FISHERMAN	0.7337	920	-1.5	0.7
RESIDENT	0.6900	970	-1.4	0.7

D Human Health Risk Assessment (Quantitative)

Table C-132
Margins of Safety For Exposed Members of the Public

ACCIDENTAL SPRAYING
HERBICIDE: Bromacil

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (3998.0)	SYSTEMIC NOEL (6.25)	REPRODUCTIVE NOEL (12.50)

For Single Route of Exposure

DERMAL, SPRAY	0.4171	9600	15	30
VEGETATION CONTACT				
HIKER	0.0060	670000	1000	2100
PICKER	1.0752	3700	5.8	12
DRINKING WATER	0.1467	27000	43	85
EATING BERRIES	0.1165	34000	54	110
EATING VEGETS.	0.2419	17000	26	52
EATING DEER	0.0261	150000	240	480
EATING BIRD	0.1654	24000	38	76
EATING FISH	0.0587	68000	110	210

For Combined Routes of Exposure:

HIKER	0.5698	7000	11	22
BERRY PICKER	1.7555	2300	3.6	7.1
HUNTER	0.7613	5300	8.2	16
FISHERMAN	0.6285	6400	9.9	20
RESIDENT	0.8117	4900	7.7	15

Table C-133
Margins of Safety For Exposed Members of the Public

ACCIDENTAL SPRAYING
HERBICIDE: 2,4-D

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (375.0)	SYSTEMIC NOEL (1.00)	REPRODUCTIVE NOEL (5.00)

For Single Route of Exposure

DERMAL, SPRAY	0.1026	3700	9.7	49
VEGETATION CONTACT				
HIKER	0.0015	250000	680	3400
PICKER	0.2645	1400	3.8	19
DRINKING WATER	0.0602	6200	17	83
EATING BERRIES	0.0478	7900	21	100
EATING VEGETS.	0.0992	3800	10	50
EATING DEER	0.0103	37000	97	490
EATING BIRD	0.0645	5800	16	78
EATING FISH	0.0241	16000	42	210

For Combined Routes of Exposure:

HIKER	0.1642	2300	6.1	30
BERRY PICKER	0.4750	790	2.1	11
HUNTER	0.2390	1600	4.2	21
FISHERMAN	0.1883	2000	5.3	27
RESIDENT	0.2634	1400	3.8	19

D Human Health Risk Assessment (Quantitative)

Table C-134
Margins of Safety For Exposed Members of the Public

ACCIDENTAL SPRAYING
HERBICIDE: 2,4-DP

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (532.0)	SYSTEMIC NOEL (5.00)	REPRODUCTIVE NOEL (6.25)

For Single Route of Exposure

DERMAL, SPRAY	0.0021	260000	2400	3000
VEGETATION CONTACT				
HIKER	0.0000	1000000+	170000	210000
PICKER	0.0054	99000	930	1200
DRINKING WATER	0.0734	7300	68	85
EATING BERRIES	0.0582	9100	86	110
EATING VEGETS.	0.1210	4400	41	52
EATING DEER	0.0117	45000	430	530
EATING BIRD	0.0726	7300	69	86
EATING FISH	0.0293	18000	170	210

For Combined Routes of Exposure:

HIKER	0.0755	7000	66	83
BERRY PICKER	0.1391	3800	36	45
HUNTER	0.1597	3300	31	39
FISHERMAN	0.1048	5100	48	60
RESIDENT	0.1964	2700	25	32

Table C-135
Margins of Safety For Exposed Members of the Public

ACCIDENTAL SPRAYING
HERBICIDE: Dalapon

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (7577.0)	SYSTEMIC NOEL (8.00)	REPRODUCTIVE NOEL (12.50)

For Single Route of Exposure

DERMAL, SPRAY	0.4171	18000	19	30
VEGETATION CONTACT				
HIKER	0.0060	1000000+	1300	2100
PICKER	1.0752	7000	7.4	12
DRINKING WATER	0.1467	52000	55	85
EATING BERRIES	0.1165	65000	69	110
EATING VEGETS.	0.2419	31000	33	52
EATING DEER	0.0261	290000	310	480
EATING BIRD	0.1654	46000	48	76
EATING FISH	0.0587	130000	140	210

For Combined Routes of Exposure:

HIKER	0.5698	13000	14	22
BERRY PICKER	1.7555	4300	4.6	7.1
HUNTER	0.7613	10000	11	16
FISHERMAN	0.6285	12000	13	20
RESIDENT	0.8117	9300	9.9	15

D Human Health Risk Assessment (Quantitative)

Table C-136
Margins of Safety For Exposed Members of the Public

ACCIDENTAL SPRAYING
HERBICIDE: Dicamba

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (757.0)	SYSTEMIC NOEL (15.80)	REPRODUCTIVE NOEL (2.50)

For Single Route of Exposure

DERMAL, SPRAY	0.1161	6500	140	22
VEGETATION CONTACT				
HIKER	0.0017	450000	9500	1500
PICKER	0.2993	2500	53	8.4
DRINKING WATER	0.0587	13000	270	43
EATING BERRIES	0.0466	16000	340	54
EATING VEGETS.	0.0968	7800	160	26
EATING DEER	0.0101	75000	1600	250
EATING BIRD	0.0637	12000	250	39
EATING FISH	0.0235	32000	670	110

For Combined Routes of Exposure:

HIKER	0.1765	4300	90	14
BERRY PICKER	0.5207	1500	30	4.8
HUNTER	0.2503	3000	63	10.0
FISHERMAN	0.1999	3800	79	13
RESIDENT	0.2732	2800	58	9.1

Table C-137
Margins of Safety For Exposed Members of the Public

ACCIDENTAL SPRAYING
HERBICIDE: Diuron

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (3750.0)	SYSTEMIC NOEL (0.63)	REPRODUCTIVE NOEL (6.25)

For Single Route of Exposure

DERMAL, SPRAY	0.6673	5600	-1.1	9.4
VEGETATION CONTACT				
HIKER	0.0096	390000	65	650
PICKER	1.7203	2200	-2.8	3.6
DRINKING WATER	0.2348	16000	2.7	27
EATING BERRIES	0.1864	20000	3.4	34
EATING VEGETS.	0.3871	9700	1.6	16
EATING DEER	0.0418	90000	15	150
EATING BIRD	0.2647	14000	2.4	24
EATING FISH	1.8780	2000	-3.0	3.3

For Combined Routes of Exposure:

HIKER	0.9117	4100	-1.5	6.9
BERRY PICKER	2.8088	1300	-4.5	2.2
HUNTER	1.2181	3100	-1.9	5.1
FISHERMAN	2.7897	1300	-4.5	2.2
RESIDENT	1.2987	2900	-2.1	4.8

D Human Health Risk Assessment (Quantitative)

Table C-138
Margins of Safety For Exposed Members of the Public

ACCIDENTAL SPRAYING
HERBICIDE: Fosamine

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (24400.0)	SYSTEMIC NOEL (25.00)	REPRODUCTIVE NOEL (50.00)

For Single Route of Exposure

DERMAL, SPRAY	0.5005	49000	50	100
VEGETATION CONTACT				
HIKER	0.0072	1000000+	3500	7000
PICKER	1.2902	19000	19	39
DRINKING WATER	0.1761	140000	140	280
EATING BERRIES	0.1398	170000	180	360
EATING VEGETS.	0.2903	84000	86	170
EATING DEER	0.0313	780000	800	1600
EATING BIRD	0.1985	120000	130	250
EATING FISH	0.0704	350000	350	710

For Combined Routes of Exposure:

HIKER	0.6838	36000	37	73
BERRY PICKER	2.1066	12000	12	24
HUNTER	0.9136	27000	27	55
FISHERMAN	0.7542	32000	33	66
RESIDENT	0.9741	25000	26	51

Table C-139
Margins of Safety For Exposed Members of the Public

ACCIDENTAL SPRAYING
HERBICIDE: Glyphosate

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (4320.0)	SYSTEMIC NOEL (31.00)	REPRODUCTIVE NOEL (10.00)

For Single Route of Exposure

DERMAL, SPRAY	0.2085	21000	150	48
VEGETATION CONTACT				
HIKER	0.0030	1000000+	10000	3300
PICKER	0.5376	8000	58	19
DRINKING WATER	0.0734	59000	420	140
EATING BERRIES	0.0582	74000	530	170
EATING VEGETS.	0.1210	36000	260	83
EATING DEER	0.0131	330000	2400	770
EATING BIRD	0.0827	52000	370	120
EATING FISH	0.0293	150000	1100	340

For Combined Routes of Exposure:

HIKER	0.2849	15000	110	35
BERRY PICKER	0.8777	4900	35	11
HUNTER	0.3807	11000	81	26
FISHERMAN	0.3142	14000	99	32
RESIDENT	0.4059	11000	76	25

D Human Health Risk Assessment (Quantitative)

Table C-140
 Margins of Safety For Exposed Members of the Public

ACCIDENTAL SPRAYING
 HERBICIDE: Hexazinone

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (1690.0)	SYSTEMIC NOEL (10.00)	REPRODUCTIVE NOEL (50.00)
<hr/> For Single Route of Exposure				
DERMAL, SPRAY	0.2503	6800	40	200
VEGETATION CONTACT				
HIKER	0.0036	470000	2800	14000
PICKER	0.6451	2600	16	78
DRINKING WATER	0.0880	19000	110	570
EATING BERRIES	0.0699	24000	140	720
EATING VEGETS.	0.1452	12000	69	340
EATING DEER	0.0157	110000	640	3200
EATING BIRD	0.0993	17000	100	500
EATING FISH	0.0352	48000	280	1400
<hr/> For Combined Routes of Exposure:				
HIKER	0.3419	4900	29	150
BERRY PICKER	1.0533	1600	9.5	47
HUNTER	0.4568	3700	22	110
FISHERMAN	0.3771	4500	27	130
RESIDENT	0.4870	3500	21	100

Table C-141
Margins of Safety For Exposed Members of the Public

ACCIDENTAL SPRAYING
HERBICIDE: Picloram

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (8200.0)	SYSTEMIC NOEL (7.00)	REPRODUCTIVE NOEL (50.00)

For Single Route of Exposure

DERMAL, SPRAY	0.0038	1000000+	1900	13000
VEGETATION CONTACT				
HIKER	0.0001	1000000+	130000	930000
PICKER	0.0097	850000	720	5200
DRINKING WATER	0.0734	110000	95	680
EATING BERRIES	0.0582	140000	120	860
EATING VEGETS.	0.1210	68000	58	410
EATING DEER	0.0117	700000	600	4300
EATING BIRD	0.0726	110000	96	690
EATING FISH	0.0293	280000	240	1700

For Combined Routes of Exposure:

HIKER	0.0772	110000	91	650
BERRY PICKER	0.1450	57000	48	340
HUNTER	0.1615	51000	43	310
FISHERMAN	0.1065	77000	66	470
RESIDENT	0.1981	41000	35	250

D Human Health Risk Assessment (Quantitative)

Table C-142
Margins of Safety For Exposed Members of the Public

ACCIDENTAL SPRAYING
HERBICIDE: Simazine

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (5000.0)	SYSTEMIC NOEL (5.00)	REPRODUCTIVE NOEL (5.00)

For Single Route of Exposure

DERMAL, SPRAY	0.2085	24000	24	24
VEGETATION CONTACT				
HIKER	0.0030	1000000+	1700	1700
PICKER	0.5376	9300	9.3	9.3
DRINKING WATER	0.0734	68000	68	68
EATING BERRIES	0.0582	86000	86	86
EATING VEGETS.	0.1210	41000	41	41
EATING DEER	0.0131	380000	380	380
EATING BIRD	0.0827	60000	60	60
EATING FISH	0.0293	170000	170	170

For Combined Routes of Exposure:

HIKER	0.2849	18000	18	18
BERRY PICKER	0.8777	5700	5.7	5.7
HUNTER	0.3807	13000	13	13
FISHERMAN	0.3142	16000	16	16
RESIDENT	0.4059	12000	12	12

Table C-143
Margins of Safety For Exposed Members of the Public

ACCIDENTAL SPRAYING
HERBICIDE: Tebuthiuron

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (644.0)	SYSTEMIC NOEL (12.50)	REPRODUCTIVE NOEL (5.00)

For Single Route of Exposure

DERMAL, SPRAY	0.2503	2600	50	20
VEGETATION CONTACT				
HIKER	0.0036	180000	3500	1400
PICKER	0.6451	1000	19	7.8
DRINKING WATER	0.0880	7300	140	57
EATING BERRIES	0.0699	9200	180	72
EATING VEGETS.	0.1452	4400	86	34
EATING DEER	0.0157	41000	800	320
EATING BIRD	0.0993	6500	130	50
EATING FISH	0.3521	1800	35	14

For Combined Routes of Exposure:

HIKER	0.3419	1900	37	15
BERRY PICKER	1.0533	610	12	4.7
HUNTER	0.4568	1400	27	11
FISHERMAN	0.6940	930	18	7.2
RESIDENT	0.4870	1300	26	10

D Human Health Risk Assessment (Quantitative)

Table C-144
 Margins of Safety For Exposed Members of the Public

ACCIDENTAL SPRAYING
 HERBICIDE: Triclopyr

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (630.0)	SYSTEMIC NOEL (2.50)	REPRODUCTIVE NOEL (2.50)

For Single Route of Exposure

DERMAL, SPRAY	0.0551	11000	45	45
VEGETATION CONTACT				
HIKER	0.0008	800000	3200	3200
PICKER	0.1419	4400	18	18
DRINKING WATER	0.1174	5400	21	21
EATING BERRIES	0.0932	6800	27	27
EATING VEGETS.	0.1935	3300	13	13
EATING DEER	0.0191	33000	130	130
EATING BIRD	0.1186	5300	21	21
EATING FISH	0.0470	13000	53	53

For Combined Routes of Exposure:

HIKER	0.1732	3600	14	14
BERRY PICKER	0.4075	1500	6.1	6.1
HUNTER	0.3109	2000	8.0	8.0
FISHERMAN	0.2202	2900	11	11
RESIDENT	0.3668	1700	6.8	6.8

Table C-145
Margins of Safety For Doses Due To Spills of Amitrole
Accidental-Worst Case Scenario

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:			
	LD50 (4080.0)	SYSTEMIC NOEL (0.03)	REPRODUCTIVE NOEL (4.00)	
<hr/>				
Spills Onto Skin				
CONCENTRATE	1.2000	3400	-48	3.3
SPRAY MIX	0.2400	17000	-9.6	17
Spills Into Bodies of Water (Drinking One Liter of Water)				
POND, HELO.	0.0737	55000	-2.9	54
RESERVOIR,HELO	0.0023	1000000+	11	1700
POND, TRUCK	1.4730	2800	-59	2.7
RESERV.,TRUCK	0.0460	89000	-1.8	87
<hr/>				

D Human Health Risk Assessment (Quantitative)

Table C-146
 Margins of Safety For Doses Due To Spills of Asulam
 Accidental-Worst Case Scenario

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (4000.0)	SYSTEMIC NOEL (50.00)	REPRODUCTIVE NOEL (50.00)
<hr/>			
Spills Onto Skin			
CONCENTRATE	240.0000	17	-4.8
SPRAY MIX	20.0400	200	2.5
Spills Into Bodies of Water (Drinking One Liter of Water)			
POND, HELO.	0.0615	65000	810
RESERVOIR, HELO	0.0019	1000000+	26000
POND, TRUCK	1.2300	3300	41
RESERV., TRUCK	0.0384	100000	1300

Table C-147
Margins of Safety For Doses Due To Spills of Atrazine
Accidental-Worst Case Scenario

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (672.0)	SYSTEMIC NOEL (0.48)	REPRODUCTIVE NOEL (0.5)

Spills Onto Skin

CONCENTRATE	240.0000	2.8	-500	-120
SPRAY MIX	24.0000	28	-54	12

Spills Into Bodies of Water (Drinking One Liter of Water)

POND, HELO.	0.0737	9100	6.5	7
RESERVOIR, HELO	0.0023	290000	210	215
POND, TRUCK	1.4730	460	-3.1	-0.8
RESERV., TRUCK	0.0460	15000	10	11

D Human Health Risk Assessment (Quantitative)

Table C-148
 Margins of Safety For Doses Due To Spills of Bromacil
 Accidental-Worst Case Scenario

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:			
	LD50 (3998.0)	SYSTEMIC NOEL (6.25)	REPRODUCTIVE NOEL (12.50)	
<hr/>				
Spills Onto Skin				
CONCENTRATE	240.0000	17	-38	-19
SPRAY MIX	12.0000	330	-1.9	1.0
Spills Into Bodies of Water (Drinking One Liter of Water)				
POND, HELO.	---	---	---	---
RESERVOIR,HELO	---	---	---	---
POND, TRUCK	0.7365	5400	8.5	17
RESERV.,TRUCK	0.0230	170000	270	540

Table C-149
Margins of Safety For Doses Due To Spills of 2,4-D
Accidental-Worst Case Scenario

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (375.0)	SYSTEMIC NOEL (1.00)	REPRODUCTIVE NOEL (5.00)

Spills Onto Skin

CONCENTRATE	144.0000	2.6	-140	-29
SPRAY MIX	14.4000	26	-14	-2.9

Spills Into Bodies of Water (Drinking One Liter of Water)

POND, HELO.	0.0737	5100	14	68
RESERVOIR,HELO	0.0023	160000	430	2200
POND, TRUCK	1.4730	250	-1.5	3.4
RESERV.,TRUCK	0.0460	8100	22	110

D Human Health Risk Assessment (Quantitative)

Table C-150

Margins of Safety For Doses Due To Spills of 2,4-DP
Accidental-Worst Case Scenario

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:			
	LD50 (532.0)	SYSTEMIC NOEL (5.00)	REPRODUCTIVE NOEL (6.25)	
<hr/>				
Spills Onto Skin				
CONCENTRATE	3.6000	150	1.4	1.7
SPRAY MIX	0.1500	3500	33	42
Spills Into Bodies of Water (Drinking One Liter of Water)				
POND, HELO.	0.0460	12000	110	140
RESERVOIR,HELO	0.0014	370000	3500	4300
POND, TRUCK	0.9206	580	5.4	6.8
RESERV.,TRUCK	0.0288	18000	170	220

Table C-151
Margins of Safety For Doses Due To Spills of Dalapon
Accidental-Worst Case Scenario

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (7577.0)	SYSTEMIC NOEL (8.00)	REPRODUCTIVE NOEL (12.50)

Spills Onto Skin

CONCENTRATE	----	----	----	----
SPRAY MIX	60.0000	130	-7.5	-4.8
Spills Into Bodies of Water (Drinking One Liter of Water)				
POND, HELO.	0.1841	41000	43	68
RESERVOIR, HELO	0.0058	1000000+	1400	2200
POND, TRUCK	3.6825	2100	2.2	3.4
RESERV., TRUCK	0.1151	66000	70	110

D Human Health Risk Assessment (Quantitative)

Table C-152
 Margins of Safety For Doses Due To Spills of Dicamba
 Accidental-Worst Case Scenario

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:			
	LD50 (757.0)	SYSTEMIC NOEL (15.80)	REPRODUCTIVE NOEL (3.00)	
Spills Onto Skin				
CONCENTRATE	167.0400	4.5	-11	-56
SPRAY MIX	16.7040	45	-1.1	-5.6
Spills Into Bodies of Water (Drinking One Liter of Water)				
POND, HELO.	0.0737	10000	210	41
RESERVOIR,HELO	0.0023	330000	6900	1300
POND, TRUCK	1.4730	510	11	2.0
RESERV.,TRUCK	0.0460	16000	340	65

Table C-153
Margins of Safety For Doses Due To Spills of Diuron
Accidental-Worst Case Scenario

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:			
	LD50 (3750.0)	SYSTEMIC NOEL (0.63)	REPRODUCTIVE NOEL (6.25)	
Spills Onto Skin				
CONCENTRATE	240.0000	16	-380	-38
SPRAY MIX	19.2000	200	-31	-3.1
Spills Into Bodies of Water (Drinking One Liter of Water)				
POND, HELO.	---	---	---	---
RESERVOIR,HELO	---	---	---	---
POND, TRUCK	1.1784	3200	-1.9	5.3
RESERV.,TRUCK	0.0368	100000	17	170

D Human Health Risk Assessment (Quantitative)

Table C-154
 Margins of Safety For Doses Due To Spills of Fosamine
 Accidental-Worst Case Scenario

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:			
	LD50 (24400.0)	SYSTEMIC NOEL (25.00)	REPRODUCTIVE NOEL (50.00)	
<hr/>				
Spills Onto Skin				
CONCENTRATE	240.0000	100	-9.6	-4.8
SPRAY MIX	72.0000	340	-2.9	-1.4
Spills Into Bodies of Water (Drinking One Liter of Water)				
POND, HELO.	0.2210	110000	110	230
RESERVOIR, HELO	0.0069	1000000+	3600	7200
POND, TRUCK	4.4191	5500	5.7	11
RESERV., TRUCK	0.1381	180000	180	360

Table C-155
Margins of Safety For Doses Due To Spills of Glyphosate
Accidental-Worst Case Scenario

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:			
	LD50 (4320.0)	SYSTEMIC NOEL (31.00)	REPRODUCTIVE NOEL (10.00)	
<hr/>				
Spills Onto Skin				
CONCENTRATE	180.0000	24	-5.8	-18
SPRAY MIX	30.0000	140	1.0	-3.0
Spills Into Bodies of Water (Drinking One Liter of Water)				
POND, HELO.	0.0921	47000	340	110
RESERVOIR,HELO	0.0029	1000000+	11000	3500
POND, TRUCK	1.8413	2300	17	5.4
RESERV.,TRUCK	0.0575	75000	540	170

D Human Health Risk Assessment (Quantitative)

Table C-156
 Margins of Safety For Doses Due To Spills of Hexazinone
 Accidental-Worst Case Scenario

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:			
	LD50 (1690.0)	SYSTEMIC NOEL (10.00)	REPRODUCTIVE NOEL (50.00)	
<hr/>				
Spills Onto Skin				
CONCENTRATE	120.0000	14	-12	-2.4
SPRAY MIX	18.0000	94	-1.8	2.8
Spills Into Bodies of Water (Drinking One Liter of Water)				
POND, HELO.	0.0552	31000	180	910
RESERVOIR,HELO	0.0017	980000	5800	29000
POND, TRUCK	1.1048	1500	9.1	45
RESERV.,TRUCK	0.0345	49000	290	1400

Table C-157
Margins of Safety For Doses Due To Spills of Picloram
Accidental-Worst Case Scenario

	EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
		LD50 (8200.0)	SYSTEMIC NOEL (7.00)	REPRODUCTIVE NOEL (50.00)
<hr/>				
Spills Onto Skin				
CONCENTRATE	2.1600	3800	3.2	23
SPRAY MIX	0.5400	15000	13	93
Spills Into Bodies of Water (Drinking One Liter of Water)				
POND, HELO.	0.0921	89000	76	540
RESERVOIR, HELO	0.0029	1000000+	2400	17000
POND, TRUCK	1.8413	4500	3.8	27
RESERV., TRUCK	0.0575	140000	120	870

D Human Health Risk Assessment (Quantitative)

Table C-158
 Margins of Safety For Doses Due To Spills of Simazine
 Accidental-Worst Case Scenario

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (5000.0)	SYSTEMIC NOEL (5.00)	REPRODUCTIVE NOEL (5.00)
<hr/>			
Spills Onto Skin			
CONCENTRATE	240.0000	21	-48
SPRAY MIX	30.0000	170	-6.0
Spills Into Bodies of Water (Drinking One Liter of Water)			
POND, HELO.	0.0921	54000	54
RESERVOIR, HELO	0.0029	1000000+	1700
POND, TRUCK	1.8413	2700	2.7
RESERV., TRUCK	0.0575	87000	87

Table C-159
Margins of Safety For Doses Due To Spills of Tebuthiuron
Accidental-Worst Case Scenario

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50	SYSTEMIC NOEL	REPRODUCTIVE NOEL
	(644.0)	(12.50)	(5.00)

Spills Onto Skin

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CONCENTRATE				
SPRAY MIX	36.0000	18	-2.9	-7.2
Spills Into Bodies of Water (Drinking One Liter of Water)				
POND, HELO.	0.1105	5800	110	45
RESERVOIR, HELO	0.0035	190000	3600	1400
POND, TRUCK	2.2095	290	5.7	2.3
RESERV., TRUCK	0.0690	9300	180	72

D Human Health Risk Assessment (Quantitative)

Table C-160
 Margins of Safety For Doses Due To Spills of Triclopyr
 Accidental-Worst Case Scenario

EXPOSURE (MG/KG/DAY)	MARGIN OF SAFETY RELATIVE TO:		
	LD50 (630.0)	SYSTEMIC NOEL (2.50)	REPRODUCTIVE NOEL (2.50)
Spills Onto Skin			
CONCENTRATE	39.6000	16	-16
SPRAY MIX	7.9200	80	-3.2
Spills Into Bodies of Water (Drinking One Liter of Water)			
POND, HELO.	0.1473	4300	17
RESERVOIR,HELO	0.0046	140000	540
POND, TRUCK	2.9460	210	-1.2
RESERV.,TRUCK	0.0921	6800	27

LIFETIME CANCER RISK TO THE PUBLIC

Table C-161
LIFETIME CANCER RISK - EXPOSED PUBLIC FOR SMALL BACKPACK, 6.0 ACRES, ROUTINE REALISTIC CASE

	EXPOSURES PER LIFETIME	RISK FROM EXCLUSIVE USE OF:							
		AMITROLE	ASULAM	ATRAZINE	BROMACIL	2,4-D	2,4-DP	GLYPHOSATE	PICLORAM
FOR A SINGLE EXPOSURE:									
DERMAL, SPRAY	1	5.07E-10	7.50E-11	1.63E-09	6.67E-10	1.09E-10	4.49E-12	1.69E-12	1.86E-13
VEGETATION CONTACT									
HIKER	1	7.28E-12	1.08E-12	2.34E-11	9.57E-12	1.57E-12	6.45E-14	2.42E-14	2.67E-15
PICKER	1	2.01E-09	2.97E-10	6.45E-09	2.64E-09	4.33E-10	1.78E-11	6.69E-12	7.36E-13
DRINKING WATER	1	4.73E-08	6.99E-11	1.52E-09	6.22E-10	1.70E-10	4.19E-10	1.57E-12	9.62E-12
EATING BERRIES	1	8.72E-08	1.29E-10	2.80E-09	1.15E-09	3.13E-10	7.72E-10	2.90E-12	1.77E-11
EATING VEGETS.	1	1.74E-07	2.58E-10	5.60E-09	2.29E-09	6.26E-10	1.54E-09	5.81E-12	3.55E-11
EATING DEER	1	1.08E-08	1.68E-11	3.65E-10	1.49E-10	4.01E-11	9.61E-11	3.78E-13	2.21E-12
EATING FISH	1	1.89E-08	2.79E-11	3.04E-09	2.49E-10	6.79E-11	1.67E-10	6.30E-13	3.85E-12
Combined Routes of Exposure:									
HIKER	1	4.78E-08	1.46E-10	3.17E-09	1.30E-09	2.81E-10	4.23E-10	3.29E-12	9.81E-12
BERRY PICKER	1	1.37E-07	5.71E-10	1.24E-08	5.08E-09	1.03E-09	1.21E-09	1.29E-11	2.83E-11
HUNTER	1	8.97E-08	2.14E-10	4.66E-09	1.91E-09	4.41E-10	7.94E-10	4.83E-12	1.84E-11
FISHERMAN	1	6.67E-08	1.74E-10	6.21E-09	1.55E-09	3.49E-10	5.91E-10	3.92E-12	1.37E-11
RESIDENT	1	2.22E-07	4.04E-10	8.78E-09	3.59E-09	9.07E-10	1.97E-09	9.10E-12	4.53E-11
FOR 30 EXPOSURES:									
DERMAL, SPRAY	30	1.52E-08	2.25E-09	4.89E-08	2.00E-08	3.28E-09	1.35E-10	5.07E-11	5.58E-12
VEGETATION CONTACT									
HIKER	30	2.18E-10	3.23E-11	7.02E-10	2.87E-10	4.71E-11	1.93E-12	7.27E-13	8.00E-14
PICKER	30	6.02E-08	8.91E-09	1.94E-07	7.92E-08	1.30E-08	5.33E-10	2.01E-10	2.21E-11
DRINKING WATER	30	1.42E-06	2.10E-09	4.56E-08	1.86E-08	5.09E-09	1.26E-08	4.72E-11	2.89E-10
EATING BERRIES	30	2.62E-06	3.87E-09	8.41E-08	3.44E-08	9.40E-09	2.32E-08	8.71E-11	5.32E-10
EATING VEGETS.	30	5.23E-06	7.73E-09	1.68E-07	6.88E-08	1.88E-08	4.63E-08	1.74E-10	1.06E-09
EATING DEER	30	3.25E-07	5.03E-10	1.09E-08	4.48E-09	1.20E-09	2.88E-09	1.13E-11	6.63E-11
EATING FISH	30	5.67E-07	8.38E-10	9.11E-08	7.46E-09	2.04E-09	5.02E-09	1.89E-11	1.15E-10
Combined Routes of Exposure:									
HIKER	30	1.43E-06	4.38E-09	9.52E-08	3.89E-08	8.42E-09	1.27E-08	9.86E-11	2.94E-10
BERRY PICKER	30	4.11E-06	1.71E-08	3.72E-07	1.52E-07	3.08E-08	3.64E-08	3.86E-10	8.49E-10
HUNTER	30	2.69E-06	6.43E-09	1.40E-07	5.72E-08	1.32E-08	2.38E-08	1.45E-10	5.51E-10
FISHERMAN	30	2.00E-06	5.22E-09	1.86E-07	4.64E-08	1.05E-08	1.77E-08	1.18E-10	4.10E-10
RESIDENT	30	6.66E-06	1.21E-08	2.63E-07	1.08E-07	2.72E-08	5.90E-08	2.73E-10	1.36E-09

Table C-162
 LIFETIME CANCER RISK - EXPOSED PUBLIC FOR LARGE BACKPACK, 60 ACRES, ROUTINE WORST CASE

	EXPOSURES PER LIFETIME	RISK FROM EXCLUSIVE USE OF:							
		AMITROLE	ASULAM	ATRAZINE	BROMACIL	2,4-D	2,4-DP	GLYPHOSATE	PICLORAM
FOR A SINGLE EXPOSURE:									
DERMAL, SPRAY	1	2.44E-09	4.02E-10	4.18E-09	3.21E-09	4.21E-10	1.86E-11	1.08E-11	1.43E-12
VEGETATION CONTACT									
HIKER	1	3.50E-11	5.76E-12	6.00E-11	4.61E-11	6.04E-12	2.67E-13	1.56E-13	2.05E-14
PICKER	1	6.29E-09	1.04E-09	1.08E-08	8.28E-09	1.08E-09	4.79E-11	2.79E-11	3.69E-12
DRINKING WATER	1	1.36E-07	2.24E-10	2.33E-09	1.79E-09	3.91E-10	1.04E-09	6.04E-12	4.43E-11
EATING BERRIES	1	2.63E-07	4.32E-10	4.50E-09	3.45E-09	7.55E-10	2.00E-09	1.17E-11	8.55E-11
EATING VEGETS.	1	5.25E-07	8.65E-10	9.00E-09	6.91E-09	1.51E-09	4.00E-09	2.33E-11	1.71E-10
EATING DEER	1	3.29E-08	5.68E-11	5.91E-10	4.54E-10	9.73E-11	2.51E-10	1.53E-12	1.07E-11
EATING FISH	1	5.44E-08	8.96E-11	4.66E-09	7.16E-10	1.56E-10	4.15E-10	2.42E-12	1.77E-11
Combined Routes of Exposure:									
HIKER	1	1.39E-07	6.31E-10	6.58E-09	5.05E-09	8.18E-10	1.06E-09	1.70E-11	4.58E-11
BERRY PICKER	1	4.07E-07	2.09E-09	2.18E-08	1.67E-08	2.65E-09	3.10E-09	5.65E-11	1.35E-10
HUNTER	1	2.68E-07	8.67E-10	9.03E-09	6.93E-09	1.21E-09	2.04E-09	2.34E-11	8.80E-11
FISHERMAN	1	1.93E-07	7.21E-10	1.12E-08	5.76E-09	9.74E-10	1.47E-09	1.95E-11	6.35E-11
RESIDENT	1	6.64E-07	1.50E-09	1.56E-08	1.20E-08	2.33E-09	5.06E-09	4.04E-11	2.17E-10
FOR 30 EXPOSURES:									
DERMAL, SPRAY	30	7.32E-08	1.21E-08	1.26E-07	9.63E-08	1.26E-08	5.58E-10	3.25E-10	4.29E-11
VEGETATION CONTACT									
HIKER	30	1.05E-09	1.73E-10	1.80E-09	1.38E-09	1.81E-10	8.00E-12	4.67E-12	6.16E-13
PICKER	30	1.89E-07	3.11E-08	3.24E-07	2.48E-07	3.25E-08	1.44E-09	8.38E-10	1.11E-10
DRINKING WATER	30	4.08E-06	6.72E-09	7.00E-08	5.37E-08	1.17E-08	3.11E-08	1.81E-10	1.33E-09
EATING BERRIES	30	7.88E-06	1.30E-08	1.35E-07	1.04E-07	2.26E-08	6.00E-08	3.50E-10	2.57E-09
EATING VEGETS.	30	1.58E-05	2.59E-08	2.70E-07	2.07E-07	4.53E-08	1.20E-07	7.00E-10	5.13E-09
EATING DEER	30	9.87E-07	1.70E-09	1.77E-08	1.36E-08	2.92E-09	7.52E-09	4.59E-11	3.22E-10
EATING FISH	30	1.63E-06	2.69E-09	1.40E-07	2.15E-08	4.69E-09	1.24E-08	7.25E-11	5.32E-10
Combined Routes of Exposure:									
HIKER	30	4.16E-06	1.89E-08	1.97E-07	1.51E-07	2.45E-08	3.17E-08	5.11E-10	1.37E-09
BERRY PICKER	30	1.22E-05	6.28E-08	6.54E-07	5.02E-07	7.96E-08	9.31E-08	1.69E-09	4.05E-09
HUNTER	30	8.04E-06	2.60E-08	2.71E-07	2.08E-07	3.64E-08	6.13E-08	7.02E-10	2.64E-09
FISHERMAN	30	5.79E-06	2.16E-08	3.37E-07	1.73E-07	2.92E-08	4.41E-08	5.84E-10	1.90E-09
RESIDENT	30	1.99E-05	4.49E-08	4.67E-07	3.59E-07	.98E-08	1.52E-07	1.21E-09	6.51E-09

Table C-163
 LIFETIME CANCER RISK - EXPOSED PUBLIC FOR SMALL RIGHT OF WAY, ROUTINE REALISTIC CASE

	EXPOSURES PER LIFETIME	RISK FROM EXCLUSIVE USE OF:							
		AMITROLE	ASULAM	ATRAZINE	BROMACIL	2,4-D	2,4-DP	GLYPHOSATE	PICLORAM
FOR A SINGLE EXPOSURE:									
DERMAL, SPRAY	1	9.83E-11	2.91E-11	3.16E-10	1.29E-10	2.65E-11	1.09E-12	4.36E-13	3.60E-14
VEGETATION CONTACT									
HIKER	1	1.41E-12	4.17E-13	4.53E-12	1.85E-12	3.80E-13	1.56E-14	6.26E-15	5.17E-16
PICKER	1	5.32E-10	1.57E-10	1.71E-09	6.99E-10	1.43E-10	5.89E-12	2.36E-12	1.95E-13
DRINKING WATER	1	2.12E-08	6.27E-11	6.81E-10	2.79E-10	9.52E-11	2.35E-10	9.42E-13	4.32E-12
EATING BERRIES	1	2.91E-08	8.61E-11	9.36E-10	3.83E-10	1.31E-10	3.23E-10	1.29E-12	5.93E-12
EATING VEGETS.	1	5.83E-08	1.72E-10	1.87E-09	7.66E-10	2.62E-10	6.45E-10	2.59E-12	1.19E-11
EATING DEER	1	3.50E-09	1.07E-11	1.17E-10	4.77E-11	1.61E-11	3.87E-11	1.61E-13	7.12E-13
EATING FISH	1	8.48E-09	2.51E-11	1.36E-09	1.12E-10	3.81E-11	9.39E-11	3.77E-13	1.73E-12
Combined Routes of Exposure:									
HIKER	1	2.12E-08	9.22E-11	1.00E-09	4.10E-10	1.22E-10	2.36E-10	1.38E-12	4.35E-12
BERRY PICKER	1	5.10E-08	3.35E-10	3.64E-09	1.49E-09	3.96E-10	5.64E-10	5.03E-12	1.05E-11
HUNTER	1	3.34E-08	1.31E-10	1.43E-09	5.85E-10	1.80E-10	3.70E-10	1.97E-12	6.83E-12
FISHERMAN	1	2.98E-08	1.17E-10	2.36E-09	5.22E-10	1.60E-10	3.30E-10	1.76E-12	6.08E-12
RESIDENT	1	7.96E-08	2.64E-10	2.87E-09	1.18E-09	3.84E-10	8.81E-10	3.97E-12	1.62E-11
FOR 30 EXPOSURES:									
DERMAL, SPRAY	30	2.95E-09	8.72E-10	9.47E-09	3.88E-09	7.94E-10	3.26E-11	1.31E-11	1.08E-12
VEGETATION CONTACT									
HIKER	30	4.23E-11	1.25E-11	1.36E-10	5.56E-11	1.14E-11	4.68E-13	1.88E-13	1.55E-14
PICKER	30	1.60E-08	4.72E-09	5.13E-08	2.10E-08	4.30E-09	1.77E-10	7.08E-11	5.85E-12
DRINKING WATER	30	6.36E-07	1.88E-09	2.04E-08	8.37E-09	2.86E-09	7.04E-09	2.82E-11	1.29E-10
EATING BERRIES	30	8.74E-07	2.58E-09	2.81E-08	1.15E-08	3.92E-09	9.68E-09	3.88E-11	1.78E-10
EATING VEGETS.	30	1.75E-06	5.17E-09	5.62E-08	2.30E-08	7.85E-09	1.94E-08	7.76E-11	3.56E-10
EATING DEER	30	1.05E-07	3.22E-10	3.50E-09	1.43E-09	4.82E-10	1.16E-09	4.84E-12	2.14E-11
EATING FISH	30	2.54E-07	7.52E-10	4.09E-08	3.35E-09	1.14E-09	2.82E-09	1.13E-11	5.18E-11
Combined Routes of Exposure:									
HIKER	30	6.39E-07	2.77E-09	3.01E-08	1.23E-08	3.66E-09	7.07E-09	4.15E-11	1.31E-10
BERRY PICKER	30	1.53E-06	1.01E-08	1.09E-07	4.47E-08	1.19E-08	1.69E-08	1.51E-10	3.14E-10
HUNTER	30	1.00E-06	3.94E-09	4.29E-08	1.75E-08	5.39E-09	1.11E-08	5.92E-11	2.05E-10
FISHERMAN	30	8.93E-07	3.52E-09	7.09E-08	1.56E-08	4.80E-09	9.89E-09	5.28E-11	1.82E-10
RESIDENT	30	2.39E-06	7.93E-09	8.62E-08	3.53E-08	1.5E-08	2.64E-08	1.19E-10	4.86E-10

Table C-164
 LIFETIME CANCER RISK - EXPOSED PUBLIC FOR LARGE RIGHT OF WAY, ROUTINE WORST CASE

	EXPOSURES PER LIFETIME	RISK FROM EXCLUSIVE USE OF:							
		AMITROLE	ASULAM	ATRAZINE	BROMACIL	2,4-D	2,4-DP	GLYPHOSATE	PICLORAM
FOR A SINGLE EXPOSURE:									
DERMAL, SPRAY VEGETATION CONTACT	1	1.37E-09	2.10E-10	3.11E-09	1.12E-09	1.51E-10	7.57E-12	3.79E-12	2.50E-13
HIKER	1	1.96E-11	3.02E-12	4.46E-11	1.61E-11	2.17E-12	1.09E-13	5.44E-14	3.59E-15
PICKER	1	3.52E-09	5.43E-10	8.02E-09	2.90E-09	3.89E-10	1.95E-11	9.78E-12	6.45E-13
DRINKING WATER	1	1.13E-07	1.75E-10	2.58E-09	9.33E-10	2.09E-10	6.28E-10	3.15E-12	1.15E-11
EATING BERRIES	1	1.77E-07	2.72E-10	4.02E-09	1.45E-09	3.25E-10	9.78E-10	4.90E-12	1.80E-11
EATING VEGETS.	1	3.53E-07	5.44E-10	8.05E-09	2.91E-09	6.51E-10	1.96E-09	9.81E-12	3.60E-11
EATING DEER	1	2.15E-08	3.44E-11	5.09E-10	1.84E-10	4.05E-11	1.19E-10	6.21E-13	2.19E-12
EATING FISH	1	4.54E-08	6.99E-11	5.17E-09	3.73E-10	8.36E-11	2.51E-10	1.26E-12	4.62E-12
Combined Routes of Exposure:									
HIKER	1	1.15E-07	3.88E-10	5.74E-09	2.07E-09	3.62E-10	6.36E-10	7.00E-12	1.18E-11
BERRY PICKER	1	2.95E-07	1.20E-09	1.77E-08	6.41E-09	1.07E-09	1.63E-09	2.16E-11	3.04E-11
HUNTER	1	1.92E-07	5.19E-10	7.68E-09	2.77E-09	5.13E-10	1.07E-09	9.36E-12	1.97E-11
FISHERMAN	1	1.60E-07	4.58E-10	1.09E-08	2.45E-09	4.46E-10	8.87E-10	8.26E-12	1.64E-11
RESIDENT	1	4.68E-07	9.33E-10	1.38E-08	4.98E-09	1.01E-09	2.59E-09	1.68E-11	4.78E-11
FOR 30 EXPOSURES:									
DERMAL, SPRAY VEGETATION CONTACT	30	4.10E-08	6.31E-09	9.33E-08	3.37E-08	4.53E-09	2.27E-10	1.14E-10	7.51E-12
HIKER	30	5.88E-10	9.06E-11	1.34E-09	4.84E-10	6.50E-11	3.26E-12	1.63E-12	1.08E-13
PICKER	30	1.06E-07	1.63E-08	2.41E-07	8.69E-08	1.17E-08	5.85E-10	2.93E-10	1.94E-11
DRINKING WATER	30	3.40E-06	5.24E-09	7.75E-08	2.80E-08	6.27E-09	1.88E-08	9.45E-11	3.46E-10
EATING BERRIES	30	5.30E-06	8.16E-09	1.21E-07	4.36E-08	9.76E-09	2.93E-08	1.47E-10	5.40E-10
EATING VEGETS.	30	1.06E-05	1.63E-08	2.41E-07	8.72E-08	1.95E-08	5.87E-08	2.94E-10	1.08E-09
EATING DEER	30	6.44E-07	1.03E-09	1.53E-08	5.51E-09	1.22E-09	3.57E-09	1.86E-11	6.56E-11
EATING FISH	30	1.36E-06	2.10E-09	1.55E-07	1.12E-08	2.51E-09	7.54E-09	3.78E-11	1.39E-10
Combined Routes of Exposure:									
HIKER	30	3.45E-06	1.16E-08	1.72E-07	6.22E-08	1.09E-08	1.91E-08	2.10E-10	3.54E-10
BERRY PICKER	30	8.85E-06	3.50E-08	5.32E-07	1.92E-07	3.22E-08	4.90E-08	6.49E-10	9.13E-10
HUNTER	30	5.77E-06	1.56E-08	2.30E-07	8.32E-08	1.54E-08	3.20E-08	2.81E-10	5.91E-10
FISHERMAN	30	4.81E-06	1.37E-08	3.27E-07	7.34E-08	1.34E-08	2.66E-08	2.48E-10	4.93E-10
RESIDENT	30	1.40E-05	2.80E-08	4.14E-07	1.49E-07	3.04E-08	7.78E-08	5.04E-10	1.43E-09

Table C-165
LIFETIME CANCER RISK - EXPOSED PUBLIC FOR ACCIDENTAL WORST CASE SPRAYING

	EXPOSURES PER LIFETIME	RISK FROM EXCLUSIVE USE OF:							
		AMITROLE	ASULAM	ATRAZINE	BROMACIL	2,4-D	2,4-DP	GLYPHOSATE	PICLORAM
FOR A SINGLE EXPOSURE:									
DERMAL, SPRAY	1	9.51E-07	1.46E-07	2.16E-06	7.82E-07	1.05E-07	5.26E-09	2.64E-09	4.35E-10
VEGETATION CONTACT									
HIKER	1	1.36E-08	2.10E-09	3.11E-08	1.12E-08	1.51E-09	7.55E-11	3.79E-11	6.25E-12
PICKER	1	2.45E-06	3.77E-07	5.58E-06	2.01E-06	2.71E-07	1.36E-08	6.80E-09	1.12E-09
DRINKING WATER	1	3.34E-05	5.15E-08	7.61E-07	2.75E-07	6.16E-08	1.85E-07	9.28E-10	8.51E-09
EATING BERRIES	1	2.66E-05	4.09E-08	6.05E-07	2.18E-07	4.89E-08	1.47E-07	7.37E-10	6.76E-09
EATING VEGETS.	1	5.51E-05	8.49E-08	1.26E-06	4.53E-07	1.02E-07	3.05E-07	1.53E-09	1.40E-08
EATING DEER	1	5.34E-06	9.17E-09	1.36E-07	4.89E-08	1.05E-08	2.96E-08	1.65E-10	1.36E-09
EATING FISH	1	1.34E-05	2.06E-08	1.52E-06	1.10E-07	2.46E-08	7.41E-08	3.71E-10	3.40E-09
Combined Routes of Exposure:									
HIKER	1	3.44E-05	2.00E-07	2.96E-06	1.07E-06	1.68E-07	1.90E-07	3.61E-09	8.95E-09
BERRY PICKER	1	6.34E-05	6.16E-07	9.11E-06	3.29E-06	4.86E-07	3.51E-07	1.11E-08	1.68E-08
HUNTER	1	7.28E-05	2.67E-07	3.95E-06	1.43E-06	2.45E-07	4.03E-07	4.82E-09	1.87E-08
FISHERMAN	1	4.78E-05	2.21E-07	4.48E-06	1.18E-06	1.93E-07	2.65E-07	3.98E-09	1.24E-08
RESIDENT	1	8.96E-05	2.85E-07	4.21E-06	1.52E-06	2.70E-07	4.96E-07	5.14E-09	2.30E-08
FOR 30 EXPOSURES:									
DERMAL, SPRAY	30	2.85E-05	4.39E-06	6.49E-05	2.34E-05	3.15E-06	1.58E-07	7.92E-08	1.31E-08
VEGETATION CONTACT									
HIKER	30	4.09E-07	6.30E-08	9.32E-07	3.36E-07	4.52E-08	2.27E-09	1.14E-09	1.87E-10
PICKER	30	7.35E-05	1.13E-05	1.67E-04	6.04E-05	8.12E-06	4.07E-07	2.04E-07	3.37E-08
DRINKING WATER	30	1.00E-03	1.55E-06	2.28E-05	8.25E-06	1.85E-06	5.55E-06	2.78E-08	2.55E-07
EATING BERRIES	30	7.97E-04	1.23E-06	1.81E-05	6.55E-06	1.47E-06	4.41E-06	2.21E-08	2.03E-07
EATING VEGETS.	30	1.65E-03	2.55E-06	3.77E-05	1.36E-05	3.05E-06	9.16E-06	4.59E-08	4.21E-07
EATING DEER	30	1.60E-04	3.75E-07	4.07E-06	1.47E-06	3.15E-07	8.87E-07	4.96E-09	4.08E-08
EATING FISH	30	4.01E-04	6.18E-07	4.57E-05	3.30E-06	7.39E-07	2.22E-06	1.11E-08	1.02E-07
Combined Routes of Exposure:									
HIKER	30	1.03E-03	6.00E-06	8.87E-05	3.20E-05	5.04E-06	5.71E-06	1.08E-07	2.69E-07
BERRY PICKER	30	1.90E-03	1.85E-05	2.73E-04	9.87E-05	1.46E-05	1.05E-05	3.33E-07	5.05E-07
HUNTER	30	2.18E-03	8.02E-06	1.19E-04	4.28E-05	7.34E-06	1.21E-05	1.45E-07	5.62E-07
FISHERMAN	30	1.43E-03	6.62E-06	1.34E-04	3.53E-05	5.78E-06	7.94E-06	1.19E-07	3.71E-07
RESIDENT	30	2.68E-03	8.55E-06	1.26E-04	4.56E-05	8.09E-06	1.49E-05	1.54E-07	6.90E-07

Table C-166
 LIFETIME CANCER RISK - EXPOSURE DUE TO SPILLS

	EXPOSURES PER LIFETIME	RISK FROM EXCLUSIVE USE OF:							
		AMITROLE	ASULAM	ATRAZINE	BROMACIL	2,4-D	2,4-DP	GLYPHOSATE	PICLORAM
FOR A SINGLE EXPOSURE:									
SPILLS ONTO SKIN:									
CONCENTRATE	1	3.42E-04	1.69E-04	1.46E-03	4.50E-04	1.47E-04	9.09E-06	2.28E-06	2.51E-07
SPRAY MIX	1	6.84E-05	1.41E-05	1.47E-04	2.25E-05	1.47E-05	3.79E-07	3.80E-07	6.26E-08
SPILLS INTO WATER (1 LITER DRUNK):									
POND, HELO.	1	2.10E-05	3.23E-08	4.50E-07	---	7.54E-08	1.16E-07	1.16E-09	1.07E-08
RESERV., HELO.	1	6.56E-07	1.35E-09	1.41E-08	---	2.36E-09	3.63E-09	3.64E-11	3.34E-10
POND, TRUCK	1	4.20E-04	8.64E-07	8.99E-06	1.38E-06	1.51E-06	2.32E-06	2.33E-08	2.14E-07
RESERV., TRUCK	1	1.31E-05	2.70E-08	2.81E-07	4.31E-08	4.71E-08	7.26E-08	7.28E-10	6.68E-09

Appendix D

Human Health Risk Assessment (Quantitative)



References

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All documents referenced in the Supplement are available at universities, at libraries, or from Federal agencies such as the Forest Service or the U.S. Environmental Protection Agency (EPA). All EPA documents can be obtained through requests to EPA's Freedom of Information Office, Washington, D.C. 20460.

In the text of this document references are cited in parentheses using the author-year system of citation. When an organization (such as a Government agency or scientific society) is listed as the author in the parenthetical citation, an acronym or an abbreviated form of that organization's name generally is used in place of its full title. Below is a list of acronyms and abbreviations that are used in citations, along with the corresponding full titles that are used in this reference section.

BLM	U.S. Department of the Interior, Bureau of Land Management
CDFA	California Department of Food and Agriculture
DHHS	U.S. Department of Health and Human Services
DOE	U.S. Department of Energy
EPA	U.S. Environmental Protection Agency
HSDB	Hazardous Substances Data Bank
NCI	National Cancer Institute
NRC	National Research Council
OSTP	U.S. Office of Science and Technology Policy
USDA	U.S. Department of Agriculture
WSSA	Weed Science Society of America

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Appendix D

**Human Health
Risk Assessment
(Quantitative)**



Glossary



GLOSSARY

A

- Acceptable Daily Intake (ADI).** The maximum dose of a substance that is anticipated to be without lifetime risk to humans when taken daily.
- Acetone.** A colorless, volatile liquid that is useful as a solvent. It is found in the blood and urine when fats are not properly metabolized.
- Acid Equivalent (a.e.).** The amount of active ingredient expressed in terms of the parent acid.
- Active Ingredient (a.i.).** The chemical in a herbicide that is primarily responsible for its phytotoxic or herbicidal action.
- Acute Toxicity.** The quality or potential of a substance to cause injury or illness shortly after exposure to a relatively large dose.
- Adenoma.** An abnormal growth of glandular tissue.
- Adenocarcinomatous.** Referring to a malignant (cancerous) adenoma.
- Adsorption.** Adhesion of substances to the surfaces of solids or liquids. Technically, the attraction of ions of compounds to the surfaces of solids or liquids.
- Ames Assay.** A type of short-term test using bacteria in laboratory cultures to assess the mutagenic potential of a substance.
- Assay.** A test or measurement used to evaluate a characteristic of a chemical. See Bioassay.
- Atopic.** Displaced or not located in the usual position.

B

- Bacteriophage.** A group of transmissible agents (bacterial viruses) capable of destroying certain bacterial cells.
- Bile Ducts.** Passages that convey the bile from the liver and gall bladder to the small intestine.
- Bioaccumulation.** The process of a plant or animal selectively taking in or storing a persistent substance. Over a period of time, a higher concentration of the substance is found in the organism than in the organism's environment.
- Bioassay.** A method for quantitatively determining the concentration of a substance by its effect on a suitable animal, plant, or microorganism under controlled conditions.

D Human Health Risk Assessment (Quantitative)

Boom (herbicide spray). A tubular metal device that conducts an herbicide mixture from a tank to a series of spray nozzles. It may be mounted beneath a helicopter or a fixed-wing aircraft or behind a tractor.

Buffer Strip/Zone. A strip of vegetation that is left or managed to reduce the impact that a treatment or action on one area would have on another area.

C

Carcinogenic. Capable of producing or inciting cancer.

Carcinoma. A malignant or cancerous tumor.

Chemical Degradation. The breakdown of a chemical substance into simpler components through chemical reactions.

Cholangiofibrosis. An abnormal formation of fibrous tissue within the bile duct of the gall bladder.

Chromosome. Microscopic structures within the cell that are composed of DNA and the genes (hereditary determiners).

Chronic (effects or toxicity). Having poisonous or deleterious effects from prolonged exposure or repeated administration of a chemical.

Conifer. An order of the Gymnospermae, comprising a wide range of trees, mostly evergreens that bear cones and have needle-shaped or scalelike leaves; timber commercially identified as softwood.

Crossing Over. The breaking and exchanging of parts of chromosomes between chromosome pairs during cell division.

Cytogenetic. Refers to the structure or function of chromosomes within cells.

D

Degradation. See chemical degradation.

Dermal Exposure. That portion of an amount of toxic substance that an organism receives as a result of the substance coming into contact with the organism's body surface.

Dislodgeable Residue. A pesticide residue that can be removed from surfaces such as foliage by physical contact.

DNA. Deoxyribonucleic acid. Any of various nucleic acids that are the molecular basis of heredity in many organisms.

Dominant Lethal Assay. A toxicity test whereby a male animal (usually a rodent) is exposed to a chemical substance and later sequentially mated with two female animals. The females are sacrificed, and the number and status of the fetuses is recorded.

Dose. The amount of chemical administered or received by an organism, generally at a given point in time.

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

E

Ecosystem. An interacting system of organisms considered together with their environment; for example, marsh, watershed, and lake ecosystems.

Environmental Impact Statement (EIS). A formal document to be filed with the Environmental Protection Agency that considers significant environmental impacts expected from implementation of a major Federal action.

E. coli or Escherichia coli. A common species of bacteria used in many areas of biological research, including mutagenicity testing.

Ester. A compound formed by the reaction of an acid and an alcohol, generally accompanied by the elimination of water.

Exposure Analysis. The estimation of the amount of chemical that is in an organism's environment and available for uptake into the body.

F

F₀. In genetics and reproduction studies, it pertains to the first parents' generation.

F₁. In genetics, it refers to the first generation of offspring from the F₀ generation.

Fate. The course of an herbicide in an ecosystem or biological system after it has been applied; including metabolism, microbial degradation, leaching, and photodecomposition.

Fetotoxic. Capable of producing adverse effects in a developing fetus.

Fibroblast. Any cell from which connective tissue is developed.

Formulation. A chemical mixture that includes a certain percentage of active ingredient (technical chemical) with an inert carrier.

D Human Health Risk Assessment (Quantitative)

G

Gavage. Feeding by way of a tube inserted into the stomach.

Gene. The basic unit of heredity. Each gene occupies a specific place (locus) on a chromosome.

Genotoxic. Harmful to genetic material (DNA).

Germ Cell. A functional sex cell that combines with the opposite sex cell for fertilization, for example, sperm, egg.

Global 82. A computer program by Howe and Crump (1982) used to fit the multistage or one-hit models to experimental cancer data.

H

Half-Life. The amount of time required for half of a compound to degrade.

Hazard. The characteristic of an item or substance that renders it capable of producing injury or illness.

Hazard Analysis. The determination of whether a particular chemical is or is not causally linked to particular harmful effects.

HDT. Highest dose tested.

Hectare (ha). 10,000 square meters, or approximately 2.47 acres.

HeLa Cell Line. A human cell line originally derived from cancerous breast cells.

Hematocrit. The percentage by volume of red blood cells in a given volume of blood.

Hemoglobin. The iron-containing compound in red blood cells that functions to carry oxygen from the lungs to the tissues.

Hepatoma. A tumor of the liver.

Herbaceous. A plant that does not develop persistent woody tissue above the ground.

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

Heritable. Capable of being passed on from parents to offspring.

Histology. The study of the microscopic structure of tissue.

Histopathologic. Referring to tissue changes characteristic of disease.

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

Hyperplasia. An excessive proliferation of normal cells in the tissue of an organ.

Hypertrophy. An increase in size of an organ or structure that does not involve tumor formation.

Hypohatchet. A tool used to inject herbicide into a tree trunk or woody stem.

I

In Vitro. Pertaining to a test that is conducted outside the living body and in an artificial environment such as a test tube or petri dish.

In Vivo. Pertaining to a test that is performed within the living body of the organism.

Intraperitoneal. Related to a structure or process occurring within the peritoneum, a membranous lining of the body cavity.

Intravenous. Within or into a vein.

K

Kilogram (kg). One thousand grams; or approximately 2.2 pounds.

L

Label. All printed material on or attached to a pesticide container as required by law.

Latency Period. The time between a stimulus and its response.

LC50. A lethal concentration rate at which 50 percent of the test animals will be killed. It is usually used in the testing of fish or other aquatic animals.

LD50. The dosage of toxicant, expressed in milligrams of toxicant per kilogram of animal body weight, required to kill 50 percent of the animals in a test population when given orally.

LDT. Lowest dose tested.

Leach. Usually refers to the movement of chemicals through soil by water; may also refer to the movement of herbicides out of leaves, stems, or roots into the air or soil.

Least Squares Estimation. A mathematical approach used to fit a straight line (or other models) so that the sum of the squares of the vertical distances of the data points from the line will be a minimum.

D Human Health Risk Assessment (Quantitative)

Lowest Effect Level (LEL). The lowest dose tested that results in an effect in a test organism.

Linear Regression. A mathematical procedure used to draw a straight line that best fits a set of data points on a graph.

Log-Probit Model. An equation used to describe the relationship between dose and the probability of contracting cancer. This equation can be derived by assuming that humans (or animals) have various susceptibilities, but that at very low doses none has a significant risk.

Lymphocyte. A cell of the lymphatic system, or a special type of white blood cell.

Lymphoma. A general term for the growth of new tissue in the lymphatic system.

M

Malignant. Used in reference to a tumor; indicating the presence of cancer and tending to grow worse and spread within an organism.

Margin of Safety (MOS). The ratio between the no-observed-effect level (NOEL) and the estimated dose.

Metabolism. The chemical changes in living cells by which energy is provided for vital processes and new material is assimilated.

Metabolite. A product of the chemical changes in living cells that provide energy and assimilate new material.

Microbial Degradation. The breakdown of a chemical substance into simpler components by bacteria or other microorganisms.

Microgram (ug). One millionth of a gram.

Mitigation Measures. Means taken to avoid, compensate for, rectify, or reduce the potential adverse impacts of a proposed action.

Mitotic. Pertaining to the process of cell division that results in two cells having the same number of chromosomes as the original cell.

Multistage Model. An equation used to describe the relationship between dose and the probability of contracting cancer. This equation, commonly used by EPA, assumes that several successive events must occur to produce cancer.

Mutagen. A substance that tends to increase the frequency or extent of genetic mutations (changes in hereditary material).

Mutagenic. Capable of producing genetic defects in an organism.

N

- Necrosis.** Death of a cell or group of cells as a result of injury, disease, or other pathologic state.
- Neoplastic.** Pertaining to new abnormal tissue formation (neoplasms).
- Neuropathy.** Any disease affecting neurons, the fundamental functional units of nervous tissues.
- NOEL (no-observed-effect level).** The dose level at which no toxic effects are observed in a test organism.
- Noxious Weed.** A plant regulated or identified by law as being undesirable, troublesome, and difficult to control.
- Nucleic Acid.** A group of complex molecules found in cells, composed of phosphoric acid, sugars, and nitrogen bases. Includes DNA and RNA.

O

- ODT.** Only dose tested.
- Omphalocele.** A congenital hernia of the navel.
- Oncogenic.** Capable of producing or inducing tumors in animals, either benign (noncancerous) or malignant (cancerous).
- Oncology.** The branch of medicine which studies tumors.
- One-Hit Model.** An equation used to describe the relationship between dose and the probability of contracting cancer. This equation, used at one time by EPA, predicts the greatest cancer probability at low doses of all commonly used models.
- Organic Material.** An accumulation of decayed and resynthesized plant and animal residues with a high capacity for holding water and nutrients.
- Ossification.** The formation of bone.

P

- Papillary.** Resembling or composed of small protuberances or elevations.
- Parenteral.** Injection of a substance into the body through any route other than the digestive tract.
- Particulates.** Finely divided solid or liquid particles in the air or in an emission; includes dust, smoke fumes, mist, spray, and fog.

D Human Health Risk Assessment (Quantitative)

Pathology. The study of the nature and cause of disease with respect to functional and structural changes.

Persistence. The resistance of a pesticide to metabolism and environmental degradation.

Pesticide. As defined by FIFRA, any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest, and any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant.

Photochemically Reactive. A property of substances or particles whose structures may be changed when solar energy is absorbed.

Photolysis (photodecomposition). The breakdown of a substance, especially a chemical compound, into simpler components by the action of radiant energy such as sunlight.

Photosynthesis. Formation of carbohydrates in the tissues of plants exposed to light.

Phytotoxic. Injurious or lethal to plants.

Pituitary Gland. A small, oval endocrine gland attached by a stalk to the base of the brain and consisting of an anterior and a posterior lobe; it secretes hormones that influence body growth, metabolism, and so forth; hypophysis.

ppm (parts per million). A unit for measuring the concentration of a substance, such as a pesticide, in a carrier medium, such as food or water. For example, where the concentration is 1 ppm, the weight of the substance is 1 millionth the weight of the carrier medium; thus, 1 ppm is equal to 1 milligram of substance per kilogram of food or organism body weight, and it is equal to 1 milligram of substance per liter of water.

Proliferation. The rapid and repeated reproduction of new cells.

Pulmonary. Concerning or involving the lungs.

Pyrolysis. Chemical breakdown caused in the process of combustion.

R

Recreation Visitor Day (RVD). Twelve visitor hours, which may be aggregated continuously, intermittently, or simultaneously for one or more persons.

Reentry. The return of a worker to an area that has recently been treated with a pesticide.

Renal Tubule. The functional unit of the kidney where urine is formed; nephron.

Residue. The quantity of a herbicide or its metabolites remaining in or on soil, water, plants, animals, or surfaces.

Resorption. Act of removal by absorption.

Risk. The likelihood that a given exposure to an item or substance that presents a certain hazard will produce illness or injury.

Risk Analysis. The description of the nature and often the magnitude of risk to organisms, including attendant uncertainty.

Runoff. That part of precipitation, as well as any other flow contributions, that appears in surface streams, either perennial or intermittent.

S

Safety Factor. A factor conventionally used to extrapolate human tolerances for chemical agents from no-observed-effect levels in animal test data.

Salmonella. A genus of bacteria used in mutagenicity testing.

Sediment. Organic matter or soil that settles to the bottom of a liquid.

Shrub. A plant with persistent woody stems and relatively low growth form; usually produces several basal shoots as opposed to a single bole; differs from a tree by its low stature and nonarborescent form.

Silviculture. The branch of forestry dealing with the care, development, and reproduction of forest trees or stands of timber.

Sister Chromatid Exchange (SCE). A short-term test conducted with laboratory cell cultures to assess the genetic damage caused by a chemical or physical influence.

Spot Treatment. Application of a herbicide to a small selected area as opposed to broadcast application.

Subchronic. The effects observed from doses that are of intermediate duration, usually 3 months (90 days).

Subcutaneous. Beneath the skin, or to be introduced beneath the skin.

Surfactant. A material that improves the emulsifying, dispersing, spreading, wetting, or other surface-modifying properties of liquids.

Systemic Herbicide. An herbicide that is moved within the plant. In a more restricted sense, refers to herbicides that are applied to the foliage and move downward through the living tissue to underground parts.

D Human Health Risk Assessment (Quantitative)

Systemic Toxicity. Effects produced as a result of the distribution of a poison or foreign substance from the point of exposure to a distant site within the body.

T

T₃. Triiodothyronine. A chemical measured in tests which evaluate the functioning of the thyroid gland.

T₄. Tetraiodothyronine. A chemical measured in tests which evaluate the functioning of the thyroid gland.

Teratogen. A substance tending to cause developmental malformations in unborn human or animal offspring.

Teratogenesis. The development of abnormal structures in an embryo.

Teratogenic. Capable of producing or inciting the development of malformations in an embryo.

Teratology. The study of malformations in organisms.

Thiourea. A colorless crystalline form of urea containing sulfur in place of oxygen.

Thymus. A relatively small organ located in the upper chest that is important in the development of the immune system in newborn and young animals.

Thyroid Gland. A large, ductless gland lying in front of and on either side of the trachea and secreting thyroxine which regulates the growth of the body.

Thyroid Stimulating Hormone (TSH). A chemical secreted by the pituitary gland intended to cause the thyroid gland to produce its hormones.

Toxicity. A characteristic of a substance that makes it poisonous.

Toxicology. The science dealing with the study of the adverse biological effects of chemicals.

Tumor. A new growth of tissue that forms an abnormal mass and performs no physiologic function. It usually develops independent of and unrestrained by the normal principles of biological growth.

Tumorigenesis. The formation and/or development of a tumor (oncogenesis).

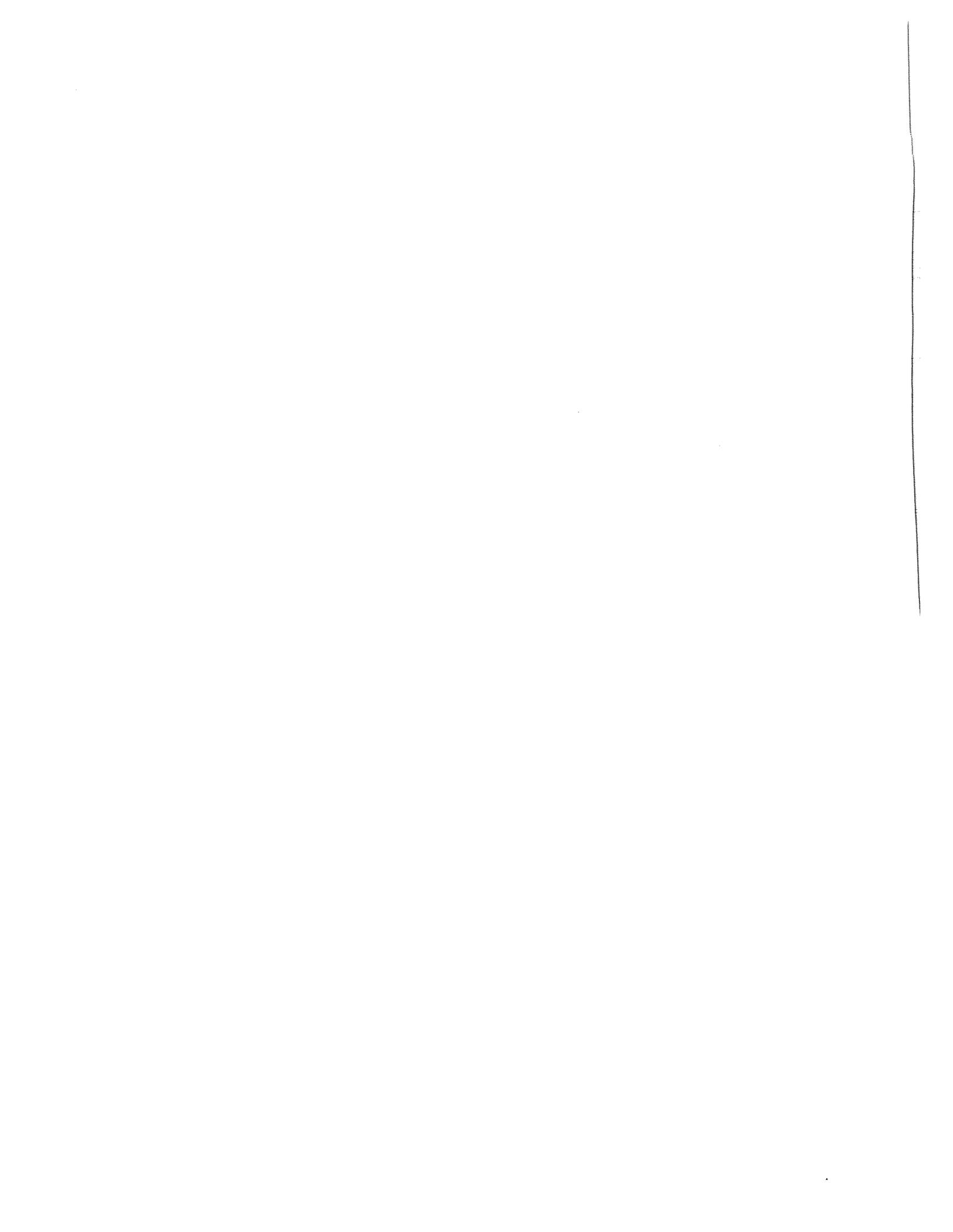
V

Volatility. The quality of evaporating readily at normal temperatures and pressures.

Volatilization. The vaporizing or evaporating of a chemical substance.

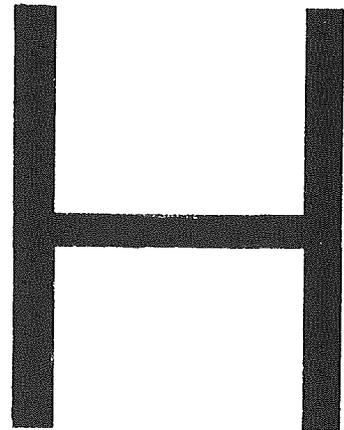
W

Wettable Powder (WP). A finely divided dry formulation that can be readily suspended in water.



Appendix H

Resource Programs and Human Health Risk Assessment (Qualitative)





Appendix H

**Human Health
Risk Assessment
(Qualitative)**



Section 1

**Qualitative Risk
Assessment**

Qualitative Risk Assessment

Why a Qualitative Risk Assessment?

Human health risk management by the U.S. Forest Service has been troubled by strongly conflicting views on the potential for health risk in vegetation management. Various sides embrace very different scientific judgments and policy choices on both the risk assessment and risk management levels. The debate, however, has not generally recognized these differences, and has been argued on an item by item, right vs. wrong basis.

Part of the problem is that there is a great deal of uncertainty in the data on health effects of herbicides. This uncertainty has to be bridged with human judgment. These controversial decisions have not been clearly presented, and perceived health risks have become a major focus of public input and concern.

However, by more clearly stating the various unknowns, and the limits of our judgments, we hope to clarify these issues. Thus, the concept of a qualitative risk assessment. We hope to put equal emphasis upon the information the data contains and the quality of that information. We will avoid stating numerical risks where we do not have confidence in the numbers.

The Debate

Risk assessments face two types of information gaps gaps in test data and gaps in testing theory. Actually, it is the interaction of the two that makes our work so uncertain. The lack of accurate measurement tools makes the task of gathering information much more difficult.

Looking at the Uncertainty

It is important to understand that the biological models we use to measure health risks are very simple compared to the complexity of life. When we try to measure the effect of a chemical on any living organisms, individual variability is extremely large.

Because of this biological variation, a dose that may seriously affect one test animal may produce no observable effect on another of the same species. To deal with this individual variability, we have developed methods of statistically measuring the probability of observing an effect in a test population exposed to a chemical.

In an effort to evaluate the cancer potency of various chemicals, a group of researchers (Gold et al. 1984) reviewed over 3,000 long-term animal experiments for 770 different chemicals. They evaluated the dose that would cause 50 percent of the test animals to contract cancer (Tumor Dose 50), and found a ten million-fold variation in potencies between the various chemicals, and a thousand-fold variation within some individual chemicals.

This information tells us that toxicity studies are useful because the variation in potency in tests for a particular substance is small compared to the variation between substances. In other words, we can make some distinction between the carcinogenic potency of various chemicals.

However, this also demonstrates that the results of different studies evaluating the cancer potency of a single chemical could disagree by a factor of 1,000. This wide range might be due to species differences, different methods of administering the chemicals, or other factors. Whatever the reason, we must use caution in trying to quantify specific toxicity using published studies.

Two Types of Errors

Much of the disagreement around human health risk assessment is based upon how to weigh studies showing differing results. Because there is biological variability, it is unreasonable to expect that all test results will agree. Statistical methods allow for a certain number of false conclusions.

When testing a substance for toxicity, it is usual to start with the hypothesis that assumes no effect the null hypothesis. Statistical methods are applied to the test results to determine if the null hypothesis is consistent with the data. If the null hypothesis is not too discordant with the data, it cannot be rejected, and the study is considered negative. If it is discordant with the data, then it is rejected for an alternative hypothesis, and the test is considered positive.

Thus, when we use statistical tests to determine whether or not an effect occurs (such as whether or not a substance is a carcinogen), there are two types of errors that can be made. First, the null hypothesis may be rejected, and the conclusion made that the chemical does cause cancer when, in fact, it does not. This is called a false positive.

The second type of error occurs when the null hypothesis is not rejected. The test is then considered negative, and the conclusion may be made that the chemical does not cause cancer, when it actually does. This is called a false negative.

Both false positives and false negatives are extremely important types of errors, but their treatment by the scientific community has been inconsistent. Most authors report the probability of making a false positive conclusion, but not the probability of a false negative conclusion. This may lead readers to discount the importance of false negatives.

On the other hand, those involved in developing risk assessment and risk management policies frequently consider false negative conclusions more costly than false positives. For example, Lave and Omenn (1986) make the assumption that, in evaluating chemicals for

Qualitative Risk Assessment

carcinogenicity, a false negative may have ten times the social cost of a false positive.

A study is called significant when the probability of the the test data occurring under the null hypothesis falls below some preset level. By convention, this level is five per cent. When a study is considered positive, the statistical probability of this conclusion being false (a false positive) is the level of significance of the study. The lower the probability of a false positive, the stronger the significance of the study. This probability, often expressed as the p value, is a universally reported statistic. Only when a study reaches the preset p value criteria is it considered to support the positive conclusion (a single study does not prove a conclusion it can only support it).

When the p value of a study is greater than 0.05 (or 5 percent), by convention it is considered not significant and does not support the rejection of the null hypothesis and acceptance of an alternative hypothesis. This is not, in itself, evidence that there is no effect. In fact, this is where the importance of the second type of error the false negative comes in.

It is possible, and at times probable, that a true effect will not meet the criteria for significance. It is important to know the probability of being able to reject the null hypothesis when there is a true effect (probability of seeing the effect). This probability is dependent upon the design of the study as well as the strength of the actual effect being measured, and is called the power of the study.

The power of a study is always less than one (there is no certainty of seeing the effect). The probability of missing the effect (coming to a false negative conclusion) is one minus the power. While there is no strong convention on what an acceptable level of power is, 80 percent is generally considered strong. This would mean that there is a 20 percent chance of missing a true effect. The power of a study is usually considered part of the study design rather than part of its conclusion, and is often not reported in the scientific literature.

In order to appreciate the function of the power of a study, it is necessary to understand that studies do not measure safety (the total lack of effect), but only levels of effect. The smaller the effect, the harder it is to measure. A study designed with a good level of power to detect a doubling of risk, may have virtually no chance of seeing a true increased risk of only ten percent.

Thus, the power of a study is dependent upon the level of effect you are interested in measuring. The most important parameter of a study design in determining its power is the size of the test popula-

Significance

Power

tion. If you are interested in observing an effect that occurs in a very low percentage of the population, then you must test a very large number of subjects. But it is very expensive to design large, high powered studies for low level effects. Thus, the probability of false negatives is generally much higher than the accepted preset five per cent level for false positives.

Interpreting False Positives

What do false positives mean in terms of public health and the decisions facing the Forest Service? A false positive means that a chemical will be considered dangerous when, in fact, it is not. It will mean that the chemical may not be used, or may be used in reduced amounts and in restricted circumstances.

It may also mean that alternative ways of doing the job may be chosen. These alternative methods may have their own risks. Thus, using a less-tested chemical or alternative method for one that is well-tested and demonstrated to have some toxic effects, may not reduce true health risks.

What is of particular concern to those who believe chemical use is beneficial is that a single chemical may be tested many times, and any ONE of these tests, if significant, could be used to label the chemical as toxic. Clearly, as the number of tests increase, the probability that any one of them may be significant simply by chance (false positive) goes up. For this reason, supporters of chemical use suggest that consistent positive results be required to determine toxicity.

Interpreting False Negatives

What do false negatives mean in terms of public health and the decisions facing the Forest Service? A false negative means that a chemical will be considered safe when, in fact, it is dangerous. It will mean that the chemical may continue to be used in situations where people are exposed, and where it may be harmful to their health.

It also means that alternative ways of doing the job may not be fully explored. These alternative methods may have reduced risks. Thus, opportunities for doing the job in a safer way may be overlooked.

What is of particular concern to those who are worried about the extent of chemical use is that a single chemical may only be tested in a few minimally adequate tests with high likelihood of producing false negatives. If these tests do not show a significant effect, then the chemical is labeled as not toxic.

Finally, those concerned about use of chemicals point out that unknown situations are frequently considered safe situations. Use of chemicals is not generally restricted without clear evidence of harm,

Qualitative Risk Assessment

Looking at the Degree of Uncertainty

Additional Gaps in Testing Theory

and many chemicals are used with little or no information about their toxicity.

The degree of uncertainty for yes-no answers is quite high. Consider the paper sponsored by the International Commission for Protection Against Environmental Mutagens and Carcinogens (Clayson & Krewski 1986):

For example, with an agent affecting as much as 1% of the population, there is a better than even chance of observing no responses in a sample size of $n=50$.

Also:

with 50 animals per group, the false negative rate can be more than 50% with an agent causing an excess risk of 10% over and above background rate.

The authors continued by pointing out that to detect low level effects with any reliability could require thousands of test animals per experiment.

One method of avoiding this uncertainty is the use of upper 95 percent confidence intervals. This is a statistical technique for answering the question: What is the largest effect with 95 percent certainty that would occur after a given exposure.

Clayson and Krewski point out, however, that when this method is applied, it can have very conservative results. They give a hypothetical example of testing 50 animals with distilled water and observing no adverse health effect. Nevertheless, using the upper 95 percent confidence limit approach, the authors calculated that a maximum:

dose of 833 ppb (parts per billion of distilled water in the food) would be required in order to limit the population risk to one in a million.

The statistical methods discussed above are primarily used in the analysis of data from animal studies. Additional uncertainty arises from the extrapolation of these results to humans and to the lower doses humans are likely to encounter.

The way animals and humans metabolize various chemicals can be quite different, and may mean that the test results in one have no direct application to the other. In addition, test animals are generally selected for being healthy, and are maintained in otherwise healthy environments. These conditions do not apply to the general human population.

Questions on how to relate animal doses to humans, and which

animals are the best predictors of human toxicity, have not been completely resolved.

Major concerns exist around the interactions between various chemicals. A mixture of chemicals is generally considered to have a toxicity equal to the sums of the toxicity of the various chemicals in the mixture. This is not necessarily true. Many chemicals interact with each other. Mixtures of chemicals may be either less toxic, or more toxic than the sum of their parts. This may be due to chemical to chemical interactions, or the altering of the host susceptibility to one chemical by another. Current testing methods seldom take this into account.

There are also considerations about various types of toxicity and our ability to test them. For example, standard test protocols have not been developed for neurological and immunological toxicity. Concern has also been expressed about the problem of hypersensitive individuals people who are much more reactive to chemicals than would be predicted by general population reactions. Hyper-sensitive individuals are not accounted for in statistical tests which are based upon normal population distributions. One type of hypersensitivity is the allergic reaction, but other types of hyper-sensitivity also exist, and are poorly measured and poorly understood.

The above examples clearly indicate limitations in current methods of testing for toxicity. A manager for regulatory response for a chemical producer, in a review article on calculating carcinogenic potency (Barr 1985), stated:

A completely acceptable method of estimating relative or absolute potency values relevant to humans has not yet become available. The nearest approximation is the upper limit on risk which can be estimated from epidemiological data.

Gaps in Test Data Data gaps exist which are not based upon gaps in theory, but on gaps in experiments. No matter how good or bad experimental methods may be, they cannot provide answers unless the chemicals of concern have been tested by currently acceptable methods.

Unfortunately, many of the chemicals being reviewed by the Forest Service have not been sufficiently tested. Furthermore, many methods available at the time of the initial testing do not meet current standards for acceptable test procedures.

This can be most clearly seen in the current review of pesticides being conducted by the state of California under the Birth Defect Reduction Act (SB 950). Reviews were available from California on 13 of the 16 herbicides being considered. Many of the tests reviewed were not considered to be of adequate quality by the State of California.

Qualitative Risk Assessment

Finally, when testing pesticides, most chronic tests do not use the full formula, but test only the active ingredient. However, a high proportion of most formulas are made up of the so called inert ingredients. These inerts are often neither chemically nor biologically inert and may have substantial toxicity themselves.

Inert ingredients are generally not reported on labels or safety sheets. The Environmental Protection Agency reports that many inerts have not been tested for toxicity, and there is virtually no information on possible interactions within these mixtures.

Some limitations of toxicity testing and rating have been presented. These limitations, particularly as applied to the 16 herbicides being evaluated by the Forest Service are the reasons for doing a qualitative risk assessment.

In Summary



Evaluation of Herbicide Chronic Toxicity Information Base Used for Draft EIS

An evaluation was made of the information/data base cited in support of the chronic toxicity thresholds (lowest systemic NOELs) contained in the Supplement to the Western Oregon Program Management of Competing Vegetation Draft Environmental Impact Statement, (USDI-BIM, February, 1986).

For this evaluation, only studies involving repeated exposures of several weeks to lifetime durations were considered. Information and data on the general toxic effects of the sixteen herbicides cited in the draft EIS referenced above was compared with that contained in several other information sources.

Because chronic toxicity test studies of pesticides are most often not reported in the open literature, very few useful original reports were available for examination. Hence, most of the information used for comparison was from secondary sources which had had access to original contract reports submitted to regulatory or other agencies. Therefore, the approach was to examine the data cited in each review or report examined, and to compare the findings with respect to consistency among the reports and specifically with respect to the conclusion reached in the Draft EIS.

The overall quality of the information was judged on the basis of apparent thoroughness of the studies (a range of doses including no effect; sufficient duration (minimally three months or greater); whether multiple species had been tested; identification of the most sensitive effect or target site); and general quantitative agreement on the NOEL among the studies, and with the draft EIS specifically.

A qualitative evaluation of the toxicity information available was expressed according to the following rating scheme:

I = Inadequate to make judgement concerning a chronic systemic NOEL (e.g., wide variation in values found in different studies, target effects/sites not identified, limited time, doses or species);

M = Minimally adequate to make a judgement (e.g., two or more reports with a range of doses, which agree in general on NOEL, but which give little information on nature of effects and with limited confidence that the toxicity has been well characterized).

A = Adequate (numerous studies have been conducted, driving target effects clearly identified in more than one study, and quantitative values for NOEL agree well).

This evaluation did not consider effects of teratogenicity, mutagenicity, carcinogenicity, neurotoxicity, or immunotoxicity, as these are evaluated separately. Of the 16 herbicides for which chronic toxicity information was evaluated, three (2,4-D, 2,4-DP, and picloram) were judged to have adequate information that could be used for risk assessment with confidence. Six were judged to have minimally adequate information (amitrole, asulam, atrazine, bromacil, dalapon, hexazinone, and simazine), but more complete information or additional studies would enhance confidence for risk assessment. For four herbicides (fosamine, glyphosate, tebuthiuron, and triclopyr), the information available for this evaluation was considered borderline between minimally adequate and inadequate. Essentially, this translates to a low level of confidence in the NOEL conclusion. For two compounds (dicamba and diuron), the information cited in the Draft EIS or available for review from these sources was inadequate to judge suitability for risk assessment.

It is important to note that these evaluations of adequacy of information refer to the information contained in the Draft EIS or available from other, generally secondary, sources of information supplied. There may well be additional information extant which has not been made available for examination. A comprehensive search of the open literature for chronic toxicity studies is beyond the scope of this project. However, quite frequently routine chronic toxicity studies are not reported in the peer-reviewed literature.

Given the limitations of this effort, it is of interest that the NOEL estimated after examination of several information sources do not differ greatly from those reported in the Draft EIS, although the basis for the EIS values is better developed in this document.

Appendix H

**Human Health
Risk Assessment
(Qualitative)**



Section 2

**Data for Analysis
of General Systemic
Toxicity**

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GENERAL TOXICITY AND SELECTED
ORGAN EFFECTS OF CHRONIC AND
SUBCHRONIC EXPOSURES TO HERBICIDES

AMITROLE

<u>Source</u>	<u>Effects</u>	<u>Rt</u>	<u>Sp</u>	<u>Dose-schedule-duration</u>	<u>NOEL</u>	<u>LOEL</u>	<u>Notes</u>
EPA 1985a	thyroid effects	F	R		0.5 ppm 0.025 mg/kg/day		
Cal one liners (no author, 10/83)	thyroid effects	F	R	13 weeks	0.5 ppm	2 ppm	
Hazleton Labs 1959	thyroid effects (50 ppm) fatty liver changes (100 ppm)	F	R	0, 10, 50, 100, 500 ppm for 26 weeks	10 ppm		"unacceptable"
Hazleton Labs 1960	dec. wt. gain; enlargement/ congestion of thyroid	F	R	28 days		<250 ppm (LDT)	
Bayer 1978	dec. food cons.; wt. gain inc. mortality	F	H	0, 1, 10, 100 ppm	10 ppm		oncology study "unacceptable"
Bayer 1978	dec. maternal wt. gain	G	W	0, 4, 40, 400 mg/kg/day days 6-18 of gestation	4 mg/kg/day		"acceptable"

ASULAM

Source	Effects	Rt	Sp	Dose-schedule-duration	NOEL	LOEL	Notes
EPA 1984b	fatty deposits in liver	F	R	90 days	2000 ppm 100 mg/kg/day		
EPA 1984b		F	D	6 mos.	60 mg/kg/day		
EPA 1985d		F	R	107 wks.	50 mg/kg/day		
May and Baker LTD. 1968	myocarditis; kidney lesions; testicular abnormalities	F	D	0, 50, 500 mg/kg/day 90 days	>500 mg/kg/day		
May and Baker LTD. 1970	fatty liver	F	R	0,16,80,400,2000,10,000 ppm 90 days	2000 ppm	10,000 ppm	60% Asulox
May and Baker LTD. (no date)	inc. thyroid, body wts.	F	D	0, 60, 300, 1500 mg/kg	60 mg/kg	300 mg/kg	"guideline"
IBT 8/75 651-05129	inc. relative liver wts.	F	R	2 yrs.	400 ppm (LDT)	2200 ppm	1 year interim report
Pathology Lab Rhodia, Inc. #CH-2, 7/78	inc. thyroid, heart, kidney wts.	F	M	0, 1500, 5000 ppm 18 mos.	<1500 ppm		oncology study "guideline"

ATRAZINE

FL-14

Source	Effects	Rt	Sp	Dose-schedule-duration	NOEL	LOEL	Notes
EPA 1984c		F	D	2 years	150 ppm 3.7 mg/kg/day		
EPA 1984c		F	R	3 generations	100 ppm 5mg/kg/day (HDT)		
Suschetet et al., 1974	dec. growth, food cons.; dec. relative, absolute kidney/liver wts.; altered N, Ca, excretion.	F	R	0, 100, 500 ppm or 0, 5, 25 mg/kg/day	none established		
EPA 1984		F	D	0, 15, 150, 1500 ppm 2 years	150 ppm or 3.75 mg/kg/day		used to calculate margins of safety
Ciba-Geigy 1971	maternal weight loss	G	R		100 mg/kg	500 mg/kg	terat. study "minimum"
Ciba-Geigy 1984	dec. maternal wt gain; dec. food cons.	G	W	0, 1, 5, 75 mg/kg/day	1 mg/kg/day		terat. study "unacceptable", "ungradeable"
Woodard Research lab 1964	dec. body wt., food cons., hemoglobin, hematocrit	F	D	0, 15, 150, 1500 ppm 2 years	150 ppm	1500 ppm	"supplementary"
American Biogenics Corp., 1986	dec. body wt. gain	F	R	0, 10, 70, 500, 1000 ppm	70 ppm		
Binns and Johnson 1970		?	S	maternal exposure throughout gestation and 1st 30 days of nursing	>15 mg/kg/day <30 mg/kg/day		

BROMACIL

<u>Source</u>	<u>Effects</u>	<u>Rt</u>	<u>Sp</u>	<u>Dose-schedule-duration</u>	<u>NOEL</u>	<u>LOEL</u>	<u>Notes</u>
EPA 1984d	dec. weight gain	F	D	2 years	250 ppm 6.25 mg/kg/day		
Hazleton 1966 #201-163	maternal toxicity	?	W	0, 50, 250 ppm	250 ppm (HDT)		teratology study "minimum"
EI Dupont (no date)	dec. growth; low RBC; inc. thyroid activity; enlargement of liver centolobular cells (all at 5000 ppm)	F	R	0, 50, 500, 2500/5000 ppm 80% WP for 90 days	500 ppm	2500 ppm	"minimum"
EI Dupont	dec. growth	F	R	0.005, 0.025, 0.125% for 2 years	250 ppm (0.025%)	0.125%	"minimum"
		F	D		1250 ppm		"minimum"
EI Dupont	dec. wt. gain	F	D	0.005, 0.025, 0.125% of 80% bromacil for 2 years	0.025%	0.125%	"acceptable"
Haskel Labs 1980 #893-80	testicular abnormalities inc. liver wt. at 5000 ppm	F	M	0, 250, 1250, 5000 ppm for 2 years	<250 ppm (LDT)		"minimum"

2,4-D

<u>SOURCE</u>	<u>EFFECT(S)</u>	<u>RT</u>	<u>SP</u>	<u>DOSE-SCHEDULE-DURATION</u>	<u># TESTED</u>	<u>#AFFECTED</u>	<u>NOEL</u>	<u>LOEL</u>	<u>NOTES</u>
Drill and Hiratzka 1953	bleeding gums buccal mucosa necrosis stiff hind limbs liver/kidney alts. dec. lymphocyte counts	O/P	D	0,2,5,10,20 mg/kg/day 5 days per w for 13 w			10 mg/kg/ day		
Hansen et al 1971		F	D	0, 10, 50, 100 or 500 ppm for 2 yrs	3 female, 3 males per group		500 ppm or 20 mg/kg/day		
EPA 1984	Histo changes in renal Tubules	F	M	0, 5, 15, 45, 90 mg/kg/day for 90 days			None est.		
EPA 1984	Histo changes in renal cortical tubules and inc. thyroid wt. at 1 mg/kg/day	F	R	0, 1, 5, 15, 45 mg/kg/day for 90 days			None est.		
Kociba et al 1949	mineralized deposits in, renal pelvis inc excr of coproporphyrin	F	R	3-30 mg/kg/day - 2 yrs			3 mg/kg/ day	10 mg/kg/ day	
Whitehead 1973	Food cons. & growth	F	Ch	10, 50, 100 ppm for 8wks			(5ppm)	(10ppm)	chicks
Hazleton labs (1986)	Kidney effects	F	R	1-45 mg/kg/day 10 for wks			1 mg/kg/ day	5 mg/kg/ day	
Chem et al 1981	Kidney histo changes	?	R	13 weeks			15 mg/kg/ day		
Whitehead and Pettigrew 1972	Kidney enlargement at 5000 mg/kg	F	Ch	1000mg/kg (142 mg/kg bw) or 5000 mg/kg for 3 wks			1000 mg/kg		adults

2,4-D

<u>SOURCE</u>	<u>EFFECT(S)</u>	<u>RT</u>	<u>SP</u>	<u>DOSE-SCHEDULE-DURATION</u>	<u># TESTED</u>	<u># AFFECTED</u>	<u>NOEL</u>	<u>LOEL</u>	<u>NOTES</u>
(WHO 1984) Fabacher & Chambers 1974 Gambusia. Affins. Environ. Lett. 7:15-20 Meehan et al 1974 J.Fisher Res.Board Can. 31:480-485 King and Penfound 1946 Ecology 27:327-374 Ehiteneva & Chesuokova 1973 1973 Eksp. Vod. Toksikol. 4:56-67 (Russian)			Poikilo- Therms				1 mg/l water		2,4-D esters

2, 4-DP

<u>Source</u>	<u>Effects</u>	<u>Rt</u>	<u>Sp</u>	<u>Dose-schedule-duration</u>	<u>NOEL</u>	<u>LOEL</u>	<u>Notes</u>
EPA 1984f	blood enz. effects inc. liver/kidney wts.	F	R	90 days	5 mg/kg/day		
EPA 1984f	inc. liver wt.	F	M	18 months	100 mg/kg/day		
EPA 1984f	dec. wt. gain, hematocrit RBC count; prostatitis; kidney degeneration	F	R	2 years	50 mg/kg/day		
Hazleton labs no date	ataxia; dec. food intake	?	W	0, 25, 100 mg/kg	25 mg/kg (LDT)	100 mg/kg (HDT)	teratology study "minimum"
Litton Bionetics #7286 2-8-73		?	R	0, 10, 30, 100 mg/kg	>100 mg/kg		teratology study "minimum"
Huntington Research center #1-361	dec. body wt.	F	R	0, 125, 500, 1000, 2000 ppm	1000 ppm	2000 ppm	3 generation "minimum"
Central Inst. Vor Voedingsonderzoek (TNO) #R5419/a; 12/77	dec. blood Na, PCV; inc. liver/kidney wt.	F	R	0, 100, 500, 2500 ppm for 90 days	5 mg/kg (as reported)	25 mg/kg	"guideline"
TNO #R5555 6/78		F	D	0, 8, 20, 32 mg/kg for 4 wks	<8 mg/kg		"supplementary"
CDC research #CDC-AM-002-77 12-14-79	inc. bile retention liver wt., regeneration, degeneration	F	M	0, 25, 100, 300 mg/kg for 18 months	100 mg/kg	300 mg/kg	oncology study "guideline"
CDC research #CDC-AM-001-77 4-18-80	dec. wt. gain, hematocrit, RBC count; renal degen., chronic prostatitis; testicular atrophy	F	R	0, 25, 50, 200/150 mg/kg for 2 years	50 mg/kg	150 mg/kg	oncology study "guideline"
Inst. Env. Tox., Japan no date	dec. urinary specific gravity and/or protein	F	R	0, 100, 300, 1000, 3000 ppm for 2 years	100 ppm	300 ppm	oncology study "guideline"
Inst. Env. Tox., Japan 12-14-81	dec. hematocrit, hemo- globin, A/G ratio; inc. in Alk. phosphatase, total bilirubin, albumin	F	R	100, 300, 1000, 3000 ppm for 90 days	300 ppm	1000 ppm	"supplementary"

DALAPON

<u>Source</u>	<u>Effects</u>	<u>Rt</u>	<u>Sp</u>	<u>Dose-schedule-duration</u>	<u>NOEL</u>	<u>LOEL</u>	<u>Notes</u>
Paynter et al 1960 in USDA 1984	inc. kidney wts.	F	R	2 years	15 mg/kg/day		
Paynter et al 1960 in USDA 1984	inc. kidney wts.	F	D	52 weeks	50 mg/kg/day		no abnormal pathology/histol.
Paynter et al 1960	inc. kidney wts.; dec. growth; slight changes in kidney, liver histology	F	R	0, 10, 30, 100, 300, or 1000 mg/kg/day for 97 days	100 mg/kg/day (male) 10 mg/kg/day (female)		
Thompson et al 1971 Kenaga et al 1974	maternal toxicity	G	R	0, 250, 500, 1000, 1500 or 2000 mg/kg/day days 6-15 of gestation	500 mg/kg/day		teratology study
Dow Chemical 1983	inc. liver wt.	F	D	0, 2, 60 or 200 mg/kg/day for 2 years	60 mg/kg/day		
Hazleton labs 1956		F	R	0, 0.01 or 0.03% in diet for 2 years	not established		"unacceptable" according to Cal.
Hazleton labs 1956		OC	D	0, 15, 50, 100 mg/kg for 52 weeks	not established		"unacceptable" according to Cal.

DICAMBA

H-20

Source	Effects	Rt	Sp	Dose-schedule-duration	NOEL	LOEL	Notes
EPA 1985d		?	R		250 mg/kg/day		EPA "in house value"
EPA 1985d	slight liver cell alts.	?	R	90 days	500 ppm/25 mg/kg/day		
IRDC #163-436 9/77	maternal toxicity (mortality; dec. wt. gain)	?	W	0, .5, 1, 3, 10, or 20 mg/kg/day	10 mg/kg/day	20 mg/kg/day	teratology study "supplemental"
IRDC #163-436 10/78	dec. weight gain	?	W	0, 1, 3, or 10 mg/kg/day	3 mg/kg/day	10 mg/kg/day	"supplementary" teratology study
Toxigenics #450-0460	dec. food cons.; wt loss	G	R	0, 64, 160, 400 mg/kg days 6-19 of gestation	160 mg/kg/day	400 mg/kg/day	"minimum" teratology study
U of Cincinnati 1962	dec. food cons; wt. loss	F	D	0, 5, 25, 50 ppm in food for 2 years	5 ppm (male body wt.) 25 ppm (female body wt.) 50 ppm (hematology, histopathology, urinalysis, organ wts.)		"supplementary" chronic study
U of Illinois 1962	slight liver cell necrosis and cytoplasmic vacuolization	F	R		500 ppm	800 ppm	dimethylamine salt of Banvel
Edson and Sanderson 1965	Inc. liver weight	F	R	0 to 3162 ppm	316 ppm	1000 ppm	

DIURON

<u>Source</u>	<u>Effects</u>	<u>Rt</u>	<u>Sp</u>	<u>Dose-schedule-duration</u>	<u>NOEL</u>	<u>LOEL</u>	<u>Notes</u>
EPA 1984i		F	R	2 years	125 ppm or 6.25 mg/kg/day		
EPA 1984i		F	D		25 ppm or .625 mg/kg/day		
Hodge et al 1967	dec. growth; slight anemia; abnormal pigments; hemosiderosis	F	R	2 years	250 ppm		
Hodge et al 1967		F	D	2 years	250 ppm		
EPA memorandum; Diuron 8-20-82		F	R	0, 25, 125, 250, 2500 ppm for 2 years	25 ppm		no core grade
EPA memorandum; Diuron 8-20-82	wt. loss; dec. RBC counts; inc. liver wt.; inc. liver cell pigmentation	F	D	0, 25, 125, 250, 1250 ppm for 2 years	25 ppm		no core grade
Khera et al 1979	dec. maternal body wt.	G	R	0, 125, 250, 500 mg/kg/day days 6-15 of gestation	250 mg/kg/day		"supplemental" teratology study

FOSAMINE

<u>Source</u>	<u>Effects</u>	<u>Rt</u>	<u>Sp</u>	<u>Dose-schedule-duration</u>	<u>NOEL</u>	<u>LOEL</u>	<u>Notes</u>
Schneider and Kaplan 1983 in USDA 1984	inc. stomach wt.	F	D		100 ppm 25 mg/kg/day		
Schneider and Kaplan 1983 in USDA 1984		F	R		5000-10,000 ppm 250-500 mg/kg/day (HDT)		
Schneider and Kaplan 1983 in USDA 1984a	none	F	R	0, 200, 1000, 5000/10,000 ppm for 90 days	5000-10,000 ppm		
Schneider and Kaplan 1983 in USDA 1984a	inc. heart, stomach wts.	F	D	0, 200, 1000, 5000, 7000 ppm for 6 months	1000 ppm or 40 mg/kg/day (calc used by Crump)		worst case NOEL

GLYPHOSATE

<u>Source</u>	<u>Effects</u>	<u>Rt</u>	<u>Sp</u>	<u>Dose-schedule-duration</u>	<u>NOEL</u>	<u>LOEL</u>	<u>Notes</u>
EPA 1984k		F	R	26 months	30 mg/kg/day		
Monsanto: 1982c in 1984a	"systemic"	D	W	0, 100, 1000, 5000 mg/kg/day for "15 out of 21 days"	5000 mg/kg/day		IDRC NOEL 1000, LOEL 5000
Monsanto: 1972 in 1984a	dec. food cons., body wt.; inc. mortality	D	W	32% aq. solution by Vol. (5 X intended conc.)	3 x 6.4% by Vol.		
Monsanto: 1983a in 1984a		I	R	.36 mg aq solution/ l air 6 hrs/day, 5 days/wk, 30 days			
Monsanto: 1979h in 1984a	inc. in relative and absolute lung wt.	F	R	0, 200, 2000, 5000, 12500 ppm or 0, 13.5, 135, 340, 820 mg/kg/day, 90 days	2000 ppm or 135 mg/kg/day		
Monsanto: 1979i in 1984a	dec. growth at 50,000 ppm	F	M	up to 50,000 ppm for 90 days	10000 ppm or 2305 mg/kg/day		
Monsanto #83-137 8-22-85	apparent dec. in relative and absolute pituitary wts.	O	D	0, 20, 100, 500 mg/kg/day for 1 year	20 mg/kg/day *	100 mg/kg/day	tentative NOEL LOEL, EPA reqs. more data
Monsanto, 1985 #ML-83-137		O	D	96% glyphosate in caspsul 0, 20, 100, 500 mg/kg/day for 1 year	>500 mg/kg/day *		
Monsanto, 1983 #77-2061	central lobular hepatic necrosis/hypertrophy; chronic interstitial nephritis; proximal tubule epithelial basophilia and hypertrophy	F	M	0, 1000, 5000, 30000 ppm 99.7% glyphosate (for 2 years?)	5000 ppm		chronic feeding study
IRDC #IR-79-018 2-29-80	inc. mortality; misc. clinical signs	G	W	0, 75, 175, 350 mg/kg/day 98.7% glyposate, days 6-27 of gestation	175 mg/kg/day (maternal systemic)		teratology study EPA "minimum" Cal "acceptable"
Biodynamics #77-2062 9-18-81	inc. mortality; dec. wt. gain; clinical pathology	F	R	0, 3, 10, 31 mg/kg/day for 26 months	>31 mg/kg/day systemic		onco study "minimum"
Biodynamics #77-20663 7-6-82		?	R	3 generations	10 mg/kg/day		"minimum"
IRDC #401-054 3-21-80	maternal tox.; inc. mortality; dec. wt. gain; alt. gen. appearance	?	R	0, 300, 1000, 3500 mg/kg/day	1000 mg/kg/day maternal tox.	3500 mg/kg/day	teratology study "minimum"

* California 1 liners (12-2-86) does not acknowledge EPA's summary (Guidance for the Registration of Pesticides Containing Glyphosate, 6-30-86) that states a "tentative" NOEL of 20 mg/kg/day based upon "apparent" decreases in pituitary weight at 100 and 500 mg/kg/day. No evaluation of "tentative" or "apparent" NOEL is available. The Cal. 1 liner does, however, claim "no data gap" in their review of its chronic effects.

HEXAZINONE

H-24

<u>Source</u>	<u>Effects</u>	<u>Rt</u>	<u>Sp</u>	<u>Dose-schedule-duration</u>	<u>NOEL</u>	<u>LOEL</u>	<u>Notes</u>
EPA 1984i	inc. liver wt., liver cell size	F	R	2 years	10 mg/kg/day		
		F	M	2 years	30 mg/kg/day		
Haskel labs (Dupont) 1973	dec weight gain	F	R	0, 200, 1000, 5000 ppm 3 months	1000 ppm	5000 ppm	
	dec. wt. gain, inc. alkaline phosphatase; dec albumin: globulin ratio	F	D	0, 200, 1000, 5000 ppm 3 months	1000 ppm	5000 ppm	"minimum"
Haskel labs 1977	dec. wt. gain	F	R	0, 200, 1000, 2500 ppm 2 years	200 ppm	1000 ppm	"minimum"
IRDC #125-026 6-23-81	liver hypertrophy, hyperplastic nodules focal necrosis	F	M	0, 200, 2500, 10,000 ppm 2 years	200 ppm (30 mg/kg/day)	2500 ppm	may be same as LA EPA 1984i

PICLORAM

<u>Source</u>	<u>Effects</u>	<u>Rt</u>	<u>Sp</u>	<u>Dose-schedule-duration</u>	<u>NOEL</u>	<u>LOEL</u>	<u>Notes</u>
BarnaLloyd et al., 1982 in Mullison, 1985	inc. liver wts.	F	D	0, 7, 35, 175 mg/kg/day	7 mg/kg/day	35 mg/kg/day	
Lynn 1965	liver histo., necrosis bile duct prolifer.; alterations in: blood chem, body/organ wts., mortality	F	R	75, 225, 750 mg/kg/day or 1000, 3000, 10,000 ppm in diet for 90 days	10,000 ppm or 75 mg/kg/day (conversions reported by author)		
NCI 1978		F	R	1250 to 20,000 ppm for 6 wks	10,000 ppm		
NCI 1978		F	M	1250 to 30,000 ppm for 6 wks	5000 ppm		
Dow chemical 1984 in USDA 1984a	inc. relative, absolute liver wts. at 150 mg/kg and kidney wts. at 300 mg/kg	F	R	0, 15, 50, 150, 300, 500 mg/kg/day for 13 wks	50 mg/kg/day		
Dow chemical 1984 in USDA 1984a	unspecified toxic liver and gastric mucosa effects at 3000 mg/kg/day	F	M	0, 30, 100, 650, 1000, 3000 mg/kg/day for 32 days	1000 mg/kg/day		
Dow chemical 1984 in USDA 1984a	inc. relative, absolute liver wt	F	D	0, 7, 35, 175 mg/kg/day for 6 months	7 mg/kg/day		worst case NOEL
Dow chemical 1986	inc. size of hepatocytes, tinctorial properties of liver	O	R	0, 20, 60, 200 "mg/kg in the diet for 2 years" (97% picloram, 197 ppm hexachlorobernzene)	20 mg/kg	60 mg/kg	"acceptable"

TEBUTHIURON

<u>Source</u>	<u>Effects</u>	<u>Rt</u>	<u>Sp</u>	<u>Dose-schedule-duration</u>	<u>NOEL</u>	<u>LOEL</u>	<u>Notes</u>
EPA 1984o		F	M	119 day	554 ppm 83.1 mg/kg/day		
EPA 1984o	inc. thyroid/body wt. ratios; inc in blood enzyme levels	F	D	3 month	500 ppm 12.5 mg/kg/day		
Elli Lilly Res. lab #'s R03780 and R08780 11-81		?	R	2 generations	>100 ppm		"supplementary"
Elli Lilly Res. lab 4-75		?	R	3 generations	800 ppm (HDT)		
Elli Lilly Res. lab 1972	dec. growth; pancreatic lesions	F	R	90 days	1000 ppm	2500 ppm	
Elli Lilly Res. lab 1972	inc. thyroid, spleen wts.	F	D	90 days	12.5 mg/kg	25 mg/kg	
Elli Lilly Res. lab 1976	dec. growth	F	Cw	162 days	30 ppm	100 ppm	
Elli Lilly Res. lab 1972	dec. growth	F	Ch	30 days	1000 ppm	2500 ppm	
Elli Lilly Res. lab 1976	dec. growth	F	R	2 years	400 ppm 20 mg/kg	800 ppm 40 mg/kg	

SIMAZINE

<u>Source</u>	<u>Effects</u>	<u>Rt</u>	<u>Sp</u>	<u>Dose-schedule-duration</u>	<u>NOEL</u>	<u>LOEL</u>	<u>Notes</u>
EPA 1984n		F	R	2 years	> 100 ppm or 5 mg/kg/day		
EPA 1984n		F	D	2 years	1500 mg/kg/day (HDT)		
Woodward lab 1965		F	M	20 days	250 mg/kg/day (HDT)		
Ciba-Geigy #62-83 5-17-86	dec. food cons., wt. gain abortions	G	W	0, 5, 75, 200 mg/kg	5 mg/kg	75 mg/kg	teratology study "guideline"
Ciba-Geigy #85018 4-10-85	dec. RBC, WBC counts inc. levels of cholesterol, inorganic phosphate	F	R	3 weeks	<200 ppm (LDT)		"supplementary"
Ciba-Geigy #85022 4-12-85	dec. albumin; increased: globulin, ketone levels; urinary specific gravity	F	D	3 weeks	200 ppm	2000 ppm	"minimum"

TRICLOPYR

H-28

<u>Source</u>	<u>Effects</u>	<u>Rt</u>	<u>Sp</u>	<u>Dose-schedule-duration</u>	<u>NOEL</u>	<u>LOEL</u>	<u>Notes</u>
EPA 1984p, USDA 1984		F	R, M	2 years	30 mg/kg/day (HDT)		
Dow chemical, in USDA 1984	dec. food cons, wt. gain	F	D	228 days	<5 mg/kg/day		
40 CFR part 180 5(84) 18485 5-1-85	effects not representative of human effects	F	D	6 months	2.5 mg/kg (per day?; HDT)		
Humiston et al 1975	dec. growth; dec. liver wt. inc. brain, kidney wts.	F	R	90 days	30, 100 mg/kg/ day (male, female) (HDT)	100 mg/kg/day (HDT)	
EPA 1984	dec. wt. gain at 200, 300 mg/kg/day for females and 100 mg/kg only for males	F	R	0, 30, 100, 200, 300 mg/kg/day, 14 days	30 mg/kg/day		
Dow chemical, in USDA 1984a	dec. liver wt. in males at 60 mg/kg/day	F	M	6, 20, 60 mg/kg/day for 90 days	20 mg/kg/day (males) 60 mg/kg/day (females)		
Molello et al 1976		GI	Mk	28 days	30 mg/kg/day (HDT)		
Quast et al 1976		F	D	0, 5, 10, 20 mg/kg/day for 228 days	none established	5 mg/kg/day	
Quast et al 1977	dec. excretion of phenosulfonphthalein	F	D	0, 0.1, 0.5, 2.5 mg/kg/day for 183 days	0.5 mg/kg/day	2.5 mg/kg/day	worst case NOEL EPA "minimum" Cal "unacceptable"
Litton Bionetics #2538 11-4-86		F	R	0, 3, 10, 30 mg/kg 3 generations	>30 mg/kg/day (HDT)		reproduction study "minimum"
Smith et al 1977	maternal mortality	G	W	0, 25, 50, 100 mg/kg/day days 6-18 of gestation	not established	25 mg/kg/day (LDT)	teratology study
Dunn et al 1980 (IBT; EPA acceptable)		F	R	3, 10, 30 mg/kg/day for 2 years	30 mg/kg/day (HDT)		oncology study
Mollelo et al 1979	no effect (wt. gain; organ wt. ratios; hematology; urinalysis; clinical chem.; histology)	F	M	0, 3, 10, 30 mg/kg/day for 2 years	30 mg/kg/day (HDT)		oncology study

2,4-D

SOURCE	EFFECT(S)	RT.	SP	DOSE-SCHEDULE-DURATION	# TESTED	#AFFECTED	NOEL	LOEL	NOTES
EPA 1984e		F	D	0-500 ppm or 0-12.5 mg/kg for 2 yrs			12.5 mg/kg/day		
EPA 1984e		F	R	1250 ppm or 62.5 mg/kg/day for 2 yrs			62.5 mg/kg/day		
EPA 1985c	Kidney effects	F	R				1 mg/kg/ day	5 mg/kg/ day	
Kay et al. 1965		D	W	.636% 7 or 3.13% 7 hrs/day x 5 days/wk for 3wks			none spec		
Bucher 1946		G	M	up to 93 mg/kg/day 3 wks to 3 months			93 mg/kg/ day		
Bucher 1946	dec. growth	SQ	M	50 to 90 mg/kg once or twice daily 3 wks to 3 mos			70 mg/kg/ day	70 mg/kg/ day	
Rowe and Hymas 1954	GI irritation dec. growth rate cloudy swelling of liver	GI	R	0,3,10,30,100,300 mg/kg/day 5 times/w for 4 weeks			30 mg/kg/ day	100 mg/kg/ day	
Hill and Carlisle 1947		F	R	0, 100, 200 or 400 ppm for 30 days	7 rats/dose				No effect at 1000 ppm in food for 1 month, IARC 15, 1977
Bjorklund and Erne 1966		F	R	1000 ppm for 10 months					no detrimental effects occurred
Rowe and Hymas 1954	dec. Growth rate inc. Mortality inc. liver wt Cloudy swelling of liver (1000 mg/kg)	F	R	0,100,300,1000,3000 10k ppm mg/kg/ diet for 113 days			300 ppm 15 mg/kg/ day	1000 ppm	
Hansen et al. 1971	growth & organ wt., hematology, survival	F	R	0, 5, 25, 125 or 1250 ppm for 2 yrs			1250 ppm or 62.5 mg/kg/day		

RESOURCES

H-30

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- (Hayes) Hayes, Wayland J. Pesticides Studied in Man: Chap 11 Herbicides
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Industrial Chemicals Volume 15 International Agency for Research on Cancer Aug 1977
- (Cal one liners) California Dept. of Food and Agriculture Medical Toxicology Branch
Summary of Toxicology Data: 2,4-D . (One liners)
- (WHO 1984) Environmental Health Criteria 29. 2,4-Dichlorophenoxyacetic acid (2,4-D)
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LEGEND

RT = route: D- dermal; F- in food; G- gavage; GI- gastric intubation; I- inhalation; OC- oral capsul; O- oral, not further described;
O/P- oral pellet; SQ- subcutaneous; ?- not stated

SP = species: Ch - chicken; Cw- cow; D- dog; H- hamster; M- mouse; Mk- monkey; R- rat; S- sheep; W- rabbit

LDT = lowest dose tested (when indicated)

HDT = highest dose tested (when indicated)

ppm - For dosages in laboratory animals expressed as concentration in the diet, i.e. in parts per million (ppm), approximate conversions to mg/kg/day can be made with the following factors: rat, 1 ppm = 0.05 mg/kg/day; mouse, 1 ppm = 0.150 mg/kg/day; rabbit, 1 ppm = 0.030 mg/kg/day; dog, 1 ppm = 0.025 mg/kg/day

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Appendix H
Human Health
Risk Assessment
(Qualitative)

Section 3
Data for Analysis
of Mutagenic and
Carcinogenic
Toxicity



DATA FOR ANALYSIS OF MUTAGENIC AND CARCINOGENIC TOXICITY

Footnotes

a) Data for each compound was evaluated for: 1) the quantity and quality of available studies, 2) the consistency of effects between studies, and 3) the strength of association and/or dose-relatedness of the effect, with a consideration for the potency of the chemical in producing the effect.

I (Inadequate) = data are so limiting and / or of poor quality so as to preclude any meaningful judgement of the potential for the chemical to produce the effect in question. Further studies are necessary. The summary result of available data is shown in brackets to denote the tenuous nature of the findings.

M (Minimal) = sufficient data are available to make a *cautionary* judgement about the ability of the chemical to produce the effect in question. Further testing is desirable.

A (Adequate) = data are of sufficient abundance and quality to make a reasonably confident judgement about the ability of the chemical to produce the effect in question. Further testing would be of limited value, and is not essential.

- = effect is consistently negative or insignificant,

+ = effect is consistently positive

± = effect is equivocal, or inconsistently positive / negative.

* = no studies are available to judge

b) Although almost all of the numerous acceptable mutagenicity / cytogenicity studies on amitrole have been negative, at least 4 cell transformation studies have tested positive, suggesting that amitrole may have cancer promoting activity.

c) Although numerous different mutagenicity studies have been performed on atrazine, most have been published only as abstracts or summary reports, so detailed evaluations of quality are not possible. One reasonably consistent theme that emerges, however is that atrazine appears to be activated to mutagenic metabolite(s) by many plant activating systems, but generally not by mammalian activating systems. There is limited evidence suggesting that atrazine is positive in cell transformation assays, but only at quite high concentrations *in vitro*.

Review Table for Mutagenicity of Amitrole

<u>TEST ORGANISM TYPE</u>	<u>Response</u>	<u>Quality</u> ¹	<u>Reference</u>
I. Point Mutations or Specific Locus tests			
Microbial assays:			
1. Ames TA98,100,1535, 1537, 1538, ± S9	-	A	Moriya et al., 1983
2. Ames TA98,100,1535, 1537, 1538, + S9	-	A	Falck et al., 1985
3. Ames TA 1535, 1536, 1537, 1538 ± S9	-	A	Carere et al., 1978
4. <i>S. coelicolor</i> A3(2), <i>his A</i> ⁻¹	±	?	"
5. <i>S. cerevisiae</i> D3 (recombination), S9	-	A	Simmon, 1979
6. <i>Aspergillus nidulans</i> , 8-azaguanine resist.	-	?	Bignami et al., 1977
7. " " , somatic recombinations	±	?	"
8. " " , non-dysjunction	±	?	"
9. " " , non-dysjunction	+	A	Morpurgo et al., 1979
10. Ames test plus nitrate	+	A	Braun, 1977
11. Ames test	+	?	Venitt & Crofton-Sleigh, 1981
12. "Bacterial forward and reverse mutation" 7 additional studies negative, 1 positive	7-, 1+	R	NHMRC, 1984 ³
13. Yeast reverse mutation, mitotic gene conversion & non-dysjunction, 4 additional studies	3-, 1+	R	"
14. Ames test, "49 tests in different strains"	-	R	EPA, 1985 ²
drosophilla tests:			
1. mutation	-	A	Laamanen et al., 1977
2. non-dysjunction	-	A	"
3. recessive lethal test	-	A	"
4. non-dysjunction	-	I (abs)	Sorsa & Gripenberg, 1976
mammalian cell cultures:			
1.			
<i>in vivo</i> host mediated assays			
1. <i>S. typhimuriam</i> TA 1530, 1538	+	A	Simmon et al., 1979
2. <i>S. cerevisiae</i> D3	+	A	"
II. DNA Damage / Repair Tests			
Microbial assays:			
1. <i>E. coli pol A</i> reversion	-	?	Bamford et al., 1976
2. <i>E. coli pol A</i> reversion, ± S9	-	A	Rosenkranz & Poirer, 1979
3. <i>E. coli</i> WP2/WP100 rec (<i>uvr A</i> ⁻ recA-)	-	A	Mamber, et al., 1983
4. <i>E. coli</i> DNA DNA-cell binding assay ± S9	+	I	Kubinski et al., 1981
5. "microbial DNA repair", 2 addit. studies reviewed	-	R	NHMRC, 1984 ³
6. <i>E. coli</i> WP2 <i>her</i> , ± S9	-	A	Moriya et al., 1983
7. "SOS Chromtest" induction of <i>sfi A</i> gene in <i>E. coli</i>	-	?	Quillardet et al., 1985
8. <i>E. coli</i> WP2 <i>uvr A</i>	-	A	Falck et al., 1985

Mammalian Cell culture:

1. unscheduled DNA synthesis	+	I (abs)	Begnini & Dogliotti, 1980
2. UDS in HeLa cells, \pm S9	+S9	?	Martin & McDermid, 1981 in EPA, 1985 ²

Other:

1. <i>in vivo</i> inhibition of testicular DNA synthesis	-	A	Seiler, 1977
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III. Chromosomal Abberations / Cytogenetic tests

Drosophila tests:

1. recessive lethal assay	-	A	Vogel et al., 1980
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mammalian cell cultures:

1. sister chromatid exchange, CHO cells	-	R	EPA, 1985 ²
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in vivo animal studies:

1. sperm head abnormalities, mice	-	A	Topham, 1980
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in vivo / *in vitro* human studies:

1. aneuploidy / aberrations	-	?	Meretoja et al., 1976
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plant material assays:

1. <i>Pelargonium zonale</i> , chlorophyll defects	+++	I (abs)	Polheim et al., 1976
2. "mutations & chromosomal effects	-	R	NHMRC, 1984 ³

IV. Cell Transformation Assays

Mammalian cell cultures:

1. human lymphoblast transformation	+	?	Meretoja et al., 1976
2. 4 <i>in vitro</i> transformation studies, rat & hamster	4+	R	cited in EPA, 1985 ²
3. Syrian Hamster embryo, HGPRT and TAPase loci	+	A	Tsutsui et al., 1984

FOOTNOTES:

1.

1. Quality assessment is a judgement of the overall validity of the study. A = acceptable (this indicates that useful information is provided), I = inadequate (this indicates flaws in study design, data interpretation, or questionable significance), ? = unable to judge (when uncommon study is used with little basis for comparison or no reference compounds, but apparently acceptable study design and interpretation. May also be used when there is inadequate information to make a judgement), R = signifies that the study was cited in a review, but original study was not evaluated. If the review (e.g. EPA or CDFA) gave a quality rating, this is indicated prior to the R.

2 U.S.E.P.A.: Amitrole Position Document 2/3, dated 9/30/85. Mutagenicity summary:

" Amitrole has been evaluated in a variety of mutagenicity test systems. Although positive results were reported [in 2 studies], 49 other *Salmonella* gene mutation tests and 9 other *E. coli* tests were negative. The validity of the two positive studies is questionable. The weakly positive results by Carere *et al.* were in an unvalidated system using unusual bacteria. The mechanisms for this [*sic*] positive results

reported for the DNA repair assays can not be determined without positive gene mutation or chromosome aberration assays. The negative results in the sister chromatid exchange assay in mammalian cells in culture (which is a very sensitive assay) and the chromosome aberration assay in culture human lymphocytes or *in vivo* mouse bone assays. [sic] Amitrole does not present a potential for heritable genetic effects.

Amitrole induces transformation in cultured cells and was positive in four *in vitro* transformation studies using rat and hamster cells ... following treatment of 0.1 to 100 µg/ml. This test is used to establish the malignant activities of test compounds on mammalian cells *in vitro*. Cells treated *in vitro* with chemical carcinogens give rise to foci of cellular growth superimposed on the cell monolayer. If these foci are picked from the cultures, grown to larger numbers, and injected into animals, a malignant tumor will be obtained, in most cases. Therefore, the appearance of piled-up colonies in treated cell cultures is correlated with malignant transformation. In addition, weak cellular transformation capacity was observed in EUE cells (no data presented, only summary) (Benigni, 1980.)

The Agency concludes that "available transformation assays neither determined a mechanism for tumor formation nor necessarily demonstrated that a transformation inducer is genotoxic. These results support oncogenicity potential but not necessarily mutagenicity potential"

3. National Health and Medical Research Council [of Canada]: Report of the Working Party on Amitrole, ninety-seventh session, June 1984. Mutagenicity summary:

"Although sporadic positive responses have been recorded in various microbial assays as well as in assays for aneuploidy in yeast, and for transformation, sister chromatid exchanges and unscheduled DNA synthesis in mammalian cells, these reports suffer certain statistical or technical deficiencies and are not considered to provide adequate evidence for amitrole as a DNA-damaging, mutagenic or transforming chemical". This report is a review of 201 references related to amitrole mutagenicity and carcinogenicity.

Because of the large number of studies available on the mutagenicity of amitrole, and because these studies have been thoroughly reviewed previously by qualified agencies (see above), this review table is not exhaustive, but represents an independent review of many of the most useful mutagenicity studies available.

Review Table for Mutagenicity of Asulam

<u>TEST ORGANISM TYPE</u>	<u>Response</u>	<u>Quality</u> ¹	<u>Reference</u>
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I. Point Mutations or Specific Locus tests

Microbial assays:

1. Ames TA 98, 100, 1535, 1537, 1538, ±S9	-	IR ² AR ³	CDFA, 1986; EPA, 1986;
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mammalian cell cultures:

1.

in vivo host mediated assays:

1.

II. DNA Damage / Repair Tests

Microbial assays:

1.

Mammalian Cell culture:

1. UDS in HeLa S3 cells	-	IR ³	CDFA, 1986
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III. Chromosomal Abberations / Cytogenetic tests

drosophila tests:

1.

mammalian cell cultures:

1.

in vivo animal studies:

1. dominant lethal test, mice	-	IR ² ?R ³	CDFA, 1986; EPA, 1986;
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in vivo / *in vitro* Human studies:

1. PHA-M stimulated human lymphocytes	-	IR ³	CDFA, 1986
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plant material assays:

1.

IV. Cell Transformation Assays

1. C3H/10T ^{1/2} cell transformation	-	IR ² AR ³	CDFA, 1986; EPA, 1986;
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Footnotes:

1. Quality assessment is a judgement of the overall validity of the study. A = acceptable (this indicates that useful information is provided), I = inadequate (this indicates flaws in study design, data interpretation, or questionable significance), ? = unable to judge (when uncommon study is used with little basis for comparison or no reference compounds, but apparently acceptable study design and interpretation. May also be used when there is inadequate information to make a judgement), R = signifies that the study was cited in a review, but original study was not evaluated. If the review (e.g. EPA or CDFA) gave a quality rating, this is indicated prior to the R.

2. CDFA, California Department of Food and Agriculture, Medical Toxicology Branch, Summary of Toxicology Data- Asulam, SB#950-219, Tolerance # 360, dated December 4, 1986.

3. EPA Tox one liners, No.62A, Asulam, dated 1/29/85

Review Table for Mutagenicity of Atrazine

<u>TEST ORGANISM TYPE</u>	<u>Response</u>	<u>Quality</u> ¹	<u>Reference</u>
I. Point Mutations or Specific Locus tests			
Microbial assays:			
1. Ames TA98, 100, 1535,1537, ±S9 (SRI)	-	IR ² AR ³	CDFA, 1986 ² , EPA 1986 ³
2. Ames TA 100, 1535, 1537, ± S9 (Ciba-Geigy)	-	IR ²	CDFA, 1986
3. Ames, old nomenclature, -S9	-	I	Andersen et al., 1972
4. Reversion of bacteriophages N17 and AP72 to T ₄	-	I	" " "
5. Ames TA98, 100, 1535,1537, ±S9 (SRI)	-	A	Eisenbeis et al., 1981
6. <i>S. cerevisiae</i> , ± mouse S9	-	I(abs)	deBertoldi et al., 1980
7. <i>Aspergillus nidulans</i> , ± mouse S9	-	I(abs)	deBertoldi et al., 1980
8. Ames test, "9 strains"	-	R ⁴	Loprieno & Adler, 1980
9. <i>S. typhimuriam</i> , 8-azaguanine resistance	-	R ⁴	Loprieno & Adler, 1980
10. <i>S. coelicolor</i> , strp resistance (with potato micros)	+	R ⁴	Loprieno & Adler, 1980
11. <i>S. cerevisiae</i> , + potato microsomes	-	R ⁴	Loprieno & Adler, 1980
12. <i>E. coli</i> , ampicillin resist.	-	R ⁴	Loprieno & Adler, 1980
13. <i>Schizosaccharomyces pombe</i> , ± mouse S9, ± maize S9	-	I(abs)	Chollet et al., 1980
14. Ames, TA98, + <i>Z. maize</i> (plant) metabolic activation	+	A	Plewa et al., 1984
mammalian cell cultures:			
1. V79 cells, 6-thioguanine resist., + potato microsomes	+	R ⁴	Loprieno & Adler, 1980
<i>in vivo</i> host mediated assays:			
1. <i>Salmonella</i> TA 1535 or 1538, in mice	-	R ²	CDFA, 1986
2. <i>E. coli</i> forward mutation	-	I(abs)	deBertoldi et al., 1978
3. <i>E. coli</i> forward mutation	+	I(abs)	Solte and Neale, 1980
II. DNA Damage / Repair Tests			
Microbial assays:			
1.			
Mammalian Cell culture:			
1. UDS, EUE human cells, with potato microsomes	+	R ⁴	Loprieno & Adler, 1980
III. Chromosomal Abberations / Cytogenetic tests			
drosophila tests:			
1. dominant lethals (egg hatching success)	+	I(abs)	Murnik, 1976
2. recessive lethal	-	I(abs)	Loprieno et al., 1980
mammalian cell cultures:			
1. chinese hamster ovary cells	-	R ⁴	Loprieno & Adler, 1980

2. mouse bone marrow cells	+	R	Ehling, 1980, in Crump et al., 1986
3. mouse bone marrow cells	-	R ⁴	Loprieno & Adler, 1980
4. sister chromatid exchange, hamster cells	-	R ⁴	Loprieno & Adler, 1980
<i>in vivo</i> animal studies:			
1. mouse dominant lethal mutations	-	R	Ehling 1980, in Crump, 1986;
2. mouse dominant lethal mutations (spermatids)	+	R ⁴	Loprieno & Adler, 1980
3. mouse bone marrow, "chromosome analysis"	+	I(abs)	Kliesch & Adler, 1983
4. mouse bone marrow, micronucleus test	-	I(abs)	Kliesch & Adler, 1983
5. mouse bone marrow, "clastogenic activity"	-	I(abs)	Chollet et al., 1980
6. bone marrow cells, "spermatogonia and diakinesis"	-	I(abs)	Chollet et al., 1980
7. mouse dominant lethal, post-implantation loss	-	I(abs)	Chollet et al., 1980
8. mouse dominant lethal, pre-implantation loss	+	I(abs)	Chollet et al., 1980
<i>in vivo / in vitro</i> Human studies:			
1. cultured human lymphocytes	-	I(abs)	Ghiazza et al., 1984
plant material assays:			
1. <i>Tradescantia</i> micronucleus test	-	I	Ma et al., 1984
2. <i>Pelargonium zonale</i> chlorophyll defects	-	I(abs)	Pohleim et al., 1976
3. <i>Vicia</i> root tip SCE and aberrations	+	R	Ma, 1982
4. Maize wx locus assay	+	A	Plewa et al., 1984

IV. Cell Transformation Assays

1. fibroblasts, SHEM cells (early passage), no S9	+	A	Dunkel et al., 1981
2. virus infected, R-MuLV-RE cells	+	A	Dunkel et al., 1981

Footnotes:

1. Quality assessment is a judgement of the overall validity of the study. A = acceptable (this indicates that useful information is provided), I = inadequate (this indicates flaws in study design, data interpretation, or questionable significance), ? = unable to judge (when uncommon study is used with little basis for comparison or no reference compounds, but apparently acceptable study design and interpretation. May also be used when there is inadequate information to make a judgement), R = signifies that the study was cited in a review, but original study was not evaluated. If the review (e.g. EPA or CDFA) gave a quality rating, this is indicated prior to the R.

2. California Department of Food and Agriculture, Medical Toxicology Branch, Summary of Toxicology Data - Atrazine SB950-008, Tolerance #220, dated August 11, 1986.

3. EPA one liner no. 63 - Atrazine, dated 07/09/85

4. This paper is a preliminary report of "a coordinated comparative test programme to assess the mutagenic effects of five chemical in as many different assay systems as possible." This study was sponsored by the European Economic Community. Few details of experimental protocols and design are provided, so no evaluation of adequacy of studies can be made.

Review Table for Mutagenicity of Bromacil

<u>TEST ORGANISM TYPE</u>	<u>Response</u>	<u>Quality</u> ¹	<u>Reference</u>
I. Point Mutations or Specific Locus tests			
Microbial assays:			
1. Ames test, TA100, 98, 1535, 1537, 1538 ± S9	-	A	Moriya et al., 1983
2. Ames test, TA 100, 1535, 1537, 1538, +mouse S9	-	R ²	Waters et al., 1981
4. <i>S. cerevisiae</i> D3 recombination	-	R ²	"
6. <i>S. cerevisiae</i> D3 and D7 assays, ±S9	-	I(abs)	Riccio et al., 1981
7. Ames test, strains & methods unspecified	+	I	Njagi & Gopalan 1980
9. bacteriophage AP72 of <i>E. coli</i>	-	I,R	McGahen and Hoffman, 1966, cited in CDFA, 1986 ³ .
mammalian cell cultures:			
1. mouse lymphoma L5178Y forward mutation for TK±	+	R	Waters et al., 1982, cited in CDFA, 1986 ³ .
<i>in vivo</i> host mediated assays:			
1.			
II. DNA Damage / Repair Tests			
Microbial assays:			
1. <i>E. coli</i> WP2 <i>hcr</i>	-	A	Moriya et al., 1983
2. <i>E. coli</i> WP2 <i>uvrA</i> ⁻	-	R ²	Waters et al., 1981
3. <i>E. coli</i> W3110 & P3478 repair deficient, (Pol A)	-	R ²	"
4. <i>B. subtilis</i> H17 and M45 <i>rec</i> ⁺	-	R ²	"
Mammalian Cell culture:			
1. UDS in human fetal lung fibroblasts (WI-38 cells)	-	R ²	Waters et al., 1981
III. Chromosomal Abberations / Cytogenetic tests			
drosophila tests:			
1. complete and/or partial loss of chromosomes <i>mus</i> - 302 repair defective females	-	A	Woodruff et al., 1983
2. sex-linked recessive lethal test	+	R ²	Waters et al., 1981
3. dominant lethal test	+	I(abs)	Murnik, 1976
4. non-dysjunction and chromosome loss	-	I(abs)	"
mammalian cell cultures:			
1.			
<i>in vivo</i> animal studies:			
1. mouse dominant lethal test	-	R ²	Waters et al., 1981
2. Sister chromatid exchange in CHO cells	-	R	Waters, et al., 1982, cited in CDFA, 1986 ³ .
3. mouse micronucleus test	-	R	" "

in vivo / in vitro Human studies:

1.

plant material assays:

1.

IV. Cell Transformation Assays

Footnotes:

1. Quality assessment is a judgement of the overall validity of the study. A = acceptable (this indicates that useful information is provided), I = inadequate (this indicates flaws in study design, data interpretation, or questionable significance), ? = unable to judge (when uncommon study is used with little basis for comparison or no reference compounds, but apparently acceptable study design and interpretation. May also be used when there is inadequate information to make a judgement), R = signifies that the study was cited in a review, but original study was not evaluated. If the review (e.g. EPA or CDFA) gave a quality rating, this is indicated prior to the R.

2. This reference is a summary of several contract studies performed on Bromacil and other pesticides over several years. The contracts were sponsored by the EPA and performed at SRI International, Menlo Park, CA, and WARF Institute, Inc, Madison WI. This review is apparently written by the EPA contract officer as lead author, with the scientists at SRI and WARF as co-authors. We did not review the original EPA contract reports.

3. California Department of Food and Agriculture (1986). Summary of toxicology Data - Bromacil, SB 950-020, Tolerance #210, dated December 8, 1986.

Review Table for Mutagenicity of Dalapon

<u>TEST ORGANISM TYPE</u>	<u>Response</u>	<u>Quality</u> ¹	<u>Reference</u>
I. Point Mutations or Specific Locus tests			
Microbial assays:			
1. Ames test, strains identified by old nomenclature; -S9	-	I	Anderson et al., 1972
2. Ames TA 98, 100, ±S9	-	A	Moriya et al., 1983
3. <i>Aspergillus nidulans</i> , 8-azaguanine resist.	-	?	Bignami et al., 1977
4. " " , somatic recombinations .	-	?	"
5. " " , non-dysjunction	-	?	"
6. " " , non-dysjunction	-	A	Morpurgo et al., 1979
7. Ames test, TA1535, 1536, 1537, 1538; ± S9	-	A	Carere <i>et al.</i> , 1978
8. <i>S. coelicolor his A1A</i> , forward mutation (S9 ?)	+	?	" "
mammalian cell cultures:			
1.			
<i>in vivo</i> host mediated assays:			
1.			
II. DNA Damage / Repair Tests			
Microbial assays:			
1.			
Mammalian Cell culture:			
1.			
III. Chromosomal Abberations / Cytogenetic tests			
drosophila tests:			
1.			
mammalian cell cultures:			
1. CHO cells ±S9	-	IR	CDFA, 1986 ²
2. mouse bone marrow, no study details	+	I(abs)	Kurinyi et al., 1982
<i>in vivo</i> animal studies:			
1.			
<i>in vivo</i> / <i>in vitro</i> Human studies:			
1.			
plant material assays:			
1. <i>Pelargonium zonale</i> growth inhibition	+	?	Pohleim et al., 1976

IV. Cell Transformation Assays

Footnotes:

1. Quality assessment is a judgement of the overall validity of the study. A = acceptable (this indicates that useful information is provided), I = inadequate (this indicates flaws in study design, data interpretation, or questionable significance), ? = unable to judge (when uncommon study is used with little basis for comparison or no reference compounds, but apparently acceptable study design and interpretation. May also be used when there is inadequate information to make a judgement), R = signifies that the study was cited in a review, but original study was not evaluated. If the review (e.g. EPA or CDFA) gave a quality rating, this is indicated prior to the R.

2. California Department of Food and Agriculture, Medical Toxicology Branch, Summary of Toxicology Data - Dalapon SB 950-502, tolerance #150, "super summary" dated May 12, 1986. Most of the above referenced studies were reviewed, but individual rankings were provided for only a few. However, CDFA indicated data gaps, based on "inadequate studies", in all three areas of mutagenicity for dalapon (gene mutation, chromosome and DNA damage).

3. No mutagenicity data were reviewed in EPA Tox one liners.

Summary of Mutagenicity Studies of 2,4-D

<u>TEST ORGANISM TYPE</u>	<u>Response</u>	<u>Quality</u> ¹	<u>Reference</u>
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I. Point Mutations or Specific Locus tests

Microbial assays:

1. Ames TA 98, 100, 1535, 1527, 1538, ±S9	-	A	Moriya et al, 1983
2. Ames, strains unspecified, - S9	-	I	Anderson et al. 1972
3. " "	-	I	Nagy et al., 1975
4. " "	-	R	Fahrig, 1974
5. Ames TA 98, 100, 1535, 1527, 1538, ±S9	-	R	Waters et al., 1981b
6. <i>Streptomyces</i>	±	A	Zetterberg, 1977
7. <i>Saccharomyces cerevisiae</i>	-	R	Fahrig, 1974
8. <i>Saccharomyces cerevisiae</i> (low pH)	+	A	Siebert & Lemperle, 1974
9. " " "	+	A	Zetterberg et al., 1977
10. " " mitotic recom.	-	A	Waters et al., 1981b

Mammalian cell cultures:

1. Chinese hamster V79 cells	+	A	Ahmed et al., 1977a
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II. DNA Damage / Repair Tests

Microbial assays:

1. <i>E. Coli</i> (WP2 <i>hcr</i>)	-	A	Moriya et al., 1983
2. "	-	I	Ficsor Piccolo, 1972
3. " (WP2 <i>uvr A</i> ⁻)	-	R	Waters et al., 1981b
4. " (Pol A)	+	R	Water et al., 1981b
5. <i>Bacillus subtilis</i>	+	R	Waters et al., 1981b

Mammalian Cell culture:

1. UDS rat hepatocytes	-	A	Probst et al., 1981
2. human fetal lung fibroblasts	-	R	Waters et al., 1981b

Other:

1. inhibition of testicular DNA synthesis	+	R	Seiler, 1979
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III. Chromosomal Abberations / Cytogenetic tests

Drosophila tests:

1. somatic mutations (eye color)	±	A	Rasmusson et al., 1976
2. sex-linked recessive lethality	-	?	Vogel & Chandler, 1974
3. " " "	+	A	Magnusson et al., 1977
4. chromosome loss, non-dysj., X-Y recomb.	-	A	Ramel, 1977
5. chromosome loss	-	A	Woodruff et al., 1983

Mammalian cell cultures:

1. human lymphocyte SCE	+	A	Korte & Jalal, 1982
2. CH bone marrow cells	±	A	Linnainmaa, 1984
3. bovine lymphocyte mitogenesis	-	A	McCabe & Nowak, 1986
4. bovine kidney cells & blood cells	±	I	Bongso & Basrur, 1973
5. human embryonic fibroblasts	+	I	Berin et al., cited in Seiler, 1978 (in russian)

In vivo animal studies:

1. rat lymphocyte SCE	-	A	Linnainmaa, 1984
2. CH bone marrow cells	-	A	Linnainmaa, 1984
3. micronucleus/mouse	-	A	Jenssen and Renberg, 1976
4. micronucleus mouse	-	R	Seiler, 1978
5. Dominant lethal test	-	A	Epstein, et. al, 1972
6. chromosomal breakage (mouse)	+	R	three Russian studies, cited in Selier, 1978

In vivo human studies:

1. Lymphocyte chromosomal abber.	+	I	Yoder et al., 1973
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Plant material assays:

1. <i>Pelargonium zonale</i> mutation	±	?	Pohlheim et al., 1977
2. Chromosomal abber. in <i>Vicia faba</i>	+	?	Amer & Ali, 1974
3. anaphase abberations in plant cells	-	?	Singh & Harvey, 1975
4. <i>Nicotiana</i> chromosomal abberations	+	?	Ronchi et al., 1976
5. polyploidy, fragmentation in plants	++	?	Grant, 1973

IV. Cell Transformation

1. SV-40 transformation of human fibroblasts	+	A	Ahmed et al., 1977b
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Footnotes:

1. Quality assessment is a judgement of the overall validity of the study. A = acceptable (this indicates that useful information is provided), I = inadequate (this indicates flaws in study design, data interpretation, or questionable significance), ? = unable to judge (when uncommon study is used with little basis for comparison or no reference compounds, but apparently acceptable study design and interpretation. May also be used when there is inadequate information to make a judgement), R = signifies that the study was cited in a review, but original study was not evaluated. If the review (e.g. EPA or CDFA) gave a quality rating, this is indicated prior to the R.

Review Table for Mutagenicity of 2,4-DP (Dichlorprop)

<u>TEST ORGANISM TYPE</u>	<u>Response</u>	<u>Quality</u> ¹	<u>Reference</u>
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I. Point Mutations or Specific Locus tests

Microbial assays:

1. Ames TA 98, 1537, 1538, ± S9	-	AR ²	EPA, 1984 ²
2. <i>S. cerevisiae</i> D7, mitotic cross over, no S9	-	AR ²	EPA, 1984 ²
3. <i>S. cerevisiae</i> D7, mitotic gene conversion, no S9	+	AR ²	EPA, 1984 ²
4. <i>S. cerevisiae</i> D7, reverse mutation, no S9	+	AR ²	EPA, 1984 ²

mammalian cell cultures:

1.

in vivo host mediated assays:

1.

II. DNA Damage / Repair Tests

Microbial assays:

1. E coli W3110 & p3478, UDS (?)± S9	±	AR ²	EPA, 1984 ²
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Mammalian Cell culture:

1.

Other:

1. inhibition of testicular DNA synthesis	-	I	Seiler, 1979
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III. Chromosomal Abberations / Cytogenetic tests

drosophila tests:

1.

mammalian cell cultures:

1.

in vivo animal studies:

1.

in vivo / *in vitro* Human studies:

1.

plant material assays:

1.

IV. Cell Transformation Assays

Footnotes:

1. Quality assessment is a judgement of the overall validity of the study. A = acceptable (this indicates that useful information is provided), I = inadequate (this indicates flaws in study design, data interpretation, or questionable significance), ? = unable to judge (when uncommon study is used with little basis for comparison or no reference compounds, but apparently acceptable study design and interpretation. May also be used when there is inadequate information to make a judgement), R = signifies that the study was cited in a review, but original study was not evaluated. If the review (e.g. EPA or CDFA) gave a quality rating, this is indicated prior to the R.

2. EPA Tox One-liner, Tox Chem No. 320 - 2,4-DP, dated 8/20/84.

Review Table for Mutagenicity of Dicamba

<u>TEST ORGANISM TYPE</u>	<u>Response</u>	<u>Quality¹</u>	<u>Reference</u>
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I. Point Mutations or Specific Locus tests

Microbial assays:

1. Ames TA 98, 100, 1535, 1537, 1538, ±S9	-	A	Eisenbeis et al., 1981
2. Ames TA 98, 100, ±S9	-	A	Moriya et al., 1983
3. Ames Test, strains identified by old nomenclature; -S9	-	I	Andersen et al., 1972
4. rII mutants of T ₄ Bacteriophage	-	I	" " "
5. Ames test, TA 100, 1535, 1537, 1538, +mouse S9	-	AR ³	Waters et al., 1981
6. <i>S. cerevisiae</i> D3 recombination	-	I,R ³	"

mammalian cell cultures:

1.

in vivo host mediated assays:

1.

II. DNA Damage / Repair Tests

Microbial assays:

1. <i>B. subtilis</i> H17 and M45 rec+	+	A,R ³	Waters et al., 1981
2. <i>E. Coli</i> WP2 <i>uvrA</i> ⁻	-	A,R ³	"
3. <i>E. Coli</i> W3110 & P3478 repair deficient, (Pol A)	+	A,R ³	"

Mammalian Cell culture:

1. Unscheduled DNA synthesis, primary rat hepatocytes	-	AR ^{4,5}	EPA, 1986; CDFA, 1986
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III. Chromosomal Abberations / Cytogenetic tests

drosophila tests:

1. sex-linked recessive lethal test	±	A,R ³	Waters et al., 1981
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mammalian cell cultures:

1.

in vivo animal studies:

1.

in vivo / *in vitro* Human studies:

1.

plant material assays:

1. tradescantia-micronucleus tests	+	?	Ma et al., 1984
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IV. Cell Transformation Assays

Footnotes:

1. Quality assessment is a judgement of the overall validity of the study. A = acceptable (this indicates that useful information is provided), I = inadequate (this indicates flaws in study design, data interpretation, or questionable significance), ? = unable to judge (when uncommon study is used with little basis for comparison or no reference compounds, but apparently acceptable study design and interpretation. May also be used when there is inadequate information to make a judgement), R = signifies that the study was cited in a review, but original study was not evaluated. If the review (e.g. EPA or CDFA) gave a quality rating, this is indicated prior to the R.

2. This extensive study of herbicide mutagenicity was conducted by SRI International and WARF Research Institute under contract to EPA. The results of each of these studies have been reported in numerous forms, including the book citation listed, as well as in the *Journal of Environmental Science and Health*, B15(6), 867-906, 1980. These same studies have also been evaluated by CDFA and EPA (see notes 3 and 4 below), and have been judged to be adequate, with the exception of the yeast mutation assay (D3 recombination) in which no positive control was reported.

3. CDFA, California Department of Food and Agriculture, Medical Toxicology Branch, Summary of Toxicology Data - Dicamba, SB950 - 070, tolerance #227, dated August 8, 1986.

4. EPA Tox one liners, No. 295 - Dicamba, dated 06/11/85.

Review Table for Mutagenicity of Diuron

<u>TEST ORGANISM TYPE</u>	<u>Response</u>	<u>Quality</u> ¹	<u>Reference</u>
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I. Point Mutations or Specific Locus tests

Microbial assays:

- | | | | |
|---|---|---------------------------------|--------------------------|
| 1. Ames TA 98, 100, 1535, 1537, 1538, ±S9 | - | A | Moriya et al, 1983 |
| 2. Ames, strains identified by old nomenclature; - S9 | - | I | Anderson et al., 1972 |
| 3. Ames test, strains unidentified, - S9 | - | R | Fahrig, 1973 |
| 4. Ames test, strains unspecified, ± S9 | - | IR ² AR ³ | EPA, 1986;
CDFA, 1986 |

mammalian cell cultures:

- | | | | |
|-------------------------------------|---|-------------------|--------------------------|
| 1. CHO/HGPRT forward mutation assay | - | AR ^{2,3} | EPA, 1986;
CDFA, 1986 |
|-------------------------------------|---|-------------------|--------------------------|

in vivo host mediated assays:

- 1.

II. DNA Damage / Repair Tests

Microbial assays:

- 1.

Mammalian Cell culture:

- | | | | |
|---|---|-----------------------------------|--------------------------|
| 1. Unscheduled DNA synthesis, primary rat hepatocytes | - | AR ² IR ^{3,4} | EPA, 1986;
CDFA, 1986 |
|---|---|-----------------------------------|--------------------------|

III. Chromosomal Abberations / Cytogenetic tests

drosophila tests:

- 1.

mammalian cell cultures:

- 1.

in vivo animal studies:

- | | | | |
|--------------------------|---|-------------------|-------------------------|
| 1. rat bone marrow cells | ± | AR ^{2,3} | EPA, 1986
CDFA, 1986 |
|--------------------------|---|-------------------|-------------------------|

in vivo / *in vitro* Human studies:

- 1.

plant material assays:

- 1.

IV. Cell Transformation Assays

Footnotes:

1. Quality assessment is a judgement of the overall validity of the study. A = acceptable (this indicates that useful information is provided), I = inadequate (this indicates flaws in study design, data interpretation, or questionable significance), ? = unable to judge (when uncommon study is used with little basis for comparison or no reference compounds, but apparently acceptable study design and interpretation. May also be used when there is inadequate information to make a judgement), R = signifies that the study was cited in a review, but original study was not evaluated. If the review (e.g. EPA or CDFA) gave a quality rating, this is indicated prior to the R.

2. EPA Tox one liners, No. TL-9, Diuron, dated 10/14/86

3. CDFA (California Department of Food and Agriculture), Medical Toxicology Branch, Summary of Toxicology Data - Diuron, SB 950-018, Tolerance # 106, dated December 8, 1986.

4. CDFA classified this study as inadequate because pages were missing from the report at the time of review, so no review was completed.

Review Table for Mutagenicity of Fosamine

<u>TEST ORGANISM TYPE</u>	<u>Response</u>	<u>Quality</u> ¹	<u>Reference</u>
I. Point Mutations or Specific Locus tests			
Microbial assays:			
1. Ames TA 98, 100, 1535, 1537, 1538, ±S9	-	IR	CDFA, 1986 ²
2. Ames TA 98, 100, 1535, 1537, 1538, ±S9	-	A	Moriya et al., 1983
mammalian cell cultures:			
1. CHO/HGPRT	-	AR	CDFA, 1986 ² , EPA, 1986 ³
<i>in vivo</i> host mediated assays:			
1.			
II. DNA Damage / Repair Tests			
Microbial assays:			
1. <i>E. coli</i> WP2 <i>hcr</i>	-	A	Moriya et al., 1983
Mammalian Cell culture:			
1. rat hepatocytes UDS	-	I ² A ³ R	CDFA, 1986 ² , EPA, 1985 ³
III. Chromosomal Abberations / Cytogenetic tests			
drosophila tests:			
1.			
mammalian cell cultures:			
1. Chinese hamster cells, ± S9	+	I ² A ³ R	CDFA, 1986 ² , EPA, 1985 ³
<i>in vivo</i> animal studies:			
1. rat cytogenetics, tissue unspecified	-	I ² A ³ R	CDFA, 1986 ² , EPA, 1985 ³
<i>in vivo</i> / <i>in vitro</i> Human studies:			
1.			
plant material assays:			
1.			

IV. Cell Transformation Assays

Footnotes:

1. Quality assessment is a judgement of the overall validity of the study. A = acceptable (this indicates that useful information is provided), I = inadequate (this indicates flaws in study design, data interpretation, or questionable significance), ? = unable to judge (when uncommon study is used with little basis for comparison or no reference compounds, but apparently acceptable study design and interpretation. May also be used when there is inadequate information to make a judgement), R = signifies that the study was cited in a review, but original study was not evaluated. If the review (e.g. EPA or CDFA) gave a quality rating, this is indicated prior to the R.

2. California Department of Food and Agriculture, Medical Toxicology Branch, Summary of Toxicology Data - Fosamine, SB 950-312, Tolerance # 50097, dated August 6, 1986

3. EPA Tox one liners, No. 465G-Fosamine, dated 7/14/85.

4. An exhaustive computer-based search of the literature revealed only a single published study of fosamine mutagenicity.

Review Table for Mutagenicity of Glyphosate

<u>TEST ORGANISM TYPE</u>	<u>Response</u>	<u>Quality</u> ¹	<u>Reference</u>
I. Point Mutations or Specific Locus tests			
Microbial assays:			
1. Ames assay, TA 100, 98, 1535, 1537, 1538 ± S9	-	A	Moriya et al., 1983
2. Ames test, TA100, 98, 1535, 1537, 1538 +S9	-	A	Long & Li, 1987 ²
drosophila tests:			
1.			
mammalian cell cultures			
1. CHO/HGPRT forward mutation, ±S9	-	A	Long & Li, 1987
<i>in vivo</i> host mediated assays:			
1. host mediated, rats and mice	-	I, R	EPA, 1986 ³
II. DNA Damage / Repair Tests			
Microbial assays			
1. <i>B. Subtilis</i> H17 (rec+), M45 (rec-); recombination	-	A, (I ⁴)	Long & Li, 1987 ²
2. <i>E. coli</i> WP2 <i>hcr</i>	-	A	Moriya et al., 1983
Mammalian Cell culture:			
1. UDS in hepatocytes	± ⁵	A(I ⁵)	Long & Li, 1987
III. Chromosomal Abberations / Cytogenetic tests			
mammalian cell cultures:			
1.			
<i>in vivo</i> animal studies:			
1. mouse bone marrow, chromosome abberations	-	A	Long & Li, 1987
2. mouse dominant lethal	-	A(I ⁶)	Long & Li, 1987
<i>in vivo / in vitro</i> Human studies:			
1. Sister chromatid exchange in cultured lymphocytes	+	I	Vigfusson & Vyse 1980
2.			
plant material assays:			
1.			
IV. Cell Transformation Assays			

Footnotes:

1. Quality assessment is a judgement of the overall validity of the study. A = acceptable (this indicates that useful information is provided), I = inadequate (this indicates flaws in study design, data interpretation, or questionable significance), ? = unable to judge (when uncommon study is used with little basis for comparison or no reference compounds, but apparently acceptable study design and interpretation. May also be used when there is inadequate information to make a judgement), R = signifies that the study was cited in a review, but original study was not evaluated. If the review (e.g. EPA or CDFA) gave a quality rating, this is indicated prior to the R.

2. This reference is cited as an abstract presented at the 1987 meeting of the Society of Toxicology. However, descriptions of methods and actual results were provided by the author for our independent review. A manuscript of this work is currently in preparation and will be submitted for publication in a peer-reviewed journal.

3. Environmental Protection Agency, (1986). EPA-Tox one liners, No. 661A - Glyphosate, dated 04/08/86.

4. CDFA, 1986: California Department of Food and Agriculture, Chemical Toxicology Branch, Summary Review of Glyphosate, dated Dec. 2, 1986. This particular study was judged "incomplete, unacceptable" because "only single plates per treatment, doses tested from 20 - 200 µg/disk but reported as 20 - 2000". However, data provided to us shows full range to to 2000 µg per plate. EPA³ has accepted this study as "core minimal".

5. CDFA judged this study to be "because authors did not provide justification for "dismissing the high dose result ... without further information". Although the authors reported no effect, the highest dose did show a small but significant increase in nuclear grains. Thus, we report the effects as ±, as there was no indication of any effect except at the highest dose (0.125 mg/ml). the design and the conduct of the assay appear adequate. The EPA³ has classified this study as negative study with "core acceptable" grade.

6. CDFA judges this study to be "Incomplete, unacceptable" because "too few animals, individual data missing". We believe 10 males per treatment group, mated to 2 females for 8 weeks post-dosing is an adequate number of animals to be of some scientific value. The data we were provided did not indicate that any data were missing, although original records were not provided. Never-the-less, the information provided us indicates that all animals are accounted for, and appears to be adequately conducted and reported, and thus is judged to be scientifically valid. EPA³ has accepted this negative study as a "core minimum" .

Review Table for Mutagenicity of Hexazinone

<u>TEST ORGANISM TYPE</u>	<u>Response</u>	<u>Quality</u> ¹	<u>Reference</u>
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I. Point Mutations or Specific Locus tests

Microbial assays:

1. Ames TA 98, 100, 1535, 1537, 1538, ±S9	-	AR	EPA, 1984 ²
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mammalian cell cultures:

1.

in vivo host mediated assays:

1.

II. DNA Damage / Repair Tests

Microbial assays:

1.

Mammalian Cell culture:

1. rat hepatocytes UDS	-	AR	EPA, 1984 ²
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III. Chromosomal Abberations / Cytogenetic tests

drosophila tests:

1.

mammalian cell cultures:

1. Chinese hamster cells, without S9	+	AR	EPA, 1984 ²
2. Chinese hamster cells, with S9	+	AR	EPA, 1984 ²

in vivo animal studies:

1. rat bone marrow cytogenetic	-	AR	EPA, 1984 ²
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in vivo / *in vitro* Human studies:

1.

plant material assays:

1.

IV. Cell Transformation Assays

Footnotes:

1. Quality assessment is a judgement of the overall validity of the study. A = acceptable (this indicates that useful information is provided), I = inadequate (this indicates flaws in study design, data interpretation, or questionable significance), ? = unable to judge (when uncommon study is used with little basis for comparison or no reference compounds, but apparently acceptable study design and interpretation. May also be used when there is inadequate information to make a judgement), R = signifies that the study was cited in a review, but original study was not evaluated. If the review (e.g. EPA or CDFA) gave a quality rating, this is indicated prior to the R.

2. EPA Tox one liners, No. 271 AA - Hexazinone, dated 9/20/84. Hexazinone Registration Standard, dated February, 1982, indicates that no further mutagenicity testing is required for hexazinone under FIFRA (Table A, p. 3-9).

3. An exhaustive computer based search of the literature revealed no published studies of hexazinone mutagenicity. No California Department of Food and Agriculture review was available for Hexazinone.

Review Table for Mutagenicity of Picloram (Tordon)

<u>TEST ORGANISM TYPE</u>	<u>Response</u>	<u>Quality</u> ¹	<u>Reference</u>
I. Point Mutations or Specific Locus tests			
Microbial assays:			
1. Ames test, TA1535, 1536, 1537, 1538; ± S9 (EPA ³ has classified this study as "partially satisfying gene mutation requirement")	-	A (I ²)	Carere <i>et al.</i> , 1978
2. <i>S. coelicolor his A1A</i> , forward mutation (S9 ?)	+	? (I ²)	Carere <i>et al.</i> , 1978
3. <i>Aspergillus nidulans</i> , non-dysjunction	-	? (I ²)	Bignami <i>et al.</i> , 1977
4. <i>Aspergillus nidulans</i> , non-dysjunction	-	A (I ²)	Morpurgo <i>et al.</i> , 1979
5. <i>S. cerevisae</i> (unspecified)	+	I	L'Vova, 1984
6. <i>S. cerevisae</i> (unspecified)	+	I	Guerzoni <i>et al.</i> , 1976, cited in Dow Technical Data Sheet ⁴
7. Ames test, 8 strains unspecified, - S9	-	I	Anderson <i>et al.</i> , 1972
8. Ames test, TA100, 98, 1535, 1537; +S9 (this study is part of NTP-sponsored study with good quality assurance protocols)	-	A	Mortelmans <i>et al.</i> , 1986
mammalian cell cultures:			
1. mouse bone marrow cells (unspecified test)	-	I	L'Vova, 1984
<i>in vivo</i> host mediated assays:			
1.			
II. DNA Damage / Repair Tests			
Microbial assays:			
1.			
Mammalian cell culture:			
1.			
III. Chromosomal Abberations / Cytogenetic tests			
drosophila tests:			
1. complete and partial chromosome loss, <i>mus</i> -302 repair defective females	-	A	Woodruff <i>et al.</i> , 1983
mammalian cell cultures:			
1. human peripheral lymphocytes (unspecified test)	-	I	L'Vova, 1984
<i>in vivo</i> animal studies:			
1. rat bone marrow cells	-	I,R	Johnston <i>et al.</i> , 1976 (also CDFA ³ , 1986)

in vivo Human studies:

1. lymphocyte chromosome aberrations in applicators + I Yoder et al., 1973.

plant material assays:

- 1.

IV. Cell Transformation Assays

mammalian cell cultures:

- 1.

Footnotes:

1. Quality assessment is a judgement of the overall validity of the study. A = acceptable (this indicates that useful information is provided), I = inadequate (this indicates flaws in study design, data interpretation, or questionable significance), ? = unable to judge (e.g. when an unusual test system is used with little basis for comparison or no reference compounds, but apparently acceptable in design and interpretation. May also be used when there is inadequate information to make a judgement), R = signifies that the study was cited in a review, and original study was not evaluated. If a review (e.g. EPA or CDFA) gave a quality rating, this is indicated prior to the R. In certain circumstances, there may be disagreement between our evaluations and those of others. If this occurs, two contradictory ratings may appear, with the rating and source of the contradictory evaluation in parentheses.

2. California Department of Food and Agriculture, Toxicology Branch. Summary of Data - Picloram, SB950-306, Tolerance #292, July 30, 1986. Details of why studies were judged inadequate by CDFA were not provided, so no rational comparison of CDFA judgements with ours can be made.

3. EPA, 1985. Guidance for the Reregistration of pesticide products containing Picloram as the active ingredient. EPA case number 0096, March, 1985.

4. Dow Chemical Company Technical Data Sheet, undated, #137-1640-1183.

5. No "EPA-one liners" were available to compare EPA's "core mutagenicity" evaluations of these studies with ours or CDFA's.

Review Table for Mutagenicity of Simazine

<u>TEST ORGANISM TYPE</u>	<u>Response</u>	<u>Quality</u> ¹	<u>Reference</u>
I. Point Mutations or Specific Locus tests			
Microbial assays:			
1. Ames TA98, 199, 1535, 1537, ±S9	-	I R	CDFA, 1986 ²
2. <i>S. cerevisiae</i> D3 and D7 assays, ±S9	-	I(abs)	Riccio et al., 1981
3. Ames test, TA 100, 1535, 1537, 1538, +mouse S9	-	R ³	Waters et al., 1981
4. <i>S. cerevisiae</i> D3 recombination	-	R ³	"
mammalian cell cultures:			
1. mouse lymphoma L5178Y TK+/-, ±S9	-	I R	CDFA, 1986 ²
2. UDS in human fetal lung fibroblasts (WI-38 cells)	-	R ³	Waters et al., 1981
<i>in vivo</i> host mediated assays:			
1. <i>Salmonella</i> host mediated assay in mice	-	?R	CDFA, 1986 ²
II. DNA Damage / Repair Tests			
Microbial assays:			
1. <i>B. subtilis</i> H17 and M45 rec+	-	R ³	Waters et al., 1981
2. <i>E. Coli</i> WP2 <i>uvrA</i> ⁻	-	R ³	"
3. <i>E. Coli</i> W3110 & P3478 repair deficient, (Pol A)	-	R ³	"
Mammalian Cell culture:			
1. primary rat hepatocytes UDS	-	AR	CDFA, 1986 ²
2. DNA repair (UDS), human fibroblasts, no S9	-	I R	CDFA, 1986 ²
III. Chromosomal Abberatlons / Cytogenetic tests			
drosophila tests:			
1. sex-linked recessive lethal	±	?	Valencia, R. 1981
2. sex-linked recessive lethal	+	R ³	Waters et al., 1981
3. dominant lethal mutations	+	I(abs)	Murnick, 1976
mammalian cell cultures:			
1. Chinese hamsters, micronucleus test	-	I R	CDFA, 1986 ²
<i>in vivo</i> animal studies:			
1.			
<i>in vivo</i> / <i>in vitro</i> Human studies:			
1. cultured human lymphocytes, SCE	+	I	Ghiazza et al., 1984
plant material assays:			
1. <i>Pelargonium zonale</i> chlorophyll defects	+	I(abs)	Pohleim et al., 1976

2. *Vicia* root tip SCE and aberrations + R Ma, 1982

IV. Cell Transformation Assays

Footnotes:

1. Quality assessment is a judgement of the overall validity of the study. A = acceptable (this indicates that useful information is provided), I = inadequate (this indicates flaws in study design, data interpretation, or questionable significance), ? = unable to judge (when uncommon study is used with little basis for comparison or no reference compounds, but apparently acceptable study design and interpretation. May also be used when there is inadequate information to make a judgement), R = signifies that the study was cited in a review, but original study was not evaluated. If the review (e.g. EPA or CDFA) gave a quality rating, this is indicated prior to the R.

2. California Department of Food and Agriculture, Medical Toxicology Branch, Summary of Toxicology Data - Simazine SB950-129, Tolerance #213, dated August 11, 1986.

3. This reference is a summary of several contract studies performed on Simazine and other pesticides over several years. The contracts were sponsored by the EPA and performed at SRI International, Menlo Park ,CA, and WARF Institute, Inc, Madison WI. This review is apparently written by the EPA contract officer as lead author, with the scientists at SRI and WARF as co-authors. We did not review the original EPA contract reports.

Review Table for Mutagenicity of Tebuthiuron

<u>TEST ORGANISM TYPE</u>	<u>Response</u>	<u>Quality</u> ¹	<u>Reference</u>
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I. Point Mutations or Specific Locus tests

Microbial assays:

1. Ames TA 98, 100, 1535, 1537, 1538, ±S9	-	AR	EPA, 1986 ²
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mammalian cell cultures:

1. mouse lymphoma cell forward mutation	±	AR	EPA, 1986 ²
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in vivo host mediated assays:

1.

II. DNA Damage / Repair Tests

Microbial assays:

1.

Mammalian Cell culture:

1. primary rat hepatocytes	?	IR	EPA, 1986 ²
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III. Chromosomal Abberations / Cytogenetic tests

drosophila tests:

1.

mammalian cell cultures:

1.

in vivo animal studies:

1. Chinese hamster bone marrow SCE	?	IR	EPA, 1986 ²
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in vivo / *in vitro* Human studies:

1.

plant material assays:

1.

IV. Cell Transformation Assays

Footnotes:

1. Quality assessment is a judgement of the overall validity of the study. A = acceptable (this indicates that useful information is provided), I = inadequate (this indicates flaws in study design, data interpretation, or questionable significance), ? = unable to judge (when uncommon study is used with little basis for comparison or no reference compounds, but apparently acceptable study design and interpretation. May also be used when there is inadequate information to make a judgement), R = signifies that the study was cited in a review, but original study was not evaluated. If the review (e.g. EPA or CDFA) gave a quality rating, this is indicated prior to the R.

2. EPA-Tox one-liner, number 366AA - tebuthiuron, dated 10/31/86. this is the only source of information on mutagenicity of tebuthiuron available to us for this review.

3. An exhaustive computer-based literature search did not reveal any published mutagenicity studies on tebuthiuron. No California Department of Agriculture review is available.

Review Table for Mutagenicity of Triclopyr (Garlon)

<u>TEST ORGANISM TYPE</u>	<u>Response</u>	<u>Quality</u> ¹	<u>Reference</u>
I. Point Mutations or Specific Locus tests			
Microbial assays:			
1. Ames test, TA 98, 100, 1537, 1538, ±S9	-	AR	EPA, 1985 ² , CDFA, 1986 ³
2. Ames test, TA 98, 100 (different laboratory)	-	I ³ A ² R	EPA, 1985 ² , CDFA, 1986 ³
3. Ames test, TA 98, 100, ±S9	-	A	Moriya et al., 1983
mammalian cell cultures:			
1.			
<i>in vivo</i> host mediated assays:			
1. male mice, <i>Salmonella</i> TA1530 and G46,	?	I	CDFA, 1986 ³
2. male mice, <i>Saccharomyces</i> D3	?	I	CDFA, 1986 ³
II. DNA Damage / Repair Tests			
Microbial assays:			
1. <i>B. subtilus</i> H17/M45 recombination	-	I ³ A ² R	EPA, 1985 ² , CDFA, 1986
Mammalian Cell culture:			
1. primary rat hepatocytes	-	A	CDFA, 1986 ³
III. Chromosomal Abberations / Cytogenetic tests			
drosophila tests:			
1. rat cytogenetic	-	I ³ A ² R	EPA, 1985 ² , CDFA, 1986 ³
mammalian cell cultures:			
1.			
<i>in vivo</i> animal studies:			
1. mouse, dominant lethal assay	-	A, R	EPA, 1985 ² , CDFA, 1986 ³
2. rat, dominant lethal	±	I ³ A ² R	EPA, 1985 ² , CDFA, 1986 ³
3. mouse micronucleus test	-	A	CDFA, 1986 ³
<i>in vivo / in vitro</i> Human studies:			
1.			

plant material assays:

1.

IV. Cell Transformation Assays

Footnotes:

1. Quality assessment is a judgement of the overall validity of the study. A = acceptable (this indicates that useful information is provided), I = inadequate (this indicates flaws in study design, data interpretation, or questionable significance), ? = unable to judge (when uncommon study is used with little basis for comparison or no reference compounds, but apparently acceptable study design and interpretation. May also be used when there is inadequate information to make a judgement), R = signifies that the study was cited in a review, but original study was not evaluated. If the review (e.g. EPA or CDFA) gave a quality rating, this is indicated prior to the R.

2. EPA Tox-one liner, No. 882-I, Garlon, Dated 2/7/85. Evaluations for mutagenicity were all ranked acceptable, supplementary or minimum.

3. California Department of Food and Agriculture, Medical Toxicology Branch, Summary of Toxicology data for Triclopyr, SB 950-227, tolerance #417, dated October 27, 1986. All of the above studies were thoroughly reviewed and ranked as indicated above. In their summary for mutagenicity, CDFA showed "no data gap" for all mutagenicity categories.

4. An exhaustive computer-based literature search revealed only one published mutagenicity study with triclopyr.

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SUMMARY OF ONCOGENICITY STUDIES OF HERBICIDES ¹

<u>Species</u>	<u>Dose</u>	<u>Route</u>	<u>Time</u>	<u>#/group</u>	<u>Effect</u> ²	<u>Quality</u> ³	<u>Study</u>
<u>Amitrole</u>							
Rat	0, 10, 50, 100, 500 ppm	diet	2 y	?	thyroid adenomas at 50, 100, 500 ppm	I	Hazelton, '59
Rat	0, 1, 10, 100 ppm	diet	2 y	75	thyroid adenomas in 100 ppm; pituitary adenomas and carcinomas at 100 ppm	M	Steinhoff, '83
mice	0, 1, 10, 100 ppm	diet	2 y	?	increase thyroid weight at 100 ppm; no tumors	M	"
mice	1000 mg/kg/day; 2192 ppm	gav. diet	day 7-28 18 m	18	liver tumors; thyroid tumors (shortened lifespan)	I	Innes, '69
Hams.	0, 1, 10, 100 ppm	diet	2 year		no effects reported	M	Steinhoff, '83
Rat	20-25 mg/kg/day	water	10 - 32 m	55(?)	increased thyroid tumors, increased liver tumors	I	Napulkov, '69
Rat	250 - 5000 ppm	diet	10 - 32 m	52(?)	increased thyroid tumors, increased liver tumors	I	"
Rat	1, 3, 5, 10 ppm; 20, 60, 100, 100 ppm, respectively	diet diet	39 w then 78 w	75	increased thyroid tumors; increased pituitary tumors in high (10 + 100 ppm) group only	M	FDA, '81
Rat	?	inhal	?	?	increased thyroid tumors	I	Johnson, '81
<u>Asulam</u>							
mice	0, 1500, 5000 ppm	diet	18 m	60	questionable incidence of skin and subcutaneous undifferentiated sarcomas at 5000 ppm (rated as "guideline" by EPA)	A	Rhodia, Inc, '78
rats	0,1000, 5000 25000 ppm	diet	107 w	65	follicular thyroid hyperplasia at 5000 and 25000 ppm; possible pheochromocytoma in 25000 ppm males.	M	Huntingdon, '81

<u>Species</u>	<u>Dose</u>	<u>Route</u>	<u>Time</u>	<u>#/group</u>	<u>Effect</u>	<u>Quality</u>	<u>Study</u>
<u>Atrazine</u>							
Rat	0, 1, 10, 100, 1000 ppm	diet	2 yr	?	no apparent effect; poor survival from infections	I	see Crump, '86
Rat	0, 10, 100, 1000 ppm	diet	2 yr	?	no apparent effect; histopathology incomplete	I	see Crump, '86
mice	21.5 m/k/d 82 ppm	gav diet	3 w 18 m	18	no apparent effect; insufficient detail to evaluate	I	Innes, '69
Rat	0, 10, 70, 500, 1000 ppm	diet	2 y	70	dose related increase in female mammary adenocarcinomas (min. 70 ppm) and fibroadenomas (500 ppm); testicular interstitial tumors increased at 1000 ppm; non-oncogenic NOEL set at 70 ppm.	A	Toxigenics, '86
<u>Bromacil</u>							
rats	0, 50, 250, 1250 ppm	diet	2 y	36	possible adverse effect on thyroid; systemic NOEL 250 ppm; no tumors reported; CDFA states "inadequate evaluation."	M	Haskell, '66
mice	0, 250, 1250, 5000 ppm	diet	18 m	80	increased liver adenomas + carcinomas and liver damage at 5000 ppm; testicular atrophy at all doses - systemic NOEL < 250 ppm; doses in excess of MTD.	M	Haskell, '80
<u>Dalapon</u>							
Rats	0, 100, 300, 1000 ppm	diet	2 y	24 m/20 f	no adverse effect apparent (Data published in summary form in 1960)	M	Hazelton, '56 (Paynter, 1960)
mice	0, 2, 60, 200 mg/kg/day	diet	2 y	50	no oncogenic effects reported; NOEL set at 60 mg/kg/day	A(M)	Dow, '83

<u>Species</u>	<u>Dose</u>	<u>Route</u>	<u>Time</u>	<u>#/group</u>	<u>Effect</u>	<u>Quality</u>	<u>Study</u>
					<u>2,4-D</u> ¹		
rat	0, 1, 5, 15, 45 mg/kg/day	diet	2 year	60	chronic NOEL set at 1 mg/kg/day (kidney effect at 5 mg/kg/day); increased glial cell brain tumors in high dose males; of questionable statistical significance (CDFA - "distribution with clustering in high dose group is most likely by chance based on a number of criteria for significance")	A	Hazelton, '86
mice	47, 100 m/k/d 149, 323 ppm (used acid,	gav diet isopropyl,	d 7- 28 74 w isobutyl or n-octyl	?	no significant increase in tumors (esters)	M	Innes , '69
mice	same study as above - reinterpreted				increase in some tumors (reticulum cell sarcoma, neoplasms of liver and lung) with ester formulations, but not 2,4-D acid.	M	Reuber, '83
rats	0, 5, 25, 125, 625, 1250 ppm	diet	2 y	25	no specific target organ tumors; dose related increase in total and malignant tumors, but only 1250 ppm dose was significant (6, 8, 7, 7, 8, 14 tumors in control and consecutive doses, respectively)	M	Hansen, '71
rats	same study as above - reinterpreted*				increase in total malignant tumors, lympho-sarcomas and mammary tumors in females	M	Reuber, '83
rats	1/10 LD50	diet	27 m	120 m/ 45 f	no significant carcinogenic effects with 2,4-D amine	I	Archipov & Kozlova, '74
mice	1/10 LD50	diet	27 m	100 f	no significant carcinogenic effects reported	I	"
mice	skin painting with 2,4-D amine following 3-MC				significant increase in skin papillomas	I	"

* using the same assumptions and model, Crump et al (1986) found that Reuber's interpretation of data resulted in a 3 fold increase in risk compared with NCI interpretation.

<u>Species</u>	<u>Dose</u>	<u>Route</u>	<u>Time</u>	<u>#/group</u>	<u>Effect</u>	<u>Quality</u>	<u>Study</u>
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Dicamba

rats	0, 5, 50, 100, 250, 500 ppm	diet	2 y	32	multiple tissue lesions at all doses, but not dose related; increase in malignant neoplasms at 5, 250 & 500, but not dose-related.	I	Kettering, '62
rats	0, 50, 250, 2500 ppm	diet	2+ y	60	increase in thyroid parafollicular cell carcinoma & malignant lymphoma, high dose males only	A	IRDC, '85
mice	0, 100, 1000, 10000 ppm	diet	2 y	60	possible increase in angiosarcoma at 1000 ppm males; IBT test; not yet validated by EPA	I	IBT, '80

Diuron

rats	0, 25, 125, 250, 2500 ppm	diet	2 y	35	effects on bone marrow erythropoiesis at high dose; no oncogenic effects reported, but histopathology was stated by CDFA to be inadequate/incomplete	M	U. Rochester, '64
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2,4-DP

rats	0, 25, 50, 250/150 m/k/d (switched at 60 weeks)	diet	2 y	?	dose-related increase in pituitary and thyroid medullary tumors at all doses (in males); oncogenic NOEL < 25 m/k/d - increase in rare malignant brain tumors at low dose only (classified as "guideline" by EPA; EPA one-liner only available information; CDFA did not review).	A	CDC Res., '80
mice	0, 25, 100, 300 m/k/d	diet	18 mo	?	no oncogenic response noted; oncogenic NOEL >300 m/k/d; systemic NOEL (liver effects) 100 m/k/d. (this study classified as "guideline" by EPA; EPA one-liner is only available information on this study)	A	CDC Res., '80

Fosamine

no studies available

<u>Species</u>	<u>Dose</u>	<u>Route</u>	<u>Time</u>	<u>#/group</u>	<u>Effect</u>	<u>Quality</u>	<u>Study</u>
<u>Glyphosate</u>							
rat	0, 3, 10, 32 mg/kg/day	diet	2+ y	50	possible increase in testicular tumors in high dose group, but questionable significance; NOEL > 32 mg/kg/day, MTD never reached; (rated "supplemental" by EPA)	M	BioDynamics, '81
mice	0, 1000, 5000, 30,000 ppm	diet	2 y	50	possible increase in renal adenomas in high dose males compared with concurrent control initially reported; re-evaluation of histopathology resulted in no signif. increase in renal tumors.	A	BioDynamics, '81
<u>Hexazinone</u>							
rat	0, 200, 1000, 2500 ppm	diet	2 y	36	no apparent oncogenic effects; NOEL (decreased body wt) set at 200 ppm. (satisfies EPA requirem.)	A	Haskell Lab., '77
mice	0, 200, 2500, 10000 ppm	diet	2 y	80	effects on liver at 2500 and 10000 ppm; no oncogenic effects reported.	A	IRDC, '81
<u>Picloram</u>							
rats	0, 7437, 14875 ppm	diet	80 w	50	no treatment related increases in any tumors in males; increase in benign liver tumors in high dose females	M	NCI, '78
rats	re-review of above study*				high incidence of malignant tumors (adrenal, pituitary, liver, mammary and thyroid); tumors in control animals were unusually high	M	Reuber, '81
mice	0, 2531, 5062 ppm	diet	80 w	50	no apparent oncogenic effects reported	M	NCI, '78
mice	re-review of above study*				increased neoplasms of spleen in high dose group	M	Reuber, '81
rats	0, 20, 60, 200 mg/kg/day	diet	2 y	70	mild hepatic hypertrophy at 60 and 200 mg/kg/d; no oncogenic effects reported. This study judged adequate by both EPA and CDFA.	A	Dow, '86

* using the same assumptions and model, Crump et al (1986) found that Reuber's interpretation of data resulted in a 6 fold increase in risk compared with NCI interpretation.

<u>Species</u>	<u>Dose</u>	<u>Route</u>	<u>Time</u>	<u>#/group</u>	<u>Effect</u>	<u>Quality</u>	<u>Study</u>
<u>Simazine</u>							
rats	0, 1, 10, 100 ppm	diet	2 y	30	no observed effects; NOEL set at > 100 ppm	I	Hazelton '60
mice	2 ppm solution of 25% atrazine; 37.5% simazine	ip inj			increased incidence of malignant lymphoma	I	Donna, '81
<u>Tebuthiuron</u>							
rats	0, 400, 800, 1600 ppm	diet	2 y	40	vacuolization of pancreatic acinar cells at high dose; no oncogenic effect reported; systemic NOEL set at 400 ppm (20 mg/kg/day)	M	Lilly Res, '76
mice	0, 400, 800 1600 ppm	diet	2 y	40	no evidence of toxicity or oncogenicity	M	Lily Res., '76
<u>Triclopyr (Garlon)</u>							
rats	0, 3, 10, 30 m/k/d	diet	2 y	50	no apparent oncogenic effects	M	IBT, '78
mice	0, 24, 80, 240 ppm	diet	2y	50	questionable increase in benign lung tumors at 24 & 240 ppm in males; in females at 240 ppm; significance depends upon control group used. Independent evaluation concluded that lung tumor effect "could not be substantiated."	M	Dow, '79

- ¹ Data reviewed for this table were obtained primarily from notes of the California Department of Food and Agriculture (CDFA) review of these herbicides. CDFA notes were available for all herbicides except Amitrole. In addition to CDFA documents, EPA reregistration standards and other documents that serves as the source for EPA "one-liners" were used, as well as evaluations in the Crump et al., 1986 review of herbicides for Washington State Department of Natural Resources. Where published studies appear, the reference is given under study source. If the study was a contract study, the contracting laboratory responsible for conduct of the study is noted.
 - ² Any significant oncogenic effects reported in any review were noted here. Non-oncogenic chronic effects are also listed and a NOEL for systemic chronic effects is shown, if available.
 - ³ Each study was evaluated for its overall usefulness in making a judgement about potential oncogenic (carcinogenic) properties. I = inadequate study; little meaningful conclusions can be drawn from study; M = minimal; although there are deficiencies in design, data evaluation and/ or interpretation, the study provides useful information on oncogenic potential of chemical; additional studies would be necessary to make definitive conclusions; A = adequate; study meets currently accepted standards for design, data evaluation and interpretation. Further studies with this species are not essential to make a definitive statemnt about oncogenicity in this species.
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Developmental and Reproductive Toxicity Assessment

Two main types of toxicology tests have been used to assess the reproductive and developmental toxicity of these pesticides. Most of these tests are conducted in mouse, rat, or rabbit test populations. The attached tables give experimental details.

The potential adverse reproductive effects of pesticides have been evaluated using multigeneration exposure studies. These studies have been especially designed to evaluate the effects of compounds where a long-term, low-level human exposure pattern exists. The majority of these studies have been three generation reproduction studies. The experiment, if conducted using weanlings, uses animals (30-40 days of age, parental generation) which are randomly assigned to control or treated groups.

Exposure to test conditions starts 60 days prior to mating. The exposed males and females are mated, and litters from this mating are examined for adverse developmental effects. The offspring are sacrificed for internal examination.

A second litter from the parental generation is produced, and this litter is also examined for adverse reproductive effects. These animals are then mated as male-female within the same treatment group (brother-sister matings are avoided).

A similar pattern of examination occurs, where the first litter produced is examined both grossly and visorally, then sacrificed. The second litters produced are mated to produce the third generation.

These offspring are then also examined. Exposure to control or test conditions continues throughout the entire three-generation study.

Modifications of this general protocol are common. However, current recommendations suggest three dose levels plus a control group. The highest dose level is frequently a multiple of the human exposure level, or 10 percent of the LD_{50} . Ideally, the lowest dose tested should be a no effect level. Test protocol should allow for a minimum of 20 pregnant females per treatment group per generation.

Multigeneration reproduction studies are designed to provide data on gonadal function, estrus cycle, mating behavior, conception, implantation, abortion, fetal and embryonic development, parturition, post natal survival, lactation, maternal behavior, and post partum growth (Dixon 1986). In addition to identifying altered reproductive capability (including genetic and behavioral effects), these studies often are able to identify other systemic effects, since treatment continues throughout the animals' life.

Developmental toxicity is usually assessed using Phase II Teratology tests.

These tests are designed to assess effects on viability, growth, and birth defects. Routinely, one rodent and one non-rodent species (normally rabbits) is tested with control and two dose groups, each containing 20 rodents or 10 non-rodents. Time-mated females are treated only during the organogenesis period (days 6-15, rodents; and days 6-18, rabbits).

Doses should be selected so that the highest dose group produces some maternal toxicity. Frequently a 10 percent decrease in normal maternal body weight is used as an indication that maternal toxicity has occurred. One day prior to birth, the females are sacrificed and the fetuses are examined for viability and growth parameters and gross, visceral, and skeletal abnormalities.

Classification systems are used to order major and minor malformations dependent upon their severity and irreversibility. Minor skeletal variations such as incomplete ossification of sternum, vertebrae, or phalanges are frequently used as indicators of developmental retardation, since these effects are frequently reversible during the post natal period.

In this worst-case analysis, these endpoints will be included in identifying NOELs if these endpoints appear to be treatment related. Early and late developmental deaths are scored to determine if the test compounds may be causing lethality during gestation.

Developmental NOELs are compared to maternal NOELs to determine if the test compound causes adverse developmental effects at or below maternally toxic doses. The following ranking (score) system has been used to identify the relative developmental toxicity of test compounds:

- 1) little or no evidence of developmental toxicity in the absence of maternally toxic effects;
- 2) evidence of developmental toxicity, primarily minor abnormalities and variation observed;
- 3) evidence of developmental toxicity, including some major malformations; and
- 4) evidence of severe adverse developmental effects. Dose-related increases in major malformation in the absence of maternal toxicity.

REPRODUCTIVE TOXICITY STUDIES

Herbicide	Chemical Grade Purity	Description of Study	Doses Tested	Qualitative Ranking on Adq. Testing	Effect Level	Comments
Amitrole ^{1,6,12,13}	Technical	2-generation rats	25,100, 500,1000ppm (variable treat time)	CG=Invalid	LEL=25ppm (5mg/kg/day) NOEL=ND (50mg/kg/day)	Hyperplasia thymus No info. on exp. details Adequate #'s?
Ansulam ^{1,12,13}	Technical	2-generation rats (oral)	1000,5000, 25000ppm	Incomplete ¹² Inadequate ¹² CG=minimal ¹³	LOAEL=5000ppm (250mg/kg/day) NOEL=1000ppm (50mg/kg/day)	Decreased live births
Atrazine ^{1,2,6,12,13}	Atrazine	3-generation (rats)	50,100ppm	Unacceptable ¹² CG=Supplementary ¹³	NOEL> 100ppm 5mg/kg/day	Dietary regime altered
	Unknown ¹⁴	Rats - Feed throughout gestation	50,100,200, 300,400,500, 1000ppm	Unknown	NOEL<50ppm	Examined pup wt and number only No teratology examination
	Unknown ¹⁴	Rats - sub Q inj days 3,6,9	50,100,200, 800,1000. 2000mg/kg	Unknown	LEL=800mg/kg NOEL=200mg/kg	Embryotoxicity Increased reabsorbtion No standard teratology evaluations done
Bromocil ^{1,6,12,13}	80% (formulated)	3-generation Rats	250ppm 12.5mg/kg/day	Unacceptable ¹² CG=minimum	NOEL>250ppm	Inadequate numbers of animals No diet analysis Inadequate histopathology Formulated versus technical grade Only one dose tested mat. tox. N.D.

Reproductive Toxicity Studies (continued)

2,4D ^{1,2,12,13}	97.5%	2 generation Rats	5,20,80 mg/kg/day	Acceptable ¹²	NOEL=5mg/kg/day (?)	Decreased mat. survival Increased fetal loss Dramatic effects in litters Adverse Reprod. effects (Data may suggest NOEL=20mg/kg/day ¹²)
	Unknown	3 generation Rats	0,100,500, 1500ppm	Unknown	NOEL=500ppm (25mg/kg/day)	Viability, effects at high doses No adverse effects on fertility or avg. litter size at any of the doses tested
	Unknown	1 + generation Rats (oral)	1000ppm	Unknown	-----	No adverse effects on reproduction *however 2 year treatment of offspring caused systemic effects of growth retardation, poor general health, diarrhea and increased mortality
	Unknown	1 generation (treated only) Rats (oral)	1000,2000ppm	Unknown	LEL=1000ppm (lowest dose tested)	Adverse effects on pup viability observed at both doses

Reproductive Toxicity Studies (continued)

2,4DP ^{1,13}	Acid, Technical	3 generation Rats (oral)	125,500,1000, 2000ppm	CG=Minimal ¹³	Mat. NOEL=1000ppm Mat. LEL=2000ppm Dev. NOEL=125ppm (6.25mg/kg/day)	Decreased Bulk Increase in small litters Increased postmated pup mortality
Dalapon ^{1,2,13,12}	Purity Unknown	3 generation Rats (oral)	0.03,0.1,0.3% (3000ppm) (300mg/kg/day)?	Inadequate ¹² Incomplete ¹²	NOEL> 300mg/kg/day	Insufficient data! No evidence of reproductive effect, ^{12?} NOEL not established ^{12?}
	Technical	1 generation Dog (diet)	50,100,200 mg/kg/day	Incomplete ¹² Unacceptable ¹²	ND	Insufficient data! Few animals Dosing started after breeding
Dicamba ^{1,12,29,Z10}	Technical Banvel D (87.2% a.i.)	3 generation Rat (CD) Oral (diet) 10 males/group 20 females/group	0,50,125,250, 500ppm	Unacceptable ¹²	NOEL> 500ppm (HDT)	No adverse effects on reproduction Supplement to next study Same problems as listed below ¹² Inadequate
1,12,13,29,Z10	Technical DMA Salt	3 generation Rat (CD) Oral (diet)	0,50,125,250, 500 ppm	Unacceptable ¹² CG=Minimum ¹³	NOEL> 500ppm (HDT)	No adverse effects on reproduction. Problems with age, animal numbers, dose selection (no sign of tox.) short dosing prior to mating? Inadequate pathology
13,Z10	Technical	Reproduction Chickens		valid ¹³		

96-H

Reproductive Toxicity Studies (continued)

Diuron ^{1,5,13,12}	Technical 80% (Source 1)	3 generation Rat (oral)	125ppm	Unacceptable ¹² Inadequate ²	Reprod. NOEL> 125ppm (?) Systemic NOEL< 125ppm (?)	No adv. reprod. effect observed Body wt. decreases in F ₂ b and F ₃ a litters Inadequate numbers of preg. animals (8 males 16 females per group) Parental animals not necropsied, no diet analysis, no food consump. info. Single dose tested
	Technical 80% (Source 2)	3 generation Rat (oral)	125ppm	Unacceptable ¹² Inadequate ²	Reprod. NOEL> 125ppm(?) Systemic NOEL> 125ppm(?)	No adv. reprod. effect observed No systemic effects observed Inadequate numbers of preg. animals (8 males 16 females per group) Parental animals not necropsied, no diet analysis, no food consump. info. Single dose tested
Fosamine ^{1,2,12}	Unformulated fosamine ammonium	One generation Rats (oral)	200,1000, 5000/10000ppm (90 days)	Unacceptable ¹²	NOEL=5000ppm (250mg/kg/day)	Only 2 litters examined for each dose group No adverse reprod. effects observed Dose selection unjustified Minimal exp. details

Reproductive Toxicity Studies (continued)

Glyphosate ^{12,13}	Technical	3-generation Rat (CP)	0,30,100,300 ppm	CG=Invalid ¹³		Unacceptable ¹³ Invalid per Canadian revaluation ¹³
1,12,13,Z,GRP-11,Z6		3-generation Rat (CD) Oral (diet)	0,3,10,30 mg/kg/day	CG=Supplementary upgraded to Minimum ¹³ Unacceptable ¹²	Reprod. NOEL=10 mg/kg/day	No adverse reproductive effects observed, however Renal focal tubular dilatation observed in weanling males in F36 generation at high dose (30mg) - systemic or reproductive effect? Called reproductive based on 1985 review ¹²
Hexazinone ^{1,13,Z4}	Technical	3-generation Rats Oral (diet)	0,200,1000, 2500ppm	CG=Minimum ¹³	NOEL=1000ppm 50mg/kg/day	No differences in treated versus control groups on reproductive or lactation performance. Aug. B. Wt. of pups at weaning for F2A & F3A litters was decreased at 2500 ppm.
Picloram ^{1,2,12,Z3}	95%	3-generation (2 litter) Rat Oral (diet) 4 males 12 females	0,0.03,0.1,0.3% 0 - 3000ppm 0,15,50,150mg/kg	Unacceptable, ¹² non-upgradeable.	NOEL=1000ppm ²³ 50mg/kg/day	No obvious effects on reproduction however, reduced fertility at highest dose (treatment related?).

Reproductive Toxicity Studies (continued)

Picloram (con't.)

Insufficient number of animals, only 4 weeks of exposure prior to 1st mating, mating in groups inadequate number necropsied, data not clearly presented
 No record of total consumption
 Reduced fertility observed at 3000ppm in one generation-EPA stated not treatment related.
 However, Note that NOEL I.D. by Ref 12Z and 1 was 1000ppm (50mg/kg/day)

1,2

Fertility Mice Oral (diet) 4 days before mating 14 days after mating	0.01% 15mg/kg/day	NOEL> 15mg/kg/day	No adverse effects observed on fertility or litter size
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Simazine^{1,12,13,Z1,Z2}Simazine
80W

3-generation Rat (CR) Oral (diet) 20 males/group 20 females/group	0,100ppm	CG=Minimum Unacceptable with insufficient info. ¹²	Reprod. NOEL> 100ppm 5mg/kg/day	Only 1 dose tested for F2 gen. a 50ppm group added, No reprod. effects observed, some missing info. on matings, F0 not necropsied.
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0,100ppm

CG=Minimum
Unacceptable with
insufficient
info.¹²Reprod. NOEL>
100ppm
5mg/kg/day

3-generation Rat (CR) Oral (diet) 20 males/group 20 females/group	0,100ppm	CG=Minimum Unacceptable with insufficient info. ¹²	Reprod. NOEL> 100ppm 5mg/kg/day	Only 1 dose tested for F2 gen. a 50ppm group added, No reprod. effects observed, some missing info. on matings, F0 not necropsied.
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Terbuthurion^{1,13}Technical
(95%)2-generation
RatDose groups
unknownCG=Supplementary¹³Reproductive
NOEL>400ppm
(20mg/kg/day)
Systemic NOEL>
100ppm

Reproductive Toxicity Studies (continued)

Terbuthurion ^{1,13} (continued)	Technical	3-generation Rat	Dose groups unknown		Reproductive NOEL=<400ppm Systemic NOEL=800ppm	Reproductive effects observed were decreased body ₃ wt. of weanling pups
Triclopyr ^{1,2,12,13}	Technical	3-generation Rat (SD) Oral (diet) 11-12 males 23 females	0,3,10,30 mg/kg/day	Unacceptable ¹² CG=Minimum ₃	Reproductive NOEL>30 mg/kg/day Systemic NOEL>30 mg/kg/day	

H-100 Herbicide	DEVELOPMENTAL TOXICITY STUDIES						
	Chemical Grade	Description of Study	Doses Tested	Qualitative Ranking on Adq. Testing	Maternal Toxicity Effect Level	Developmental Toxicity Effect	Comments
Amitrole ^{1,6,12}		Teratology ³ Rats Oral	20,100 mg/kg/day	Inadequate No visceral or skeletal exam	ND	NOEL= 100mg/kg/day	
		Teratology ¹² Rats	400,1000 mg/kg/day	Inadequate ¹²	ND		Very limited summaries Histolog. change in thyroid at all tested doses
		Teratology ¹² Rats (CD)	100,500, 1000 mg/kg/day	Complete ¹² Acceptable ¹² No indic. of adv. effect	NOEL= 100mg/kg/day	NOEL= 500mg/kg/day	Decreased fetal weight gain
		Teratology ⁴ Mice Oral	500,1000, 2500,5000 ppm comp. in water)	Inadequate ¹² (no water consump. info.)	ND(?)	LOAEL= 1,000 ppm	Fetotoxicity, decreased body wt., sm. fetuses under-develop. fetuses w/ immature skeletons)
	Technical 91.8%	Teratology ¹² Phase II rabbits (oral)	4,40,400 mg/kg/day	Acceptable ¹² No data gap ¹² Possible adv. effect due to freq. and sev. of defects	NOEL= 4mg/kg/day	NOEL= 4mg/kg/day	Increased incidence of structural changes
Ansulam ¹	60% w/v	Teratology ⁷ Phase II Rabbits (oral)	2,4,8,40 mg/kg/day	Incomplete ¹² Unacceptable ¹²	ND	NOEL> 40mg/kg	

Developmental Toxicity Studies (continued)

Ansulam (con't.)	Technical (98-99%)	Teratology Phase II rabbits (oral)	150,300, 750,1500 mg/kg/day	Incomplete ¹² Unacceptable ¹² CG=Minimum ¹³	LOEL (?) 750 mg/kg/day	NOEL (?) 300 mg/kg	Insufficient info. Many technical errors Poorly conducted, confounded study
60% w/v		Teratology	8,40 mg/kg/day	Incomplete ¹² Unacceptable ¹²	ND	NOEL 40 mg/kg/day	Insufficient info. Only 2 dose levels Mat. tox. N.D.
60% w/v		Teratology Phase II Rats (oral)	8,40	Unacceptable ¹² CG= Unacceptable ¹³	ND	NOEL 40mg/kg/day	Insufficient info. Only 2 dose levels Mat. tox. N.D.
Technical (98-99%)		Teratology Phase II Rats (oral)	500,1000, mg/kg/day	Incomplete ¹² Unacceptable ¹² CG=Minimum ¹³	ND(?) (Insig. decrease at 1500 mg/kg/day	LOEL(?) 500mg/kg (non-stat. sig. increase in pre- implantation loss)	Insufficient info. Inadequate dose Inappropriate dosing schedule (prior to implantation) No historical control values
Atrazine ^{1,2,6,12,13}	Technical	Teratology ¹⁰ Phase II rats (oral)	10,70,700 mg/kg/day	Unacceptable ¹²	NOEL= 70mg/kg/day	NOEL< 10mg/kg/day	Increased visceral and skeletal variability
Unknown		Teratology Phase II Rats (oral)	100,500, 1000 mg/kg/day	Unacceptable ¹² CG=Minimum ¹³	NOEL 100 mg/kg/day	NOEL= 100mg/kg/day LEL= 500mg/kg/day	Fetal loss, wt. loss

Developmental Toxicity Studies (continued)

Atrazine (con't.)	Technical	Teratology Phase II	1,5,75 mg/kg/day	Unacceptable ¹²	NOEL= 1mg/kg/day	NOEL= 5mg/kg/day	Maternal effects observed were decreased wt gain and food consumption Developmental effects observed were increased resorptions decreased fetal wt and number of fetuses
		Teratology Phase II Mouse	46mg/kg/day	Unacceptable ²	ND	NOEL= 46mg/kg/day	Used DMSO as vehicle One dose tested Insufficient info. on evaluation
Bromocil ^{1,6,12,13}	Unknown	Teratology Phase II Rat (Inhalation)	38,78, ₃ 165 mg/m (=1.8,3.8, 7.9mg/kg)	Unacceptable ¹² CG=Minimum ¹³	ND	NOEL> 165mg/m ³ >7.9mg/kg	Inadequate number of animals tested No individual information No comments on visceral exam. Mat. tox. N.D. Unjustified dose selection Inadequate number of animals No comments on visceral exam or other exp. changes
2,4D ^{1,2,9,12,13}	97.5%	Teratology Phase 2 Rats (oral)	8,25,75 mg/kg/day	Incomplete ¹² CG=Minimum ¹³	NOEL> 75mg/kg/day	NOEL= 25mg/kg/day	No analysis of dosing solution Delayed ossification Fetotoxicity

Developmental Toxicity Studies (continued)

2,4D (cont'd),
12,13

Unknown	Teratology Phase 2	75,100,150, 200,250	CG= Supplementary ¹³ LEL=	NOEL= 100mg/kg/day 150mg/kg/day	ND	Evidence of develop- mental toxicity Range finding for above study. Was conducted to support dose selection in this full teratology study however, use of 75mg/kg not fully justified.
Rats(F344)	mg/kg (oral) gavage	d6-15				
Acid	Teratology Phase II Rats (oral)	25,50,100, 150mg/kg/day	Unknown	ND	NOEL=	Mat. deaths (cerebral hemorrhage at 200 and 250mg/kg/day) Skeletal abnormalities Fetotoxicity Several different sources of 2,4D tested, some inconsistency observed
Acid	Teratology Phase II Rats (oral)	12.5,25,50, 75,87.5 mg/kg/day	Unknown	ND	LEL= 12.5mg/kg/day (delayed ossifici)	Fetotoxicity Delayed ossification Skeletal abnormalities Hydrocephaly
Acid	Teratology Mice (?)	147mg/kg (single dose)	Inadequate	ND	NOEL=147 mg/kg	Inadequate summary only available

Developmental Toxicity Studies (continued)

2,4D (con't.)	Acid	Teratology Phase II Hamster (oral)	20,40,60, 100mg/kg/day	Inadequate ²	ND	NOEL= 40mg/kg/day	Insufficient info. on abnormalities Mat. tox. N.D.
2,4DP ^{1,13}	Acid Technical	Teratology Phase II Rats	25,100mg/kg	CG=Guideline ¹³	ND	NOEL> 100mg/kg/(HDT)	Range finding
	Acid (94%)	Teratology Phase II Rats	10,30, 100mg/kg	CG=Minimum ¹³	NOEL> 100mg/kg (HDT)	NOEL> 100mg/kg	Mat. tox. N.D.
	Acid Technical	Teratology Phase II Rabbits	25,100mg/kg	CG=Minimum ¹³	NOEL= 25mg/kg (LDT)	NOEL< 25mg/kg (LDT)	Range finding Omphalocele Skeletal malformations Growth retardation
Dalapon ^{1,2,12,13}	Technical	Teratology Phase II Rats (oral)	500,1000, 1500 mg/kg/day	Incomplete ¹² Unacceptable ¹²	NOEL= 1000mg/kg (see comments)	NOEL= 500 mg/kg/day ¹³	Decreased mat. wt. gain Some evidence of dev. tox. without mat. effect ¹² No individual data Experimental design problems Skeletal effects at all doses(?) ¹²

Developmental Toxicity Studies (continued)

Dalapon (con't.)	Unknown	Teratology Rats (oral)	250,500,1000 1500,2000 mg/kg/day	Unknown	NOEL= 500mg/kg/day	NOEL= 1500mg/kg/day	Decreases in mat. wt. gain Decrease in mat. food consumption Fetal resorptions (NS) Decreased pup wts. No teratog. effects observed
Dicamba ^{1,13} 1,Z10,13	Technical Acid	Teratology Rats (CD) Oral (gavage)	0,50,150, 350,600,750 mg/kg/day d6-19	CG=Minimum ¹³	NOEL=350 mg/kg/day LEL=600 mg/kg/day	See next study	Pilot study Mat. tox. included behavioral reactions and gross stomach lesions.
1,Z10,13	Technical Acid	Teratology Rats (CD) Oral (gavage)	0,64,160, 400 mg/kg/day 20-24 rats/gr d6-19	Acceptable ¹² CG=Minimum ¹³ Inadequate (see comments)	NOEL= 160mg/kg/day LEL=400 mg/kg/day	NOEL<64 mg/kg/day LEL=64 mg/kg/day	Mat. tox. observed including ataxia, salivation decreased motor activ., mortality and decreased body wts. and food consumption. Problems with study since skeletal malf. were observed in all groups (non dose- related) however, incidence of misshapen inter- parietal, occipital and parietal skeletal bones only in treated groups was suggestive and resulted in a LEL=64mg/kg/day (lowest dose tested). ²¹⁰

Developmental Toxicity Studies (continued)

Dicamba (con't.)	Unknown	Teratology Rabbits Oral (gavage) 21-22/group	0,1,3,10 mg/kg/day	Inadequate ¹² Unacceptable ¹² CG= Supplementary ¹³	ND		Inadequate numbers of preg., combined this study with repeat below. No individual animal data given. No teratogenic effect observed.
Bonnel Technical (87.7%)	Teratology Rabbits Oral (gavage) 31-35/group	0,1,3,10 mg/kg/day d6-18	Unacceptable ¹² Inadequate ² CG= Supplementary ¹³	ND	?NOEL=3.0 mg/kg/day	No individual data etc Supplement to above observed study due to disease and mortality Difficult to identify treatment related effects. Possible effects on male/ female ratio and fetal body wt. on 10mg/kg/day group.	
Technical	Teratology Rabbits (NZ) Oral (gavage) 10/group	0,0.5,1,3, 10,20 d6-18	CG= Supple- mentary ¹³ ,Z ¹⁰	NOEL 10mg/kg/day	NOEL= 0.5mg/kg/day LEL= 1.0mg/kg/day	Mat. toxicity observed included reduced wt. gain and decreased activity. Data on skeletal and soft tissues not given. Too few animals (10/group) Increased fetal resorbtions noted in in 1.0mg/kg/day group	

Developmental Toxicity Studies (continued)

Diuron ^{1,5,13,12}	Karmex (80% Diuron)	Teratology Phase II Rat (oral)	125,250, 500 mg/kg/day	Unacceptable ¹² CG= Supplementary ¹³	NOEL= 250mg/kg/day	LEL= 125mg/kg/day (lowest dose tested)	Insufficient Fetal wt. decreased Wavy ribs Mat. wt. reduced Dev. NOEL not determined Stat. Sig. Delayed ossification in lowest dose tested No individual data given
	Unknown	Teratology Phase II Mouse (?)	215mg/kg	Unacceptable ¹²		NOEL=215 mg/kg	No adv. develop. tox. observed at 215mg/kg No study details Tabular summary only Totally unacceptable
Fosamine ^{1,2,12}	Krenite	Teratology Phase II Rats (oral) (28 females/ group)	200,1000, 10000ppm (equiv. to 207mg/kg/day a.i.)	Unacceptable ¹²	ND	NOEL= 1000ppm(?) (21mg/kg/day a.i.)	Mat. tox. N.D. Stat. Sig. Hydronephrosis noted at high dose (P=.04) Minimal exp. details available Dose selection not justified Test material not described No individual data available

Developmental Toxicity Studies (continued)

Glyphosate ^{1,2,12,13,27}	Technical 98.7%	Teratology Rat (CD) Oral (gavage) 25/group	0,300,1000, 3500 mg/kg/day d6-19	Complete ¹² Acceptable ¹² CG=Minimum ¹³	NOEL=1000 mg/kg/day LEL=3500 mg/kg/day	NOEL=1000 mg/kg/day LEL=3500 mg/kg/day	Mat. toxicity observed included inactivity, death, stomach hemorrhages, decreased wt. gain. Developmental toxicity observed was delayed ossification (high dose) and structural malformations (high dose - single litter) Developmental toxicity only observed at doses causing significant maternal toxicity.
1,2,12,13,Z8	Technical 98.7%	Teratology Rabbit Oral (gavage) @6-27 (16/group)	0,75,175,350 mg/kg/day	Complete ¹² Acceptable ¹² CG=Minimum ¹³	NOEL=175 mg/kg/day LEL=350 mg/kg/day	NOEL=75 mg/kg/day	Signs of mat. tox. observed at 350 mg/kg/day included death, soft stools, diarrhea, nasal discharge. Note: major structural malformations were observed in 2 fetuses in 175 mg/kg/day group and 1 fetus in 350 mg/kg/day group. Were not stat. sig. and were not considered to be related to ^Z treatment. For worst case analysis, will set developmental tox. NOEL at 75 ^Z mg/kg/day.

Developmental Toxicity Studies (continued)

Glyphosate (con't.)	12,13	Technical	Teratology Rabbit d6-18	10,30 mg/kg	Invalid ¹² CG=Invalid ¹³ (IBT)			
	13	Technical	Teratology Rabbit		CG=Invalid ¹³ (IBT)			
Hexazinone	1,2,Z4	Technical	Teratology Rat Oral (diet) 25-27 rats/grp. d6-15	0,200,1000, 5000ppm		NOEL=1000ppm	NOEL>5000ppm	Mat. effects observed at 5000ppm included decreased food consumption and body wt. No adverse develop- mental effects were observed at any test doses.
	1,13,Z4	Technical 100%	Teratology Rabbit Oral (gavage) d6-19	0,20,50,125 mg/kg/day	CG= Minimum ¹³	NOEL>125 mg/kg/day	NOEL=50 mg/kg/day	No maternal effects. The highest dose level showed a higher per- centage (16.2%) of fetuses showing skeletal variants than controls in skeletal development. These differences included delayed ossification in extremities and extra ribs.
	1,Z5		Teratology Rabbit			NOEL=20		No exp. details known

Developmental Toxicity Studies (continued)

Picoloram ^{1,2,Z3,12}	No purity stated 35/group d6-15	Teratology Rat (SD) Oral (gavage) mg/kg/day	0,500,750, 1000	CG= Supplemental ¹² Unacceptable ¹² Upgradable ¹²	NOEL=500 mg/kg	NOEL<500 mg/kg/day ^{Z3} LOAEL=500 mg/kg/day	No NOEL for develop. tox. determined. Mat. tox. observed. Ref 12 - Unacceptable due to lack of purity info., no analysis of dosing solution, poor copies of individual data. Decreased viability index at highest dose. Presence of minor variations and no sig. major malf. Treatment related?
	12	Teratology Rabbit Oral (gavage) d6-18 18-23/group	0,40,200, 400mg/kg	Unacceptable ¹² Upgradable ¹²	NOEL=40mg/kg	NOEL>400 mg/kg(?)	No teratogenic effects observed. ¹² Insufficient info. to evaluate (no individual data). ¹²
Simazine ^{1,13,12}	Technical 97%	Teratology Rabbit Oral (gavage) 18/group	0,5,75,200 mg/kg	CG= Supplementary, Guideline Acceptable with no adverse effect ¹²	NOEL=5mg/kg	NOEL=75 mg/kg/day ¹³ NOEL=5 mg/kg/day ¹²	Maternal effects observed at 75mg/kg included tumors, abortions, & decreased body wt. gain and food consumption. Decreased fetal wt. and increased skeletal variations at 200mg/kg. Late resorptions observed at 75 and 200mg/kg. ¹²

Developmental Toxicity Studies (continued)

Terbuthiuron ^{1,13}	Technical	Teratology Rabbit	Unknown			NOEL>25mg/kg	Minimal details known, doses, route, of exposure, etc. Maternal tox.? Not given.
	1,13	Technical	Teratology Rat	Highest dose 1800ppm		NOEL>1800ppm 90mg/kg	Minimal details known doses, route, of exposure, etc. Maternal tox.? Not given.
	1	Unknown	Teratology Rat Dermal			NOEL=237 mg/kg/day	No experimental details known.
Triclopyr ^{1,2,12,13}	Technical (98.5%)	Teratology Rat (SD) Oral (gavage) 25/group	0,50,100, 200 mg/kg/day d6-15	Acceptable ¹² CG=Minimal ¹³	NOEL<50 mg/kg/day	NOEL=100 mg/kg/day	Maternal toxicity observed was change in wt. gain, food consumption. Fetal effects (delayed ossification) at 200mg/kg/day were ascribed to maternal effects.
	Technical (>95%) Oral (gavage)	Teratology Rabbit d6-18 15/test groups 25/control groups	0,25,50,100 mg/kg/day	Unacceptable ¹² CG=Supplementary ¹²			Heavy mortality at all doses and among controls. Attributed by investigators to volume administered by gavage. Insufficient info. to evaluate

Developmental Toxicity Studies (continued)

Triclopyr (con't.) Technical (Dow w 233)	Teratology Rabbit Intubation 20/group	0, 10, 25 mg/kg d6-18	Unacceptable ¹² CG=Minimum ¹³	NOEL=?	NOEL<10 mg/kg/day	Enteritis deaths in all groups. Treatment related effects at 25mg/kg in dams? No other signs of mat. tox. Minor anomalies were increased (not sig.) above control values.
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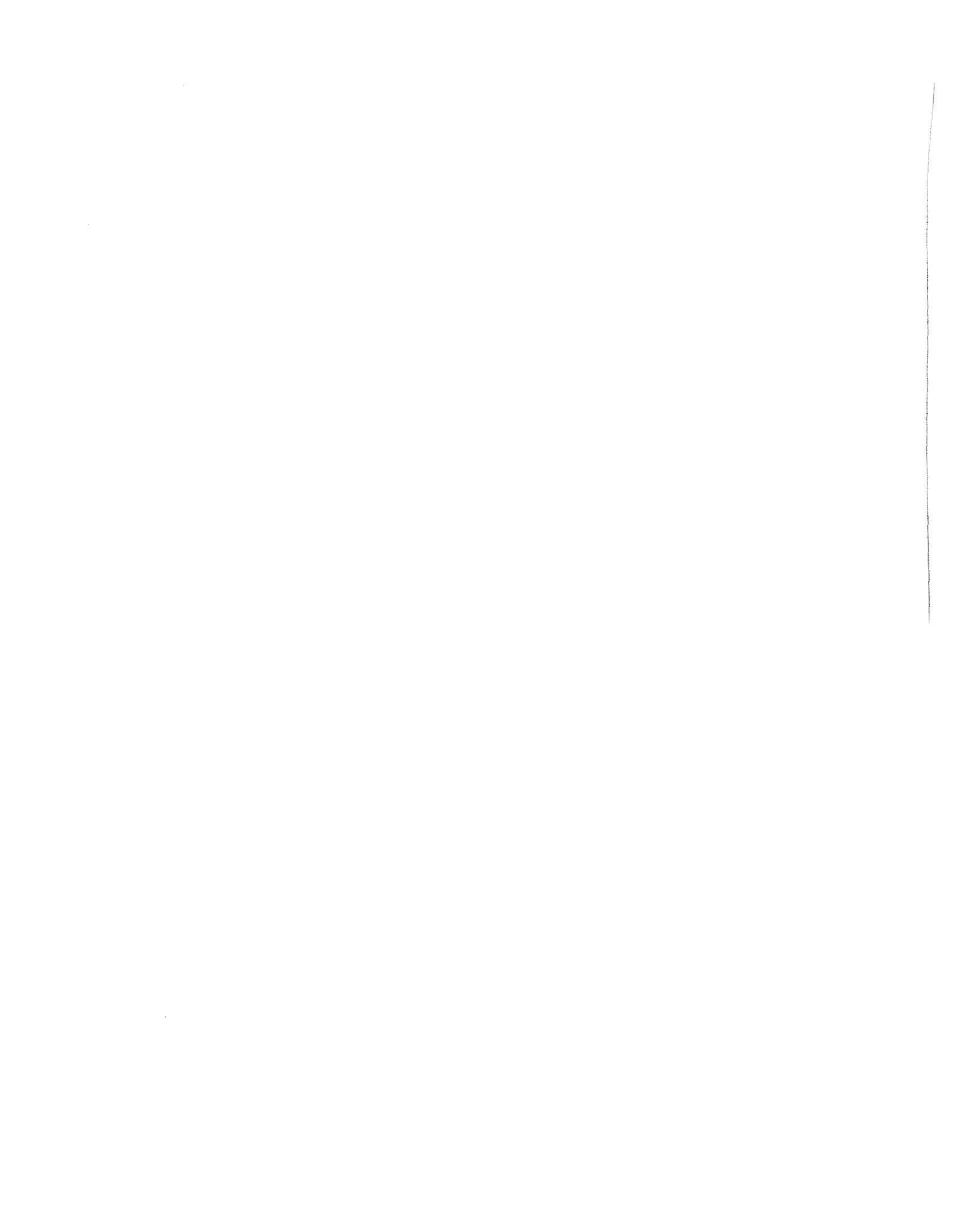
Appendix H

**Human Health
Risk Assessment
(Qualitative)**



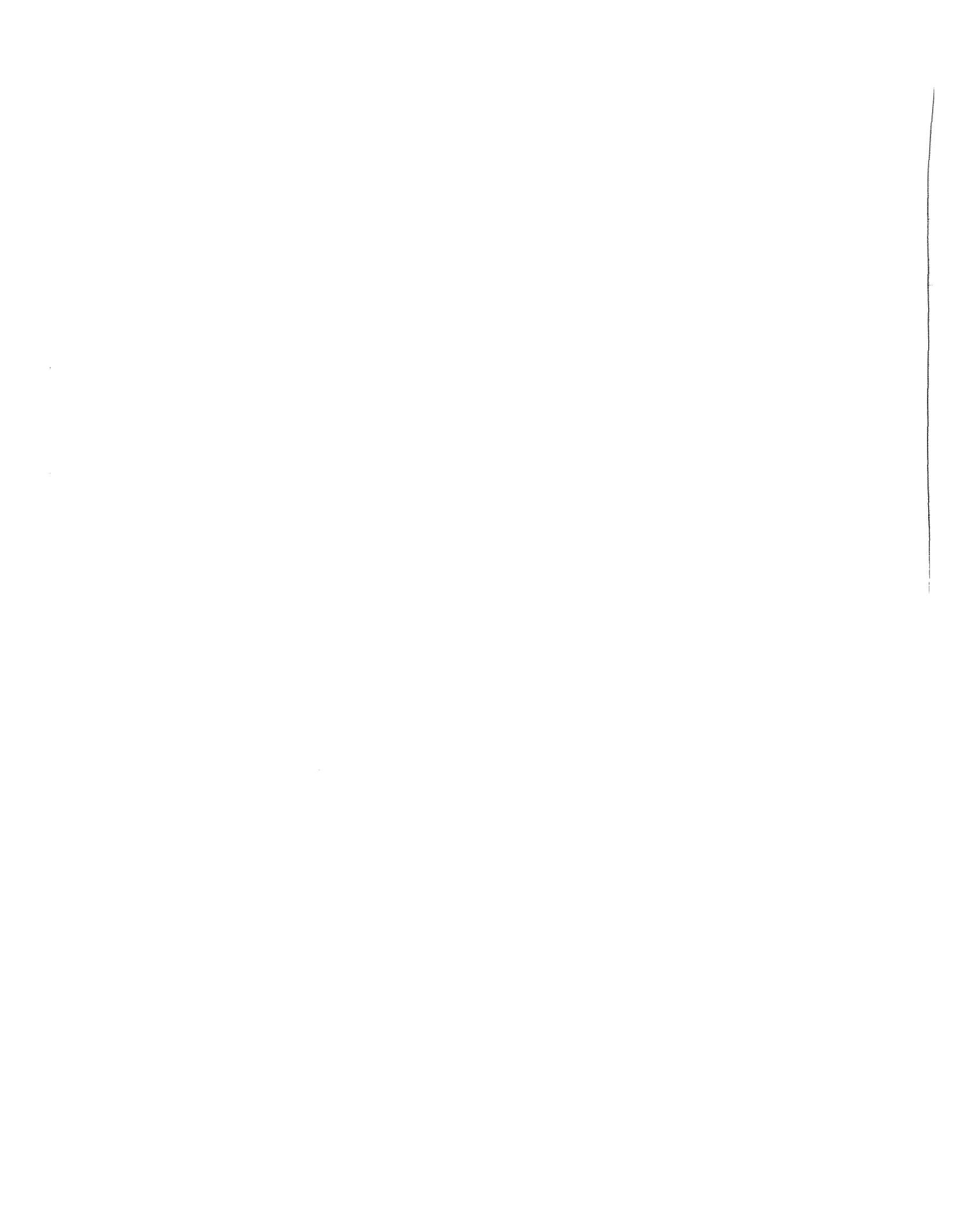
Section 4

**Data for Analysis
of Reproductive
and Development
Toxicity**



References for Developmental and Reproductive Toxicity

1. Draft Environmental Impact Statement to the Western Oregon Program-Management of Competing Vegetation. U.S. Dept. of Interior, Bureau of Land Management, February 1986.
2. A.M. Shipp, M.L. Hogg, K.S. Crump, and R.L. Kodell. Worst case analysis study on forest plantation herbicide use. Forest Land Management Division, Department of Natural Resources, State of Washington, May 1986.
3. T.B. Gaines, R.D. Kimbough, and R.E. Linder. The toxicity of amitrole in rats. *Tox. Appl. Pharm.* 26:118-129 (1973).
4. H. Tjalve. Fetal uptake and embryotoxic effects of amino triazole in mice. *Arch. of Tox.* 33:41-48 (1974).
5. EPA, 1985a (EIS pg 1-32).
6. J.L. Shardein. Chemically induced birth defects. *Drug and Chemical Toxicology Vol. 2*, Marcel Dekker, Inc., New York 1985 pp. 577-617.
7. EPA, 1984b.
8. EPA, 1984c.
9. Ciba Geigy, 1985.
10. EPA, 1984c.
11. Hayes, 1982 EPA stated study evaluation.
12. Medical Toxicology Reviews. California Department of Food and Agriculture Reports, Pest Management, Environmental Protection and Worker Safety, State of California, February 1987.
13. Tox 1-liners. We have not adjusted any of the doses for percent purity of compound tested.
14. Peters and Cook (from Crump pg. 161).
15. EPA Dicamba Registration Standard (6/11/85?) (SC-8).



Neurotoxicity of Herbicides

1. Summary of data

For 10 of the herbicides studied (amitrole, bromacil, 2,4-DP, dalapon, dicamba, diuron, glyphosate, hexazinone, picloram, triclopyr), there is no reported evidence of any sign of toxicity involving the central and/or peripheral nervous system.

For atrazine, fosamine, simazine, and tebuthiuron, signs indicative of a nervous system involvement were reported for doses equivalent to their ID50s.

For simazine, nervous symptoms were also observed following 21-day exposure (1,000–2,000 mg/kg) in rabbits; for atrazine following 6-month exposure in dogs (1,500 ppm) and after 3-month exposures in rats (75 mg/kg); and for asulam following 5-day exposure of dogs to 2,000 mg/kg.

2,4-D caused no neuropathy in animals, but caused brain lesions and EEG alterations following exposure to 100–300 mg/kg. Peripheral neuropathy and brain lesions have been observed in humans exposed to high or lethal doses. A decreased nerve conduction velocity has been found in workers chronically exposed to 2,4-D and 2,4,5-T.

2. Evaluation

With the exception of the delayed neurotoxicity test required for all new organophosphates, no other test for central or peripheral nervous system toxicity is required for registration of pesticides. Therefore, specific tests aimed at detecting neurotoxicity are not normally done with compounds such as the herbicides under consideration. However, any sign of toxicity, including those suggestive of a nervous system involvement, are usually recorded and reported during acute, subchronic, and chronic studies. No such indications were reported for 10 out of 16 herbicides, suggesting that no specific signs were observed.

For five additional herbicides, certain signs suggestive of a possible nervous system involvement were reported; however, these occurred mostly when lethal or very high doses were administered. Atrazine provided some indications of neurotoxicity at doses well below its lethal dose; although the doses are still quite high and only two animal studies are available, this potential effect should be kept in consideration.

2,4-D has caused peripheral neuropathy and brain lesions in humans exposed to very high doses (accidental poisoning or suicide).

One study reported a decrease in nerve conduction velocity in chronically 2,4-D exposed workers. However, there was a concomitant exposure to 2,4,5-T (and most probably dioxins), which makes it impossible to ascribe this effect to 2,4-D.

Neuropathy has not been observed in laboratory animals, but exposure of mice and rats to doses as low as 100 mg/kg of 2,4-D were found to cause brain lesions in one study. No determination of NOEL is possible from the available studies. 2,4-D should be reported as a potentially neurotoxic compound, possibly only in a few susceptible individuals and only at high doses.

Immunotoxicity of Herbicides

1. Summary of Data

There is no reported evidence of immunotoxicity for 13 herbicides (amitrole, asulam, bromacil, 2,4-DP, dalapon, dicamba, fosamine, glyphosate, hexazinone, picloram, simazine, tebuthiuron and triclopyr). Diuron (250 mg/kg in the diet) increased spleen weights, and atrazine (100 mg/kg in the diet) caused lymphopenia (decreased white cells count). 2,4-D had some immunotoxic effects at high doses (200 mg/kg and up), and a breakdown product of 2,4-D depressed cell-mediated immunity in rats at the dosage of 30 ppm.

2. Evaluation

No specific tests for immunotoxicity are required for pesticide registration, and therefore no experiments aiming at detecting alternations in immune function are performed. Some evidence of toxicity to the thymus or the spleen could surface during autopsies following subchronic and/or chronic studies, but these have not been reported for the herbicides under consideration.

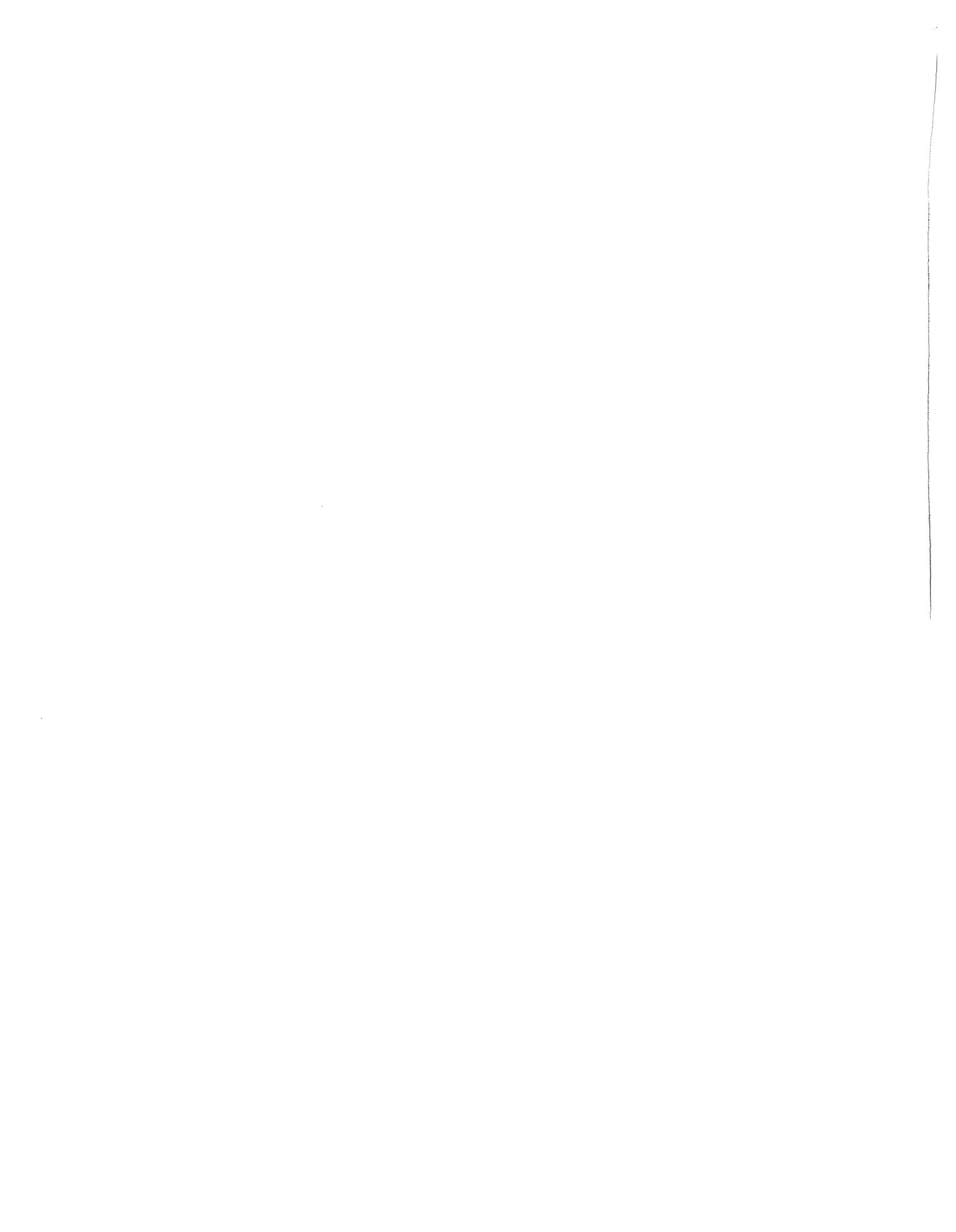
Atrazine-caused lymphopenia at a dose level (100 mg/kg) similar to that which caused some evidence of neurotoxicity. Although the information available is limited, exposure levels should be kept below these values.

Acute administration of 2,4-D caused alteration of cell-mediated responses at 200 mg/kg and of humoral responses at 500 mg/kg, when overt clinical manifestations of toxicity and histopathological alterations in brain were also present. No effects were found following repeated exposures. Exposure to such high doses of 2,4-D are unlikely to occur. Exposure to 2,4-dinitrophenol a breakdown product of 2,4-D alters cell-mediated immunity at doses of 30 ppm. Safe exposure levels should be kept below these values.

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Section 5
Data for Analysis
of Immunotoxicity
and Neurotoxicity



Data for Analysis of Immunotoxicity and Neurotoxicity

1. Amitrole:	NEUROTOX .	: No reported evidence of neurotoxicity in subchronic studies.
	IMMUNOTOX .	: No reported evidence of immunotoxicity in acute and subchronic studies.
2. Asulam:	NEUROTOX	: Vomiting and anorexia in dogs given 2,000 mg/kg/day for 5 days (only dose tested) .
	IMMUNOTOX .	: No reported evidence of immunotoxicity in acute and subchronic studies.
3. Atrazine:	NEUROTOX .	: Tremor, ataxia, hypoactivity in rats after ID_{50} doses.
		Rear limb muscular tremors in dogs following 6 months feeding of 1,500 ppm.
		Impairment of learning and alteration in EEG activity in rats given 1/40 of the ID_{50} (i.e. 75 mg/kg/day) of Toxurazine (15% atrazine, 15% chlorinol, 30% aminotriazole) for 3 months. (Desi et al., Acta Physiol. Acad. Scient. Hung. 60-:1-8, 1982) .
	IMMUNOTOX	: 100 mg/kg in diet caused lymphopenia in rats (Vos et al. In Pesticide Chemistry. Human Welfare and the Environment, Vol. 3, p. 497-506, 1983) .

Summary of Neurotoxicity and Immunotoxicity of Herbicides

al. *Fund. Appl. Toxicol.* 6, 175, 1986; *Neurobehav. Toxicol. Teratol.* 8, 255, 1986).

No brain lesions in rats fed 500 ppm for 2 years (Hansen et al. *Toxicol. Appl. Pharmacol.* 20, 122, 1971).

EEG alternations in rats following acute and chronic treatment (200 mg/kg) (Desi and Sos, *Med. Acad. Sci. Hung* 18, 429, 1962); Desi et al. *Arch. Env. Health* 4, 95, 1962).

Acute doses (200 mg/kg and up) cause myotonia in rats and dogs (Brody, *Arch. Neurol.* 28, 243, 1973; Drill and Hiratzka, *Arch. Ind. Hyg. Occup. Med* 7, 61, 1953).

Previous exposure to 250 mg/kg increases concentration of [14C] 2,4-D in brain by sevenfold and in other tissues by two-three fold (Elo and Ylitalo, *Toxicol. Appl. Pharmacol.* 51, 439, 1979).

Acute dermal dose of 500 mg/kg or subacute (3 weeks) dermal doses of 100-300 mg/kg in mice cause histopathological lesions in CNS including perivascular edema and ganglial cells necrosis (Blakley and Shiefer; *J. Appl. Toxicol.* 6, 291, 1986).

IMMUNOTOX . : Altered immune functions in rats following 3 months

exposure to 30 and 300 ppm 2,4-dichlorophenol, breakdown product of 2,4-D. (Exon et al., J. Toxicol. Ev. Health 14, 723, 1984).

Exposure in utero to 200 mg/kg reduces lymphocyte mitogen responsiveness in 6 week-old offspring (subtle injury to lymphocyte precursors?). No changes in humoral immunity. (Blakley and Blakley, Teratology 33, 15, 1986).

Acute dermal dose of 200 and 500 mg/kg in mice suppressed antibody production against sheep RBC but not the proliferative responses induced by other mitogens. Subacute dermal exposure to 100-300 mg/kg had no effect on these parameters (Blakley and Schiefer, J. Appl. Toxicol. 6, 291, 1986).

6. 2,4-DP	NEUROTOX.	: No reported evidence of neurotoxicity in acute and subchronic studies.
	IMMUNOTOX.	: No reported evidence of immunotoxicity in acute and subchronic studies.
7. Dalapon	NEUROTOX.	: No reported neurotoxicity in acute and subchronic studies.
	IMMUNOTOX.	: No reported evidence of immunotoxicity in acute and subchronic studies.

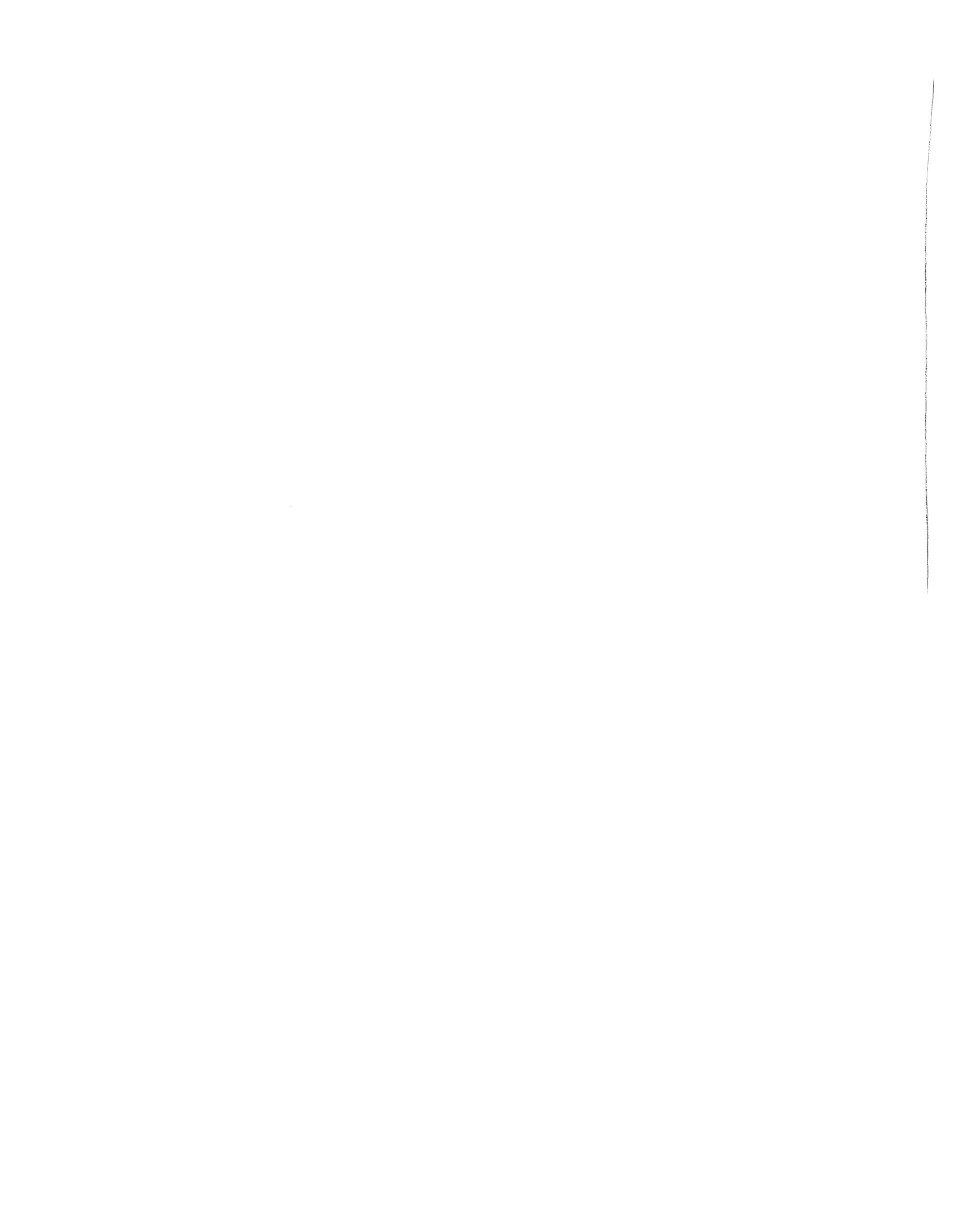
8. Dicamba NEUROTOX : Sciatic nerve damage observed in hens at LD50 dose.
- IMMUNOTOX : No reported evidence of immunotoxicity in acute and subchronic studies.
9. Diuron NEUROTOX : No reported evidence of neurotoxicity in acute and subchronic studies.
- IMMUNOTOX : 250 mg/kg in diet increased spleen weight in rats (Vos et al. IN Pesticide Chemistry. Human Welfare and the Environment, Vol. 3, p. 497-506, 1983) .
10. Fosamine NEUROTOX : Tremors and convulsions at LD₅₀ dosage.
- IMMUNOTOX : No reported evidence of immunotoxicity in acute and subchronic studies.
11. Glyphosate NEUROTOX : No reported evidence of neurotoxicity in acute and subchronic studies.
- IMMUNOTOX : No reported evidence of immunotoxicity in acute and subchronic studies.
12. Hexazinone NEUROTOX : No reported evidence of neurotoxicity in acute and subchronic studies.
- IMMUNOTOX : No reported evidence of immunotoxicity in acute and subchronic studies.
13. Picloram NEUROTOX : No reported evidence of neurotoxicity in acute and subchronic studies.

	IMMUNOTOX	: No reported evidence of immunotoxicity in acute and subchronic studies.
14. Simazine	NEUROTOX	: 1,000 and 2,000 mg/kg to rabbits in 21-day dermal exposure caused uncoordination, paralysis, and decreased brain weight.
		LD ₅₀ dose in rabbit caused paralysis, tremor, convulsions.
		LD ₅₀ dose in rat caused hypoactivity, muscular weakness, labored breathing, convulsions, ataxia.
	IMMUNOTOX	: No reported evidence of immunotoxicity in acute and subchronic studies.
15. Tebuthiuron	NEUROTOX	: At LD ₅₀ doses in mice, rat, cat, and dog caused hyper-irritability, loss of sighting reflex, ataxia, emesis, tremors, convulsions.
	IMMUNOTOX	: No reported evidence of immunotoxicity in acute and subchronic studies.
16. Triclopyr	NEUROTOX	: No reported evidence of neurotoxicity in acute and subchronic studies.
	IMMUNOTOX	: No reported evidence of immunotoxicity in acute and subchronic studies.

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Section 6
Data for Evaluation
of Human
Epidemiology



Observational Epidemiology

I. Discussion

A. Strengths & Weaknesses

Almost all the human epidemiology information on health effects of pesticides is from observational studies. These studies take real life exposure situations for evaluation (such as groups of workers) rather than controlled and deliberate exposures (as in animal experiments). This approach has its strengths and weaknesses.

The most important strengths in these studies are as follows. First, actual human, as opposed to animal, health effects are being observed. Second, exposures levels that actually occur in the environment and workplace are being evaluated, as opposed to the very high exposures used in animal studies. And third, exposures to total commercial products, and not just one active ingredient, are evaluated. Thus, the questions about "inerts" are reduced, and the need for extrapolation to a different species at much lower exposure levels are eliminated.

On the other hand, humans are much less homogeneous than laboratory animals. They differ greatly both in genetic makeup and life environment. The actual exposure being evaluated is often associated with other exposures which can confound the results. Thus, it is very unlikely that a worker using or manufacturing pesticides will come into contact with only one pesticide.

One of the major concerns in studies relating to the phenoxy herbicides 2,4-D and 2,4-DP is confounding by other phenoxy herbicides, in particular 2,4,5-T. The latter is contaminated with significant amounts of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), a highly toxic compound. The herbicides 2,4-D and 2,4,5-T were frequently used together and manufactured at the same facilities.

Finally, human studies involve many more subjects, take a long time and can be expensive. Almost all of the sixteen herbicides under consideration have not been evaluated in exposed human populations. The only herbicide group with considerable information is the phenoxy acid herbicides (including 2,4-D and 2,4-DP).

B. The Scope of the Studies

The studies presented here all involve phenoxy acid herbicides. One study also looks at workers exposed to amitrole. Only for the phenoxy acid herbicides have sufficient human studies been identified to make even a tentative evaluation.

Most of the studies involved mixed exposure to various phenoxy herbicides, chlorophenols and/or other chemicals. Exposure to TCDD, not associated with 2,4-D or 2,4-DP, is of concern in these studies. However, several studies involve only minimal confounding with dioxins. These include the following:

Lynge (1985): a cohort study of workers exposed primarily to 2,4-D and other phenoxy herbicides not contaminated with TCDD.

Eriksson et al (1981): a case control study independently analyzed for non 2,4,5-T exposure.

Hoar et al (1987): a case-control study independently analyzed for 2,4-D use.

In addition, an observational animal study showed positive results which were unchanged by analysis for herbicides contaminated with TCDD and those not contaminated (Newell et al, 1984).

Other studies looked primarily at mixed 2,4-D and 2,4,5-T exposures. These include the Swedish studies (Hardell, 1981; Hardell & Bengtsson, 1983; Hardell et al, 1981; Hardell & Sandstrom, 1979), as well as others (Pearce et al, 1986; Riihimaki et al, 1982; Smith et al, 1984; Smith et al, 1982; Woods et al, 1987; Singer et al, 1982).

Still other studies looked primarily at 2,4,5-T exposures (Ott et al, 1980; Smith et al, 1982; Suskind & Hertzberg, 1984; Zack and Gaffey, 1983), or to mixtures of chemicals including phenoxy herbicides (Axelson et al, 1980).

Finally, reproductive effects were looked at in several ecological studies (Nelson et al, 1979; Thomas, 1980; Field & Kerr, 1979; Hanify et al, 1981; Balarajan & McDowall, 1983). These studies look at the experience of a general population over time and area, and compare these results to herbicide use levels over the same time and area.

The concern about confounding cannot be overcome in many of these studies. However, 2,4-D and 2,4-DP are contaminated with chlorinated dioxins other than TCDD or may have toxic effects of their own. The assumption that all the toxicity of phenoxy herbicides is only associated with TCDD exposure does not necessarily follow, and there is evidence that other dioxins may be important factors (Woods, 1987). To ignore the observed human health effects of this group of herbicides based upon the assumption that all effects are attributable to TCDD would be overly simplistic and not consistent with a conservative approach to assessing human health.

C. Study Descriptions

The studies evaluated include five worker cohort studies, a number of case-control studies, and a few miscellaneous studies. The worker cohort studies

define an exposed population and look for any disease (in this case any cancers) that might occur more frequently than expected. Case-control studies, on the other hand, define the study population by the type of disease (cancer) being studied, and then look to see if subjects with this disease had more than expected exposure to the chemical (herbicide) of concern.

The five cohort studies look at cancer deaths and incidence among groups of workers exposed to phenoxy acids. One also evaluates a group exposed to Amitrole. These studies will be referred to repeatedly throughout this section as they may be used to evaluate any number of cancers. They will be presented in greater detail at the beginning of the following charts, and will be referenced later simply by the name of the author.

The cohort studies are ordered according to the total number of deaths or cases observed. These studies include fairly small cohorts and some rarer diseases may not be represented in their findings. All the studies except that by Lynge (1985) look only at mortality. Lynge used information on the incidence of cancer in his cohort.

The other studies will be referred to and described only under the heading of the cancer being evaluated in the tables below.

D. Evaluations of Association

The following evaluations are based upon all the studies described above and listed in the table below. Due to the fact that very few of the studies evaluated exposure to 2,4-D or 2,4-DP separately from other associated exposures, the extension of these findings to these herbicides must be done with care.

Nevertheless, those studies which specifically looked at 2,4-D exposure did not differ greatly in results from the other studies. There is no evidence here that 2,4-D is any less or more toxic than other phenoxy herbicides. A cautious observer would have to conclude that the evidence is suggestive of some carcinogenic effect.

1. Lung Cancer

Based upon fairly small studies, there is a suggestion that exposure to phenoxy acids and/or dioxins may cause lung cancer. One difficulty of applying these findings to the use of 2,4-D and 2,4-DP is the question of the role of the TCDD dioxin. It is very difficult to clearly separate these exposures. However, the only statistically significant increase in lung cancer was reported by Lynge, a study with only minor exposure to 2,4,5-T and the TCDD dioxin.

2. Stomach Cancer

Based upon very small studies, there is a suggestion that exposure to phenoxy acids and/or dioxins may cause stomach cancer.

3. Leukemia

The association between leukemia and phenoxy herbicide exposure has not been explicitly studied. Several of the cohort studies have reported cases of leukemia, but no clear pattern emerges.

4. Hodgkin's Disease

Several case-control studies have looked specifically at the occurrence of Hodgkin's disease and exposure to phenoxy herbicides. Two studies (Hardell, Eriksson et al, 1979 and Hardell & Bengtsson, 1983), both done in Sweden on separate populations, reported statistically significant five fold risks. A recent study in the U.S. (Hoar, Blair et al, 1986) found no excess risk. The differences for this disparity is not clear. The studies all appear to have sufficient quality to be given credibility.

Given the variability of the data, we conclude that the possibility of risk for Hodgkin's disease with exposure to phenoxy herbicides has been raised and should be of concern.

5. Non-Hodgkin's Lymphoma

Several case-control studies have looked specifically at the occurrence of Non-Hodgkin's Lymphoma and exposure to phenoxy herbicides. Two studies, one in Sweden (Hardell, Eriksson et al, 1981) and one in the U.S. (Hoar, Blair et al, 1986) reported statistically significant five to six fold risks. A recent study in New Zealand (Pearce, Smith et al, 1986) found a non-significant mild increase of risk around 1.4 fold.

The authors of the New Zealand study felt that their findings were not consistent with the other studies, because their study population was likely to have high exposure.

Given the variability of the data, we conclude that the possibility of risk for Non-Hodgkin's Lymphoma with exposure to phenoxy herbicides has been raised and should be of concern.

6. Soft Tissue Sarcomas

Several case-control studies have looked specifically at the occurrence of Soft Tissue Sarcomas (STS) and exposure to phenoxy herbicides. Two studies (Hardell, Eriksson et al, 1979 and Hardell & Bengtsson, 1983), both done in Sweden on separate populations, reported statistically significant five to seven fold risks. Two recent studies, one in the U.S. (Hoar, Blair et al, 1986) and one in New Zealand (Smith, Pearce et al, 1984) found little or no excess risk.

STS, a fairly rare tumor, was seen in four of the five cohort studies. In each case this represented an excess. A statistically significant excess of five fold was reported by Lynge (1985) for workers in the manual services (maintenance) category.

A number of small manufacturer cohorts also reported individual cases. A review by Honchar & Halperin (1981) estimated an excess risk of over 40 fold based upon three cases in four cohorts and compared to national statistics. Additional case reports claim to have found additional cases who worked in manufacture, some possibly from these four cohorts. A total of seven cases diagnosed by pathologists have been reported.

STS is a difficult diagnosis even for pathologists. The National Institute of Occupational Safety and Health (Fingerhut et al, 1983) reviewed these cases. Two pathologists familiar with STS concurred in the diagnosis in only five cases.

In addition to the difficulty of diagnosis, there are problems coding STS on death certificates. The International Code for Diseases (ICD) is site oriented. Thus, an STS of the stomach may be coded as a stomach cancer. This may be an explanation of the increased stomach cancers noted in some of the cohort studies.

Of more immediate concern is that the two Swedish case-control studies selected their cases using primarily histopathologic characteristics, and did not limit selection by site. The New Zealand and U.S. studies identified their cases using the more site specific ICD classification of 171 (malignant neoplasm of connective and other soft tissue). Thus, while all the studies used cancer registries and cases confirmed by pathology examination, the Swedish studies probably included more sites (such as STS of the stomach). The differences between these studies could well be due to different diagnostic criteria.

The problems with both diagnosis and coding of STS mean that comparisons using death certificates must be questioned. Thus, while there is some variability of the data, there are some clear difference in technique which could explain these differences. Both case control and cohort studies in various countries have found associations with STS and phenoxy acid exposures. We conclude that the possibility of risk for Hodgkin's disease with exposure to phenoxy herbicides has been raised and should be of concern.

7. Summary of Cancer Associations

Suggestions of association with at least five types of cancer have been found in the epidemiology literature. Each of the five cancers has had both statistically significant associations in some studies and negative findings in others. While there is no conclusive demonstration of any individual association, the suggestion is that phenoxy herbicides in some way initiate or promote cancers, and that this is done at a level of exposure experienced in various work settings.

One observational studies on sheep exposed through feed treated with herbicide demonstrated a dose-response relationship with intestinal cancer.

8. Reproductive Effects

There are no good epidemiology studies of reproductive outcomes associated with exposure to phenoxy herbicides. Much of the information comes from studies in Vietnam where research conditions and records are poor. The results of the Vietnamese studies, as well as those of U.S. soldiers exposed in Vietnam and the few other studies, are generally inconsistent.

The mixed results of studies on reproductive effects could be expected, as these effects are very difficult to study. The possibility of some reproductive effects has been raised and should be of concern.

9. Neurologic Effects

While only two small studies are presented, there are numerous case reports of neurologic effects with 2,4-D exposure. 2,4-D should be considered a potential human neurotoxin.

II. Tables of Cohort Studies

The following five cohort studies look at cancer deaths (or incidence) among groups of workers exposed to phenoxy acids. One also evaluates a group exposed to Amitrole. These studies will be referred to throughout this section as they pertain to the specific cancer being evaluated. They are presented here in more detail.

The studies are ordered according to the total number of deaths or cases observed. These studies include fairly small cohorts and some rarer diseases may not be represented in their findings.

All the studies except that by Lyngø (1985) look only at mortality. Lyngø used information on the incidence of cancer in his cohort.

COHORT STUDIES

Lynge 1985	4,459 workers at two factories in Denmark
Denmark	3,390 males and 1,069 females
Manufacturer Cohort	940 worked in mfg & pkg of phenoxy herbicides
Total observed	1,226 worked in manual service functions
cancer incidence	1,667 worked in mfg & pkg of other chemicals
= 208 among	Remainder worked office and unspecified jobs
200 individuals	59% males and 50% females worked less than 1 year.
	Study reports results by department and for the entire cohort. Little TCDD contamination.

Zack & Gaffey 1983 USA Manufacturer Cohort	884 white male hourly workers at Monsanto in Nitro, West Virginia employed at least one year. Exposure to 2,4,5-T was determined only for deceased
Total observed deaths = 163	Study reports SMR's for the entire cohort and PMR's for the deceased by exposed and unexposed. Only 58 of the 163 deaths were 2,4,5-T exposed.
Riihimaki et al 1982 Finland Herbicide Applicators	1,971 male herbicide applicators of four employers with at least two weeks exposure to 2,4-D or 2,4,5-T 75% worked less than eight weeks total.
Total observed deaths = 144	
Axelsson et al 1980 Sweden Railroad Sprayers	348 RR herbicide sprayers with exposure > 45 days Study reports SMR's for the total cohort and three distinct subgroups: phenoxy acid, amitrole and combined exposure.
Total observed deaths = 45	
Ott et al 1980 USA Manufacturer Cohort	204 male workers at Dow Chemical who worked in a 2,4,5-T area for at least one month - 157 worked less than one year.
Total observed deaths = 11	

III. Case Control Studies

Various case-control studies have been conducted to look at risk factors for specific cancers. All the case control studies reported in this section were specifically concerned about associations between phenoxy acid exposures and the cancer being studied.

The case control studies are summarized under the headings of the specific cancers being evaluated.

IV. Presentation of Epidemiology Studies by Type of Cancer

Summaries of all cohort studies and relevant case-control studies are presented below for several types of cancers. Relative risks (risks compared to a general population) are presented when available. Relative risks greater than one represents a risk greater than that expected in the general population.

All the cohort studies have been included for each cancer to provide completeness. In some cases, several small cohort studies, with little information on their own, combine to present possible patterns of disease.

Human Epidemiology

TOXICITY/ STUDY	POINT ESTIMATE OF RELATIVE RISK		COMMENT
	>1.0	<=1.0	
 OVERALL CANCERS			
-----Cohort Studies-----			
Lynge 1985 Manufacturer Cohort		0.99 0.88	Based on all 159 male cases. Based on all 49 female cases.
	1.05		Based on 28 male cases in phenoxy acid manufacture and packaging.
		0.87	Based on 13 female cases in phenoxy acid manufacture and packaging.
Zack & Gaffey 1983 Manufacturer Cohort	1.13		Based on all 35 male deaths.
		0.82	PRM based on 9 male deaths among 2,4,5-T exposed workers.
Riihimaki et al 1982 Herbicide Applicators		0.71 0.82	Based on all 26 male deaths. Based on 20 male deaths with ten year latency period.
Axelson et al 1980 Railroad Sprayers	1.4 1.1 (1.9)		Based on all 17 male deaths. Based on 6 male deaths with only phenoxy acid exposure. (with a ten year latency period)
	2.1 (3.4*)		Based on 6 male deaths with phenoxy acid and amitrole exposure. (with a ten year latency period)
	1.5 (1.5)		Based on 5 male deaths with only amitrole exposure. (with a ten year latency period)
Ott et al 1980 Manufacturer Cohort		0.28	Based on the 1 male death.

* = Significant at the p=0.05 level.

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TOXICITY/ STUDY	POINT ESTIMATE OF RELATIVE RISK		COMMENT
	>1.0	<=1.0	
LUNG CANCER			
-----Cohort Studies-----			
Lynge 1985 Manufacturer Cohort	1.19		Based on 38 male cases.
	2.21		Based on 6 female cases.
	2.06*		Based on 11 male cases in phenoxy acid manufacture and packaging.
	1.28		Based on 1 female case in phenoxy acid manufacture and packaging.
Zack & Gaffey 1983 Manufacturer Cohort	1.41		Based on 14 male deaths.
	1.68		PRM based on 6 male deaths among 2,4,5-T exposed workers.
Riihimaki et al 1982 Herbicide Applicators	1.1		Based on 12 male deaths with ten year latency period.
Axelson et al 1980 Railroad Sprayers	1.4		Based on 3 male deaths.
		0.0	Based on 0 male deaths with only phenoxy acid exposure.
	1.9 (2.9)		Based on 1 male death with phenoxy acid and amitrole exposure. (with a ten year latency period)
	3.2 (2.6)		Based on 2 male deaths with only amitrole exposure. (with a ten year latency period)
Ott et al 1980 Manufacturer Cohort	+		Based on 1 male death.

* = Significant at the p=0.05 level.

TOXICITY/ STUDY	POINT ESTIMATE OF RELATIVE RISK		COMMENT
	>1.0	<=1.0	
STOMACH CANCER			
-----Cohort Studies-----			
Lynge 1985 Manufacturer Cohort	1.29	0.68	Based on 12 male cases. Based on 1 female case.
	1.36	0.0	Based on 2 male cases in phenoxy acid manufacture and packaging. Based on 0 female cases in phenoxy acid manufacture and packaging.
Zack & Gaffey 1983 Manufacturer Cohort		0.63	Based on 1 male death.
		0.0	PRM based on 0 male deaths among 2,4,5-T exposed workers.
Riihimaki et al 1982 Herbicide Applicators	1.1		Based on 4 male deaths with ten year latency period.
Axelson et al 1980 Railroad Sprayers	2.2		Based on 3 male deaths.
	3.1 (6.1*)		Based on 2 male deaths with only phenoxy acid exposure. (with a ten year latency period)
	3.1 (5.6)		Based on 1 male death with phenoxy acid and amitrole exposure. (with a ten year latency period)
		0.0	Based on 0 male deaths with only amitrole exposure.
Ott et al 1980 Manufacturer Cohort		0.0	Based on 0 male death.

* = Significant at the p=0.05 level.

TOXICITY/ STUDY	POINT ESTIMATE OF RELATIVE RISK		COMMENT
	>1.0	<=1.0	
LEUKEMIA			
-----Cohort Studies-----			
Lynge	1.11		Based on 5 male cases.
1985	2.08		Based on 2 female case.
Manufacturer Cohort			
	1.35		Based on 1 male case in phenoxy acid manufacture and packaging.
	4.0		Based on 1 female case in phenoxy acid manufacture and packaging.
Riihimaki et al		0.0	Based on 0 male deaths with ten year latency period.
1982			
Herbicide Applicators			
Axelsson et al	+		Based on 2 male deaths.
1980			
Railroad Sprayers	+		Based on 1 male deaths with only phenoxy acid exposure.
	(+)		(with a ten year latency period)
	+		Based on 1 male death with phenoxy acid and amitrole exposure.
	(+)		(with a ten year latency period)
Ott et al		0.0	Based on 0 male death.
1980			
Manufacturer Cohort			

* = Significant at the p=0.05 level.
+ = Unquantified excess risk.

TOXICITY/ STUDY	POINT ESTIMATE OF RELATIVE RISK		COMMENT
	>1.0	<=1.0	
HODGKIN'S			
-----Case-Control Studies-----			
Hardell, Eriksson et al 1981	4.8*		169 cases of malignant lymphoma (including 60 Hodgkins lymphomas) and 338 controls. Controls were from the general population. Cases and controls with exposure to chlorophenol were excluded. A dose response was observed. SMR is reported for the entire cohort - it was reported that there was no observable difference in risk between the Hodgkin's and non-Hodgkin's cases.
Hardell 1981	5.5*		169 malignant lymphoma cases (including 60 Hodgkins lymphomas and 154 controls. This is the same case population as above (Hardell & Eriksson 1981), but new controls were chosen from males with colon cancer. A dose response observed. SMR is reported for the entire cohort.
Hardell & Bengtsson 1983	5.0*		60 cases and 335 controls. Controls were from the general population. Cases & controls with high exposure to chlorophenols were excluded. This is a refinement of the two studies presented above (Hardell 1981 / Hardell et al 1981)
Hoar, Blair et al 1986		0.9	71 cases and 984 controls. Controls were from the general population. Exposure was based on reported herbicide use.

* = Significant at the p=0.05 level.

TOXICITY/ STUDY	POINT ESTIMATE OF RELATIVE RISK		COMMENT
	>1.0	<=1.0	
HODGKIN'S			
-----Cohort Studies-----			
Riihimaki et al 1982		0.0	Based on 0 male deaths.
Axelsson et al 1980	+		Based on 2 male deaths
	+		Based on 1 male death with
	(+)		only phenoxy acid exposure
			(with ten year latency period).
		0.0	Based on 0 male deaths with
			phenoxy acid & amitrole exposure
	+		Based on 1 male deaths with
	(+)		only amitrole exposure
			(with ten year latency period).
Ott et al 1980		0.0	Based on 0 male deaths.

+ = Unquantified excess risk.

TOXICITY/ STUDY	POINT ESTIMATE OF RELATIVE RISK	>1.0	<=1.0	COMMENT
NON-HODGKIN'S				
-----Case-Report-----				
Hardell 1979				Pilot study of 17 cases. 14 cases had employment consistent with exposure (farming, forestry, sawmill, painting and building).
-----Case-Control Studies-----				
Hardell, Eriksson et al 1981	4.8*			169 cases of malignant lymphoma (including 109 non-Hodgkins lymphomas) and 338 controls. Controls were from the general population. Cases and controls with exposure to chlorophenol were excluded. A dose response was observed. SMR is reported for the entire group - it was reported that there was no observable difference in risk between the Hodgkin's and non-Hodgkin's cases.
Hardell 1981	5.5*			169 malignant lymphoma cases (including 109 non-Hodgkins lymphomas) and 154 controls. This is the same case population as above (Hardell & Eriksson 1981), but new controls were chosen from males with colon cancer. A dose response observed. SMR is reported for the entire cohort.
Hoar, Blair et al 1986	1.6 (6.0*)			170 cases and 948 controls. Controls were from the general population. Exposure was based on reported herbicide use. (SMR increased to a significant 6.0 for herbicide use of at least 20 times per year). A dose response was demonstrated.
Pearce, Smith et al 1986	1.4			83 cases matched with two sets of controls - 168 controls with other cancers and 228 controls from the general population.
Woods et al 1987	1.07 (4.80*) ((1.71*))			576 cases and 694 random controls from the general population: ever exposed. (forestry herbicide applicator). ((15 years exposure 15 years prior to diagnosis - a latency response was demonstrated))

* = Significant at the p=0.05 level.

TOXICITY/ STUDY	POINT ESTIMATE OF RELATIVE RISK		COMMENT
	>1.0	<=1.0	
NON-HODGKIN'S			
-----Cohort Studies-----			
Riihimaki et al 1982		0.0	Based on 0 male deaths.
Axelsson et al 1980		0.0	Based on 0 male deaths
Ott et al 1980		0.0	Based on 0 male deaths.

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TOXICITY/ STUDY	POINT ESTIMATE OF RELATIVE RISK		COMMENT
	>1.0	<=1.0	
SOFT TISSUE SARCOMA (STS)			
-----Case-Control Studies-----			
Hardell & Sandstrom 1979	5.3*		46 cases and 201 controls. Controls were from the general population. Cases & controls with chlorophenol exposures were excluded.
Eriksson, Hardell et al 1981	6.8*		110 cases & 220 controls. Controls were from the general population Cases & controls with chlorophenol exposures were excluded.
Smith, Pearce et al 1984	1.3		82 cases and 92 controls. Controls were selected from males with other cancers. Case & controls with chlorophenol exposures were excluded.
Hoar, Blair et al 1986		0.9	71 cases and 948 controls. Controls were from the general population Exposure was based on reported herbicide use.
Woods et al 1987		0.99 (0.0) (-)	576 cases and 694 random controls from the general population: ever exposed. (forestry herbicide applicator = no cases). ((15 years exposure 15 years prior to diagnosis = a latency response was demonstrated))

* = Significant at the p=0.05 level.

- = No association (number not reported).

TOXICITY/ STUDY	POINT ESTIMATE OF RELATIVE RISK		COMMENT
	>1.0	<=1.0	
SOFT TISSUE SARCOMA (STS)			
-----Cohort Studies-----			
Lynge 1985	2.72		Based on 5 male cases.
		0.0	Based on 0 female cases.
	3.33		Based on 1 male case in phenoxy acid manufacturing and packing.
		0.0	Based on 0 female cases in phenoxy acid manufacturing and packing.
	5.19*		Based on 3 male cases in manual services.
		0.0	Based on 0 female cases in manual services.
	1.38		Based on 1 male case in other chemical manufacturing and packing.
		0.0	Based on 0 female cases in other chemical manufacturing and packing.
Zack & Gaffey 1983	+		Based on 1 male death in plant.
	+		PMR based on 1 male death to a 245-T exposed worker.
Riihimaki et al 1982		0.0	Based on 0 male deaths.
Axelson et al 1980	+		Based on 1 male death.
		0.0	Based on 0 male deaths with only phenoxy acid exposure.
		0.0	Based on 0 male deaths with phenoxy acid & amitrole exposure.
	+	(+)	Based on 1 male death with only amitrole exposure (with ten year latency period).
Ott et al 1980		0.0	Based on 0 male deaths.

Honchar & Halperin 1981	41.4*		Summary of the 4 USA studies (one unpublished at the time)/ total deaths=105/ three STS cases.

* = Significant at the p=0.05 level.
+ = Unquantified excess risk.

TOXICITY/ STUDY	POINT ESTIMATE OF RELATIVE RISK		COMMENT
	>1.0	<=1.0	
SOFT TISSUE SARCOMA (STS)			
-----Case-Report-----			
Cook 1981			Case report/ one more STS case discovered in the Dow cohort described in Cook, Townsend & Ott.
Moses & Selikoff 1981			Case report/ one more STS case discovered in the Monsanto cohort.
Johnson, Kugler & Brown 1981			Case reports/ two more STS cases with work histories at Monsanto/ not identified a part of above cohorts.
-----Other Studies-----			
Milham 1982	1.2		Proportional Mortality Death certificate study/ 49 STS deaths/ looked at occupations with possible 2,4-D exposure including farming and forestry.

REPRODUCTIVE OUTCOMES

-----Cohort Studies-----

Smith, Fischer, Pearce & Chapman 1982	548 sprayers in New Zealand and 441 controls. 427 exposed & 352 not exposed one year before or after conception.
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Exposed group had 1.19 RR of congenital defect and 0.89 risk of miscarriage. Stillbirths (3) occurred only in the exposed group.

-----Other Studies-----

Nelson et al 1979	Cleft palate occurrence by county with herbicide use by county based on rice acreage. No association observed.
Thomas 1980	Congenital malformation and 245-T use over time in Hungary. No association observed.
Hanify et al 1980	New Zealand malformations in association with spraying herbicides by area and time. Mixed results
Field & Kerr 1979	Australia - neural-tube defects and spraying of 2,4,5-T over time. Mild positive association
Balarajan & McDowall	England & Wales - malformations and occupations with likely exposure to 2,4,5-T. Facial cleft malformation consistently high. Spina bifida high in gardeners and agricultural workers. Anencephaly high in gardeners. Association are soft.
Erikson et al 1984	Review of Vietnamese studies for both paternal and maternal studies Mixed positive results - no clear pattern
Hatch 1984	Review of reproductive effects of dioxins/ no definite conclusions.

NEUROLOGICAL EFFECTS

-----Cohort Studies-----

Singer, Moses et al
1982

56 workers in a 2,4-D & 2,4,5-T
plant were compared with 25
unexposed controls.

Median motor, median sensory and sural nerve velocities were measured. 46% of exposed group had slowed velocities compared to 5% in the control group ($p < .001$). The mean velocities of the median motor and sural nerves were significantly slower than the controls. There was a highly significant inverse relation between the sural nerve velocity and length of employment. All these relationships remained true when adjusted for alcohol consumption, age and other parameters.

Suskind & Hertzberg
1984

204 workers at Monsanto's Nitro,
West Virginia plant exposed to
dioxin and 163 workers not exposed.

Nerve conduction velocities in ulnar and peroneal nerves was non-significantly reduced in exposed group. Sural nerve conduction was slightly reduced in unexposed.

ANIMAL STUDIES

SHEEP AND SMALL INTESTINAL ADENOCARCINOMA

Newell, Ross & Renner

Sheep from 88 farms in New Zealand
20,678 female sheep/ 125 cases
(6/1000) from 61 farms
Exposure to phenoxy herbicides,
picolinic herbicide and combined.

Significant positive trends for treatment of feed with either herbicide or both combined, and with how recently the feed had been treated before consumption.

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