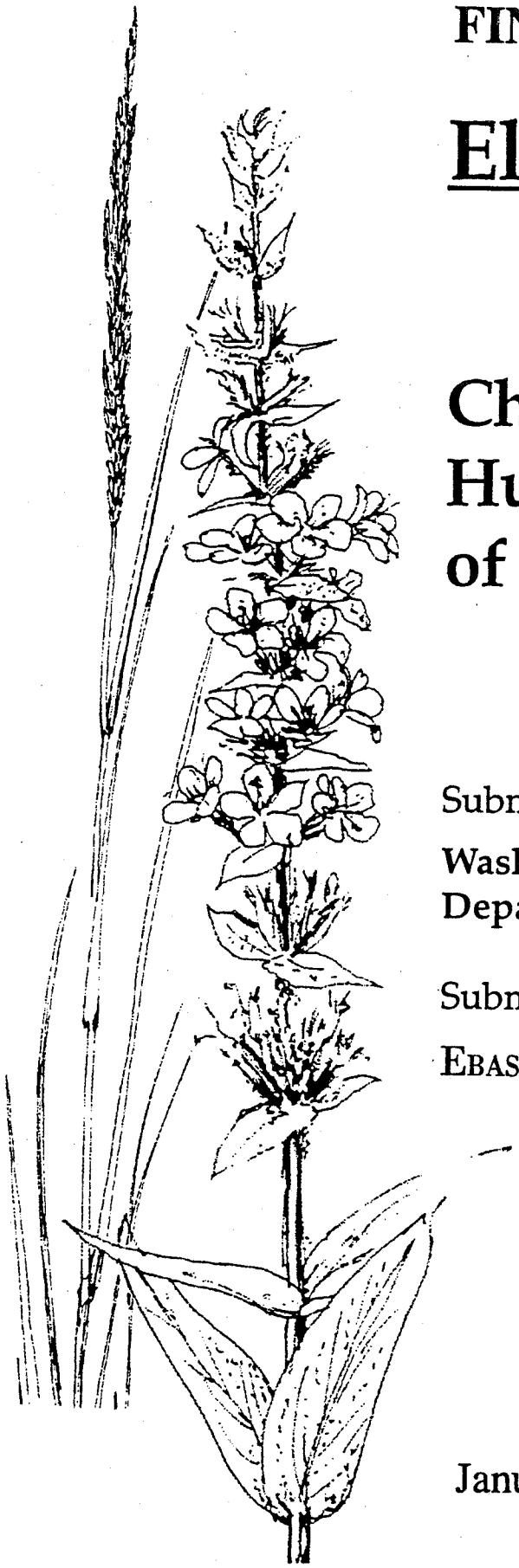

FINAL REPORT

Element G

Chemical Methods Only: Human Health Effects of 2,4-D

Submitted to

Washington State Department of Ecology

Submitted by

EBASCO ENVIRONMENTAL

January 1993

FINAL REPORT

Element G: Chemical Methods Only: Human Health Effects of 2,4-D

Submitted to:

Washington State Department of Ecology

Submitted by:

Ebasco Environmental

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ADDENDUM FOR 2,4-D RISK ASSESSMENT, ELEMENT G
FINAL REPORT, JANUARY 1993

This addendum outlines technical and editorial revisions to the 2,4-D Risk Assessment prepared for the Washington State Department of Ecology by Ebasco Environmental. The revisions include a review of additional 2,4-D carcinogenicity studies and a discussion of the evaluation of 2,4-D by the Environmental Protection Agency 2-4,D scientific advisory panel. This information was not available at the time the 2,4-D Risk Assessment was finalized. The paragraph numbering for the revisions specified below begins with the first full paragraph on the given page.

Page	Para	Line	Change
2	2	3	Capitalize "assessment", "assessment", and "analysis"
6	2	4	Change "does" to "doses"
18	1	2	Change to "nonvolatile"
18	1	7	Equation 2 should read "$[2,4\text{-D}]_{water}$ + $[2,4\text{-D}]_{sediment}$"
18	1	10	Equation 5 should read "$[2,4\text{-D}]_{water}$ + Kp ($[2,4\text{-D}]_{water}$)"
37	heading		Change to "2.2.3.1 Exposure Data"
61	1	1	Instead of "agricultural workers" should read "two farmers and one home gardener"
61	1	6	Add: "by USDA (1984)" between "estimated" and "to be...."
61	2	2	Add sentence: "All of these case reports failed to indicate whether patients were questioned about other chemical exposures and, more importantly, about alcohol intake or use of prescription medications."
61	2	4	Change to "is an unlikely cause"
61	2	6	Change "illness" to "symptoms"
61	2	10	After (Casarett and Doull, 1986) add: ", and symptoms and physical evidence of nerve damage may not occur for several weeks after the actual chemical or infectious insult (Harrison, 1977)."
61	3	3	After "2,4,5-T." add: "Herbicides at this factory were also found to be contaminated with TCDD (dioxins)."
62	top	2	After "control group." add: "Since workers were exposed to both 2,4-D and 2,4,5-T (and possibly to TCDD) it is impossible to attribute the findings to 2,4-D specifically. These results do raise questions about neurotoxicity of phenoxyherbicides as a chemical group. The few case reports that are available suffer from very poor exposure histories and failure to control for other exposures that could cause peripheral neuropathy. Most of the patients had symptoms that were suggestive of other illness in addition to the neuropathy. When added to the lack of specific information regarding exposures of the pesticide manufacturing cohort, there is no compelling evidence that 2,4-D alone has significant neurotoxic effects in humans."

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Page	Para	Line	Change
62	1	6	Add the following new paragraph after "persisted." "This study was highly flawed in several areas. The authors failed to determine level of exposure to 2,4-D in their subjects and failed to ask about other chemical exposures. There was also no information on comparison of study and control groups to determine if they were matched by age or any other factors. Therefore, no conclusions regarding the neurological effects associated with human exposure to 2,4-D can be drawn from this study."
63	2	2,6	Change "doseage" to "dosage"
63	2	6	Change to "shortly after the start of the test."
65	3	4	Change to "Maternal toxicity"
70	Dog study		Under Comments change to "Although one dog at the 500 ppm"
70	"	2	Change to "developed an adrenal hemangioma"
72	2	4	After "May,1992." delete next sentence and add: "EPA convened a panel of experts in April 1993 to evaluate the weight of evidence of the human and animal carcinogenicity data. The majority of the panelists found the data to be 'weakly suggestive' of carcinogenicity but felt that exposures to multiple chemicals and the inability to control for other confounders were major flaws in the epidemiology studies. The final report from the panel is due in July 1993, and EPA expects to make a regulatory decision about special review in the fall. The implication...."
72	3	4	Change to "single large dose (Casarett and Doull, 1986)."
74	2	7	Change "100," to "100."
74	3	2,3	Add abbreviations for Hodgkin's disease (HD), soft-tissue sarcoma (STS),and non-Hodgkin's lymphoma (NHL)
75	3	2	Delete right sided) after "OR = 1.5"
75	3	5	Replace "*p*" with "(p for trend)"
76	top line		Replace "*p*" with "(p for trend)"
76	2	1	Change to "link between STS and farm..."
77	3	5	Delete second) after 1.9
78		after1	Add heading and paragraph: "Animal Case-Control Study In an article that received much media coverage, Hayes, *et al* . (1991) reported the results of a case-control study of dogs with canine malignant lymphoma (the canine equivalent of NHL) and two control groups, one with other cancers and one with non-cancer illnesses or

Page	Para	Line	Change
			injuries. Owners were asked by questionnaire or phone interview about use of chemicals in the home, use of lawn chemicals, and opportunity for exposure of the dog to these chemicals. The OR for dogs having access to a yard where the owner had applied 2,4-D and/or had commercial lawn service was 1.3 (95% CI 1.04-1.67). There was also a positive trend for association of cancer with yearly number of owner applications but not for years of use or yearly number of commercial lawn treatments. A recent review of this study (Carlo, 1992) offered several criticisms of the study techniques. First, failure to separate the two control groups when analyzing data could have increased the effect of recall bias. Second, there was no knowledge of the chemicals used by the commercial applicators, and the OR was only significant when the three exposure groups (owner application only, commercial application only, and both owner and commercial application) were combined. Third, it is likely that the dogs were exposed to other pesticides in addition to 2,4-D since most lawn chemicals for public use are combinations. The reviewers also questioned the positive trend for increasing cancer incidence with number of applications since it was driven by a significant number of owners who reported using 2,4-D more than four times per year. They felt it was unlikely that even a small percentage of dog owners would use 2,4-D that often. In addition, the study authors incorrectly included the unexposed group when analyzing this trend. In view of the lack of good exposure history and an OR result that barely achieved statistical significance, the reviewers concluded that these results should not be accepted as definite evidence of carcinogenicity in animals."
80	4	5	After "carcinogen." add: "Eleven out of thirteen panelists felt it was 'possible' that 2,4-D can cause cancer in humans and two believed that it was 'unlikely.'"
81	top	1	Change sentence and add following paragraph: "However, they state that '...the epidemiological evidence for an association between 2,4-D use and non-Hodgkin's lymphoma is suggestive and requires further investigation.'

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Page	Para	Line	Change
			Another comprehensive review of the 2,4-D literature sponsored by the Industry Task Force II on 2,4-D Research Data recently became available (Munro, 1992). They conclude that 'epidemiological studies provide, at best, only weak evidence of an association between 2,4-D and the risk of cancer.' They felt that the structure of 2,4-D does not suggest carcinogenicity and that the lack of animal evidence made it unlikely that 2,4-D was a human carcinogen. They also commented that present rigorous standards and the proposed label changes would indicate that present and future exposures will be less than those in the studies and conclude that the public health impact of 2,4-D is 'negligible.'"
81	after 4		Add new paragraph between paragraphs 4 and 5: "Some of the new regulations on the use of 2,4-D should help to decrease exposure of the general public after weed-spraying. These include limiting the amount of 2,4-D that can be applied and limiting the number of applications to two per year. However, the new regulations for workers that include wearing complete protective gear with gloves and eye protection, washing skin surfaces immediately after contact, and keeping and washing contaminated clothing separately from other laundry will not protect the general public who may experience the accidental exposures that were analyzed in this risk assessment."
81	4	4	Change to "risk from 2,4-D"
81	5	2	Change to "some of the studies (Hoar, 1986; Bond,1988; Zahm, 1990),"
82	1	2	Replace "it is likely" with "it is possible"
83	3	1	Change to "exposure pathway"
83	3	6	Change to "chronic daily intake/RfD ratio"
83	4	2	Change to "NOELs from animal toxicity studies for specific toxic"
84	1	7	MOSs
84	2	6	NOELs
84	2	7	LELs
84	3	3	Change to "are greater than 100, ranging..."
84	bet. 4-5		Insert heading <u>Chronic Exposures</u> between paragraphs 4 and 5
99	3	1	MOSs
99	3	8	Change to "is exposed to a constant"
99	4	2	Change to "chronically exposed"

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Page	Para	Line	Change
101	2	1	MOSs
102	3		Add this paragraph: "Although almost all of the animal studies thus far have been negative, there is some evidence from human epidemiology studies that 2,4-D may be carcinogenic with prolonged exposures. Conclusions from Industry Task Force panels have varied, ranging from the opinion that 2,4-D is a possible cause of human cancer to the opinion that the public health impact of 2,4-D, including risk of cancer, is negligible. Although it is currently classified as Group D (not classifiable as to carcinogenicity), EPA recently convened an expert panel to review all of the available data in order to determine if a special review of 2,4-D is warranted. That panel concluded that the animal and human data was 'weakly suggestive' of carcinogenicity. EPA is expected to make a regulatory decision about special review of 2,4-D in the fall of 1993. The implication of a decision by EPA to call for a special review is that the evidence for carcinogenicity is compelling enough that it might lead to a change in the carcinogenicity classification of 2,4-D. However, until EPA has decided whether a special review is warranted and until the results of that special review are available, the uncertainty regarding the carcinogenicity of 2,4-D should be considered in any decision about its use."
105			Add reference: Cantor, K.P., Blair, A., Everett, G., Gibson, R, Burmeister, L.F., Brown, L.M., Schuman, L., Dick, F.R. 1992. Pesticides and Other Agricultural Risk Factors for Non-Hodgkin's Lymphoma among Men in Iowa and Minnesota. Cancer Research. 52:2447-2455.
105			Add reference: Carlo, G.L., Cole, P., Miller, A.B., Munro, I.C., Solomon, K.R., Squire, R. A. 1992. Review of a Study Reporting an Association between 2,4-Dichlorophenoxyacetic Acid and CanineMalignant Lymphoma: Report of an Expert Panel. Reg Tox and Pharm 16:245-52.
109			Add reference: Harrison, T.R. 1977. Harrison's Principles of Internal Medicine. Eighth edition. 1809-11.
113			Add reference: Munro, I.C., Carlo G.L., Orr, J.C., Sund, K.G., Wilson, R.M., Kennepohl, E., Lynch, B.S., Jablinske, M., Lee, N.L. 1992. A Comprehensive, Integrated Review and Evaluation of the Scientific Evidence Relating to the Safety of the Herbicide 2,4-D. Journal Amer Coll Tox 11(5):559-664.

CONTENTS

TABLES

FIGURES

EXECUTIVE SUMMARY

This risk assessment was performed to assess potential risks to the general public from exposure to the herbicide 2,4-Dichlorophenoxyacetic acid (2,4-D) associated with its use for noxious weed control in the state of Washington. Noncarcinogenic risks were evaluated for both acute and chronic exposures. Chronic exposure pathways include dermal contact with vegetation, dermal contact with water (swimming), dermal contact with sediments, ingestion of fish, ingestion of surface water, and incidental ingestion of sediments. Acute pathways include ingestion of fish, dermal contact with sediments, dermal contact with water (swimming) and dermal contact with vegetation. Each exposure pathway was evaluated for three different environmental scenarios: small pond, irrigation ditch, and large lake. A review of available epidemiology/carcinogenicity studies was also conducted.

The likelihood of adverse public health impacts associated with single acute exposure to 2,4-D was determined using the Margin of Safety approach, in which "safe" doses from mammalian laboratory experiments are compared to expected environmental doses. The likelihood of effects associated with chronic exposures was evaluated using the RfD approach, in which expected chronic intakes are compared to a USEPA derived "safe" intake value.

Results of this investigation indicate that adverse public health risks are probably not associated with acute exposure to 2,4-D via ingestion of fish, dermal contact with sediments, dermal contact with water or dermal contact with vegetation.

Hazard quotients for all chronic exposure pathways range from 8E-10 to 3E-01, indicating that human health should not be adversely impacted from chronic exposure to 2,4-D via dermal contact with sediments, dermal contact with water (swimming), ingestion of fish, incidental ingestion of sediments, or ingestion of surface water.

1.0 INTRODUCTION

1.1 STUDY OBJECTIVE

The Washington State Department of Ecology (DOE) contracted with Ebasco Environmental Services (Ebasco) to provide data concerning human health impacts from the herbicides glyphosate and 2,4-D. These two herbicides are currently being considered for use to control noxious plants in the State of Washington.

The purpose of this study is to provide information to the Washington State Department of Ecology on the potential toxicological risks to public health associated with 2,4-D use, and to assist the agencies in making a decision concerning herbicide use. A review of previously performed health risk assessments of glyphosate is provided in a separate document.

The objectives of this study were: 1) develop a public health risk assessment for 2,4-D as it applies to use of noxious plant control, 2) provide an overview of epidemiology and carcinogenicity of 2,4-D; and 3) present the information in a quantitative manner that permits direct comparison of the estimated exposure concentrations with concentrations that are expected to protect public health.

1.2 STUDY APPROACH

1.2.1 Information Compilation

Toxicology, carcinogenicity, and fate and transport information were obtained from 3 primary sources, including a computerized search of the scientific literature, EPA office of Pesticide Programs (OPP), and a herbicide manufacturer (Monsanto Agricultural Company).

The computerized Dialogue Information retrieval system was used to search the scientific literature. The databases were searched using both the chemical names and manufacturers names. The search was limited to the years from 1980 to present. However, many pre-1980 summary papers were also retrieved as references. The following databases were searched:

- Biosis Previews
- National Technical Information Services (NTIS)
- Aquatic Sciences and Fisheries Abstracts
- Agricola
- Medline
- Toxline
- CAB Abstracts
- Cancerlit
- Life Sciences Collection
- The New England Journal of Medicine Online
- Registry of Toxic Effects of Chemical Substances (RTECS)
- Dissertation Abstracts Online
- Agris International
- Pascal

Descriptions of these databases are provided at the end of this document.

In addition, the U.S. Department of Agriculture funded an extensive literature review in 1988. This information is summarized in their 1988 publication "Managing Competing and Unwanted Vegetation - Final Environmental Impact Statement." Therefore, this document was also used as an information source.

1.2.2 Risk Assessment Methodology

This risk assessment is structured according to guidelines described by the USEPA (1989) and USEPA Region 10 guidance, and is comprised of four basic units: Exposure assessment, Toxicity assessment, Risk Characterization, and Uncertainty analysis.

Exposure Assessment

The exposure assessment involves determination of potentially exposed populations and estimating doses likely to result from these potential exposures. The results of contaminant fate and transport analyses are used to evaluate the extent and magnitude of 2,4-D in environmental mediums. This information is used to determine exposure pathways, such as inhalation or ingestion of groundwater. Some pathways will naturally be ruled out, depending on the fate and transport of the chemical in the environment. In

this step, the individual chemical-specific exposure estimates for each exposure route (i.e., dermal, inhalation, ingestion) are developed.

Also integral to the exposure assessment is a determination of potentially exposed populations. This involves the identification, enumeration, and characterization of those population segments likely to be exposed. The goal of this analysis is not only to determine which population groups will potentially be exposed but also to determine how and with what frequency and duration such exposure occurs. Only the general public was evaluated as part of this assessment; applicators and mixers of 2,4-D were not considered in the exposed population.

The herbicide 2,4-D may be applied in the State of Washington using several different application methods at vastly different sites. In Washington, 2,4-D can only legally be applied to terrestrial sites. Control programs may be large or small, and may involve several treatment units. Individual treatment units may be as large as 1,000 acres or as small as 1 acre (USDA, 1988; WDOE, 1992).

In order to account for variability in treatment area size and location, and in human activities associated with these areas in Washington State, several "generic" exposure scenarios were developed (Table 1). These scenarios are intended to be representative of typical activities undertaken within Washington. Both the amine and ester forms of 2.4-D were evaluated.

For acute exposure scenarios it was assumed that "worst case" conditions exist for both 2,4-D environmental concentrations and exposure parameters. Chronic exposures were calculated for three different types of environments (small pond, irrigation ditches, large lake) and assumed "worst case" exposures. This is further discussed in section 2.0.

Toxicity Assessment

The purpose of the toxicity assessment is (1) to weigh the available evidence regarding the potential for contaminants to cause adverse effects in exposed individuals (i.e., hazard identification) and (2) to provide a quantitative estimate of the relationship between the magnitude of exposure and the likelihood or severity of adverse effects (i.e., the dose-response assessment) (USEPA, 1989). These elements are discussed in the subsections which follow.

Table 1. Potential Exposure Routes

Application Method	Dermal	Oral	Inhalation
Helicopter	Contact with sediment/soil Contact with vegetation Contact with water	Ingestion of fish Incidental ingestion of sediment	Not Applicable
Helicopter with ball	Same as above	Same as above	Not Applicable
Backpack sprayer	Same as above	Same as above	Not Applicable
Wicking	Contact with vegetation	Not Applicable	Not Applicable

As part of the hazard identification step of the toxicity assessment, information is assembled on the potential for a chemical to cause adverse health effects (e.g., carcinogenic, noncarcinogenic) in humans. A hazard identification is intended to characterize the nature and extent of the health hazards associated with chemical exposures. Generally, this step is addressed through the development of a toxicological summary for each chemical which discusses parameters such as pharmacokinetics, various critical health effects (e.g., carcinogenic effects, reproductive, developmental, or other systemic effects) and the association of these effects with exposure at different chemical concentrations over varying time periods. The sources for this information include human epidemiological studies and clinical cases, experimental animal studies, and supporting data such as in vitro studies (USEPA, 1989). Generally, the preferred sources of information for dose-response assessment are properly conducted epidemiologic studies. Where appropriate human studies are available, they are weighted more heavily, with animal studies used as supporting evidence.

When human data are lacking, as is usually the case, animal studies are used to evaluate potential adverse effects and quantify dose-response. Differences between animals and humans in relation to metabolic processes, behavior, and physiology, etc., result in a high degree of uncertainty in the dose-response values derived from these sources. However, the likelihood of a chemical causing adverse effects in humans increases as similar effects are observed among sexes, species, and exposure routes in well-conducted animal studies (USEPA, 1989).

The dose-response assessment is intended to quantify the relationship between the magnitude of exposure to a chemical and the occurrence of adverse health effects. This step involves a analysis of correlations between the severity or frequency of adverse effects and the levels of exposure at which these effects occur for each chemical. Typically, this entails a review of the toxicological literature to identify chemical-specific dose-response estimates through oral, inhalation and dermal routes of exposure.

Chemicals may elicit two general categories of adverse health impacts in exposed individuals--noncarcinogenic and carcinogenic effects. Noncarcinogenic effects, or any health impact other than cancer, may result from acute, subchronic or chronic exposures. For most noncarcinogenic effects, protective mechanisms within an individual are assumed to exist that must be overcome before an adverse effect is elicited. The level above or below which effects may or may not be elicited is referred to as a threshold level. Examples of noncarcinogenic effects include central nervous system disorders (e.g., neurological damage or impairment), blood disorders (e.g., anemia), organ toxicity (e.g., kidney, liver, heart) and reproductive toxicity (e.g., gametotoxicity, fetal toxicity, etc.).

In developing dose-response values for noncarcinogenic effects (i.e., the reference dose or RfD), the goal is to identify the highest no-observed-adverse-effect-level, NOAEL (i.e., the upperbound of the tolerance range) or the lowest-observed-adverse-effect-level, LOAEL, from well designed human or animal studies. One or more order-of-magnitude uncertainty factors are incorporated to adjust this level based on considerations of the following: (1) the duration of the experimental exposure, (2) effects elicited (if any), (3) extrapolation of the data to other species (i.e., interspecies variability, such as extrapolation to humans), and (4) sensitive subgroups (i.e., intraspecies variability). Additional modifying factors varying between a value of 1 and 10 may also be incorporated in the derivation of the RfD if additional considerations are necessary. The general formula to derive a RfD is as follows:

$$\underset{\text{(mg/kg-day)}}{\text{RfD}} = \frac{\text{NOAEL or LOAEL}}{\text{Uncertainty} * \text{Modification Factors}} \qquad (1)$$

RfDs are generally taken from the preferred source of dose-response values--EPA's computerized Integrated Risk Information System (IRIS) - and represent "verified" (interagency reviewed) quantities.

The RfD approach was designed to predict risk to human health from low level, chronic exposures over the course of a lifetime. Potential risks associated with acute exposures were assessed using the "Margin of Safety" approach, detailed in Section 4.1.

Risk Characterization

The risk characterization involves comparing the dose estimates for the different exposure pathways with the hazard information and determining the probability that health effects could occur. This is accomplished by comparing expected environmental doses to those does which elicit a toxicological response in laboratory animals.

Human doses are calculated from expected environmental concentrations (EEC's) of 2,4-D. The EEC's are calculated from herbicide application rates and information regarding chemical fate and transport. The methods of calculating EEC's are detailed in Section 2.2.2.1.

Non-carcinogenic risk from single, acute 2,4-D exposures was estimated using the Margin of Safety Approach. The methodology of Shipp et al. (1986) was used to determine potential reproductive, systemic, and teratogenic effects. In this method 2,4-D doses which are shown to cause toxic effects in laboratory animals are compared to predicted human doses.

Details of the margin of safety approach and risk characterization methodology are discussed in section 4.1. MOSs are calculated for each pathway on a daily basis, starting from immediately after 2,4-D application and ending 22 days after application. Once an initial environmental concentration was calculated degradation rates were used to calculate change in concentration over time. Daily doses were then calculated using these EEC's.

For chronic exposures the RfD approach was used. Hazard indices were calculated for each exposure pathway. The hazard index is the ratio of the chronic daily intake to a reference (RfD) intake.

Uncertainty Analysis

In this section of the risk assessment, each step is reviewed to identify the uncertainties involved and to evaluate their impact on the assessment results. For example,

uncertainties may result from the use of default exposure parameter values or the use of simplified estimation procedures in the event of lack of data. The Uncertainty analysis is generally presented in a qualitative format.

1.3 CHEMICAL FORMULATIONS

Several formulations of 2,4-D are available, including various salts and esters. The organic esters consist mainly of the butoxyethyl ester but also include the butyl ester and propylene glycol ether esters as well. The 2,4-D salts include free acid, dimethylamine and sodium salts. As further discussed in sections 3.3.3 and 3.3.4 there is insufficient data available to support development of separate human health risk assessments for every chemical form of 2,4-D. DOE has requested that only the amine and ester forms of 2,4-D be considered in this health assessment. In addition, 2,4-D is rarely available commercially in the acid form due to its poor water solubility.

2.0 EXPOSURE ASSESSMENT

2.1 EXPOSED POPULATION

In this Risk Assessment, the exposed population refers to the general public and does not include people who may be exposed to 2,4-D occupationally (i.e., while mixing, loading, or applying the chemical). The general public as considered in this document includes people of both sexes.

2.2 POTENTIAL ROUTES OF EXPOSURE

The potential routes of public exposure to 2,4-D include those which occur during recreational activities. Application techniques vary widely with exposure route being dependent upon application technique, mixing processes, and fate and transport processes (decay and removal rates). Methods most likely to be utilized are wicking, back-pack sprayer, helicopter, and helicopter with ball. Each method will result in different concentrations of 2,4-D in air, water, or sediments. Several exposure pathways were initially considered:

- inhalation during spraying
- dermal contact while swimming
- dermal contact with sediments
- incidental ingestion of sediments
- ingestion of surface water
- ingestion of fish/seafood
- ingestion of garden fruits/vegetables
- ingestion of wild berries
- ingestion of wild game
- ingestion of crops irrigated with herbicide containing water.

Inhalation is not an important exposure pathway for 2,4-D. In a study of Florida airboat sprayers, inhalation of 2,4-D has been shown to comprise only 0.03% of total body exposure. Inhalation constituted 0.17% of dermal exposure in a study of truck applicators, and was up to 50 times lower than dermal exposure in a study of right-of-

way applicators (USDA, 1988). It is likely that inhalation exposure will account for the same or less of the total body exposure among the public.

The ingestion of crops irrigated with herbicide-containing water should not occur as use of potentially treated water is restricted following application. If accidentally treated water was used to irrigate crops before degradation, the plants would likely be damaged, thereby reducing the potential for human ingestion. 2,4-D is especially designed to kill broadleaf plants, which includes many crops (not including wheat, corn, or rice).

Human health impacts due to the ingestion of wild berries has been investigated by the USDA (1988). They calculated that the lifetime cancer risk from the ingestion of wild berries after 2,4-D application is 4.14×10^{-8}, or the chance that approximately 4 people out of every 100,000,000 exposed will contract cancer. This risk was calculated using conservative "worst case" conditions and is well below the range of 1×10^{-4} to 1×10^{-7} designated as acceptable by the USEPA. For noncarcinogenic effects the margin of safety (ratio of a "safe" dose derived from a laboratory study to an expected environmental dose) for eating wild berries ranged from 96 to greater than 1 million for various application methods. These results indicate that under absolute worst-case conditions the dose received would be at least 96 times lower than the estimated "safe dose." Given that the cancer risk and margins of safety were calculated using extremely conservative, worst case assumptions and that they indicate little if any potential for harm, berry eating will not be addressed further in this assessment. The conservative nature of the exposure assumption indicate that the assessment applies to sensitive sub-groups such as the elderly and ill.

Ingestion of wild game has also been addressed by the USDA (1988). Results of their "worst case" analysis also indicates that there is little or no risk from ingestion of wild meat after 2,4-D application. However, the USDA risk assessment also modeled exposure and risk to the public from procuring berries and wild meat (i.e., berry picking and hunting) and determined that most of the health risk was due to dermal contact with freshly sprayed vegetation. Thus, this risk assessment will focus on dermal exposure to 2,4-D rather than those ingestion pathways which have been shown to present little risk. Other pathways to be considered are ingestion of aquatic organisms, ingestion of surface water, dermal contact with water, dermal contact with sediments, and incidental ingestion of sediments.

2.2.1 Dermal Contact with Vegetation

2.2.1.1 Exposure Data

Absorption of 2,4-D varies in different anatomical areas (Feldmann and Maibach, 1974). The forehead, face, and neck absorb two to six times more than the forearm. Larger areas such as the back allow for even greater absorption than the forearm.

Several studies were conducted in the 1970s and 1980s to determine dermal 2,4-D exposures to workers using various application techniques. However, it was not until 1992 that research was published concerning exposures to homeowners and bystanders.

Harris and Solomon (1992) determined total body dose of 2,4-D amine in volunteers following exposure to sprayed turf 1 hour and 24 hours following application. Each group of 10 volunteers was divided in half. Five volunteers wore long pants, short sleeved shirt, socks and covering footwear. The other five wore shorts, short sleeved shirt, and were barefoot. Volunteers were exposed to a 2 by 15 meter area of sprayed turf for 1 hour during which they alternated between walking, sitting, or lying down for 5 minute intervals. 2,4-D dose was determined by urinalysis. Dislodgeable residues were also determined.

Total dose of 2,4-D found in 96 hour urine samples indicate that the highest dose occurred in a volunteer who removed his shirt for 30 minutes (426 μg). Exposure levels were 103 to 153 μg in two other members of the 1-hour post-application exposure group. Assuming an average human body weight of 70 kg the doses range from 0.0015 to 0.006 mg/kg. No detectable residues were found in urine samples supplied by volunteers exposed to sprayed turf 24 hours after application.

The public may be exposed to pesticides by dislodging them from plant surfaces. Dislodgeable residues of 2,4-D taken during the exposure sessions showed a rapid decline from 1 hour after application to 24 hours following application (8% to 1%). This is in good agreement with the findings of Thompson et al. (1982) who report that a maximum of 6% of the original applied 2,4-D can be dislodged from turf immediately after spraying at a rate of 2.24 kg a.e./ha and 4.5% when sprayed at a rate of 1.0 kg a.e/ha.

Harris et al. (1992) also studied exposures in homeowners and bystanders after a 2,4-D amine formulation was used on home gardens. Both granular and liquid forms of 2,4-D were used during separate trials. Groups consisted of applicator or bystanders with or without protective clothing. Results of urinalysis indicate that total body doses ranged from non-detectable to 0.0071 mg/kg of body weight. Exposure is believed to have occurred via accidental spills, mowing the lawn, and handling of 2,4-D containers and applicators, as 2,4-D was either not detected or detected at extremely low concentrations in the air. No exposures to bystanders (people living in the household) were detected.

The dose of 0.0071 mg/kg is consistent with the study of Frank et al. (1985) in which aerial spray application of 1/4lb/acre resulted in a dose of 0.0045 mg/kg to an unprotected worker. The amount of 2,4-D absorbed was 0.44% of the total deposited on the skin and clothing. Newton and Dost (1984) and Nigg and Stamper (1983) report slightly higher dermal absorptions of 2.5% (application rate = 1.45 lb/ac) and 2-4% of the total deposition on the skin.

2.2.1.2 Estimated Dose

The studies discussed above indicate that doses to the public from dermal contact with fresh-sprayed vegetation range from 0.0015 mg/kg to 0.006 mg/kg when 2,4-D is applied at typical rates. The dose of 0.0045 mg/kg reported by Frank et al. (1985) fall within the mid-range of these doses. Thus, 0.0015 mg/kg is assumed to be a "low dose" and 0.006 mg/kg a "high dose" for the acute exposure scenario.

Risks from every other exposure pathway in this assessment are estimated as a function of time (days after 2,4-D application) by using degradation data to calculate environmental concentrations. As actual human dose data was available for dermal adsorption of 2,4-D it was not necessary to estimate human dose by first calculating concentrations on vegetation and then using an intake equation.

The data in Section 2.2.1.1 are from people exposed 1 hour and 24 hours post-application. No 2,4-D residues were detected in the group exposed 24 hours post application. Therefore, it is not necessary to evaluate 2,4-D exposure via contact with vegetation for periods longer than 24 hours after application, as data indicate 2,4-D is only available for human uptake from vegetation for a very short period.

2.2.2 Dermal Contact with Water (Swimming)

Although 2,4-D is not currently permitted for use on water bodies in Washington State it is labeled for such use. If 2,4-D is used near water, as is currently permitted in Washington, it may drift onto water. Drift estimates are very low (1%). This risk assessment assumes that 2,4-D is applied directly to water, thus presenting an overestimate of risk.

The possibility exists that treated bodies of water may be used for swimming, even if precautions are taken to post warnings. This pathway has not been evaluated before and is, therefore, addressed below.

2.2.2.1 Exposure Data

In order to estimate the environmental concentrations of 2,4-D in aquatic systems, information on the formulation, application rate, persistence, partitioning, and location of purple loosestrife must be evaluated. This document utilizes this information for potential 2,4-D application in Washington State to control purple loosestrife in order to calculate environmental concentrations. These concentrations will represent the highest concentrations while remaining within label compliance.

Formulations

Although approximately 30 2,4-D formulations are registered for use in Washington State, this analysis will focus on two representative formulations: Weedar 64® and Aqua-Kleen®. Weedar 64®, which is manufactured by Rhone-Poulenc, contains 46.4% dimethylamine salt of 2,4-Dichlorophenoxyacetic acid (DMA). Aqua-Kleen® is manufactured by Rhone-Poulenc is contains 27.6% 2,4-Dichlorophenoxyacetic acid, butoxyethyl ester (BEE). Aqua-Kleen® is a granular formulation, and is thus less likely used for emergent noxious weeds such as purple loosestrife than for submergent vegetation.

Other formulations registered for use in Washington State include different concentrations of DMA or BEE. However, the application rate reflects these differences. In addition, some formulations contain other 2,4-D compounds such as the acid, sodium salt, isooctyl(2-octyl) ester, isooctyl 2-ethylhexyl ester, and the alkyl amine C12. DMA

containing herbicides are the most frequently applied formulations near the aquatic environment.

Application Rate

According to the Weedar® 64 label, an application rate of 1 to 2 lbs a.e./acre is recommended for control of aquatic weeds in irrigation canal ditchbanks and an application rate of 2 to 4 lbs. a.e./acre is recommended for control of water hyacinth in ponds, lakes, reservoirs, marshes, bayous, drainage ditches, canals, rivers and streams that are quiescent or slow moving. An application rate for purple loosestrife is not specifically identified. Application rates suggested for other DMA formulations, such as Amine 6-D (66.3% DMA) and Amine 4 (47.3%) DMA, are slightly lower than those recommended for Weedar® 64 on an acid equivalent basis. Therefore, to be conservative an application rate of 4 lbs. a.e./acre of Weedar® 64 will be used to calculate initial concentrations.

The Aqua-Kleen label suggests 100 lbs/acre for susceptible weeds and 150 to 200 lbs/acre for slightly to moderately resistant weeds. Purple loosestrife is not identified on the label. On a BEE basis, these rates correspond to 27 lbs/acre to 55 lbs/acre. On an acid equivalent basis, these rates correspond to 19 lbs/acre to 38 lbs/acre. Guidance on the label states, "Rates of application vary with resistance to weed species to the chemical, density of weed mass at time of treatment, water depth, and rate of water flow through the treated area. Use the higher rate for dense weeds, when water is more than 8 feet deep, and where there is a large volume turnover." Therefore, to be conservative an application rate of 38 lbs. a.e./acre will be used in the calculations.

Persistence

Available information on the persistence of 2,4-D formulations indicates half-lives of days to months in surface water (EPA 1987) and half-lives up to several months in sediments (Smith and Isom, 1967; Frank and Comes, 1967; Cope et al., 1970; Wojtalik et al., 1971). Persistence increases with low temperature, low oxygen, and low unacclimated microbial populations.

Using field data, Reinert and Rodgers (1987) report water half-lives for 2,4-D from 1 to 11 days. This is consistent with the range of values reported for DMA (Table 2). Field

studies of BEE persistence in water report half-lives from 0.11 to 3 days. Using the longest half-life to be conservative, 11 days is selected for both DMA and BEE.

Table 2. Degradation half lives of 2,4-D in water

Half life, days	Reference
2,4-D acid: 1 - 11	Reinert and Rodgers 1987
2,4-D DMA: 3.9	Robson 1968
2,4-D DMA: 10 - 11	Schultz and Harman 1973
2,4-D DMA: 6.6	Westerdahl and Getsinger 1988
2,4-D DMA: 2.2 - 4.2	Averitt and Gangstad 1976
2,4-D DMA: 0.5 - 0.8	Gangstad 1983
2,4-D DMA: 2.5 - 6.2	Otto et al. 1983
2,4-D BEE: 3	Dynamac 1988
2,4-D BEE: 0.11 - 2.3	Reinert and Rodgers 1987
2,4-D BEE: 2.2 - 2.3	Oklahoma Water Research 1975; Frank and Comes 1967

Longer half-lives have been reported in sediment, with values of months reported (Schultz and Harman, 1973; Martin et al., 1986; EPA, 1987). Since more precise information is not available, the half-life in sediment must be estimated. Since 2,4-D residues following application of Aqua-Kleen® have persisted for 182 days in artificial ponds (Birmingham and Colman (1985), this can be used as an upper bound for the half-life in sediment. As a very rough approximation, the half-life will be assumed to be one third of the persistence, or 60 days (2 months). Due to the scarcity in sediment half-life information, a distinction can not be made between DMA and BEE in the calculations.

Partitioning

The extent of partitioning of compounds between water and sediment is generally site specific (i.e. a function of pH, TOC, redox potential, ionic strength, sediment substrate). Reported values for sediment-water partitioning (Kd) are 0.13 to 0.25 for DMA (Reinart and Rodgers 1987). Kd values for BEE are not reported. Due to the lower solubility of BEE, however, the Kd value should be lower than that for DMA. Rough calculations of

reported field concentrations indicate Kd values from 21 to 88. Simply using average values for both, Kd will be assumed to be 0.19 for DMA and 55 for BEE.

Water Scenarios

In order to estimate the dimensions and characteristics of water bodies with purple loosestrife, guidance from ACOE (1993) and Andy Driscoll (personal communication) was incorporated. As a result, three water scenarios can be envisioned to include a small lake, a wasteway or irrigation canal, and a portion of a large lake such as Lake Washington's Montlake Fill area (Table 3). In the second scenario (wasteway and irrigation canals), dimensions are given for the wasteway. Note that in a scaled down wasteway (i.e. irrigation canal) the concentration would be similar.

Both overall dimensions of the water body as well as the area of treatment are important considerations. In order to calculate the treatment area, the landward portion of the water area with water depths of less than 2 feet was approximated. For the small lake, the whole perimeter was considered, whereas for the large lake, only one third of the perimeter was used because mixing would then extend out into the rest of the lake. In the wasteway, approximately one half of the width was used. It should be emphasized that these are only representative scenarios, and a great deal of variability exists within water bodies in Washington State.

Table 3. Three scenarios for 2,4-D application

Parameter	Scenario 1: Small Lake or Pond	Scenario 2: Wasteway (large irrigation canal)	Scenario 3: Portion of a Large Lake (e.g. Lake Washington)
Water dimensions	1 acre x 4 feet	200 feet x 3 miles x 3 feet	20 acre x 8 feet
Water volume	4,934,000 L	2.701×10^8 L	1.974×10^8 L
Treatment area	740 ft x 3 feet (0.051 acre)	100 feet x 3 miles (36 acres)	1,100 feet (1/3 perimeter) x 12 feet (0.03 acre)

Initial Concentrations

In order to calculate the initial concentration, the treatment area must be multiplied by the application rate to determine the mass of acid equivalent herbicide added to the system. This mass is then divided by the water volume to determine an initial concentration. This initial concentration is then subject to partitioning to sediment (Kd) and degradation. Partitioning is assumed to be fast relative to degradation.

Mixing is assumed to be immediate and complete throughout the water depth considered in each scenario for both formulations. Although this is clearly not the case with the granular formulation of Aqua-Kleen, which has been estimated to take up to 8 days to dissolve, this assumption will err on the conservative side with respect to water concentration. Although it would be expected to underestimate the impact on sediment concentration, this effect should be at least partially compensated for since both BEE partitioning and half-life values were derived from field studies.

Initial Concentrations

Using an application rate for 2,4-D DMA of 4 lb a.e./acre, the concentration can be calculated as shown in Equations 1 (Martin et al., 1986). An example calculation for DMA in Scenario 1 is included. BEE calculations were done in an analogous manner, with an application rate of 38 lbs a.e./acre. Results for all the scenarios are presented in Table 4.

$$\frac{(\ application\ rate\ )(\ treated\ area\ )}{(\ volume\ of\ water\ )} \qquad \text{Equation 1}$$

$$\frac{[\ (4\ lbs\ a.e./acre)(0.051\ acre)(4.545 \times 10^5\ mg/lb)\ ]}{(4{,}934{,}000\ L)} = 0.018\ mg/l$$

Table 4. Initial concentrations of 2,4-D DMA and 2,4-D BEE in Scenarios 1 - 3

Scenario	2,4-D DMA concentration (mg/L)	2,4-D BEE concentration (mg/L)
1 (small lake)	0.018	0.18
2 (wasteway)	0.24	2.3
3 (large lake)	0.00028	0.0026

The Effect of Partitioning

Assuming rapid partitioning into sediment, initial water concentrations will be rapidly decreased following application of 2,4-D. Since 2,4-D is nonvolative, the water/sediment system can be approximated as a closed system and measured partitioning coefficients can be used to predict the initial distribution of 2,4-D. Sediment-water partitioning coefficients (Kp) are assumed to be 0.19 for DMA and 55 for BEE. The distribution of 2,4-D DMA can be calculated as follows:

$$TOTAL\ 2,4\text{-}D = [2,4\text{-}D]_{water} + [2,4\text{-}D] \qquad \text{Equation 2}$$

$$Kp = \frac{[2,4\text{-}D]_{sediment}}{[2,4\text{-}D]_{water}} \qquad \text{Equation 3}$$

$$[2,4\text{-}D]_{sediment} = Kp\ (\ [2,4\text{-}D]_{water}\ ) \qquad \text{Equation 4}$$

$$TOTAL = [2,4\text{-}D]_{water} + Kp\ (\ [2,4\text{-}D]_{w} \qquad \text{Equation 5}$$

From the above expressions, ranges can be calculated for dissolved 2,4-D concentration and 2,4-D associated with sediment in the 3 scenarios (Table 5). This distribution would occur immediately after application and partitioning and before degradation has occurred to a significant extent.

Table 5. Sediment and water concentrations of DMA and BEE immediately following application

Scenario	2,4-D DMA Concentration		2,4-D BEE Concentration	
	Water (mg/L)	Sediment (mg/kg)	Water (mg/L)	Sediment (mg/kg)
1	0.015	0.0028	0.0032	0.17
2	0.20	0.044	0.041	2.26
3	0.00024	0.00004	0.00004	0.0025

Effect of Degradation

Assuming a first-order reaction rate degradation equation (Equation 6) (Shipp et al., 1986), information regarding the initial concentration and the half-life of a compound can be used to predict the persistence of 2,4-D in water and sediment.

$$A = A_o 2^{-\frac{t}{h}} \qquad \text{Equation 6}$$

Where:

A = the compound concentration at time, t
A_o = the initial compound concentration at t = 0
t = elapsed time in days since application
h = half-life of a chemical in days (i.e. the time require for the chemical concentration to reach half its initial value).

Equation 6 was applied to the initial concentrations presented in Table 5 with an 11 day half-life for water and a 60 day half-life for sediment. Results are given in Appendix A and are shown graphically in figures 1 through 12.

In order to calculate chronic exposures, 22 days was chosen as a reference time. Twenty-two days is the average number of days/year that Washington residents swim. Applying Equation 7, "average" concentrations could be calculated from initial concentrations and half-lives. The results are presented in Table 6.

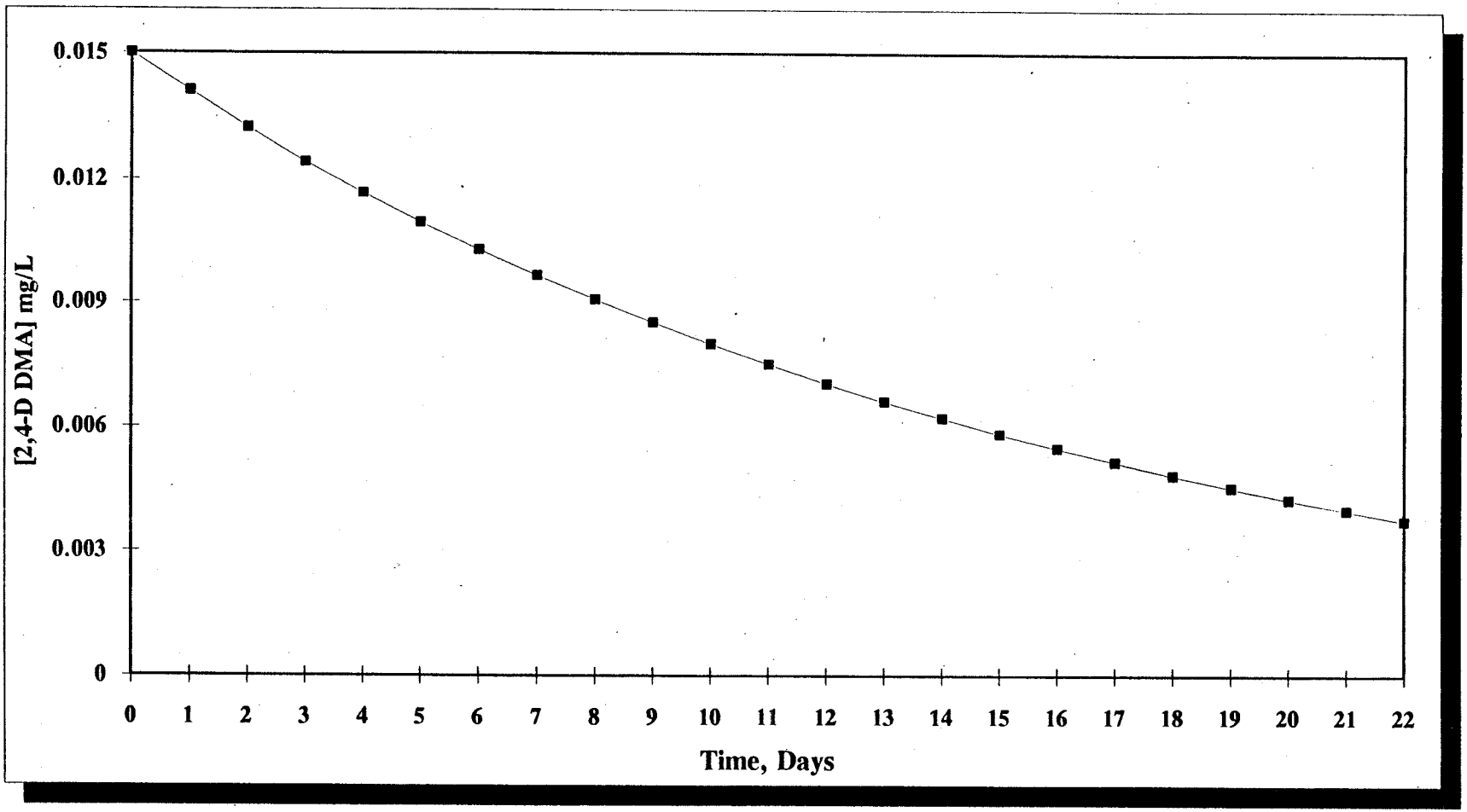


Figure 1. 2,4-D DMA concentration in water as a function of ti in Scenario 1 (initial concentration = 0.015, half life = 11 days

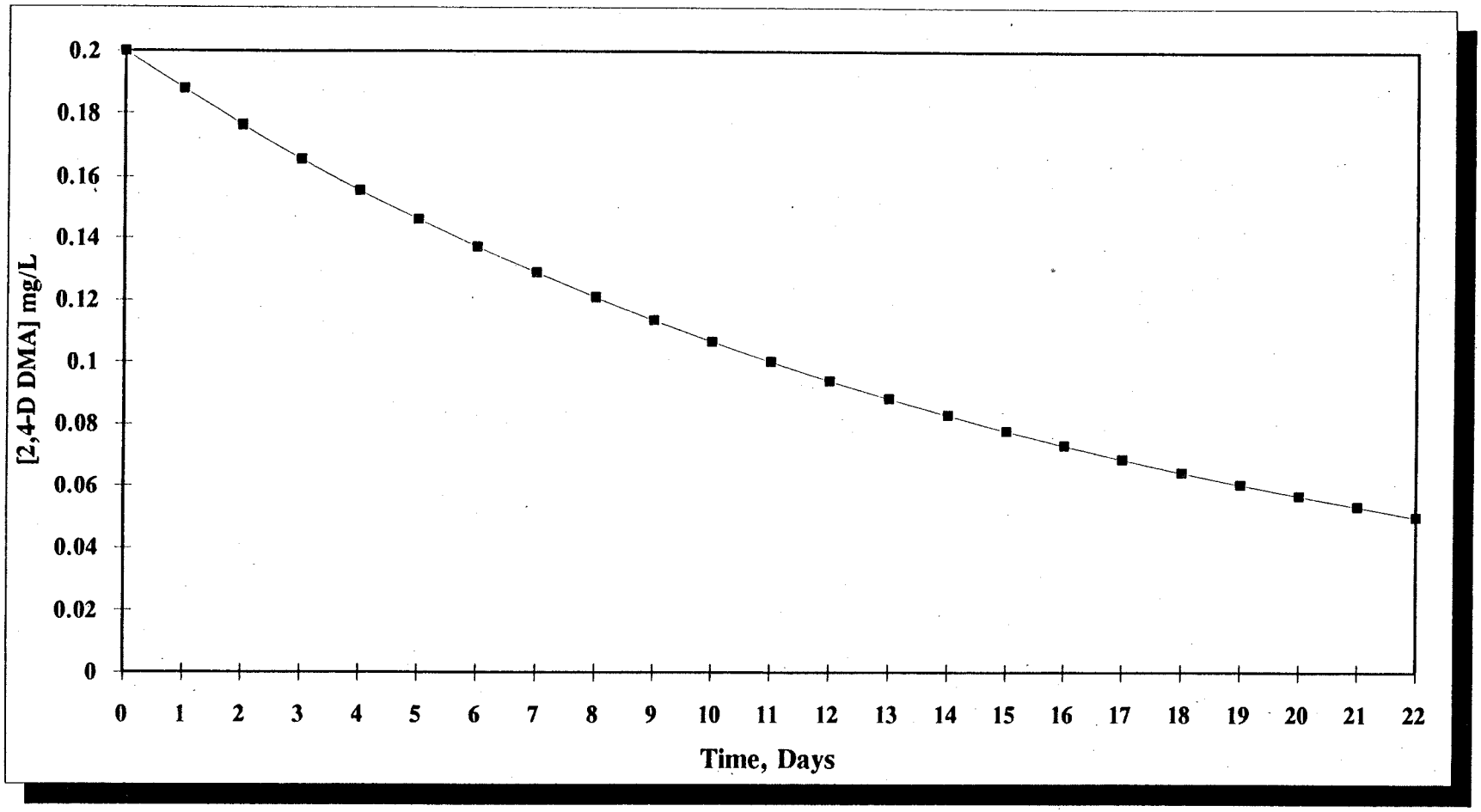
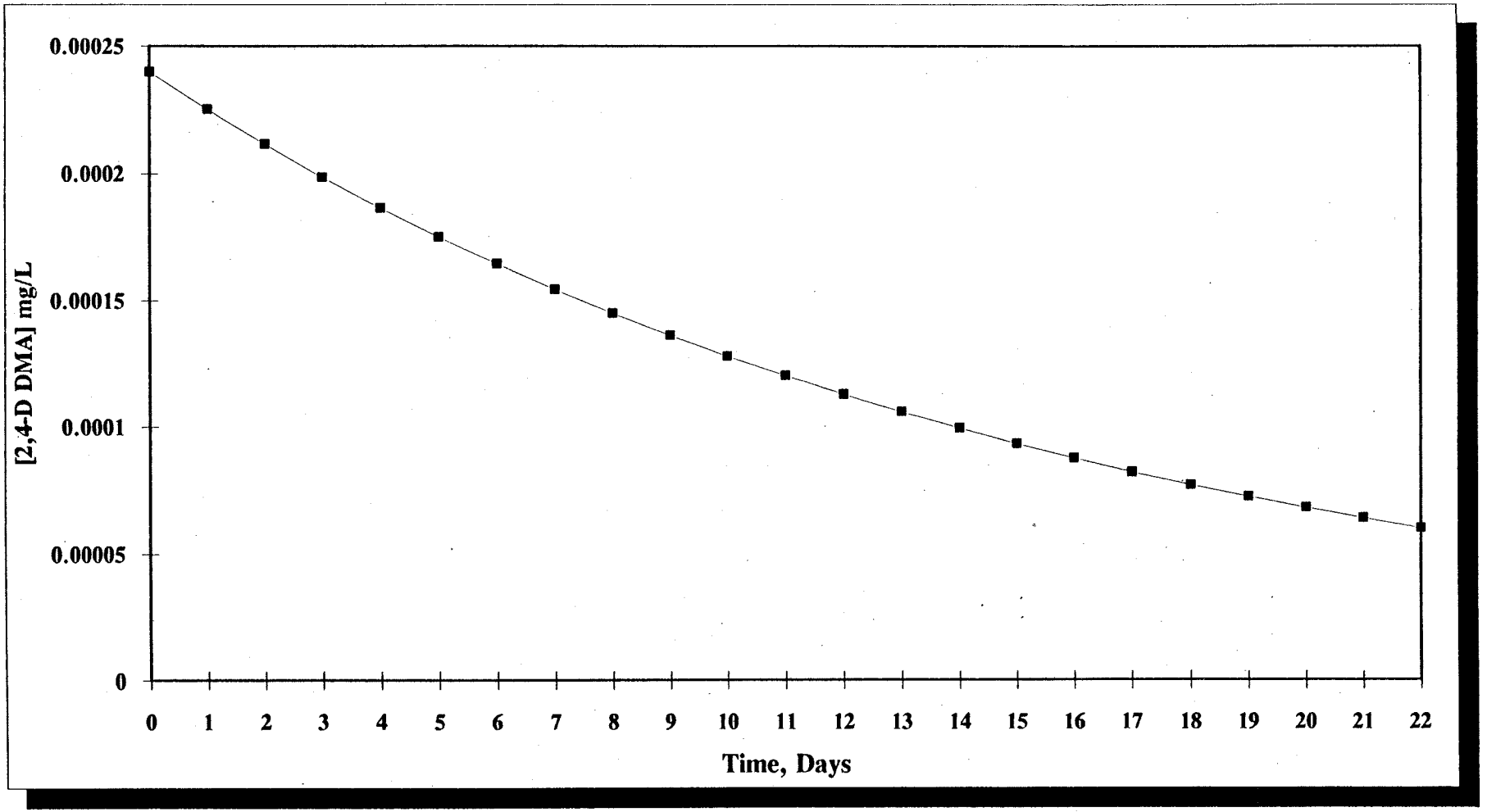


Figure 2. 2,4-D DMA concentration in water as a function of time in Scenario 2 (initial concentration = 0.2 ppm, half-life = 11 days).



ure 3. 2,4,D DMA concentration in water as a function of time Scenario 3 (initial concentration = 0.00024 ppm, half-life = 11 s).

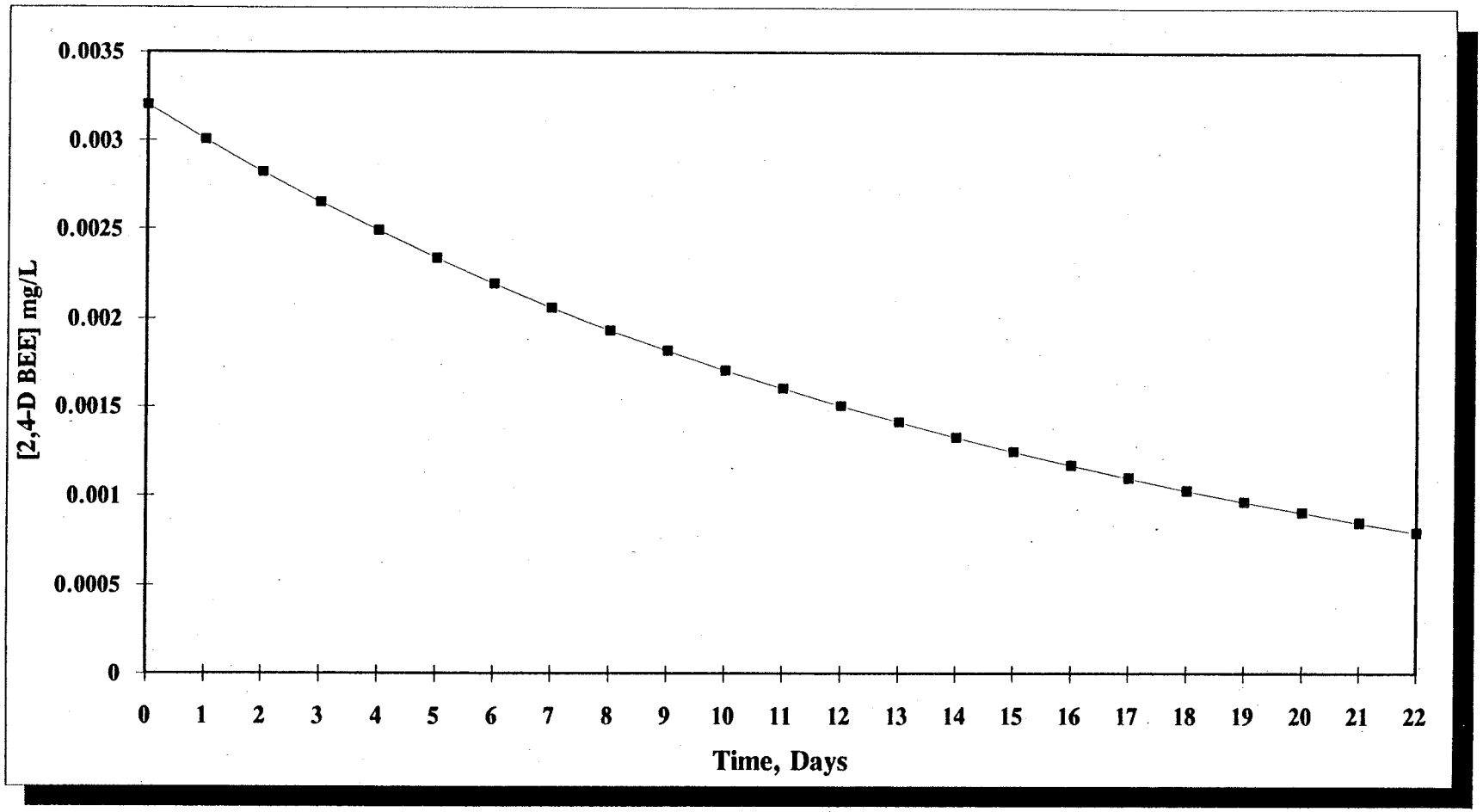
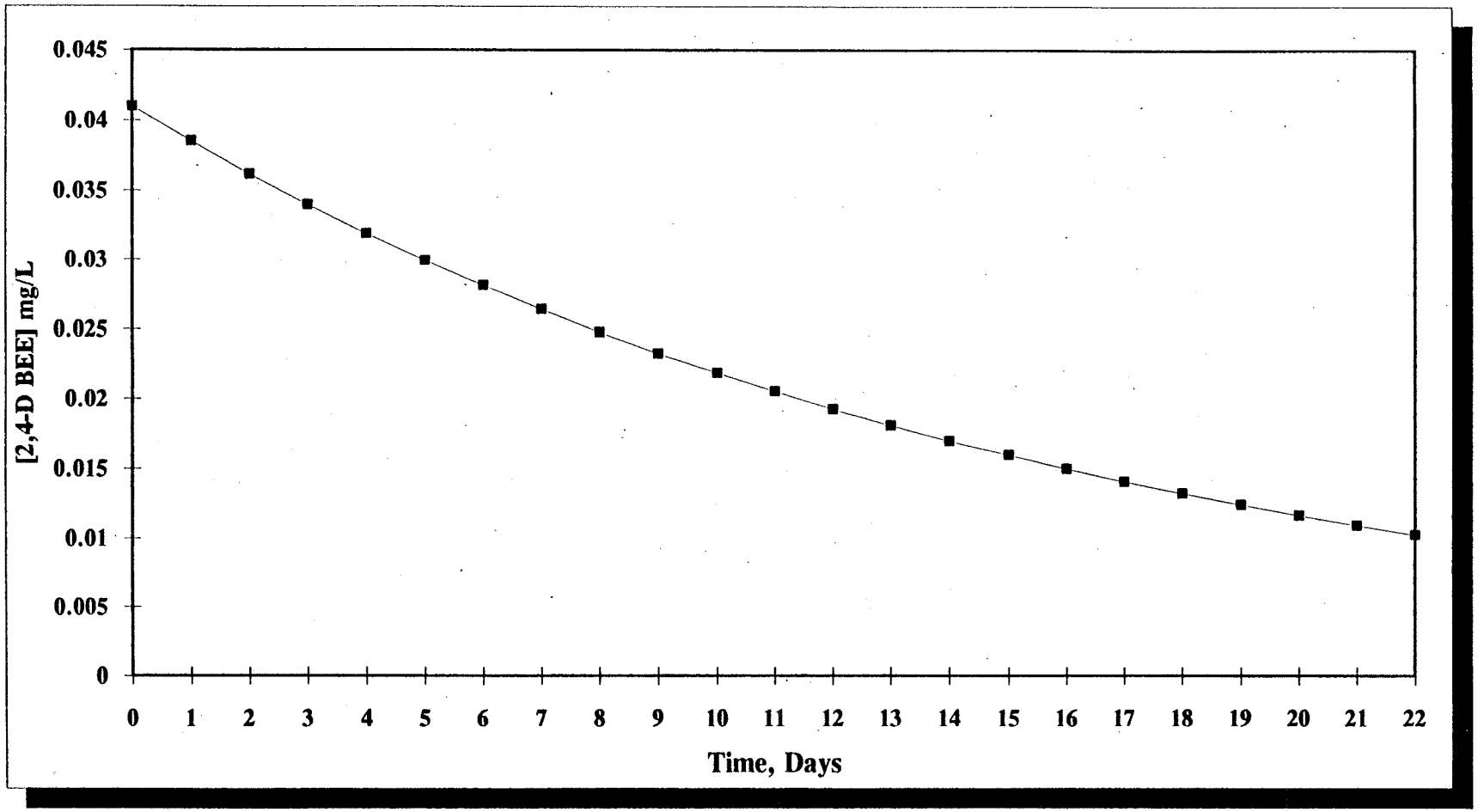


Figure 4. 2,4-D BEE concentration in water as a function of time in Scenario 1 (initial concentration = 0.0032 ppm, half-life = 11 days).



'gure 5. 2,4-D BEE concentration in water as a function of time Scenario 2 (initial concentration = 0.041 ppm, half-life = 11 d:

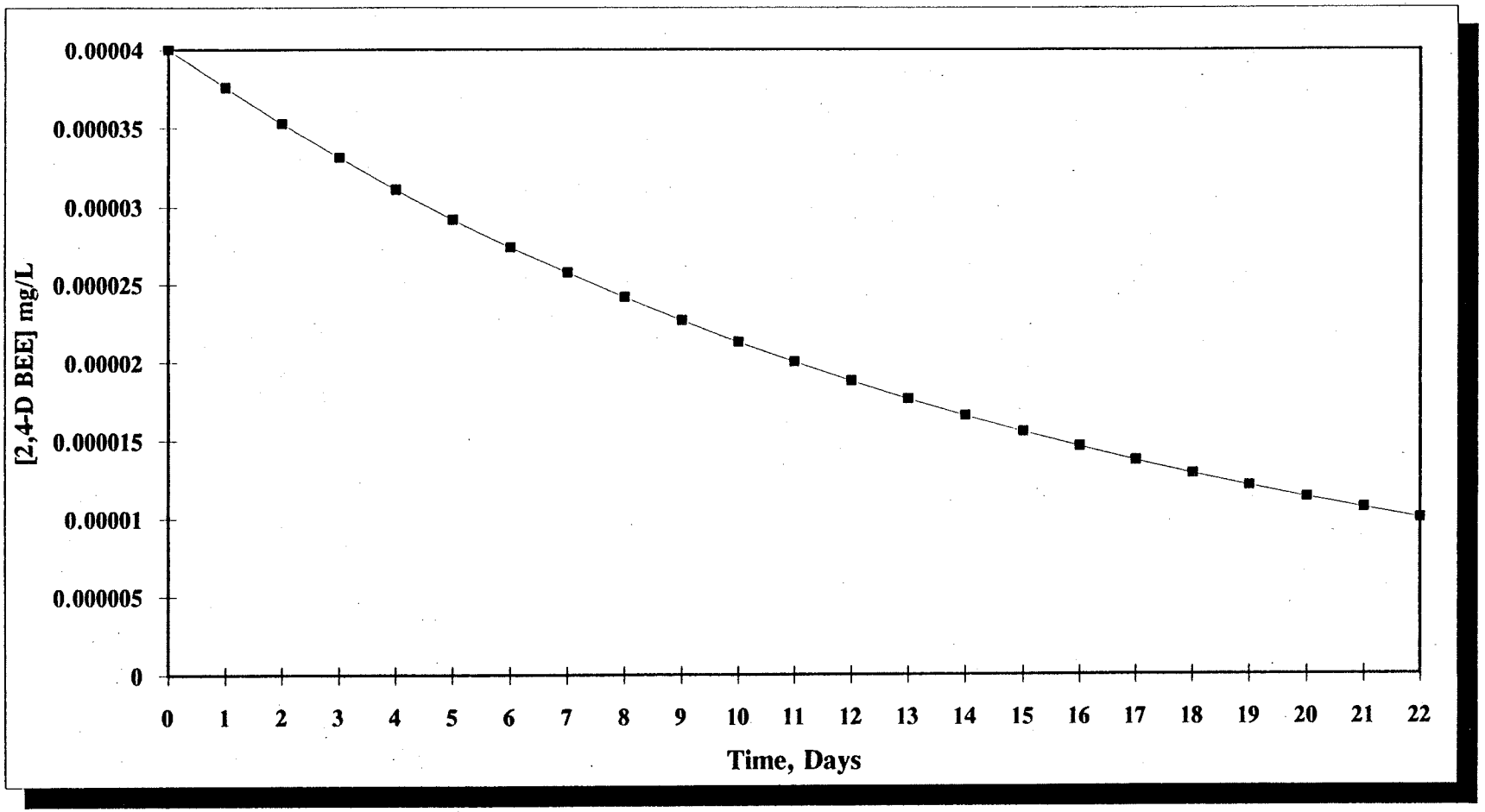
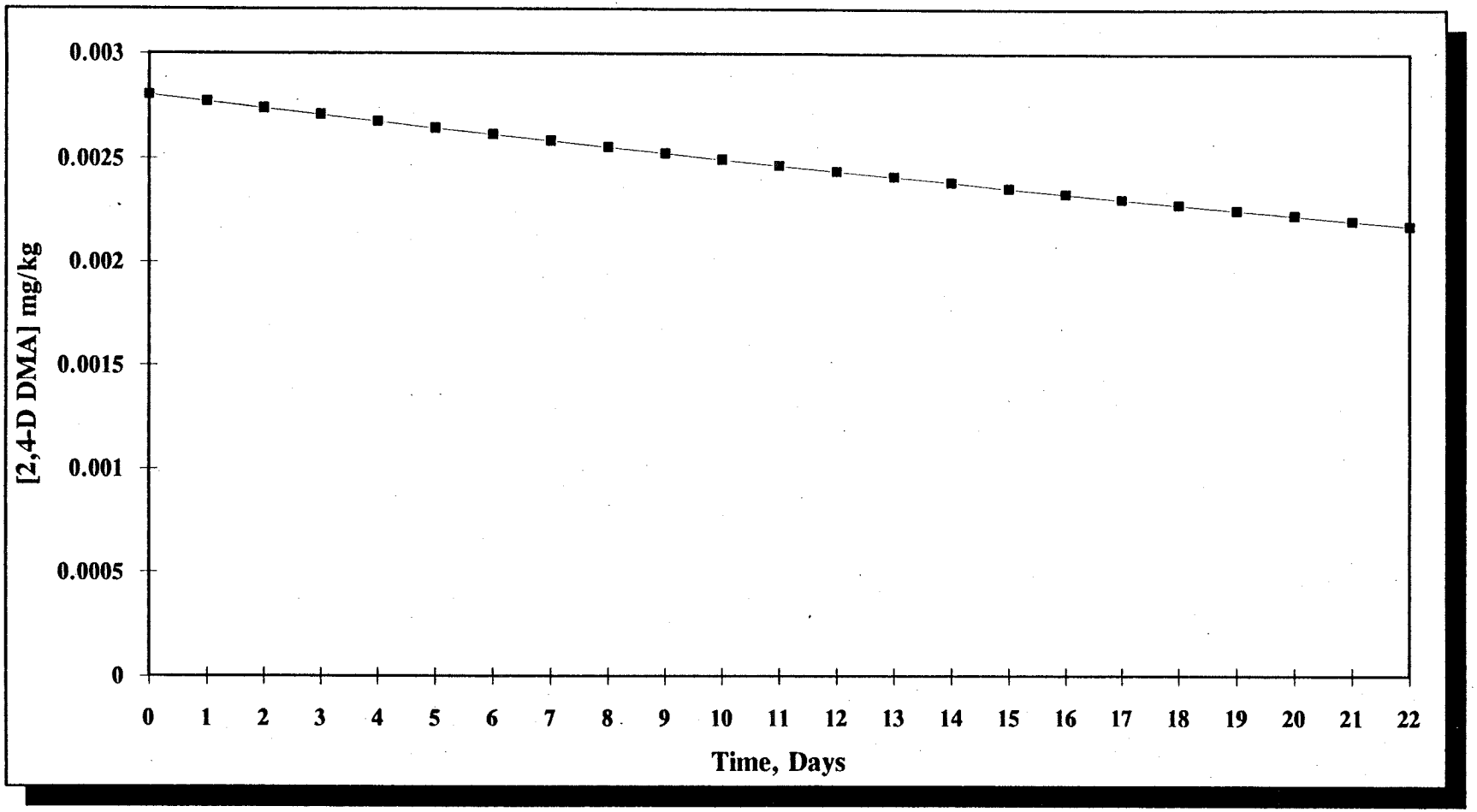


Figure 6. 2,4-D BEE concentration in water as a function of time in Scenario 3 (initial concentration = 0.00004 ppm, half-life = 11 days).



F' -e 7. 2,4-D DMA concentration in sediment as a function of tir ' Scenario 1 (initial concentration = 0.0028 ppm, half-life = 6('s).

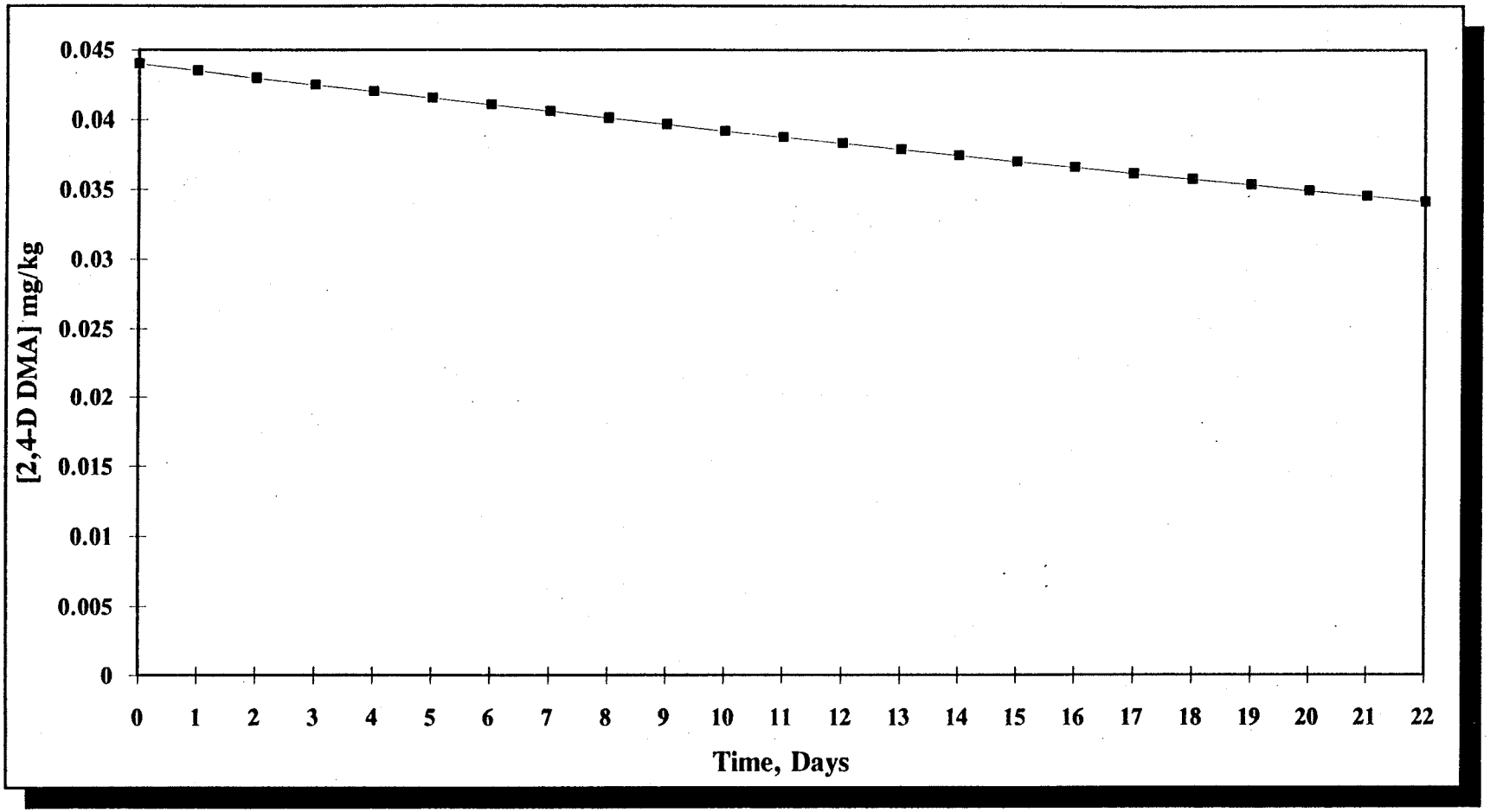


Figure 8. 2,4-D DMA concentration in sediment as a function of time in Scenario 2 (initial concentration = 0.044 ppm, half-life = 60 days).

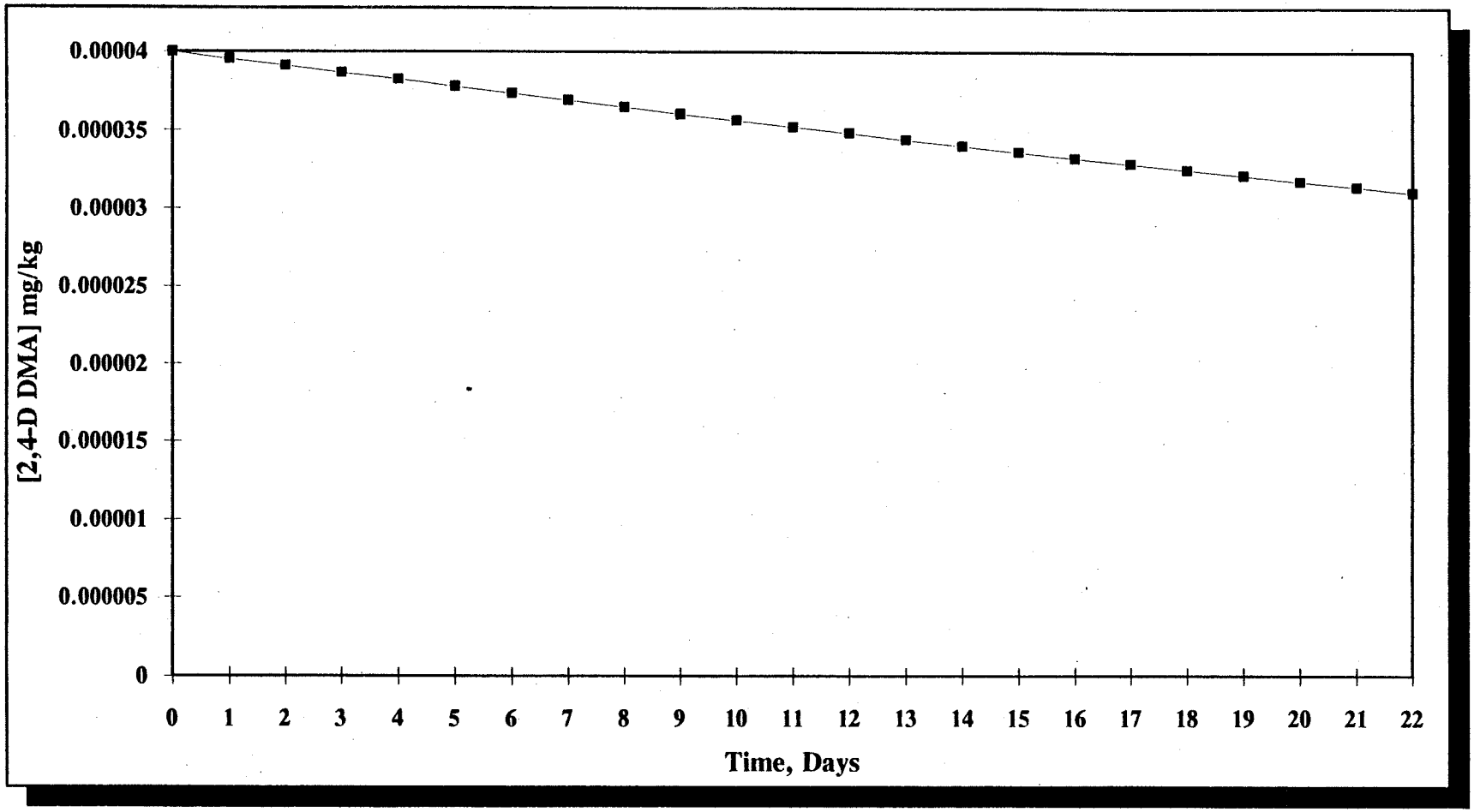


Figure 9. 2,4-D DMA concentration in sediment as a function of time Scenario 3 (initial concentration = 0.00004 ppm, half-life = 60 days).

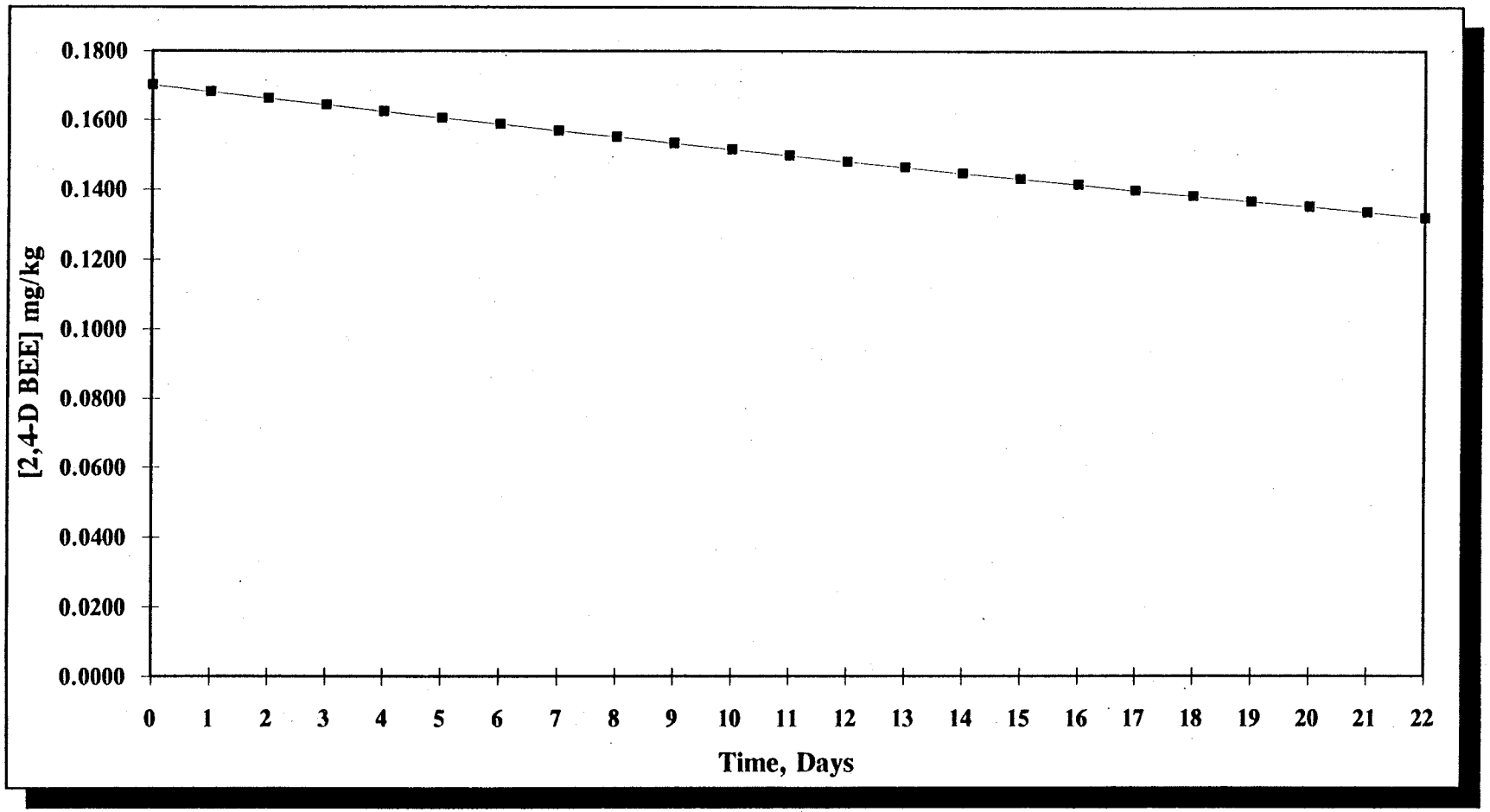


Figure 10. 2,4-D BEE concentration in sediment as a function of time in Scenario 1 (initial concentration = 0.17 ppm, half-life = 60 days).

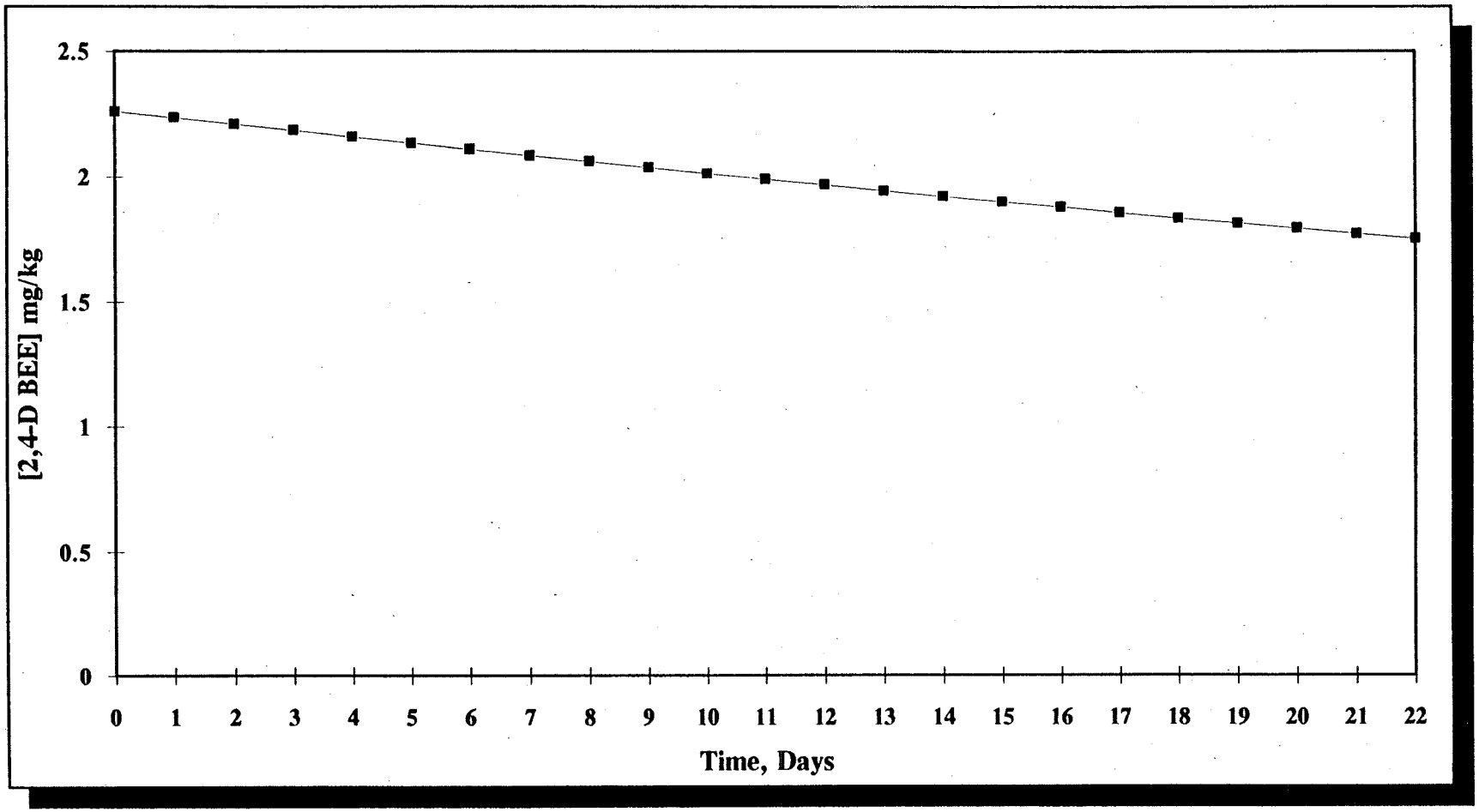


Figure 11. 2,4-D BEE concentration in sediment as a function of time in Scenario 2 (initial concentration = 2.26 ppm, half-life = 60 days).

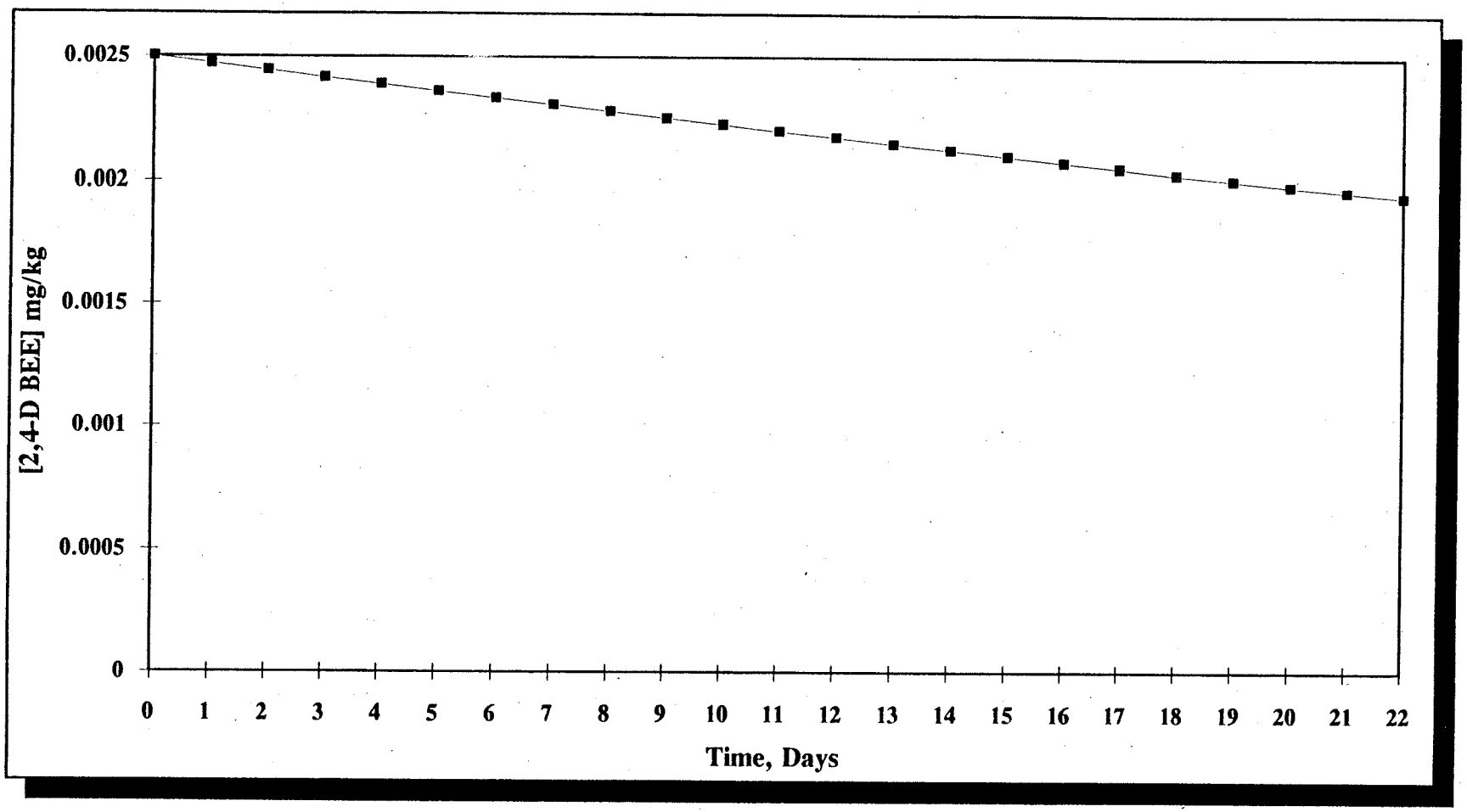


Figure 12. 2,4-D BEE concentration in sediment as a function of time in Scenario 3 (initial concentration = 0.0025 ppm, half-life = 60 days).

$$A_{ave} = \frac{[\,(A_o \cdot (1 - 2^{-22/h})\,]}{(\,22 \cdot \ln 2\,)}$$

Equation 7

Where:

A_{ave} = the average concentration within 22 days following application, and Ao and h are as above.

Table 6. Average concentrations (A_{ave}) of 2,4-D within a 22 day period following application

Scenario	2,4-D DMA Concentration		2,4-D BEE Concentration	
	Water (mg/L)	Sediment (mg/kg)	Water (mg/L)	Sediment (mg/kg)
1	8.10×10^{-3}	2.47×10^{-3}	1.73×10^{-3}	0.15
2	0.108	3.89×10^{-2}	2.22×10^{-2}	2.00
3	1.30×10^{-4}	3.53×10^{-5}	2.16×10^{-5}	2.21 x 10-3

2.2.2.2 Estimated Dose

The acute dermal dose of 2,4-D from contact with water is calculated according to the equation from USEPA (1992):

$$\text{Dermal Dose(mg/kg)} = \frac{PC \times ED \times SA \times Cw}{BW}$$

Where:

PC (amine) = Permeability Constant [1 E-05 cm/hr]
PC (ester) = Permeability Constant [0.0107 cm/hr]
ED = Exposure Duration (1 hr)
SA = Surface Area of Body (23,000 cm^2)
Cw = Concentration in water (mg/L)
BW = human body weight (70 kg)

Recent guidance (USEPA Dermal Exposure Guidance, 1992) recommends 0.5 hours for a recreational swimmer and 1 hour for a competitive swimmer. One hour was chosen as the exposure duration. The permeability constants were derived using the method of Flynn (1990), as cited in the USEPA Dermal Exposure Guidance (1992).

Acute doses are presented in Table 7. Water concentrations are taken from those calculated in Section 2.2.2.1 and shown in Appendix A.

Chronic dose is calculated for both the amine and ester formulations of 2,4-D as follows (USEPA, 1989).

$$\text{Intake (mg/kg-day)} = \frac{Cw \times SA \times ET \times ED \times EF \times CF \times PC}{BW \times AT}$$

Where:

Cw = Concentration in water (mg/L)
SA = Surface Area of Body (23,000 cm^2)
ET = Exposure Time (1 hr/event)
ED = Exposure Duration (30 years)
EF = Exposure Frequency (22 events/year)
CF = Conversion Factor (1 L/1,000 cm^3)
PC (amine) = Permeability Constant [1 E-05 cm/hr]
PC (ester) = Permeability Constant [0.0107 cm/hr]
BW = human body weight (70 kg)
AT = Averaging Time (30 years x 365 days/year = 10,950 days)

All parameters are taken from the USEPA Dermal Exposure Guidance (1992) with the exception of exposure frequency. This value was taken from a Washington State recreation survey (Interagency Committe for Outdoor Recreation, 1979). Chronic intake values for the three exposure scenarios are presented in Table 8.

Table 7. Single Doses from Dermal Contact with Water (Swimming). (Page 1 of 3)

Scenario 1: Small Pond

Days After application	Water Concentration (mg/L)		Dose Swimming (mg/kg)	
	Amine	Ester	Amine	Ester
Immediately	1.50E-02	3.20E-03	4.93E-08	1.13E-05
1	1.41E-02	3.00E-03	4.63E-08	1.06E-05
2	1.32E-02	2.82E-03	4.34E-08	9.92E-06
3	1.24E-02	2.65E-03	4.08E-08	9.31E-06
4	1.17E-02	2.49E-03	3.83E-08	8.74E-06
5	1.09E-02	2.34E-03	3.60E-08	8.21E-06
6	1.03E-02	2.19E-03	3.38E-08	7.71E-06
7	9.64E-03	2.06E-03	3.17E-08	7.24E-06
8	9.06E-03	1.93E-03	2.98E-08	6.80E-06
9	8.51E-03	1.81E-03	2.80E-08	6.38E-06
10	7.99E-03	1.70E-03	2.62E-08	5.99E-06
11	7.50E-03	1.60E-03	2.46E-08	5.63E-06
12	7.04E-03	1.50E-03	2.31E-08	5.28E-06
13	6.61E-03	1.41E-03	2.17E-08	4.96E-06
14	6.20E-03	1.32E-03	2.04E-08	4.66E-06
15	5.83E-03	1.24E-03	1.92E-08	4.37E-06
16	5.47E-03	1.17E-03	1.80E-08	4.10E-06
17	5.14E-03	1.10E-03	1.69E-08	3.85E-06
18	4.82E-03	1.03E-03	1.59E-08	3.62E-06
19	4.53E-03	9.66E-04	1.49E-08	3.40E-06
20	4.25E-03	9.07E-04	1.40E-08	3.19E-06
21	3.99E-03	8.52E-04	1.31E-08	3.00E-06
22	3.75E-03	8.00E-04	1.23E-08	2.81E-06

Table 7. Single Doses from Dermal Contact with Water (Swimming). (Page 2 of 3)

Scenario 2: Irrigation Ditch

Days After application	Water Concentration (mg/L)		Dose Swimming (mg/kg)	
	Amine	Ester	Amine	Ester
Immediately	2.00E-01	4.10E-02	6.57E-07	1.44E-04
1	1.88E-01	3.85E-02	6.17E-07	1.35E-04
2	1.76E-01	3.61E-02	5.79E-07	1.27E-04
3	1.66E-01	3.39E-02	5.44E-07	1.19E-04
4	1.55E-01	3.19E-02	5.11E-07	1.12E-04
5	1.46E-01	2.99E-02	4.80E-07	1.05E-04
6	1.37E-01	2.81E-02	4.50E-07	9.88E-05
7	1.29E-01	2.64E-02	4.23E-07	9.27E-05
8	1.21E-01	2.48E-02	3.97E-07	8.71E-05
9	1.13E-01	2.33E-02	3.73E-07	8.18E-05
10	1.07E-01	2.18E-02	3.50E-07	7.68E-05
11	1.00E-01	2.05E-02	3.29E-07	7.21E-05
12	9.39E-02	1.92E-02	3.09E-07	6.77E-05
13	8.82E-02	1.81E-02	2.90E-07	6.35E-05
14	8.28E-02	1.70E-02	2.72E-07	5.97E-05
15	7.77E-02	1.59E-02	2.55E-07	5.60E-05
16	7.30E-02	1.50E-02	2.40E-07	5.26E-05
17	6.85E-02	1.40E-02	2.25E-07	4.94E-05
18	6.43E-02	1.32E-02	2.11E-07	4.64E-05
19	6.04E-02	1.24E-02	1.98E-07	4.35E-05
20	5.67E-02	1.16E-02	1.86E-07	4.09E-05
21	5.33E-02	1.09E-02	1.75E-07	3.84E-05
22	5.00E-02	1.03E-02	1.64E-07	3.60E-05

Table 7. Single Doses from Dermal Contact with Water (Swimming). (Page 3 of 3)

Scenario 3: Large Lake

Days After application	Water Concentration (mg/L)		Dose Swimming (mg/kg)	
	Amine	Ester	Amine	Ester
Immediately	2.40E-04	4.00E-05	7.89E-10	1.41E-07
1	2.25E-04	3.76E-05	7.40E-10	1.32E-07
2	2.12E-04	3.53E-05	6.95E-10	1.24E-07
3	1.99E-04	3.31E-05	6.53E-10	1.16E-07
4	1.87E-04	3.11E-05	6.13E-10	1.09E-07
5	1.75E-04	2.92E-05	5.75E-10	1.03E-07
6	1.64E-04	2.74E-05	5.40E-10	9.64E-08
7	1.54E-04	2.57E-05	5.07E-10	9.05E-08
8	1.45E-04	2.42E-05	4.76E-10	8.49E-08
9	1.36E-04	2.27E-05	4.48E-10	7.98E-08
10	1.28E-04	2.13E-05	4.20E-10	7.49E-08
11	1.20E-04	2.00E-05	3.94E-10	7.03E-08
12	1.13E-04	1.88E-05	3.70E-10	6.60E-08
13	1.06E-04	1.76E-05	3.48E-10	6.20E-08
14	9.93E-05	1.36E-05	3.26E-10	4.77E-08
15	9.33E-05	1.55E-05	3.06E-10	5.46E-08
16	8.76E-05	1.46E-05	2.88E-10	5.13E-08
17	8.22E-05	1.37E-05	2.70E-10	4.82E-08
18	7.72E-05	1.29E-05	2.54E-10	4.52E-08
19	7.25E-05	1.21E-05	2.38E-10	4.25E-08
20	6.81E-05	1.13E-05	2.24E-10	3.99E-08
21	6.39E-05	1.07E-05	2.10E-10	3.74E-08
22	6.00E-05	1.00E-05	1.97E-10	3.52E-08

Table 8. Chronic intake values from dermal contact with water (swimming).

Scenario	Amine Average Concentration in Water (mg/L)	Ester Average Concentration in Water (mg/L)	Amine Intake (mg/kg-day)	Ester Intake (mg/kg-day)
1 (small pond)	8.10 E-03	1.73 E-03	1.60 E-09	3.67 E-07
2 (irrigation ditch)	0.108	2.22 E-02	2.14 E-08	4.70 E-06
3 (large lake)	1.30 E-04	2.16 E-05	2.57 E-11	4.58 E-09

2.2.3 Dermal Contact with Sediments

2.2.3.1 Exposure Date

Studies regarding uptake of 2,4-D via dermal contact with sediments do not exist. When this is the case USEPA recommends that data regarding uptake from soils be used. However, exposure data regarding absorption of chemicals from a soil matrix is also lacking, as only nine chemicals have been studied (USEPA, 1992).

An absorption factor was not available for 2,4-D. Therefore, in accordance with the USEPA Dermal Exposure Guidance it was attempted to substitute an ABS for a structurally similar chemical. However, this proved impossible. Thus, absorption factors derived from human studies using liquid 2,4-D were utilized. As discussed in section 3.1.1.1 dermal absorption of 2,4-D in a non-solvent vehicle ranges from 6 % to 10.5 %.

2.2.3.2 Estimated Dose

Acute doses are derived by the formula:

$$\text{Dermal Dose (mg/kg)} = \frac{Cs \times CF \times SA \times AF \times ABS}{BW}$$

Where:

Cs = Concentration in sediment (mg/kg)
CF = Conversion factor (0.000001 kg/mg)

SA = Surface are exposed (1840cm^2)
AF = Adherence factor (0.95 mg/cm^3)
ABS = Absorption factor (10.5%)
BW = Body weight (70 kg)

The only body parts assumed to contact sediments are the feet and lower legs. Acute doses from a single incident of dermal contact with sediment are shown in Table 9.

Chronic intake from dermal contact with sediments is calculated as follows (USEPA, 1989):

$$\text{Intake (mg/kg-day)} = \frac{Cs \times CF \times SA \times AF \times ABS \times EF \times ED}{BW \times AT}$$

Where:

CS = Contaminant concentration in Sediment (mg/kg)
CF = Conversion Factor (0.000001 kg/mg)
SA = Surface Area (1,840 cm^2)
AF = Adherence Factor (0.95 mg/cm^2-event)
ABS = Absorption factor (10.5 %)
EF = Exposure Frequency (22 events/year)
ED = Exposure Duration (30 years)
BW = Body Weight (70 kg)
AT = Averaging Time (30 years x 365 days/year = 10,950 days)

In this scenario it is assumed that both lower legs and feet contact sediment. Intake values from dermal contact with sediments are shown in Table 10.

2.2.4 Ingestion of Aquatic Organisms

2.2.4.1 Exposure Data

The herbicide 2,4-D generally does not bioaccumulate to a great extent, and the small amounts which do accumulate will be rapidly eliminated once exposure ceases (Norris, 1982). Reinert and Rodgers (1987) report that bioconcentration factors ratio of 2,4-D concentrations in organisms to that in water range from 1 to 7 in various species of fish.

Table 9. Single Doses from Dermal Contact with Sediment. (Page 1 of 3)

Scenario 1: Small Pond

Days After Application	Concentration in Sediment (mg/kg)		Dose Dermal Contact with Sediment (mg/kg)	
	Amine	Ester	Amine	Ester
Immediately	2.80E-03	1.70E-01	7.34E-09	4.46E-07
1	2.77E-03	1.68E-01	7.26E-09	4.41E-07
2	2.74E-03	1.66E-01	7.17E-09	4.36E-07
3	2.70E-03	1.64E-01	7.09E-09	4.31E-07
4	2.67E-03	1.62E-01	7.01E-09	4.26E-07
5	2.64E-03	1.60E-01	6.93E-09	4.21E-07
6	2.61E-03	1.59E-01	6.85E-09	4.16E-07
7	2.58E-03	1.57E-01	6.77E-09	4.11E-07
8	2.55E-03	1.55E-01	6.69E-09	4.06E-07
9	2.52E-03	1.53E-01	6.62E-09	4.02E-07
10	2.49E-03	1.51E-01	6.54E-09	3.97E-07
11	2.47E-03	1.50E-01	6.47E-09	3.93E-07
12	2.44E-03	1.48E-01	6.39E-09	3.88E-07
13	2.41E-03	1.46E-01	6.32E-09	3.84E-07
14	2.38E-03	1.45E-01	6.25E-09	3.79E-07
15	2.35E-03	1.43E-01	6.17E-09	3.75E-07
16	2.33E-03	1.41E-01	6.10E-09	3.71E-07
17	2.30E-03	1.40E-01	6.03E-09	3.66E-07
18	2.27E-03	1.38E-01	5.96E-09	3.62E-07
19	2.25E-03	1.36E-01	5.89E-09	3.58E-07
20	2.22E-03	1.35E-01	5.83E-09	3.54E-07
21	2.20E-03	1.33E-01	5.76E-09	3.50E-07
22	2.17E-03	1.32E-01	5.69E-09	3.46E-07

Table 9. Single Doses from Dermal Contact with Sediment. (Page 2 of 3)

Scenario 2: Irrigation Ditch

Days After Application	Concentration in Sediment (mg/kg)		Dose Dermal Contact with Sediment (mg/kg)	
	Amine	Ester	Amine	Ester
Immediately	2.80E-03	1.70E-01	1.15E-07	5.93E-06
1	2.77E-03	1.68E-01	1.14E-07	5.86E-06
2	2.74E-03	1.66E-01	1.13E-07	5.79E-06
3	2.70E-03	1.64E-01	1.11E-07	5.72E-06
4	2.67E-03	1.62E-01	1.10E-07	5.66E-06
5	2.64E-03	1.60E-01	1.09E-07	5.59E-06
6	2.61E-03	1.59E-01	1.08E-07	5.53E-06
7	2.58E-03	1.57E-01	1.06E-07	5.47E-06
8	2.55E-03	1.55E-01	1.05E-07	5.40E-06
9	2.52E-03	1.53E-01	1.04E-07	5.34E-06
10	2.49E-03	1.51E-01	1.03E-07	5.28E-06
11	2.47E-03	1.50E-01	1.02E-07	5.22E-06
12	2.44E-03	1.48E-01	1.00E-07	5.16E-06
13	2.41E-03	1.46E-01	9.93E-08	5.10E-06
14	2.38E-03	1.45E-01	9.81E-08	5.04E-06
15	2.35E-03	1.43E-01	9.70E-08	4.98E-06
16	2.33E-03	1.41E-01	9.59E-08	4.93E-06
17	2.30E-03	1.40E-01	9.48E-08	4.87E-06
18	2.27E-03	1.38E-01	9.37E-08	4.81E-06
19	2.25E-03	1.36E-01	9.26E-08	4.76E-06
20	2.22E-03	1.35E-01	9.16E-08	4.70E-06
21	2.20E-03	1.33E-01	9.05E-08	4.65E-06
22	2.17E-03	1.32E-01	8.95E-08	4.60E-06

Table 9. Single Doses from Dermal Contact with Sediment. (Page 3 of 3)

Scenario 3: Large Lake

Days After Application	Concentration in Sediment (mg/kg)		Dose Dermal Contact with Sediment (mg/kg)	
	Amine	Ester	Amine	Ester
Immediately	2.80E-03	1.70E-01	1.05E-10	6.56E-09
1	2.77E-03	1.68E-01	1.04E-10	6.48E-09
2	2.74E-03	1.66E-01	1.02E-10	6.41E-09
3	2.70E-03	1.64E-01	1.01E-10	6.33E-09
4	2.67E-03	1.62E-01	1.00E-10	6.26E-09
5	2.64E-03	1.60E-01	9.90E-11	6.19E-09
6	2.61E-03	1.59E-01	9.79E-11	6.12E-09
7	2.58E-03	1.57E-01	9.67E-11	6.05E-09
8	2.55E-03	1.55E-01	9.56E-11	5.98E-09
9	2.52E-03	1.53E-01	9.45E-11	5.91E-09
10	2.49E-03	1.51E-01	9.34E-11	5.84E-09
11	2.47E-03	1.50E-01	9.24E-11	5.77E-09
12	2.44E-03	1.48E-01	9.13E-11	5.71E-09
13	2.41E-03	1.46E-01	9.03E-11	5.64E-09
14	2.38E-03	1.45E-01	8.92E-11	5.58E-09
15	2.35E-03	1.43E-01	8.82E-11	5.51E-09
16	2.33E-03	1.41E-01	8.72E-11	5.45E-09
17	2.30E-03	1.40E-01	8.62E-11	5.39E-09
18	2.27E-03	1.38E-01	8.52E-11	5.32E-09
19	2.25E-03	1.36E-01	8.42E-11	5.26E-09
20	2.22E-03	1.35E-01	8.32E-11	5.20E-09
21	2.20E-03	1.33E-01	8.23E-11	5.14E-09
22	2.17E-03	1.32E-01	8.13E-11	5.08E-09

Table 10. Chronic intake values for dermal contact with sediments

Scenario	Amine Average Concentration in Sediment (mg/kg)	Ester Average Concentration in Sediment (mg/kg)	Amine Intake (mg/kg-day)	Ester Intake (mg/kg-day)
1 (small pond)	2.47 E-03	0.15	3.90 E-10	2.37 E-08
2 (irrigation ditch)	3.89 E-02	2	6.51 E-09	3.16 E-07
3 (large lake)	3.53 E-03	2.21 E-05	5.58 E-12	3.49 E-10

These values are for the DMA (dimethylamine salt) formulation of 2,4-D. Shipp et al. (1986) utilized a BCF of 1 for prediction of fish tissue 2,4-D concentration, and the USDA (1988) utilized a BCF of 5. A review of BCFs (USEPA, 1993) indicate that these values are representative of those typical for freshwater fish. A BCF of 5 was utilized to calculate fish tissue concentrations from water concentrations. Bioaccumulation factors (BAF) describe the ratio of 2,4-D in fish tissue to that in sediment and were not available for fish.

2.2.4.2 Estimated Dose

The species of fish found in ponds and lakes in Washington State very widely. Thus, generalizations regarding applicability of the above BCFs to these fish must be made. A BCF of 5 was assumed to be representative of BCFs for resident fish. This low BCF is further supported by negligible and below detection limit concentrations of 2,4-D measured in numerous fish species (Schultz and Harmon, 1973; Grangstad, 1983, Hoeppel and Westerdahl, 1983).

Concentrations of 2,4-D in fish were calculated using a standard methodology (Rand and Petrocelli, 1985) in which concentrations are multiplied by the BCF, so that

$$C_{fish} = C_{water} \times BCF \left(\frac{C_{fish}}{C_{water}} \right)$$

Estimated water concentrations are taken from section 2.2.2.1, and resulting fish concentrations and acute human doses are presented in Table 11. Fish 2,4-D

Table 11. Single Doses from Ingestion of Fish. (Page 1 of 3)

Scenario 1: Small Pond

Days After Application	Concentration in Water (mg/L)		BCF	Concentration in Fish (mg/kg)		Dose Ingestion of Fish (mg/kg)	
	Amine	Ester		Amine	Ester	Amine	Ester
Immediately	1.50E-02	3.20E-03	5	7.50E-02	1.60E-02	4.29E-04	9.14E-05
1	1.41E-02	3.00E-03	5	7.04E-02	1.50E-02	4.02E-04	8.58E-05
2	1.32E-02	2.82E-03	5	6.61E-02	1.41E-02	3.78E-04	8.06E-05
3	1.24E-02	2.65E-03	5	6.21E-02	1.32E-02	3.55E-04	7.57E-05
4	1.17E-02	2.49E-03	5	5.83E-02	1.24E-02	3.33E-04	7.11E-05
5	1.09E-02	2.34E-03	5	5.47E-02	1.17E-02	3.13E-04	6.67E-05
6	1.03E-02	2.19E-03	5	5.14E-02	1.10E-02	2.94E-04	6.26E-05
7	9.64E-03	2.06E-03	5	4.82E-02	1.03E-02	2.75E-04	5.88E-05
8	9.06E-03	1.93E-03	5	4.53E-02	9.66E-03	2.59E-04	5.52E-05
9	8.51E-03	1.81E-03	5	4.25E-02	9.07E-03	2.43E-04	5.19E-05
10	7.99E-03	1.70E-03	5	3.99E-02	8.52E-03	2.28E-04	4.87E-05
11	7.50E-03	1.60E-03	5	3.75E-02	8.00E-03	2.14E-04	4.57E-05
12	7.04E-03	1.50E-03	5	3.52E-02	7.51E-03	2.01E-04	4.29E-05
13	6.61E-03	1.41E-03	5	3.31E-02	7.05E-03	1.89E-04	4.03E-05
14	6.20E-03	1.32E-03	5	3.10E-02	6.62E-03	1.77E-04	3.78E-05
15	5.83E-03	1.24E-03	5	2.91E-02	6.22E-03	1.67E-04	3.55E-05
16	5.47E-03	1.17E-03	5	2.74E-02	5.84E-03	1.56E-04	3.34E-05
17	5.14E-03	1.10E-03	5	2.57E-02	5.48E-03	1.47E-04	3.13E-05
18	4.82E-03	1.03E-03	5	2.41E-02	5.15E-03	1.38E-04	2.94E-05
19	4.53E-03	9.66E-04	5	2.27E-02	4.83E-03	1.29E-04	2.76E-05
20	4.25E-03	9.07E-04	5	2.13E-02	4.54E-03	1.22E-04	2.59E-05
21	3.99E-03	8.52E-04	5	2.00E-02	4.26E-03	1.14E-04	2.43E-05
22	3.75E-03	8.00E-04	5	1.88E-02	4.00E-03	1.07E-04	2.29E-05

Scenario 2: Irrigation Ditch

Days After Application	Concentration in Water (mg/L)		BCF	Concentration in Fish (mg/kg)		Dose Ingestion of Fish (mg/kg)	
	Amine	Ester		Amine	Ester	Amine	Ester
Immediately	2.00E-01	4.10E-02	5	1.00E+00	2.05E-01	5.71E-03	1.17E-03
1	1.88E-01	3.85E-02	5	9.39E-01	1.92E-01	5.37E-03	1.10E-03
2	1.76E-01	3.61E-02	5	8.82E-01	1.81E-01	5.04E-03	1.03E-03
3	1.66E-01	3.39E-02	5	8.28E-01	1.70E-01	4.73E-03	9.70E-04
4	1.55E-01	3.19E-02	5	7.77E-01	1.59E-01	4.44E-03	9.10E-04
5	1.46E-01	2.99E-02	5	7.30E-01	1.50E-01	4.17E-03	8.55E-04
6	1.37E-01	2.81E-02	5	6.85E-01	1.40E-01	3.92E-03	8.03E-04
7	1.29E-01	2.64E-02	5	6.43E-01	1.32E-01	3.68E-03	7.54E-04
8	1.21E-01	2.48E-02	5	6.04E-01	1.24E-01	3.45E-03	7.08E-04
9	1.13E-01	2.33E-02	5	5.67E-01	1.16E-01	3.24E-03	6.64E-04
10	1.07E-01	2.18E-02	5	5.33E-01	1.09E-01	3.04E-03	6.24E-04
11	1.00E-01	2.05E-02	5	5.00E-01	1.03E-01	2.86E-03	5.86E-04
12	9.39E-02	1.92E-02	5	4.69E-01	9.62E-02	2.68E-03	5.50E-04
13	8.82E-02	1.81E-02	5	4.41E-01	9.04E-02	2.52E-03	5.16E-04
14	8.28E-02	1.70E-02	5	4.14E-01	8.48E-02	2.37E-03	4.85E-04
15	7.77E-02	1.59E-02	5	3.89E-01	7.97E-02	2.22E-03	4.55E-04
16	7.30E-02	1.50E-02	5	3.65E-01	7.48E-02	2.08E-03	4.27E-04
17	6.85E-02	1.40E-02	5	3.43E-01	7.02E-02	1.96E-03	4.01E-04
18	6.43E-02	1.32E-02	5	3.22E-01	6.59E-02	1.84E-03	3.77E-04
19	6.04E-02	1.24E-02	5	3.02E-01	6.19E-02	1.73E-03	3.54E-04
20	5.67E-02	1.16E-02	5	2.84E-01	5.81E-02	1.62E-03	3.32E-04
21	5.33E-02	1.09E-02	5	2.66E-01	5.46E-02	1.52E-03	3.12E-04
22	5.00E-02	1.03E-02	5	2.50E-01	5.13E-02	1.43E-03	2.93E-04

Table 11. Single Doses from Ingestion of Fish. (Page 3 of 3)

Scenario 3: Large Lake

Days After Application	Concentration in Water (mg/L)		BCF	Concentration in Fish (mg/kg)		Dose Ingestion of Fish (mg/kg)	
	Amine	Ester		Amine	Ester	Amine	Ester
Immediately	2.40E-04	4.00E-05	5	1.20E-03	2.00E-04	6.86E-06	1.14E-06
1	2.25E-04	3.76E-05	5	1.13E-03	1.88E-04	6.44E-06	1.07E-06
2	2.12E-04	3.53E-05	5	1.06E-03	1.76E-04	6.05E-06	1.01E-06
3	1.99E-04	3.31E-05	5	9.93E-04	1.66E-04	5.68E-06	9.46E-07
4	1.87E-04	3.11E-05	5	9.33E-04	1.55E-04	5.33E-06	8.88E-07
5	1.75E-04	2.92E-05	5	8.76E-04	1.46E-04	5.00E-06	8.34E-07
6	1.64E-04	2.74E-05	5	8.22E-04	1.37E-04	4.70E-06	7.83E-07
7	1.54E-04	2.57E-05	5	7.72E-04	1.29E-04	4.41E-06	7.35E-07
8	1.45E-04	2.42E-05	5	7.25E-04	1.21E-04	4.14E-06	6.90E-07
9	1.36E-04	2.27E-05	5	6.82E-04	1.13E-04	3.90E-06	6.48E-07
10	1.28E-04	2.13E-05	5	6.39E-04	1.07E-04	3.65E-06	6.09E-07
11	1.20E-04	2.00E-05	5	6.00E-04	1.00E-04	3.43E-06	5.71E-07
12	1.13E-04	1.88E-05	5	5.63E-04	9.39E-05	3.22E-06	5.37E-07
13	1.06E-04	1.76E-05	5	5.29E-04	8.82E-05	3.02E-06	5.04E-07
14	9.93E-05	1.36E-05	5	4.97E-04	6.78E-05	2.84E-06	3.87E-07
15	9.33E-05	1.55E-05	5	4.66E-04	7.77E-05	2.66E-06	4.44E-07
16	8.76E-05	1.46E-05	5	4.38E-04	7.30E-05	2.50E-06	4.17E-07
17	8.22E-05	1.37E-05	5	4.11E-04	6.85E-05	2.35E-06	3.92E-07
18	7.72E-05	1.29E-05	5	3.86E-04	6.43E-05	2.21E-06	3.68E-07
19	7.25E-05	1.21E-05	5	3.62E-04	6.04E-05	2.07E-06	3.45E-07
20	6.81E-05	1.13E-05	5	3.40E-04	5.67E-05	1.94E-06	3.24E-07
21	6.39E-05	1.07E-05	5	3.20E-04	5.33E-05	1.83E-06	3.04E-07
22	3.00E-04	5.00E-05	5	3.00E-04	5.00E-05	1.71E-06	2.86E-07

concentrations are calculated from water concentrations. The calculated fish concentrations are very likely to be overestimates of actual tissue values as bioconcentration is a dynamic process of uptake and depuration, particularly for a hydrophilic chemical such as 2,4-D.

A single acute human dose is calculated by the formula (USEPA, 1989):

$$\text{Dose (mg/kg)} = \frac{C_{fish}\text{(mg/kg)} * \text{kg fish consumed}}{\text{human body weight (kg)}}$$

Where:

Kg fish consumed = 0.4 kg
human body weight = 70 kg

Chronic intake is calculated using the following equation (USEPA, 1989):

$$\textit{Intake (mg/kg-day)} = \frac{CF \times IR \times FI \times EF \times ED}{BW \times AT}$$

Where:

CF = Contaminant concentration in Fish (mg/kg)
IR = Intake Rate (0.4 kg/meal)
FI = Fraction Ingested (100%)
EF = Exposure Frequency (52 meals/year)
ED = Exposure Duration (30 years)
BW = Body Weight (70 kg)
AT = Averaging Time (30 years x 365 days/year = 10,950 days)

The fraction ingested describes the percent of a person's total fish intake which is derived from the site of interest. For this conservative analysis it was assumed that 100% of a person's fish diet is taken from a 2,4-D treated water body. A BCF of 5 was used to calculate 2,4-D concentrations in fish. All other values are standard USEPA default values (Region 10 guidance). The chronic intake values are shown in Table 12.

Table 12. Chronic intake values for ingestion of fish

Scenario	Amine Average Conc. in Water (mg/l)	Ester Average Conc in Water (mg/l)	Amine Average Conc. in Fish (mg/kg)	Ester Average Conc. in Fish (mg/kg)	Amine Intake (mg/kg-day)	Ester Intake (mg/kg-day)
1 (small pond)	8.10 E-03	1.73 E-03	4.05 E-02	8.65 E-03	3.30 E-05	7.04 E-06
2 (irrigation ditch)	0.108	2.22 E-02	0.54	1.11 E-01	4.40 E-04	9.04 E-05
3 (large lake)	1.30 E-04	2.16 E-05	6.5 E-04	1.10 E-04	5.29 E-07	8.79 E-08

2.2.5 Ingestion of Surface Water

2.2.5.1 Exposure Data

The herbicide 2,4-D may be utilized on lakes or ponds which are used as residential drinking water sources. This assessment assumes that water is drawn directly from lakes, ponds, or irrigation ditches and utilized without any chemical or physical pre-treatments.

2.2.5.2 Estimated Dose

Chronic daily intake is calculated as follows (USEPA, 1989):

$$Intake\ (mg/kg\text{-}day\ ) = \frac{CW \times IR \times EF \times ED}{BW \times AT}$$

Where:

CW = Contaminant concentration in Water (mg/L)
IR = Intake Rate (2 L/day)
EF = Exposure Frequency (365 days/year)
ED = Exposure Duration (30 years)
BW = Body Weight (70 kg)
AT = Averaging Time (30 years x 365 days/year = 10,950 days)

All exposure values are standard USEPA region 10 guidance default values and represent very conservative assumptions. Estimated intakes are presented in Table 13.

2.2.6 Incidental Ingestion of Sediment

2.2.6.1 Exposure Data

Incidental ingestion of sediment may occur during recreational activities such as swimming or wading. The intake equation includes different intake scenarios for children and adults to account for the likelihood that children will ingest more sediment than adults.

Table 13. Chronic intake values for ingestion of surface water

Scenario	Amine Average Concentration in Water (mg/kg)	Ester Average Concentration in Water (mg/kg)	Amine Intake (mg/kg-day)	Ester Intake (mg/kg-day)
1 (small pond)	8.10 E-03	1.73 E-03	2.31 E-04	4.94 E-05
2 (irrigation ditch)	0.108	2.22 E-02	3.09 E-03	6.34 E-04
3 (large lake)	1.30 E-04	2.16 E-05	3.71 E-06	6.17 E-07

2.2.6.2 Estimated Dose

Chronic daily intake of incidental ingestion of sediment is estimated as follows (USEPA Region 10 Guidance, 1991):

$$Intake\ (mg/kg\text{-}day\ ) = CS \times CF_1 \times \left(\frac{\frac{IR_C \times EF \times ED_C}{BW_C} + \frac{IR_A \times EF \times ED_A}{BW_A}}{AT \times CF_2} \right)$$

Where:

CS = Contaminant concentration in Sediment (mg/kg)
CF_1 = Conversion Factor (0.000001 kg/mg)
CF_2 = Conversion Factor (365 days/year)
IR_C = Intake Rate, child (200 mg/day)
IR_A = Intake Rate, adult (100 mg/day)
EF = Exposure Frequency (22 days/year)
ED_C = Exposure Duration, child (6 years)
ED_A = Exposure Duration, adult (24 years)
BW_C = Body Weight, child (15 kg)
BW_A = Body Weight, adult (70 kg)
AT = Averaging Time (30 years x 365 days/year = 10,950 days)

All exposure parameter values are standard default values from USEPA region 10 guidance with the exception of exposure frequency, taken from the statewide recreation survey. Chronic daily intake values are shown in Table 14.

Table 14. Chronic intake values for incidental ingestion of sediment

Scenario	Amine Average Concentration in Sediment (mg/kg)	Ester Average Concentration in Sediment (mg/kg)	Amine Intake (mg/kg-day)	Ester Intake (mg/kg-day)
1 (small pond)	2.47 E-03	0.15	5.67 E-10	3.44 E-08
2 (irrigation ditch)	3.89 E-02	2	8.93 E-09	4.59 E-07
3 (large lake)	3.53 E-05	2.21 E-03	8.11 E-12	5.07 E-10

3.0 TOXICITY ASSESSMENT

3.1 PHARMACOKINETICS

3.1.1 Uptake

3.1.1.1 Dermal

Studies are available concerning pharmacokinetics of 2,4-D in both man and laboratory animals. An early study by Feldman and Maibach (1974) involved applying ^{14}C labeled 2,4-D acid in acetone to the forearms of human subjects and quantifying the urinary excretion of the labeled 2,4-D. Approximately 6 percent of a dermally applied dose is absorbed, as 5.8 percent was recovered within 5 days after application. This study indicates that skin absorption is incomplete probably because much of the applied dose is lost by washing or evaporation.

A similar study by Moody et al. (1990) reported on the absorption of 2,4-D applied to the foreheads of human volunteers. Treatment consisted of either ^{14}C-2,4-D amine in acetone, or 2,4-D isooctyl in acetone or Esteron LV96. The dose site was washed 24 hours post-treatment and urine samples collected at 4, 8, and 12 hours and daily for 7 days post-treatment. Results of urinalysis indicate that total percent cumulative absorption of 2,4-D amine in water is 58. Absorption of 2,4-D isooctyl in acetone is 6 percent, as is 2,4-D isooctyl in Esteron LV96 Vehicle.

The same authors published results of a follow-up study in 1992 in which ^{14}C labeled 2,4-D amine was applied to the palm and forearm of human volunteers. The effect of two vehicles (water and acetone) and the mosquito repellant N,N-diethyl-m-toluamide (DEET) was also investigated. Sixteen male subjects were divided into four groups to receive the following treatments: 1) ^{14}C-2,4-D-amine in water to left palm; 2) ^{14}C-2,4-D-amine with DEET in water to left palm; 3) ^{14}C-2,4-D-amine in water to left ventral forearm; and 4) 2,4-D-amine in acetone to left ventral forearm. The 2,4-D-amine dose rate was 1.7 $\mu g/cm^2$. When DEET was part of the treatment, it was applied to the skin just before application of 2,4-D. Treatment areas were covered, and washed 24 hours post-treatment. Urine samples were collected for 5 days at 24-hour intervals.

Results of urinalysis indicate that DEET has no significant effect on the total cumulative palmar permeability of 2,4-D, and that there was no significant differences between percent recovery with water or acetone vehicles. DEET appears to accelerate urinary ^{14}C excretion. The following cumulative average percent recoveries were recorded: 1) 2,4-D + DEET applied to palm (acetone vehicle) = 14 percent; 2) 2,4-D applied to palm (water vehicle) = 10.5 percent; 3) 2,4-D applied to forearm (acetone vehicle) = 13 percent; and 4) 2,4-D applied to forearm (water vehicle) = 7 percent. These results indicate that even though a rigorous washing at 24-hour post-treatment occurred, up to 14 percent of the dose was dermally absorbed when administered with a solvent vehicle.

Absorption of 2,4-D has also been studied in the rat and results are similar to those in humans. A 1992 study by Knopp and Schiller investigated absorption and excretion of sodium 2,4-D and 2,4-Dimethylammonium salts (2,4-DMA) after dermal application of 2.6 mg/kg (2,4-D) and 1.9 mg/kg (2,4-DMA). Urinary excretion reached 10 percent and 15 percent of 2,4-D and 2,4-DMA, respectively, by 5 days post-treatment.

Several dermal pre-treatments were tested using Fischer 344 rats in a 1990 study by Pelletier et al. The mid-back of the rat was pretreated with one of four treatments: 1) hair clipping only; 2) hair clipping followed by an epilatory cream; 3) hair clipping plus shaving with an electric razor; and 4) hair clipping, electric shaving followed by washing with soap and water. Dose sites were cleansed with soap and water after 7 hours (8-hour sacrifice) or 7 and 23 hours (24-hour sacrifice).

Results indicate that after 24 hours, the rats prepared by clipping plus shaving or clipping, shaving, and washing excreted 18 to 21 percent of the dose while those treated by clipping alone excreted 4 percent. Clipping plus epilatory-treated rats excreted 11 percent of the dose after 24 hours.

3.1.1.2 Oral

Two comprehensive studies (Erne, 1966; Khanna and Fang, 1966) report that absorption, distribution, and elimination of 2,4-D is rapid and complete following oral administration. Khanna and Fang reported that 94 to 99 percent of the dose is excreted unchanged within 48 hours. In general, the ester form is poorly absorbed compared the amine form, probably due to its low water solubility (Erne, 1966).

A more recent study (Pelletier et al., 1989) in which rats were dosed orally (1 and 0.4 mg/kg) with ^{14}C-2,4-D confirmed past studies with results indicating that 94 to 96 percent of the dose was absorbed with 6 hours. The absorbed dose was almost completely excreted within 24 hours. Absorption is similar in orally dosed dogs. Arnold et al. (1991) reported rapid absorption of 2,4-D followed by rapid elimination in urine. Their findings indicate that the amine salt of 2,4-D is hydrolyzed to 2,4-D acid in the stomach and is then available for absorption.

3.1.2 Metabolism/Distribution/Excretion

Two studies involving oral administration of 2,4-D to man are also available. Kohli et al. (1974) report on six male volunteers who ingested 5 mg/kg 2,4-D in gelatin capsules. Almost all of the administered dose was quickly absorbed and detected in plasma 1 hour after ingestion. Seventy-five percent of the dose was excreted unchanged in the urine 96 hours after administration. In this study, 2,4-D did not appear to undergo metabolic transformation and was rapidly excreted.

Sauerhoff et al. (1977) also administered a single dose of 2,4-D (5 mg/kg) in a slurry of milk (two subjects) or in powder form (three subjects) to five volunteers. Most (82 percent) of the 2,4-D was excreted unchanged in the urine. No metabolites were detected in the urine, and 95 percent of the dose was recovered within 6 days.

Metabolism is similar in dogs. Khanna and Fang (1966) dosed dogs orally with radiolabelled 2,4-D. The chemical was distributed widely throughout the body, and detected unchanged in all organs and tissues examined.

In rats, pigs, calves, and chickens 2,4-D amine salt administered orally was rapidly absorbed. 2,4-D butyl ester was less rapidly absorbed, and hydrolyzed during absorption was all that was found circulating was in the acid form. Absorbed 2,4-D was rapidly distributed throughout the body, with highest levels in kidneys, liver, spleen, and lungs.

3.2 SYNERGISM WITH SEVIN AND OTHER PESTICIDES

[TO BE ADDED IN THE EIS]

3.3 ACUTE TOXICITY

In general, acute toxicity of 2,4-D is dependent upon the amount of 2,4-D acid involved, as all forms are metabolized to the acid form before they are absorbed (Hayes, 1982). Thus, the salts and esters have approximately the same toxicity as the acid forms.

3.3.1 Dermal Toxicity

The LD_{50} from a single dermal exposure of 2,4-D (unspecified formulation) was 1,500 mg/kg in rats and 1,400 mg/kg in rabbits (USDA, 1984). However, application of doses up to 3,980 mg/kg 2,4-D (butyl ester or diethanolamine salt) to shaved skin of rabbits produced no toxic symptoms. 2,4-D has been shown to be a dermal sensitizer in guinea pigs, and has not been tested for such in other species (USEPA, 1988).

A 1986 study by Dow Chemical determined the acute dermal LD_{50} for rabbits to be >2,000 mg/kg. Erythema and edema were observed on day one in all animals tested. A second dermal study by Dow Chemical involved a single application of 0.5 ml 2,4-D (diethanolamine salt) to the shaved backs of white rabbits. Treatment produced no signs of dermal irritation.

In a subacute study sytemic effects were seen in rats treated dermally for 3 weeks with a 12% 2,4-D amine solution. Three groups of rats (15 rats/group) were painted with the solution for 2 hours/day, 5 days/week for 3 weeks. Control animals were treated with tap water. Treated rats exhibited two systemic effects: 1) they weighed less than control rats, and 2) kidney weights of treated rats were elevated relative to controls (USEPA, 1986d).

An earlier, similarly designed study reported no systemic effects in rabbits treated with lower doses of 2,4-D (Kay, et al, 1965). Formulations of 2,4-D (amine and ester) in solvent were applied to normal or abraded skin at 0.636% or 3.13% concentrations 7 hours/day, 5days/week for 3 weeks. While localized skin inflammation was seen in both treated and control groups (probably caused by the solvent vehicle) no effects were

observed on weights, survival, blood, histopathology, or organ/body weight ratios. However, the localized skin inflammation was accompanied by subepithelial fibrosis and mononuclear infiltration of the skin in treated rats.

3.3.2 Oral Toxicity

The oral LD_{50} for 2,4-D compounds ranges from 300 mg/kg to 1,000 mg/kg (WHO, 1984), depending on the animal tested and formulation used. Studies are summarized in Table 15. Dogs are more sensitive to 2,4-D's lethal effect than other species tested. The LD_{50} for dogs is approximately 100 mg/kg. Also reported as effects were pathologic changes of the gastrointestinal tract, hepatic recrosis, and mild renal tubular degeneration (Drill and Hiratzka, 1953).

Hill and Carlisle (1947) determined oral LD_{50}s of 375, 666, 800, and 1,000 mg/kg for 2,4-D sodium salt in mice, rats, rabbits, and guinea pigs, respectively. The maximum doses tolerated (not causing death) in these species were: 125 mg/kg (mice), 33 mg/kg (rats), 200 mg/kg (rabbits), and 333 mg/kg (guinea pigs). The LD_{50}s for 2,4-D compounds following a single oral dose range from 368 to 713 mg/kg in mice, 375 to 620 mg/kg in rats, 424 to 800 mg/kg in rabbits, and 469 to 1,000 mg/kg in guinea pigs.

A 1991 study by Arnold et al. determined toxicity and serum concentrations of 2,4-D (dimethylamine) in orally dosed dogs. Dogs dosed with encapsulated 2,4-D acid at 1.3, 8.8, 43.7, 175, or 220 mg/kg failed to exhibit abnormalities in hematologic, serum biochemical, urinalysis, or electrocardiogram parameters. However, at the two highest doses changes were noted in electroencephalograms (EEGs).

3.3.3 Inhalation Toxicity

Very few studies are available concerning toxicity of 2,4-D via inhalation. Hill and Carlisle (1947) reported no adverse systemic effects on guinea pigs exposed to 2,4-D dust.

3.3.4 Human Studies

There have been several conflicting reports in the literature regarding neurological effects in workers applying or handling 2,4-D (Goldstein et al., 1959; Mullison, 1981; Todd,

Table 15. Summary of Mammalian Systemic Toxicity Studies for 2,4-Dichlorophenoxyacetic Acid (2,4-D)*

Type of Test		Effects				
Formulation Species	Route of Exposure	NOEL	LEL	LD50	Comments	Reference
ACUTE, ORAL			mg/kg			
2,4-D (Acid)						
Rat Mouse Guinea Pig	Single dose, administered by intubation in olive oil; observed two weeks; male rats, mice, male and female guinea pits.	—	—	375(rat) 368(mouse) 469(g.pig)	In general, adverse effects in animals, including rats, mice, guinea pigs, and dogs, exposed to acutely toxic doses of 2,4-D include anorexia, weight loss, dipsesis (excessive thirst), depression, roughness of coat, tremors, myasthenia (muscle weakness), rapid breathing and salivation. Post-mortem findings include stomach irritation, liver and kidney damage, and occasional lung congestion.	Rowe and Hymas, 1954
Rat	Single dose, administered by intubation in a 5% gelatin solution at dosage levels of 0, 333, 666 or 1,000 mg/kg; 4 rats/ dose level.	—	—	666	Adverse effects for all species tested included myatonia, stiffness of extremities, ataxia, paralysis and coma with death caused by ventricular fibrillation.	Hill and Carlisle, 1947
Dog	Administered by capsule, at dosage levels of 0, 25, 100, 250 or 400 mg/kg; 2-4 dogs per dose.	25	100	100	Anorexia, weight loss, amyotonia, and pathological changes in the gastrointestinal tract,lungs, and liver with death resulting from hepatic congestion or pneumonia.	Drill and Hiratzka, 1953
Monkey	Single injections either oral (up to 214 mg/kg) or intraperitoneal (up to 428 mg/kg); combined oral or intra-peritoneal for 500 mg/kg total dose.	—	—	—	Tolerated 214 mg/kg by the oral route or 428 mg/kg by the intraperitoneal route; 500 mg/kg resulted in nausea, vomiting, lethargy and muscle incoordination.	Hill and Carlisle, 1947
2,4-D (isopropyl ester)						
Mouse Rat Guinea Pig	Single doses, administered by intubation in olive oil; observed two weeks. Male mice, guinea pigs, male and female rats.	—	—	541(mouse) 700(rat) 550(g.pig)	—	Rowe and Hymas, 1954
ACUTE, ORAL			mg/kg			
2,4-D (mixed butyl esters)						

Table 15. Summary of Mammalian Systemic Toxicity Studies for 2,4-Dichlorophenoxyacetic Acid (2,4-D)*

Type of Test / Formulation Species	Route of Exposure	Effects NOEL	Effects LEL	Effects LD50	Comments	Reference
Mouse Rat Guinea Pig Rabbit	Single doses, administered by intubation to females in corn oil; observed two weeks.	—	—	713(mouse) 620(rat) 848(g.pig) 424(rabbit)	—	Rowe and Hymas, 1954
2,4-D (sodium salt)						
Mouse	Single dose, administered by intubation at dosage levels of 1, 2.5, 5.0, 7.5 or 10 mg (equivalent to 1, 125, 250, 375 or 500 mg/kg); 10 mice per dose level.	—	—	375	Adverse effects included myotonia, stiffness of extremities, ataxia, paralysis and coma with death caused by ventricular fibrillation.	Hill and Carlisle, 1947
Rat	Single doses by intubation in water; observed two weeks.	—	—	666	Adverse effects for all species tested included myotonia, stiffness of extremities, ataxia, paralysis and coma with death caused by ventricular fibrillation.	Hill and Carlisle, 1947
Rat	Single doses by intubation in water to females; observed two weeks.	—	—	805	—	Rowe and Hymas, 1954
Rabbit	Single dose, administered by intubation at 4 or 5 dosage levels; 4 rabbits per dose level.	—	—	800	Adverse effects included myotonia, stiffness of extremities, ataxia, paralysis and coma with death caused by ventricular fibrillation.	Hill and Carlisle, 1947
Guinea Pig	Single doses by intubation in water to moles; observed two weeks.	—	—	551	—	Rowe and Hymas, 1954
Guinea Pig	Single dose, administered by intubation at dosage levels of 0, 100, 150, 200, 250 or 300 mg (equivalent to 0, 330, 500, 666, 833 or 1,000 mg/kg); 6 guinea pigs per dose level.	—	—	1,000	Adverse effects included myotonia, stiffness of extremities, ataxia, paralysis and coma with death caused by ventricular fibrillation.	Hill and Carlisle, 1947
ACUTE, DERMAL		mg/kg				
2,4-D (acid)						
Rat	Details not specified.	—	—	1,500	—	USDA, 1984a
Mouse	Details not specified.	—	—	1,400	—	USDA, 1984a/

Table 15. Summary of Mammalian Systemic Toxicity Studies for 2,4-Dichlorophenoxyacetic Acid (2,4-D)*

Type of Test		Effects				
Formulation Species	Route of Exposure	NOEL	LEL	LD50	Comments	Reference
2,4-D (butyl ester or diethanolomine salt)						
Rabbit	Applied to shaved skin of rabbits.	—	—	>3,980	—	Kay et al., 1965
INHALATION						
2,4-D (sodium salt)						
Guinea Pig	Exposed to 2,4-D dust; no details specified.	—	—	—	No signs of adverse systemic effects.	Hill and Carlisle, 1947
EYE IRRITATION						
2,4-D (acid salt, and esters)						
Species not specified	Applications of dry powder or highly concentrated solutions.	—	—	—	Produced irritation of conjunctival membranes and possible corneal damage.	Gehring and Betso, 1978 in USDA, 1984a
SUBCHRONIC, DERMAL		% solution				
2,4-D (dimethyl-amine salt, and isooctyl or butyl esters)						
Rabbit	Formulations of 2,4-D were applied to intact and abraded rabbit skin at 0.636% and 3.13% 7 hours/day, 5 days/week for 3 weeks.	No NOEL	0.636	—	Adverse reactions were limited to localized skin inflammations in both treated and control groups that were apparently produced by the oil-based solvents used as the vehicle. Treated animals had an increased incidence and severity of subepithelial fibrosis and accompanying mononuclear infiltration of the skin.	Kay et al., 1965
SUBCHRONIC AND CHRONIC, ORAL		mg/kg/day a.e.				
2,4-D (sodium salt)						
Mouse	Fed at dosage levels up to 93 mg/kg/day for 3 weeks to 3 months.	>93	—	—	No adverse effects measured.	Bucher, 1946

Table 15. Summary of Mammalian Systemic Toxicity Studies for 2,4-Dichlorophenoxyacetic Acid (2,4-D)*

Type of Test		Effects				
Formulation Species	Route of Exposure	NOEL	LEL	LD50	Comments	Reference
Guinea Pig	Groups of 6 guinea pigs were fed 0, 50 or 100 mg daily for 10 days over a 12-day period (doses equivalent to 0, 167 or 333 mg/kg).	333	—	—	No adverse treatment-related effects reported.	Hill and Carlisle, 1947
2,4-D (acid)						
Mouse	Once or twice daily subcutaneous injections at dosage levels of 50 to 90 mg/kg for 3 weeks to 90 days.	<70	70	—	No adverse effects below 70 mg/kg; levels of 70 mg/kg and above resulted in growth retardation.	Bucher, 1946
Mouse	Fed diet containing 0, 5, 45 or 90 mg/kg/day for 90 days.	No NOEL	—	—	Histopathological changes in renal tubules occurred in both sexes at the lowest dose tested.	EPA, 1984
Rat	Fed diets containing 0, 100, 200 or 400 ppm daily for 30 days (equivalent to up to 20 mg/kg/day); 7 rats/dose level.	20	—	—	Doses up to 400 ppm (20 mg/kg/day) produced no adverse effects. One death occurred at 400 ppm.	Hill and Carlisle, 1947
Rat	Groups of 5 or 6 female rats fed dosage levels of 0, 3, 10, 30, 100 or 300 mg/kg 5 days/week, for 4 weeks	30	100	—	At dosage levels of 30 mg/kg/day and below, no adverse effects were observed. At doses of 100 mg/kg/day, varying degrees of gastrointestinal irritation, depressed growth rates, and cloudy swelling of the liver were reported. At 300 mg/kg/day animals failed rapidly and died.	Rose and Hymas, 1954
Rat	Groups of 5 female rats fed diets containing 0, 100, 300, 1,000, 3,000 or 10,000 ppm daily for 113 days; doses equivalent to 0, 5, 15, 50, 150 or 500 mg/kg/day.	15	50	—	No adverse effects at doses below 300 ppm. At 1,000 ppm toxic effects were characterized by depressed growth rate, increased mortality, increased liver weights, and cloudy swelling of the liver.	Rowe and Hymas, 1954
Rat	Fed at dietary levels of 0, 5, 25, 125, or 1,250 ppm (equivalent to 0, 0.25, 1.25, 6.25 or 62.5 mg/kg/day) daily for two years, 25/sex/group.	62.5	—	—	No significant differences in growth rate, survival rate, organ weights, or hematological values as compared to controls were observed.	Hansen et al., 1971

Table 15. Summary of Mammalian Systemic Toxicity Studies for 2,4-Dichlorophenoxyacetic Acid (2,4-D)*

Type of Test		Effects				
Formulation Species	Route of Exposure	NOEL	LEL	LD50	Comments	Reference
Rat	Fed diets containing 0, 1, 5, 15 or 45 mg/kg/day for 90 days.	No NOEL	—	—	Histopathological changes in renal cortical tubules and increased thyroid weight occurred in the 1 mg/kg/day dose group.	EPA, 1984
Dog	Fed capsules containing 0, 2, 5, 10 or 20 mg/kg daily for 5 days/week for 13 weeks, four/group.	10	20	—	All dogs survived dosages up to 10 mg/kg/day and no significant changes in body weight, organ weights, or blood counts weights, or blood counts were observed. At 20 mg/kg/day, three or four dogs died between 18 and 49 days. All four dogs displayed ataxia, weakness, dysphagia, (difficulty in swallowing), bleeding gums, buccal mucosa necrosis, stiff hind legs, liver and kidney alterations, and decreased lymphocyte counts.	Drill and Hiratzka, 1953
Dog	Groups of male and female dogs were fed 0, 10, 50, 100 or 500 ppm daily in the diet for two years (equivalent to 0, 0.4, 2, 4 or 20 mg/kg/day); three/sex/group.	20	—	—	No treatment-related effects were noted at any dose tested.	Hansen et al., 1971

1962). Ingestion of 2,4-D has been reported to cause muscle twitching and/or central nervous system depression.

Goldstein et al. (1959) reported three cases of peripheral neuropathy in agricultural workers following dermal exposure to 2,4-D. The neuropathy was characterized by numbness, aching of arms and legs, muscle spasms, denervation of muscles, and decreased nerve conduction velocity. The condition may be totally or partially reversible, as indicated by one patient reporting incomplete recovery after 3 years of treatment. His exposure was estimated to be 60 mg 2,4-D/kg body weight.

Goldstein's report was followed by three similar case reports (Monarca and DiVito, 1961; Todd, 1962; Berkley and Magee, 1963). Mattsson and Eisenbrandt (1990) provided a critical review of these and other studies and concluded that the weight of evidence indicates that 2,4-D is the unlikely cause of polyneuropathy. The authors argue that in all of the above mentioned case reports every patient had some varying additional illness not usually associated with peripheral neuropathy (fever, respiratory illness, GI upset). In addition, the authors cite studies on the pharmokinetics of 2,4-D, which shows that it is rapidly eliminated from the body. As most of the cases of neuropathy did not occur until several days after 2,4-D exposure, they conclude that 2,4-D was not the causal agent. However, toxic responses are often delayed (Cassarett and Doull, 1986). Mattsson and Eisenbrandt also cite evidence against 2,4-D induced polyneuropathy by referring to two studies of heavily exposed military personnel in which no significant neurological differences were found between those exposed and those unexposed (Chesney, 1983; Lathrop et al., 1984). The authors also point out that no valid epidemiological evidence exists to support the relationship between 2,4-D and polyneuropathy.

One of the larger human studies criticized by Mattsson and Eisenbrandt is that by Singer et al. (1982). Conduction velocities of the median motor, median sensory, and sural nerves were measured in 56 workers involved in the manufacture of 2,4-D and 2,4,5-T. The control group consisted 25 subjects without exposure to phenoxy herbicides. Nerve conduction velocity (NCV) is considered to be an early indicator of neuropathy.

Results indicate that sural sensory and median motor nerve conduction velocities were significantly slower in the study versus control group. Duration of phenoxy herbicide manufacture employment was significantly correlated with slowing of sural nerve

velocity. Overall, 46% of the study group had some type of slowed nerve conduction velocity compared with 5% of the control group.

A recent area of study focus in humans has been reproductive effects associated with 2,4-D exposure. Lerda and Rizzi (1991) studied the reproductive function of 32 male farm sprayers who were exposed to 2,4-D. Significant changes in three male reproductive parameters (asthenospermia, necrospermia, teratospermia) were found in exposed workers. Over time, asthenospermia and necrospermia diminished but teratospermia (abnormal sperm) persisted.

3.4 CHRONIC TOXICITY

3.4.1 Dermal Toxicity

While there are two subchronic dermal studies available (section 3.3.1) no chronic dermal studies were found in the literature.

3.4.2 Oral Toxicity

A NOEL of 1 mg/kg/day for renal effects was established in a chronic feeding study on rats (USEPA, 1985e). The lowest effect level was 5 mg/kg/day. Hill and Carlisle (1947) fed rats diets containing 0, 50, or 100 mg/kg/day 2,4-D daily for 30 days. No adverse effects related to treatment were observed. Similarly, Bjorklund and Erne (1966) observed no detrimental effects on rats fed up to 1000 mg/kg 2,4-D amine salt daily for 10 months.

These findings do not support earlier findings (Rowe and Hymas, 1954) on rats fed 2,4-D. Groups of female rats were fed diets containing 0,100,300,1000, 3000, or 10000 mg/kg 2,4-D for 113 days. No adverse effects on growth, mortality, blood, body chemistry, or histopathology were noted at doses below 300 mg/kg. Food consumption and appearance were also normal in these groups. In the 1000 mg/kg group a depressed growth rate was noted, along with increased mortality and liver effects. All of the animals in the 3000 and 10000 mg/kg groups were sacrificed after 12 days for humane reasons. The NOEL in this study was 300 mg/kg or 15 mg/kg/day.

A higher NOEL of 1250 mg/kg or 62.5 mg/kg/day was established in a two year feeding study on rats. Animals were maintained on diets containing 0, 5, 25, 125, 625, or 1250 mg/kg 2,4-D. Adverse effects on blood, growth rate, mortality, or organ weights were not significantly different from controls.

A NOEL of 30 mg/kg/day was established for rats given 2,4-D acid by intubation (via a tube passed down the esophagus) five times weekly for four weeks at doseage levels of 0,3,10,30,100, or 300 mg/kg/day (Rowe and Hymas, 1954). Various systemic effects were seen among the 100 mg/kg/day groups and above. These include gastrointestinal irritation, decreased growth rates, and liver effects. At 300 mg/kg/day animals died shortly after strat of the test. At doseage levels of 30 mg/kg/day (the NOEL) and below there were no adverse effects observed on mortality, blood, biochemistry, body weight, or organ weights.

3.5 DEVELOPMENTAL/REPRODUCTIVE TOXICITY

Most tests conducted to evaluate reproductive and developmental toxicity of herbicides involve mouse, rat, or rabbit test populations (Table 16). Multigenerational studies are the generally accepted test protocol, and are designed to provide data on both maternal/paternal reproductive capabilities and offspring defects, development and growth.

To date, four reproductive studies have been conducted using 2,4-D. A three-generation study by Hansen, et al. (1971) determined the NOEL to be 500 ppm (25 mg/kg/day) in food for Osborne-Mendel rats. Groups of male and female rats were fed 0, 100, 500, and 1,500 ppm 2,4-D in food throughout their lifetimes. There were no effects on average litter size or fertility at any of the doses tested. The number of pups surviving until 21 days after birth was not affected at the 0, 100, or 500 ppm dose but was significantly decreased at the 1500 ppm dose.

A 1966 study by Bjorklund and Erne indicated that 1,000 ppm 2,4-D administered in drinking water to rats during pregnancy and continuing for an additional 10 months was not teratogenic to offspring, and did not affect fertility of the adults. However, offspring which were continued on 2,4-D treatment for 2 years exhibited general poor health, diarrhea, growth inhibition, and increased mortality. The dose of 1000 ppm is roughly equivalent to 35 mg/kg/day, based on the average daily water intake for rats.

Table 16. Summary of Mammalian Reproductive Studies for 2,4-Dichlorophenoxyacetic Acid (2,4D)[a/]

Type of Test		Effects				
Formulation Species	Nature of Exposure	NOEL	LEL	LD50	Comments	Reference
		mg/kg/day g.e.				
2,4-D (acid)						
Rat	Three-generation study. Groups of 20 females and 10 males maintained on diets containing 0, 100, 500 or 1,500 ppm through-out life; total of six litters produced by three successive generations	25	75	—	No apparent adverse effects on fertility or average litter size occurred at any of the doses tested. The viability index (number of pups surviving until 21 days post-partum) was significantly decreased at the 1,500 ppm level.	Hansen et al., 1971
Rat	Groups of 10 female rats fed dietary levels of 0, 1,000 or 2,000 ppm for 95 days, then mated to untreated males; treatment continued through gestation and location, approximately 7 additional weeks.	No NOEL	50	—	An increase in pup death was observed at both dosage levels tested.	Gaines and Kimbrough, 1970 in Hansen, 1971
Rat	Groups of 10 females rats receiving 0 or 1,000 ppm in drinking water during pregnancy and for 10 additional months.	35	—	—	No adverse effects reported.	Bjorklund and Erne, 1966

A third study, summarized by Hansen, et al. (1971) reported an increase in pup death from mothers fed 1,000 or 2,000 ppm 2,4-D for 95 days. After 95 days the treated females were mated to untreated males. Treatment of pregnant females continued after the birth of pups and until they were weaned. A NOEL could not be determined as effects occurred at both dosages.

3.6 TERATOGENIC EFFECTS

A fairly large database exists concerning teratogenic effects of 2,4-D in laboratory animals. The teratogenic potential of 2,4-D formulation varies with dose, route of administration and species and strain tested. Results of available teratology studies are summarized in Table 17.

In a 1973 study by Aleksashina et al. involved 76 female rats injected intraperitoneally with a dose of 2,4-D equal to half the LD_{50}. The rats were injected one time during various stages of gestation. The number of fetal resorptions and fetal mortality was significantly increased in the treated groups. Material toxicity consisted of myotonia, depressed activity, and a significant increase in abdominal hemorrhaging. In a follow-up study by the same group, rats were injected intraperitoneally with 0.1 or 0.5 mg/kg/day throughout gestation. Adverse effects were limited to decreased fetal weight in the 0.5 mg/kg/day dose group.

Several studies in which animals were administered 2,4-D via gavage are also reported in the literature. Collins and Williams (1971) administered 2,4-D acid via gavage to Syrian Golden Hamsters at dosage levels of 0, 20, 40, 60, or 100 mg/kg/day. Doses were given on days 6 through 10 of gestation. While there were some increases of unidentified abnormalities in the 60 and 100 mg/kg/day-dose groups, they were not statistically significant. A NOEL of 40 mg/kg/day was selected.

A similarly designed study by Rodwell et al. (1984) using Fischer 344 rats also reported no significant adverse effects (maternal or fetotoxic). Pregnant rats were administered 0, 8, 25, or 75 mg/kg/day of 2,4-D by gavage. No specific information as to number or type of anomalies was given, except that they were nonsignificant.

Table 17. Summary of Mammalian Teratology Studies for 2,4-Dichlorophenoxyacetic Acid (2,4-D)

Type of Test Formulation Species	Nature of Exposure	Effects NOEL	 LEL	 LD50	Comments	Reference
		mg/kg/day a.e.				
2,4-D (acid or isopropyl, butyl or osooctyl esters)						
Mouse	Unspecified daily doses administered either orally or subcutaneously or subcutaneously at days 6 to 14 of gestation, several strains of mice were tested.	—	—	—	There was a significant increased incidence of fetal anomalies in certain mouse strains (BL6, AKR, and A1Ha), while in other strains treatment had no effect. Interpretation of results was reported to be complicated by the fact that adverse effects appeared to be both strain and route specific, and DMSO had been used as the vehicle in parenteral administrations.	Bionetics Research Laboratory, 1970 in Young et al., 1978
Hamsters, Syrian Golden	Administered by gavage at dosage levels of 20, 40, 60 or 100 mg/kg/day from days 6 to 10 of gestation; 6 hamsters per dose.	100	—	—	No consistent fetotoxic or teratogenic effects observed; the percentage abnormalities per live litter was increased at 60 and 100 mg/kg/day, but not significantly different from control.	Collines and Williams, 1971
2,4-D (acid, or isooctyl, butyl or butoxy-ethanol esters)						
Rat	Daily oral (gavage) doses of the acid at 0,25,50,100 or 150 mg/kg/day from day 6 to 15 of gestation. M = maternal F = fetotoxic T = teratogenic	M: 150 F: 50 T: 50	— 100 100	— — —	No maternal toxicity at any dose, but fetotoxicity and teratogenicity increased at 100 and 150 mg/kg/day. The abnormalities not detected in the control group included fused ribs, distorted scapula, defects in the bones of both the forelimb and the hind limb, and micromelia. An increased incidence of spontaneously occurring anomalies, such as wavy ribs, additional ribs, and sternal defects, also occurred at 100 and 150 mg/kg/day levels. Interpretation of the results of this study were complicated by several factors.	Khera and McKinley, 1972

Table 17. Summary of Mammalian Teratology Studies for 2,4-Dichlorophenoxyacetic Acid (2,4-D)

Type of Test		Effects				
Formulation Species	Nature of Exposure	NOEL	LEL	LD50	Comments	Reference
2-4-D (acid)						
Rat, Fischer 344	Oral doses of 0, 8, 25 or 75 mg/kg/day from days 6 through 15 of gestation. M = maternal, F = fetotoxic, T = teratogenic	M: 25 F: 25 T: 25	75 75 —	— — —	No maternal or fetotoxic effects were observed at dosages of 25 mg/kg/day or less; no significant differences in the number or type at any level tested when compared to the control group; however, no specific information as to number or type was reported.	Rodwell et al., 1984
2,4-D (acid, propylene glycol butyl ether, or isooctyl ester)						
Rat	Oral (gavage) dosage levels of 0,12.5, 25, 50, 75 or 87.5 mg/kg/day (on an acid equivalent basis) on days 6 through 15 of gestation. M = maternal, F = fetotoxic, T = teratogenic.	M: 87.5 F: NO NOEL T: 87.5	— — —	— — —	No treatment-related maternal toxicity was observed. Gross anomalies, such as exencephaly, acaudate state, an umbilical hernia, were not significantly different from control, but the actual incidence in control or treated groups was not given. Fetotoxic effects, such as decreased fetal body weight and subcutaneous edema were increased at dosages of 50 mg/kg/day and above. Delayed ossification of skull bones was significantly increased at 12.5 mg/kg/day and above. Significant increases in the occurrence of wavy ribs and missing sternebrae occurred at the 87.5 mg/kg/day level, which significant increases in lumbar ribs occurred at 75 and 87.5 mg/kg/day. In addition, the percentage of hydrocephalus among the fetal populations was significantly increased at only the 50 mg/kg/day dosage level. The authors state that this response occurred in a single litter and was not treatment-related.	Schwetz et al., 1971
2,4-D (diethylamine salt)						

Table 17. Summary of Mammalian Teratology Studies for 2,4-Dichlorophenoxyacetic Acid (2,4-D)

Type of Test		Effects				
Formulation Species	Nature of Exposure	NOEL	LEL	LD50	Comments	Reference
Rat	Single intraperitoneal injection of 50% LD50 at various stages of gestation.	—	—	—	Treatment-related increases in fetal resorptions and live births; hemorrhaging into abdominal cavity observed.	Aleksashina et al., 1973
Rat	Repeated injections of 0.1 and 0.5 mg/kg/day throughout gestation.	0.1	0.5	—	Adverse effects limited to decreased fetal weight in the high dose group.	Aleksashina et al., 1973

A 1972 study by Khera and McKinley used slightly higher doses of 2,4-D acid (0, 25, 50, 100, or 150 mg/kg/day) and reported significant increases above control of skeletal defects in the 100 and 150 mg/kg/day groups. Skeletal abnormalities included fused or wavy ribs, distorted scapula, and fore- and hind-limb deformation. Sternal defects and additional ribs also occurred in the 100 and 150 mg/kg/day-dose groups. In this same study, groups of rats were dosed orally with 0, 50, or 150 mg/kg/day of 2,4-D isooctyl, butyl, or butoxyethanol esters from day 6 to 15 of gestation. The results of this study are difficult to interpret, as the overall incidence of malformations was statistically significantly elevated in the 25 mg/kg/day group but not the 50 mg/kg/day group (isooctyl 2,4-D). An elevation in malformations was also observed in the 25 and 50 mg/kg/day-dose groups using butyl and butoxyethanol 2,4-D.

Schwertz et al. (1971) also performed studies in which rats were dosed by gavage. 2,4-D and its esters (isooctyl) were administered to rats at dosage levels of 0, 12.5, 25, 50, 75, or 87.5 mg/kg/day on days 6 through 15 of gestation. Gross abnormalities (i.e., exencephaly, acaudate state) were not significantly elevated above control. The incidence of delayed ossification of skull bones was significantly increased above control at dosages of 12.5 mg/kg/day and above. Decreased fetal body weight and subcutaneous edema were significantly increased above control at dosages of 50 mg/kg/day and above. At 87.5 mg/kg/day and above, the occurrence of wavy ribs and missing sternebrae was significantly increased, and significant increases in lumbar ribs occurred in the 75 and 87.5 mg/kg/day groups. It is noted that the authors do not consider wavy ribs, missing sternebrae, or lumbar ribs to be teratogenic responses. Rather, they were considered to be fetotoxic responses. This study derived a NOEL of 25 mg/kg/day for teratogenic effects and a NOEL of 8 mg/kg/day for fetotoxic effects.

3.7 CUMULATIVE EFFECTS

[TO BE ADDED TO THE EIS]

3.8 CARCINOGENICITY REVIEW/EPIDEMIOLOGY REVIEW

The results of carcinogenicity and epidemiology studies regarding 2,4-D have led to much controversy among the scientific community. WHO has stated that the carcinogenic potential of 2,4-D has not been adequately tested, and that the reports to date on animal studies (summarized in Table 18) do not contain enough information to properly evaluate

Table 18. Summary of Mammalian Carcinogenicity Studies for 2,4-Dichlorophenoxyacetic acid (2,4-D)

Type of Test / Formulation Species	Nature of Exposure	Effects NOEL	LEL	LD50	Comments	Reference
CARCINOGENIC		mg/kg/day a.e.				
2,4-D (acid or isopropyl, n-butyl, and isooctyl esters)						
Mouse (C57BL/6xC3H/Anf)F_1 or (C57BL/6xAFR)F_1	Mice were administered by gavage doses of 46.4 or 100 mg/kg/day from 7 to 28 days, then maintained on diets containing 149 or 323 ppm 2,4-D until termination of the experiment at 78 weeks. Mice treated with isopropyl, n-butyl, or isooctyl esters were initially treated with 46.4 mg/kg/day for days 7 to 28, then fed diets containing 111, 149 or 130 ppm respectively, until termination at 78 weeks.	Highest Dose Treated	—	—	The tumor incidence in any group was not significantly different from that in control animals.	Innes et al., 1969
2,4-D (acid)						
Dog	Groups of male and female beagle dogs, three per sex dose group, were fed 0, 10, 50, 100 or 500 ppm 2,4-D in the diet for two years (equivalent to 0, 0.4, 2, 4 or 20 mg/kg/day).	20	—	—	Although _____ dog at the 500 ppm dosage level developed on adrenal hemangioma, the authors stated that there were no treatment-related lesions or tumors.	Hansen et al., 1971
Rat	Groups of 25 rats/sex/dose group were fed diets containing 0, 5, 25, 125, 625 or 1,250 ppm for two years (equivalent to 0, 0.25, 1.25, 6.25, 31.25 or 62.5 mg/kg/day)	31.25	62.5	—	No target organ tumors were observed and the individual tumor types, normally age-related in this strain, were randomly and widely distributed. A dose-related increase in total tumors and malignant tumors occurred in both male and females. Only the 1,250 ppm level in males showed a significant increase in the incidence of malignant tumors.	Hansen et al., 1971
Rat	Groups of 10 male and 12 female offspring of dams treated during pregnancy received 0 or 1,000 ppm in drinking water for two years (doses equivalent to 0 or 35 mg/kg/day).	35	—	—	No significant differences in hematology or clinical chemistry values or in pathology. Elevated mortality, decreased food and water intake, poor general condition observed in treated group.	Bjorklund and Erne, 1966

Table 18. Summary of Mammalian Carcinogenicity Studies for 2,4-Dichlorophenoxyacetic acid (2,4-D)

Type of Test		Effects				
Formulation Species	Nature of Exposure	NOEL	LEL	LD50	Comments	Reference
2,4-D (amine)						
Rat	Groups of 120 male and 45 female rats were fed diets containing no 2,4-D or levels equivalent to one-tenth the LD50 for 27 months.	—	—	—	No treatment-related adverse effects reported.	Archipov and Kozlova, 1974
Mice	Groups of 100 female mice were fed diets containing no 2,4-D or levels equivalent to one-tenth the LD50 for 27 months.	—	—	—	No treatment-related adverse effects reported.	Archipov and Kozlova, 1974

[a/] The NOEL, LEL and LD50s for 2,4-D formulations were expressed as the acid equivalent.
[b/] Information not available or applicable.

carcinogenicity (1984). The USEPA agreed with WHO, and classified it as a "D-not classifiable as to carcinogenicity" chemical. A weight of evidence category (WOEC) determines the likelihood that the chemical will cause cancer in humans according to the strength of the supporting human and/or animal data. The weight of evidence categories defined by EPA are presented below (USEPA, 1986):

Group A - Human Carcinogen
Group B - Probable Human Carcinogen
  Group B1 - At least limited evidence of carcinogenicity to humans
  Group B2 - A combination of sufficient evidence in animals and inadequate evidence in humans
Group C - Possible Human Carcinogen (limited evidence of carcinogenicity in animals in the absence of human data)
Group D - Not classifiable as to human carcinogenicity
Group E - Evidence of noncarcinogenicity in humans (no evidence in at least two adequate animal tests in different species or in both epidemiological and animal studies)

EPA ruled in March, 1988, that a special review of 2,4-D was not warranted. However, in October, 1989, EPA became aware of two epidemiologic studies (Zahm, 1990; Cantor, 1992) sponsored by the National Cancer Institute which were near completion that could impact the EPA decision. The last of these studies was released in May, 1992. EPA has convened a panel of experts to review these studies and plans to announce in April, 1993, its decision on conducting a special review. The implication of deciding for a special review is that evidence from the studies is compelling enough that it could lead to a change in the carcinogenicity classification for 2,4-D.

Chemical carcinogenesis is a complex process that makes epidemiologic investigation difficult. The latent period between exposure to the carcinogen and the development of recognizable disease is usually measured in decades. Repeated small doses of a carcinogen may be more hazardous than a single large dose. At each step in the carcinogenic process, from the initial DNA damage in a single cell to the development of a tumor, the process may be stopped by the body's immune mechanisms.

Carcinogens may act directly on the DNA of a cell (genotoxic carcinogens) or may act indirectly as promoters of tumor growth or as suppressors of the body's immune response to abnormal cells (epigenetic carcinogens). Some carcinogens act by both mechanisms. Genotoxic carcinogens may be effective after a single exposure, and the effects may be cumulative with repeated exposures, whereas most epigenetic carcinogens have effects only with repeated or high-dose exposures.

2,4-D is considered to be non-genotoxic and the mechanism by which it would exert a carcinogenic effect is unknown. Therefore, prolonged or high-dose exposure to 2,4-D may be required for carcinogenesis to occur.

Sources of Error in Epidemiologic Studies

Numerous epidemiologic studies of 2,4-D, including those sponsored by the National Cancer Institute, are available in the literature. Information on exposure to the potential carcinogenic agent is a crucial piece of information in an epidemiology study, the other being accurate diagnosis of the disease (O'Brien, 1984). Before a causal relationship can be defined between a disease and a chemical the actual incidence of disease and a realistic estimation of exposure must first be determined for both case and control groups. Precautions must be taken to avoid bias introduced when individuals answer questions inaccurately or when diseases are misdiagnosed. Assessments of exposure to a specific chemical are difficult because researchers must rely on the memories of subjects or relatives and because almost all exposures involve multiple chemicals.

Often, living relatives of a deceased person may be called upon to recall complex lifetime herbicide exposures. Thus, every epidemiological study has some sort of criticism associated with it. In addition, there exists a publishing bias, in which authors of studies are more likely to publish studies with positive result than those with negative results. Results that are significant are more likely to be published than those that are non-significant (McNamee, 1989).

There are two types of epidemiology studies: case-control and cohort. In case-control studies individuals with specific diseases are identified and comparable controls chosen, usually by means of interviews. Case-control studies have the advantage of being able to identify almost all cases of the disease of interest which is especially important when the disease is rare. The disadvantage is that exposures to the chemical of interest have

usually occurred years before and are subject to errors of recall. It is often impossible to separate exposure to the chemical of interest from exposures to other chemicals.

In a cohort study the experiences of an unexposed group from the general population are followed in comparison with an exposed group. Cohort studies offer the advantage of following a group of subjects with a specific exposure (i.e. workers in a pesticide plant). The disadvantages are that the number of subjects in the cohort may be too small to detect a rare disease and that it is difficult to follow a cohort for the length of time necessary to account for the latent period of chemical carcinogenesis.

These studies often employ a technique for expressing excess occurrence of disease called the "odds ratio," in which the number of cases of disease in an exposed group is divided by the number of cases in the control group. The odds ratio is also referred to as "relative risk." For example, an odds ratio (OR) of 2.4 indicates that the exposed group has a 2.4-fold increased risk of a disease over the control group. Standardized mortality ratio (SMR) is used to look at mortality rather than disease incidence and is calculated as the ratio of observed to expected deaths multiplied by 100, It is important to realize that even though the OR is high, if the confidence interval includes 1.0 (or, in the case of SMR, includes 100) the OR cannot be considered significantly elevated.

Epidemiologic Studies

Case Control Studies

Several well-designed studies were sponsored by NCI to determine if there is a link between herbicide use and three types of cancer: Hodgkin's disease, soft-tissue sarcoma, and non Hodgkin's lymphoma. A recent study of pesticide exposure and NHL in men from Iowa and Minnesota used personal interviews of 62 cases and 1,245 controls (Cantor, 1992). Significantly elevated risks were found for use of certain insecticides, and a small, non-significant increased risk was found for 2,4-D use (OR 1.2, 95% CI 0.9-1.6). There was no quantification of exposure in this study. The authors found no increase with latency or with failure to use protective equipment.

A population-based case-control study was conducted among Kansas farmers (Hoar, et al., 1986). Of all herbicides used by farmers in Kansas, 2,4-D is the most commonly used, along with substantial amounts of 2,4,5-T and other chemicals. Only histologically

confirmed cases were included in this analysis. Herbicide exposures were further defined by type of herbicide, years of use, days of exposure per year, and use of protective equipment. Types and amount of pesticides used by some of the subjects were corroborated by checking records of their pesticide suppliers. Smoking, caffeine intake, non-farming pesticide use, and concurrent immunosuppressive disease did not affect the risk.

The authors of this study report that farm herbicide use is associated with non-Hodgkin's lymphoma (OR = 1.6, 95% CI 0.9-2.6). Relative risk of non-Hodgkin's lymphoma (NHL) increased significantly with number of days of herbicide exposure per year and latency. Farm workers (men only surveyed) exposed to herbicides more than 20 days per year had an NHL odds ratio of 6.0 (95% CI 1.9-19.5). Farmers who began using herbicides prior to 1946 had an OR of 2.2 while those who began use after 1965 had an OR of 1.3. Risk was higher for those who did not use protective equipment (OR 2.1) than for those who did (OR 1.5). Use of 2,4-D exclusively was associated with an OR of 2.6 (95% CI 1.4-5.0). Controlling for concurrent insecticide use did not affect the OR for herbicide use. Neither soft tissue sarcoma nor Hodgkin's disease was associated with herbicide exposure.

The results of this study prompted the authors to undertake a similar population-based case-control study in Nebraska (Zahm et al., 1990). This study evaluated the role of 2,4-D in the development of non-Hodgkin's lymphoma (NHL) among people residing in 66 counties in Nebraska. The study involved 201 white men diagnosed with NHL between July 1, 1983 and June 30, 1986 and with 725 controls. Only people with histologically confirmed cases of NHL were included.

There was a non-significant 50% excess of NHL among men who mixed or applied 2,4-D (OR = 1.5), 95% CI 0.9-2.5). Among those exposed to 2,4-D for 20 or more days per year the risk of NHL increased threefold (OR = 3.3; 95% CI 0.5-22.1). Although the individual OR were not significant, the trend of higher OR with increasing days of exposure was significant (ρ for trend = .051). Risk also increased with degree of exposure, as measured by time spent in contaminated clothing and application method, but not with number of years of use. The lack of association between risk and number of years of use is consistent with the Kansas study. Risk increased substantially among those men who usually waited to change into clean clothes after handling or using pesticides. Farmers who changed immediately, at the end of the workday, or who wore

the clothes for more than one day had odds ratios of 1.1, 1.5, and 4.7, respectively (ρ for trend = 0.15). Risk was unaffected by the use or lack of use of personal protective equipment.

This study also investigated the histology, tumor grade, degree of maturation, and immunologic type of NHL associated with 2,4-D exposure. Exposure to 2,4-D did not appear to be specific to any subgroup of NHL. Adjusting for use of organophosphate insecticides decreased the risk from 2,4-D while adjusting for fungicide use increased the risk. The authors conclude, based on this study and their previous Kansas study (Hoar-Zahm et al., 1986) that the use of 2,4-D in an agricultural setting increases the risk of NHL among persons who handle the 2,4-D frequently.

This study is in agreement with reports from Sweden of a link between NHL and farm herbicides, specifically phenoxyacetic acid herbicides. Hardell and Sandstrom (1979) reported a case control study in which the odds ratio of soft tissue sarcoma was 5.3 in those exposed to phenoxy herbicides in agriculture and farming. These findings were confirmed by Hardell (1981).

Eriksson et al (1981) report the results of another study focussing on a different group of workers in south Sweden. Persons exposed to non- 2,4,5-T phenoxy herbicides, including 2,4-D, have a relative risk of 4.2 of having soft tissue sarcoma.

Two studies were conducted in New Zealand, a country in which phenoxyacetic acids are used extensively. A 1984 study by Smith et al found that the odds ratio of soft tissue sarcoma for those potentially exposed to phenoxy herbicides (one day/year but not in the five years before cancer registration with the county) was 1.3. A second New Zealand study (Pearce et al, 1986) examined occurrence of non-Hodgkin's lymphoma among two groups of people: those who had ever sprayed an agricultural chemical involving phenoxyacetic acid herbicides, and those using any agricultural spray. The odds ratios was 1.5 for those using any agricultural spray. The relative risk was 1.3 for cancer controls and 1.6 for population controls for those who ever sprayed a phenoxyacetic acid herbicide containing chemical. Both of these studies demonstrate a small, though not significant, elevation of risk. Both cases and controls were restricted to those from public hospitals, and the interview process appeared to be less specific and extensive than that used in the Swedish studies. This may have contributed to the relatively low odds ratio in both studies (Canadian Centre for Toxicology 1987).

Vineis et al (1987) studied soft tissue sarcomas among men and women in northern Italy. The herbicides to which workers were exposed included 2,4-D, MCPA, and 2,4,5-T. No excess risk of cancer associated with phenoxyacetic acid herbicide exposure was found for men. However, the relative risk among living women was 2.7. When the comparison group was restricted to women alive at the time of interview (1981-83), less than 75 years old, and exposed during the period 1950-1955 the age adjusted odds ratio was 15.5 (90% CI 1.3-180). These women had been employed as rice weeders during a period starting in 1950 in which phenoxy herbicides were being used experimentally to control weeds. When only those living women who had regular jobs in agriculture were considered the age adjusted odds ratio was 3. This study was limited by low statistical power and the lack of a dose-response evaluation.

Recently a case-control study was conducted in the state of Washington (Woods et al, 1987) which included 128 cases of soft tissue sarcoma, 575 of non-Hodgkin's lymphoma, and 694 population controls. All data were obtained by personal interview, as opposed to telephone or next of kin interviews. There was no excess risk of NHL or STS for people with past occupational exposure to phenoxy herbicides. However, there was an elevated risk of NHL among several subgroups. Men who had been farmers had a relative risk of 1.33 (95% CI 1.03-1.7), while forestry herbicide applicators had a relative risk of 4.8 (95% CI 1.2-19.4). Those potentially exposed to phenoxy herbicides in any occupation for 15 years or more during the period prior to 15 years before cancer diagnosis had a statistically significant relative risk of 1.71. An increased risk of both STS and NHL was observed among those who had previous occurrence of chloracne, a chemically induced skin rash.

A 1990 study by Brown et al focused on farmers in Iowa and Minnesota who had used herbicides and/or insecticides. Analyses showed a small but significant risk for all leukemias (OR = 1.2, 95% CI 1.0-1.5) among persons who lived or worked on a farm as an adult. Significantly elevated risks were also seen for chronic lymphocytic leukemia among farmers (OR = 1.4, 95% CI 1.1-1.9)) compared to non-farmers. The authors then analyzed leukemia occurrence among farmers who reported using different classes of herbicides, one of which was phenoxy acids (2,4-D and 2,4,5-T). There were no significantly elevated increases in leukemia among this group (OR=1.2, 95% CI 0.9-1.6). There were non-significant excesses for specific leukemia cell types but no evidence of a dose-response effect. Interestingly, there was a significantly increased risk

for leukemia (OR = 1.9, 95% CI 1.3-2.9) among farmers who reported no exposure to pesticides. This finding was seen only among the Iowa group.

All of these studies have the potential for misclassifying subjects in regard to pesticide exposure because of difficulty in recalling information by subjects or inaccurate information given by next-of-kin. However, this type of misclassification is likely to be "random" (affecting cases and controls equally) which would tend to underestimate an association if one exists.

Cohort Studies

As in the case control studies there are few groups who are known to have been exposed exclusively to 2,4-D. In the majority of cases exposure has included both 2,4-D and 2,4,5-T, thus it may not be clear as to which agent is responsible. Thus, the most informative studies are those on workers involved in the manufacture of specific chemicals.

One study in Denmark (Lynge, 1985) followed 3,844 workers in one manufacturing plant and 615 in another. The workers had been employed from 1947 and 1951 respectively were followed until December 31, 1982. Exposure was largely to 2,4-D although a small amount of 2,4,5-T was manufactured in the larger plant between 1951 and 1959. This study showed an excess of soft tissue sarcomas, the only cohort study to do so. When only those cases in which the latency periods exceeded 10 years were examined there were 4 observed with 1.09 expected. When the same analysis was completed for malignant lymphomas a non-significant increase was observed (4 observed, 3.04 expected). However, it can not be concluded that either of these increases were due to 2,4-D as workers were also exposed to 2,4,5-T.

Bond et al. (1988) studied all causes of mortality in a cohort of 878 Dow Chemical employees who were potentially exposed to 2,4-D between 1945 and 1983. The employees were potentially exposed in any of four separate buildings in which 2,4-D was manufactured, esterified, aminated, formulated, or packaged. The study was designed to determine whether or not cancer or other causes of death had occurred excessively and in relation to exposure. Since a subject may have cancer but die from another condition, a study of cancer mortality would tend to underestimate the risk of developing cancer. Exposures were estimated using historical plant 2,4-D air monitoring data and employee

work histories. A total of 111 deaths were identified among the 878 cohort members. This study employed a standardized mortality ratio (SMR) which was calculated as the ratio of observed to expected deaths multiplied by 100.

The SMR for all causes of death was 100. There was a non-significant increase in mortality (SMR=115) from malignant neoplasms. Non-significant excesses were noted for cases of cancer of the large intestine (SMR=212, 95% CI 57-544) and lymphatic and hematopoietic cancer (SMR=202, 95% CI 65-472). An analysis of mortality was also completed allowing for a latency period of 15 years, thus eliminating from the analysis all persons exposed after 1967. There was no significant effect on the mortality patterns described above. When the analysis was limited to the 2,4-D production area, the SMR for lymphopoietic cancer was 312, which was statistically significant. There was no apparent relationship with cumulative dose of 2,4-D, however.

Every other cohort study reported to date has been negative. A small cohort study of Swedish railroad workers exposed to herbicides at least 40 days per year revealed no soft tissue sarcomas or non-Hodgkin's lymphoma in the group (Axelson and Sundell, 1974; Axelson et al., 1980). However, an excess of stomach cancer (2 cases vs 0.33 expected) was noted among those workers exposed to phenoxy herbicides or phenoxy herbicides plus amitrole. The small number of workers (348) involved in the study renders it lacking in power to clearly indicate the role of herbicides in these cancers.

In Finland 1,971 male herbicide applicators who were exposed to 2,4-D and 2,4,5-T at least two weeks per year from 1955 to 1971 were followed until 1980. There were no excess cancers, STS, or NHL reported (Riihimaki, et al., 1982). A Canadian study (Green, 1986) focused on Hydro plant workers exposed to phenoxy herbicides, and reported that no cases of STS or NHL were identified. This study has the potential for prolonged follow-up although exposures included herbicides other than 2,4-D.

The results of a very large study in Sweden were published in 1986 by Wiklund and Holm. A cohort of 354,620 men born between 1891 and 1940 who were identified as agricultural or forestry workers were studied. A reference cohort of nearly 2 million men having other occupations was also followed, from 1961 through 1979. The cohort was divided into subgroups based on occupation and presumed herbicide exposure. Although large numbers of soft tissue sarcomas occurred, there was no significant excess in any of the subgroups. Relative risks ranged from 0.9 to 1.0.

A 1991 study by Coggon et al. studied four British cohorts of chemical manufacturers comprising a total of 2,239 men employed during 1963-85. The subjects were traced from 31 December 1987 to 1990. Exposures were to phenoxyherbicides and related chlorophenols, and dioxins. Levels of exposure to specific chemicals could not be estimated. Non-significant increases in lung cancer were observed for all cohorts, as was an overall increase in death from all causes. The latter increase was probably due to an excess of circulatory diseases and deaths from injury and poisoning (Coggon et al., 1991). There were no deaths from Hodgkin's disease or soft tissue sarcoma. A non-significant increase in deaths due to non-Hodgkin's lymphoma was reported.

Reviews of Epidemiology Studies

To date, three review papers have been published in which epidemiology data from previous studies is critically re-evaluated. In their 1989 paper, Bond et al. reviewed all available cohort and case-control studies published up to 1987. The authors created graphs of the probability densities for the odds ratios from the eight case-control studies of soft tissue sarcoma (STS), Hodgkin's disease (HD) or non-Hodgkin's lymphoma (NHL). The results demonstrate gross inconsistencies which are not attributable to chance. The combined results of the cohort studies of workers exposed to phenoxy herbicides provide little or no evidence of carcinogenicity (Bond et al., 1989), and do not support a conclusion that phenoxyherbicides present a carcinogenic hazard to humans.

A 1990 paper by Johnson et al reviewed epidemiology studies found in the literature between 1979 and 1987, which focused on the association between phenoxy herbicides and chlorophenols and soft tissue sarcoma (STS). Cohort studies and case control studies were considered separately. The authors concluded that the case-control studies, with the exception of the earliest reports, do not support a chemical-disease association. The cohort studies give inconclusive results, confirming the 1989 review by Bond et al.

The latest review of studies is provided by Ibrahim et al. (1991). This study contains the results of a panel convened at the Harvard School of Public Health, funded by the Industry Task Force II on 2,4-D Research. After review (no statistical analysis involved) of all available toxicology and epidemiology data the panel agreed that the data do not provide a strong basis for predicting that 2,4-D is a human carcinogen. The panel also concluded that there is little epidemiological evidence for an association between 2,4-D

use and STS or HD. However, they state that the evidence for an association between 2,4-D use and non-Hodgkin's lymphoma is suggestive and requires further investigation.

Discussion

It is possible that the vast differences in study findings may in part be due to differences in spraying practices. For example, spraying in Sweden is usually carried out intensively over a two to three month period, whereas spraying in Washington State and New Zealand occurs over a longer period. These differences may result in Swedish herbicide sprayers receiving a relatively high dose. Pearce (1989) reviewed studies from Sweden, New Zealand, and the U.S.A. and concluded that this difference in frequency of phenoxy herbicide use may account for the differences in relative risk estimates obtained in these studies.

Although the exposures in the case-control studies were relatively short-term (<30 days per year), they were often repeated on a yearly basis. Exposures in the pesticide manufacturing cohort studies were chronic and long-term. It is likely that a weed-spraying program would cause short-term and possibly repeated exposures which would resemble those in the case-control studies. It is unlikely that any member of the general public would be exposed to as large a dose as the farmers in these studies were.

These studies almost exclusively examined the risks to men since men have more occupational exposure to 2,4-D. The one study which did involve women (Vineis, 1987) showed a non-significant increased risk and suffered from low statistical power. The risk to women and children who could be exposed to 2,4-D by a weed-spraying program is unknown.

Most of these studies involved exposure to multiple chemicals, although there were attempts to separate out the effects of 2,4-D in some of the studies. In the past, many of these herbicides contained significant amounts of TCDD, a known potent carcinogen. Therefore it is impossible to know how much of the apparent risk form 2,4-D is actually due to contaminants or to concurrent exposures to other chemicals.

Although there is conflicting epidemiological evidence and no animal evidence of the carcinogenicity of 2,4-D, the positive findings of some of the studies, including some evidence of a dose-response relationship, are cause for concern. The International

Agency for Research on Cancer (IARC) is currently compiling data from a large cohort survey of pesticide manufacturing workers. In view of these studies, it is likely that the EPA will recommend a special review of 2,4-D which could lead to a change in its carcinogenicity classification. The uncertainty of the status of 2,4-D should be considered in any decision about its use.

4.0 RISK ANALYSIS

4.1 APPROACH FOR DETERMINING RISKS

The evaluation of potential risk of non-carcinogenic effects is usually evaluated by comparing an environmental dose to a reference, or "safe" dose. Under the reference dose (RfD) approach uncertainty factors are added to the lowest NOEL dose reported in animal studies. An uncertainty factor of 10 is generally used to estimate a safe human exposure level from experimental studies when there is no indication of carcinogenicity and valid human studies are available. A more conservative uncertainty factor of 100 is supplied when there are few or no valid human studies available but there are valid long-term animal studies.

Thus, the RfD represents a lifetime "safe" dose for protection against threshold (non-carcinogenic) health effects. The EPA promulgated RfD for 2,4-D is derived from a study in which liver, kidney, and blood disorders were produced in rats dosed orally. The oral RfD is converted to a dermal RfD when evaluating dermal exposure according to USEPA guidance (USEPA, 1992).

In the RfD method, hazard quotients are calculated for each exposure papthway by dividing the chronic daily intake by the RfD. Hazard quotients are then summed to obtain a hazard index. A hazard quotient of "1" indicates that the chronic daily intake is the same as the RfD (the level of exposure below which adverse health effects are unlikely to occur for even sensitive populations). Thus, the greater the value of the chronic daily intake/RfD ration, the greater the level of concern. Hazard quotients should not be interpreted as statistical probabilities. A hazard quotient of 0.001 does not mean that there is a one in one thousand chance of an effect occurring.

A similar method, the Margin of Safety (MOS) approach was used to evaluate acute exposures. In this approach NOEL's from animal toxicity studies for specific toxics effects, such as reproduction, systemic, or teratogenic effects are compared to estimated human doses. This method allows the risk assessor to use a variety of "safe" doses specific to each human route of exposure. The RfD approach was not used for single acute exposures as the RfD is designed to be protective of long term, chronic exposures.

The MOSs computed in this risk assessment are direct comparisons of NOELs and LELs from animal studies to estimated doses. Thus, the lower the MOSs, the greater the risk of toxic effects occurring (indirect contact to the RfD approach). For example, an MOS of 1,000 means the laboratory determined "safe" dose is 1,000 times higher than the estimated human dose. The standard margin of safety is 100 (Shipp et al., 1986)). A margin of safety greater than 100 is considered to represent negligible risk, and a margin of safety less than 100 is considered to represent a risk of toxic effects. MOS's are meant to be general indicators of potential risk.

NOELs and LELs used to calculate margins of safety are taken from three animal studies. Shipp et al. (1986) provided an excellent review of available mammalian toxicity data and chose three toxic endpoints to estimate risk: systemic toxicity, reproductive effects and teratogenic effects. Table 19 summarizes the studies and resulting NOEL's and LEL's.

4.2 PROJECTED NONCARCINOGENIC RISKS

Acute Exposures

Noncarcinogenic risks for each acute exposure pathway are summarized in Tables 20 through 23. MOSs for every pathway and scenario except dermal contact with vegetation are greater than 1,000, ranging up to over 1×10^{11} for all pathways, indicating that there is essentially no risk of these effects occurring. The lowest MOS (167) occurred in the high dose, dermal contact with vegetation scenario. If interpreted in light of the fact that the standard default USEPA safety factor for extrapolation from laboratory animal "safe" doses to human "safe" doses is 100, the MOS is acceptable.

Margins of safety are also consistently lower (i.e., higher risk) for all pathways in scenario 2:irrigation ditch due to the high sediment and water concentrations predicted. All MOSs rapidly increase with increasing days after application, and should be interpreted in light of the uncertainties discussed in Section 5.0.

Noncarcinogenic effects for chronic exposures are summarized in Table 24. Hazard quotients range from 3E-01 to 8E-10 for all exposure pathways and scenarios. Hazard quotients less than "1" indicate that the chronic daily intake is lower than the USEPA reference or "safe" dose (RfD). The cumulative hazard index, in which hazard quotients

Table 19. NOEL and LEL Used to Calculate Margins of Safety for Noncarcinogenic Effects Resulting from Exposure to 2,4-D.

Effect	Study	NOEL	LEL	Reference
		mg/kg-day		
Systemic Toxicity	Subchronic-oral-rats. Fed diets containing 0, 1, 5, 15, 45 mg/kg/day for 90 days.	--	1[a/]	EPA, 1964
Reproductive	Three generation study-rats. Groups of 20 females and 10 males maintained on diets containing 0, 100, 500, or 1,500 ppm throughout life; total of six litters produced by three successive generations (doses equivalent to 0, 5, 25, or 75 mg/kg/day).	25	75[b/]	Hansen et al., 1971
Teratogenic	Oral (gavage) rat dosage levels of 0, 12.5, 25, 50, 75, or 87.5 mg/kg/day (on an acid equivalent basis) on days 6 through 15 of gestation.	25	50[c/]	Schwetz et al., 1971

a/ Altered histopathology in renal cortical tubles occurred at the lowest dose tested.

b/ Decrease viability index (number of pups surviving until 21 days postpartum) at 75 mg/kg/day.

c/ At 50 mg/kg/day level, increased incidence in hydrocephalus occurred in 7/69 fetuses (1/13 litters). Authors concluded that incidence was not treatment-related, but for this worst case analysis, it will be considered. The NOEL reported by the authors was 87.5 mg/kg/day.

Adapted from Shipp et al., 1986.

Table 20 - Margins of Safety for Various Effects from a Single Exposure to 2,4-D Through Dermal Contact with Vegetation

Days After Application	Single Human Dose (mg/kg)		MOS Systemic Effects NOEL = 1mg/kg/day		MOS Reproductive and Teratogenic Effects NOEL = 25 mg/kg/day	
	Amine (low dose)	Amine (high dose)	Amine (low dose)	Amine (high dose)	Amine (low dose)	Amine (high dose)
Immediately	1.50E-03	6.00E-03	667	167	16667	4167
1	NA	NA	NA	NA	NA	NA

Table 21. Margins of Safety for Various Effects from a Single Exposure to 2,4-D Through Dermal Contact with Water (Swimming).

Scenario 1 : Small Pond

Days After Application	Single Human Dose (mg/kg)		MOS Systemic NOEL = 1 mg/kg/day		MOS Reproductive/ Teratogenic Effects NOEL = 25 mg/kg/day	
	Amine	Ester	Amine	Ester	Amine	Ester
Immediately	4.93E-08	1.13E-05	2.03E+07	8.85E+04	5.07E+08	2.21E+06
1	4.63E-08	1.06E-05	2.16E+07	9.47E+04	5.40E+08	2.37E+06
2	4.34E-08	9.92E-06	2.30E+07	1.01E+05	5.76E+08	2.52E+06
3	4.08E-08	9.31E-06	2.45E+07	1.07E+05	6.13E+08	2.68E+06
4	3.83E-08	8.74E-06	2.61E+07	1.14E+05	6.53E+08	2.86E+06
5	3.60E-08	8.21E-06	2.78E+07	1.22E+05	6.95E+08	3.05E+06
6	3.38E-08	7.71E-06	2.96E+07	1.30E+05	7.40E+08	3.24E+06
7	3.17E-08	7.24E-06	3.16E+07	1.38E+05	7.89E+08	3.45E+06
8	2.98E-08	6.80E-06	3.36E+07	1.47E+05	8.40E+08	3.68E+06
9	2.80E-08	6.38E-06	3.58E+07	1.57E+05	8.94E+08	3.92E+06
10	2.62E-08	5.99E-06	3.81E+07	1.67E+05	9.53E+08	4.17E+06
11	2.46E-08	5.63E-06	4.06E+07	1.78E+05	1.01E+09	4.44E+06
12	2.31E-08	5.28E-06	4.32E+07	1.89E+05	1.08E+09	4.73E+06
13	2.17E-08	4.96E-06	4.60E+07	2.02E+05	1.15E+09	5.04E+06
14	2.04E-08	4.66E-06	4.91E+07	2.15E+05	1.23E+09	5.37E+06
15	1.92E-08	4.37E-06	5.22E+07	2.29E+05	1.31E+09	5.72E+06
16	1.80E-08	4.10E-06	5.56E+07	2.44E+05	1.39E+09	6.09E+06
17	1.69E-08	3.85E-06	5.92E+07	2.59E+05	1.48E+09	6.49E+06
18	1.59E-08	3.62E-06	6.31E+07	2.76E+05	1.58E+09	6.91E+06
19	1.49E-08	3.40E-06	6.72E+07	2.94E+05	1.68E+09	7.36E+06
20	1.40E-08	3.19E-06	7.16E+07	3.13E+05	1.79E+09	7.84E+06
21	1.31E-08	3.00E-06	7.62E+07	3.34E+05	1.91E+09	8.35E+06
22	1.23E-08	2.81E-06	8.12E+07	3.56E+05	2.03E+09	8.89E+06

Table 21 cont'd. Margins of Safety for Various Effects from a Single Exposure to 2,4-D Through Dermal Contact with Water (Swimming).

Scenario 2: Irrigation Ditch

Days After Application	Single Human Dose (mg/kg)		MOS Systemic NOEL = 1 mg/kg/day		MOS Reproductive/ Teratogenic Effects NOEL = 25 mg/kg/day	
	Amine	Ester	Amine	Ester	Amine	Ester
Immediately	6.57E-07	1.44E-04	1.52E+06	6.94E+03	3.81E+07	1.74E+05
1	6.17E-07	1.35E-04	1.62E+06	7.39E+03	4.05E+07	1.85E+05
2	5.79E-07	1.27E-04	1.73E+06	7.87E+03	4.32E+07	1.97E+05
3	5.44E-07	1.19E-04	1.84E+06	8.38E+03	4.60E+07	2.10E+05
4	5.11E-07	1.12E-04	1.96E+06	8.93E+03	4.89E+07	2.23E+05
5	4.80E-07	1.05E-04	2.09E+06	9.51E+03	5.21E+07	2.38E+05
6	4.50E-07	9.88E-05	2.22E+06	1.01E+04	5.55E+07	2.53E+05
7	4.23E-07	9.27E-05	2.37E+06	1.08E+04	5.91E+07	2.70E+05
8	3.97E-07	8.71E-05	2.52E+06	1.15E+04	6.30E+07	2.87E+05
9	3.73E-07	8.18E-05	2.68E+06	1.22E+04	6.71E+07	3.06E+05
10	3.50E-07	7.68E-05	2.86E+06	1.30E+04	7.14E+07	3.26E+05
11	3.29E-07	7.21E-05	3.04E+06	1.39E+04	7.61E+07	3.47E+05
12	3.09E-07	6.77E-05	3.24E+06	1.48E+04	8.10E+07	3.69E+05
13	2.90E-07	6.35E-05	3.45E+06	1.57E+04	8.63E+07	3.93E+05
14	2.72E-07	5.97E-05	3.68E+06	1.68E+04	9.19E+07	4.19E+05
15	2.55E-07	5.60E-05	3.92E+06	1.79E+04	9.79E+07	4.46E+05
16	2.40E-07	5.26E-05	4.17E+06	1.90E+04	1.04E+08	4.75E+05
17	2.25E-07	4.94E-05	4.44E+06	2.03E+04	1.11E+08	5.06E+05
18	2.11E-07	4.64E-05	4.73E+06	2.16E+04	1.18E+08	5.39E+05
19	1.98E-07	4.35E-05	5.04E+06	2.30E+04	1.26E+08	5.74E+05
20	1.86E-07	4.09E-05	5.37E+06	2.45E+04	1.34E+08	6.12E+05
21	1.75E-07	3.84E-05	5.72E+06	2.61E+04	1.43E+08	6.51E+05
22	1.64E-07	3.60E-05	6.09E+06	2.77E+04	1.52E+08	6.94E+05

Table 21 cont'd. Margins of Safety for Various Effects from a Single Exposure to 2,4-D Through Dermal Contact with Water (Swimming).

Scenario 3: Large Lake

Days After Application	Single Human Dose (mg/kg)		MOS Systemic NOEL = 1 mg/kg/day		MOS Reproductive/ Teratogenic Effects NOEL = 25 mg/kg/day	
	Amine	Ester	Amine	Ester	Amine	Ester
Immediately	7.89E-10	1.41E-07	1.27E+09	7.09E+06	3.17E+10	1.77E+08
1	7.40E-10	1.32E-07	1.35E+09	7.57E+06	3.38E+10	1.89E+08
2	6.95E-10	1.24E-07	1.44E+09	8.07E+06	3.60E+10	2.02E+08
3	6.53E-10	1.16E-07	1.53E+09	8.59E+06	3.83E+10	2.15E+08
4	6.13E-10	1.09E-07	1.63E+09	9.15E+06	4.08E+10	2.29E+08
5	5.75E-10	1.03E-07	1.74E+09	9.74E+06	4.34E+10	2.44E+08
6	5.40E-10	9.64E-08	1.85E+09	1.04E+07	4.63E+10	2.59E+08
7	5.07E-10	9.05E-08	1.97E+09	1.11E+07	4.93E+10	2.76E+08
8	4.76E-10	8.49E-08	2.10E+09	1.18E+07	5.25E+10	2.94E+08
9	4.48E-10	7.98E-08	2.23E+09	1.25E+07	5.58E+10	3.13E+08
10	4.20E-10	7.49E-08	2.38E+09	1.34E+07	5.95E+10	3.34E+08
11	3.94E-10	7.03E-08	2.54E+09	1.42E+07	6.34E+10	3.56E+08
12	3.70E-10	6.60E-08	2.70E+09	1.51E+07	6.75E+10	3.79E+08
13	3.48E-10	6.20E-08	2.88E+09	1.61E+07	7.19E+10	4.03E+08
14	3.26E-10	4.77E-08	3.06E+09	2.10E+07	7.66E+10	5.25E+08
15	3.06E-10	5.46E-08	3.26E+09	1.83E+07	8.16E+10	4.57E+08
16	2.88E-10	5.13E-08	3.48E+09	1.95E+07	8.69E+10	4.87E+08
17	2.70E-10	4.82E-08	3.70E+09	2.08E+07	9.25E+10	5.19E+08
18	2.54E-10	4.52E-08	3.94E+09	2.21E+07	9.86E+10	5.53E+08
19	2.38E-10	4.25E-08	4.20E+09	2.35E+07	1.05E+11	5.89E+08
20	2.24E-10	3.99E-08	4.47E+09	2.51E+07	1.12E+11	6.27E+08
21	2.10E-10	3.74E-08	4.76E+09	2.67E+07	1.19E+11	6.68E+08
22	1.97E-10	3.52E-08	5.07E+09	2.84E+07	1.27E+11	7.11E+08

Table 22. Margins of Safety for Various Effects from a Single Exposure to 2,4-D Through Dermal Contact with Sediments.

Scenario 1: Small Pond

Days After Application	Single Human Dose (mg/kg)		MOS Systemic Effects NOEL = 1mg/kg/day		MOS Reproductive/ Teratogenic Effects NOEL = 25 mg/kg/day	
	Amine	Ester	Amine	Ester	Amine	Ester
Immediately	7.34E-09	4.46E-07	1.36E+08	2.24E+06	3.41E+09	5.61E+07
1	7.26E-09	4.41E-07	1.38E+08	2.27E+06	3.44E+09	5.67E+07
2	7.17E-09	4.36E-07	1.39E+08	2.30E+06	3.48E+09	5.74E+07
3	7.09E-09	4.31E-07	1.41E+08	2.32E+06	3.53E+09	5.81E+07
4	7.01E-09	4.26E-07	1.43E+08	2.35E+06	3.57E+09	5.87E+07
5	6.93E-09	4.21E-07	1.44E+08	2.38E+06	3.61E+09	5.94E+07
6	6.85E-09	4.16E-07	1.46E+08	2.40E+06	3.65E+09	6.01E+07
7	6.77E-09	4.11E-07	1.48E+08	2.43E+06	3.69E+09	6.08E+07
8	6.69E-09	4.06E-07	1.49E+08	2.46E+06	3.73E+09	6.15E+07
9	6.62E-09	4.02E-07	1.51E+08	2.49E+06	3.78E+09	6.22E+07
10	6.54E-09	3.97E-07	1.53E+08	2.52E+06	3.82E+09	6.30E+07
11	6.47E-09	3.93E-07	1.55E+08	2.55E+06	3.87E+09	6.37E+07
12	6.39E-09	3.88E-07	1.56E+08	2.58E+06	3.91E+09	6.44E+07
13	6.32E-09	3.84E-07	1.58E+08	2.61E+06	3.96E+09	6.52E+07
14	6.25E-09	3.79E-07	1.60E+08	2.64E+06	4.00E+09	6.59E+07
15	6.17E-09	3.75E-07	1.62E+08	2.67E+06	4.05E+09	6.67E+07
16	6.10E-09	3.71E-07	1.64E+08	2.70E+06	4.10E+09	6.75E+07
17	6.03E-09	3.66E-07	1.66E+08	2.73E+06	4.14E+09	6.83E+07
18	5.96E-09	3.62E-07	1.68E+08	2.76E+06	4.19E+09	6.91E+07
19	5.89E-09	3.58E-07	1.70E+08	2.79E+06	4.24E+09	6.99E+07
20	5.83E-09	3.54E-07	1.72E+08	2.83E+06	4.29E+09	7.07E+07
21	5.76E-09	3.50E-07	1.74E+08	2.86E+06	4.34E+09	7.15E+07
22	5.69E-09	3.46E-07	1.76E+08	2.89E+06	4.39E+09	7.23E+07

Table 22 cont'd. Margins of Safety for Various Effects from a Single Exposure to 2,4-D Through Dermal Contact with Sediments.

Scenario 2: Irrigation Ditch

Days After Application	Single Human Dose (mg/kg)		MOS Systemic Effects NOEL = 1mg/kg/day		MOS Reproductive/ Teratogenic Effects NOEL = 25 mg/kg/day	
	Amine	Ester	Amine	Ester	Amine	Ester
Immediately	1.15E-07	5.93E-06	8.67E+06	1.69E+05	2.17E+08	4.22E+06
1	1.14E-07	5.86E-06	8.77E+06	1.71E+05	2.19E+08	4.27E+06
2	1.13E-07	5.79E-06	8.87E+06	1.73E+05	2.22E+08	4.32E+06
3	1.11E-07	5.72E-06	8.97E+06	1.75E+05	2.24E+08	4.37E+06
4	1.10E-07	5.66E-06	9.08E+06	1.77E+05	2.27E+08	4.42E+06
5	1.09E-07	5.59E-06	9.18E+06	1.79E+05	2.30E+08	4.47E+06
6	1.08E-07	5.53E-06	9.29E+06	1.81E+05	2.32E+08	4.52E+06
7	1.06E-07	5.47E-06	9.40E+06	1.83E+05	2.35E+08	4.57E+06
8	1.05E-07	5.40E-06	9.51E+06	1.85E+05	2.38E+08	4.63E+06
9	1.04E-07	5.34E-06	9.62E+06	1.87E+05	2.40E+08	4.68E+06
10	1.03E-07	5.28E-06	9.73E+06	1.89E+05	2.43E+08	4.74E+06
11	1.02E-07	5.22E-06	9.84E+06	1.92E+05	2.46E+08	4.79E+06
12	1.00E-07	5.16E-06	9.96E+06	1.94E+05	2.49E+08	4.85E+06
13	9.93E-08	5.10E-06	1.01E+07	1.96E+05	2.52E+08	4.90E+06
14	9.81E-08	5.04E-06	1.02E+07	1.98E+05	2.55E+08	4.96E+06
15	9.70E-08	4.98E-06	1.03E+07	2.01E+05	2.58E+08	5.02E+06
16	9.59E-08	4.93E-06	1.04E+07	2.03E+05	2.61E+08	5.08E+06
17	9.48E-08	4.87E-06	1.05E+07	2.05E+05	2.64E+08	5.13E+06
18	9.37E-08	4.81E-06	1.07E+07	2.08E+05	2.67E+08	5.19E+06
19	9.26E-08	4.76E-06	1.08E+07	2.10E+05	2.70E+08	5.25E+06
20	9.16E-08	4.70E-06	1.09E+07	2.13E+05	2.73E+08	5.32E+06
21	9.05E-08	4.65E-06	1.10E+07	2.15E+05	2.76E+08	5.38E+06
22	8.95E-08	4.60E-06	1.12E+07	2.18E+05	2.79E+08	5.44E+06

Table 22 cont'd. Margins of Safety for Various Effects from a Single Exposure to 2,4-D Through Dermal Contact with Sediments.

Scenario 3: Large Lake

Days After Application	Single Human Dose (mg/kg)		MOS Systemic Effects NOEL = 1mg/kg/day		MOS Reproductive/ Teratogenic Effects NOEL = 25 mg/kg/day	
	Amine	Ester	Amine	Ester	Amine	Ester
Immediately	1.05E-10	6.56E-09	9.53E+09	1.53E+08	2.38E+11	3.81E+09
1	1.04E-10	6.48E-09	9.65E+09	1.54E+08	2.41E+11	3.86E+09
2	1.02E-10	6.41E-09	9.76E+09	1.56E+08	2.44E+11	3.90E+09
3	1.01E-10	6.33E-09	9.87E+09	1.58E+08	2.47E+11	3.95E+09
4	1.00E-10	6.26E-09	9.99E+09	1.60E+08	2.50E+11	3.99E+09
5	9.90E-11	6.19E-09	1.01E+10	1.62E+08	2.53E+11	4.04E+09
6	9.79E-11	6.12E-09	1.02E+10	1.64E+08	2.55E+11	4.09E+09
7	9.67E-11	6.05E-09	1.03E+10	1.65E+08	2.58E+11	4.14E+09
8	9.56E-11	5.98E-09	1.05E+10	1.67E+08	2.61E+11	4.18E+09
9	9.45E-11	5.91E-09	1.06E+10	1.69E+08	2.64E+11	4.23E+09
10	9.34E-11	5.84E-09	1.07E+10	1.71E+08	2.68E+11	4.28E+09
11	9.24E-11	5.77E-09	1.08E+10	1.73E+08	2.71E+11	4.33E+09
12	9.13E-11	5.71E-09	1.10E+10	1.75E+08	2.74E+11	4.38E+09
13	9.03E-11	5.64E-09	1.11E+10	1.77E+08	2.77E+11	4.43E+09
14	8.92E-11	5.58E-09	1.12E+10	1.79E+08	2.80E+11	4.48E+09
15	8.82E-11	5.51E-09	1.13E+10	1.81E+08	2.83E+11	4.54E+09
16	8.72E-11	5.45E-09	1.15E+10	1.84E+08	2.87E+11	4.59E+09
17	8.62E-11	5.39E-09	1.16E+10	1.86E+08	2.90E+11	4.64E+09
18	8.52E-11	5.32E-09	1.17E+10	1.88E+08	2.93E+11	4.70E+09
19	8.42E-11	5.26E-09	1.19E+10	1.90E+08	2.97E+11	4.75E+09
20	8.32E-11	5.20E-09	1.20E+10	1.92E+08	3.00E+11	4.81E+09
21	8.23E-11	5.14E-09	1.22E+10	1.94E+08	3.04E+11	4.86E+09
22	8.13E-11	5.08E-09	1.23E+10	1.97E+08	3.07E+11	4.92E+09

Table 23. Margins of Safety for Various Effects from a Single Exposure to 2,4-D Through Ingestion of Fish.

Scenario 1: Small Pond

Days After Application	Single Human Dose (mg/kg)		MOS Systemic Effects NOEL = 1mg/kg/day		MOS Reproductive/ Teratogenic Effects NOEL = 25 mg/kg/day	
	Amine	Ester	Amine	Ester	Amine	Ester
Immediately	4.29E-04	9.14E-05	2.33E+03	1.09E+04	5.83E+04	2.74E+05
1	4.02E-04	8.58E-05	2.49E+03	1.17E+04	6.22E+04	2.91E+05
2	3.78E-04	8.06E-05	2.65E+03	1.24E+04	6.61E+04	3.10E+05
3	3.55E-04	7.57E-05	2.82E+03	1.32E+04	7.04E+04	3.30E+05
4	3.33E-04	7.11E-05	3.00E+03	1.41E+04	7.51E+04	3.52E+05
5	3.13E-04	6.67E-05	3.19E+03	1.50E+04	7.99E+04	3.75E+05
6	2.94E-04	6.26E-05	3.40E+03	1.60E+04	8.50E+04	3.99E+05
7	2.75E-04	5.88E-05	3.40E+03	1.70E+04	9.09E+04	4.25E+05
8	2.59E-04	5.52E-05	3.64E+03	1.81E+04	9.65E+04	4.53E+05
9	2.43E-04	5.19E-05	3.86E+03	1.93E+04	1.03E+05	4.82E+05
10	2.28E-04	4.87E-05	4.12E+03	2.05E+04	1.10E+05	5.13E+05
11	2.14E-04	4.57E-05	4.39E+03	2.19E+04	1.17E+05	5.47E+05
12	2.01E-04	4.29E-05	4.67E+03	2.33E+04	1.24E+05	5.83E+05
13	1.89E-04	4.03E-05	5.29E+03	2.48E+04	1.32E+05	6.20E+05
14	1.77E-04	3.78E-05	5.65E+03	2.65E+04	1.41E+05	6.61E+05
15	1.67E-04	3.55E-05	5.99E+03	2.82E+04	1.50E+05	7.04E+05
16	1.56E-04	3.34E-05	6.41E+03	2.99E+04	1.60E+05	7.49E+05
17	1.47E-04	3.13E-05	6.80E+03	3.19E+04	1.70E+05	7.99E+05
18	1.38E-04	2.94E-05	7.25E+03	3.40E+04	1.81E+05	8.50E+05
19	1.29E-04	2.76E-05	7.75E+03	3.62E+04	1.94E+05	9.06E+05
20	1.22E-04	2.59E-05	8.20E+03	3.86E+04	2.05E+05	9.65E+05
21	1.14E-04	2.43E-05	8.77E+03	4.12E+04	2.19E+05	1.03E+06
22	1.07E-04	2.29E-05	9.35E+03	4.37E+04	2.34E+05	1.09E+06

Table 23 cont'd. Margins of Safety for Various Effects from a Single Exposure to 2,4-D Through Ingestion of Fish.

Scenario 2: Irrigation Ditch

Days After Application	Single Human Dose (mg/kg)		MOS Systemic Effects NOEL = 1mg/kg/day		MOS Reproductive/ Teratogenic Effects NOEL = 25 mg/kg/day	
	Amine	Ester	Amine	Ester	Amine	Ester
Immediately	5.71E-03	1.17E-03	1.75E+02	8.55E+02	4.38E+03	2.14E+04
1	5.37E-03	1.10E-03	1.86E+02	9.09E+02	4.66E+03	2.27E+04
2	5.04E-03	1.03E-03	1.98E+02	9.71E+02	4.96E+03	2.43E+04
3	4.73E-03	9.70E-04	2.11E+02	1.03E+03	5.29E+03	2.58E+04
4	4.44E-03	9.10E-04	2.25E+02	1.10E+03	5.63E+03	2.75E+04
5	4.17E-03	8.55E-04	2.40E+02	1.17E+03	6.00E+03	2.92E+04
6	3.92E-03	8.03E-04	2.55E+02	1.25E+03	6.38E+03	3.11E+04
7	3.68E-03	7.54E-04	2.72E+02	1.33E+03	6.79E+03	3.32E+04
8	3.45E-03	7.08E-04	2.90E+02	1.41E+03	7.25E+03	3.53E+04
9	3.24E-03	6.64E-04	3.09E+02	1.51E+03	7.72E+03	3.77E+04
10	3.04E-03	6.24E-04	3.29E+02	1.60E+03	8.22E+03	4.01E+04
11	2.86E-03	5.86E-04	3.50E+02	1.71E+03	8.74E+03	4.27E+04
12	2.68E-03	5.50E-04	3.73E+02	1.82E+03	9.33E+03	4.55E+04
13	2.52E-03	5.16E-04	3.97E+02	1.94E+03	9.92E+03	4.84E+04
14	2.37E-03	4.85E-04	4.22E+02	2.06E+03	1.05E+04	5.15E+04
15	2.22E-03	4.55E-04	4.50E+02	2.20E+03	1.13E+04	5.49E+04
16	2.08E-03	4.27E-04	4.81E+02	2.34E+03	1.20E+04	5.85E+04
17	1.96E-03	4.01E-04	5.10E+02	2.49E+03	1.28E+04	6.23E+04
18	1.84E-03	3.77E-04	5.43E+02	2.65E+03	1.36E+04	6.63E+04
19	1.73E-03	3.54E-04	5.78E+02	2.82E+03	1.45E+04	7.06E+04
20	1.62E-03	3.32E-04	6.17E+02	3.01E+03	1.54E+04	7.53E+04
21	1.52E-03	3.12E-04	6.58E+02	3.21E+03	1.64E+04	8.01E+04
22	1.43E-03	2.93E-04	6.99E+02	3.41E+03	1.75E+04	8.53E+04

Table 23 cont'd. Margins of Safety for Various Effects from a Single Exposure to 2,4-D Through Ingestion of Fish.

Scenario 3: Large Lake

Days After Application	Single Human Dose (mg/kg)		MOS Systemic Effects NOEL = 1mg/kg/day		MOS Reproductive/ Teratogenic Effects NOEL = 25 mg/kg/day	
	Amine	Ester	Amine	Ester	Amine	Ester
Immediately	6.86E-06	1.14E-06	1.46E+05	8.77E+05	3.64E+06	2.19E+07
1	6.44E-06	1.07E-06	1.55E+05	9.35E+05	3.88E+06	2.34E+07
2	6.05E-06	1.01E-06	1.65E+05	9.90E+05	4.13E+06	2.48E+07
3	5.68E-06	9.46E-07	1.76E+05	1.06E+06	4.40E+06	2.64E+07
4	5.33E-06	8.88E-07	1.88E+05	1.13E+06	4.69E+06	2.82E+07
5	5.00E-06	8.34E-07	2.00E+05	1.20E+06	5.00E+06	3.00E+07
6	4.70E-06	7.83E-07	2.13E+05	1.28E+06	5.32E+06	3.19E+07
7	4.41E-06	7.35E-07	2.27E+05	1.36E+06	5.67E+06	3.40E+07
8	4.14E-06	6.90E-07	2.42E+05	1.45E+06	6.04E+06	3.62E+07
9	3.90E-06	6.48E-07	2.56E+05	1.54E+06	6.41E+06	3.86E+07
10	3.65E-06	6.09E-07	2.74E+05	1.64E+06	6.85E+06	4.11E+07
11	3.43E-06	5.71E-07	2.92E+05	1.75E+06	7.29E+06	4.38E+07
12	3.22E-06	5.37E-07	3.11E+05	1.86E+06	7.76E+06	4.66E+07
13	3.02E-06	5.04E-07	3.31E+05	1.98E+06	8.28E+06	4.96E+07
14	2.84E-06	3.87E-07	3.52E+05	2.58E+06	8.80E+06	6.46E+07
15	2.66E-06	4.44E-07	3.76E+05	2.25E+06	9.40E+06	5.63E+07
16	2.50E-06	4.17E-07	4.00E+05	2.40E+06	1.00E+07	6.00E+07
17	2.35E-06	3.92E-07	4.26E+05	2.55E+06	1.06E+07	6.38E+07
18	2.21E-06	3.68E-07	4.52E+05	2.72E+06	1.13E+07	6.79E+07
19	2.07E-06	3.45E-07	4.83E+05	2.90E+06	1.21E+07	7.25E+07
20	1.94E-06	3.24E-07	5.15E+05	3.09E+06	1.29E+07	7.72E+07
21	1.83E-06	3.04E-07	5.46E+05	3.29E+06	1.37E+07	8.22E+07
22	1.71E-06	2.86E-07	5.85E+05	3.50E+06	1.46E+07	8.74E+07

Table 24. Hazard Quotients* for all Pathways.

Scenario	Ingestion of Fish		Dermal Contact With Water (Swimming)		Dermal Contact With Sediments		Incidental Ingestion of Sediments		Drinking Water		Cumulative Hazard Index	
	Amine	Ester	Amine	Ester	Amine	Ester	Amine	Ester	Amine	Ester	Amine	Ester
1: Small Pond	3.30E-03	7.04E-04	1.69E-07	3.86E-05	4.11E-08	2.50E-06	5.67E-08	3.44E-06	2.31E-02	4.94E-03	2.64E-02	5.69E-03
2: Irrigation Ditch	4.40E-04	9.04E-03	2.25E-06	4.95E-04	6.47E-07	3.33E-05	8.93E-07	4.59E-05	3.09E-01	6.34E-02	3.53E-01	7.30E-02
3: Large Lake	5.29E-05	8.79E-06	2.71E-09	4.82E-07	5.87E-10	3.68E-08	8.11E-10	5.07E-08	3.71E-04	6.17E-05	4.26E-04	7.11E-05

*Hazard Quotients calculated using USEPA-derived RfD's (IRIS, 1992)
Oral RfD = 1.00E-02 mg/kg/day
Dermal RfD = 9.50E-03 mg/kg/day

are summed across pathways are all well below "1" for the three environmental exposure scenarios. The highest cumulative hazard index is 3.5E-01, for amine formulation, irrigation ditch scenario.

Among the hazard quotients (chronic daily intake/RfD for each exposure pathway) the largest value was calculated for the drinking water exposure scenario, amine formulation, irrigation ditch scenario. This value was 3.09 E-01 and is still considered to be low (i.e., "safe") in light of the fact that the hazard quotient is "1" when the chronic daily intake and RfD are equal.

5.0 UNCERTAINTY ANALYSIS

Uncertainty is inherently introduced at a number of steps in the risk assessment process. Generally, sources of uncertainty include variability in exposure input parameters, contaminant transport modeling, toxicological evaluation of contaminants, and analytical data. To compensate for such uncertainties, risk assessments are commonly conducted by incorporating conservative assumptions and input parameters favoring the protection of public health. This same approach has been incorporated here. Although a rigorous quantitative evaluation of these uncertainties is beyond the scope of this assessment, it is important to consider, at least qualitatively, the effect various assumptions used throughout this analysis are likely to have on the final risk estimates.

Assumptions are a necessary and innate part of risk assessment, and each assumption usually has a technically correct alternative. This risk assessment required that a greater than usual number of assumptions be made regarding 2,4-D exposure scenarios, as no one particular site was designated to be evaluated. A discussion of this and other sources of uncertainty are discussed below.

5.1 ENVIRONMENTAL CONCENTRATIONS

Uncertainty in risk predictions was introduced during the calculation of expected environmental 2.4-D concentrations. 2,4-D concentrations in environmental media were calculated assuming particular application rates, depth of water, and type of sediment. If any of these parameters vary in an actual 2,4-D application scenario environmental concentrations will vary, as will resulting risks.

Sediment and water concentrations were calculated using published application and degradation rates. Application rates are expected to vary with site, method, and 2,4-D formulation. Thus, the calculated environmental concentrations, and resulting risks represent values around which variation is expected to occur.

5.2 EXPOSURE SCENARIOS AND ASSUMPTIONS

Generally, the inhabitants or visitors to a specific geographical area are designated as the exposed population in a risk assessment. For example, residents living near a contaminated site, recreational users of a specific body of water, or people living within the zone of deposition of an incinerator all represent specific groups. As 2,4-D is proposed for use across the entire state of Washington, it was impossible to evaluate human health risks from exposures which take place at one specific site.

Thus, uncertainty is introduced through the use of the necessary "generic" exposure scenarios. These generic scenarios represent the most likely routes of public exposure and are not intended to be site-specific. Thus, they may underestimate risks if, for example, people live near a lake particularly well suited for swimming and are thus exposed for longer periods of time than are built into the swimming exposure scenario. Likewise, risks may be overestimated for a lake in which conditions (i.e., cold temperature) cause people to spend very little time swimming. However, margins of safety are so large for this pathway that any variation in exposure parameters is unlikely to influence them to any great extent.

For the ingestion of fish pathway, it is likely that the MOS's are slightly underestimated (i.e., risk is overestimated) due to the use of a BCF to calculate fish tissue concentration of 2,4-D. The bioconcentration of 2,4-D by fish is a dynamic process of uptake and elimination and may take hours to days before a fish reaches an equilibrium or "steady state" concentration. Thus, the 2,4-D tissue concentrations calculated for the "immediately after spraying" scenario may be overestimates of actual concentrations, as fish may eliminate 2,4-D very rapidly (Rand and Petrocelli, 1985). The calculation of fish tissue concentration also assume that a fish is exposed to an constant concentration of 2,4-D in water, which is rarely the case in a natural setting. The ingestion of surface water pathway represents an extremely conservative assessment as it was assumed people drink 2,4-D containing water 365 days/year. Given that 2,4-D is not labelled for application on a daily basis and that it degrades rapidly in water it is most likely not found in potable surface water 365 days/year.

For chronic exposures the hazard index is calculated by summing hazard quotients across exposure pathways. It is highly unlikely that a person will be chronically expsoed to 2,4-D via <u>every</u> pathway. Thus, the hazard index represents a very conservative value.

5.3 RISK EVALUATION

It is important to recognize that acute and chronic non-carcinogenic risk was evaluated using two separate approaches: the MOS and RfD approach, respectively. Given this, the results of the separate assessments should be interpreted independently, without comparison of the results of an acute exposure to that of a chronic exposure.

6.0 MITIGATION MEASURES

MOSs indicate that there is very little risk to public health associated with 2,4-D use, except when vegetation is contacted one hour after spraying. The time-dependent MOSs can be used to place restrictions on public use of treated areas. For example, risk characterization results indicate that it may be unsafe for the public to recreate in areas within one hour of spraying but risk decreases to "safe" levels 24 hours after spraying. Thus, warning could be posted for the public to avoid treated areas for 24 hours.

All the MOS's and hazard indices indicate that 2,4-D should not pose acute or chronic risk to the public.

7.0 SUMMARY

Results indicate that 2,4-D should present little or no risk to the public from acute exposures via dermal contact with sediment, dermal contact with water, or ingestion of fish. Dermal contact with vegetation may present limited risk if it is contacted one hour after application. By 24 hours post-application non-carcinogenic risk is essentially non-existent, as 2,4-D is unavailable for dermal uptake. Margins of safety for all acute exposure scenarios are greater than "100", implying that risk of systemic, teratogenic, or reproductive effects to humans is negligable.

Results of chronic exposure assessments indicate that human health should not be adversely impacted from chronic 2,4-D exposure via ingestion of fish, ingestion of surface water, incidental ingestion of sediments, dermal contact with sediments, or dermal contact with water (swimming). Hazard quotients for every exposure pathway and scenario are small (8E-10 to 3E-01). Hazard quotients are consistently higher (i.e., higher risk) for the irrigation ditch scenario.

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9.0 GLOSSARY

Absorbed Dose -	A quantity of a substance taken into the body, generally expressed in mass of a substance taken into the body per unit body weight per unit time.
Absorption -	The movement of a chemical into the body or cell(s).
Bioconcentration -	The transport process by which an organism accumulates a chemical from water, usually resulting in tissue concentrations greater than those in the water.
Bioconcentration Factor (BCF) -	The ratio of concentration of a chemical in an organism to that in water.
Carcinogen -	A chemical or substance which produces uncontrollable changes in cells, after resulting in a tumor.
Conservative -	A moderate of safe procedure designed to protect human health.
Deoxyribonucleic acid (DNA) -	in genetics, the part of a cell which carries the "genetic code".
Edema -	The presence of abnormally large amounts of fluid in the intercellular tissue spaces.
Fetal Resorption -	Resorption of a nonviable fetus(es) by the maternal reproductive organs.
Hepatic -	Pertaining to the liver.
LD_{50} -	Median lethal dose - the dose which theoretically causes mortality on 50 percent of a population.

LOEL -	Lowest Observable Effect Level - a series of doses used in a test, the lowest level at which adverse effects are observed in test organisms at a rate which is statistically significantly higher than that observed in controls.
Mg/kg -	Milligrams of chemical per kilgram of body weight. Equivalent to 1 part per million.
Necrosis -	Morphological changes indicative of cell death and caused by the progressive degradation action of enzymes.
NOEL -	No Observable Effect Level - In a series of doses used in a test, the highest level at which no adverse effects are observed in the test organisms.
Teratogen -	A substance which produces birth defects not attributable to genetic defects.

APPENDIX A - 2,4-D CONCENTRATIONS IN SEDIMENT AND WATER

A = Ao * 2^(-t/h)			
Scenario 1, DMA			
Conc at time t, ppm	**Initial conc, ppm**	**half-life, days**	**time, days**
A	Ao	h	t
0.15	0.015	11	0
0.014083964	0.015	11	1
0.013223869	0.015	11	2
0.012416299	0.015	11	3
0.011658047	0.015	11	4
0.010946101	0.015	11	5
0.010277632	0.015	11	6
0.009649987	0.015	11	7
0.009060671	0.015	11	8
0.008507344	0.015	11	9
0.007987808	0.015	11	10
0.0075	0.015	11	11
0.007041982	0.015	11	12
0.006611934	0.015	11	13
0.00620815	0.015	11	14
0.005829024	0.015	11	15
0.00547305	0.015	11	16
0.005138816	0.015	11	17
0.004824993	0.015	11	18
0.004530335	0.015	11	19
0.004253672	0.015	11	20
0.003993904	0.015	11	21
0.00375	0.015	11	22
Scenario 2, DMA			
Conc at time t, ppm	**Initial conc, ppm**	**half-life, days**	**time, days**
A	Ao	h	t
0.2	0.2	11	0
0.187786182	0.2	11	1
0.176318251	0.2	11	2
0.165550656	0.2	11	3
0.155440628	0.2	11	4
0.145948011	0.2	11	5
0.137035098	0.2	11	6
0.12866649	0.2	11	7
0.120808944	0.2	11	8
0.113431252	0.2	11	9
0.106504109	0.2	11	10
0.1	0.2	11	11
0.093893091	0.2	11	12

Scen. 2, DMA, Cont.			
Conc at time t, ppm	Initial conc, ppm	half-life, days	time, days
0.088159125	0.2	11	13
0.082775328	0.2	11	14
0.077720314	0.2	11	15
0.072974005	0.2	11	16
0.068517549	0.2	11	17
0.064333245	0.2	11	18
0.060404472	0.2	11	19
0.056715626	0.2	11	20
0.053252054	0.2	11	21
0.05	0.2	11	22
Scenario 3, DMA			
Conc at time t, ppm	Initial conc, ppm	half-life, days	time, days
A	Ao	h	t
0.00024	0.00024	11	0
0.000225343	0.00024	11	1
0.000211582	0.00024	11	2
0.000198661	0.00024	11	3
0.000186529	0.00024	11	4
0.000175138	0.00024	11	5
0.000164442	0.00024	11	6
0.0001544	0.00024	11	7
0.000144971	0.00024	11	8
0.000136118	0.00024	11	9
0.000127805	0.00024	11	10
0.00012	0.00024	11	11
0.000112672	0.00024	11	12
0.000105791	0.00024	11	13
9.93304E-05	0.00024	11	14
9.32644E-05	0.00024	11	15
8.75688E-05	0.00024	11	16
8.22211E-05	0.00024	11	17
7.71999E-05	0.00024	11	18
7.24854E-05	0.00024	11	19
6.80588E-05	0.00024	11	20
6.39025E-05	0.00024	11	21
0.00006	0.00024	11	22

Scenario 1, BEE			
Conc at time t, ppm	Initial conc, ppm	half-life, days	time, days
A	Ao	h	t
0.0032	0.0032	11	0
0.003004579	0.0032	11	1
0.002821092	0.0032	11	2
0.00264881	0.0032	11	3
0.00248705	0.0032	11	4
0.002335168	0.0032	11	5
0.002192562	0.0032	11	6
0.002058664	0.0032	11	7
0.001932943	0.0032	11	8
0.0018149	0.0032	11	9
0.001704066	0.0032	11	10
0.0016	0.0032	11	11
0.001502289	0.0032	11	12
0.001410546	0.0032	11	13
0.001324405	0.0032	11	14
0.001243525	0.0032	11	15
0.001167584	0.0032	11	16
0.001096281	0.0032	11	17
0.001029332	0.0032	11	18
0.000966472	0.0032	11	19
0.00090745	0.0032	11	20
0.000852033	0.0032	11	21
0.0008	0.0032	11	22
Scenario 2, BEE			
Conc at time t, ppm	Initial conc, ppm	half-life, days	time, days
A	Ao	h	t
0.041	0.041	11	0
0.038496167	0.041	11	1
0.036145241	0.041	11	2
0.033937884	0.041	11	3
0.031865329	0.041	11	4
0.029919342	0.041	11	5
0.028092195	0.041	11	6
0.02637663	0.041	11	7
0.024765834	0.041	11	8
0.023253407	0.041	11	9
0.021833342	0.041	11	10
0.0205	0.041	11	11
0.019248084	0.041	11	12
0.018072621	0.041	11	13
0.016968942	0.041	11	14

Scen. 2, BEE Cont.			
Conc at time t, ppm	Initial conc, ppm	half-life, days	time, days
0.015932664	0.041	11	15
0.014959671	0.041	11	16
0.014046098	0.041	11	17
0.013188315	0.041	11	18
0.012382917	0.041	11	19
0.011626703	0.041	11	20
0.010916671	0.041	11	21
0.01025	0.041	11	22
Scenario 3, BEE			
Conc at time t, ppm	Initial conc, ppm	half-life, days	time, days
A	Ao	h	t
0.00004	0.00004	11	0
3.75572E-05	0.00004	11	1
3.52637E-05	0.00004	11	2
3.31101E-05	0.00004	11	3
3.10881E-05	0.00004	11	4
2.91896E-05	0.00004	11	5
2.7407E-05	0.00004	11	6
2.57333E-05	0.00004	11	7
2.41618E-05	0.00004	11	8
2.26863E-05	0.00004	11	9
2.13008E-05	0.00004	11	10
0.00002	0.00004	11	11
1.87786E-05	0.00004	11	12
1.76318E-05	0.00004	11	13
1.65551E-05	0.00004	11	14
1.55441E-05	0.00004	11	15
1.45948E-05	0.00004	11	16
1.37035E-05	0.00004	11	17
1.28666E-05	0.00004	11	18
1.20809E-05	0.00004	11	19
1.13431E-05	0.00004	11	20
1.06504E-05	0.00004	11	21
0.00001	0.00004	11	22

A = Ao * 2^(-t/h)			
Scenario 1, DMA			
Conc at time t, ppm	**Initial conc, ppm**	**half-life, days**	**time, days**
A	Ao	h	t
0.0028	0.0028	60	0
0.002767839	0.0028	60	1
0.002736048	0.0028	60	2
0.002704622	0.0028	60	3
0.002673556	0.0028	60	4
0.002642848	0.0028	60	5
0.002612492	0.0028	60	6
0.002582485	0.0028	60	7
0.002552823	0.0028	60	8
0.002523501	0.0028	60	9
0.002494516	0.0028	60	10
0.002465864	0.0028	60	11
0.002437542	0.0028	60	12
0.002409544	0.0028	60	13
0.002381868	0.0028	60	14
0.00235451	0.0028	60	15
0.002327466	0.0028	60	16
0.002300733	0.0028	60	17
0.002274307	0.0028	60	18
0.002248184	0.0028	60	19
0.002222361	0.0028	60	20
0.002196835	0.0028	60	21
0.002171603	0.0028	60	22
Scenario 2, DMA			
Conc at time t, ppm	**Initial conc, ppm**	**half-life, days**	**time, days**
A	Ao	h	t
0.044	0.044	60	0
0.043494617	0.044	60	1
0.042995039	0.044	60	2
0.042501198	0.044	60	3
0.042013031	0.044	60	4
0.04153047	0.044	60	5
0.041053452	0.044	60	6
0.040581913	0.044	60	7
0.040115789	0.044	60	8
0.03965502	0.044	60	9
0.039199544	0.044	60	10
0.038749298	0.044	60	11
0.038304225	0.044	60	12

Scen. 2, DMA Cont.			
Conc at time t, ppm	**Initial conc, ppm**	**half-life, days**	**time, days**
0.037864263	0.044	60	13
0.037429355	0.044	60	14
0.036999442	0.044	60	15
0.036574467	0.044	60	16
0.036154374	0.044	60	17
0.035739105	0.044	60	18
0.035328607	0.044	60	19
0.034922823	0.044	60	20
0.0345217	0.044	60	21
0.034125185	0.044	60	22
Scenario 3, DMA			
Conc at time t, ppm	**Initial conc, ppm**	**half-life, days**	**time, days**
A	Ao	h	t
0.00004	0.00004	60	0
3.95406E-05	0.00004	60	1
3.90864E-05	0.00004	60	2
3.86375E-05	0.00004	60	3
3.81937E-05	0.00004	60	4
3.7755E-05	0.00004	60	5
3.73213E-05	0.00004	60	6
3.68926E-05	0.00004	60	7
3.64689E-05	0.00004	60	8
3.605E-05	0.00004	60	9
3.56359E-05	0.00004	60	10
3.52266E-05	0.00004	60	11
3.4822E-05	0.00004	60	12
3.44221E-05	0.00004	60	13
3.40267E-05	0.00004	60	14
3.36359E-05	0.00004	60	15
3.32495E-05	0.00004	60	16
3.28676E-05	0.00004	60	17
3.24901E-05	0.00004	60	18
3.21169E-05	0.00004	60	19
3.1748E-05	0.00004	60	20
3.13834E-05	0.00004	60	21
3.10229E-05	0.00004	60	22

Scenario 1, BEE			
Conc at time t, ppm	Initial conc, ppm	half-life, days	time, days
A	Ao	h	t
0.17	0.17	60	0
0.168047383	0.17	60	1
0.166117195	0.17	60	2
0.164209176	0.17	60	3
0.162323073	0.17	60	4
0.160458633	0.17	60	5
0.158615609	0.17	60	6
0.156793753	0.17	60	7
0.154992823	0.17	60	8
0.153212579	0.17	60	9
0.151452782	0.17	60	10
0.149713199	0.17	60	11
0.147993596	0.17	60	12
0.146293744	0.17	60	13
0.144613417	0.17	60	14
0.142952391	0.17	60	15
0.141310442	0.17	60	16
0.139687353	0.17	60	17
0.138082907	0.17	60	18
0.13649689	0.17	60	19
0.134929089	0.17	60	20
0.133379297	0.17	60	21
0.131847305	0.17	60	22
Scenario 2, BEE			
Conc at time t, ppm	Initial conc, ppm	half-life, days	time, days
A	Ao	h	t
2.26	2.26	60	0
2.234041686	2.26	60	1
2.208381529	2.26	60	2
2.183016103	2.26	60	3
2.157942025	2.26	60	4
2.133155947	2.26	60	5
2.108654561	2.26	60	6
2.084434598	2.26	60	7
2.060492824	2.26	60	8
2.036826046	2.26	60	9
2.013431103	2.26	60	10
1.990304874	2.26	60	11
1.967444273	2.26	60	12
1.944846248	2.26	60	13
1.922507784	2.26	60	14

Scen. 2, BEE Cont.			
Conc at time t, ppm	Initial conc, ppm	half-life, days	time, days
1.900425898	2.26	60	15
1.878597645	2.26	60	16
1.857020111	2.26	60	17
1.835690416	2.26	60	18
1.814605713	2.26	60	19
1.793763189	2.26	60	20
1.773160061	2.26	60	21
1.752793581	2.26	60	22
Scenario 3, BEE			
Conc at time t, ppm	Initial conc, ppm	half-life, days	time, days
A	Ao	h	t
0.0025	0.0025	60	0
0.002471285	0.0025	60	1
0.0024429	0.0025	60	2
0.002414841	0.0025	60	3
0.002387104	0.0025	60	4
0.002359686	0.0025	60	5
0.002332582	0.0025	60	6
0.00230579	0.0025	60	7
0.002279306	0.0025	60	8
0.002253126	0.0025	60	9
0.002227247	0.0025	60	10
0.002201665	0.0025	60	11
0.002176376	0.0025	60	12
0.002151379	0.0025	60	13
0.002126668	0.0025	60	14
0.002102241	0.0025	60	15
0.002078095	0.0025	60	16
0.002054226	0.0025	60	17
0.002030631	0.0025	60	18
0.002007307	0.0025	60	19
0.001984251	0.0025	60	20
0.00196146	0.0025	60	21
0.001938931	0.0025	60	22

APPENDIX B - DESCRIPTIONS OF DATABASES SEARCHED FOR HUMAN HEALTH RISK ASSESSMENTS

DESCRIPTIONS OF DATABASES SEARCHED FOR THE HUMAN HEALTH RISK ASSESSMENTS

AGRICOLA

Coverage: 1970 to the present.
Updates: Monthly
Provider: US National Agricultural

This massive file provides comprehensive coverage of worldwide journal literature and monographs on agriculture and related subjects, including: animal studies, botany, chemistry, entomology, fertilizers, forestry, hydroponics, soils, and more.

AGRIS INTERNATIONAL

Coverage: 1975 to the present.
Updates: Monthly
Provider: US National Agricultural Library

This is an inventory of worldwide agricultural literature that reflect research results, food production, and rural development. Subject coverage focuses on topics including general agriculture, plant production, protection of plants, animal production, aquatic sciences, fisheries and pollution.

AQUATIC SCIENCE AND FISHERIES ABSTRACTS

Coverage: 1978 to the present.
Updates: Monthly
Provider: NOAA, Bethesda. MD

This is a comprehensive database on the science, technology and management of marine and freshwater environments. The database corresponds to the publication of the same title. It includes citations to 5,000 primary journals, monographs, conference proceedings, and technical reports.

BEILSTEIN ONLINE

Coverage: 1779 to the present.
Updates: Periodic
Provider: Beilstein Institute, Heidelberg, Germany

Beilstein is the database version of Beilstein's Handbuch der Organischen Chemie, or the Beilstein Handbook. This is the world's most extensive collection of data on known organic compounds, including heterocyclics, isocyclics, and acyclics.

BIOSIS PREVIEWS

Coverage: 1969 to the present.
Updates: Weekly
Provider: BIOSIS, Philadelphia, PA

Contains citations from Biological Abstracts, Biological Abstracts/RRM, Bioresearch Index the major publications of Biosis. Together these publications constitute the major English-language service providing comprehensive worldwide coverage of research in the biological and biomedical sciences.

CA SEARCH

Coverage: 1967 to the present.
Updates: Biweekly
Provider: Chemical Abstracts Service, Columbus, OH

This database contains citations to the literature of chemistry and its applications. It is an expanded database that contains the basic bibliographic information appearing in the spring Chemical Abstracts.

CAB ABSTRACTS

Coverage: 1972 to the present.
Updates: Monthly
Provider: CAB International, Slough, UK

This is a comprehensive file of agricultural and biological information and contains all records in the 26 main abstract journals published by Commonwealth Agricultural Bureaux. Over 8,500 Journals in 37 different languages are scanned for inclusion, as well as books, reports, theses, conference proceedings, patents, annual reports, and guides. CAB covers agricultural engineering, animal breeding, animal disease, arid lands, dairy science, forestry, forest products, horticulture, nutrition, veterinary science, entomology, plant breeding, plant pathology, rural recreation and tourism, soils, fertilizers, weeds, and world agricultural economics.

CANCERLIT:

Coverage: 1963 to the present.
Updates: Monthly
Provider: US National Cancer Institute

This is a bibliographic database containing citations and abstracts of published cancer literature selected from more than 3,500 biomedical journals, meeting proceedings, books, reports, and doctoral theses.

CONFERENCE PAPERS INDEX

Coverage: 1973 to the present.
Updates: 6 times per year
Provider: Cambridge Scientific Abstracts

Provides access to records of the more than 100,000 scientific & technical papers presented at over 1,000 major regional, national and international meetings each year. Also included are announcements of any publications issued from the meetings.

CURRENT CONTENTS SEARCH:

Coverage: Current 6 months to 1 year.
Updates: Weekly
Provider: ISI

An online version of the weekly service that reproduces the tables of contents from current issues of leading journals in the sciences, social sciences, arts and humanities.

DISSERTATION ABSTRACTS

Coverage: 1861 to the present.
Updates: Monthly
Provider: University Microfilms International

A definitive subject, title, and author guide to virtually every American dissertation accepted at an accredited institution since 1861, when academic doctoral degrees were first granted in the United States. British, Canadian and European dissertations are included in the database from January, 1988 forward. Master abstracts are also included from Spring 1988 to present.

EMBASE

Coverage: June, 1974 to the present.
Updates: Weekly
Provider: Elseview Science Publishers, Amsterdam, the Netherlands.

Excerpta Medica, EMBASE, is one of the leading sources for searching the biomedical literature. It consists of abstracts and citations to over 3,500 biomedical and pharmacological journals published throughout the world. Over 350,000 records are added each year to the database.

FEDERAL RESEARCH IN PROGRESS

Coverage: Current
Updates: Monthly
Provider: NTIS

Provides access to information about ongoing, federally funded research projects in the fields of physical sciences, engineering, and life sciences, research information is provided to NTIS by the sponsoring US government agencies.

LIFE SCIENCES COLLECTION

Coverage: 1978 to the present.
Updates: Monthly
Provider: Cambridge Scientific Abstracts, Bethesda, MD

This file contains abstracts of literature in the field of animal behavior, biochemistry, ecology, endocrinology, entomology, genetics, immunology, microbiology, oncology, neuroscience, toxicology, and virology.

MEDLINE

Coverage: 1966 to the present.
Updates: Weekly
Provider: US National Library of Medicine

One of the major sources for biomedical literature, Medline corresponds to three print indices: Index Medicus, Index to Dental Literature, and International Nursing Index.

MEDTEXT:

Coverage: 1982 to the present.
Updates: Weekly
Provider: AMA and the Massachusetts Medical Society.

A collection of full-text medical journals available on Dialog. Included on this database are the journals published by the American Medical Association and the New England Journal of Medicine.

NTIS

Coverage: 1964 to the present.
Updates: Biweekly
Provider: National Technical Information Service

This database consists of government-sponsored research, development, and engineering, plus analyses prepared by federal agencies, their contractors, or grantees. It is the means through which unclassified, publicly available, unlimited distribution reports are made available for sale from agencies such as NASA, DOE, etc. 240 federal agencies contribute their reports plus some state and local agencies.

PASCAL

Coverage: 1973 to the present.
Updates: Monthly
Provider: Centre de Documentation Scientifique et Technique, Paris, France

Multidisciplinary database equivalent to the 79 print Pascal journals. Major subjects include: life sciences, biology, medicine, chemistry, applied chemistry, pollution, energy, food and agricultural sciences, earth sciences and engineering. This file is bilingual in French and English.

REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES

Coverage: 1971 to the present.
Updates: Quarterly
Provider: National Institute for Occupational Safety and Health

A comprehensive database of the basic toxicity information for over 100,000 chemical substances including: prescription and non-prescription drugs, food additives, pesticides, fungicides, herbicides, solvents, diluents, chemical wastes, reaction products of chemical waste, and substance used in both industrial and household situations. Toxicity information appearing in RTECS is derived from reports of acute, chronic, lethal and non-lethal effects of chemical substances. The reviewed information from the scientific literature and published government reports, plus unpublished test data from the EPA TSCA test submissions database (TSCATS), are included in the file.

SCISEARCH

Coverage: 1974 to the present.
Updates: Weekly
Provider: Institute for Scientific Information, Philadelphia, PA

A multidisciplinary index to the literature of science and technology. It contains all records published in Science Citation Index and additional records from Current Contents series of publications.

TOXLINE

Coverage: 1950 to the present.
Updates: Monthly
Provider: US National Library of Medicine

Toxline covers the adverse effects of chemicals, drugs, and physical agents on living systems. About 45% of the approximate 120,000 records added per year are from the TOXBIB subfile, which is derived from MEDLINE.

WATER RESOURCES ABSTRACTS

Coverage: 1968 to the present.
Updates: Monthly
Provider: US Department of the Interior, Geological Survey.

WRA is prepared from materials collected by over 50 water research centers and institutes in the United States. Covered are water resource economics, ground and surface hydrology, metropolitan water resources planning and management and water-related aspects of nuclear radiation and safety. The literature is particularly strong in the area of water quality.