CHEMICALS MEETING THE CRITERIA FOR LISTING VIA THE AUTHORITATIVE BODIES MECHANISM: (2,4-DICHLOROPHENOXY) ACETIC ACID (2,4-D), 2,4-D N-BUTYL ESTER, 2,4-D ISOPROPYL ESTER, 2,4-D ISOOCTYL ESTER, 2,4-D PROPYLENE GLYCOL BUTYL ETHER ESTER (2,4-D PGBE), 2,4-D BUTOXYETHANOL ESTER AND 2,4-D DIMETHYLAMINE SALT

November 2005

Reproductive and Cancer Hazard Assessment Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

(2,4-Dichlorophenoxy) acetic acid (2,4-D), 2,4-D n-butyl ester, 2,4-D isopropyl ester, 2,4-D isooctyl ester, 2,4-D propylene glycol butyl ether ester (2,4-D PGBE), 2,4-D butoxyethanol ester and 2,4-D dimethylamine salt meet the criteria for listing as known to the State to cause reproductive toxicity under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Health and Safety Code Section 25249.5 et seq.), more commonly known as Proposition 65, via the authoritative bodies mechanism. The regulatory requirements for listing by this mechanism are set forth in Title 22, California Code of Regulations §12306[1]. The regulations include provisions covering the criteria for evaluating the documentation and scientific findings by the authoritative body which the Office of Environmental Health Hazard Assessment (OEHHA) uses to determine whether listing under Proposition 65 is required.

The U.S. Environmental Protection Agency (U.S. EPA) is one of five institutions that have been identified as authoritative bodies for identification of chemicals as causing reproductive toxicity for the purposes of Proposition 65 (§12306(1)(3)). U.S. EPA has identified 2,4-D, 2,4-D n-butyl ester, 2,4-D isopropyl ester; 2,4-D isooctyl ester, 2,4-D PGBE, 2,4-D butoxyethanol ester and 2,4-D dimethylamine salt as causing reproductive toxicity. OEHHA has found that these chemicals have been "formally identified" by U.S. EPA as causing reproductive toxicity as required by §12306(d). 2,4-D, 2,4-D n-butyl ester, 2,4-D isopropyl ester, 2,4-D isooctyl ester, 2,4-D PGBE, 2,4-D butoxyethanol ester and 2,4-D dimethylamine salt are the subject of a report published by the authoritative body that concludes that the chemicals cause reproductive toxicity (U.S. EPA 1988). 2,4-D, 2,4-D isopropyl ester, 2,4-D butoxyethanol ester and 2,4-D dimethylamine salt are also otherwise identified as causing reproductive toxicity in a document that indicates that the identification is a final action (U.S EPA 2005). These documents specifically and accurately identify the chemicals and the documents meet one or more of the criteria required by §12306(d)(2).

OEHHA also finds that the criteria in regulation for "as causing reproductive toxicity" (§12306(g)) have been satisfied for 2,4-D, 2,4-D n-butyl ester, 2,4-D isopropyl ester,

[1] All further references are to Title 22 of the California Code of Regulations unless otherwise indicated.

2,4-D isooctyl ester, 2,4-D propylene glycol butyl ether ester (2,4-D PGBE), 2,4-D butoxyethanol ester and 2,4-D dimethylamine salt. In making this evaluation, OEHHA relied upon the discussion of data by the authoritative body in making it's finding that the specified chemical causes reproductive toxicity. A brief discussion of the relevant reproductive and developmental toxicity studies providing evidence for the findings is presented below.

Chemicals Meeting Criteria for Listing as Reproductive Toxicants

Chemical	CAS No.	Toxicological Endpoints	Identity of chemical	Reference
(2,4-dichlorophenoxy) acetic acid	94-75-7	developmental toxicity	herbicide (2,4-D)	U.S. EPA (1988, 2005[1])
2,4-D n-butyl ester	94-80-4	developmental toxicity	ester of 2,4-D	U.S. EPA (1988)
2,4-D isopropyl ester	94-11-1	developmental toxicity	ester of 2,4-D	U.S. EPA (1988, 2005)
2,4-D isooctyl ester	25168-26-7	developmental toxicity	ester of 2,4-D	U.S. EPA (1988)
Propylene glycol butyl ether ester (of 2,4-D)	1928-45-6	developmental toxicity	ester of 2,4-D	U.S. EPA (1988)
2,4-D butoxyethanol ester	1929-73-3	developmental toxicity	ester of 2,4-D	U.S. EPA (1988, 2005)
2,4-D dimethylamine salt	2008-39-1	developmental toxicity	salt of 2,4-D	U.S. EPA (1988, 2005)

[1] Documents included in the U.S. EPA administrative record that provide additional information on these chemicals (U.S. EPA 2004a,b) are included by reference in U.S. EPA (2005)

A U.S. EPA document entitled *Drinking Water Criteria Document for 2,4-D* (U.S. EPA 1988) meets the criteria for formal identification of 2,4-D and various esters and salts as causing reproductive toxicity (§12306(d) and §12306(g)). This document is provided as Attachment 1. In addition, a recent U.S. EPA Reregistration Eligibility Decision (RED) for 2,4-D and various esters and salts (U.S. EPA 2005) also meets the criteria for formal identification of 2,4-D and various esters and salts, some of which were previously formally identified in U.S. EPA (1988). A related document, the *2,4-D Revised Occupational and Residential Exposure and Risk Assessment and Response to Phase One Comments for the Registration Eligibility Decision (RED) Document* (U.S. EPA 2004a), is incorporated by reference into the RED and reviews the data for developmental and reproductive toxicity of 2,4-D and these various esters and salts. These documents are provided as Attachments 2 and 3.

The ***developmental toxicity*** of 2,4-D and certain of its derivatives has been evidenced by embryotoxicity.

The US Environmental Protection Agency (US EPA, 1988) concluded that, "Teratogenicity testing has been conducted with 2,4-D, several of its esters (n-butyl,

isopropyl, isooctyl, PGBE, butoxyethanol [and] the dimethylamine salt…. in mice, rats and hamsters (Courtney, 1977; Khera and McKinley, 1972; Schwetz et al., 1971; Unger et al., 1981; Konstantinova et al., 1976; Collins and Williams, 1971). Overall these studies indicate that 2,4-D and its derivatives are embryotoxic but only weakly teratogenic or nonteratogenic." All of the studies cited by the EPA document are reviewed in detail. Information such as species and number of animals used; doses, route, and days of treatment; and details of toxicological findings is provided in the document, and is summarized below.

The six research reports cited by U.S. EPA (1988) as containing data on 2,4-D and its esters and salts are referenced as follows:

a. Courtney 1977: 2,4-D; PGBE ester of 2,4-D' n-butylester of 2,4-D, isopropyl ester of 2,4-D, isooctyl ester of 2,4-D
b. Khera and McKinley 1972: 2,4-D; isooctyl ester of 2,4-D; butyl ester of 2,4-D; butoxyethanol ester of 2,4-D; dimethylamine salt of 2,4-D
c. Schwetz et al. 1971: 2,4-D; PGBE ester of 2,4-Disooctyl ester of 2,4-D
d. Unger et al. 1981: PGBE ester of 2,4-D; isooctyl ester of 2,4-D
e. Konstantinova et al. 1976: 2,4-D
f. Collins and Williams 1971: 2,4-D

With regard to the studies cited supporting U.S. EPA's identification of 2,4-D and certain esters and salts as causing developmental toxicity, OEHHA finds that the evidence for DART effects meets the criteria of §12306(g). Relevant parameters of the studies described in Attachment 1 (U.S. EPA 1988) are summarized as follows:

1. **Adequacy of the experimental design:**
   a. Developmental toxicity study with dosing during organogenesis
   b. Developmental toxicity study with dosing during organogenesis
   c. Developmental toxicity study with dosing during organogenesis.
   d. Developmental toxicity study with dosing during organogenesis
   e. Developmental toxicity study with dosing during organogenesis
   f. Developmental toxicity study with dosing during organogenesis

2. **Route of administration:**
   a. CD-1 mouse teratology study- oral-gastric intubation-corn oil or acetone vehicle
   b. Wistar rat teratology study-oral administration , corn oil or aqueous gelatin vehicle
   c. Sprague-Dawley rat teratology study-oral, corn oil vehicle
   d. CD rat teratology study- oral, corn oil vehicle
   e. rat teratology study- oral , gastric intubation, in emulsifying agent
   f. hamster teratology study, oral, in acetone, corn oil or carboxymethyl cellulose

3. **The frequency and duration of exposure:**
   a. gestation day 7 through 15, 12 through 15, or 11 through 13
   b. gestation day 6 through 15
   c. gestation day 6 through 15
   d. gestation day 6 through 15
   e. gestation day 7 through 14
   f. gestation day 6 through 10

4. **The numbers of test animals:**
   a. group size =7 to 16
   b. group size = 4 to 17
   c. group size control = 36 and 41; treated = 13-21
   d. group size control =~35, 37; treated =19-28
   e. group size not stated
   f. group size control=86; treated =7-12

5. **The choice of species:** Rats, mice and hamsters are standard test species for developmental toxicity studies.

6. **The choice of dosage levels:**
   a. 0.56 or 1.0 mM/kg
   b. 25, 50, 100, 150, or 300 mg/kg/day
   c. 12.5, 25, 50, 75 or 87.5 mg/kg/day equimolar to 2,4-D
   d. 6.25, 12.5, 25, 75, or, 87.5 mg/kg/day equimolar to 2,4-D
   e. 50 mg/kg/day
   f. 20, 40, 80, or 100 mg/kg/day

7. **Maternal toxicity:**
   a. no effect on maternal weight gain; increased relative maternal liver weight at some doses
   b. no effects on maternal body weight, except for dimethylamine salt at the highest dose (300 mg/kg/day)
   c. no effects on maternal body weight
   d. no adverse effect on maternal body weight or survival
   e. details of maternal toxicity not reported
   f. details of maternal toxicity not reported

Developmental toxicity, characterized mainly as an increased incidence of skeletal abnormalities in the rat, was observed following exposure to 2,4-D and its amine salts and esters at or above the threshold of saturation of renal clearance.

The U.S. EPA Reregistration Eligibility Decision (RED) for 2,4-D and various esters and salts (U.S. EPA 2005) and the *2,4-D Revised Occupational Residential Exposure and Risk Assessment and Response to Phase One Comments for the Registration Eligibility*

Decision (RED) Document (U. S. EPA 2004a) state that the database for developmental toxicity is considered complete, and identify two studies of prenatal development and one study of reproduction and fertility effects. These studies are all of 2,4-D acid form, which the RED states is representative of all members of the 2,4-D reregistration case (i.e., 2,4-D, 2,4-D dimethylamine salt , 2,4-D isopropyl ester, 2,4-D butoxyethyl ester, 2,4-D isopropylamine salt, 2,4-D sodium salt, 2,4-D diethanolamine salt, 2,4-D triisopropanolamine salt and 2,4-D 2-ethylhexyl ester). As a final action, these documents identify the sole basis for the acute dietary reference dose (RfD) for females 13-50 years of age as the rat developmental toxicity study that demonstrated skeletal abnormalities. In addition, these documents identify the basis for the short term dermal and inhalation RfDs as decreased maternal body-weight gain and skeletal abnormalities in the same rat developmental toxicity study. Additional information on the details of the studies was obtained from the Toxicology Disciplinary Chapter for the Registration Eligibility Decision Document (U.S. EPA 2004b), which is included in the administrative record for the Reregistration Eligibility Decision.

1. **Adequacy of the experimental design:**
   Study a) (MRID 00130407, 00130408 [1983]) prenatal developmental study in Fisher 344 rats. This study was rated Acceptable/Guideline.
   Study b) (MRID 41747601 [1990]) prenatal developmental study in rabbits. This study was rated Acceptable/Guideline.
   Study c) (MRID 00150557, 00163996 [1985]) reproduction and fertility effects study in Fisher 344 rats. This study was rated Acceptable/Guideline.
2. **Route of Administration:**
   Study a) rat prenatal developmental study: gavage.
   Study b) rabbit prenatal developmental study: not stated, but appears to be gavage.
   Study c) rat reproduction and fertility effects study: via diet.
3. **The frequency and duration of exposure:**
   Study a) rat prenatal developmental study: daily on days 6 through 15 of gestation.
   Study b) rabbit prenatal developmental study: daily on days 6 through 18 of gestation.
   Study c) rat reproduction and fertility effects study: from 105 days prior to gestation through gestation and lactation of two litters.
4. **The numbers of test animals:**
   Study a) rat prenatal developmental study: 35 per group.
   Study b) rabbit prenatal developmental study: 20 per group.
   Study c) rat reproduction and fertility effects study: 30 males and 30 females per group.
5. **The choice of species:**
   Rat and rabbit are standard test species.
6. **The choice of dosage levels:**
   Study a) rat prenatal developmental study - 0, 8, 25, 75 mg/kg/day.

Study b) rabbit prenatal developmental study – 0, 10, 30, 90 mg/kg/day (corrected for the 96.1% purity of the test substance).

Study c) rat reproduction and fertility effects study – 0, 5, 20, 80 mg/kg/day highest dose group discontinued due to excess toxicity).

7. **Maternal toxicity:**

Study a) rat prenatal developmental study - maternal body weight gain was decreased at the highest dose tested (75 mg/kg/day), not statistically significant. Survival was not affected.

Study b) rabbit prenatal developmental study – clinical signs (ataxia, decreased motor activity, loss of righting reflex, cold extremities), two abortions, decreased body weight gain at the highest dose tested (90 mg/kg/day), not statistically significant. Survival was not affected.

Study c) rat reproduction and fertility effects study – decreased body weight gain at 20 and 80 mg/kg/day.

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U.S. Environmental Protection Agency (U.S. EPA 2004b) Toxicology Disciplinary Chapter for the Reregistration Eligibility Decision Document. Health Effects Division, Reregistration Branch, Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency, Docket OPP-0167-0019, available at: http://docket.epa.gov/edkpub/do/EDKStaffItemDetailView?objectId=090007d4802c9079

U.S. Environmental Protection Agency (U.S. EPA 2005). Reregistration Eligibility Decision for 2,4-D. Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency, available at: http://www.epa.gov/oppsrrd1/REDs/24d_red.pdf. [Attachment 2.]

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DRINKING WATER CRITERIA DOCUMENT FOR
2,4-DICHLOROPHENOXYACETIC ACID (2,4-D)

Prepared for

OFFICE OF DRINKING WATER

Prepared by

Environmental Criteria and Assessment Office
Office of Health and Environmental Assessment
U.S. Environmental Protection Agency
Cincinnati, OH 45268

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The Office of Drinking Water (ODW), Environmental Protection Agency has prepared a Drinking Water Criteria Document on 2,4-D. This Criteria Document is an extensive review of the following topics:

- Physical chemical properties of 2,4-D
- Toxicokinetics and human exposure to 2,4-D
- Health Effects of 2,4-D in humans and animals
- Mechanisms of toxicological effects of 2,4-D
- Quantification of toxicological effects of 2,4-D

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FOREWORD

Section 1412 (b)(3)(A) of the Safe Drinking Water Act, as amended in 1986, requires the Administrator of the Environmental Protection Agency to publish maximum contaminant level goals (MCLGs) and promulgate National Primary Drinking Water Regulations for each contaminant, which, in the judgment of the Administrator, may have an adverse effect on public health and which is known or anticipated to occur in public water systems. The MCLG is nonenforceable and is set at a level at which no known or anticipated adverse health effects in humans occur and which allows for an adequate margin of safety. Factors considered in setting the MCLG include health effects data and sources of exposure other than drinking water.

This document provides the health effects basis to be considered in establishing the MCLG. To achieve this objective, data on pharmacokinetics, human exposure, acute and chronic toxicity to animals and humans, epidemiology and mechanisms of toxicity are evaluated. Specific emphasis is placed on literature data providing dose-response information. Thus, while the literature search and evaluation performed in support of this document has been comprehensive, only the reports considered most pertinent in the derivation of the MCLG are cited in the document. The comprehensive literature data base in support of this document includes information published up to 1984; however, more recent data may have been added during the review process.

When adequate health effects data exist, Health Advisory values for less than lifetime exposures (1-day, 10-day and longer-term, ~10% of an individual's lifetime) are included in this document. These values are not used in setting the MCLG, but serve as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur.

Michael B. Cook
Director
Office of Drinking Water

DOCUMENT DEVELOPMENT

Michael L. Dourson, Document Manager
Environmental Criteria and Assessment Office, Cincinnati
U.S. Environmental Protection Agency

Helen H. Ball, Project Officer
Environmental Criteria and Assessment Office, Cincinnati
U.S. Environmental Protection Agency

Authors

Stephen J. Bosch
Syracuse Research Corporation
Syracuse, New York
(EPA Contract #68-03-3112)

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Office of Drinking Water,
U.S. Environmental Protection Agency
Washington, DC

Scientific Reviewers

Michael W. Neal
Syracuse Research Corporation
Syracuse, New York

Steven D. Lutkenhoff
Environmental Criteria and Assessment Office, Cincinnati
U.S. Environmental Protection Agency

David Bayliss
Charles H. Ris
Bernard Haberman
Carcinogen Assessment Group
U.S. Environmental Protection Agency
Washington, DC

Krishan Khanna
Office of Drinking Water
U.S. Environmental Protection Agency
Washington, DC

James O. Pierce
University of Southern California

Editorial Reviewers

Erma Durden
Environmental Criteria and Assessment Office, Cincinnati
U.S. Environmental Protection Agency

Judith Olsen
Environmental Criteria and Assessment Office, Cincinnati
U.S. Environmental Protection Agency

Document Preparation

Technical Support Services Staff: B. Zwayer, K. Davidson and J. Moore
Environmental Criteria and Assessment Office, Cincinnati

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LIST OF ABBREVIATIONS

bw	Body weight
CNS	Central nervous system
CSF	Cerebral spinal fluid
DNA	Deoxyribonucleic acid
DWEL	Drinking water equivalent level
EEG	Electroencephalogram
FEL	Frank-effect level
GI	Gastrointestinal
HA	Health advisory
i.p.	Intraperitoneal
i.v.	Intravenous
LD_{50}	Dose lethal to 50% of recipients
LDH	Lactic dehydrogenase
LOAEL	Lowest-observed-adverse-effect level
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
PCDD	Polychlorinated dibenzo-p-dioxins
ppb	Parts per billion
ppm	Part per million
ppt	Parts per trillion
RfD	Reference dose
RNA	Ribonucleic acid
s.c.	Subcutaneous
SGOT	Serum glutamic oxalacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
STEL	Short-term exposure limit

LIST OF ABBREVIATIONS (cont.)

TLV	Threshold limit value
TWA	Time-weighted average
V_d	Volume of distribution

I. SUMMARY

2,4-Dichlorophenoxyacetic acid (2,4-D) (molecular weight, 221; water solubility, 540 mg/ℓ at 20°C; pK_a, 2.87) is a white to yellow crystalline powder that is used as a herbicide for both terrestrial and aquatic plants and to prevent preharvest fruit drop in citrus trees, and also to increase the storage life of citrus fruit and increase the latex output of old rubber trees. 2,4-D has not been shown to contain 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD), but does contain low concentrations (<60 ppb) of some other chlorinated dioxins. 2,4-D is degraded rapidly in water by chemical hydrolysis, photolysis and biological processes (the major removal mechanism).

Toxicokinetic studies have shown that most of the 2,4-D that is orally administered to animals (>90%) is excreted in the urine unchanged within 24-48 hours, suggesting fairly rapid and complete absorption and little metabolism of the compound. 2,4-D is widely distributed following absorption, but the highest concentrations are found in the liver, kidney, spleen, heart and lungs and the lowest levels in the muscle, brain and fat. Elimination from animals at low levels of exposure (<100 mg/kg) follows firstorder kinetics, but biphasic patterns are observed as concentrations increase. Limited human toxicokinetic data are consistent with the animal data, but considerable interindividual variations are noted in rates of absorption and elimination and the amount of the 2,4-D excreted as conjugates.

Acute exposure to 2,4-D by oral administration or injection by various routes results in progressive symptoms of muscular incoordination, hind-quarter paralysis, stupor, coma and death in animals. Myotonia is a dominant effect of exposure, and lethal levels of 2,4-D have been shown to cause kidney and skeletal muscle damage in rodents. Oral LD_{50} values are generally in the range of 350-500 mg/kg bw for rodents; significant differences in toxicity are not apparent between 2,4-D and its salts and esters.

Subchronic oral administration of 2,4-D at daily doses of ~15.0 mg/kg/day caused alterations in hematology, in kidney and brain weights, and alterations in pituitary and adrenal weights, as well as in the liver enzymes LDH, SGOT, SGPT and alkaline phosphatase, which were biologically and stat- istically significant in mice and rats. Effects at 45 mg/kg/day or higher included GI disturbances as well as acute toxicity to hepatic tissues. Effects of higher doses included GI irritation and mild hepatic effects as well as symptoms and signs characteristic of acute exposures. Dogs appear to be more sensitive and guinea pigs less sensitive to subchronic oral administration of 2,4-D. Repeated s.c. or i.p. injection of 100-200 mg/kg bw 2,4-D cause pathological and functional effects in the liver, kidneys, lungs, thyroid, and nervous system of rats and mice, but systemic toxicity is not produced by daily dermal application of 2,4-D dimethylamine salt or esters to rabbits.

Chronic oral administration of 2,4-D at levels of up to ~78 mg/kg bw/day has no effect on hematological indices, clinical chemistry indices or non-tumor pathology in rats. Administration of 2,4-D in the diet of dogs for 2 years at levels up to ~14.5 mg/kg bw/day did not produce adverse gross or histopathological effects.

There are conflicting and unresolved reports of induction of lymphosarcoma in rats that were administered 2,4-D in the diet at levels in the range of 0.25-62.5 mg/kg bw/day for 2 years, but administration of 2,4-D or the isopropyl, butyl or isooctyl esters by intubation before weaning (46-100 mg/kg bw/day) and subsequently in the diet (~14-42 mg/kg bw/day) for 73-90 weeks was not tumorigenic. Rats or mice fed 2,4-D amine salt at 0.10% of the LD_{50} level for life reportedly did not develop a significant increase in tumors. Single s.c. injections of 2,4-D isooctyl ester were associated with reticulum cell carcinomas in mice after 78 weeks of latency, but similar injections of 2,4-D acid or the isopropyl or isobutyl esters were not tumorigenic. Repeated dermal applications of 2,4-D to mice produced skin papillomas only when treatment was preceded by application of the initiator 3-methylcholanthrene. A 1985 industry sponsored rat and mouse bioassay is available but on an interim basis has not been critically evaluated in this document. Note is made that EPA's Office of Pesticide Programs, in a March 23, 1988 Federal Register Notice proposes that the available animal evidence be viewed as inadequate to assess the carcinogenic potential in animals.

Five epidemiologic studies provide evidence of cancer induction from exposure to a class of compounds-chlorophenoxy herbicides. Both EPA and IARC have judged this evidence to be limited according to weight-of-evidence guidelines. The evidence for 2,4-D alone prior to a 1986 study by Hoar et al. was clearly inadequate, the Hoar et al. study raises questions as to whether the epidemiologic evidence for 2,4-D is now more substantial.

On an interim basis this document defers an evaluation of the human weight of evidence by the CAG in recognition of additional data forthcoming from NCI epidemiologic investigators. Note is made that the Office of Pesticide Programs (March 23, 1988) has proposed that the human data base including the Hoar et al., 1986 findings be considered inadequate for OPP regulatory use. The Pesticide Programs also propose that new animal studies be conducted and that the cancer evidence be reconsidered depending on the findings of such studies or the availability of newer epidemiologic information.

2,4-D has been tested for mutagenicity in a variety of assays (e.g., plant, bacteria, yeast, fruit flies, in vitro and in vivo mammalian systems), but there is a preponderance of negative and inconsistent results in the animal assays. It appears that these varied results may be attributed to differences in pH. At physiological pH, 2,4-D exists in the ionized state, where it less readily crosses cell membranes than when in the non-ionized state; the inconsistent results may indicate that sufficient levels of 2,4-D did not reach the target sites.

Teratogenicity testing with several species of rodents indicates that 2,4-D and several of its esters and other derivatives are embryotoxic, but only weakly teratogenic or non-teratogenic. Malformations generally consisted of cleft palate and other skeletal effects, but the threshold for adverse fetal effects is not clearly defined; sporadic evidence of mild fetotoxicity was reported in orally treated rats at doses as low as 12.5-25 mg 2,4-D/kg bw/day for both 2,4-D and 2,4-D esters. Multigeneration studies indicated that 2,4-D caused increased mortality in preweanling rats, but produced no adverse effects on litter size or fertility.

Reports of humans who acutely ingested 2,4-D solutions or were exposed to 2,4-D formulations via industrial or agricultural exposure indicate that symptoms of gastritis, vomiting, loss of consciousness, neurological signs (e.g., reflex disorders) and muscular paralysis precede death. Autopsies of fatal poisoning cases have shown widespread pathologic effects (e.g., congestion and hyperemia of most organs, hepatic necrosis). An inadequately reported epidemiology study concluded that chronic exposure to 2,4-D did not produce adverse clinical effects.

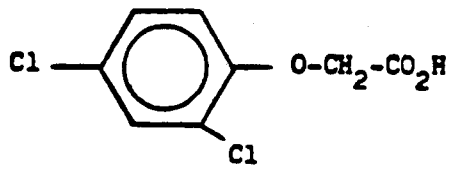
A non-lethal single oral dose in mice that represents a lowest-observed-adverse-effect level (LOAEL) was used to derive a 1-day HA for ingestion of 2,4-D in drinking water of 1.1 mg/ℓ for children. A 10-day HA of 0.30 mg/ℓ for children was derived from subchronic NOAELs in rats. A lifetime Drinking Water Equivalent Level (DWEL) of 0.35 mg/ℓ is recommended at this time based on a subchronic rat NOAEL.

II. PHYSICAL AND CHEMICAL PROPERTIES

Description

2,4-Dichlorophenoxyacetic acid (2,4-D) is a white to yellow crystalline powder that is used almost exclusively as an herbicide and to increase the latex output of old rubber trees, prevent preharvest drop in citrus trees and increase storage life of citrus fruit (Hawley, 1977; Ayers et al., 1976; Bovey and Young, 1980). It is also used as an herbicide for aquatic plants.

The chemical structure of 2,4-D, the Chemical Abstracts Service (CAS) Registry Number and the Registry of Toxic Effects of Chemical Substances (RTECS) number are given below.



CAS Number: 94-75-7

RTECS Number: AG6825000

Physical Properties

The physical properties of 2,4-D and four derivatives are presented in Table II-1.

Solubility in Organic Solvents (Herbicide Handbook, 1979)

acetone	-	850,000 mg/ℓ at 25°C
ethanol (95%)	-	1,300,000 mg/ℓ at 25°C
isopropanol	-	316,000 mg/ℓ at 31°C
benzene	-	10,700 mg/ℓ at 28°C

TABLE II-1

Physical Properties of Some 2,4-D Compounds[a]

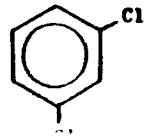
Compounds	Structure	Molecular Formula	Molecular Weight	Melting Point (°C)	Boiling Point (°C)	Density	Vapor Pressure (Torr)	Physical State	Water Solubility
2,4-D	$ArOCH_2COOH$	$C_8H_6Cl_2O_3$	221.04	140-141 135-138 (tech.)	160 (at 0.4 torr)	1.57 (at 30°C)	NA	white crystals, odorless when pure	540 mg/ℓ at 20°C (Melnikov, 1971); 725 mg/ℓ at 25°C (Bailey and White 1965); 900 mg/ℓ at 25°C (Herbicide Handbook, 1979)
2,4-D Sodium Salt	$ArOCH_2COONa$	$C_8H_5Cl_2O_3Na$	243.03	216-218	NA	NA	NA	white crystals	27.5 g/100 g H_2O at 0°C: 33.5 g/100 g H_2O at 20°C: 50.6 g/100 g H_2O at 30°C
2,4-D Dimethylamine Salt	$ArOCH_2COONH_2(CH_3)_2$	$C_{10}H_{13}Cl_2NO_3$	266.12	85-87	NA	NA	10^{-6} at 20°C[b]	white odorless crystalline solid	300 g/100 g H_2O at 20°C
2,4-D Butoxyethyl Ester	$ArOCH_2COOCH_2CH_2OCH_2CH_2CH_2CH_3$	$C_{14}H_{18}Cl_2O_4$	321.20	NA	156-162 (at 1-1.5 torr) 185-190 (at 5.5-7 torr)	NA	see Table II-2	viscous, colorless, odorless liquid when pure	12 mg/ℓ at 25°C
2,4-D n-Butyl Ester	$ArOCH_2COOCH_2CH_2CH_2CH_3$	$C_{12}H_{14}Cl_2O_3$	277.15	9	146-147 (at 1 torr)	1.235-1.245 at 25°C	see Table II-2	clear, colorless when pure	46 mg/ℓ at 25°C

[a]Sources: Weast, 1980; Herbicide Handbook, 1979; Melnikov, 1971; Zepp et al., 1975

[b]No reference or experimental method was provided for this value

NA - Not available

tech. - technical

Ar = 

toluene	-	6,700 mg/ℓ at 25°C
xylene	-	5,800 mg/ℓ at 25°C
diethyl ether	-	270,000 mg/ℓ at 25°C
dioxane	-	785,000 mg/ℓ at 31°C
n-heptane	-	1,100 mg/ℓ at 25°C (Melnikov, 1971)
carbon tetrachloride	-	1,000 mg/ℓ at 25°C
carbon disulfide	-	5,000 mg/ℓ at 29°C

pK_a Values for 2,4-D

The pK_a values for 2,4-D in water at 25°C are listed below with the method of determination (2,4-D is a weakly acidic herbicide, pK_a is the negative log of the ionization constant):

pK_a	Method	Reference
2.87±0.6	spectrophotometric	Cessna and Grover, 1978
2.73	potentiometric	Nelson and Faust, 1969
2.96	potentiometric	Wedding et al., 1954
2.90	conductimetric	Matell and Lindenfors, 1957
2.92	conductimetric	Wershaw et al., 1967
3.28	unspecified	Andus, 1949

According to Cessna and Grover (1978), their spectrophotometric method yields the most accurate pK_a value claiming that potentiometric titration is not ideal for many herbicides because of their low solubilities; that the conductimetric method, although suitable at low concentrations, has to be performed at a number of dilutions, with each conductimetric value requiring different activity corrections; and that activity corrections are quite tedious. This results in the wide range of pK_a values (Cessna and Grover, 1978).

Vapor Pressures of 2,4-D Esters

Vapor pressures of several 2,4-D esters are listed in Table II-2. These data are not consistent, which is probably the result of the experimental method; however, even measurements using the same method can vary almost an order of magnitude. For example, 2,4-D isopropyl ester vapor pressure measured by gas liquid chromatography is reported to be 1.40×10^{-3} and 4.60×10^{-5} mm Hg at 25°C (see Table II-2). This variation makes calculations based on the vapor pressure difficult to interpret. Conversion factors for those esters listed in Table II-2 are presented in Table II-3.

Ultraviolet Absorption Data for 2,4-D

λ max = absorption wavelength, ε = extinction coefficient values

ionized		unionized	
λ max	ε	λ max	ε
290	1490	288	1310
283	1680	281	1500
229	7240	226	6960
202	26300	202	25500
in solution of 0.001 M KOH		in solution of 0.2 M HCl	

There is little difference in absorption spectra between the anionic and molecular forms (NRCC, 1978).

Aqueous Degradation

Chemical hydrolysis plays an important role in 2,4-D ester degradation in basic natural water but is minimal in neutral or acidic water (Zepp et al., 1975; Mill, 1980). Zepp et al. (1975) estimated that the hydrolytic half-life of the methyl, isopropyl, n-butyl, n-octyl and isooctyl esters at

TABLE II-2

Summary of Vapor Pressure Data for Various 2,4-D Esters*

Ester	Vapor Pressure (mm Hg)	Temperature (C°)	Method	Reference
Methyl	1.55×10^{-3}	26.6	Boiling point determinations	Mullison and Hummer, 1949
	12.70×10^{-3}	25	Transpiration	Warren and Gillies, 1952
	2.30×10^{-3}	25	Gas liquid chromatography	Jensen and Schall, 1966
Ethyl	0.86×10^{-3}	26.6	Boiling point determinations	Mullison and Hummer, 1949
	11.50×10^{-3}	25	Transpiration	Warren and Gillies, 1952
	1.10×10^{-3}	25	Gas liquid chromatography	Jensen and Schall, 1966
n-Propyl	7.20×10^{-3}	25	Transpiration	Warren and Gillies, 1952
Isopropyl	1.20×10^{-3}	26.6	Boiling point determinations	Mullison and Hummer, 1949
	10.50×10^{-3}	25	Transpiration	Warren and Gillies, 1952
	1.05×10^{-2}	25	Transpiration	Vernetti and Freed, 1963
	1.40×10^{-3}	25	Gas liquid chromatography	Jensen and Schall, 1966
	4.60×10^{-5}	25	Gas liquid chromatography	Flint et al., 1968
	2.32×10^{-4}	25	Knudson cell	Kybett et al., 1976
n-Butyl	4.50×10^{-3}	25	Radioactive tracer	Warren and Gillies, 1952
	3.92×10^{-3}	25	Transpiration	Vernetti and Freed, 1963
	3.97×10^{-4}	25	Gas liquid chromatography	Jensen and Schall, 1966
	6.16×10^{-5}	25	Knudson cell	Kybett et al., 1976
n-Pentyl	3.00×10^{-3}	25	Transpiration	Warren and Gillies, 1952
n-Hexyl	2.10×10^{-3}	25	Transpiration	Warren and Gillies, 1952
n-Heptyl	1.35×10^{-3}	25	Radioactive tracer	Warren and Gillies, 1952
	0.02×10^{-3}	25	Gas liquid chromatography	Jensen and Schall, 1966
Tridecyl	0.40×10^{-3}	25	Transpiration	Warren and Gillies, 1952
2-Ethyl hexyl	2.00×10^{-6}	25	Gas liquid chromatography	Flint et al., 1968
Isooctyl	2.00×10^{-6}	25	Gas liquid chromatography	Flint et al., 1968
	7.06×10^{-6}	25	Knudson cell	Kybett et al., 1976
Butoxy ethyl	1.70×10^{-3}	25	Radioactive tracer	Warren and Gillies, 1952
	4.50×10^{-6}	25	Gas liquid chromatography	Flint et al., 1968
Propylene glycol butyl ether	3.00×10^{-6}	25	Gas liquid chromatography	Flint et al., 1968

*Source: NRCC, 1978

TABLE II-3

Conversion Factors for 2,4-D Esters

Ester	Conversion Factor
Methyl	1 ppm = 9.66 mg/m³ 1 mg/m³ = 0.104 ppm
Ethyl	1 ppm = 10.2 mg/m³ 1 mg/m³ = 0.0978 ppm
n-Propyl Isopropyl	1 ppm = 10.8 mg/m³ 1 mg/m³ = 0.0926 ppm
n-Butyl	1 ppm = 11.4 mg/m³ 1 mg/m³ = 0.0879 ppm
n-Pentyl	1 ppm = 11.95 mg/m³ 1 mg/m³ = 0.0837 ppm
n-Hexyl	1 ppm = 12.5 mg/m³ 1 mg/m³ = 0.0798 ppm
n-Heptyl	1 ppm = 13.1 mg/m³ 1 mg/m³ = 0.0763 ppm
Tridecyl	1 ppm = 16.5 mg/m³ 1 mg/m³ = 0.0605 ppm
2-Ethyl-hexyl Isooctyl	1 ppm = 13.7 mg/m³ 1 mg/m³ = 0.0731 ppm
Butoxy ethyl	1 ppm = 13.2 mg/m³ 1 mg/m³ = 0.0413 ppm
Propylene glycol butyl ether	1 ppm = 14.4 mg/m³ 1 mg/m³ = 0.0694 ppm

pH 9.0 and 6.0 were 1.1 hours and 44 days, 17.0 hours and 710 days, 5.2 hours and 220 days, 5.2 hours and 220 days and 37 hours and 1500 days, respectively. 2,4-D esters are photolytically degraded in water by >290 nm light, but limited data suggest that this rate is significantly slower than hydrolysis (Binkley and Oakes, 1974a,b; Zepp et al., 1975). Although abiotic degradation of 2,4-D may be rapid and is clearly a significant removal mechanism, 2,4-D appears to be degraded predominantly by biological processes (half-life of 1-2 weeks once biodegradation is detected) (Aly and Faust, 1964; Demarco et al., 1967; Boethling and Alexander, 1979).

Dioxins in 2,4-D

A number of studies have reported the presence of chlorinated dibenzodioxins in phenoxy herbicides including 2,4-D (Table II-4). In addition to these samples with positive contamination, Cochrane et al. (1980) analyzed 1 mixed butyl ester, 3 dimethylamine salts and 10 acid samples that contained no detectable dioxins. Thomas (1980) detected dichlorodibenzodioxins in 3 of 30 samples. Norstrom et al. (1979) analyzed five older 2,4-D samples and found no dioxins. There are few toxicology data available on these dioxins.

Summary

2,4-D is a crystalline powder used as an herbicide for both terrestrial and aquatic plants. It does not volatilize from water (although some of the esters are volatile) but is not persistent in water. Biodegradation is the major removal mechanism from water, although chemical hydrolysis of the esters is rapid at basic pH and photolysis may be significant. 2,4-D has not been shown to contain 2,3,7,8-TCDD but does contain low concentrations (<60 ppb) of some other chlorinated dioxins.

TABLE II-4

Dioxins in 2,4-D Samples

2,4-D Form	2,4-D Acid % (ppb)	Concentration of PCDDs					Country of Manufacture	Reference
		Di- (ppb)	Tri- (ppb)	1,3,6,9- or 1,3,6,8-Tetra- (ppb)	2,3,7,8-Tetra- (ppb)	Hexa- (ppm)		
Acid	44.6	ND	ND	ND	ND	NA	Canada[4]	Cochrane et al., 1980
	NR	ND	ND	ND	ND	NA	Canada	Cochrane et al., 1980
	NR	ND	ND	ND	ND	NA	Canada	Cochrane et al., 1980
	41.3	ND	ND	ND	ND	NA	Canada	Cochrane et al., 1980
	NR	ND	ND	ND	ND	NA	Canada	Cochrane et al., 1980
	41.7	ND	ND	ND	ND	NA	Canada	Cochrane et al., 1980
	37.9	ND	ND	ND	ND	NA	Canada	Cochrane et al., 1980
	NR	ND	ND	ND	ND	NA	Canada	Cochrane et al., 1980
	42.44	316	490	132	ND	NA	Canada	Cochrane et al., 1980
	43.10	275	587	136	ND	NA	Canada	Cochrane et al., 1980
	NR	ND	ND	ND	ND	NA	Canada	Cochrane et al., 1980
	NR	ND	ND	ND	ND	NA	Canada	Cochrane et al., 1980
	42.9	409	551	210	ND	NA	Canada	Cochrane et al., 1980
	42.9	ND	ND	ND	ND	NA	Canada	Cochrane et al., 1980
	NR	ND	ND	ND	ND	NA	Canada	Cochrane et al., 1980
	NR	ND	ND	ND	ND	NA	Canada	Cochrane et al., 1980
	NR	ND	ND	ND	ND	NA	Canada	Cochrane et al., 1980
	NR	ND	ND	ND	ND	NA	Canada	Cochrane et al., 1980
	42.55	140	230	96	ND	NA	Canada	Cochrane et al., 1980
	42.66	ND	38	54	ND	NA	Canada	Cochrane et al., 1980
	42.74	ND	584	278	ND	NA	Canada	Cochrane et al., 1980
	42.74	5	54	20	ND	NA	Canada	Cochrane et al., 1980
	49.59	33	533	208	ND	NA	Canada	Cochrane et al., 1980
	42.74	ND	ND	ND	ND	NA	Canada	Cochrane et al., 1980
	NR	ND	ND	ND	ND	NA	Canada	Cochrane et al., 1980
	NR	ND	ND	ND	ND	NA	Canada	Cochrane et al., 1980
	NR	NA	NA	ND[a]	ND[a]	5-10	USA	Woolson et al., 1972
	NR	52.9	ND	ND	ND	NA	USA	Thomas, 1980
	NR	25.4	ND	ND	ND	NA	USA	Thomas, 1980
Iso-octyl ester	65.4	NA[b]	346	226	ND	ND	Canada	Cochrane et al., 1982
	65.4	722	79	717	ND	ND	Canada	Cochrane et al., 1982
	50	200	632	1752	ND	ND	Canada	Cochrane et al., 1982
	65.1	104	639	315	ND	ND	Canada	Cochrane et al., 1982
	60	238	825	852	ND	ND	Canada	Cochrane et al., 1982
	70	109	929	486	ND	ND	Canada	Cochrane et al., 1982
	48.1	NA[b]	NA[b]	384	ND	ND	Canada	Cochrane et al., 1982
	42.9	474	450	8730	ND	ND	Canada	Cochrane et al., 1981
								Cochrane et al., 1981

TABLE II-4 (cont.)

2,4-D Form	2,4-D Acid % (ppb)	Concentration of PCDDs: Di- (ppb)	Tri- (ppb)	1,3,6,9- or 1,3,6,8-Tetra- (ppb)	2,3,7,8-Tetra- (ppb)	Hexa- (ppm)	Country of Manufacture	Reference
Iso-octyl ester	55.2	674	422	466	ND	ND	Canada	Cochrane et al., 1981
	55.0	110	385	127	ND	ND	Canada	Cochrane et al., 1981
	55.0	362	53	414	ND	ND	Canada	Cochrane et al., 1981
	52.36	NA[b]	346	226	ND	ND	Canada	Cochrane et al., 1981
	52.17	722	79	717	ND	ND	Canada	Cochrane et al., 1981
	46.55	200	632	1752	ND	ND	Canada	Cochrane et al., 1981
	NR	104	639	315	ND	ND	Canada	Cochrane et al., 1981
	45.46	238	825	852	ND	ND	Canada	Cochrane et al., 1981
	61.57	109	929	486	ND	ND	Canada	Cochrane et al., 1981
	54.3	151	102	120	ND	ND	Canada	Cochrane et al., 1981
Mixed butyl ester	68.3	815	273	219	ND	ND	Canada	Cochrane et al., 1981
	67.2	503	659	311	ND	ND	Canada	Cochrane et al., 1981
	69.5	295	371	314	ND	ND	Canada	Cochrane et al., 1981
	67.8	293	385	175	ND	ND	Canada	Cochrane et al., 1981
	NR	NA[b]	NA[b]	317	ND	ND	Canada	Cochrane et al., 1981
	47.26	NA	NA	NA	NA	NA	Canada	Cochrane et al., 1981
	67.68	151	102	120	ND	ND	Canada	Cochrane et al., 1981
	67.57	264	35	148	ND	ND	Canada	Cochrane et al., 1981
	NR	102	684	317	ND	ND	Canada	Cochrane et al., 1981
	50.0	ND	ND	ND	ND	ND	Canada	Cochrane et al., 1982
	NR	200	160	210	ND	ND	Canada	Cochrane et al., 1982
Dimethyl amine salt	50.0	ND	38	54	ND	ND	Canada	Cochrane et al., 1982
	50.0	ND	584	278	ND	ND	Canada	Cochrane et al., 1982
	50.0	5	54	20	ND	ND	Canada	Cochrane et al., 1982
	50.0	ND	ND	ND	ND	ND	Canada	Cochrane et al., 1982
	60.0	33	533	208	ND	ND	Canada	Cochrane et al., 1982
	50.0	ND	ND	ND	ND	ND	Canada	Cochrane et al., 1982
	50.0	ND	ND	ND	ND	ND	Canada	Cochrane et al., 1982
Propylene glycol butyl ester	48.8	134	418	384	ND	ND	Canada	Cochrane et al., 1982
Butoxy propyl ester	NR	59.7	ND	ND	ND	ND	USA	Thomas, 1980

[a]<0.5 ppm

[b]Not analyzed due to coeluting interferences

NA = Not analyzed; ND = Not detected at <1 ppb; NR = Not reported

III. TOXICOKINETICS

Absorption

Available data for nonruminant mammals indicate that absorption of 2,4-D from the GI tract is rapid and virtually complete.

Erne (1966a) administered various forms of 2,4-D by gavage to rats and pigs that were fasted overnight. When a single oral dose of 2,4-D triethanolamine salt equivalent to 100 mg/kg 2,4-D was given to male rats, peak plasma concentrations of 200 µg/mℓ 2,4-D were reached by 7 hours. Pigs that received 50 or 100 mg/kg of the compound had peak plasma levels of 120 and 210 µg/mℓ, respectively, by 5 hours postexposure. When rats were given single doses of the potassium-sodium salt of 2,4-D (equivalent to 100 mg/kg 2,4-D), absorption was similar to that of the 2,4-D amine. Similar administration of 2,4-D butyl ester (100 mg 2,4-D/kg) to rats resulted in much lower plasma levels (~20 µg/mℓ) than were reached at a later time (~7 hours). Erne (1966a) suggested that incomplete and delayed absorption of 2,4-D butyl ester accounted for the observed lower plasma levels, since its solubility in water is poor. Only the acid form of 2,4-D, rather than the intact ester, could be found in plasma at any time after dosing; thus, the author concluded that the ester underwent complete hydrolysis during absorption.

Khanna and Fang (1966) reported that 93-96% of an oral dose of 3-30 mg/kg of ^{14}C-2,4-D (acid) to rats was excreted almost entirely in the urine within 24 hours of dosing. Smith et al. (1980) recovered 90% of an administered dose in the urine of rats of up to 150 mg/kg 2,4-D as the sodium salt in 12 hours and 95% in 24 hours, indicating >95% absorption.

When ^{14}C-2,4-D was administered to rats as a bolus of 10 µmole/kg (containing 10 µCi/kg in a volume of 0.5 mℓ/kg) through the duodenal cannula, ~92% of the administered radioactivity was recovered in the urine after 24 hours (Sieber, 1976).

The rapid absorption of 2,4-D observed in experimental animals has been confirmed by studies that used human volunteers. Although individual variation was appreciable, significant levels of 2,4-D were detected in six men as early as 1 hour following ingestion of 5 mg/kg. Peak plasma levels were obtained within 7-24 hours and averaged ~35 µg/mℓ (Kohli et al., 1974; Khanna and Kohli, 1977).

In a similar study by Sauerhoff et al. (1977), oral administration of the same dose, 5 mg/kg 2,4-D, to three men also resulted in rapid absorption with peak levels of between 9 and 25 µg 2,4-D/mℓ plasma, achieved within 4 hours after ingestion. Values for absorption rate coefficients (k_a) were calculated using a nonlinear parameter estimation program and were reported as 0.165, 0.202 and 0.415 h^{-1} for the three subjects.

Dermal application of 4 µg/cm² of 2,4-D acid in acetone to the forearms of six men resulted in total excretion of 5.8% of the administered dose in the urine collected over 5 days. Measurable amounts were detected in the urine as early as 4 hours after exposure, indicating rapid percutaneous absorption (Feldman and Maibach, 1974).

An abstract of a study by Draper and Street (1982) reported dermal exposure to 2,4-D (1.2-18 mg of 2,4-D was washed from the hands of men engaged

in spray applications) resulted in maximum urinary excretion between 16 and 40 hours after the exposure. Inhalation exposure was minimal; further details were not reported.

Distribution

Erne (1966a) conducted a study on the distribution of 2,4-D as the triethanolamine salt using rats and pigs. The animals were given single oral doses of 2,4-D equivalent to 100 mg 2,4-D/kg and were killed by exsanquination. Tissues containing the highest levels of 2,4-D in both species at 6 hours were the liver, kidney, lungs and spleen. These levels declined after 24 hours. Brain levels of 2,4-D in the pigs were relatively low, ~5% of plasma levels, but could be increased by repeated administration of toxic doses. Only trace amounts of 2,4-D were found in fat. The butyl ester form of 2,4-D was distributed in a similar manner, but lower tissue levels were achieved. Apparent volumes of distribution (V_d) of different 2,4-D compounds (amine, potassium-sodium salt, butyl ester), estimated from elimination data plotted on a semi-logarithmic scale, ranged between 25 and 50% of the body weight, intermediate between extracellular body volume and total body water. These estimates suggested that some of the compound entered cells. The results of the *in vitro* study by Erne (1966a) support this concept by reporting ~10% of plasma levels of 2,4-D were found in blood cells.

Khanna and Fang (1966) reported tissue levels of 2,4-D in rats killed at various times between 1 and 41 hours after receiving 1 or 80 mg of ^{14}C 2,4-D by gavage. Distribution was widespread; radioactivity was detected in all of 12 tissues examined. Peak concentrations were reached in the tissues

between 6 and 8 hours at the low dose with no detectable radioactivity after 24 hours. At the high-dose level, peak concentrations were reached at 8 hours, remained fairly constant for 17 hours and then declined; however, radioactivity was still detected after 41 hours. The highest levels of radioactivity were found in blood, liver, kidney, heart, lungs and spleen, with lower levels in muscle and brain. At 17 hours after the high dose and at 1 hour after the low dose, the kidney level exceeded that of plasma. The intracellular distribution of 2,4-D was also investigated in kidney, liver, spleen, brain, heart and lungs. Higher levels of radioactivity were found in the soluble and nuclear fraction and relatively low levels were found in the mitochondrial and microsomal fractions.

The observations of low accumulations of 2,4-D in adipose tissue (Erne, 1966a; Khanna and Fang, 1966) and the low level of absorption by intestinal lymphatics observed by Sieber (1976) are not surprising. Sieber (1976) collected samples of perirenal or mesenteric fat from rats killed 24 hours after administration of a bolus dose of ^{14}C-2,4-D (10 μmoles/kg) through a duodenal cannula during infusion with physiological salt solution. Only 1.0±1.7% of the administered radioactivity was found in body fat (estimated as 12% of body weight). This finding was consistent with the low chloroform: buffer partition coefficient (0.007±0.002) for 2,4-D, indicating very low lipid solubility.

Some studies (Erne, 1966a; Khanna and Fang, 1966) report that relatively low levels of 2,4-D were found in the brain. Erne (1966a) found that brain levels of 2,4-D could be increased by increasing the dose. In support of this observation are the results of Elo and Ylitalo (1977, 1979), who demon-

strated that 2,4-D levels in the brain and CSF of rats could be greatly increased if the animals were pretreated with high (250 mg/kg) s.c. injections of 2,4-D sodium salt before i.v. administration of 8 μCi/kg ^{14}C-2,4-D with a specific activity of 0.9 μCi/mg. The measure of radioactivity in tissues as a percentage of plasma levels 3.5 and 4.5 hours after ^{14}C-2,4-D administration showed plasma levels reduced to 67%, while liver levels increased ~3.5 times, and testis, lung, heart and muscle levels increased ~2-fold when compared with levels in saline-pretreated controls. Pretreatment greatly increased the brain level by 6.5 times (2.3% in controls, 15% in pretreated rats) and the CSF level by 23.5 times (0.4% in control, 9.4% in pretreated rats).

The low levels of 2,4-D in brain tissue after a low dose is assumed to be due to the functioning of the blood-brain barrier. Based on experiments investigating 2-chloro-2-methyl phenoxyacetic acid (MCPA) binding to plasma protein in vitro, the authors suggested that if plasma protein binding sites are saturated by the high exposure levels, more unbound ^{14}C-2,4-D is free to be distributed to tissues (Elo and Ylitalo, 1979). The binding of 2,4-D to serum protein has been confirmed by in vitro studies (Mason, 1975; Haque et al., 1975; Kuhne et al., 1979; Fang and Lindstrom, 1980). The greater enhancement of brain and CSF accumulation of 2,4-D at high doses may be due to disruption (by high circulating levels of unbound 2,4-D) of the blood-brain barrier, with increased influx or decreased efflux or a combination of both processes (Elo and Ylitalo, 1979).

This hypothesis is supported by a study by Pritchard (1980), who demonstrated that ^{14}C-2,4-D was capable of being actively transported by rabbit choroid plexus preparations in vitro. The uptake of 2,4-D by the choroid plexus was shown to be energy dependent (inhibited by metabolic inhibitors), saturable, and specific for organic anions. 2,4-D was also shown to inhibit the transport of 5-hydroxy-3-indole-acetic acid, a metabolite of the neurotransmitter, serotonin. Since 2,4-D has been found in brain tissues, Pritchard (1980) suggested that 2,4-D can be accumulated in the brain in much the same way as the kidney accumulates this substance (see Elimination Sections). Intracellular binding before efflux may account for the observed brain levels of 2,4-D and for the CNS toxicity.

The distribution of 2,4-D in pregnant animals has also been studied. Lindquist and Ullberg (1971) subjected late stage pregnant mice (gestational day not specified) to whole body autoradiography following i.v. injection of ^{14}C-2,4-D (10 μCi = 0.05 mg/mouse) and killing at 5 minutes, 20 minutes, 1 hour, 4 hours and 24 hours. The autoradiograms showed that 2,4-D accumulated in the visceral yolk sac epithelium to a small degree, entered the fetus and was eliminated from all tissues within 24 hours.

The ability of 2,4-D to cross the placenta was also investigated by Fedorova and Belova (1974), who administered a single intragastric dose of 0.05 mg/kg ^{14}C-2,4-D to pregnant rats on the 19th day of gestation. The rats were killed 24 hours later and the levels of radioactivity present in the uterus, placenta, fetus and intrauterine fluid were 2.7, 3.5, 4.7 and 4.9% of the administered dose, respectively.

Erne (1966a) also found that 2,4-D crossed the placenta of a sow fed 500 ppm 2,4-D during the entire term of pregnancy. Tissue levels of 2,4-D found in dead piglets (10 of 15 died) were 35 µg/g of liver, 27 µg/kg of kidney and 30 µg/g of lung. Upon delivery, the level of 2,4-D in the placenta was 45 µg/g.

Several forensic investigations have determined levels of 2,4-D in human tissue samples obtained at autopsy from people who had ingested fatally high doses. Nielsen et al. (1965) determined the following tissue levels (in micrograms of 2,4-D per gram of tissue) in an apparent suicide victim (a 23-year-old man who ingested ~62 g of 2,4-D): muscle, 70; spleen, 134; liver, 183; blood, 669; kidney, 63; brain, 12.5; adipose tissue, 165. Analysis of tissue samples taken at autopsy from an elderly man who died 6 days after ingesting an unknown quantity of 2,4-D revealed the following tissue concentrations of 2,4-D (in µg/g tissue): blood, 57.6; brain, 93.4; kidney, 193.4; liver, 407.9; and muscle, 117.5 (Dudley and Thapar, 1972). Geldmacher et al. (1966) reported the following tissue levels of 2,4-D (µg/g tissue) in two fatalities: case one (33-year-old woman) - blood, 480; brain, 62; kidney and liver combined, 113; and case two (51-year-old woman) - blood, 25; brain 164; liver, 116; lungs, 88; and heart, 63. Levels of 2,4-D determined in the tissues of a female suicide victim (in µg/g tissue) were reported in an abstract (Coutselinis et al., 1977): liver, 21; spleen, 12; and kidney, 82.

Quantitative comparisons of the above information are difficult to make because of the unknown amounts of 2,4-D ingested and the uncertainty of the time of death after ingestion (the elderly man died 6 days after ingesting

2,4-D). There was also much variation between the victims with respect to relative blood to kidney or liver to kidney ratios. These studies do, however, confirm the findings in animal investigations that 2,4-D is widely distributed throughout the body tissues after oral administration of high doses.

Sauerhoff et al. (1977) calculated apparent V_d for three men who ingested 5 mg/kg 2,4-D. The changes in plasma levels with time indicated a one-compartment model for subjects 2 and 3, while a two-compartment model seemed more appropriate for the data of subject 1 (biphasic plasma elimination curve). The Vd values were 238 and 294 mℓ/kg for subjects 2 and 3, respectively. Vd_1 (for the central compartment) was 83 and Vd_2 (for the slow exchange compartment) was 218 mℓ/kg for subject 1. These small values indicated that 2,4-D was not widely distributed to tissues. Kohli et al. (1974) determined a Vd of ~100 mℓ/kg by averaging the data from six men who had ingested 5 mg/kg of 2,4-D, which is additional evidence of little distribution into the tissues of 2,4-D at low doses.

Metabolism

In studies to determine the extent of metabolism of 2,4-D, Erne (1966b) administered the amine salt of the compound to pigs, either in 3 oral doses of 50 mg/kg each, in 23 oral doses of 50 mg/kg each, or in the feed at 500 ppm for 5 months. The percent conjugation of 2,4-D in the urine of 6 pigs ranged from 0-18% conjugation as determined by differential acid hydrolysis. No correlation between the different exposure regimens and the amount of conjugation was evident. No significant amount of conjugation was detected in plasma. When 2,4-D butyl ester was administered orally to pigs (either 3

or 23 doses of 50 mg/kg each) or to rats (single dose of 100 mg/kg), only trace amounts of esterified compound could be detected in plasma, urine, red blood cells or liver, indicating complete hydrolysis of the ester linkage in vivo. The report did not state at what time after exposure these determinations were made.

Khanna and Fang (1966) found only unchanged 2,4-D in urine and tissue extracts from rats given oral doses of ~3-300 mg/kg ^{14}C-2,4-D when determined by paper chromatography. Countercurrent separation of urine and tissue extracts, however, indicated the presence of a very small amount of a metabolite of 2,4-D. This metabolite accounted for ~0.25% of the radioactivity in urine samples, 0.7% in the lung extracts and 6.1% in the liver. Paper chromatography of the metabolite using a 2-propanol-NH_4OH-H_2O solvent system gave an R_f of 0.67-0.69, compared with an R_f of 0.55-0.59 for 2,4-D. Further characterization was not performed.

Whole body extracts of mice prepared after an s.c. injection of 100 mg/kg 2,4-D, 2,4-D butyl ester or 2,4-D isooctyl ester in dimethylsulfoxide failed to show the presence of 2,4-dichlorophenol, suggesting that cleavage of the ether linkage is not a major metabolic pathway in animals (Zielinksi and Fishbein, 1967). Grunow and Boehme (1974) found primarily unchanged 2,4-D in the urine of rats administered 200 mg/kg of 2,4-D; ~3% of the administered dose was identified as the glycine and taurine conjugates of the compound.

Limited human data also indicate that 2,4-D does not undergo biotransformation to any great extent. Of five men who ingested 5 mg/kg of 2,4-D,

four excreted between 4.8 and 27.1% of the administered dose as conjugated 2,4-D. The rest of the 2,4-D excreted (82%) was detected as unchanged compound (Sauerhoff et al., 1977). Similarly, ~10% of the total 2,4-D excreted in the urine of a man who had ingested an herbicide containing 2,4-D and mecoprop [i.e., 2-(4-chloro-2-methylphenoxy)propanoic acid], as the amine salts, was in the form of acid-labile conjugates. The total dose was unknown but was sufficient to result in unconsciousness and myotonia (Park et al., 1977). Urine samples, collected from six men who ingested 5 mg 2,4-D/kg, were analyzed by gas chromatography and found to contain no metabolic products of the compound (Kohli et al., 1974).

Elimination

The elimination of 2,4-D (administered as the triethanolamine salt, the potassium-sodium salt, or the butyl ester) from the tissues of rats and pigs was studied by Erne (1966a) following single oral doses equivalent to 100 mg 2,4-D/kg. Blood samples were collected at 2-3 hour intervals for 12 hours after dosing and then less frequently for up to 50 hours, and then were analyzed for 2,4-D. Plasma half-life values (Table III-1) were calculated from semilogarithmic dose-elimination curves. The linearity of the terminal curves indicated first order elimination rates. As seen from Table III-1, the elimination of 2,4-D from the plasma in rats occurred at a slightly slower rate after administration of the butyl ester than after administration of the amine salt or potassium-sodium salt. Intact butyl ester was detected only in trace amounts in plasma; 2,4-D acid was the predominant form present in plasma (and tissues) after oral administration of the ester.

TABLE III-1

Plasma Half-Life Values of 2,4-D After Administration of a Single Oral Dose of 2,4-D Salt or Ester Equivalent to 100 mg 2,4-D/kg*

Administered Compound	Species	Plasma Half-life (hours)
2,4-D amine	Rat, male	2.9 ± 0.4
	Rat, female	3.3 ± 0.5
	Pig	12 ± 2
2,4-D K-Na salt	Rat, male	3.5 ± 0.5
2,4-D butyl ester	Rat, male	6 ± 1
	Pig	10 ± 0.8

*Source: Erne, 1966a

Erne (1966a) observed lower rates of elimination of 2,4-D from tissue (tissue half-life values for rats ranged between 5 and 10 hours, for pigs between 10 and 30 hours) than from plasma. Elimination of 2,4-D was essentially complete within 72 hours. Thus, 2,4-D did not accumulate in the tissues examined (Erne, 1966a).

Zielinski and Fishbein (1967) compared the differences in whole body elimination from mice given single s.c. injections of 100 mg/kg 2,4-D, 2,4-D butyl ester, or 2,4-D isooctyl ester in dimethylsulfoxide. The mice were killed various times after dosing, homogenized, and the extracts analyzed by gas chromatography for each compound. The whole body half-life values (assuming first order kinetics) were reported as 4.1 hours for 2,4-D, 1.1 hours for 2,4-D butyl ester and 3.4 hours for 2,4-D isooctyl ester. The esters did not appear to be hydrolyzed, as 2,4-D was not detected upon methylation of the whole mouse extracts. Differences between the results of this experiment and the data of Erne (1966a) may be attributable to route of administration and the use of dimethylsulfoxide as a vehicle by Zielinski and Fishbein (1967). Erne (1966a) administered the butyl ester of 2,4-D as an emulsion of the ester in petroleum solvent, with water.

Fedorova and Belova (1974) reported that, following oral administration of ^{14}C-2,4-D to rats at a level of 0.05 mg/kg, 92.1% of the administered dose was excreted in the urine within 3 days, while 6.1% of the radioactivity was detected in the feces in this time period. The study demonstrated that 2,4-D was excreted in the milk of nursing rats given a single oral dose of 100 mg/kg ^{14}C-2,4-D immediately after delivery. Radioactivity was

detected in the GI tract of pups killed up to 7 days after birth, with the maximum amount of 2,4-D excreted during the second or third day.

The excretion pattern of ^{14}C-1-2,4-D or ^{14}C-2-2,4-D in rats was studied by Khanna and Fang (1966). No radioactivity was found in the expired carbon dioxide of rats that were given oral doses of 3-300 mg/kg, although 93-96% and 94-98% of the radioactivity was detected in the urine and feces within 24 and 48 hours, respectively, after dosing with 3-30 mg/kg ^{14}C-2,4-D. Almost all of the 2,4-D had been excreted in the urine, with a small unspecified amount in the feces. As the dose of ^{14}C-2,4-D was increased (60-300 mg/kg), the percentage of radioactivity recovered in the urine and feces declined in a linear fashion; excretion was not complete even 144 hours after administration of 300 mg/kg.

Elimination of 2,4-D from tissues appeared to be complete within 24 hours after low doses were given (Khanna and Fang, 1966). When the dose was raised to ~240 mg/kg ^{14}C-2,4-D, radioactivity was still detected at 41 hours and the elimination appeared to be biphasic, with the second phase becoming apparent ~30 hours after dosing. The half-life values for the initial phase of elimination from blood, liver, kidney, heart, lungs and spleen were averaged and reported as 3.1 hours (range: 3.0-3.5 hours) as opposed to ~0.58 hours when the dose was 3 mg/kg. These values were crude estimates based upon levels of radioactivity determined from animals killed sequentially at various times after dosing.

Smith et al. (1980) also observed a dose-dependent biphasic urinary excretion pattern of 2,4-D in rats. A maximum urinary excretion rate of 7 mg/kg/hour was determined for rats given single oral doses of 10-150 mg/kg of the compound or injected i.v. with doses of 5 or 75 mg/kg of the 2,4-D sodium salt. Urinary excretion showed a biphasic pattern, with half-life values of 2 and 21 hours estimated for the fast phase and for the slow phase, respectively.[47] Urinary excretion patterns became nonlinear at dose levels ≥100 mg/kg 2,4-D. The observations of Khanna and Fang (1966) and Smith et al., (1980) on delayed elimination of 2,4-D at high doses suggest a saturation mechanism.

Sauerhoff et al. (1977) studied the pharmacokinetic profile of 2,4-D administered orally to five human male volunteers. Following ingestion of 5 mg/kg of the compound, the subjects excreted an average of 82% of the dose as unchanged 2,4-D in the urine collected over 6 days (range: 48-97%). The average urinary half-life of 2,4-D was estimated to be 17.7 hours (range: 10.2-28.5 hours), using a one-compartment linear model for each individual set of data. Plasma clearance of the compound occurred by apparent first-order process with an average half-life of 11.6 hours; however, one of the three subjects investigated showed plasma clearance kinetics that suggested a two-compartment model rather than a one-compartment model. The researchers did not establish the factors that accounted for the wide range of calculated kinetic values; the authors suggested that changes in levels of protein binding and kidney function may be important. A delayed peak in urine excretion was also observed in the subject for whom a two-compartment model was indicated (on the basis of biphasic plasma elimination).

The elimination of 2,4-D was similarly studied by Kohli et al. (1974) in six men who also ingested 5 mg/kg of the compound. Gas chromatography analysis of urine samples detected 2,4-D as early as 2 hours after ingestion. By 4 days, an average of 77% of the administered dose of 2,4-D had been excreted as unchanged compound. The calculated half-life for plasma clearance was 33±3.1 hours, which represents the mean for the six subjects. This half-life value for plasma clearance is ~3 times longer than that calculated by Sauerhoff et al. (1977); however, there were wide individual variations and small numbers of subjects in the two studies. After i.v. injection of 1 μCi of ^{14}C-2,4-D as a solution of 1 Ci/mℓ in propylene glycol to six men, 100% of the administered dose was recovered in the urine after 5 days. The estimated half-life of elimination of 2,4-D administered by this route was 13 hours (Feldmann and Maibach, 1974).

Young and Haley (1977) analyzed data collected from a case in which a young woman had survived the ingestion of a mixture of 2,4-D and Dicamba and was being treated for the intoxication. These investigators made certain assumptions: that the initial dose, D_0, was 12.29 g [20.1% of 100 mℓ mixture or 20.1 g x 0.9 (10% was lost because of gastric lavage) x 0.6788 (67.88% of the 2,4-D salt is free acid)]; that by the time of lavage, all 2,4-D had been absorbed; and an assumed time zero blood concentration (C_0) of an arbitrary value higher than the first measured blood level was picked. This value, 1100 μg/mℓ, was used to estimate the V_d.

$$D_0/C_0 = V_d = \frac{12.29\ g}{1100\ \mu g/m\ell} = 11.2\ \ell$$

Thus the data collected over 219 minutes for blood and urinary levels of 2,4-D were analyzed for best fit using an E.A.I. Pacer 500 Hybrid computer, and a one-compartment model for 2,4-D with an "interactive urinary excretion

pathway" (k' blood-urine) to account for Dicamba elimination. First-order rate constants (hr^{-1}) for the 2,4-D best-fit model were $k_{blood-feces}$ = 0.010; $k_{blood-urine}$ = 0.002; $k'_{blood-urine}$ = 0.030; k_e = 0.012 (without $k'_{blood-urine}$), k_e = 0.042 (with $k'_{blood-urine}$). The $t_{1/2}$ was 16.7 hours when the interactive urinary excretion pathway was not shared with Dicamba and 59 hours when Dicamba used this pathway. When a "tissue compartment" for the 2,4-D model was included in the computer analysis, no better fit was obtained. Even though many assumptions were made in the analysis, the results supported the view that 2,4-D is rapidly absorbed following oral exposure, is not accumulated to any great extent in tissues, and is rapidly eliminated from the body.

In urine collected over 5 days after the application of 4 mg/cm² of 2,4-D in acetone to the forearms of six volunteers, 5.8% of the applied dose was recovered (Feldmann and Maibach, 1974). The discussion of absorption of 2,4-D suggests that the exposure to humans engaged in 2,4-D spraying in experiments simulating operations is mainly dermal. Draper and Street (1982) reported in an abstract that maximum elimination of 2,4-D in the urine of male ground spray applicators occurred 16-40 hours after termination of exposure. Taskav et al. (1982) reported a relatively long retention time for 2,4-D in some of 11 subjects who participated in spraying with the herbicide, since an average of 5.05 µg of 2,4-D was detected in 12-hour pooled urine samples 5 days after exposure. The results of this study were widely variable and very poorly reported.

The half-life for elimination of 2,4-D calculated from data collected from men engaged in agricultural spraying of 2,4-D ranged from 35-48 hours

after a single exposure (Nash et al., 1982). One-time ground application of 2,4-D by 26 men resulted in mean 24-hour urinary excretion levels of 0.002 mg/kg for applicators, 0.003 mg/kg for mixer-loaders and 0.004 mg/kg for mixer-load applicators. Maximum mean 24-hour urinary excretion of 2,4-D by 17 men exposed intermittently during aerial spraying were 0.006 mg/kg for pilots and 0.02 mg/kg for mixer-loaders.

Blood and urine levels of 2,4-D have been determined in humans who were exposed to 2,4-D during spraying operations, but exposure occurred by both the inhalation and dermal routes. The limited data available suggest that exposure is mainly by the dermal route, but do not provide a basis for estimating the contribution of the dermal route to total absorption.

A poorly reported study by Taskav et al. (1982) reported mean serum levels of 106.63 ng/mℓ, ranging from trace amounts to 482 ng/mℓ, from blood collected immediately after spraying 6 gallons (3.8 lb acid equivalent/gal) of 2,4-D for 3 hours by 11 male volunteers. Exposures were determined from denim patches on the necks, chests and backs (dermal) and from air filter monitors (inhalation). Average amounts of residues on the denim patches were 131.45 µg/sq ft, while air filter residues averaged 43.1-60.1 ppt.

Plasma levels of 2,4-D in four men during a workweek of spraying a 2% emulsion of 2,4-D in kerosene ranged from undetectable amounts (<0.02 µg/mℓ) to 0.1-0.2 µg/mℓ. In this study, the exposures were intermittent and occurred by both dermal and inhalation routes (Kolmodin-Hedman and Erne, 1980).

In contrast, Lavy et al. (1982) detected very little, if any, 2,4-D in the urine of 18 men engaged in aerial spraying of the herbicide. Of 524 urine samples collected during the day of exposure and for 5 days afterward, only ~150 contained detectable amounts of 2,4-D. Those men with detectable levels were crew members who actually performed the spraying. Denim patches analyzed for dermal exposure and air filters analyzed for inhalation exposure contained very little 2,4-D, indicating minimal exposure by either route.

Summary

2,4-D triethanolamine and potassium-sodium salts are readily absorbed from the GI tract of nonruminant mammals and reach peak plasma concentrations as early as 7 hours in rats and 5 hours in pigs (Erne, 1966a). 2,4-D butyl ester is less completely absorbed and appears to be hydrolyzed to the free acid before absorption. That 2,4-D is rapidly and almost completely absorbed from the gut is suggested by reports of high urinary recoveries (90-96%) of intact 2,4-D within 24-48 hours in rats after oral administration (Khanna and Fang, 1966; Smith et al., 1980; Sieber, 1976). Studies with limited numbers of human volunteers have confirmed that 2,4-D is absorbed rapidly; significant levels have been detected in the plasma as early as 1 hour and peak plasma levels have been reached as early as 4-7 hours after ingestion (Kohli et al., 1974; Khanna and Kohli, 1977; Sauerhoff et al., 1977).

The presence of 2,4-D in the blood and urine of humans who were exposed to 2,4-D during spraying indicate that absorption can occur by dermal or respiratory routes or both (Kolmodin-Hedman and Erne, 1980; Taskav et al.,

1982; Lavy et al., 1982; Draper and Street, 1982). Rapid percutaneous absorption is indicated by the detection of 2,4-D in the blood as early as 4 hours after experimental dermal application (Feldmann and Maibach, 1974).

Animal Jies indicate that distribution of absorbed 2,4-D is widespread and rapid, with peak tissue concentrations occurring as early as 6-8 hours after oral exposure (Erne, 1966a; Khanna and Fang, 1966). The highest concentrations are found in the liver, kidney, spleen, heart and lungs, and the lowest levels in the muscle, brain and fat. Distribution of 2,4-D to tissues other than those involved with excretion of the compound is enhanced relative to plasma levels at high doses. 2,4-D can cross the placenta of mice, rats and sows (Lindquist and Ullberg, 1971; Fedorova and Belova, 1974; Erne, 1966a), an observation that is notable in view of the ionization of 2,4-D (pK ~3) at plasma pH (Erne, 1966a). Forensic investigators in humans confirm the findings of animal studies that 2,4-D is widely distributed throughout the body tissues after oral administration of high doses (Nielsen et al., 1965; Geldmacher et al., 1966; Dudley and Thapar, 1972; Coutselinis et al., 1977).

2,4-D appears to be excreted essentially unchanged regardless of dose, route of administration or animal species (Erne, 1966b; Khanna and Fang, 1966). More sensitive detection techniques have, however, provided evidence of metabolism to 2,4-dichlorophenol (Zielinski and Fishbein, 1967) and of conjugation with amino acids (Grunow and Boehme, 1974). Limited data from humans also indicate that 2,4-D is not biotransformed to a large extent, although some conjugation may occur (Kohli et al., 1974; Sauerhoff et al., 1977).

Elimination of low levels (<100 mg/kg) of 2,4-D from the plasma, tissues and bodies of animals is rapid (generally complete in 24-72 hours) and follows first-order kinetics (Erne, 1966a). 2,4-D is excreted almost completely in the urine. As the concentration increases, biphasic patterns are observed, indi[illegible]g that the saturation of some process takes place (Khanna and Fang, 1966; Smith et al., 1980). Toxicokinetic studies of humans who ingested 5 mg/kg of 2,4-D have estimated (using one-compartment assumptions) a urinary half-life of ~17.7 hours (Sauerhoff et a[illegible]., 1977) and a plasma half-life of ~33 hours (Kohli et al., 1974). An elimination half-life of 35-48 hours was calculated from data collected from men engaged in agricultural spraying of 2,4-D (Nash et al., 1982).

IV. HUMAN EXPOSURE

Humans may be exposed to chemicals such as 2,4-D from a variety of sources, including drinking water, food, ambient air, occupational settings and consumer products. This analysis of human exposure to 2,4-D is limited to drinking water, food and ambient air because those media are considered to be sources common to all individuals. Even in limiting the analysis to these three sources, it must be recognized that individual exposure will vary widely based on many personal choices and on several factors over which there is little control. Where one lives, works and travels, what one eats, and physiologic characteristics related to age, sex and health status can all profoundly affect daily exposure and intake. Individuals living in the same neighborhood or even in the same household can experience vastly different exposure patterns.

Detailed information concerning the occurrence of and exposure to 2,4-D in the environment is presented in another document entitled "Occurrence of Pesticides in Drinking Water, Food and Air" (Johnston et al., 1984). This chapter summarizes the pertinent information presented in that document in order to assess the relative source contribution from drinking water, food and air.

In the Exposure Estimation section of this chapter, available information is presented on the range of human exposure and intake for 2,4-D from drinking water, food and ambient air for the 70 kg adult male. It is not possible to provide an estimate of the number of individuals experiencing specific combined exposures from those three sources. However, the Summary section of this chapter provides some insight into the range of intake values suggested by the available data.

Exposure Estimation

Drinking Water. Levels of 2,4-D in drinking water vary from one location to another. The highest level of 2,4-D monitored in the available studies was 50 µg/ℓ in Oregon (Elliott, 1979), below the Maximum Contaminant [illegible] (MCL) of 100 µg/ℓ. In the national studies, the highest level of 2,4-D was 1.1 µg/ℓ (Boland, 1981). However, levels of 2,4-D in drinking water typically appear to be lower than these levels. Analysis of the National Screening Program for Organics in Drinking Water (NSP) (Boland, 1981) and the Rural Water Survey (RWS) (U.S. EPA, 1984) suggests that median levels of 2,4-D in drinking water systems would be below 0.5 µg/ℓ, and possibly below 0.01 µg/ℓ, because only 1 of 117 systems sampled in the NSP contained a level of 2,4-D above 0.5 µg/ℓ, and none of 92 systems sampled in the RWS contained a level above 0.01 µg/ℓ. 2,4-D may not be present in drinking water in some areas. The available monitoring data are not sufficient to determine regional variations in exposure levels for 2,4-D.

The daily intake of 2,4-D from drinking water was estimated using the assumptions presented in Table IV-1 and the values presented above. The estimates in Table IV-1 indicate that the daily intake of 2,4-D from drinking water ranges from 0.0-1.4 µg/kg/day. However, the values presented do not account for variances in individual exposure or uncertainties in the assumptions used to estimate exposure.

A tolerance level for 2,4-D in potable water of 100 µg/ℓ (negligible residues) has been established from certain specific aquatic uses of 2,4-D (21 CFR 193.100, April 1, 1979).

Diet. Data are limited on the dietary intake of 2,4-D in the United States. Dietary exposure to 2,4-D appears to be low; there have been no findings of 2,4-D in FDA adult market basket surveys since 1973. The

TABLE IV-I

Estimated Intake of 2,4-D from Drinking Water*

Drinking Water Concentration (µg/ℓ)	Intake (µg/kg/day)
0.0	0.0
0.01	0.0003
0.5	0.014
1.1	0.031
50	1.4

*Assumptions: 70 kg adult male consuming 2 ℓ of water/day.

average total daily intakes of 2,4-D, based on detectable levels of 2,4-D in market basket studies performed between 1965 and 1973, were calculated to range from 0.0006-0.07 µg/kg/day (FDA, 1982).

Detectable residues of 2,4-D were found in the FY 76 market basket survey for toddlers. The average daily intake, based on the residue levels detected in the toddler diet in that year, was calculated to be 0.0058 µg/kg/day (FDA, 1980).

It is expected that dietary levels of 2,4-D vary somewhat with geographical location, with higher levels occurring in foods from areas near the sources of 2,4-D exposure. However, because of insufficient data, no estimates could be made of variations in intake by geographical region.

Tolerance levels for residues of 2,4-D in foods and in and on raw agricultural commodities are presented in Table IV-2.

Air. Data on levels of 2,4-D in ambient air are limited. A maximum level of 4 ng/m³ (0.004 µg/m³) of 2,4-D was reported from air monitoring studies of 16 cities (Grover et al., 1976). Using a range of air levels of 2,4-D of 0.0-0.004 µg/m³, the respiratory intake of 2,4-D was estimated. Assuming that a 70 kg adult male inhales 23 m³ of air/day (ICRP, 1975), a range of respiratory intake of 0.0-0.0013 µg/kg/day was estimated. The values presented do not account for variances in individual exposure or uncertainties in the assumptions used to estimate exposure.

Summary

Data on the intake of 2,4-D from drinking water, food and ambient air are insufficient for use in determining which of the three sources is the major contributor to total intake. FAO/WHO and EPA have established acceptable daily intakes (ADIs) for 2,4-D of 300 and 125 µg/kg/day, respectively

TABLE IV-2

Tolerances for 2,4-D in Foods and In and On Raw Agricultural Commodities[a]

Commodity	Tolerance (µg/kg)
Food	
Barley, milled fractions (exc. flour)	2,000
Oats, milled fractions (exc. flour)	2,000
Rye, milled fractions (exc. flour)	2,000
Sugarcane, molasses	5,000
Wheat, milled fractions (exc. flour)	2,000
Raw agricultural commodity	
Apples	5,000
Asparagus	5,000
Avocados	100 N[c] 1,000[d]
Barley	
forage	20,000
grain	500
Blueberries	100
Cattle	
fat	200
kidney	2,000
meat byproducts (exc. kidney)	200
meat	200
Citrus fruits	100 N[c] 1,000[d]
including pre- and post-harvest	5,000
Corn	
fodder	20,000
forage	20,000
fresh, including sweet[b]	500
grain	500
Cottonseed	100 N[c] 1,000[d]
Cranberries	500

TABLE IV-2 (cont.)

Commodity	Tolerance (µg/kg)
Cucurbits	
	100 N[c]
	1,000[d]
Eggs	
	50
Fish	
	1,000[d]
	1,000[f]
Fruits	
pome	
	100 N[c]
small	1,000[d]
	100 N[c]
stone	1,000[d]
	100 N[c]
	1,000[d]
Goats	
fat	
kidney	200
meat byproducts (exc. kidney)	2,000
meat	200
	200
Grain crops	
	100 N[c]
	1,000[d]
Grapes	
	500
Grasses	
forage	
	100 N[c]
hay	1,000[d]
pasture	300,000
rangeland	1,000,000
	1,000,000
Hogs	
fat	
kidney	200
meat byproducts (exc. kidney)	2,000
meat	200
	200
Hops	
	100 N[c]
	1,000[d]

TABLE IV-2 (cont.)

Commodity	Tolerance (µg/kg)
Horses	
fat	200
kidney	2,000
meat byproducts (exc. kidney)	200
meat	200
Legumes, forage	100 N[c]
	1,000[d]
Lemons, post-harvest	5,000
Milk	100
Nuts	100 N[c]
	1,000[d]
Oats	
forage	20,000
grain	500
Pears	5,000
Potatoes	200
Poultry	50
Quinces	5,000
Rice	100
straw	20,000
Rye	
forage	20,000
grain	500
Sheep	
fat	200
kidney	2,000
meat byproducts (exc. kidney)	200
meat	200
Shellfish	1,000[d]
Sorghum	500
fodder	20,000
forage	20,000

TABLE IV-2 (cont.)

Commodity	Tolerance (µg/kg)
Strawberries	50
	100 N[c]
	1,000[d]
Sugarcane	
forage	2,000
	20,000
Vegetables	
fruiting	100 N[c]
	1,000[d]
leafy	100 N[c]
	1,000[d]
root crop	100 N[c]
	1,000[d]
seed and pod	100 N[c]
	1,000[d]
Wheat	
forage	20,000
grain	500

[a]Sources: 40 CFR 180.142, July 1, 1981; 21 CFR 193.100, April 1, 1979.

[b]Kernel plus cob with husks removed

[c]From application to irrigation ditch banks in the Western United States

[d]From application to control water hyacinth

[e]For 2,4-D and/or its metabolite 2,4-dichlorophenol

[f]From application for Eurasian water milfoil control in dams and reservoirs of the TVA system

N = Negligible residues

(FDA, 1982). In addition, EPA has reported a maximum safe level of 2,4-D (from all sources) of 16 µg/kg/day (U.S. EPA, 1976). The intake of 2,4-D from drinking water, food and air appears to be below these levels.

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V. HEALTH EFFECTS IN ANIMALS

Acute Toxicity

Acute toxic levels of 2,4-D and certain of its salts and esters by different routes of administration are summarized in Table V-1. The LD_{50} range is generally betwee[illegible]0 and 1000 mg/kg; there do not appear to be significant differences in toxicity between the free acid and the various salt and ester derivatives. Hill and Carlisle (1947) determined oral LD_{50}s of 666, 375, 800 and 1000 for 2,4-D sodium salt in rats, mice, rabbits and guinea pigs, respectively; the maximum doses in these species not causing death were 333, 125, 200 and 333 mg/kg, respectively. Individual monkeys that were fed single doses of ~286 or 428 mg/kg of 2,4-D sodium salt or 286 mg/kg of 2,4-D ammonium salt regurgitated a large portion of the material, precluding determinations of lethal doses (Hill and Carlisle, 1947). Symptoms other than nausea were not described in these monkeys. Approximately 214 mg/kg of 2,4-D sodium salt was fed to another monkey without development of vomiting or "serious illness" (Hill and Carlisle, 1947). Comparison of the species sensitivity to 2,4-D indicates that dogs may show greater sensitivity to this compound (Rowe and Hymas, 1954). This greater sensitivity observed in dogs may reflect an inability of kidney processes in this species to effectively clear phenoxyacetic acids (Seiler, 1978).

Hill and Carlisle (1947) noted that fatal poisoning of several types of laboratory animals (mice, rats, guinea pigs, rabbits and monkeys) with the sodium and ammonium salts of 2,4-D produced similar symptoms. Animals died within several hours to 3 days following oral or i.p. administration of the salts. Progressive symptoms included muscular incoordination, lethargy, paralysis of the hindquarters, stupor, coma and death. The authors noted

TABLE V-1

Acute Toxicity of 2,4-D Compounds

2,4-D Form	Vehicle	Route	Species	Dose (mg/kg)	Response	Reference
Acid	olive oil	oral	mice	368	LD_{50}	Rowe and Hymas, 1954
Acid	olive oil	oral	guinea pigs	469	LD_{50}	Rowe and Hymas, 1954
Acid	olive oil	oral	rats	375	LD_{50}	Rowe and Hymas, 1954
Acid	gelatin	oral	rats	666 333	3/4 deaths 0/4 deaths	Hill and Carlisle, 1947
Acid	capsule	oral	dogs	100	LD_{50}	Drill and Hiratzka, 1953
Sodium salt	saline	oral	mice	375 125	LD_{50} tolerated dose*	Hill and Carlisle, 1947
Sodium salt	saline	oral	guinea pigs	1000 333	LD_{50} tolerated dose*	Hill and Carlisle, 1947
Sodium salt	saline	oral	rabbits	800 200	LD_{50} tolerated dose*	Hill and Carlisle, 1947
Sodium salt	saline	oral	rats	666 333	LD_{50} tolerated dose*	Hill and Carlisle, 1947
Sodium salt	H_2O	oral	rats	805	LD_{50}	Rowe and Hymas, 1954
Sodium salt	H_2O	oral	guinea pigs	551	LD_{50}	Rowe and Hymas, 1954
Sodium salt	saline	i.p.	mice	375 125	LD_{50} tolerated dose*	Hill and Carlisle, 1947
Sodium salt	saline	i.p.	guinea pigs	666 333	LD_{50} tolerated dose*	Hill and Carlisle, 1947
Sodium salt	saline	i.p.	rats	666 25	LD_{50} tolerated dose*	Hill and Carlisle, 1947
Sodium salt	saline	i.p.	rabbits	400 200	LD_{50} tolerated dose*	Hill and Carlisle, 1947
Sodium salt	saline	i.v.	rabbits	400 200	LD_{50} tolerated dose*	Hill and Carlisle, 1947
Sodium salt	saline	s.c.	mice	280	LD_{50}	Bucher, 1946

TABLE V-1 (cont.)

2,4-D Form	Vehicle	Route	Species	Dose (mg/kg)	Response	Reference
Ammonium salt	saline	oral	rats	333	0/6 deaths	Hill and Carlisle, 1947
Ammonium salt	saline	oral	guinea pigs	33	0/6 deaths	Hill and Carlisle, 1947
Ammonium salt	saline	oral	rabbits	200	0/4 deaths	Hill and Carlisle, 1947
Isopropyl ester	olive oil	oral	mice	541	LD_{50}	Rowe and Hymas, 1954
Isopropyl ester	olive oil	oral	rats	700	LD_{50}	Rowe and Hymas, 1954
Isopropyl ester	olive oil	oral	guinea pigs	550	LD_{50}	Rowe and Hymas, 1954
Butyl esters	corn oil	oral	mice	713	LD_{50}	Rowe and Hymas, 1954
Butyl esters	corn oil	oral	guinea pigs	848	LD_{50}	Rowe and Hymas, 1954
Butyl esters	corn oil	oral	rabbits	424	LD_{50}	Rowe and Hymas, 1954
Butyl esters	corn oil	oral	rats	620	LD_{50}	Rowe and Hymas, 1954
Butyl esters	NR	oral	cats	820	LD_{50}	Konstantinova, 1970
Butyl esters	NR	oral	rats	920	LD_{50}	Konstantinova, 1970
Butyl esters	NR	oral	mice	380	LD_{50}	[illegible] ntinova, 1970
PGBE esters	corn oil	oral	rats	570	LD_{50}	Rc[illegible] and Hymas, 1954
Crotyl ester	NR	oral	mice	580	LD_{50}	Fetisov, 1966
Crotyl ester	NR	oral	rats	452	LD_{50}	Fetisov, 1966

*Tolerated dose - largest amount causing no deaths

NR - Not reported; PGBE - propylene glycol butyl ether

that the skeletal muscle changes resembled those observed in congenital myotonia. Pathological examination showed cloudy swelling and enlargement of the kidneys in all species; liver damage (centrilobular degeneration and parenchymal damage) was noted only in dogs succumbing to massive doses of 2,4-D.

Drill and Hiratzka (1953) described myotonia with pathologic changes of GI mucosa irritation, moderate hepatic necrosis and mild renal tubular degeneration in dogs that were lethally poisoned by acute oral administration of 2,4-D at doses of 100-400 mg/kg.

Bucher (1946) found that myotonia persisted for 8-24 hours in strain A mice that were injected i.p. with sublethal doses (100-200 mg/kg) of 2,4-D. No significant differences were found in the effects produced when 2,4-D was administered s.c., i.p. or i.v.

Subchronic Toxicity

In a subchronic exposure feeding study, 200 $B6C3F_1$ mice were sorted into five groups of 40 animals, 20 of each sex per group, and fed the diet chow mixed with 97.5% pure 2,4-D (Hazelton Laboratories, 1983). Mice were fed 0.0 (controls), 5.0, 15.0, 45.0 or 90.0 mg/kg/day (calculated doses) of the diet-chemical mixture for 91 days. Criteria used to determine toxicity were survival, daily exam for clinical symptomology, weekly changes in body weights, growth rates, food intake, ophthalmological alterations, organ weight changes, and clinical, gross and histopathological alterations.

The results of the study demonstrated increases in mean white blood cell counts (both sexes) at 15.0 mg/kg/day, and increased platelet and reticulocyte counts (females only) at the 15-45 mg/kg/day dose levels. There were also statistically significant reductions in absolute brain weights (males only) at the 15.0 mg/kg/day or higher dose. Alteration of relative brain-to-body weight was found (females only) at the 15.0 mg/kg/day or higher groups. Statistically significant reductions in kidney weights (absolute and relative) were found in males (45.0 mg/kg/day or higher) and in females at the 90.0 mg/kg/day dose level. Statistically significant reductions in liver weights were found only in the 90.0 mg/kg/day groups of males. Pituitary glands were hypertrophied (statistically significant) (absolute and relative weights) in both sexes at 15.0 or 90.0 mg/kg/day groups. Adrenal glands were also increased (statistically significant) at the 15.0 mg/kg/day dose in males and at the 5.0 mg/kg/day dose in females. Ovarian weights were reduced (statistically significant) in the 15.0 mg/kg/day dose level. One control female died at week 12 and one female in the high-dose group died at week 1. These deaths were not treatment-related.

Hematological, hepatic and renal toxicity were demonstrated in a sister study in Fischer rats (strain #344) during a subchronic exposure feeding study performed at the Hazelton Laboratories (1983). 2,4-D (97.5% pure) was added to the diet chow and fed to the rats for 91 days at doses calculated to be 0.0 (controls), 1.0, 5.0, 15.0 or 45.0 mg/kg/day. In each of the five groups were 20 animals of each sex, 40 animals per treatment group or a total of 200 animals. Criteria examined to determine toxicity were survival, daily exam for clinical symptomology, weekly change in body weights, growth rates, food intake, ophthalmological changes, changes in organ weights, and clinical, gross and histopathological alterations.

The results of the study demonstrated statistically significantly reductions in mean hemoglobin (both sexes), mean hematocrit and red blood cell levels (both sexes), mean reticulocyte counts (both sexes), mean platelet counts (females only) and mean leucocyte levels (males only) at the 5.0 mg/kg/day dose or higher after 7 weeks. There were also statistically significant reductions in liver enzymes LDH, SGOT, SGPT and alkaline phosphatase at week 14 in animals treated at the 15.0 mg/kg/day or higher doses. Kidney weights (absolute and relative) showed statistically significant increases in all animals at the 15.0 mg/kg/day dose or higher at the end of the experimental protocol. Histopathological examination correlated well with kidney organ weight changes showing cortical and subcortical pathology. Increases in ovarian weights, T-4 levels and a decrease in BUN were reported but not considered to be treatment related.

Rowe and Hymas (1954) administered doses of 0, 30, 100 or 300 mg/kg/day 2,4-D to groups of 5 or 6 female rats (strain not specified) by intubation 5 times/week for 4 weeks (Table V-2). The 2,4-D was administered in olive oil that was emulsified in 5-10% aqueous gum arabic, and the controls were vehicle treated. Rats that received 30 mg/kg/day or less reportedly showed no adverse treatment-related clinical or pathological effects; but treatment with 100 mg/kg/day elicited GI irritation, depressed growth rate and slight cloudy swelling of the liver. Rats that received 300 mg/kg/day 2,4-D succumbed rapidly (additional details were not given) and died; severe GI irritation was reportedly the principal adverse effect observed.

TABLE V-2

Subchronic Toxicity of Orally Administered 2,4-D Compounds

Species/ Strain	Sex/No.	Vehicle	Purity	Dosage/Exposure	Dose[a] (mg/kg/day)	Response	Reference
Mice/B6C3F1	20 each sex per group	diet chow	97.5%	NS	5.0, 15, 45 or 90	Significant reduction in brain weight and increased white blood cell counts at 15 mg/kg bw/day or higher; significant reductions in liver weights at high doses; pituitary gland hypertrophy at 15 mg/kg bw/day or higher; other effects also noted.	Hazelton Laboratories, 1983
Rats/Fischer 344	20 each sex per group	diet chow	97.5%	NS	1.0, 5.0, 15 or 45	Significant reductions in measured blood parameters at 5.0 mg/kg bw/day or higher; liver enzyme activities were reduced and increased kidney weights occurred with corresponding histopathology at 15 mg/kg bw/day or higher.	Hazelton Laboratories, 1983
Rat/NS young adult	5-6 F/group	olive oil/ gum arabic	NS	3, 30, 100 or 300 mg/kg/day by gavage 5 days/week for 4 weeks	2.14, 21.4, 71.4, 214	2.14 or 21.4 mg/kg had no adverse effects as judged by growth, behavior, mortality, hematologic and BUN values, organ weights, and gross and microscopic appearance of tissues; 71.4 mg/kg caused GI irritation, depressed growth, slight cloudy swelling in liver; 214 mg/kg caused rapid deterioration and death; GI irritation	Rowe and Hymas, 1954
Rats/ Long-Evans	No. ambiguous: ~8 treated or control M/ treatment period	diet	analytical standard grade	2000 ppm in diet x 4, 5 or 7 weeks	200	No effect on food consumption, no overt signs of toxicity, slight increase in amount glycogen/liver, slight decrease in amount RNA/liver, slight decrease in absolute and relative liver weights	Chang et al., 1974

TABLE V-2 (cont.)

Species/ Strain	Sex/No.	Vehicle	Purity	Dosage/Exposure	Dose[a] (mg/kg/day)	Response	Reference
Rats/NS young adult	5 F/group	diet	NS	100, 300, 1000, 3000 or 5000 ppm in diet x 113 days	10, 30, 100, NA, NA	No effect at 2 lowest doses as judged by mortality, growth, food consumption, hematologic and BUN values, organ weights, gross and microscopic appearance of tissues; 100 mg/kg produced "excessive" mortality, decreased growth, slight cloudy swelling in liver, food consumption NS at this dose; at 2 highest dosages, rats refused to eat	Rowe and Hymas, 1954
Rats/NS young	7 M/group	diet	purified commercial	0, 200 or 400 ppm in diet x 31 days, 100 ppm x 21 days, then 1000 ppm for the subsequent 10 days (390 ppm TWA)	0, 10, 20 or 40 39[b]	No adverse effects as judged by food consumption, growth, mortality or other characteristic signs of intoxication (i.e., muscular signs or paralysis)	Hill and Carlisle, 1947
Guinea pigs/NS	6/group sex NS	saline	purified commercial	50 or 100 mg/day of 2,4-D sodium salt by intubation 10 daily doses in 12 days	139.8 or 252.6[c]	No treatment-related signs of intoxication or mortality	Hill and Carlisle, 1947
Dogs/mongrel 7-15 kg	Control, 2 F; 2 mg/kg, 1 M, 1 F; 5 mg/kg, 1 M, 1 F; 10 mg/kg, 3 M; 20 mg/kg, 3 M, 1 F	capsule	98.5% commercial	0, 2, 5, 10 or 20 mg/kg/day, 5 days/week x 13 weeks	0, 1.4, 3.6, 7.1 or 14.3	1.4, 3.6 and 7.1 mg/kg caused no signs of toxicity, no significant effects on body weight, organ weight, gross and histological appearance of organs, and hematologic values; 14.3 mg/kg caused death of 3 by day 49, ataxia, stiffness of hind legs, difficulty in swallowing, no significant lesions	Drill and Hiratzka, 1953

[a]When the chemical was given in the diet, the dose was calculated by assuming that a young rat or dog consumes the equivalent of 0.1 or 0.029, respectively, of its body weight per day as food.

[b]Time-weighted average dose

[c]2,4-D acid-equivalent dose

NS = Not specified; NA = not applicable because food was not eaten

In a related study, groups of five young adult female rats (strain not specified) were maintained on diets that contained 0, 100, 300 or 1000 ppm 2,4-D in the diet for 113 days (Rowe and Hymas, 1954). If it is assumed that young rats consume 10% of their weight in food per day, the corresponding daily doses are 0, 10, 30 and 100 mg/kg/day. Rats that were exposed at the 1000 ppm level experienced excessive mortality (not quantified), depressed growth rate and slight cloudy swelling of the liver. These effects were not observed at the two lowest doses (see Table V-2). Groups of five rats that were given diets that contained higher concentrations of 2,4-D (3000 or 5000 ppm) were sacrificed after 12 days because they were not eating and were rapidly losing weight; examinations revealed increased liver and kidney weights and slight but unspecified pathologic changes.

Chang et al. (1974) reported that dietary administration of 2,4-D to rats at levels of 2000 ppm in the diet (~200 mg/kg/day) for 4-7 weeks produced a slight increase in liver glycogen content, a slight decrease in liver RNA content and slight decreases in absolute and relative liver weights, but no overt signs of toxicity (see Table V-2).

Administration of 0, 100, 200 or 400 ppm dietary 2,4-D (~0, 10, 20 or 40 mg/kg/day, respectively) to groups of seven rats for 1 month did not adversely affect food intake or rate of growth, or elicit characteristic signs of intoxication (skeletal muscular signs or paralysis) (Hill and Carlisle, 1947). Dietary administration of 2,4-D at a level of 100 ppm for 21 days and subsequently 1000 ppm for 10 days (average total dose ~39.0 mg/kg/day) was similarly nontoxic for rats. Groups of six guinea pigs that

were given 10 daily doses of 50 or 100 mg 2,4-D in 12 days (~88 or 177 mg/kg/day) by intubation also did not develop characteristic evidence of intoxication.

Drill and Hiratzka (1953) administered 2,4-D orally in capsules to groups of 2-4 dogs at doses of 0, 2, 5, 10 or 20 mg/kg/day, 5 days/week, for 13 weeks. When adjusted for a 7-day week, the respective daily doses were 0, 1.4, 3.6, 7.1 and 14.3 mg/kg/day. As detailed in Table V-2, toxic effects were only observed at the high dose. Treatment at 20 mg/kg/day produced death in 3/4 dogs between days 18 and 49, and symptoms in the moribund animals included hind leg stiffness, ataxia, weakness, gum bleeding and difficulty in chewing and swallowing. A terminal decrease in the percentage of blood lymphocytes was noted in the three dogs that died, but significant effects on the hemoglobin, red cell count or total white cell count were not observed. The dog that survived 2,4-D treatment at the high dose, as well as the dogs exposed to the lower levels of 2,4-D, showed no significant hematologic, gross or histopathologic effects.

In a study of limited design, pigs (Lantras strain, 18-25 kg, 8-12 weeks old) were administered 50 mg/kg commercial grade 2,4-D triethanolamine (water solvent) or 2,4-D butyl ester (diluted in petroleum solvent and emulsified in water) by intubation (Bjorklund and Erne, 1966). The compounds were administered at different frequencies and durations, but only one pig per exposure schedule was tested. Four pigs were exposed to the triethanolamine salt for 3 doses in 5 days or 15 doses in 20 days, and three pigs were exposed to the butyl ester for 5 doses in 8 days or 12 doses in 17 days.

Effects (e.g., anorexia, diarrhea, catarrhal gastroenteritis, fatty degeneration in the kidneys) were noted in 3/4 pigs exposed to 2,4-D triethanolamine and in 2/3 pigs exposed to 2,4-D butyl ester. Single pigs exposed to fifty-one 50 mg/kg doses of triethanolamine salt, to 100 mg/kg triethanolamine salt (3 doses in 7 days or 7 doses in 9 days), to twenty-three 50 mg/kg doses of butyl ester in 39 days, or to 300 mg/kg butyl ester (2 doses in 4 days or 3 doses in 6 days) exhibited similar effects.

Repeated s.c. injections of 93 mg/kg levels of 2,4-D sodium salt daily for 90 days did not produce significant symptoms in treated mice and histological examination did not show abnormalities (Bucher, 1946). Dilated lungs, liver and kidneys, however, were noted in moribund animals injected with 200 mg/kg levels of compound; the significance of these changes is unknown.

Effects of s.c. injected 2,4-D sodium salt on the thyroid gland of treated rats have been reported (Florsheim and Velcoff, 1962; Florsheim et al., 1963). These investigators showed that thyroid weight was decreased following seven daily injections of 2,4-D at a level of 100 mg/kg. Administration of 2,4-D at 80 mg/kg over this period increased radioactive iodine uptake by the thyroid, lowered the binding of radiolabeled thyroxine by serum proteins, and increased the amount of radiolabeled compound in the liver of treated rats.

Desi et al. (1962) described the toxic effects of 2,4-D on the nervous system of rats administered lethal doses of the compound i.p. Animals injected daily with 200 mg/kg of 2,4-D (form not specified) died within 6

days. Progressively decreased conditioned reflex responses were observed over this period, as well as the appearance of large slow waves in the EEG. Histological examination indicated that demyelinization was present in the dorsal portion of the spinal tract. Within 10-15 minutes following a single i.p. injec[illegible] of the compound, EEG changes were observed (decreased cerebral and reticular desynchronization); recovery was seen in ~1 hour. The authors postulate that the neurological effects produced by 2,4-D in this study are due initially to action of the compound on the reticular formation, followed by later effects on cerebral tissue. Histological examination, however, failed to show any morphological changes in the cortex or subcortical regions of treated animals. The demyelinization observed in the spinal cord may be responsible for the hind limb paralysis noted by other investigators after poisoning of animals with 2,4-D.

The subchronic dermal toxicity of the dimethylamine salt and the isooctyl and butyl esters of 2,4-D has been studied in rabbits (Kay et al., 1965). Solutions containing the salt or esters at levels corresponding to 0.6 and 3.1% 2,4-D were applied to gauze patches, occluded, and left in place for 7-hour periods, 5 times/week for 3 weeks. No nervous system damage, body weight effects or hematological changes were observed following these levels of treatment. Local skin inflammation was noted in both control and treated animals, but subepithelial fibrosis and mononuclear infiltration appeared to be increased only in those animals treated with the oil dilutions of either of the 2,4-D esters.

Chronic Toxicity

Hansen et al. (1971) conducted 2-year feeding studies with technical grade (96.7% pure) 2,4-D in Osborne-Mendel rats. In the rat study, 25 animals of each sex were exposed to 0, 5, 25, 125, 625 or 1250 ppm 2,4-D in the diet (or 0, 0.25, 1.25, 6.25, 31.25 or 62.5 mg/kg bw//day, respectively, assuming a rat consu[illegible] 5% of its body weight per day) from 3 weeks of age. At the conclusion of treatment, all rats were autopsied, but comprehensive histopathologic examinations were performed only on 6 rats/sex from the high-dose and control groups; the liver, kidneys, spleen, ovaries or testes and other tissues that contained gross lesions were histologically examined in the remaining rats in the high exposure and control groups and in the rats at the other dose levels. Significant differences in survival, mean body weight and organ-to-body weight ratios (liver, kidney, heart, spleen or testes) were not found between any of the treated groups and the control group during the 2-year treatment or at the end of the study. Significant treatment-related pathologic effects were not observed and, as detailed in the Carcinogenicity Section, the incidence of tumors did not differ significantly between the groups. Several hematologic indices (hemoglobin, hematocrit, total white cell count) were similar in the treated and control groups, but the red blood cell count of the treated rats (1250, 625 and 5 ppm groups) showed a "tendency" toward macrocytosis, "very slight to slight" polychromasia, and "slight to moderate" hypochromasia. The tendency toward macrocytosis was reportedly not present and the other red cell abnormalities were of a "minor degree" in the control rats. The toxicological significance of these vaguely reported effects is unclear.

In a 2-generation reproduction study by Bjorklund and Erne (1966) that is also discussed in the Other Reproductive Effects Section, administration of 1000 ppm 2,4-D in the drinking water (~50-100 mg/kg/day) of rats (5/group) during pregnancy and for a further 10 months had no significant effects on the maternal animals (not specified) or offspring (clinical signs or malformations). Similar exp[illegible] of 22 weaned offspring (10 males, 12 females) for up to 2 years was also nontoxic as judged by normal clinical chemistry [indices were hematocrit, hemoglobin, plasma GOT, plasma elimination rate of 2,4-D (3 hours)], relative organ weights (heart, spleen, liver, kidneys, lungs, testes, ovaries), or gross or microscopic pathology. However, reduced food and water intake and consequent growth retardation, temporary diarrhea and poor general condition were observed. Other reproduction studies that are detailed in the Teratogenicity and Other Reproductive Effects Section reported that dietary exposure to 1500 ppm (~75 mg/kg bw) 2,4-D for 2 years (Hansen et al., 1971) and dietary exposure to 1000 ppm (~100 mg/kg) for 3 months (Gaines and Kimbrough, 1970) before mating and during pregnancy and lactation caused an increase in preweanling mortality.

Hansen et al. (1971) also fed 6- to 8-month-old beagle dogs (3 of each sex/group) 0, 10, 50, 100 or 500 ppm technical grade 2,4-D in the diet (~0, 0.29, 1.45, 2.9 or 14.5 mg/kg/day) for 2 years. Treatment-related effects based on observations of mortality as well as gross and microscopic tissue examinations were not indicated in any of the treated groups or the control group.

Santolucito (1975) reported EEG changes in a group of six squirrel monkeys (sex unspecified) that were exposed orally (method unspecified) to 0.2 mg 2,4-D/kg bw/day for 3 years. EEG recordings were apparently made only once, at the end of 3 years, at which time the treated monkeys were compared with seven concurrent controls. Changes during anaesthetized sleep included an increased proportion of high-frequency EEG waves and an increased number of zero potential crossovers per EEG recording. The data were obtained by on-line computer-assisted interval analysis of 5 minutes of each recording, but the toxicological significance of these changes is not known.

Carcinogenicity

Several studies have investigated the ability of 2,4-D and related compounds to produce tumors in laboratory rats and mice.

Bionetics Research Laboratories (Bionetics, 1968a; Innes et al., 1969) conducted a broad survey of the potential carcinogenic activity of several pesticides and industrial chemicals, including 2,4-D (90% pure) and its isopropyl (99% pure), butyl (99% pure) and isooctyl (97% pure) esters. Carcinogenic effects following chronic oral administration or a single s.c. injection were investigated in two strains of C57Bl/6 mice designated $B6C3F_1$ and $B6AKF_1$.

The oral administration regime consisted of intubation of the compound suspended in 0.5% gelatin to groups of 18 male and 18 female mice from 7-28 days of age, followed by dietary administration for ~10-24 months. Both strains of mice were given 46.4 mg/kg initial bw of the isopropyl, butyl or

isooctyl ester by intubation, followed by dietary concentrations of 111, 149 and 130 ppm (~14.4, 19.4 and 16.9 mg/kg/day), respectively, for 73-83 weeks. $B6AKF_1$ mice received 2,4-D by intubation at 46.4 mg/kg initial body weight, followed by 149 ppm (~19.4 mg/kg/day) in the feed for 75 weeks. Both strains received 2,4-D by intubation at 100 mg/kg initial body weight, followed by 323 ppm (~42 mg/kg/day) in the feed for [illegible]-90 weeks. Groups of 36 male and 36 female mice of both species received 0.5% gelatin or no treatment at all. These control groups were assigned randomly to rooms housing treated animals.

Following the treatment period, all surviving mice were grossly examined on dissection, and the tissues from livers, spleens, kidneys, adrenals, stomachs, intestines and genitalia, which had been fixed and stained, were examined microscopically by a pathologist. In addition, mice that were killed when moribund were given a gross pathologic examination, and tissues were examined microscopically as deemed appropriate (criteria unspecified). No statistically significant ($p<0.05$) increase in tumor incidence over controls was found when any group or combination of groups was compared. Because of the relatively small number of animals/group and the limited nature of the histopathologic examinations, weak carcinogenic effects might not have been detected.

Groups of 18 male and 18 female mice of both strains received a single s.c. injection (neck) of 215 or 464 mg 2,4-D/kg bw dissolved in dimethylsulfoxide (DMSO) at age 28 days and were observed for 78 weeks. Similar groups of mice received a single s.c. injection of 100, 21.5 or 21.5 mg/kg bw of the isopropyl, isobutyl or isooctyl ester of 2,4-D (in corn oil),

group and the high dose level with respect to the number of male rats with malignant tumors (Table V-3). The tumors observed, however, were not associated with any specific tissue, but were randomly distributed and were of types usually observed in aging Osborne-Mendel rats.

In an unpublished evaluation of this study, Reuber (1979) reexamined the original histopathology sections, and reported substantially more tumors among dosed animals than had been reported by Hansen et al. (1971). A more detailed histopathological examination of all tissues and especially of those in the lower dose animals was apparently deemed necessary by this author. Reuber (1979) reported a greater number of lymphosarcomas in treated rats of both sexes and found a significant (Fisher exact $p<0.05$) increase in the incidence of this tumor among female rats at all five dose levels. The differences in tumor incidence reported by Hansen et al. (1971) and Reuber (1979) might be resolved if an independent reexamination of the tissue sections were performed.

The amine salt of 2,4-D has been tested for carcinogenic activity in rats and mice following oral administration (Archipov and Kozlova, 1974). Rats, 120 males and 45 females, were fed 2,4-D amine at one-tenth the LD_{50} level (not specified) for life. A similar dietary level of compound was fed to a group of 100 mice for their lifespan. Neither species of test animal developed a significant increase in tumors following oral treatment. The only tumors identified were a mammary fibroadenoma and a hemangioma of the mesenterium in two treated rats and a mammary fibroadenoma in one untreated rat. These investigators also reported that long-term application of 2 drops/week of a 10% acetone solution of compound to the shaved backs of 100 mice failed to produce tumors. When this treatment with 2,4-D was preceded

TABLE V-3

Tumor Incidence in Rats Fed 2,4-D[a]

Dose (ppm)	Rats[b] with Tumors		Rats[b] with Malignant Tumors	
	Males	Females	Males	Females
0	3	12	1	5
5	5	9	2	6
25	5	13	4	3
125	6	14	2	5
625	6	17	5	3
1250	7	15	6[c]	8

[a]Source: Hansen et al., 1971

[b]Rats/sex/dose = 25

[c]$p<0.05$

by dermal application of 1 drop of a 5% solution of 3-methylcholanthrene (MCA), an increase (0-17.7%) in skin papillomas was observed. The authors concluded that 2,4-D showed significant cocarcinogenic activity; this protocol suggests that 2,4-D was tested for tumor promoter activity. No treatment of MCA-initiated control animals was carried out over the 20-month test period. It is unclear how long after 2,4-D treatment began these papillomas developed.

An additional animal bioassay (Industry Task Force, 1985) in rats and mice has been provided to EPA, although the bioassay is not independently evaluated by the ORD Carcinogen Assessment Group in this assessment, the study will be reviewed prior to finalization of this document. On an interim basis therefore this document reports the assessment position. According to EPA, 1988, (EPA Press Release, Tuesday March 15, 1988; 2,4-D) "A rat bioassay (Industry Task Force, 1985) found an apparent treatment-related increased incidence of brain tumors in males at the highest dose level. However, the increased incidence of tumors seen in the male rats at the highest dose level was not statistically significant when compared to control male rats, although a marginally statistically significant trend was observed. No tumor response was seen in female rats or mice". The Office of Pesticides tentatively concluded that the tumor induction from the rat study provided limited evidence of carcinogenicity in animals. In June 1987, the FIFRA Scientific Advisory Panel reviewed the Office of Pesticides classification (limited evidence) and advised that the evidence should be viewed as equivocal and recommended additional testing. The Office of Pesticides has accepted the assessment of the animal data by the SAB.

Available data from laboratory animals have not provided a sufficient demonstration of carcinogenicity of 2,4-D, although increased tumor production is suggested. This question cannot be adequately resolved until more compelling evidence is available.

Epidemiology studies have associated excess tumor incidence in humans with mixed exposures to chlorophenoxy herbicides, including 2,4,5-T (which may be contaminated with 2,3,7,8-TCDD) and 2,4-D (which is not contaminated with this dioxin isomer). These studies do not specifically attribute carcinogenic effects to 2,4-D alone, and are summarized in the Subchronic and Chronic Effects Section in Chapter VI.

Mutagenicity

The mutagenic activity of 2,4-D has been investigated in a number of organisms including bacteria, yeast, *Drosophila melanogaster*, algae and several species of plants (Tables V-4 and V-5). Mammalian studies relating to the mutagenicity of 2,4-D have included the micronucleus assay, the dominant lethal assay, inhibition of testicular DNA synthesis and several *in vitro* assays of peripheral blood lymphocytes or cell lines treated with 2,4-D.

Investigations of the mutagenicity using microorganisms have generally failed to show activity of the compound. These negative results include testing with *Saccharomyces cerevisiae* (Fahrig, 1974), *Salmonella typhimurium* (Andersen et al., 1972; Styles, 1973; Andersen and Styles, 1978; Ercegovich and Rashid, 1977; Commoner, 1976; Zetterberg et al., 1977), T_4 bacteriophage (Anderson et al., 1972), *Bacillus subtilis* (Shirasu et al., 1976) and *Escherichia coli* (Fiscor and Piccolo, 1972; Ercegovich and Rashid, 1977).

TABLE V-4

Mutagenicity Testing of 2,4-D

Assay	Strain	Compound	Concentration	Mammalian Activation	Application	Response	Reference
Gene conversion *Saccharomyces cerevisiae*	D_4	2,4-D	NR	no	liquid holding, neutral pH	-	Fahrig, 1974
	D_4	2,4-D	2 mℓ of U-46 solution	no	liquid, low pH	+	Siebert and Lemperle, 1974
	D_4	2,4-D	200 mg/kg, oral intubation	host-mediated, CBA mice	i.p. injection of bacteria	-	Zetterberg et al., 1977
	D_4	2,4-D	0.6 mg/ℓ	no	liquid, low pH	+	Zetterberg et al., 1977
Gene combination *Saccharomyces cerevisiae*	D_5	2,4-D	0.3 mg/mℓ	no	liquid, low pH	+	Zetterberg et al., 1977
	D_5	2,4-D	0.2 mg/ℓ	no	liquid, low pH	-	Zetterberg et al., 1977
	RAD 18	2,4-D	0.2 mg/ℓ	no	liquid, low pH	+	Zetterberg, 1978
Reversion, *Salmonella typhimurium*	TA1535	2,4-D	0.3-0.8 mg/mℓ	no	liquid	-	Zetterberg et al., 1977
	TA1538	2,4-D	0.3-0.8 mg/mℓ	no	liquid	-	Zetterberg et al., 1977
	TA1530	2,4-D	200 mg/kg, oral intubation	host-mediated, CBA mice	i.p. injection of bacteria	-	Zetterberg et al., 1977
	TA1531	2,4-D	200 mg/kg, oral intubation	host-mediated, CBA mice	i.p. injection of bacteria	-	Zetterberg et al., 1977
	his mutants	2,4-D	1-5 μℓ technical solution	no	agar overlay	-	Anderson et al., 1972
	TA98	2,4-D acetate	4-2500 μg/plate	Aroclor induced rat S-9	agar	-	Anderson and Styles, 1978
	TA100	2,4-D acetate	4-2500 μg/plate	Aroclor induced rat S-9	agar	-	Anderson and Styles, 1978
	TA1535	2,4-D acetate	4-2500 μg/plate	Aroclor induced rat S-9	agar	-	Anderson and Styles, 1978

TABLE V-4 (cont.)

Assay	Strain	Compound	Concentration	Mammalian Activation	Application	Response	Reference
Reversion, *Salmonella typhimurium*	TA1538	2,4-D acetate	4-2500 µg/plate	Aroclor induced rat S-9	agar	-	Anderson and Styles, 1978
	his mutants	2,4-D	NR, oral	modified host-mediated, rat	bacteria incubated in serum from treated rats and plated	-	Styles, 1973
	his mutants	2,4-D	NR	NR	NR	-	Ercegovich and Rashid, 1977
	his mutants	2,4-D	10 µg/plate		agar overlay	-	Commoner, 1976
Reversion, bacteriophage	T_4, rII mutants	2,4-D technical grade	50 µg/plate	no	tryptone plates	-	Anderson et al., 1972
Point mutation, bacteriophage	T_4	2,4-D technical grade	50 µg/plate	no	agar	-	Anderson et al., 1972
DNA modification, *Escherchia coli*	DNA polymerase deficient	2,4-D	NR	NR	disc	-	Rosenkranz and Leifer, 1979
	E 3110 and p 3478	2,4-D	5 mg/plate	no	disc	+	Simmon, 1979
	WP2 try	2,4-D	20-25 µg/plate	NR	disc	-	Nagy and Antoni, 1975
	5 strains	2,4-D amine, dicamba, dimethylamine	NR	NR	disc	-	Fiscor and Piccolo, 1972
DNA cell binding, *Escherchia coli*	Q13	2,4-D	20-200 µm	± rat S-9 or egg-white lysozomes	liquid	+	Kubinski et al., 1981
DNA modification, *Bacillus subtilis*	H17 and M45	2,4-D	5 mg/plate	no	disc	+	Simmon, 1979
Recombination, *Bacillus subtilis*	H17 Rec$^+$	2,4-D	0.02 mg/plate	no	disc	-	Shirasu et al., 1976
	M45 Rec$^-$	2,4-D	0.02 mg/plate	no	disc	-	Shirasu et al., 1976
Recessive lethals, *Drosophila melanogaster*	Berlin K males, In(1)$SC^{S1}L_{SC}{}^{8R}$; S,$SC^{S1}SC^{8}{}_{w}{}^{a}{}_{8}$ females	2,4-D	9 mM	no	oral, 3 days	-	Vogel and Chandler, 1974

TABLE V-4 (cont.)

Assay	Strain	Compound	Concentration	Mammalian Activation	Application	Response	Reference
Recessive lethals, *Drosophila melanogaster*		2,4-D diethylamine	0.08-8 mg/mL	NR	NR	-	Berin et al., 1973
	ywsn/ywsn x ywsn/y⁺Y	2,4-D	100 ppm	no	larval feeding	+	Magnusson et al., 1977
	stable white locus	2,4-D	100 ppm	no	larval feeding	+	Rasmusson and Svahlin, 1978
	stable white locus	2,4-D	50 ppm	no	larval feeding	-	Rasmusson and Svahlin, 1978
	unstable white locus	2,4-D	100 ppm	no	larval feeding	+	Rasmusson and Svahlin, 1978
	unstable white locus	2,4-D	50 ppm	no	larval feeding	-	Rasmusson and Svahlin, 1978
Somatic mutations, *Drosophila melanogaster*	stable white locus	2,4-D	25 ppm	no	larval feeding	-	Rasmusson and Svahlin, 1978
	unstable white locus	2,4-D	25 ppm	no	larval feeding	+	Rasmusson and Svahlin, 1978
Nondisjunction, *Drosophila melanogaster*	$yw^af/yw^afxyw^af/y^+YB^S$	2,4-D	100 ppm	no	larval feeding	-	Ramel and Magnusson, 1979
Sex chromosome loss, *Drosophila melanogaster*	$yw^af/yw^afxyw^af/y^+YB^S$	2,4-D	100 ppm	no	larval feeding	-	Ramel and Magnusson, 1979
Ouabain resistant mutation, hamster lung cell cultures	V-79 cell line	2,4-D fluid	10 μm	none added	liquid	+	Ahmed et al., 1977
Unscheduled DNA synthesis, transformed human fibroblasts SV-40	VA-4 cell line	2,4-D fluid	1-1000 μm	none added	liquid	+	Ahmed et al., 1977
	VA-4 cell line	2,4-D fluid	1-1000 μm	rat S-9	liquid	+	Ahmed et al., 1977
Cell transformation human lung cell culture	WI-38	2,4-D acetate	0.08-250 μg/mL	none added	liquid	-	Styles, 1977
	WI-38	2,4-D acetate	0.08-250 μg/mL	rat S-9	liquid	-	Styles, 1977

TABLE V-4 (cont.)

Assay	Strain	Compound	Concentration	Mammalian Activation	Application	Response	Reference
Cell transformation Syrian hamster kidney	BKH-21	2,4-D acetate	0.08-250 µg/mL	none added	liquid	-	Styles, 1977
	BHK-21	2,4-D acetate	0.08-250 µg/mL	rat S-9	liquid	-	Styles, 1977
Micronucleus assay, mouse	male CBA	2,4-D	100 mg/kg	in vivo	i.p. injection	-	Jenssen and Renberg, 1976
Dominant lethal assay, mouse	ICR/Ha Swiss	2,4-D	125 mg/kg	in vivo	i.p. injection	-	Epstein et al., 1972
Chromosomal aberrations, mouse bone marrow	linear white	2,4-D	300 mg/kg	in vivo	i.p. injection	+	Pilinskaya et al., 1976
	linear white	2,4-D	50 mg/kg	in vivo	i.p. injection	-	Pilinskaya et al., 1976
Chromosomal aberrations, human blood lymphocytes	NR	2,4-D	20 µg/mL	none added	medium	+	Pilinskaya et al., 1976
	NR	2,4-D	2 µg/mL	none added	medium	-	Pilinskaya et al., 1976
Sister chromatid exchange, human blood lymphocytes	NR	2,4-D	10-60 µg/mL	none added	medium	+	Korte and Jalal, 1982
	NR	2,4-D	0.2 µg/mL	none added	medium	-	Korte and Jalal, 1982
Unscheduled DNA synthesis, primary rat hepatocyte cultures	F344	2,4-D	0.5-1000 nm/mL	present in hepatocyte culture	medium	-	Probst et al., 1981
Chromosomal aberrations, human blood lymphocytes	NR	2,4-D	50-60 µg/mL	none	medium	+	Korte and Jalal, 1982
	NR	2,4-D	0.2-40 µg/mL	none	medium	-	Korte and Jalal, 1982
Chromosomal aberrations, embryonic bovine kidney cells	NR	2,4-D	1-1000 µg/mL	none	medium	-	Bongso and Basrur, 1973
Inhibition of thymidine incorporation into testicular DNA, mice	NR	2,4-D	200 mg/kg	in vivo	oral	+	Seiler, 1979

NR - Not reported

TABLE V-5

Mutagenicity Testing of 2,4-D in Plants

Test	Compound	Concentration	Application	Mutagenicity	Assay	Reference
Barley	2,4-D	1.5 mL	injection into spike	+	phenotypic mutants	Denward, 1954
Barley	2,4-D	100 ppm	9-hour treatment of seeds	+	chlorophyll mutation	Khalatkar and Bhargava, 1982
Barley	2,4-D mixed butyl ester	200 ppm	6-hour treatment of seeds	+	chlorophyll mutation	Mohandas and Grant, 1972
Wheat	2,4-D amine	8 ounces	pre-boot and tillering stages	+	phenotypic mutants	Sandhu, 1957
Wheat, barley	2,4-D ester	12 ounces acid/acre	spray	+	chromosome aberrations	Unrau and Larter, 1951
5 species, weed	2,4-D amine	907 g acid/0.4 ha	spray	+	chromosome aberrations	Tomkins and Grant, 1976
Tobacco	2,4-D	0.4 ppm, 120 hours	medium	+	chromosome aberrations	Nuti-Ronchi et al., 1976
Bean	2,4-D	0.39 ppm	spray	+	chromosome aberrations	Amer and Ali, 1974
Pea	2,4-D	40 ppm, 8-12 hours	seedling	-	chromosome aberrations	Muhling et al., 1960
Geranium	2,4-D	10^{-5} M	liquid	+	somatic mutation	Pohlheim et al., 1977
Onion	2,4-D mixed butyl esters	50 ppm, 6 hours	root application	+	chromosome aberrations	Mohandas and Grant, 1972
Carrot	2,4-D	0.1 mg/L	medium	+	chromosome aberrations	Bayliss, 1973
Helianthus annuus	2,4-D	>10 ppm	NR	+	chromosome aberrations	Siddiqui et al., 1982

NR = Not reported

Positive mutagenic effects of 2,4-D were reported by Siebert and Lemperle (1974) in S. cerevisiae following treatment of cell suspensions with 2 mℓ of commercial U-46 D-Fluid (2,4-D acid) at pH 4.5; this concentration of 2,4-D produced toxicity in treated cells. Mutagenic effects have also been reported by Simmon (1979) for DNA repair-deficient strains of E. coli and B. subtilis treated with 2,4-D (.5 mg/plate). Clarification of these varied results has been provided by the work of Zetterberg et al. (1977), who illustrated a definite pH-dependency in obtaining mutagenic effects of 2,4-D in S. cerevisiae. At pH 4.5, cells showed a dose-dependent increase in gene conversion and cellular toxicity at 2,4-D concentrations from 0.1-0.6 mg/mℓ, while at neutral pH, neither effect was observed. The authors indicate that, at neutral pH, 2,4-D is primarily in a dissociated (ionized) state and does not readily penetrate cell membranes. Zetterberg (1978) also showed a pH-dependent increase in S. cerevisiae revertants exposed to 0.2 mg/mℓ of 2,4-D. Kubinski et al. (1981) reported that binding of 2,4-D to E. coli Q13 DNA was enhanced at close to neutral pH (7.2-7.4) in the presence of a cell membrane disruptor (egg-white lysozymes) or a metabolic activator (rat liver enzymes).

Detection of sex-linked recessive lethals in Drosophila melanogaster treated with 2,4-D has been used as a mutagenicity assay by several investigators (Vogel and Chandler, 1974; Magnusson et al., 1977; Rasmusson and Svahlin, 1978). Vogel and Chandler (1974) were unable to show a statistically significant increase in recessive lethals after larval feeding of 9 mM 2,4-D for 3 days; examination was for the F_1 generation. Positive mutagenic effects were reported by Magnusson et al. (1977) following 15-day larval feeding with 100 ppm 2,4-D. Lethals observed in F_1 were not significantly increased, but pooled data from the F_1 and F_2 generations

showed a 2- to 3-fold increase in lethals over controls. These investigators were unable to show chemically induced nondisjunction or loss of sex chromosomes in D. melanogaster treated with the same level of 2,4-D. This assay, however, is less sensitive than the production of recessive lethals for screening of mutagenic agents. Rasmusson and Svahlin (1978) compared phenotypic changes in eye color induced by 2,4-D in two strains of D. melanogaster. They observed that larval exposure to 25 ppm of 2,4-D produced a significant increase in mutations for an unstable D. melanogaster strain (foreign DNA inserted in the structural gene), but failed to do so for a stable strain. The positive control, ethyl methane sulfonate, at 500 ppm levels produced mutations in both strains.

Studies involving 2,4-D and its salts and esters applied to various plant species have indicated chromosomal effects of the compounds. Grant (1978) has argued that the effects of pesticides in plants correlate well with effects in cultured mammalian cells and, therefore, such effects in plants should be considered to indicate possible mutagenic activity of 2,4-D in mammals. Positive mutagenic effects in plants treated with 2,4-D have been reported by many investigators; these have included experiments with barley (Denward, 1954; Mohandas and Grant, 1972; Khalatkar and Bhargava, 1982), wheat (Sandhu, 1957), wheat and barley (Unrau and Larter, 1951), tobacco (Nuti-Ronchi et al., 1976), beans (Amer and Ali, 1974), carrots (Bayliss, 1973), geranium (Pohlheim et al., 1977) and several weed species (Tomkins and Grant, 1976). Denward (1954) recorded seven mutants in the second generation progeny of barley plants that had been injected near the spikes with 1.5 mL of a 2,4-D solution (concentration unknown). Spraying of wheat and barley plants at various stages of growth with 2,4-D ester at a level equivalent to 12 ounces of 2,4-D acid/acre has been reported by Unrau

and Larter (1951) to produce a number of meiotic abnormalities. Chromosome aberrations included bridges, fragments, aneuploidy and polyploidy, chain and ring formation, and sticky chromosomes. The incidence of these chromosome effects at different times after emergence indicated that sensitivity to 2,4-D changes throughout the growth cycle. Sandhu (1957) reported a higher number of off-plants in progeny of barley treated with 8 ounces of 2,4-D amine solution. Khalatkar and Bhargava (1982) reported the induction of mitotic and meiotic chromosomal aberrations, pollen sterility, spike and seed morphological alterations in the M_1 generation and chlorophyll-deficient mutations in the M_2 generation grown from barley seeds soaked in a 100 ppm solution of 2,4-D for 9 hours.

Treatment of germinated barley seeds with 200 ppm of a commercial herbicide preparation of the mixed butyl esters of 2,4-D for 6 hours has been reported to produce five chlorophyll mutants in M_2 seedlings during field trials (Mohandas and Grant, 1972). These investigators also noted chromosome effects similar to those described by Denward (1954) in root tip cells of Allium cepa (onion) treated with 50-100 ppm of 2,4-D for 6 hours. Data on the scoring of these chromosome effects were not presented. Two other species of plants also showed root tip effects after application of this commercial 2,4-D ester preparation, while three species tested failed to show an increase in abnormal cells. The types of aberrations described, including the finding of C-mitosis, suggest that 2,4-D may interact with the spindle apparatus during cell division. Seiler (1978) points out that cereals are generally insensitive to the auxin-like activity of chlorophenoxy acetic acids, but whether the in vitro effects observed in plant cells treated with 2,4-D are the result of physiological effects on cell growth or direct effects on chromosomal material is not clear.

Tomkins and Grant (1976) found increased chromosome aberrations in 5 of 12 weed species sprayed with a 2,4-D amine solution at a dose of 907 g of 2,4-D acid equivalent per 0.4 ha. These included chromosome fragments, bridges and lagging chromosomes. Similar chromosome effects were observed by Amer and Ali (1974) in bean plants following spraying with 0.39 ppm 2,4-D for 5 days. These workers found that the growth stage of the plants influenced the sensitivity to 2,4-D treatment. Disturbed metaphases and anaphases indicated effects on the mitotic spindle. Siddiqui et al. (1982) observed abnormalities in meiotic chromosomes of Helianthus annuus treated with 10 or 20 ppm of 2,4-D, but not 5 ppm. These aberrations included chromosome pairing failure, stickiness, bridges, irregular separation, laggards and fragments. Muhling et al. (1960) were unable to show increases in chromosome breaks following treatment of pea seedling roots with 40 ppm levels of a 2,4-D solution; however, colchicine-like effects observed in mitotic preparations suggested that 2,4-D may have acted as a spindle poison. Bayliss (1973) noted similar chromosomal and mitotic abnormalities in root tip preparations of carrots treated in vitro with 0.1 mg/ℓ of 2,4-D. Increased chromosome breakage in tissue cultures of tobacco plant cells following in vitro exposure to 0.4 ppm 2,4-D has also been reported by Nuti-Ronchi et al. (1976). These effects were also produced in this habituated line of plant cells by the addition of a synthetic auxin, kinetin. Nonhabituated cells that required the presence of growth factor for survival in culture showed no chromosome breakage from treatment with 2,4-D or kinetin.

Assays using in vivo mammalian metabolic activation have failed to show mutagenic activity of 2,4-D, including the host mediated assay with S. typhimurium (Styles, 1973) and the host mediated assay with S. cerevisiae

(Zetterberg et al., 1977). Similarly, two mammalian assays, the dominant lethal assay (Epstein et al., 1972) and the micronucleus test (Jenssen and Renberg, 1976), have not demonstrated genotoxic effects. This lack of activity in mammalian systems may correlate with the finding of Jenssen and Renberg (1976) that <5% of a 100 mg/kg dose of 2,4-D injected i.p. into mice was available for penetration into bone marrow cells within 24 hours. Pilinskaya et al. (1976), however, reported an increase in chromosome aberrations of bone marrow cells from mice treated with 100 or 300 mg/kg oral doses of 2,4-D. No data on the scoring of these cells were presented, but the authors stated that the chromosome aberrations were primarily single fragments. The purity of the 2,4-D and the vehicle used in this study were not described.

Conflicting results for the genotoxicity of 2,4-D have been observed in several in vitro assays using mammalian cells. Probst et al. (1981) reported that 2,4-D did not stimulate unscheduled DNA synthesis in primary rat hepatocyte cultures that retain metabolic capability. Murakami and Fukami (1980, 1982) reported the absence of 2,4-D binding to human embryonic DNA in cultured cells. Ahmed et al. (1977), however, found an increase in oubain resistant mutants following treatment of cultured V-79 Chinese hamster lung cells with a 2,4-D concentration of 10 µM. Further, they found increased unscheduled DNA synthesis and increased bromodeoxyuridine photolysis in SV-40 transformed human fibroblasts treated with or without a source of metabolic activation using the same concentration range of 2,4-D. Calculations to determine the number of breaks produced in 2,4-D-treated cells in the photolysis assay indicated very little increase as the dose of 2,4-D was increased from 10-100 µM. Styles (1977) was unable to show increased transformation of cultured baby hamster kidney or human lung cell lines

treated in vitro with or without a source of metabolic activation at concentrations of 0.08-250 µg 2,4-D/mℓ.

Peripheral blood lymphocytes have been cultured in the presence of 2,4-D and scored for chromosome damage (Bongso and Basrur, 1973; Pilinskaya et al., 1976; Korte and Jalal, 1982). Pilinskaya et al. (1976) reported an increase in chromosome aberrations following treatment of cultured human lymphocytes with 20 µg/mℓ. Data on controls were not presented, nor were scoring data reported. Bovine peripheral blood cells exposed to 10-1000 ppm levels of 2,4-D showed altered mitosis and an elevated mitotic index, but no chromosomal aberrations (Bongso and Basrur, 1973).

Korte and Jalal (1982) incubated cultured human blood cells with 0.2-60 µg 2,4-D/mℓ for 48 hours and examined the chromosomes for evidence of aberration and sister chromatid exchange. They observed statistically significant increases in gaps and deletions in lymphocytes treated with 50 and 60 µg/mℓ ($p=0.05$), and in sister chromatid exchanges in lymphocytes treated with 10, 20, 30, 40, 50 and 60 µg/mℓ ($p=0.05$) over untreated controls.

A recent report has found that oral administration of 2,4-D to mice inhibited thymidine incorporation into testicular DNA (Seiler, 1979). This inhibition was observed when 200 mg/kg of 2,4-D was administered to mice 1 hour after an i.p. injection of ^{14}C-thymidine. The author noted that the order of mutagenic activity (MCPA > 2,4,5-T > 2,4-D) suggested by the work of other investigators was also observed in this assay (which has not been validated as a mutagenicity screening test).

These studies suggest that 2,4-D may have mutagenic activity in certain systems; however, the general lack of positive genotoxic effects in vivo for mammalian assays may indicate that sufficient levels of 2,4-D are not able to reach the target tissues. No information is available on mammalian mutagenicity testing conducted with the esters of 2,4-D; these forms could theoretically show higher levels of penetration into target cells.

Teratogenicity and Other Reproductive Effects

Teratogenicity. The teratogenic and embryotoxic effects of 2,4-D and several derivatives of 2,4-D have been investigated in several species of laboratory animals. Overall, 2,4-D and its derivatives appear to be embryotoxic but only weakly teratogenic or nonteratogenic. The teratogenic or embryotoxic (or both) effects observed following oral administration of 2,4-D and its derivatives during gestation are summarized in Table V-6.

Courtney (1977) investigated the ability of 2,4-D (no dioxins detected) and several derivatives of 2,4-D (no dioxins detected), including isopropyl, n-butyl, isooctyl and propylene glycol butyl ether (PGBE) esters of 2,4-D, and 2,4-D butyric acid, to induce cleft palates in CD-1 mice. Daily gastric intubation of 2,4-D and the propylene glycol butyl ether (PGBE) and n-butyl ester derivatives were given at levels of 124 mg/kg/day of 2,4-D on days 7-15 of gestation and 221 mg/kg/day of 2,4-D on days 12-15 of gestation. The isooctyl and isopropyl esters and butyric acid derivatives were administered at 124 mg/kg/day of 2,4-D on days 7-15 of gestation for the two esters and on days 11-13 of gestation for butyric acid. The day of detection of a vaginal plug was taken as day 1 of gestation; the animals were killed on day 18 of gestation. Control animals were given daily gastric intubations of the vehicle, consisting of 0.1 mℓ corn oil:acetone (in a ratio of 9:1).

TABLE V-6

Teratogenicity of Orally Administered 2,4-D and Derivatives of 2,4-D

Compound	Species/ Strain	No. Dams at Start	Vehicle	Purity	Dosage/Exposure	Dose as mg/kg/day of 2,4-D	Maternotoxic, Fetotoxic and Teratogenic Effects	Reference
2,4-D	mice/CD-1	vehicle controls: 4 groups, 7-16/ group; treated: 8/low dose, 14/high dose	corn oil: acetone	90%	0.56 mM/kg on days 7 through 15 of gestation	124	2% cleft palate/litter as compared with 0% for controls; no other effect on fetal parameters; no effect on maternal weight gain; increase ($p<0.05$) in maternal relative liver weight	Courtney, 1977
					1.00 mM/kg on days 12 through 15 of gestation	221	6% cleft palate/litter as compared with 0% for controls; decreased ($p<0.05$) fetal weight among litters; no effect on maternal weight gain; increase ($p<0.05$) in maternal relative liver weight	
PGBE ester of 2,4-D	mice/CD-1	vehicle controls: 4 groups, 7-16/ group; treated: 10/low dose, 7/high dose	corn oil: acetone	99.9%	0.56 mM/kg on days 7 through 15 of gestation	124	8% cleft palate/litter as compared with 0% for controls; decreased ($p<0.05$) fetal weight among litters; no effect on maternal weight gain; increase ($p<0.05$) in maternal relative liver weight	Courtney, 1977
					1.00 mM/kg on days 12 through 15 of gestation	221	16% cleft palate/litter as compared with 0% for controls; decreased ($p<0.05$) fetal weight among litters; no effect on maternal weight gain or relative liver weight	
n-Butyl ester of 2,4-D	mice/CD-1	vehicle controls: 4 groups, 7-16/ group; treated: 9/dose level	corn oil: acetone	98.4%	0.56 mM/kg on days 7 through 15 of gestation	124	No effect on fetal parameters or on maternal weight gain or relative liver weight	Courtney, 1977
					1.00 mM/kg on days 12 through 15 of gestation	221	15% cleft palate/litter as compared with 0% for controls; decreased ($p<0.05$) fetal weight among litters; no effect on maternal weight gain; increase ($p<0.05$) in maternal relative liver weight	

TABLE V-6 (cont.)

Compound	Species/ Strain	No. Dams at Start	Vehicle	Purity	Dosage/Exposure	Dose as mg/kg/day of 2,4-D	Maternotoxic, Fetotoxic and Teratogenic Effects	Reference
Isopropyl ester of 2,4-D	mice/CD-1	vehicle controls: 4 groups, 7-16/ group; treated: 10	corn oil: acetone	99%	0.56 mM/kg on days 7 through 15 of gestation	124	No incidence of cleft palate; decreased ($p<0.05$) fetal weight among litters; no effect on maternal weight gain or relative liver weight	Courtney, 1977
Isooctyl ester of 2,4-D	mice/CD-1	vehicle controls: 4 groups, 7-16/ group; treated: 11	corn oil: acetone	96.8%	0.56 mM/kg on days 7 through 15 of gestation	124	No incidence of cleft palate; decreased ($p<0.05$) fetal weight among litters; no effect on maternal weight gain or relative liver weight	Courtney, 1977
Butyric acid of 2,4-D	mice/CD-1	vehicle controls: 4 groups, 7-16/ group; treated: 8	corn oil: acetone	99.6%	0.56 mM/kg on days 11 through 13 of gestation	124	No incidence of cleft palate; no effect on other fetal parameters; no effect on maternal weight gain; increase ($p<0.05$) in maternal relative liver weight	Courtney, 1977
2,4-D	rats/ Wistar	6-14/dose/expt.	corn oil or aqueous gelatin	no dioxins detected	0, 25, 50, 100, 150 mg/kg/day on days 6 through 15 of gestation	0, 25, 50, 100, 150	Dose-related increased fetal mortality and decreased fetal weight significant ($p<0.05$) at 100 and 150 mg/kg/day; increased incidence of skeletal malformations* among litters significant ($p<0.05$) at 25, 100 and 150 mg/kg/day as compared with controls; no effect on maternal body weights.	Khera and McKinley, 1972
Isooctyl ester of 2,4-D	rats/ Wistar	17 controls, 5-6 treated/dose	corn oil	NR	50 mg/kg/day on days 6 through 15 of gestation	33.2	NOAEL as judged by fetal mortality, fetal weights, occurrence of skeletal or visceral anomalies*	Khera and McKinley, 1972
					150 mg/kg/day on days 6 through 15 of gestation	99.5	Decreased ($p<0.05$) fetal weight among litters; increased ($p<0.05$) incidence of skeletal malformations* among litters; no effect on maternal body weights	

TABLE V-6 (cont.)

Compound	Species/ Strain	No. Dams at Start	Vehicle	Purity	Dosage/Exposure	Dose as mg/kg/day of 2,4-D	Maternotoxic, Fetotoxic and Teratogenic Effects	Reference
Butyl ester of 2,4-D	rats/ Wistar	17 controls, 4-5 treated/dose	corn oil	NR	50 mg/kg/day on days 6 through 15 of gestation	40	NOAEL as judged by fetal mortality, fetal weights, occurrence of skeletal or visceral anomalies*	Khera and McKinley, 1972
					150 mg/kg/day on days 6 through 15 of gestation	120	Increased ($p<0.05$) fetal mortality among litters; decreased ($p<0.05$) fetal weight among litters; increased ($p<0.05$) incidence of skeletal malformations* among litters; no effect on maternal body weights	
Butoxy-ethanol ester of 2,4-D	rats/ Wistar	15 controls, 8-9 treated/dose	corn oil	NR	50 mg/kg/day on days 6 through 15 of gestation	34.4	NOAEL as judged by fetal mortality, fetal weights, occurrence of skeletal or visceral anomalies*	Khera and McKinley, 1972
					150 mg/kg/day on days 6 through 15 of gestation	103.2	Increased ($p<0.05$) incidence of skeletal malformations* among litters; no effect on maternal body weights	
Dimethyl-amine salt of 2,4-D	rats/ Wistar	15 controls, 7-10 treated/dose	corn oil	NR	100 mg/kg/day on days 6 through 15 of gestation	41.8	NOAEL as judged by fetal mortality, fetal weights, occurrence of skeletal or visceral anomalies*	Khera and McKinley, 1972
					300 mg/kg/day on days 6 through 15 of gestation	125.5	Increased ($p<0.05$) incidence of skeletal malformations* among litters; effect on maternal body weights	
2,4-D	rats/ Sprague-Dawley	controls: 2 groups, 36 and 41; treated: 13-21/dose	corn oil	commercial grade	12.5 mg/kg/day 2,4-D on days 6 through 15 of gestation	12.5	Increased ($p<0.05$) incidence of delayed ossification of skull bones among fetuses and litters; no effect on maternal body weight	Schwetz et al., 1971
					25 mg/kg/day 2,4-D on days 6 through 15 of gestation	25	No significant effect on fetuses or on maternal body weight	

TABLE V-6 (cont.)

Compound	Species/ Strain	No. Dams at Start	Vehicle	Purity	Dosage/Exposure	Dose as mg/kg/day of 2,4-D	Maternotoxic, fetotoxic and Teratogenic Effects	Reference
2,4-D					50 mg/kg/day 2,4-D on days 6 through 15 of gestation	50	Intermediate respon: between 2 lower dosage levels (12.5 and 25 mg/kg/day) and 2 higher dosage levels (75 and 87.5 mg/kg/day)	Schwetz et al., 1971
					75 or 87.5 mg/kg/day 2,4-D on days 6 through 15 of gestation	75 or 87.5	Decreased ($p \leq 0.05$) fetal weight among litters; increased ($p<0.05$) incidences of skeletal defects (including delayed ossification of sternebrae and/or skull, wavy ribs, lumbar ribs, missing sternebrae) among fetuses and litters; increased ($p<0.05$) incidence of subcutaneous edema among fetuses and litters; no effect on maternal body weight	
PGBE ester of 2,4-D	rats/ Sprague-Dawley	controls: 2 groups, 36 and 41; treated: 13-21/dose	corn oil	commercial grade	dose equimolar to 12.5 mg/kg/day 2,4-D on days 6 through 15 of gestation	12.5	Increased ($p<0.05$) incidence of missing sternebrae among fetuses; no effect on maternal body weight	Schwetz et al., 1971
					dose equimolar to 25 mg/kg/day 2,4-D on days 6 through 15 of gestation	25	Increased ($p<0.05$) incidence of delayed ossification of skull bones among fetuses and litters; no effect on maternal body weight	
					dose equimolar to 50 mg/kg/day 2,4-D on days 6 through 15 of gestation	50	Intermediate response between 2 lower dosage levels (12.5 and 25 mg/kg/day) and 2 higher dosage levels (75 and 87.5 mg/kg/day)	

TABLE V-6 (cont.)

Compound	Species/ Strain	No. Dams at Start	Vehicle	Purity	Dosage/Exposure	Dose as mg/kg/day of 2,4-D	Maternotoxic, Fetotoxic and Teratogenic Effects	Reference
PGBE ester of 2,4-D					doses equimolar to 75 or 87.5 mg/kg/day 2,4-D on days 6 through 15 of gestation	75 or 87.5	Decreased (p<0.05) fetal weight among litters; increased (p<0.05) incidences of skeletal defects (including delayed ossification of sternebrae and/or skull, wavy ribs, lumbar ribs, missing sternebrae) among fetuses and litters; increased (p<0.05) incidence of subcutaneous edema among fetuses and litters; no effect on maternal body weight	Schwetz et al., 1971
Isooctyl ester of 2,4-D	rats/ Sprague-Dawley	controls: 2 groups, 36 and 41; treated: 13-21/dose	corn oil	commercial grade	dose equimolar to 12.5 mg/kg/day 2,4-D on days 6 through 15 of gestation	12.5	Increased (p<0.05) incidence of subcutaneous edema among fetuses; no effect on maternal body weight	Schwetz et al, 1971
					dose equimolar to 25 mg/kg/day 2,4-D on days 6 through 15 of gestation	25	Increased (p<0.05) incidence of sternebrae with split centers of ossification among litters and of delayed ossification of skull bones among fetuses; no effect on maternal body weight	
					dose equimolar to 50 mg/kg/day 2,4-D on days 6 through 15 of gestation	50	Intermediate response between 2 lower dosage levels (12.5 and 25 mg/kg/day) and 2 higher dosage levels (75 and 87.5 mg/kg/day)	
					doses equimolar to 75 or 87.5 mg/kg/day 2,4-D on days 6 through 15 of gestation	75 or 87.5	Decreased (p<0.05) fetal weight among litters; increased (p<0.05) incidences of skeletal defects (including delayed ossification of sternebrae and/or skull, wavy ribs, lumbar ribs, missing sternebrae) among fetuses and litters; increased (p<0.05) incidence of subcutaneous edema among fetuses and litters; no effect on maternal body weight	

Compound	Species/ Strain	No. Dams at Start	Vehicle	Purity	Dosage/Exposure	Dose as mg/kg/day of 2,4-D	Maternotoxic, Fetotoxic and Teratogenic Effects	Reference
PGBE ester of 2,4-D	rats/CD	~37/group for vehicle controls and 2 lower dose groups; 28 at 25 mg/kg/day; 19 at 87.5 mg/kg/day	corn oil	97.15%	doses equimolar to 6.25, 12.5 or 25.0 mg/kg/day 2,4-D on days 6 through 15 of gestation	6.25, 12.5 or 25.0	No adverse effects on fetuses or dams	Unger et al., 1981
					dose equimolar to 87.5 mg/kg/day 2,4-D on days 6 through 15 of gestation	87.5	"Minor embryo-toxicity which was not deleterious to growth and survival", i.e., statistically significantly increased incidence of lumbar (14th) rib buds; no adverse effects on body weight or survival of dams	
Isooctyl ester of 2,4-D	rats/CD	~35/group for vehicle controls and 2 lower dose groups; 28 at 25 mg/kg/day; 21 at 87.5 mg/kg/day	corn oil	96.6%	doses equimolar to 6.25, 12.5 or 25.0 mg/kg/day 2,4-D on days 6 through 15 of gestation	6.25, 12.5 or 25.0	No adverse effec or fetuses or dams	Unger et al., 1981
					dose equimolar to 87.5 mg/kg/day 2,4-D on days 6 through 15 of gestation	87.5	"Minor embryo-toxicity which was not deleterious to growth and survival", i.e., statistically significantly increased incidence of lumbar (14th) rib buds; no adverse effects on body weight or survival of dams	
2,4-D	rats/NR	NR	DP-7	NR	50 mg/kg/day 2,4-D on days 7 through 14 of gestation	50	Increased hemorrhages in the thoracic and abdominal cavities and in the liver and soft tissues of fetuses; details of maternal toxicity were not reported	Konstantinova et. al, 1976
2,4-D; three samples	golden Syrian hamsters	controls: 86; treated: 7-12/ dose/2,4-D sample	acetone, corn oil, carboxy-methyl cellulose	no dioxins detected	20, 40, 80 or 100 mg/kg/day 2,4-D on days 6 through 10 of gestation; 3 or 4 dose levels/ 2,4-D sample	20, 40, 80 or 100	Decreased ($p<0.05$) fetal viability among litters at 40 mg/kg/day with 1 of 3 samples and at 80 and 100 mg/kg/day with another sample; no other significant effects or malformations; details of maternal toxicity were not reported	Collins and Williams, 1971

*Khera and McKinley (1972) did not score minor growth retardation and delays in ossification as anomalous developmental patterns. Skeletal malformations included wavy ribs, additional ribs, fused ribs; retarded ossification of frontal and parietal bones; sternal defects; small distorted scapula laterally convex or distorted humerus shaft, and bent radius or ulna, resulting in micromelia of the forelimb.

No cleft palates were observed in control animals. In all high dose groups, fetal weight among litters was significantly decreased ($p<0.05$). The incidence of cleft palate in offspring of dams treated with 2,4-D was 2 and 6% cleft palate/litter for the low and high doses, respectively. In both groups of animals treated with 2,4-D, no effect on maternal weight gain was noted, but significant increases ($p<0.05$) in maternal relative liver weight were observed. A NOAEL for the n-butyl ester derivative may be defined at 124 mg/kg/day, as no effect on fetal parameters or on maternal weight gain or relative liver weight was observed at this dose level. At the high dose, the n-butyl ester induced 15% cleft palate/litter; a significant increase ($p<0.05$) in maternal relative liver weight without any effect on maternal weight gain was also observed. The PGBE ester of 2,4-D was the most toxic compound tested, inducing 8 and 16% cleft palate/litter at 124 and 221 mg/kg/day, respectively. In addition, treatment with 124 mg/kg/day of the PGBE ester resulted in significantly decreased ($p<0.05$) fetal weight among litters and significantly increased ($p<0.05$) maternal relative liver weight. No incidence of cleft palate or maternal toxicity was observed in animals treated with 124 mg/kg/day of either the isopropyl or isooctyl ester; fetal weight among litters was significantly decreased ($p<0.05$). 2,4-D butyric acid, administered at 124 mg/kg/day, did not induce cleft palate but significantly increased ($p<0.05$) maternal relative liver weight. Based on a calculated prenatal development index value that considered both fetotoxicity and developmental effects (cleft palate), Courtney (1977) observed that the relative order of prenatal toxicity of these compounds was PGBE ester > 2,4-D > isopropyl ester > isooctyl ester > n-butyl ester for the low level of compounds administered on days 7 through 15 of gestation.

Khera and McKinley (1972) studied the teratogenic and postnatal effects of 2,4-D; the isooctyl, butyl, and butoxyethanol esters of 2,4-D; and the dimethylamine salt of 2,4-D administered orally to rats on days 6 through 15 of gestation. Day 1 of gestation was designated as the day after mating for females having sperm in a vaginal smear; the dams were killed on day 22 of gestation. Three commercial preparations and one purified (recrystallized) preparation of 2,4-D (no dioxins detected) were tested at two or more dose levels of 25, 50, 100 and 150 mg/kg/day. The ester derivatives were administered at 50 and 150 mg/kg/day, while the dimethylamine salt derivative was tested at 100 and 300 mg/kg/day. Appropriate vehicle (corn oil or aqueous gelatin) controls were used for each compound tested. Neither administration of 2,4-D nor any of its derivatives had an effect on maternal body weight. For the purposes of this study, minor growth retardation and delayed ossification were not classified as teratogenic effects by the authors. Skeletal malformations included wavy ribs, additional ribs, fused ribs; retarded ossification of frontal and parietal bones; sternal defects; and small, distorted scapula, laterally convex or distorted humerus shaft, and bent radius or ulna, resulting in micromelia of the forelimb. 2,4-D induced a significantly increased incidence ($p<0.05$) of skeletal malformations at 25, 100 and 150 mg/kg/day; the incidence at 50 mg/kg/day was higher than in controls but was not statistically significant. The authors expressed reservations about the significance obtained at the 25 mg/kg/day level, but two of the fetuses from one of two replicate groups treated with this dosage had malformations of the forelimb (previously described). Such malformations were not observed in any control fetuses. A dose-related increase in fetal mortality and a decrease in fetal weight were also significant ($p<0.05$) at the two highest dose levels of 2,4-D. A significantly increased incidence ($p<0.05$) of skeletal malformations was observed in

offspring of dams fed 150 mg/kg/day of the isooctyl, butyl, or butoxyethanol ester of 2,4-D or 300 mg/kg/day of the 2,4-D dimethylamine salt. Fetal body weights were depressed at the 150 mg/kg/day level of the isooctyl and butyl esters. A NOAEL for the isooctyl, butyl, and butoxyethanol esters may be defined at 50 mg/kg/day, and for the dimethylamine salt at 100 mg/kg/day, as judged by no apparent adverse effect on fetal mortality, fetal weights or occurrence of skeletal or visceral anomalies. Postnatal survival was not affected at levels up to (but not including) 200 mg/kg/day of 2,4-D, 150 mg/kg/day of the ester derivatives or 300 mg/kg/day of the salt derivative, leading the authors to conclude that the observed skeletal defects were not incompatible with survival of newborn pups.

Teratogenic effects following oral administration of 2,4-D and the isooctyl and PGBE esters of 2,4-D to Sprague-Dawley rats were investigated in a three-part study by Schwetz et al. (1971). In the first part of the study, pregnant rats were treated with commercial grades of compound in corn oil suspension or solution at levels of 12.5, 25.0, 50.0, 75.0 or 87.5 mg 2,4-D/kg/day or molar equivalents of the esters on days 6 through 15 of gestation. The day sperm were first observed in a vaginal smear was considered to be day 0 of gestation; dams were killed on day 20 of gestation. The maximum tolerated dose of 2,4-D was found to be 87.5 mg/kg/day for Sprague-Dawley rats. Control animals were administered 2.5 mL corn oil/kg/day orally. No effect on maternal body weight was observed with any of the three compounds at the levels tested. At the 12.5 mg 2,4-D/kg/day dose level, treatment with 2,4-D resulted in a significantly increased incidence ($p<0.05$) of delayed ossification of skull bones among fetuses and litters, the PGBE ester resulted in a significantly increased incidence ($p<0.05$) of missing sternebrae among fetuses; and the isooctyl ester resulted in a

significantly increased incidence ($p<0.05$) of subcutaneous edema among fetuses. The NOAEL in Wistar rats of 50 mg/kg/day of isooctyl ester (equivalent to 33.2 mg/kg/day of 2,4-D) derived from the Khera and McKinley (1972) study may be indicative of strain differences, as a LOAEL of 12.5 mg/kg/day of 2,4-D as the isooctyl ester may be inferred from this study for Sprague-Dawley rats. At the 25 mg 2,4-D/kg/day level, treatment with 2,4-D had no effect on fetuses; treatment with the PGBE ester resulted in a significantly increased incidence ($p<0.05$) of delayed ossification of skull bones among fetuses and litters; and the isooctyl ester resulted in significantly increased incidences ($p<0.05$) of sternebrae with split centers of ossification among litters and of delayed ossification of skull bones among fetuses. Schwetz et al. (1971) pointed out that the incidences of these effects varied considerably between the two vehicle control groups. Treatment with 50 mg/kg/day of 2,4-D on equimolar doses of the esters gave an intermediate response between the two lower dosage levels (12.5 and 25 mg/kg/day) and the two higher dosage levels (75 and 87.5 mg/kg/day) for all three compounds tested. Treatment with 75 or 87.5 mg/kg/day of 2,4-D, or equimolar doses of PGBE ester, or the isooctyl ester yielded decreased fetal weight among litters, significantly increased incidences ($p<0.05$) of skeletal defects (including delayed ossification of sternebrae or skull (or both), wavy ribs, lumbar ribs and missing sternebrae) among fetuses and litters, and a significantly increased incidence ($p<0.05$) of subcutaneous edema among fetuses and litters. Schwetz et al. (1971) stated that, in their opinion, the "dose level essentially without effect" was 25 mg 2,4-D/kg/day for 2,4-D and its PGBE and isooctyl esters. They classified all of the anomalies as embryotoxic or fetotoxic effects rather than as teratogenic responses, because none of these anomalies adversely affected either fetal or neonatal development and survival.

In the second part of the study, Schwetz et al. (1971) evaluated the effect on implantation of the PGBE and isooctyl esters of 2,4-D, administered orally on days 5 through 8 of gestation at levels constituting the molar equivalent of 87.5 mg 2,4-D/kg/day. Neither administration of the PGBE ester nor the isooctyl ester affected the percentage of pregnancies or the number of implantations. In the third part of the study, the isooctyl ester was administered orally at a level constituting the molar equivalent of 87.5 mg 2,4-D/kg/day on days 8 through 11 or on days 12 through 15 to differentiate between effects observed in early and late organogenesis. An increased incidence of resorptions was seen in early but not late organogenesis. Isooctyl ester had no effect on fetal body measurements during either stage of organogenesis. The incidence and magnitude of sternebral anomalies was similar following treatment with isooctyl ester during either stage of organogenesis; however, subcutaneous edema was observed only in fetuses of dams treated during early organogenesis.

In a study similar to the first part of the Schwetz et al. (1971) study, Unger et al. (1981) investigated the teratogenic and postnatal effects of the PGBE and isooctyl esters of 2,4-D administered orally to CD rats. Groups of pregnant rats were dosed with the PGBE or isooctyl ester at doses equivalent to 0, 6.25, 12.5, 25.0 or 87.5 mg 2,4-D/kg/day on days 6 through 15 of gestation. The day of detection of sperm in vaginal smears was taken as day 0 of gestation; dams were killed on day 20 except for those designated for a postnatal study. In the offspring of dams ingesting 87.5 mg 2,4-D/kg/day as the PGBE or isooctyl ester, minor fetotoxicity [statistically significantly increased incidences of lumbar (14th) rib buds] was observed; however, maternal toxicity, abnormal postnatal growth and development,

reduced fetal survival or teratogenic effects were not observed. Unlike the previous study of Schwetz et al. (1971), no adverse effects were produced at any of the lower dose levels of either ester.

Konstantinova et al. (1976) have studied the possible teratogenic effects of 2,4-D, 2,4-dichlorophenol and the combination of these two compounds given orally to rats. Compounds were administered intragastrically as aqueous emulsions in OP-7, a mixture of oxyethylated alkylphenols. Increased hemorrhages in the thoracic and abdominal cavities and in the liver and soft tissues were observed in fetuses taken from animals treated with 50 mg/kg/day 2,4-D on days 7 through 14 of gestation or 1 mg/kg/day 2,4-dichlorophenol on days 1 through 20 of gestation. No other gross anatomical effects were found, and increased embryolethality was not observed. The combination of 0.1 mg/kg/day 2,4-D and 0.1 mg/kg/day 2,4-dichlorophenol administered on days 7 through 14 of gestation also produced an increased hemorrhaging in internal organs. The authors expressed concern about the positive effect seen with the combination of 2,4-D and a metabolite (2,4-dichlorophenol) occurring at a level at which neither compound alone shows toxicity.

Aleksaskina et al. (1973) investigated the embryotoxicity of the diethylamine salt of 2,4-D administered orally to rats. Administration of 0.5 mg/kg of the compound throughout pregnancy produced decreases in fetal weight and length. When single doses of the 2,4-D salt were administered on day 4, 6, 9 or 13 of gestation at one-half the LD_{50} level (~400-600 mg/kg), an increase in fetal abdominal hemorrhages was observed. The nature of these lesions was not defined in the available abstract. This level of compound given orally on day 5, 9, 10 or 13 produced increased fetal deaths,

and on day 5, 9 or 13, produced decreased fetal weights. No information was available on the strain of animals tested, the purity of the compound, or the type of vehicle used. No skeletal examinations were conducted during this investigation.

Further work by this group (Buslovich et al., 1976) compared the embryotoxic effects of the diethylamine salt with those of the sodium salt, butyl ester, and amine salt of 2,4-D following oral administration to rats. Administration of the butyl ester at a single dose of one-half the LD_{50} value produced increased fetal deaths and resorptions when the compound was given as a single dose on day 4, 5, 6, 9, 10, 11 or 13 of gestation. The sodium and amine salts given at this dose did not produce embryolethal effects; however, when administered on either day 10 or 14 of gestation, they produced a decrease in fetal weight and length. The authors indicated that the butyl ester of 2,4-D produced the most severe embryotoxic effects, followed by the diethylamine salt, and then the sodium and amine salts. This conclusion appears to be based on comparisons of effects produced by one-half the LD_{50} level, which does not necessarily represent equitoxic doses. Complete data from this study were not available for review. The purity of the compounds and the vehicles used for administration were not identified in the available abstract.

The teratogenic potential of 2,4-D administered orally to hamsters was investigated by Collins and Williams (1971). Three commercial 2,4-D samples (no dioxins detected) were fed by intubation at levels of 20-100 mg/kg/day to hamsters on days 6 through 10 of gestation. The day after mating was designated day 0 of gestation; the dams were killed on day 14 of gestation.

Controls were fed the vehicle containing acetone, corn oil and carboxymethyl cellulose. No significant teratogenic or other effects were noted with any of the preparations. Decreased fetal viability was noted with feeding of one 2,4-D sample at 80 and 100 mg/kg/day doses, while another 2,4-D sample showed this effect at 40 mg/kg/day; the authors did not consider this a clear dose-related response.

Bionetics Research Laboratories (1968b) initiated a large-scale screening program in 1964 to investigate the teratogenic potential of a number of herbicides and other chemicals under a contract with the National Cancer Institute. Included in this study were 2,4-D, the butyl, isooctyl, isopropyl, methyl, and ethyl esters of 2,4-D, and the metabolite, 2,4-dichlorophenol. All compounds were tested by daily s.c. injections in several strains of mice, usually in doses of 46-150 mg compound/kg/day, in DMSO on days 6 through 14 of gestation (days 6-15 of gestation in AKR mice); dams were killed on day 18 (or day 19 for AKR mice). Day 0 of gestation was the day of detection of a vaginal plug. 2,4-D (100 mg/kg/day in 50% honey in water, 0.1 mℓ) was also administered by gavage. Fetotoxic and teratogenic effects were observed for certain groups of mice administered 2,4-D orally or s.c., and for the butyl, isooctyl, and isopropyl esters of 2,4-D, and for 2,4-dichlorophenol injected subcutaneously. These effects were generally seen at a dose of compound corresponding to 100 mg/kg/day of 2,4-D. The methyl and ethyl esters of 2,4-D produced some decreases in fetal weights at this level of administration but failed to produce teratogenic effects. The majority of teratogenic effects observed were in one strain of mice, BL-6, and included such defects as microthalmia, agnathia and anophthalmia. This strain of mice showed inconsistent responses to the administered compound; results with BL-6 mice were therefore divided to include those animals

treated with compounds from September through November, 1966, and those animals that were treated after November, 1966. Even responses of control BL-6 mice to s.c. injection with DMSO varied widely during these two time periods. Data on maternal toxicity were not presented for animals treated with the chlorophenoxy compounds. Because these studies were conducted as part of a large-scale screening program, studies using other doses of compounds were not generally done and, thus, dose-response relationships cannot be evaluated. The s.c. route of administration further complicates the interpretation of these results when applied to the more likely routes of exposure (inhalation and oral).

Teratogenic and embryotoxic effects have been observed in mice following s.c. injection of Hormoslyr 64, a commercial preparation that contains 2,4-D at 330 g/ℓ and 2,4,5-T at 170 g/ℓ (Bage et al., 1973). DMSO, used as a vehicle for test solutions, contained an unspecified mixture of petroleum distillates. Animals were injected on days 6 through 14 of pregnancy and killed on day 18. When this preparation was injected at a dose of 110 mg/kg, an increase was observed in fetal cleft palate incidence, and fetal weight and fetal survival were decreased. Injection of 50 mg/kg doses produced a small increase in cleft palate incidence and no significant embryotoxic effects. Other skeletal and internal malformations noted after administration of the high level of the 2,4-D/2,4,5-T mixture included increased rib and vertebral abnormalities and increased renal and subcutaneous hemorrhages. The authors noted that cystic kidneys and dilation of the renal pelvis, defects reported by other investigators after administration of 2,4,5-T to rats, were not seen in this investigation. As noted previously in the Bionetics (1968b) study, the significance of this route of adminis-

tration is questionable. Some malformations and hemorrhaging were observed in vehicle-treated animals; the complicating effect of DMSO is therefore added to the combination of the two herbicides.

Lutz-Ostertag and Lutz (1970) reported embryotoxic and teratogenic effects after spraying 2,4-D amine on pheasant and partridge eggs. A commercial preparation of the herbicide was sprayed at a level of 1.1 kg/ha after eggs had been incubated for 3.5 days. These investigators found high mortality (43-77%) of embryos by days 20-22 of development. Surviving embryos showed paralysis and sterility. Morphological examinations showed fused vertebrae, curled toes, and testicular and ovarian anomalies. The type of vehicle used and impurities present in the 2,4-D preparation were not described, nor were data on controls presented. No embryonic effects were found following spraying on chicken eggs at a level of 11.2 kg/ha with a commercial 2,4-D PGBE ester formulation (Somers et al., 1978), while immersion of chicken eggs in 1% solutions of commercial 2,4-D amine preparations has also been reported to produce no significant toxic effects (Gyrd-Hansen and Dalgaard-Mikkelsen, 1974). The findings of Lutz-Ostertag and Lutz (1970) appear to be unique and suggest an effect not attributable to the 2,4-D component. Gyrd-Hansen and Dalgaard-Mikkelsen (1974), however, did find increased mortality, malformed beak and gastroschisis in chick embryos following direct injection of the yolk sac with 2-10 mg/egg of commercial 2,4-D amine. The significance of embryonic effects produced by direct injection of chicken eggs for determining the teratogenic potential of chlorophenoxys is uncertain.

Other Reproductive Effects. Hansen et al. (1971) investigated the effects of long-term dietary administration of technical grade 2,4-D in a 3-generation reproduction study in rats. Starting at 3 weeks of age, rats were maintained on diets containing 100, 500 or 1500 ppm (~5-75 mg/kg bw) of 2,4-D for 2 years. Data from the F_1, F_2 and F_3 generations indicated an increase in preweanling mortality at the 1500 ppm feeding, determined as the percentage of pups weaned. At this maximum dose of compound, a significant loss in weight of weanlings was also observed, but there was no effect on parental fertility or litter size. No deleterious effect was noted at the lower dose levels (100 and 500 ppm) on fertility, mean litter size or viability of pups during the first 21 days of age. Liver aliesterase and liver acylamidase activity did not differ between selected F_2 rats (10/sex) at 90 days of age. These authors cite unpublished work by Gaines and Kimbrough (1970), who found increased mortality of weanlings following administration of 1000 or 2000 ppm 2,4-D to groups of 10 female rats in the diet for 3 months before mating and throughout pregnancy and lactation. At 2000 ppm, the pups were small at birth and 94% died before weaning. At 1000 ppm, more deaths were seen among offspring of treated dams than were seen among offspring of control dams.

Bjorklund and Erne (1966) observed toxic effects in the offspring of a single pig fed 500 mg/kg 2,4-D triethanolamine in the diet throughout pregnancy and for 6 weeks after delivery (~25-50 mg/kg/day). Underdevelopment and increased mortality were observed in newborn piglets in the first 24 hours after parturition. "Anorexia" was observed in the sow throughout the experiment; she died ~6 weeks after delivery.

As part of a two-generation study, Bjorklund and Erne (1966) administered 0 or 1000 ppm (equivalent to 0 or ~50-100 mg/kg/day, based on water consumption) of 2,4-D in the drinking water of pregnant rats (N=5/group) throughout gestation and for 10 months following parturition, and continued with offspring for up to 2 years after weaning. Although a reduced food and water intake, with consequent growth retardation, was observed in the treated offspring, no clinical signs, malformations or distinct morphological changes were seen in treated offspring. This study is also discussed in Chapter VII.

In a reproduction and fertility study, Lamb et al. (1980) administered a mixture of 2,4-D, 2,4,5-T and 2,3,7,8-TCDD (simulated Agent Orange) to male C57Bl/6 mice. Groups of animals were given feed that contained various concentrations of the three compounds, so that the daily doses of 40 mg/kg 2,4-D, 40 mg/kg 2,4,5-T, and 2.4 µg/kg 2,3,7,8-TCDD (Group II) or 40 mg/kg 2,4-D, 40 mg/kg 2,4,5-T, and 0.16 µg/kg 2,3,7,8-TCDD (Group III) or 20 mg/kg 2,4-D, 20 mg/kg 2,4,5-T, and 1.2 µg/kg 2,3,7,8-TCDD (Group IV) would be achieved. Another group of animals, used as controls (Group I), were given feed with only the corn oil (2%) vehicle added. At the end of 8 weeks, the treated animals were reported to have dose-related liver and thymus toxicity and significantly reduced body weight gain; however, the liver and thymus recovered to normal or near normal weights following termination of treatment. No significant effect was noted on sperm abnormalities either during or following the dosing period. After 8 weeks of treatment, each treated male was mated to three untreated virgin females, for a total of 24 matings for each treated male. Exposure to the various mixtures of simulated Agent Orange did not result in a significant decrement in fertility or reproduction, as evidenced by no effect on mating frequency, average

fertility, percent implantation and resorption sites, and percent fetal malformations. Furthermore, germ cell toxicity was not observed, and the offspring of treated males were not affected by increased lethality or abnormal neonatal development.

Summary

Acute exposure to high levels of 2,4-D results in progressive symptoms of muscular incoordination, lethargy, hindquarter paralysis, stupor, coma and death in animals (Hill and Carlisle, 1947). These symptoms have been observed consistently in a variety of species regardless of route of administration, and myotonia appears to be a dominant effect of exposure (Bucher, 1946; Hill and Carlisle, 1947; Drill and Hiratzka, 1953). Pathological examinations have shown that acute exposure to high levels of 2,4-D resulted in kidney damage and skeletal muscle changes in a variety of species, but hepatic damage has been described only in dogs (Hill and Carlisle, 1947; Drill and Hiratzka, 1953). Acute oral LD_{50}s in the range of 350-500 mg/kg 2,4-D have been reported for rodents, but significant differences in toxicity are not apparent between 2,4-D and its salts and esters. Inhalation toxicity data are not available.

Subchronic oral toxicity studies have been conducted with rats that were exposed to 2,4-D at levels of 3-300 mg/kg/day, 5 days/week for 4 weeks (Rowe and Hymas, 1954), 2000 ppm in the diet for 4-7 weeks (Chang et al., 1974); 100-5000 ppm in the diet for 113 days (Rowe and Hymas, 1954) and 200-400 ppm in the diet for 31 days (Hill and Carlisle, 1947). In rats doses of 5.0 mg/kg bw/day or higher resulted in significant reductions in blood indices at all doses; liver enzyme activities were reduced at higher doses; kidney toxicity was also evident at higher doses. Effects of higher doses included

GI irritation and mild liver effects (e.g., cloudy swelling, increased weights), as well as characteristic overt signs of toxicity and mortality. In mice doses of 15.0 mg/kg bw/day or higher are associated with decreases in brain weight and increases in white blood cells and pituitary gland hypertrophy as well as other effects (Hazelton Laboratories, 1983). Treatment-related signs of intoxication or mortality were not observed in guinea pigs exposed to 10 daily 50 or 100 mg doses of 2,4-D sodium salt by intubation in 12 days (~88 or 177 mg/kg/day 2,4-D acid equivalent) (Hill and Carlisle, 1947). Administration of 20 mg/kg/day 2,4-D in capsules 5 days/week for 13 weeks produced some mortality but not significant lesions in dogs, but similar exposure to <10 mg/kg/day produced no evidence of toxicity (Drill and Hiratzka, 1953). Pathological and functional effects have been described in the liver, kidneys, lungs, thyroid and nervous system of rats and mice that were repeatedly injected (subcutaneously or intraperitoneally) with 100-200 mg/kg/day 2,4-D (Bucher, 1946; Florsheim and Velcoff, 1962; Florsheim et al., 1963; Desi et al., 1962). Systemic toxicity was not produced by the daily (5 days/week) application of 2,4-D dimethylamine salt, isooctyl ester or butyl ester to the skin of rabbits for 3 weeks at levels of 2,4-D acid corresponding to 0.6 and 3.1% (Kay et al., 1965).

Significant treatment-related gross, histopathological or hematological effects were not found in rats that were exposed to 5-1250 ppm levels of 2,4-D in the diet (~0.25-62.5 mg/kg bw/day) for 2 years (Hansen et al., 1971). In a 2-generation study, administration of 1000 ppm 2,4-D in the drinking water for up to 2 years had no effect on clinical chemistry indices or tissue histology in maternal rats or in the first or second generation offspring (Bjorklund and Erne, 1966). Treatment-related effects were not observed in dogs that were fed 10-500 ppm 2,4-D in the diet (~0.5-25

mg/kg/day) (Hansen et al., 1971). EEG changes were reported in monkeys that were exposed orally to 0.2 mg/kg/day 2,4-D for 3 years, but the toxicological significance of the changes is unknown (Santolucito, 1975).

Administration of 2,4-D to mice by intubation from days 7-28 of age at a level of 100 mg/kg initial bw and subsequently in the diet at a level of 323 ppm (~42 mg/kg bw/day) for 81-90 weeks was not tumorigenic (Bionetics Research Lab., 1968a; Innes et al., 1969). Similar administration of 2,4-D isopropyl ester, butyl ester or isooctyl ester [46.4 mg/kg by intubation, 111-130 ppm in the diet (~14.4-16.9 mg/kg bw/day) for the subsequent 73-83 weeks] was also nontumorigenic. Hansen et al. (1971) reported that administration of 2,4-D at levels of 5-1250 ppm in the diet (~0.25-62.5 mg/kg bw/day) for 2 years did not induce treatment-related tumors in rats, but reexamination of the histopathology sections by Reuber (1979) found a significant increase in the incidence of lymphosarcomas in females at all dose levels; the differences in tumor incidences have not been resolved. Rats or mice that were fed 2,4-D amine salt at one-tenth the LD_{50} level for life did not develop a significant increase in tumors (Archipov and Kozlova, 1974). Single s.c. injections of 2,4-D (215 or 464 mg/kg), 2,4-D isopropyl ester (100 mg/kg) or 2,4-D isobutyl ester (21.5 mg/kg) at age 28 days were not tumorigenic to mice after 78 weeks, but similar injection of 2,4-D isooctyl ester (21.5 mg/kg) induced a statistically significant increase in reticulum cell carcinomas (Bionetics Research Lab., 1968a). Repeated dermal application of 2,4-D reportedly produced skin papillomas in mice only when 2,4-D treatment was preceded by a single dermal application of the initiator 3-methylcholanthrene (Archipov and Kozlova, 1974). A rat bioassay (Industry Task Force, 1985) is not evaluated in this assessment. Note is made that EPA's Office of Pesticide Programs report tumor elevation at the high dose

in male rats and a marginally significant dose-response trend in the males. The female rats and mice were negative. Taken as a whole the animal evidence has been proposed by the Office of Pesticides (EPA 1988, Federal Register) to be inadequate.

2,4-D has not produced mutagenic effects in assays with Salmonella or bacteriophage T_4, although positive responses were reported by Simmon (1979) for DNA repair-deficient strains of E. coli and B. subtilis. Gene conversion/combination tests with the yeast, S. cerevisiae, were positive only when the pH of the system was lowered into the acid range (Siebert and Lemperle, 1974; Zetterberg et al., 1977; Zetterberg, 1978), where 2,4-D would be nonionized. 2,4-D was weakly mutagenic for D. melanogaster in recessive lethal and somatic mutation assays (Magnusson et al., 1977; Rasmusson and Svahlin, 1978). 2,4-D induced ouabain resistance in Chinese hamster V-79 lung cells (Ahmed et al., 1977), induced unscheduled DNA synthesis in cultured human fibroblasts (Ahmed et al., 1977), and induced chromosome aberrations and sister chromatid exchanges in cultured human lymphocytes (Pilinskaya et al., 1976; Korte and Jalal, 1982), but was inactive in other in vitro mammalian assays (cell transformation in human lung or hamster kidney cells, unscheduled DNA synthesis in rat hepatocytes, chromosome aberrations in embryonic bovine kidney cells). Intraperitoneal injection of 2,4-D induced bone marrow chromosome aberrations (Pilinskaya et al., 1976) and oral administration of 2,4-D inhibited thymidine incorporation into testicular DNA in mice (Seiler, 1979), but other in vivo mammalian assays with mice (micronucleus assay and dominant lethal assay) were negative. Information regarding the mutagenicity of 2,4-D esters in animal systems was not located, but these compounds would theoretically penetrate cells more readily than 2,4-D at physiological pH.

Teratogenicity testing has been conducted with 2,4-D, several of its esters (n-butyl, isopropyl, isoctyl, PGBE, butoxyethanol), the dimethylamine salt, and 2,4-D butyric acid in mice, rats and hamsters (Courtney, 1977; Khera and McKinley, 1972; Schwetz et al., 1971; Unger et al., 1981; Konstantinova et al., 1976; Collins and Williams, 1971). Overall, these studies indicate that 2,4-D and its derivatives are embryotoxic but only weakly teratogenic or nonteratogenic. Oral doses (expressed as 2,4-D) of 124 mg/kg/day in mice (Courtney, 1977), 75-125.5 mg/kg/day in rats (Schwetz et al., 1971; Unger et al., 1981; Khera and McKinley, 1972) and 40-100 mg/kg/day in hamsters (Collins and Williams, 1971) produced fetotoxic effects or malformations (cleft palates and other skeletal malformations). Increased preweanling mortality and weight loss were observed in the offspring of rats that were exposed to 1500 ppm levels of 2,4-D in the diet in a 3-generation reproduction study, but adverse effects on litter size or fertility were not found (Hansen et al., 1971).

VI. HEALTH EFFECTS IN HUMANS

Acute Effects

Clinical reports have described fatal poisoning in humans resulting from ingestion of 2,4-D solutions. Nielsen et al. (1965) described a suicide case involving a male agricultural student who ingested at least 6 g of a commercial herbicide preparation of the dimethylamine salt of 2,4-D (50%, by weight). Death appeared to have been preceded by vomiting and convulsions. Pathological examination revealed acute congestion in most organs as well as acute pulmonary edema, and histological examination showed degenerative ganglion cell changes in the brain. Geldmacher et al. (1966) reported two cases of poisoning with 2,4-D. Vomiting and loss of consciousness occurred in a 33-year-old woman following ingestion of an unknown quantity of 2,4-D. Terminal symptoms developed after 1 day, and included weak pulse, tachycardia and deep breathing. These authors described another case reported by Herbich and Machata (1963) of a 46-year-old man who died within 14 hours of swallowing at least 13.5 g of an uncharacterized 2,4-D solution. Constricted pupils and respiratory paralysis were noted among the terminal symptoms. At autopsy, both patients had generalized hyperemia of the organs as well as edema of the brain and the lungs. Dudley and Thapar (1972) reported the fatal poisoning of a 76-year-old male who ingested (assumedly) a pint of 2,4-D solution (in kerosene). Early symptoms included vomiting and loss of consciousness. Death occurred 6 days after the ingestion of 2,4-D. During medical treatment, the patient received pentobarbital, ampicillin and quinidine. Pathological examination indicated edema of the lungs, mid-zonal hepatic necrosis and pyelonephritis. The pulmonary effects noted may have been due to the kerosene vehicle. Multifocal perivascular plaques of demyelinization were observed during microscopic examination of the brain. The

authors attributed death to atrial fibrillation; however, in this case, as in the other fatal poisonings described, the exact cause of death is unknown.

Berwick (1970) reported an incident of nonfatal poisoning, in which a farmer swallowed a mouthful of concentrated weed killer containing 2,4-D. Initial symptoms included acute gastritis and vomiting. Eighteen hours later, intense aching of the chest, painful and tender muscles, and a tender abdomen were reported. Within the next 6 hours, the patient lost use of his intercostal muscles, and the muscles of his upper extremities exhibited spontaneous fibrillary twitchings. Hyperactive biceps and triceps reflexes were seen, but other reflexes were normal. The blood levels of several enzymes, including lactate dehydrogenase, SGOT, SGPT, aldolase and creatine phosphokinase, were increased from days 4-7; myoglobinuria was observed, indicating probable skeletal muscle damage. Although this commercial formulation of weed killer contained 49% Eptam, 35.5% 2,4-D isooctyl ester, 0.5% epichlorohydrin and 5% emulsifiers, the authors found no evidence that the Eptam produced toxicological effects or cholinesterase inhibition. Loss of sexual potency was observed in this patient and persisted for ~4 months; however, other symptoms subsided within ~2 weeks.

Neurological symptoms have been described in other reports of illness related to human exposure to 2,4-D. In most of the cases of occupational exposure to 2,4-D, the subjects had previously been exposed to a variety of pesticides; however, the neurological symptoms observed in 2,4-D exposed experimental animals (see Acute Toxicity Section in Chapter V) suggest that the compound has the potential to produce neurological effects. Monarca and DiVito (1961) reported symptoms in a farmer who became ill after applying a

40% aqueous solution of 2,4-D against the wind. The symptoms included ataxia, reflex disorders such as abolished Achilles tendon reflex and reduced patellary reflexes, and a positive Romberg's sign (damage to the dorsal column of the spinal cord). Symptoms persisted for 2-3 months and subsided slowly. Goldstein et al. (1959) described three cases of peripheral neuropathy following exposure to an ester of 2,4-D. The first patient had two dermal exposures within 2 months to spills of a 10% solution of 2,4-D ester, and experienced nausea, vomiting and diarrhea after each exposure. He experienced numbness and aching of the digits 1 week after the second exposure. During the following 5 weeks, he showed the development of peripheral neuropathy. The second patient also developed neurological symptoms after two exposures, ~1 year apart, to dermal wetting with an ester of 2,4-D. This patient developed flaccid paraparesis 5 months after the second exposure. The third patient reported wetting of his clothes with a spray solution of 2,4-D ester during application. Within 24 hours, he developed malaise, headache, nausea and vomiting, and, within 48 hours, severe vertigo. Paresthesia in the limbs appeared within 4-5 days, followed by fasiculations that became generalized. In all three cases, the symptoms of peripheral neuropathy were of prolonged duration. The authors obtained the label from one container that had been used for spraying and found that the applied material was 44% isopropyl ester and 56% inert ingredients. Another clinical report of long-term (~2 years) peripheral neuropathy in a farmer exposed to 2,4-D ester while spraying has been reported by Todd (1962). Berkley and Magee (1963) described what appeared to be a primary sensory neuropathy of the upper extremities in a farmer exposed to the

dimethylamine salt of 2,4-D while spraying a corn field. Bordas et al. (1958) also noted weight loss and sensory and motor neuropathies in workers exposed to 2,4-D during spraying operations.

Polyneuritis has been described in a farmer who became ill after spraying 2,4-D solutions of 235 and 410 g/ℓ for several days in an open cab tractor (Foissac-Gegoux et al., 1962). The patient developed facial anaesthesia and paresthesia. He subsequently lost feeling in his legs and was forced to walk with a cane. Neurological examination showed increased knee reflex and decreased Achilles tendon reflexes at 2 months; 3 months after exposure, motor and sensory symptoms of the face and legs had improved, but an electromyelogram still showed abnormalities. In these reports of agricultural exposures, the precise formulations of compounds used is not known, nor is the amount of compound present in the air or on the skin of workers.

Subchronic and Chronic Effects

Noncarcinogenic Effects. Reports on subjective clinical symptoms in workers exposed to 2,4-D during its manufacture or use have been published. Assouly (1951) reported that symptoms in workers employed in the fabrication of 2,4-D esters included gastralgia, anorexia, somnolence, a sweet taste in the mouth, increased hearing sensitivity, a sensation of drunkenness and heaviness of the legs. Bashirov (1969) examined 292 workers (248 men and 44 women) engaged in the manufacture of 2,4-D amine and butyl ester. He reported a high frequency (63%) of symptoms of rapid fatigue, weakness, headache or vertigo. Approximately 20% of these workers experienced hypotension, bradycardia, dyspepsia and gastritis. Another Russian study (Fetisov, 1966) reported rapid fatigue, headache, loss of appetite, pains in

the region of the liver and stomach and lowered acuity of taste and smell in workers using preparations of the butyl ester, crotyl ester or amine salt of 2,4-D. Health effects of exposure to chlorophenoxys in a 2,4-D and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) production plant were reported by Poland et al. (1971). A study of health records included 73 male workers with an average duration of employment of 8.3 years. Symptoms reported for these workers included chloracne, hyperpigmentation and hirsutism; these correlated together and were most probably related to exposure to 2,4,5-T and dioxin impurities. Other symptoms noted included various gastro-intestinal disturbances and decreased hearing acuity. One case reported diminished proprioception and two workers failed to demonstrate ankle jerk reflexes. None of these subjective clinical reports indicate levels of exposure, nor do they indicate other possible chemicals to which these workers may have been exposed.

Kephart (1945) reported that an individual who voluntarily ingested 500 mg of 2,4-D daily for 21 days demonstrated no ill effects. Additional information regarding this observation is not available.

Wallis et al. (1970) described neurological changes in a worker exposed to 2,4-D over a period of 1 year while spraying sugar cane fields. Over a period of 2 days, this worker developed painful paresthesias in the hands and feet. During the next 3 days, he developed painful muscular stiffness in all four limbs; this condition progressed over the next 2 years, impairing his gait and his manual dexterity. Movement was with deliberate slowness and great effort. Medical evaluation showed fasiculations of facial, masseter, trunk and extremity muscles. Electromyography indicated normal-

appearing motor units and periodic outbursts of repetitive short durations. A biopsy of the right sural nerve showed that some fibers had undergone degenerative changes. No detectable 2,4-D was found in a urine sample from the patient. Treatment with diphenylhydantoin relieved the muscular rigidity in this patient as long as blood levels of drug were maintained.

Seabury (1963) administered a total of 12,712 mg of 2,4-D sodium salt, 369 mg of indole-3-butyric acid and 38.3 mg of α-naphthalene acetic acid to a patient that had terminal coccidioidomycosis during a period of 33 days without observable toxicity. The 2,4-D salt was administered daily in a total of 23 doses; four of the first five doses were given via intramuscular injection (8-24 mg/dose), doses 6 through 21 were given intravenously (doses 11-12 were 960 mg/dose and doses 13-21 were 800 mg/dose), and dose 22 was 2000 mg. Although administration of the 2,4-D until this point had been without apparent adverse effects, a final intravenous dose of 3600 mg 2,4-D sodium salt 2 days after the 2000 mg dose, infused over a 2-hour period, elicited a lapse into a semistuporous state, fibrillary muscle movements in the mouth and both hands that persisted for several hours, and hyporeflexia in the knees, ankles and biceps that persisted for 24 hours. The patient still complained of profound muscle weakness 24 hours after the infusion. Within the next 24 hours, recovery was observed, and no subsequent abnormalities in neurological or muscular parameters were noted in the following 2 weeks.

Johnson (1971) summarized an unpublished Dow Chemical study on the health effects of exposure to 2,4-D in a production facility. In this study, 220 men exposed for 0.5-22 years to 2,4-D in a range of 30-40 mg/day

were reported to show no significant clinical effects when compared with a control population of 4600 men not engaged in 2,4-D or 2,4,5-T manufacture. A battery of "at least 20 laboratory tests" was conducted, but additional details of this unpublished study were not presented. The author noted that karyotypes of peripheral blood lymphocytes from 10 of these workers showed no chromosome aberrations.

Singer et al. (1982) assessed the nerve conduction velocities of the median motor, median sensory and sural nerves of 56 employees (mean age of 35 years) engaged in the manufacture of 2,4,5-T and 2,4-D (exposure levels not determined) for an average of 7 years. The control group consisted of 25 subjects without previous exposure to neurotoxic agents, history of diabetes, stroke, other neurological disease or excessive alcohol use. Slowed nerve conduction velocities in one or more of the three tested nerves were seen in 46% of the study group, as compared with 5% of the control group. The most dramatic change occurred with sural sensory velocity, which was significantly correlated with duration of employment. The significance of these findings in relation to 2,4-D exposure to humans was not determined. Singer et al. (1982) indicated that another study of a group of workers exposed to 2,4,5-T contaminated with dioxins but not exposed to 2,4-D has been initiated. Comparison of these two studies may shed some light on the adverse effects in humans resulting from chronic exposure to 2,4-D.

Carcinogenic Effects.* Several Swedish epidemiological studies of workers exposed to chlorophenoxyacetic acids and derivatives have been published (Axelson and Sundell, 1974, 1977; Axelson et al., 1979; Hardell, 1977; Hardell et al., 1979, 1980; Hardell and Sandstrom, 1979; Eriksson et al., 1977). Axelson and Sundell (1974) studied tumor incidence and mortality in 730 Swedish railroad workers exposed for at least 45 days to various herbicides including chlorophenoxys, aminotriazole and monuron during spraying operations. Exposed workers were divided into four cohorts, based on the type of herbicide exposure, and mortality and tumor incidence were compared with national average age and sex specific values. Mortality was reported in the following categories: 1) all causes, 2) all tumors, and 3) lung cancers. Latency periods of 0, 3 and 5 years were included in calculations (i.e., workers exposed within the last 3 or 5 years were excluded from calculations). No excess for any of these three mortality causes was found for the cohort exposed to chlorophenoxys and combinations. Data from this study were recombined and reanalyzed by Axelson and Sundell (1977) to eliminate effects from combined exposure to chlorophenoxys and other agents (primarily aminotriazole). These investigators concluded that an excess tumor incidence can be positively associated with chlorophenoxy exposure alone, or with aminotriazole alone, and that the combination of the two herbicide types may potentiate the tumorigenic effect.

Axelson et al. (1979) considered this same group of railroad workers in a new study and extended the observation period from 1972 through October, 1978. Workers were divided into three cohorts: those exposed only to

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*For additional indepth analysis of the cancer epidemiology studies for phenoxy acetic acids and chlorinated phenols see U.S. EPA (1984).

aminotriazole, those exposed only to chlorophenoxys, and those exposed to both herbicide classes. Mortality evaluation included the following: 1) total mortality, 2) mortality produced by all tumors, 3) mortality produced by tumors of the stomach, or 4) mortality produced by tumors of the lungs. When a 10-year latency period was used in calculations, the cohort with combined herbicide exposure showed excesses in total mortality and mortality produced by all tumors (7 cases vs. 1.78 expected). Those workers who were exposed to chlorophenoxys showed only a small but significant excess of tumors of the stomach (2 vs. 0.33 expected, $p<0.05$). This excess in observed mortalities was associated with exposure to herbicides before 1962. The authors suggest that either the formulations used in that period were more toxic, or that work practices may have been more lax during the earliest period covered by this study (1957-1962). No estimates of the levels of exposure to chlorophenoxys or the duration of these exposures could be made. The 2,3,7,8-TCDD content of 2,4,5-T used by these workers was not determined. This extremely toxic contaminant may produce effects in the microgram range.

The discovery that 7 of 87 patients diagnosed with malignant mesenchymal tumors had a history of exposure to chlorophenoxy herbicides 10-20 years earlier led Hardell (1977) to conduct a case-referent study of 52 cases of soft-tissue sarcoma (STS) treated at Umea, Sweden, from 1970-1977 (Hardell and Sandstrom, 1979). The cases represented 21 living and 31 deceased male patients, ranging in age from 26-80 years. Control subjects were matched for sex, age, place of residence, and vital status. Deceased cases and controls were matched for year of death. Cohorts were defined as those exposed to chlorophenoxys only, those exposed to chlorophenols only, and

those exposed to both classes of compounds. Exposure information was obtained by questionnaires and supplementary interviews. These investigators calculated a relative risk of 5.3 (i.e., 5.3 x greater than the control risk) for developing STS in workers exposed to chlorophenoxys. This cohort had been exposed primarily to 2,4,5-T, 2,4-D and MCPA. The authors noted that 2,3,7,8-TCDD contamination of 2,4,5-T may have led to significant exposure. The number of patients with exposure to only chlorophenoxys used for the relative risk calculation was small (13 cases).

Another case-referent study on malignant mesenchymal tumors was initiated by this group for workers in a southern farming area of Sweden (Eriksson et al., 1977). Cases of STS were taken from the Swedish Cancer Registry of reports made from 1974-1978. Patients were males, 72 living and 38 deceased, ranging in age from 25-75 years. The design of the earlier study was retained for this investigation (i.e., two control subjects were selected for each case) and exposed workers were divided into three cohorts. The workers exposed to chlorophenoxys only showed a relative risk of 6.8 for developing STS. Workers exposed to phenoxy herbicides not known to be contaminated with polychlorinated dibenzo-p-dioxins (MCPA, 2,4-D, mecoprop, dichloroprop) showed a relative risk of 4.2. This subgroup, however, represented only 7 of the 25 cases of sarcoma considered by Eriksson et al. (1977). The authors suggest that this increased risk found in workers exposed to "nondioxin" herbicides alone could indicate carcinogenic effects produced by the chlorophenoxy herbicides themselves; however, materials to which this group was exposed were not available for analysis. In a later update of this work by Eriksson et al. (1981), he reiterated his earlier finding of a roughly 6-fold increase in the risk of STS from exposure to phenoxy acids or chlorophenols. Again, he found that the risk

ratio given exposure to phenoxy acids free of 2,3,7,8-TCDD and dibenzofurans was 4.2. When consideration was given to persons exposed only to phenoxy acids that contain such impurities, the relative risk equalled 17.0 This case-referent study was similar to that of Hardell and Sandstrom (1979) and subject to the same critisims. Recent work by Cochrane et al. (1980) indicates that 2,4-D may be contaminated with a small amount of chlorinated dibenzo-p-dioxins other than the 2,3,7,8-isomer.

Hardell et al. (1980) conducted a fourth case-referent study correlating the incidence of malignant lymphoma (both Hodgkin's and non-Hodgkin's lymphomas) with exposure to herbicides. The cases involved were 107 living and 62 deceased male patients treated in Umea, Sweden, between 1974 and 1978. The ages of patients ranged from 25-85 years. Workers exposed to chlorophenoxys alone showed a relative risk ratio of 4.8 for developing malignant lymphomas. The nature of the herbicides included in the category "chlorophenoxys" was not known, but probably included 2,4-D, 2,4,5-T, MCPA, picloram and aminotriazole (these latter two are not chlorophenoxy herbicides). Of the 41 cases of malignant lymphoma with histories of exposure to chlorophenoxys, seven cases were considered to have had primarily 2,4-D exposure. The authors suggest that by dividing the 41 lymphoma cases into two groups, based on 90 days or more estimated exposure to chlorophenoxys, an increase in relative risk (7.0 versus 4.3) is seen with a longer duration of exposure; however, this difference is not statistically significant. Methodology used in this study was the same as that used in the two earlier case-referent studies conducted by this group. Because exposure was determined on the basis of questionnaires and telephone interviews, very little detail on the nature and duration of exposure could be determined.

No increase in total mortality or deaths caused by malignant neoplasms was found by Ott et al. (1980) in a study of 204 employees engaged in the production of 2,4,5-T. Workers included in the study had been employed for 1 or more months between 1950 and 1971 in 1 of 4 jobs that involved exposure to chlorophenoxys and probably other agents such as chlorophenols and styrene-butadiene latex. An industrial hygiene survey conducted in 1969 found airborne exposure estimates of 0.2-0.8 mg/m³ for 2,4,5-T; <0.4 mg/m³ for 2,4-D; and 1.6-9.7 mg/m³ for 2,4,5-trichlorophenol. These levels, however, reflect only a single monitoring study and may have little relationship to levels 10-15 years earlier. Comparisons of worker mortality with average values for the total United States white male population using 5-year age intervals found no significant differences for the exposed worker population. The majority of the workers considered in this study had occupational exposure of <12 months total to chlorophenoxys.

Lynge (1985), in an incidence study of 3,390 males employed in two factories manufacturing phenoxyacetic acid herbicides, chiefly 2,4-D and MCPA, found a nonsignificant excess risk of STS in male employees. The author stated that these results supported the Swedish observation of an increased risk of STS following exposure to phenoxyacetic acid herbicides, including 2,4-D, "unlikely to be contaminated with 2,3,7,8-TCDD." However, after a 10-year latency, the excess of STS was significant (4 observed vs. 1.00 expected; $p<0.05$) in male employees of the single factory where 2,4,5-T had been produced and used and where all five STS's arose. However, the author cautions that because of the limited amount of 2,4,5-T processed at that factory exposure is unlikely although not impossible. The Lynge (1985) study noted only a slight excess of lymphomas in males after a lapse of 10

years from initial exposure (4 observed vs. 3.04 expected). However, sensitivity was somewhat reduced.

Hoar et al. (1986), in a population based case-referent study found significantly high rates of non-Hodgkin's lymphoma (NHL) in farmers in Kansas who use herbicides, particularly 2,4-D and triazines.

All newly diagnosed cases of STS, Hodgkins disease (HD) and non-Hodgkins lymphoma between 1976 and 1982 among white male residents were included in the study identified from the University of Kansas Cancer data service, a population-based registry for the state of Kansas. There were 200 diagnosed with STS, 173 diagnosed with HD and a random sample of 200 out of 297 men diagnosed with NHL during the period 1979 through 1981. (The period of time for the selection of STS and HD extended from 1976 to 1982).

Three (3) white male controls (N=1005) were matched to each patient on age ($\pm$2 years) and vital status. Live controls over 65 years of age were selected from the Health Care Financing Administration file (Medicare). Live controls under age 65 were selected by telephone utilizing a two-staged random digit-dialing technique. For deceased cases the controls were selected from Kansas state mortality files with an additional match by year of death. Persons with a cause of death of STS, HD, NHL, homicide, suicide or malignancy of ill-defined site (ICD code 195) were excluded as controls.

Farm herbicide use was found to be non-significantly associated with NHL (OR = 1.6, 95% C.I. = 0.9, 2.6). The relative risk of NHL increased significantly with number of days of herbicide exposure per year and latency. Men exposed to herbicides more than 20 days per year had a sixfold increased

risk of NHL (OR = 6.0; 95% C.I. = 1.9, 19.5) relative to nonfarmers. Frequent users who mixed or applied the herbicides themselves had an OR of 8.0 (95% C.I. = 2.3, 27.9) for NHL. Dose response excesses were associated with use of phenoxyacetic acid herbicides, essentially synonymous with use of 2,4-D (OR = 2.3; 95% CI = 1.3, 4.3), since only three patients and 18 controls had used 2,4,5-T and all but two of these controls had also used 2,4-D. Use of 2,4-D only, i.e., eliminating 2,4,5-T users, was associated with an OR of 2.6 (95% CI = 1.4, 5.0). Neither STS nor HD was associated with herbicide or pesticide exposure. The authors concluded "this study confirms the reports from Sweden and several U.S. studies that NHL is associated with farm herbicide use, especially phenoxyacetic acids. It does not confirm the case-control studies or the cohort studies of pesticide manufacturers and Vietnam veterans linking herbicides to STS or HD". However, it is not contradictory to the hypothesis that 2,3,7,8-TCDD is the contaminant responsible for the development of STS, since 2,4-D does not contain 2,3,7,8-TCDD.

Few respondents could remember exposure to 2,4,5-T, which contains 2,3,7,8-TCDD. 2,4-D is not believed to contain 2,3,7,8-TCDD but does contain other polychlorinated dibenzo-p-dioxin impurities. The risk was found to increase with increasing frequency and duration of herbicide usage. Although "herbicide usage" could mean any of the herbicides identified by Hoar, she wrote that this is "essentially synonymous" with use of 2,4-D. The next most used herbicides i.e., triazines and uracils are nonsignificant when exposure to phenoxyacetic acids are controlled for in her analyses. However, this study has problems similar to the Hardell et al. (1981) study in that there is a lack of substantiation of exposure, and the information is based on questionnaire responses that are subject to some

recall bias. Moreover, there is a statistically significant risk associated with the use of other herbicides as well, i.e., triazines, amides, and trifluralin. These uncertainties, while raising concerns, do not discount the observed dose-response relationship or the observed increased incidence. A more detailed critical analysis of this study may be provided in a later version of this document.

Summary

Case reports of individuals who acutely ingested 2,4-D solutions indicate that early symptoms of exposure include gastritis, vomiting and loss of consciousness, and that muscular paralysis precedes death. Autopsies of fatal poisoning cases have shown widespread pathologic effects (e.g., congestion and hyperemia of most organs, hepatic necrosis). Reports of human poisoning from industrial or agricultural exposure to 2,4-D formulations (dermal and inhalation exposures) commonly described neurological signs and symptoms (e.g., fatigue, nausea, reflex disorders, paresthesia). Most of the clinical reports did not identify other possible chemicals to which the subjects may have been exposed, and did not indicate levels of 2,4-D exposure.

The epidemiologic studies of Hoar et al. (1986), Lynge (1985), Eriksson et al. (1981), Hardell et al. (1981), and Hardell and Sandstrom (1979) provide limited evidence of the carcinogencity of the phenoxy herbicides. The IARC (1987) has reviewed these studies and has also classified the phenoxy herbicides as having limited human evidence for carcinogenicity. The only study (Hoar et al., 1986) in which 2,4-D was specifically cited as the predominant herbicide, found a statistically significant association between exposure to 2,4-D and an elevated risk of non-Hodgkin's lymphoma.

This carefully designed and conducted study provides evidence of a dose-related excess risk of NHL with exposure to 2,4,-D. Because confidence in inferring a causal association from epidemiologic data is increased when several independent studies are concordant and with knowledge that NCI presently plans to release the results of two additional 2,4-D studies within 12 months, the CAG will withhold a weight-of-evidence judgement on the 2,4-D human data.

VII. MECHANISMS OF TOXICITY

The myotonic syndrome produced in rats by the administration of 2,4-D was studied by Ezyaguire et al. (1948). Intraperitoneal injection of 100-250 mg/kg of the 2,4-D sodium salt or intra-arterial administration of 2 mg of compound per animal produced neuromuscular effects that resembled those observed in congenital myotonia or those produced by poisoning with veratrine alkaloids. Muscles showed increased sensitivity to stimulating agents; a single spike was followed by a silent period and then a burst of repetitive firing. Increases in both twitch tension and twitch duration were noted. Constant activity of the affected muscles caused these myotonic symptoms to diminish, but following rest, the syndrome reappear.

Iyer et al. (1976) investigated the neural factors contributing to this effect in a further study of the myotonic syndrome induced by intraperitoneal injection of 2,4-D in rats (dose unspecified). These investigators found that myotonic discharges appeared within 2 hours of a single injection and disappeared after 24 hours. Nerve block or nerve section produced after the initiation of myotonia had no effect on the condition; however, denervation of the muscle before treatment with 2,4-D produced a progressive loss of its myotonic response.

Iyer et al. (1977a,b, 1981) and Ranish et al. (1977) reported in later studies that rat skeletal muscle did not become myotonic following _in vivo_ or _in vitro_ exposure to 2,4-D if the muscle was previously denervated. They concluded that 2,4-D directly affects the muscle membrane (sarcolemma) and that the resting ionic conductance of sarcolemma is influenced by the presence of neural factors. Further evidence supporting this mechanism of

2,4-D toxicity was reported by Rudel and Senges (1972), following a study of intracellular recordings of membrane potential in rat diaphragm muscle exposed to 2,4-D; the sarcolemma was altered by decreased resting membrane conductance as a result of exposure to 2,4-D. Also, in a literature summary on myotonia in mammalian skeletal muscle, Kwiecinski (1981) noted the similarity between the conditions following the direct and selective activity of compounds such as 2,4-D on the sarcolemma of rats and those resulting from hereditary myotonia in humans. In humans, hereditary myotonia is generally thought to result from a genetic change in the structure and function of the sarcolemma.

Histochemical examination of skeletal muscle from rats in which myotonia had been induced by the intraperitoneal injection of 300 mg/kg 2,4-D indicated an inhibition of phosphorylase activity (Heene, 1966a). Further experiments by Heene (1966b) demonstrated that addition of $2x10^{-4}$ to $5x10^{-4}$ M concentrations of 2,4-D to 10 μm tissue sections of skeletal muscle would also inhibit phosphorylase and transglycosidase activities.

Dux et al. (1977) reported changes in the membrane of skeletal muscles from myotonic rats induced by intraperitoneal injection of 2,4-D (50 mg/kg/day for 21 days). Using a pyroantimonate precipitation technique to localize calcium in dystrophic muscle sections, these researchers were able to show lowered calcium in muscle triads and increased calcium associated with troponin C. They suggested that this shift in muscle calcium may lead to alterations in the actinomyosin contraction system. Seiler (1978) reported ~60% <u>in vitro</u> inhibition of both sodium-potassium and magnesium stimulated ATPases in sarcolemma extracts of normal rats following the

addition of 2.5 mM concentrations of 2,4-D. Direct injection of 100-500 mg/kg 2,4-D into the pectoralis muscle has been reported to increase muscle levels of glucose-6-phosphate within 30-45 minutes, but alteration in levels of ADPases and ATPases was not found (Kuhn and Stein, 1964). They further reported an inhibition of ^{45}Ca uptake by a sarcolemma preparation in vitro following the addition of 2,4-D.

Using embryonic chick fibroblasts prepared from primary muscle cultures, Emmons et al. (1980) investigated the relationship between perturbed sterol metabolism in the sarcolemma and experimentally induced myotonia. Application of 10 μg/mℓ of 2,4-D to the fibroblast cultures resulted in decreased cholesterol biosynthesis and an accompanying accumulation of acetate derivatives in desmosterol and related sterols. The authors concluded that the results obtained in this in vitro assay are consistent with the hypothesis that experimentally induced myotonia is preceded by a prerequisite change in steroid composition of the sarcolemma.

In vitro effects of 2,4-D on lipid biosynthesis in rat liver homogenates were reported by Olson et al. (1974). The addition of 4.5 and 9.0 mM concentrations of 2,4-D to liver preparations inhibited the incorporation of ^{14}C-mevalonate into nonsaponifiable lipids and, at the same concentrations, inhibited ^{14}C-acetate incorporation into cholesterol. The authors indicated that 2,4-D may produce hypolipidemic effects in a manner similar to that of chlorophenoxyisobutyrate, a clinically used agent. Kolberg et al. (1971) noted that L cell cultures exposed to 500 mg/mℓ 2,4-D for a 24-hour period showed increased incorporation of ^{3}H-palmitate and ^{14}C-acetate into total cell lipids. The increased ^{3}H-palmitate incorp-

oration was primarily in the triglyceride fraction, suggesting that increased fatty acid uptake from the medium was produced by 2,4-D at this level.

Brody (1952) reported that 2,4-D added in vitro to rat liver mitochondria was an uncoupling agent for oxidative phosphorylation. At concentrations as low as 5×10^{-5} M, 2,4-D began to decrease the phosphate/oxygen ratio in mitochondria without significantly affecting respiration, while at 1×10^{-3} M, more than 80% inhibition of phosphorylation was observed. Effects of 2,4-D on the oxidative phosphorylation of rat liver mitochondria were also studied by Whitehouse (1964), who reported no uncoupling effects at 2,4-D levels of 1×10^{-3} M; however, at 2.5×10^{-3} M, decreases in the phosphate/oxygen ratio were demonstrated. The differences in the inhibitory levels of 2,4-D reported by these two investigators are apparently due to the nature of the rat mitochondrial preparations tested, because Brody (1952) reports an almost 2-fold higher control value for phosphate/oxygen ratio than that reported by Whitehouse (1964). Weinbach and Garbus (1965) compared the uncoupling activity of several phenols in rat liver mitochondria and showed that complete uncoupling of oxidative phosphorylation in their assay system could be produced by 2×10^{-4} M dichlorophenol; dinitrophenol was effective in producing complete uncoupling at a 15-fold lower level. The 2,4-D uncoupling effects noted are therefore occurring at relatively high in vitro levels.

Cytotoxic effects of 2,4-D on cultured cells were observed by Haag et al. (1975). Exposure of cultured chick muscle cells to 2.5 mM 2,4-D for 44 hours produced moderate cytotoxicity that increased when the concentration

was raised to 5 mM. Morphological changes in cells treated at these 2,4-D levels included partial lack of polar orientation, diminished fiber formation and an increased nuclear/cytoplasmic ratio. Murakami and Fukami (1978) noted inhibition of cell growth in a human embryonic lung cell line when 4×10^{-4} M 2,4-D was present in cultures for 48 hours. Very little of the 2,4-D present in the medium was taken up by these cells (2.6-5.0 pmol/mg cell protein). Complete growth inhibition of L cells exposed for 24 hours to 350 mg/mL of 2,4-D has been reported by Kolberg et al. (1971).

Several investigations have demonstrated effects of 2,4-D on DNA synthesis, mitosis and cell-cycle parameters when added to cultured cells. Haag et al. (1975) observed that the S phase of the cell cycle was prolonged in cultured chicken muscle cells exposed to 2.5×10^{-3} M 2,4-D for 44 hours. Bongso and Basrur (1973) found that embryonic bovine kidney cells treated with 10 ppm of 2,4-D for 24 hours showed an elevated mitotic index caused by an increase in the number of prophase cells. Treated cells at 48 hours had increases in nucleolar size, nuclear lobulation, polyploid mitotic figures and multipolar spindles. The authors suggest that these changes may be produced by interaction of 2,4-D with mitotic spindle proteins. Increased mitotic activity has also been reported by Weiss and Beckert (1975) in monkey kidney cells and Girardi heart cells treated with 10 or 50 ppm of 2,4-D for up to 72 hours. Seiler (1979) found that oral administration of 2,4-D to mice can inhibit testicular DNA synthesis. One hour following intraperitoneal injection of ^{14}C-thymidine, mice were administered 200 mg/kg 2,4-D orally; 30 minutes later they were sacrificed and testicular DNA was extracted. Treated mice showed a 29% decrease in the incorporation of labeled thymidine into DNA. Inhibition of DNA synthesis *in vitro*, as

measured by the incorporation of ^{3}H-labeled deoxyhucleoside triphosphates into DNA by DNA polymerase, has been reported by Schwimmer (1968) when 1.5×10^{-4} M 2,4-D was added to the incubation mixture.

Enzyme inhibition by 2,4-D has also been reported in several other studies. Wedding and Black (1963) showed that porcine heart malic dehydrogenase, lactic dehydrogenase (rabbit muscle) and alcohol dehydrogenase (yeast) were all inhibited by 2,4-D at levels of $\sim 10^{-3}$ M. Inhibition was competitive relative to the pyridine nucleotide cofactors; the authors suggest that other pyridine nucleotide-requiring enzymes may be inhibited by 2,4-D. Increased activities of several placental enzymes have been observed in guinea pigs following maternal administration of 2,4-D (Humiczewska and Stanosz, 1971). Subcutaneous injection of 30 mg/kg of 2,4-D for 6 days/week throughout gestation increased succinate dehydrogenase, alkaline phosphatase and acid phosphatase activities as determined by histochemical methods.

Summary

Observations that rat skeletal muscle did not become myotonic following *in vivo* or *in vitro* exposure to 2,4-D if the muscle was previously denervated (Iyer et al., 1976, 1977a,b, 1981; Ranish et al., 1977) and intracellular recordings of membrane potential in rat muscle exposed to 2,4-D (Rudel and Senges, 1972) indicate that 2,4-D directly affects the sarcolemma. Changes in sarcolemma calcium (Dux et al., 1977; Kuhn and Stein, 1964), steroid (Emmons et al., 1980), and inhibition of muscle phosphorylase and transglycosidase activities (Heene, 1966a,b) were also observed in *in vitro* and *in vivo* experiments.

Addition of 2,4-D to rat liver preparations inhibited lipid biosynthesis (Kolberg et al., 1971; Olson et al., 1974) and oxidative phosphorylation (Brody, 1952; Whitehouse, 1964). Cytotoxicity (Kolberg et al., 1971; Haag et al., 1975; Murakami and Fukami, 1978), increased mitotic activity (Bongso and Basrur, 1973; Haag et al., 1975; Weiss and Beckert, 1975), and inhibition of DNA synthesis (Schwimmer, 1968; Seiler, 1979) and nucleotide-requiring enzymes (Wedding and Black, 1963) have also been observed in mammalian cells that were exposed to 2,4-D *in vitro* and *in vivo*.

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Introduction

The quantification of toxicological effects of a chemical consists of separate assessments of noncarcinogenic and carcinogenic health effects. Chemicals that do not produce carcinogenic effects are believed to have a threshold dose below which no adverse, noncarcinogenic health effects occur, while carcinogens are assumed to act without a threshold.

In the quantification of noncarcinogenic effects, a Reference Dose (RfD), [formerly termed the Acceptable Daily Intake (ADI)] is calculated. The RfD is an estimate (with uncertainty spanning perhaps an order magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious health effects during a lifetime. The RfD is derived from a no-observed-adverse-effect level (NOAEL), or lowest-observed-adverse-effect level (LOAEL), identified from a subchronic or chronic study, and divided by an uncertainty factor(s) times a modifying factor. The RfD is calculated as follows:

$$\text{RfD} = \frac{\text{(NOAEL or LOAEL)}}{\text{[Uncertainty Factor(s) x Modifying Factor]}} = ____ \text{ mg/kg bw/day}$$

Selection of the uncertainty factor to be employed in the calculation of the RfD is based upon professional judgment, while considering the entire data base of toxicological effects for the chemical. In order to ensure that uncertainty factors are selected and applied in a consistent manner,

the U.S. EPA (1986) employs a modification to the guidelines proposed by the National Academy of Sciences (NAS, 1977, 1980) as follows:

Standard Uncertainty Factors (UFs)

- Use a 10-fold factor when extrapolating from valid experimental results from studies using prolonged exposure to average healthy humans. This factor is intended to account for the variation in sensitivity among the members of the human population. [10H]

- Use an additional 10-fold factor when extrapolating from valid results of long-term studies on experimental animals when results of studies of human exposure are not available or are inadequate. This factor is intended to account for the uncertainty in extrapolating animal data to the case of humans. [10A]

- Use an additional 10-fold factor when extrapolating from less than chronic results on experimental animals when there is no useful long-term human data. This factor is intended to account for the uncertainty in extrapolating from less than chronic NOAELs to chronic NOAELs. [10S]

- Use an additional 10-fold factor when deriving an RfD from a LOAEL instead of a NOAEL. This factor is intended to account for the uncertainty in extrapolating from LOAELs to NOAELs. [10L]

Modifying Factor (MF)

- Use professional judgment to determine another uncertainty factor (MF) that is greater than zero and less than or equal to 10. The magnitude of the MF depends upon the professional assessment of scientific uncertainties of the study and data base not explicitly treated above, e.g., the completeness of the overall data base and the number of species tested. The default value for the MF is 1.

The uncertainty factor used for a specific risk assessment is based principally upon scientific judgment rather than scientific fact and accounts for possible intra- and interspecies differences. Additional considerations not incorporated in the NAS/ODW guidelines for selection of an uncertainty factor include the use of a less than lifetime study for deriving an RfD, the significance of the adverse health effects and the counterbalancing of beneficial effects.

From the RfD, a Drinking Water Equivalent Level (DWEL) can be calculated. The DWEL represents a medium specific (i.e., drinking water) lifetime exposure at which adverse, noncarcinogenic health effects are not anticipated to occur. The DWEL assumes 100% exposure from drinking water. The DWEL provides the noncarcinogenic health effects basis for establishing a drinking water standard. For ingestion data, the DWEL is derived as follows:

$$\text{DWEL} = \frac{\text{(RfD) x (Body weight in kg)}}{\text{Drinking Water Volume in } \ell\text{/day}} = ____ \text{ mg/}\ell$$

where:

Body weight = assumed to be 70 kg for an adult
Drinking water volume = assumed to be 2 ℓ/day for an adult

In addition to the RfD and the DWEL, Health Advisories (HAs) for exposures of shorter duration (1-day, 10-day and longer-term) are determined. The HA values are used as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur. The HAs are calculated using an equation similar to the RfD and DWEL; however, the NOAELs or LOAELs are identified from acute or subchronic studies. The HAs are derived as follows:

$$\text{HA} = \frac{\text{(NOAEL or LOAEL) x (bw)}}{\text{(UF) x (___ } \ell\text{/day)}} = ____ \text{ mg/}\ell$$

Using the above equation, the following drinking water HAs are developed for noncarcinogenic effects:

1. 1-day HA for a 10 kg child ingesting 1 ℓ water per day.
2. 10-day HA for a 10 kg child ingesting 1 ℓ water per day.
3. Longer-term HA for a 10 kg child ingesting 1 ℓ water per day.
4. Longer-term HA for a 70 kg adult ingesting 2 ℓ water per day.

The 1-day HA calculated for a 10 kg child assumes a single acute exposure to the chemical and is generally derived from a study of <7 days duration. The 10-day HA assumes a limited exposure period of 1-2 weeks and is generally derived from a study of <30 days duration. The longer-term HA is derived for both the 10 kg child and a 70 kg adult and assumes an exposure period of ~7 years (or 10% of an individual's lifetime). The longer-term HA is generally derived from a study of subchronic duration (exposure for 10% of animal's lifetime).

The U.S. EPA categorizes the carcinogenic potential of a chemical, based on the overall weight-of-evidence, according to the following scheme:

> Group A: Human Carcinogen. Sufficient evidence exists from epidemiology studies to support a causal association between exposure to the chemical and human cancer.
>
> Group B: Probable Human Carcinogen. Sufficient evidence of carcinogenicity in animals with limited (Group B1) or inadequate (Group B2) evidence in humans.
>
> Group C: Possible Human Carcinogen. Limited evidence of carcinogenicity in animals in the absence of human data.
>
> Group D: Not Classified as to Human Carcinogenicity. Inadequate human and animal evidence of carcinogenicity or for which no data are available.
>
> Group E: Evidence of Noncarcinogenicity for Humans. No evidence of carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.

If toxicological evidence leads to the classification of the contaminant as a known, probable or possible human carcinogen, mathematical models are used to calculate the estimated excess cancer risk associated with the ingestion of the contaminant in drinking water. The data used in these

estimates usually come from lifetime exposure studies using animals. In order to predict the risk for humans from animal data, animal doses must be converted to equivalent human doses. This conversion includes correction for noncontinuous exposure, less than lifetime studies and for differences in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average adult human body weight is 70 kg and that the average water consumption of an adult human is 2 ℓ of water per day.

For contaminants with a carcinogenic potential, chemical levels are correlated with a carcinogenic risk estimate by employing a cancer potency (unit risk) value together with the assumption for lifetime exposure from ingestion of water. The cancer unit risk is usually derived from a linearized multistage model with a 95% upper confidence limit providing a low dose estimate; that is, the true risk to humans, while not identifiable, is not likely to exceed the upper limit estimate and, in fact, may be lower. Excess cancer risk estimates may also be calculated using other models such as the one-hit, Weibull, logit and probit. There is little basis in the current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than any other. Because each model is based upon differing assumptions, the estimates derived for each model can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of cancer risk rate levels has an inherent uncertainty that is due to the systematic and random errors in scientific measurement. In most cases, only studies using experimental animals have been performed. Thus, there is

uncertainty when the data are extrapolated to humans. When developing cancer risk rate levels, several other areas of uncertainty exist, such as the incomplete knowledge concerning the health effects of contaminants in drinking water, the impact of the experimental animal's age, sex and species, the nature of the target organ system(s) examined and the actual rate of exposure of the internal targets in experimental animals or humans. Dose-response data usually are available only for high levels of exposure and not for the lower levels of exposure closer to where a standard may be set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

Noncarcinogenic Effects

The different forms of 2,4-D (acids, salts, esters) have been discussed together in this document. Sufficient toxicokinetic data are not available to determine whether the esters should be considered separately from the acids and salts. There are no data to indicate how rapidly the esters of 2,4-D are hydrolyzed by mammals; however, at physiological pH, 2,4-D exists in the ionized form, which does not readily pass through biological membranes, as compared with the esters that would (Zetterberg, 1977). In humans, the rate of plasma uptake of orally administered 2,4-D, the degree of conjugation of the compound and the rate of elimination may vary considerably between individuals (Sauerhoff et al., 1977; Kohli et al., 1974); further characterization of this interindividual variation in the human population is needed.

The LD_{50} range of 2,4-D is generally between 300 and 1000 mg/kg; there does not appear to be significant differences in toxicity between the free acid and the various salt and ester derivatives. Hill and Carlisle (1947) determined oral LD_{50}s of 666, 375, 800 and 1000 for 2,4-D sodium salt in rats, mice, rabbits and guinea pigs, respectively; the maximum doses in these species not causing death were 333, 125, 200 and 333 mg/kg, respectively. Individual monkeys that were fed single doses of ~286 or 428 mg/kg of 2,4-D sodium salt or 286 mg/kg of 2,4-D ammonium salt regurgitated a large portion of the material, precluding determinations of lethal doses (Hill and Carlisle, 1947). Symptoms other than nausea were not described in these monkeys. Approximately 214 mg/kg of 2,4-D sodium salt was fed to another monkey without development of vomiting or "serious illness" (Hill and Carlisle, 1947). Comparison of the species sensitivity to 2,4-D indicates that dogs may show greater sensitivity to this compound (Rowe and Hymas, 1954). The higher toxicity observed in dogs may reflect an inability of kidney processes in this species to effectively clear phenoxyacetic acids (Seiler, 1978).

Drill and Hiratzka (1953) described myotonia with pathologic changes of GI mucosa irritation, moderate hepatic necrosis and mild renal tubular degeneration in dogs that were lethally poisoned by acute oral administration of 2,4-D at doses of 100-400 mg/kg.

Bucher (1946) found that myotonia persisted for 8-24 hours in strain A mice that were injected intraperitoneally with sublethal doses (100-200 mg/kg of 2,4-D). No significant differences were found in the effects produced when 2,4-D was administered subcutaneously, intraperitoneally or intravenously.

In a summary report, Rowe and Hymas (1954) described an experiment where doses of 0, 30, 100 or 300 mg/kg/day 2,4-D to groups of 5 or 6 female rats (strain not specified) by intubation 5 times/week for 4 weeks were utilized. The 2,4-D was administered in olive oil that was emulsified in 5-20% aqueous gum arabic, and the controls were vehicle treated. Rats that received 30 mg/kg/day or less reportedly showed no adverse treatment-related clinical or pathological effects, but treatment with 100 mg/kg/day elicited GI irritation, depressed growth rate and slight cloudy swelling of the liver. Rats that received 100 mg/kg/day 2,4-D succumbed rapidly (not elaborated) and died; severe GI irritation was reportedly the principal adverse effect observed.

In addition, groups of five young adult female rats (strain not specified) were maintained on diets that contained 0, 100, 300 or 1000 ppm 2,4-D in the diet for 113 days (Rowe and Hymas, 1954). If it is assumed that young rats consume 10% of their weight in food per day, the corresponding daily doses are 0, 10, 30 and 50 mg/kg/day. Rats that were exposed at the 1000 ppm level experienced excessive mortality (not quantified), depressed growth rate, excessive mortality and slight cloudy swelling of the liver. These effects were not observed at the two lowest doses. Groups of five rats that were given diets that contained higher concentrations of 2,4-D (3000 or 5000 ppm) were sacrificed after 12 days because they were not eating and were rapidly losing weight; examinations revealed increased liver and kidney weights and slight but unspecified pathologic changes.

Chang et al. (1974) reported that dietary administration of 2,4-D to rats at levels of 2000 ppm in the diet for 4-7 (~200 mg/kg/day) weeks

produced a slight increase in liver glycogen content, a slight decrease in liver RNA content and slight decreases in absolute and relative liver weights, but no overt signs of toxicity.

Administration of 0, 200 or 400 ppm dietary 2,4-D (~0, 10 or 20 mg/kg/day, respectively) to groups of seven rats for 1 month did not adversely affect food intake or rate of growth, or elicit characteristic signs of intoxication (skeletal muscular signs or paralysis) (Hill and Carlisle, 1947). Dietary administration of 2,4-D at a level of 100 ppm for 21 days and subsequently 1000 ppm for 10 days (average total dose ~39.0 mg/kg/day) was similarly non-toxic for rats. Groups of six guinea pigs that were given 10 daily doses of 50 or 100 mg 2,4-D in 12 days (~88 or 177 mg/kg/day) by intubation also did not develop characteristic evidence of intoxication.

Drill and Hiratzka (1953) administered 2,4-D orally in capsules to groups of 2-4 dogs at doses of 0, 2, 5, 10 or 20 mg/kg/day, 5 days/week, for 13 weeks. When adjusted for a 7-day week, the respective daily doses are 0, 1.4, 3.6, 7.1 and 14.3 mg/kg/day. Toxic effects were only observed at the high dose. Treatment at 20 mg/kg/day produced death in 3 or 4 dogs between days 18 and 49, and symptoms in the moribund animals included hind leg stiffness, ataxia, weakness, gum bleeding and difficulty in chewing and swallowing. A terminal decrease in the percentage of blood lymphocytes was noted in the 3 dogs that died, but significant effects on the hemoglobin, red cell count or total white cell count were not observed. The dog that survived 2,4-D treatment at the high dose, as well as the dogs exposed to the lower levels of 2,4-D, showed no significant hematologic, gross or histopathologic effects.

Effects of subcutaneously injected 2,4-D (sodium salt) on the thyroid gland of treated rats have been reported (Florsheim and Velcoff, 1962; Florsheim et al., 1963). These investigators showed that, following seven daily injections of 2,4-D at a level of 100 mg/kg, thyroid weight was decreased. Administration of 2,4-D at 80 mg/kg over this period increased radioactive iodine uptake by the thyroid, lowered the binding of radiolabeled thyroxine by serum proteins, and increased the amount of radiolabeled compound in the liver of treated rats.

Toxic effects of 2,4-D on the nervous system of rats administered lethal doses of the compound intraperitoneally have been described by Desi et al. (1962). Animals injected daily with 200 mg/kg of 2,4-D (form not specified) died within 6 days. Progressively decreased conditioned reflex responses were observed over this period, as well as the appearance of large slow waves in the EEG. Histological examination indicated that demyelinization was present in the dorsal portion of the spinal tract. Within 10-15 minutes following a single intraperitoneal injection of the compound, EEG changes were observed (decreased cerebral and reticular desynchronization); recovery was seen in ~1 hour. The authors postulate that the neurological effects produced by 2,4-D in this study are due initially to action of the compound on the reticular formation, followed by later effects on cerebral tissue. Histological examination, however, failed to show any morphological changes in the cortex or subcortical regions of treated animals. The demyelinization observed in the spinal cord may be responsible for the hind limb paralysis noted by other investigators after poisoning of animals with 2,4-D.

Hansen et al. (1971) conducted 2-year feeding studies with technical grade (96.7% pure) 2,4-D in Osborne-Mendel rats. In the rat study, 25 animals of each sex were exposed to 0, 5, 25, 125, 625 or 1250 ppm 2,4-D in the diet (~0, 0.25, 1.25, 6.25, 31.25 or 62.5 mg/kg/day) from 3 weeks of age. At the conclusion of treatment, all rats were autopsied, but comprehensive histopathologic examinations were performed only on 6 rats/sex from the high-dose and control groups; the liver, kidneys, spleen ovaries or testes and other tissues that contained gross lesions were histologically examined in the remaining rats in the high exposure and control groups and in the rats at the other dose levels. Significant differences in survival, mean bw and organ/bw ratios (liver, kidney, heart, spleen or testes) were not found between any of the treated groups and the control group during the 2-year treatment or at the end of the study. Significant treatment-related pathologic effects were not observed. The incidence of tumors did not differ significantly between the groups. Several hematologic indices (hemoglobin, hematocrit, total white cell count) were similar in the treated and control groups, but it was noted that the red blood cell count of the treated rats (1250, 625 and 5 ppm groups) showed a "tendency" toward macrocytosis, "very slight to slight" polychromasis, and "slight to moderate" hypochromasia. The tendency toward macrocytosis was reportedly not present and the other red cell abnormalities were of a "minor degree" in the control rats. The toxicological significance of these vaguely reported effects is unclear.

In a two-generation reproduction study with rats that is also discussed in Other Reproductive Effects in Chapter V (Bjorklund and Erne, 1966), administration of 1000 ppm 2,4-D in the drinking water (~50-100 mg/kg/day)

of rats (5/group) during pregnancy and for a further 10 months had no significant effects on the maternal animals (not specified) or offspring (clinical signs or malformations). Similar exposure of 22 weaned offspring (10 males, 12 females) for up to 2 years was, with the exception of reduced food and water intake and consequent growth retardation, temporary diarrhea and poor general condition, also nontoxic as judged by normal clinical chemistry indices, hematocrit, hemoglobin, plasma GOT, plasma elimination rate of 2,4-D (3 hours), relative organ weights (heart, spleen, liver, kidneys, lungs, testes, ovaries), or gross or microscopic pathology. Other reproduction studies that are detailed in Teratogenicity and Other Reproductive Effects in Chapter V reported that dietary exposure to 1500 ppm (~75 mg/kg bw) 2,4-D for 2 years (Hansen et al., 1971) and dietary exposure to 1000 ppm (~100 mg/kg) for 3 months (Gaines and Kimbrough, 1970) prior to mating and during pregnancy and lactation caused an increase in preweanling mortality.

Hansen et al. (1971) also fed 6- to 8-month-old beagle dogs (3 of each sex/group) 0, 10, 50, 100 or 500 ppm technical grade 2,4-D in the diet (~0, 0.29, 1.45, 2.9 or 14.5 mg/kg/day) for 2 years. Treatment-related effects were not indicated based on observations of mortality as well as gross and microscopic tissue examinations in any of the treated groups or control group.

Quantification of Noncarcinogenic Effects

Derivation of 1-Day HA. Clinical reports have described cases of human ingestion of 2,4-D and its derivatives (see Acute Effects in Chapter VI), but there is only one report of nonfatal poisoning in which quantitative exposure data were provided. Berwick (1970) described a farmer who

swallowed a mouthful of weed killer (49% Eptam, 35.5% 2,4-D isooctyl ester, 0.5% epichlorohydrin and 5% emulsifiers) and exhibited characteristic symptoms of 2,4-D exposure (e.g., acute gastritis, vomiting, skeletal muscle damage) that subsided within ~2 weeks. There was no evidence of cholinesterase inhibition, further indicating that the toxicological effects were not induced by the Eptam. If it is conservatively assumed that the volume of a mouthful of liquid is 25 mℓ and that the density of 2,4-D isooctyl ester is similar to that of 2,4-D n-butyl ester (1.2 g/mℓ), the quantity of isooctyl ester ingested can be estimated to be ~11 g (25 mℓ x 0.355 x 1.2 g/mℓ); the equivalent quantity of 2,4-D acid would be ~6.7 g (~96.7 mg/kg, assuming a body weight of 70 kg). Although factors such as the crude quantitation of the quantity ingested and the unknown pharmacokinetic properties of 2,4-D isooctyl ester could preclude the identification of a human single-dose nonlethal level from this study, a more serious problem is a lack of corroborating data. In other case reports, deaths were described in a male agricultural student who ingested at least 6 g of a commercial herbicide preparation of (50% w/w) 2,4-D dimethylamine salt (≥2.5 g 2,4-D acid equivalent) (Nielson et al., 1965) and in a 46-year-old man who died within 14 hours of swallowing at least 13.5 g of an uncharacterized 2,4-D solution (Herbich and Machata, 1963). It is apparent from examination of these data that the exposures in the above reports are too poorly characterized to be used to identify an unequivocal nonlethal dose that could be used to derive a 1-day HA; the estimated nonlethal adverse effect level in the Berwick (1970) report (~6.7 g) appears to be bracketed by the apparent lethal doses of Nielson et al. (1965) (≥2.5 g) and Herbich and Machata (1963) (≥13.5 g).

Most of the information on the effects of single oral exposures to 2,4-D and derivatives in laboratory animals is related to lethality (see Table VI-1). Hill and Carlisle (1947), however, reported the results of toxicological studies in which both lethal doses and tolerated doses (the largest dose that caused no deaths) for 2,4-D sodium salt were determined for four species of rodents. The lethal and tolerated oral doses for 2,4-D sodium salt in rats, mice, guinea pigs and rabbits were 666 and 333 mg/kg bw, 375 and 125 mg/kg bw, 1000 and 333 mg/kg bw, and 800 and 200 mg/kg bw, respectively. These data indicate that mice are the most sensitive species, but it must be noted that a tolerated dose, as defined in this study, does not imply a NOAEL. Although the tolerated doses caused no deaths, effects other than survival were not mentioned; symptoms and pathological changes were only specifically described in the animals that died (i.e., the lethal dose groups). Since Hill and Carlisle (1947) noted that small ranges of doses were tested (i.e., groups of 10 mice were administered 125, 250, 375 and 500 mg/kg bw of 2,4-D sodium salt), it appears probable that some of the characteristic signs or symptoms of intoxication described at the lethal doses (e.g., muscular effects and possible histological damage) would also have been evident in those animals given tolerated doses. A 1-day HA can be calculated from the tolerated single dose for mice (125 mg 2,4-D sodium salt/kg bw, equivalent to about 114 mg 2,4-D/kg bw) using an uncertainty factor (UF) of 1000. This factor, as per previous guidelines (U.S. EPA, 1980), represents 10-fold for both intra- and interspecies variability to the toxicity of a chemical when specific data are lacking and an additional 10-fold because the tolerated single dose is assumed to have caused unreported adverse effects and, therefore, is considered a LOAEL rather than a NOAEL.

Thus, for a child:

$$\text{1-day HA (child)} = \frac{(114\ \text{mg/kg bw/day} \times 10\ \text{kg bw}) \div (1000 \times 1\ \ell\text{/day})}{\sim 1.1\ \text{mg}/\ell}$$

This HA is equivalent to 1.1 mg/day or 0.1 mg/kg bw/day.

A 1-day HA can alternatively be derived from other data of Hill and Carlisle (1947). In this experiment, groups of six guinea pigs that were administered 10 doses of 50 or 100 mg/day 2,4-D sodium salt by gavage in 12 days did not develop characteristic evidence of intoxication (i.e., muscular signs) or mortality. If it is assumed that the guinea pigs weighed 0.3 kg (the reported approximate weight in the single dose studies), the lowest reported no effect dose of 50 mg/day corresponds to a daily dose of about 139 mg/kg bw/day (50 mg/day ÷ 0.3 kg bw x 10/12); the equivalent dose of 2,4-D acid is about 126 mg/kg bw/day. Although symptoms or signs of intoxication were not specifically associated with this exposure, these criteria of toxicity are still too insensitive to justify using 126 mg/kg bw/day as an animal NOAEL with an uncertainty factor of 100. If 126 mg/kg bw/day is regarded as a LOAEL (reasoning similar to representing the single tolerated doses as LOAELs) and an uncertainty factor of 1000 is used, the 1-day HA value for a child is approximately the same as the 1-day HA derived from the single tolerated dose for mice:

$$\text{1-day HA (child)} = \frac{(126\ \text{mg/kg bw/day} \times 10\ \text{kg bw}) \div (1000 \times 1\ \ell\text{/day})}{\sim 1.3\ \text{mg}/\ell}$$

This HA is equivalent to 1.3 mg/day or 0.13 mg/kg bw/day.

Either one of the above cited experiments can be used to estimate the 1-day HA. They are both of equal value and the calculated concentrations are essentially the same.

Derivation of 10-Day HA. Subchronic or shorter duration studies may be used to calculate a 10-day health advisory. The Health Effects Branch of the Office of Drinking Water has assessed the available data with the objective of estimating a 10-day health advisory and discovered several deficiencies. The National Academy of Sciences (NAS, 1977) also concluded, "There are substantial disagreements in the results of subchronic and chronic toxicity studies with 2,4-D, perhaps reflecting the use of different formulations or preparations". This section provides critical evaluation of data and attempts to generate a 10-day health advisory.

Limited human information is available that provides quantitative short-term exposure data. Kephart (1945) moderated a discussion in which an individual reported that he had taken (presumably orally) 500 mg of 2,4-D/day for 21 days with no demonstrable ill-effects. Additional information was not available, but this exposure corresponds to a daily dose of ~7 mg/kg bw if it is assumed that the person weighed 70 kg. Seabury (1963) reported a case in which a patient was administered 18 intravenous doses of 2,4-D (with indole butyric acid and naphthalene acetic acid) over a 33-day period for the treatment of coccidiodomycosis. Infusion of a total of 10.7 g did not produce observed side effects (the dosage was 800 mg/day for doses 9 through 17, and the 18th dose was increased to 2000 mg). A final 19th dose of 3.6 g that was infused over 2 hours (~67 mg/kg) elicited fibrillary muscle twitching and general hyporeflexia that completely subsided within 48 hours. Although these reports may provide a crude indication of a human tolerated dose, numerous factors preclude their use in deriving a 10-day HA [e.g., anecdotal nature of the inadequately reported Kephart (1945) data, the inappropriate route of administration in the Seabury (1963) study, the lack of sensitive indicators of toxicity].

Rowe and Hymas (1954) administered 2,4-D (purity unspecified in olive oil/gum arabic vehicle) by gavage to groups of 5 or 6 young adult female rats at doses of 0, 3, 30, 100 or 300 mg/kg bw for 5 days/week for 4 weeks (0, 2.14, 21.4, 71.4 and 214 mg/kg bw/day, respectively). Adverse effects as judged by gross appearance and behavior, growth, hematological values (not elaborated), blood urea-nitrogen concentrations, organ weights, gross and histopathological examinations (tissues not reported) and mortality were not observed at doses of 2.14 or 21.4 mg/kg bw/day. Gastrointestinal irritation, slight cloudy swelling of the liver and depressed growth rate were apparent at 71.4 mg/kg bw/day, and rats that were administered 214 mg/kg bw/day 2,4-D died; the time to death was not reported, but severe GI irritation was the principal effect observed (other pathological effects were not discussed). In another study of longer duration, the same investigators (Rowe and Hymas, 1954) administered 0, 100, 300 or 1000 ppm 2,4-D in the diet to groups of five young female rats for 114 days. If it is assumed that young rats consume 10% of their body weight in food per day, the corresponding daily doses would be 0, 10, 30 and 100 mg/kg bw/day. No effects (same indices as in the 4-week gavage study) were found at 10 or 30 mg/kg bw/day, but 100 mg/kg bw/day produced "excessive mortality" with depressed growth rate, slightly increased liver weights and slight cloudy swelling of the liver. Rats exposed to higher levels of 2,4-D in the diet (3000 and 5000 ppm) were not evaluated because they refused food and consequently lost weight and the experiment was terminated. Both of the above Dow Chemical Company studies used small groups of animals and were not reported in detail, but multiple dose levels were tested and a number of toxicity indices were evaluated.

In another briefly reported dietary study with rats (Hill and Carlisle, 1947), adverse effects as judged by signs of intoxication, decreased food consumption, growth impairment or mortality were not observed in groups of seven rats that were exposed to purified commercial 2,4-D at daily doses as high as ~40 mg/kg bw/day (200 or 400 ppm in the diet for 31 days, 100 ppm in the diet for 21 days and 1000 ppm in the diet for the subsequent 10 days). Although this study did not examine sensitive toxicity indices (e.g., clinical chemistry or hematology indices, histopathology), the reported no effect level of ~40 mg/kg bw/day is consistent with that reported by Rowe and Hymas (1954) after 4 weeks of gavage exposure (21.4 mg/kg bw/day) or 16 weeks of dietary exposure (30 mg/kg bw/day). Chang et al. (1974) found in a single dose study with an unspecified number of rats (~8) that dietary exposure to 2000 ppm analytical grade 2,4-D (~200 mg/kg bw/day) for 4-7 weeks produced mild liver effects (slight increase in glycogen, slight decrease in RNA, slight decrease in absolute and relative weights) but no effect on food consumption or overt signs of toxicity. The results of this study are somewhat supportive of the 71.4 mg/kg bw/day LOAEL in the Rowe and Hymas (1954) 4-week gavage study (cloudy swelling in liver, GI irritation, depressed growth) but are not consistent with the Rowe and Hymas (1954) 16-week diet study that found excessive mortality at 100 mg/kg bw/day and food refusal at higher levels.

In another short-term oral study with a limited number of animals (Drill and Hiratzka, 1953), dogs were given commercial grade 2,4-D in capsules at doses of 0 (2 females), 2 (1 male, 1 female), 5 (1 male, 1 female), 10 (3 males) or 20 mg/kg bw (3 males, 1 female) 5 days/week for 13 weeks (0, 1.4, 3.6, 7.1 or 14.3 mg/kg bw/day, respectively). The dogs survived exposure to

≤7.1 mg/kg bw/day without symptoms or changes in body weight, organ weights, hemoglobin content, blood count, or gross or microscopic tissue structure, but 3 of the 4 dogs that received 14.3 mg/kg/day died with neuromuscular symptoms and terminal lymphocytosis (but no significant pathological lesions). The FEL in this study (14.3 mg/kg bw/day) is therefore lower than the highest NOAELs reported in the short-term rat studies (Rowe and Hymas, 1954; Hill and Carlisle, 1947). Although corroborating short-term exposure data in dogs are not available, both acute oral lethal (Drill and Hiratzka, 1953) and longer-term oral (Hansen et al., 1971) studies also indicate that dogs are more sensitive than rats; however, 14.5 mg/kg bw/day was reported by Hansen et al. (1971) to be a 2-year oral NOAEL for dogs (see Assessment of Chronic Oral Data and Derivation of a Lifetime Adjusted Acceptable Daily Intake in this chapter).

Teratogenicity testing with rats, mice and hamsters has shown that oral administration of 2,4-D during gestation may produce fetotoxic and developmental effects at daily doses that are in the range of the rat and dog subchronic NOAELs. Khera and McKinley (1972) found increased fetal mortality and an increased incidence of skeletal malformations in rats following oral administration of 2,4-D and 2,4-D esters and salts at 100 mg/kg bw/day (or higher levels) on days 6 through 15 of gestation. Fetal mortality was not elevated at lower dosages but the incidence of skeletal malformations was slightly elevated by 2,4-D at 25 or 50 mg/kg bw/day. This increase was significant ($p<0.05$) at the 25 but not at the 50 mg/kg/day level. Schwetz et al. (1971) reported similar types of effects in rats after administration of 2,4-D or its PGBE or isooctyl ester at 75 or 87.5 mg 2,4-D/kg on days 6 through 15 of gestation. Lower doses of 12.5 or 25 mg/kg on days 6 through

15 of gestation produced statistically significant increases in the incidences of some developmental effects (e.g., delayed ossification, missing sternebrae, and subcutaneous edema), although the incidences of these effects among different control groups were variable. For 2,4-D specifically, a significant increase in the incidence of delayed ossification of skull bones was reported at doses of 12.5, 50, 75 and 87.5 mg/kg bw/day but not at 25 mg/kg bw/day. The author reported that the incidence of this response at 12.5 mg/kg bw/day was lower than the spontaneous incidence in the second control group of this study. Furthermore, at these levels of treatment, generalized fetotoxic effects were not seen. Unger et al. (1981), in a similar study with rats, detected slight fetotoxicity at 87.5 mg 2,4-D/kg, administered as the PGBE or isooctyl ester, but no effects were detected at lower doses (<25 mg/kg). Courtney (1977) observed an increased incidence of cleft palate formation and increased fetotoxicity in CD-1 mice after oral administration of 221 mg/kg 2,4-D or equimolar levels of the PGBE or n-butyl esters on days 12 through 15 of gestation. The most toxic 2,4-D ester in this assay, PGBE ester, produced cleft palates and fetotoxic effects at a dose equivalent to 124 mg 2,4-D/kg/day, while this same lower level of the isopropyl or isooctyl esters produced fetotoxic effects but no increase in cleft palates. Thus, at 2,4-D levels that are in the approximate range of half the LD_{50} value for mice, some incidences of cleft palates have been observed. Collins and Williams (1971) were unable to show teratogenic effects in hamsters following oral administration of commercial 2,4-D preparations on days 6 through 10 of gestation at levels up to 100 mg/kg; fetotoxic effects were observed at 40, 60 and 100 mg/kg/day, but not at 20 mg/kg/day.

These teratogenicity tests for 2,4-D and its esters indicate that oral doses (expressed as 2,4-D) of 40, 60 or 100 mg/kg bw/day in hamsters on days 6 through 10 of gestation (Collins and Williams, 1971), of 75-125.5 mg/kg bw/day in rats on days 6 through 15 of gestation (Schwetz et al., 1971; Unger et al., 1981; Khera and McKinley, 1972) and of 124 mg/kg bw/day in mice on days 7 through 15 of gestation (Courtney, 1977) produced fetotoxic effects or malformations. The threshold for adverse effects on the fetus is not clearly defined: sporadic evidence of mild fetotoxicity was reported in rats at doses as low as 12.5 and 25 mg 2,4-D/kg bw/day (Schwetz et al., 1971; Khera and McKinley, 1972) for both 2,4-D and 2,4-D esters, but these effects were also seen in controls. Furthermore, generalized fetotoxic effects were not seen at these levels of treatment.

Because these teratogenicity studies have shown evidence of adverse fetal effects at daily doses that are higher than the subchronic NOAELs, one of these latter NOAELs would be the most appropriate basis for derivation of a 10-day HA. The NOAEL chosen here is 30 mg/kg bw/day (Rowe and Hymas, 1954). This NOAEL is the highest available based on several toxicity end-points including histopathological analysis. The lower FEL of 14.3 mg/kg bw/day in a limited number of dogs (Drill and Hiratzka, 1953) is not considered relevant to this analysis, because it is contradicted by a 2-year feeding study with a large number of dogs (Hansen et al., 1971).

Using the same assumptions as in the 1-day HA calculation, a 100-fold uncertainty factor for an animal NOAEL, and an additional 10-fold safety factor for deficiencies in the chosen study, a 10-day HA is derived for a child as follows:

$$\text{10-day HA (child)} = \frac{(30\ \text{mg/kg bw/day} \times 10\ \text{kg bw})}{(100 \times 10 \times 1\ \ell\text{/day})} \sim 0.30\ \text{mg}/\ell$$

This HA is equivalent to 0.30 mg/day or 0.030 mg/kg bw/day.

Derivation of Longer-term HA. A longer-term HA has not been calculated because of the lack of appropriate data.

Assessment of Lifetime Exposure and Derivation of a DWEL. Lifetime DWELs are normally derived from 2-year feeding studies in animals. The animal species that is most sensitive to the toxic effects or the species that metabolizes the compound in a manner similar to that in man is selected for estimating DWELs for humans. In these studies, a no adverse health effects level is identified. This level is divided by an uncertainty factor which may vary from 10-1000 based on the overall scientific judgment to determine an DWEL.

In 1976, the U.S. EPA, Office of Drinking Water, established an interim primary drinking water standard of 0.1 mg 2,4-D/ℓ. This was developed from an article -- Summaries of Pesticide Toxicity by Lehman. A lowest long-term level of 8 mg/kg bw/day with minimal or no effects in dogs was identified. A safety factor of 500, an average daily intake of 2 ℓ of water by man and 20% of the total acceptable daily intake were the other factors taken into consideration to derive the final standard.

The National Academy of Sciences (NAS, 1977) recommended a concentration of 0.09 mg 2,4-D/ℓ in drinking water, assigning 20% of the total RfD to the drinking water source. This recommendation was based on a study in dogs by Hansen et al. (1971). The Academy applied an uncertainty factor of 1000 to the NOAEL in dogs, recognizing the deficiencies in the study. The Academy's calculations are given below:

$$\frac{12.5 \text{ mg/kg} \times 70 \text{ kg} \times 0.2}{2 \ell \times 1000} = 0.09 \text{ mg/}\ell$$

where: 12.5 mg/kg = no adverse effect level

70 kg = assumed average body weight of an adult

0.2 = factor representing 20% of total intake from water

2 ℓ = assumed average daily intake of water for man

1000 = uncertainty factor due to inter- and intraspecies variations and deficiencies in the studies

Johnson (1971) indicated that 220 Dow Chemical Company production workers who were exposed to 2,4-D in the range of 30-40 mg/day (~0.4-0.6 mg/kg bw/day, assuming a weight of 70 kg) over a period of 0.5-22 years showed no significant clinical effects when compared with an unexposed population. These data are from an unpublished study and are inadequate as reported for derivation of a lifetime DWEL. Particularly, additional information is needed regarding the exposure estimate (which presumably reflects inhalation and dermal exposures) and the effects (it was reported only that a battery of "at least 10 laboratory tests" was conducted). Singer et al. (1982) reported that nerve conduction velocities were slowed in workers who were engaged in the manufacture of 2,4-D and 2,4,5-T for an average of 7 years, but exposure levels were not determined.

Hansen et al. (1971) fed technical grade 2,4-D to groups of 25 Osborne-Mendel rats of each sex at levels of 0, 5, 125, 625 and 1250 ppm (0, ~0.25, 6.25, 31.25 and 62.5 mg/kg bw/day, respectively, assuming consumption of 5% of body weight in food/day) for 2 years. Adverse effects on growth, survival, organ weights, tissue histology or hematological values were not attributed to exposure at any of the treatment levels up to and including ~62.5 mg/kg bw/day. Although all rats were autopsied at the end of the 2-year test, comprehensive histological examinations were performed only on six rats of each sex from the high-dose and control groups; histological examinations in the remaining rats from the high-dose and control groups and in the rats in the other groups were limited to the liver, kidney, spleen, ovary or testis and other tissues that contained gross lesions.

In a similarly designed study with dogs, 6- to 8-month-old beagles (3 of each sex/group) were fed either 0, 10, 50, 100 or 500 ppm in the diet for 2 years (Hansen et al., 1971). If it is assumed that dogs consume 2.9% of their weight in food/day, the corresponding daily doses would be 0, 0.29, 1.49, 2.9 and 14.5 mg/kg bw/day, respectively. Treatment-related gross or histopathological effects were not associated with any of the exposures. Twenty-eight of the 30 treated dogs survived the test period and were clinically normal, but the report did not state if hematological analyses were performed as in the rat study.

A 3-generation, 6-litter reproduction study was also conducted by Hansen et al. (1971) in Osborne-Mendel rats. A decrease in average preweanling weight and in the survival of offspring during the first 3 weeks after birth was observed when test animals were maintained on 1500 ppm 2,4-D in the diet

(~75 mg/kg bw/day) for 2 years. These effects were not observed at 500 ppm (~25 mg/kg bw/day) or 100 ppm (~5 mg/kg bw/day). These authors also reported an unpublished study by Gaines and Kimbrough (1970) in which feeding 1000 or 2000 ppm 2,4-D in the diet (~50 or 100 mg/kg bw/day, respectively) to rats for 3 months before and during pregnancy and lactation resulted in increased mortality among the offspring. Bjorklund and Erne (1966), however, found no significant effects on dams or their offspring following administration of 1000 ppm 2,4-D in drinking water (50-100 mg/kg bw/day) to pregnant rats throughout gestation and for 10 months beyond parturition, and to the offspring for up to 2 years.

The chronic toxicity and reproduction studies of 2,4-D indicate no adverse effects at dietary levels up to 500 ppm in dogs (~14.5 mg/kg bw/day), up to 1250 ppm in rats (~62.5 mg/kg bw/day) (Hansen et al., 1971) or at levels of 1000 ppm in drinking water (50-100 mg/kg bw/day) in pregnant rats (exposed throughout gestation and for 10 months following parturition) or their offspring (exposed for up to 2 years after weaning) (Bjorklund and Erne, 1966). As previously discussed, however, a secondary reference to another study reported an increase in mortality among young rats whose dams received ~50 mg/kg bw/day of 2,4-D in the diet for 3 months before mating and throughout gestation and lactation (Gaines and Kimbrough, 1970). Moreover, the subchronic study of Hazelton Laboratories (1983) indicates that these chronic studies may not be the most appropriate basis for the derivation of an RfD. Hazelton Laboratories (1983) report multiple adverse effect at subchronic doses of 5.0 or 15 mg/kg bw/day, or higher in both mice and rats. A dose of 1.0 mg/kg bw/day was reported as a NOAEL in rats. In addition, preliminary results from a 2-year bioassay indicate no change in this latter NOAEL.

Giving consideration to all of these studies, it seems reasonable to estimate a lifetime DWEL for a 70 kg human from the rat NOAEL of 1.0 mg/kg bw/day of Hazelton Laboratories (1983) using an uncertainty factor of 100. This factor represents a 10-fold decrease in dose for both intra- and inter-species variability to the toxicity of a chemical when specific data are lacking.

$$\text{Lifetime DWEL} = (1.0 \text{ mg/kg bw/day} \times 70 \text{ kg bw}) \div (100 \times 2 \text{ ℓ/day}) = 0.35 \text{ mg/ℓ}$$

This HA is equivalent to an RfD of 0.70 mg/day or 0.010 mg/kg bw/day.

There are discrepancies in the results of the subchronic and chronic toxicity studies. The highest NOAEL for rats in the 2-year Hansen et al. (1971) study (62.5 mg/kg bw/day), for example, is higher than the highest NOAELs reported in the subchronic rat studies of 30 mg/kg bw/day of Rowe and Hymas (1954) and of 40 mg/kg bw/day of Hill and Carlisle (1947), although this result may only be due to the doses employed. The Hansen et al. (1971) rat NOAEL is also close to the frank-effect level (100 mg/kg bw/day) in the 113-day experiment (Rowe and Hymas, 1954). The highest NOAEL for dogs in the Hansen et al. (1971) 2-year study (14.5 mg/kg bw/day) is similar to the FEL (14.3 mg/kg bw/day) in the 13-week dog study (Drill and Hiratzka, 1953). Furthermore, recent data by Hazelton Laboratories (1983) indicate that subchronic doses as low as 5 mg/kg bw/day might represent adverse effect levels in rats and perhaps mice. These variable results may reflect the use of different 2,4-D formulations or the inadequacies of the short-term studies as previously discussed (e.g., small numbers of animals per dose, inadequate reporting of data). These differences in 2,4-D toxicity could also possibly be due to a sharp break in the no-effect, effect dose region. These differences may be resolved by additional testing.

Conclusions. A summary of the data used to calculate the HAs and the lifetime DWEL is provided in Table VIII-1. The values derived for the HAs and the DWEL represent estimates of the concentrations of 2,4-D in drinking water that will not cause adverse effects after 1 day, 10 days or lifetime exposures.

Carcinogenic Effects

Quantification of Carcinogenic Effects

The available animal and epidemiology carcinogenicity studies have not conclusively shown that 2,4-D alone is carcinogenic. Administration of 2,4-D or the butyl, isopropyl or isooctyl esters of 2,4-D by intubation (46-100 mg/kg bw/day) on days 7 through 28 of age and subsequently in the diet (111-323 ppm, ~14-42 mg/kg bw/day) for up to 90 weeks was not tumorigenic for mice (Bionetics Research Lab., 1968b). Administration of 2,4-D in the diet at levels as high as 1250 ppm (~62.5 mg/kg/day) for 2 years was originally reportedly not carcinogenic for rats (Hansen et al., 1971), but later examination of the histology sections by Reuber (1979) found a significant increase in the incidence of lymphosarcomas in females at all dose levels; histopathologic reevaluation and consideration of the spontaneous incidence of lymphoid tumors in Osborne-Mendel rats are needed to resolve the discrepancy. A Russian study reported that administration of 2,4-D amine salt in the diet for life at one-tenth the LD_{50} (level not specified) was not tumorigenic for rats or mice (Archipov and Kozlova, 1974). Single subcutaneous injections of 2,4-D (215 or 464 mg/kg bw), 2,4-D isopropyl ester (100 mg/kg bw) or 2,4-D isobutyl ester (21.5 mg/kg bw) were not tumorigenic for mice after 78 weeks, but similar injection of 2,4-D isooctyl ester (21.5 mg/kg bw) induced a significant increase in reticulum

TABLE VIII-1

Summary of Data Used to Derive HA and DWEL

Criteria	Animal Dose	Duration	Effect	Value of HA or AADI		Reference
				Adult	Child	
1-Day HA	114 mg/kg (assumed mouse LOAEL)	single exposure	highest dose not causing death	NA	1.3 mg/ℓ	Hill and Carlisle, 1947
10-Day HA	30 mg/kg (rat NOAEL)	113 days	NOAEL, higher doses caused liver toxicity and depressed growth rate	NA	0.30 mg/ℓ	Rowe and Hymas, 1954
Longer-term HA			Insufficient Data			
Lifetime DWEL	1.0 mg/kg (rat NOAEL)	subchronic exposure*	NOAEL, higher doses caused a variety of effects in blood, liver and kidney indices.	0.35 mg/ℓ	NA	Hazelton Laboratories, 1983

*However, recent findings from the 2-year study confirm the subchronic NOAEL of 1.0 mg/kg/day. Thus, an uncertainty factor of 100 is used to estimate the DWEL rather than the usual 1000.

NA = Not applicable

cell carcinomas (Biometics Research Lab., 1966a). Repeated applications of 2,4-D to the skin of mice only produced papillomas when treatment was preceded by a single dermal application of the initiator 3-methylcholanthrene (Archipov and Kozlova, 1974).

An additonal animal bioassay (Industry Task Force, 1985) conducted by Hazelton Labs in Virginia is available although it has not been critically evaluated by ORD's Carcinogen Assessment Group in this document.

Epidemiology studies (see Subchronic and Chronic Effects in Chapter VI) have associated excess tumor incidence (primarily soft-tissue sarcomas) in humans with mixed exposures to chlorophenoxy herbicides that contain 2,4,5-T (which may be contaminated with 2,3,7,8-TCDD) and 2,4-D (which is not contaminated with this dioxin isomer). Prior to 1986, IARC and EPA have judged the epidemiologic evidence for chlorophenoxy herbicides to be "limited", i.e. providing evidence of causality but not without the possibility of alternative explanations such as chance, bias or confounding factors. The EPA overall weight-of-evidence classification for the chlorophenoxy herbicides is Group B1; IARC (1987) is 2B. While 2,4-D is a member of the chlorophenoxy class and is known to be present as one constituent in some of the chlorophenoxy studies, it is not possible from the studies prior to 1986 to isolate 2,4-D and conclude that it is or is not a causative agent. Thus, prior to 1986, the epidemiology data for 2,4-D alone was judged to be inadequate.

A new case-control study (Hoar et al., 1986), however, is more focused on 2,4-D than the earlier data base. In a carefully designed and well-conducted study, Hoar et al. (1986) found a statistically significant association between exposure to 2,4-D (controlling for the other herbicides present) and an excess risk of non-Hodgkins lymphoma (NHL). The authors also found a dose-related increase of NHL with exposure to 2,4-D.

The CAG believes that the Hoar et al. (1986) study provides evidence of a causal association of 2,4-D exposure with NHL; however, CAG believes that alternative explanations for this association such as chance, bias or confounding factors cannot be excluded. The CAG is aware that the authors of the Hoar et al. (1986) study are currently conducting two additional case-control studies of NHL cases in populations different from those of the Hoar et al. (1986) study. Results from these studies should be available within 12 months. As the Guidelines for Carcinogen Risk Assessment indicate, confidence in inferring a causal association from epidemiologic data is increased when several independent studies are concordant in showing the association. Because the results of the two additional studies will likely be available within 12 months, the CAG has decided to withhold its weight of evidence evaluation of the human data as well as classification of the overall weight of evidence for 2,4-D. CAG's evaluation of the weight of evidence of this chemical will be made pending receipt of the expected epidemiologic studies and a critical evaluation of the Industry Task Force animal bioassay.

Note is made that OPP, by March 23, 1988 Federal Register Notice, has proposed a weight-of-evidence for the cancer data base that takes account of

the Industry Task Force (1985) animal study and the Hoar et al. (1986) epidemiologic data. OPP has proposed that the animal and human data, be viewed as inadequate for 2,4-D, resulting in an over-all weight-of-evidence for 2,4-D of Group D, i.e. data is inadequate to refute or demonstrate a human carcinogenic potential. OPP proposes that additional animal studies be conducted and that a reevaluation of the data base could be initiated at a later date. Public comment on this proposal carries through May 23, 1988.

2,4-D as a commercial product has been shown to contain chlorinated dibenzodioxins as an impurity. A rigorous characterization of the impurities is beyond the scope of this document; however, 2,3,7,8-TCDD and the hexa- isomer have not been detected, while ppb amounts (5-900) have been cited of di-, tri- and 1,3,6,9- or 1,3,6,8-tetra- isomers, depending upon 2,4-D acid %. From a risk characterization perspective, the role, if any, of the impurities warrants recognition as it may pertain to toxicologic observations as well as to the description of the human exposure to 2,4-D, e.g., exposure via drinking water pathway may be to an altered 2,4-D mixture rather than the original commercial preparation, which might not be the case for a pesticide formulator/applicator, for instance.

2,4-D has been tested for mutagenicity in a variety of systems, including microorganisms, plants, fruit flies, cultured mammalian cells, and *in vivo* mammalian assays (see Mutagenicity in Chapter V). 2,4-D induced mitotic gene conversion and recombination in *Saccharomyces cerevisiae* (Simmon, 1979); induced recessive lethal and somatic mutations (weakly mutagenic) in *Drosophila melanogaster* (Magnusson et al., 1977; Rasmusson and Svahlin, 1978); induced mutation to ouabain resistance in cultured Chinese hamster V-79 lung cells and induced unscheduled DNA synthesis in cultured

human fibroblasts (Ahmed et al., 1977); induced chromosome aberrations and sister chromatid exchanges in cultured human lymphocytes (Pilinskaya et al., 1976; Korte and Jalal, 1982); induced bone marrow chromosome aberrations (Pilinskaya et al., 1976); and inhibited thymidine incorporation into testicular DNA (Seiler, 1979) in mice exposed in vivo. Mutagenicity testing of 2,4-D in plants was almost universally positive (see Mutagenicity in Chapter V). A preponderance of negative responses in animal assays, however, indicates that pH may be a critical factor; unless the pH is in the acid range, 2,4-D will be ionized and may not readily cross cell membranes or reach the target tissues. Mutagenicity testing of 2,4-D esters has not been performed, but theoretically these compounds could show higher levels of penetration into target cells. Thus, it may be prudent to expect that these chemicals are mutagenic.

Existing Guidelines, Recommendations and Standards

The National Academy of Sciences has suggested an acceptable level in drinking water of 0.09 mg/ℓ (0.09 ppm) for 2,4-D in drinking water, assuming that 20% of exposure is attributable to drinking water (NAS, 1977). This level was calculated from a NOEL from the Hansen et al. (1971) 2-year feeding study with dogs. The interim primary drinking water standard for 2,4-D is 0.1 mg/ℓ (Federal Register, 1975).

The American Conference of Governmental Industrial Hygienists currently recommends an 8-hour TWA-TLV of 10 mg/m³ for occupational exposure to 2,4-D (ACGIH, 1980). ACGIH also recommends a STEL of 20 mg/m³ for any 15-minute exposure period. These recommendations are intended to protect against local and systemic effects by inhalation and are derived from unspecified ingestion studies.

Occupational exposure limits for 2,4-D have not been recommended by the National Institute for Occupational Safety and Health (NIOSH) or promulgated by the Occupational Safety and Health Administration (OSHA).

The U.S. EPA (1982) has established the following tolerances for 2,4-D residues in or on raw agricultural commodities: 5 ppm for apples, pears, quinces, apricots (includes residues from the preharvest of the dimethylamine salts) and citrus fruits (includes residues from the preharvest application of the isopropyl and butoxyethyl esters and the postharvest application of the alkanolamine salts or the isopropyl ester); and 0.2 ppm for potatoes. Tolerances are established for residues of 2,4-D in acid form, or in the form of several salts and esters on the following commodities: 1000 ppm for rangeland and pasture grasses; 300 ppm for grass hay; 20 ppm for barley, corn, millet straw, oats, rice straw, rye, sorghum, sugarcane and wheat used for forage and fodder; 2 ppm for sugarcane; 0.5 ppm for various grains, cranberries and grapes; and 0.1 ppm for blueberries and rice (U.S. EPA, 1982).

In instances where 2,4-D dimethylamine salt is applied to irrigation ditch banks in the western United States under various Federal programs, the established tolerance for 2,4-D residues is 0.1 ppm for the following commodities: avocadoes, various fruits and vegetables, grain crops, hops, forage grasses and legumes, curcurbits, cottonseed and nuts (U.S. EPA, 1982).

A tolerance for residues of 2,4-D sodium, ethanolamine and isopropanolamine salts calculated as 2,4-D has been established at 5 ppm for asparagus and 0.05 ppm for strawberries (U.S. EPA, 1982).

Established tolerances for residues of 2,4-D are 1 ppm from application of its dimethylamine salt for water hyacinth control in slow moving aquatic media (e.g., western United States irrigation ditch banks) and in fish and shellfish (U.S. EPA, 1982).

Tolerances are established for 2,4-D or its metabolite, 2,4-dichlorophenol, in the following animal food commodities: 2 ppm for cattle, goat, hog, horse and sheep kidney; 0.2 ppm for cattle, goat, hog, horse and sheep meats, meat by-products or fat; 0.1 ppm for milk; and 0.05 ppm in eggs and poultry. A tolerance of 1.0 ppm 2,4-D for residues of its dimethylamine salt or butoxyethanol ester is established for fish in Tennessee Valley Authority dams and reservoirs being controlled for Eurasian Watermilfoil (U.S. EPA, 1982).

A maximum ADI level of 2,4-D for man has been recommended as 0.3 mg/kg by the Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues (WHO, 1976), after considering published experimental data and national tolerances established by several countries. An odor threshold for 2,4-D in water was reported by Sigworth (1965) as 3.13 mg/ℓ.

Special Groups at Risk

People who are occupationally exposed to 2,4-D (i.e., agricultural workers and those involved in the manufacture and distribution of the chemical) should be regarded as a special group at risk because they may be exposed to high levels of this chemical. Particularly, there is evidence that humans exposed to chlorophenoxy herbicide formulations containing

mixtures of 2,4-D and 2,4,5-T may develop cancer. Toxicokinetic studies with humans indicates that considerable interindividual variation occurs in the rates of absorption and excretion and in the amount of 2,4-D conjugated; these differences might result in a wide range of sensitivity to 2,4-D among individuals. Pregnant women should also be regarded as a sensitive population because 2,4-D and some of its salts and esters have produced fetotoxic and developmental effects in experimental animals. Because 2,4-D is excreted primarily in the urine and has some toxicity to the kidneys, persons with renal disease would also be a special group at risk.

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United States
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Agency

Prevention, Pesticides
and Toxic Substances
(7508C)

EPA 738-R-05-002
June 2005

Reregistration Eligibility Decision for 2,4-D

Reregistration Eligibility Decision

for

2,4-D

List A
Case 0073

Approved By:

_____
Debra Edwards, Ph.D.
Director, Special Review and
Reregistration Division

_____
Date

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Glossary of Terms and Abbreviations

A	Acre
AGDCI	Agricultural Data Call-In
ae	Acid Equivalent
ai	Active Ingredient
aPAD	Acute Population Adjusted Dose
AR	Anticipated Residue
BCF	Bioconcentration Factor
CFR	Code of Federal Regulations
cPAD	Chronic Population Adjusted Dose
CSF	Confidential Statement of Formula
CSFII USDA	Continuing Surveys for Food Intake by Individuals
DCI	Data Call-In
DEEM	Dietary Exposure Evaluation Model
DFR	Dislodgeable Foliar Residue
DWLOC	Drinking Water Level of Comparison.
EC	Emulsifiable Concentrate Formulation
EDSP	Endocrine Disruption Screening Program
EDWC	Estimated Drinking Water Concentration
EEC	Estimated Environmental Concentration
EPA	Environmental Protection Agency
EUP	End-Use Product
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FFDCA	Federal Food, Drug, and Cosmetic Act
FQPA	Food Quality Protection Act
FOB	Functional Observation Battery
G	Granular Formulation
GENEEC	Tier I Surface Water Computer Model
GLN	Guideline Number
HAFT	Highest Average Field Trial
HAT	Hour After Treatment
IR	Index Reservoir
LC50	Median Lethal Concentration. A statistically derived concentration of a substance that can be expected to cause death in 50% of test animals. It is usually expressed as the weight of substance per weight or volume of water, air or feed, e.g., mg/l, mg/kg or ppm.
LD50	Median Lethal Dose. A statistically derived single dose that can be expected to cause death in 50% of the test animals when administered by the route indicated (oral, dermal, inhalation). It is expressed as a weight of substance per unit weight of animal, e.g., mg/kg.
LOC	Level of Concern
LOD	Limit of Detection
LOAEL	Lowest Observed Adverse Effect Level

MATC	Maximum Acceptable Toxicant Concentration
µg/g	Micrograms Per Gram
µg/L	Micrograms Per Liter
mg/kg/day	Milligram Per Kilogram Per Day
mg/L	Milligrams Per Liter
MOE	Margin of Exposure
MRID	Master Record Identification (number). EPA's system of recording and tracking studies submitted
MSWC	Maximum Swimming Water Concentration
MUP	Manufacturing-Use Product
NA	Not Applicable
NAWQA	USGS National Water Quality Assessment
NCOD	National Drinking Water Contaminant Occurrence Database
NPDES	National Pollutant Discharge Elimination System
NR	Not Required
NOAEL	No Observed Adverse Effect Level
OP	Organophosphate
OPP	EPA Office of Pesticide Programs
OPPTS	EPA Office of Prevention, Pesticides and Toxic Substances
ORETF	Outdoor Residential Exposure Task Force
PAD	Population Adjusted Dose
PCA	Percent Crop Area
PDIC	Product-Specific Data Call-In
PDP	USDA Pesticide Data Program
PHED	Pesticide Handler's Exposure Data
PHI	Preharvest Interval
ppb	Parts Per Billion
PPE	Personal Protective Equipment
ppm	Parts Per Million
PRZM/ EXAMS	Tier II Surface Water Computer Model
Q1*	The Carcinogenic Potential of a Compound, Quantified by the EPA's Cancer Risk Model
RAC	Raw Agriculture Commodity
RED	Reregistration Eligibility Decision
REI	Restricted Entry Interval
RfD	Reference Dose
RQ	Risk Quotient
SCI-GROW	Tier I Ground Water Computer Model
SAP	Science Advisory Panel
SF	Safety Factor
SLC	Single Layer Clothing
SLN	Special Local Need (Registrations Under Section 24(c)) of FIFRA)
STORET	Storage and Retrieval Environmental Data System

TGAI	Technical Grade Active Ingredient
TRR	Total Radioactive Residue
TWAM	Time Weighted Annual Mean
USDA	United States Department of Agriculture
USGS	United States Geological Survey
UF	Uncertainty Factor
UV	Ultraviolet
WPS	Worker Protection Standard

2,4-D Reregistration Eligibility Decision Team

Office of Pesticide Programs:

Biological and Economic Analysis Assessment

Elisa Rim
Rafael Prieto
Steve Jarboe
Tim Kiely

Environmental Fate and Effects Risk Assessment

Mark Corbin
Bill Evans
James Hetrick
Sid Abel

Health Effects Risk Assessment

Bill Hazel
Timothy Dole
Linda Taylor
Felecia Fort
Toiya Jimerson
Michael Metzger
Whang Phang

Risk Management

Katie Hall
Mark Seaton
Moana Appleyard
Tom Myers
Margaret Rice

Executive Summary

EPA has completed its review of public comments on the preliminary risk assessments and is issuing its risk management decision for 2,4-D. The revised risk assessments are based on review of the required target data base supporting the use patterns of the currently registered products and additional information received from the 2,4-D Task Force II. After considering the risks identified in the revised risk assessment and comments and mitigation suggestions from interested parties, EPA developed its risk management decision for uses of 2,4-D that pose risks of concern. The decision is discussed fully in this document.

2,4-D is an herbicide in the phenoxy or phenoxyacetic acid family that is used post-emergence for selective control of broadleaf weeds. 2,4-D is registered for use on a variety of food/feed sites including field, fruit, and vegetable crops. 2,4-D is also registered for use on turf, lawns, rights-of-way, aquatic and forestry applications. Residential homeowners may use 2,4-D on lawns.

Based primarily on pesticide usage information from 1992 through 2000 for agriculture and 1993 through 1999 for non-agriculture, total annual domestic usage of 2,4-D is approximately 46 million pounds, with 30 million pounds (66%) used for agriculture and 16 million pounds (34%) used for non-agriculture. In terms of pounds, total 2,4-D usage is allocated mainly to pasture/rangeland (24%), lawn by homeowners with fertilizer (12%), spring wheat (8%), winter wheat (7%), lawn/garden by lawn care operators/landscape maintenance contractors (7%), lawn by homeowners alone (without fertilizer) (6%), field corn (6%), soybeans (4%), summer fallow (3%), hay other than alfalfa (3%) and roadways (3%). Agricultural sites with at least 10% of U.S. acreage treated include spring wheat (51%), filberts (49%), sugarcane (36%), barley (36%), seed crops (29%), apples (20%), rye (16%), winter wheat (15%), cherries (15%), oats (15%), millet (15%), rice (13%), soybeans (12%), and pears (10%). For 2,4-D, rates per application and rates per year are generally less than 1.50 pounds acid equivalent (a.e.) per acre and 2.00 pounds a.e. per acre (lbs ae/A), respectively. 2,4-D is used predominantly in the Midwest, Great Plains, and Northwestern United States.

The Food Quality Protection Act (FQPA) requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to 2,4-D and any other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that 2,4-D has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs (OPP) concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

Dietary Risk

Acute and chronic dietary exposures for food and drinking water do not exceed the Agency's level of concern; therefore, no mitigation is warranted at this time for any dietary exposure to 2,4-D.

The maximum contaminant level (MCL) established by EPA's Office of Water (OW) for 2,4-D is 70 micrograms/liter (ug/l; ppb). Further, it is important to note that an MCL is an enforceable limit under the Safe Drinking Water Act (SDWA). To minimize the possibility that aquatic applications will result in drinking water concentrations in excess of the MCL, registrants and the Agency have developed label language for the direct aquatic use of 2,4-D to control aquatic weeds.

Residential Risk

Potential exposures are anticipated as a result of homeowner and commercial applications in residential areas. Applications can be made to lawns. In addition to residential areas, there are also potential postapplication exposure scenarios that may occur in public areas such as parks, recreational areas, and golf courses. The Agency evaluated 2,4-D exposures to residential handlers during mixing, loading and application to turf/ornamentals and 2,4-D postapplication exposure to residues by adults and children on treated turf.

In preliminary versions of the risk assessment, when considered alone, acute and short-term residential risks posed by the use of 2,4-D were not of concern to the Agency; however, when considered as part of an aggregate exposure with food and drinking water, exposures did exceed the Agency's level of concern. As a result, 2,4-D registrants agreed to reduce the maximum application rate to turf and residential lawns from 2.0 lbs ae/A to 1.5 lbs ae/A. Chronic residential exposures to 2,4-D are not expected due to its use pattern.

Aggregate Risk

An aggregate risk assessment looks at the combined risk from dietary exposure (food and drinking water pathways), as well as exposures from non-occupational sources (e.g., residential uses). In the preliminary and revised risk assessments, the estimated acute and short-term exposures exceeded the Agency's level of concern. As a result, 2,4-D registrants agreed to reduce the maximum application rate to turf and residential lawns from 2.0 pounds acid equivalent per acre (lbs ae/A) to 1.5 lbs ae/A. The current risk assessment considers exposures from the reduced application rate for residential turf.

Two methods of aggregate risk calculations were employed in assessing the aggregate risk of 2,4-D. The first method is the drinking water level of concern (DWLOC) method. OPP (Office of Pesticide Programs) has traditionally compared estimates of concentrations of a pesticide in drinking water to DWLOCs. A DWLOC is the portion of the acute population adjusted dose (aPAD) or chronic population adjusted dose (cPAD) remaining after estimated dietary (food only) exposures have been subtracted and the remaining exposure has been converted to a concentration (ug/liter or ppb). This concentration value (DWLOC) represents the available or allowable exposure through drinking water. The second method is the forward calculation method. In this approach, food, drinking water, and residential exposures are aggregated and compared to an appropriate endpoint. A

population adjusted dose, or PAD, is the reference dose (RfD) adjusted for the FQPA safety factor. A risk estimate that is less than 100% of the acute PAD (aPAD), the dose at which an individual could be exposed over the course of a single day and no adverse health effects would be expected, does not exceed EPA's level of concern. Likewise, risk estimate that is less than 100% of the chronic PAD (cPAD), the dose at which an individual could be exposed over the course of a lifetime and no adverse health effects would be expected, does not exceed EPA's level of concern.

In the case of 2,4-D, the DWLOCs were calculated for comparison to the MCL established by the EPA Office of Water and aggregate risks were calculated using the forward calculation approach for comparison to the appropriate endpoint. The respective DWLOCs and aggregate risks are shown for acute, chronic and short term exposures in the following sections.

Acute aggregate risk. The acute aggregate risk assessments address exposure to 2,4-D residues in food and water using both the DWLOC and forward calculation approach. Acute residential exposures from swimming in treated water bodies or playing on treated turf were not included because exposures are unlikely to co-occur with acute dietary exposures. The acute DWLOCs are 432 ppb or greater with the most sensitive population being females 13-49 years old. The estimated drinking water concentrations (EDWCs) of 118 ug/liter for surface water and 15 ug/liter for groundwater are substantially less than the DWLOCs which means that the risks are not of concern.

Acute aggregate risks were also assessed by aggregating acute food exposures and acute water exposures using Lifeline. The acute aggregate risks are not of concern because they are less than 100 percent of the aPAD. The highest risks (58 percent of the aPAD) are for females 13-49 years old because these risks are based upon the lower no-observed adverse effect level (NOAEL) of 25 mg/kg/day from a developmental study in rats.

Short-term aggregate risk. Short term aggregate risk assessments were conducted by calculating DWLOCs based upon short term turf exposures, chronic food exposures and short term endpoints. Short term exposures from swimming in treated water bodies were not included because these exposures represent high-end unlikely scenarios. The short term DWLOCs were calculated only for females 13-49 and children 1-6 because these population subgroups have the highest exposure and are protective of the other subgroups. The DWLOCS range from 24 to 54 ug/liter. These DWLOCs are all greater than the EDWCs, which range from 15 to 23 ug/liter, and indicate that short term risks are not of concern.

Short term aggregate risks were also assessed by aggregating short term turf exposures, chronic food exposures and chronic water exposures using the forward calculation approach. Short term aggregate risks were calculated only for females 13-49 and children 1-6 because these population subgroups have the highest exposure and are protective of the other subgroups. The short term aggregate margins of exposure (MOEs) indicate that the short term risks are not of concern because the MOEs equal or exceed the target MOE of 1000.

Chronic (non-cancer) aggregate risk. Chronic DWLOCs were calculated based upon chronic dietary exposures. As there are no chronic residential exposures, residential exposures were not included in the chronic DWLOC calculations. The chronic DWLOCs are 47 ug/liter or greater with the most sensitive populations being infants and children. The EDWCs, which range from 1.5 to 23 ug/liter, are less than the DWLOCs which means that the risks are not of concern. It should be noted that the master label indicates that potable water consumption from a treated water body cannot begin until the 2,4-D concentration is 70 ug/liter or below, therefore an annual average exposure at the MCL of 70 ug/liter would not occur because dissipation would reduce the initial concentration of 70 ug/liter to an annual average concentration of 11 ug/liter.

Chronic aggregate risks were also assessed by aggregating chronic food exposures and chronic water exposures using the forward calculation approach. The chronic aggregate risks are presented as percent cPAD are not of concern because they are less than 100 percent of the cPAD. The highest risks (38 percent of the cPAD) are for children 1-2 years old.

Occupational Risk

Based on current use patterns, occupational handlers (mixers, loaders, and applicators) may be exposed to 2,4-D during and after normal use. The Agency identified 18 handler scenarios resulting from mixing/loading and applying 2,4-D for crop and non-crop uses. For the occupational use of 2,4-D, EPA is concerned about any Margin of Exposure (MOE) less than 100, which incorporates uncertainty factors of 10x for interspecies variation and 10x for intraspecies variation.

With the exception of mixing/loading wettable powder, all of the short-term and intermediate-term MOEs exceed the target of 100 with baseline personal protective equipment (PPE) (i.e., long-sleeved shirt, long pants, shoes plus socks, no respirator) or single layer PPE (i.e., long-sleeved shirt, long pants, shoes plus socks, gloves, no respirator) and are not of concern. The MOEs for handling wettable powder are above 100 with engineering controls (i.e., water soluble bags).

Ecological Risk

Fish and Aquatic Invertebrates: Estimated risk quotients (RQs) from use of 2,4-D acid and amine salts in aquatic weed control through direct subsurface application to water bodies exceed the restricted use LOCs for freshwater invertebrates. There are no chronic LOC exceedances for this use. Estimated RQs from use of 2,4-D BEE in weed control through direct subsurface application to water bodies exceed the acute risk level of concern (LOC) for freshwater fish and invertebrates and chronic risk LOC for freshwater and estuarine fish and freshwater invertebrates when compared on an acid equivalent basis. Estimated RQs from use of 2,4-D acid and amine salts in rice paddies exceed the acute endangered species LOCs for freshwater invertebrates.

Non-Target Aquatic Plants: For non-target aquatic plants, estimated RQs from the runoff/drift of 2,4-D acid and amine salts from use on terrestrial crops exceed the aquatic vascular plant endangered species LOCs for use of 2,4-D acid and amine salts on pasture and apples. Consideration of average application rates and assuming a proportional reduction in EECs results in RQs below the

endangered species LOC. Likewise, there are no LOC exceedances from the drift of the ester forms to aquatic water bodies or from the runoff of the ester forms to water bodies from use on terrestrial sites.

Estimated RQs for the scenario of direct application to water for aquatic weed control for 2,4-D acid and amine salts exceed the acute and endangered species LOCs for aquatic vascular and acute the LOC for non-vascular plants, while estimated RQs from use of 2,4-D BEE (the only ester registered for aquatic weed control) for direct application to water for weed control exceed all LOCs for vascular and the acute LOC for non-vascular plants.

Estimated RQs for use of 2,4-D acid and amine salts in rice paddies exceed the acute and endangered species LOCs for aquatic vascular plants. Consideration of average application rates results in RQs below the endangered species LOCs.

Birds: For non-granular spray applications of 2,4-D acid, amine salts, and esters, estimated RQs exceed acute LOCs for most crop scenarios for short grass, tall grass, and broadleaf forage exposures. For birds that eat fruit and large insects, acute endangered LOCs are exceeded for non-cropland, forest, and cranberry scenarios. Chronic LOCs are exceeded for birds that forage on short grass when the application rate of 2,4-D ranges from 2.0 to 4.0 lbs ae/A such as with non-cropland areas, cranberries, or asparagus. For granular broadcast applications, acute LOCs are exceeded for several different crop scenarios and bird weights. The chronic LOC is not exceeded for granular broadcast applications.

Mammals: For non-granular formulations of 2,4-D, estimated RQs exceed acute LOCs for mammals feeding on plants and insects for all uses assessed for small and medium size mammals, except potatoes and citrus. There were no exceedances for granivores exposed to non-granular formulations of 2,4-D. LOCs for acute exposure to granular 2,4-D products are exceeded for all sites with the following exceptions: 1000 g mammals in turf, aquatic areas, and cranberries. Mammalian chronic RQs range from 0.05 to 200 and chronic LOCs were exceeded in all cases with the exception of potatoes and citrus (large insects, seeds). Consideration of average application rates results in acute RQs below the LOCs for non-granular and granular applications. However, consideration of average application rates for non-granular and granular applications did not result in RQs below the chronic LOC.

Insects: Since study results show that 2,4-D DMAS and 2,4-D EHE are practically non-toxic to honey bees, the potential for 2,4-D and its salts and esters is predicted to pose minimal risk to pollinators and other beneficial insects.

Non-Target Terrestrial Plants: Estimated RQs exceed acute LOCs for both non-endangered and endangered plants for non-granular and granular uses at many use sites. Consideration of average application rates did not result in RQs below LOCs.

In summary, some ecological risks are of concern on some sites for some species. The Agency's characterization of its assessment of ecological risk is provided in section III.B.3 of this document. The mitigation measures of (1) reducing maximum application rates, and (2) specifying a

required spray droplet size of "Medium to Coarse" or coarser (i.e., prohibiting "fine" sprays) are expected to lessen, but not eliminate, the risk of 2,4-D to wildlife and plants.

Summary of Mitigation Measures

EPA has determined that 2,4-D is eligible for reregistration provided the mitigation outlined in this document is implemented.

Dietary Risk

- Acute and chronic dietary exposures for food and drinking water do not exceed the Agency's level of concern; therefore, no mitigation is warranted at this time for any dietary exposure to 2,4-D.

Residential Risk

- Maximum turf rate is reduced from 2.0 lbs ae/A to 1.5 lbs ae/A.
- At the agreed-upon maximum application rate of 1.5 lbs ae/A for residential turf, acute and short-term residential risks posed by the use of 2,4-D are not of concern to the Agency. Due to its use pattern, chronic residential exposures to 2,4-D are not expected.

Occupational Risk

- Risks from handling wettable-powder products will be mitigated by requiring wettable powder products to be packaged in water-soluble packaging.
- Personal protective equipment (PPE) prescribed in the exposure reduction plan set forth in 1992 will be replaced with the PPE requirements outlined in this document.

Ecological Risk

- The measures to control spray drift are expected to reduce the risk of 2,4-D to non-target plants.
- Maximum turf rate is reduced from 2.0 lbs ae/A to 1.5 lbs ae/A.
- Implementation of the application rates set forth in the Master Label will reduce rates (as compared to current rates on existing labels) for field corn, popcorn, sweet corn, small grains, fallowland/stubble, non-cropland, turf, aquatic applications (surface), pasture, and soybean.

I. Introduction

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) was amended in 1988 to accelerate the reregistration of products with active ingredients registered prior to November 1, 1984. The amended Act calls for the development and submission of data to support the reregistration of an active ingredient, as well as a review of all submitted data by the U.S. Environmental Protection Agency (referred to as EPA or "the Agency"). Reregistration involves a thorough review of the scientific database underlying a pesticide's registration. The purpose of the Agency's review is to reassess the potential hazards arising from the currently registered uses of the pesticide; to determine the need for additional data on health and environmental effects; and to determine whether or not the pesticide meets the "no unreasonable adverse effects" criteria of FIFRA.

On August 3, 1996, the Food Quality Protection Act of 1996 (FQPA) was signed into law. This Act amends FIFRA and the Federal Food Drug and Cosmetic Act (FFDCA) to require reassessment of all existing tolerances for pesticides in food. FQPA also requires EPA to review all tolerances in effect on August 3, 1996 by August 3, 2006. In reassessing these tolerances, the Agency must consider, among other things, aggregate risks from non-occupational sources of pesticide exposure, whether there is increased susceptibility to infants and children, and the cumulative effects of pesticides with a common mechanism of toxicity. When a safety finding has been made that aggregate risks are not of concern and the Agency concludes that there is a reasonable certainty of no harm from aggregate exposure, the tolerances are considered reassessed. EPA decided that, for those chemicals that have tolerances and are undergoing reregistration, tolerance reassessment will be accomplished through the reregistration process.

As mentioned above, FQPA requires EPA to consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity" when considering whether to establish, modify, or revoke a tolerance. Potential cumulative effects of chemicals with a common mechanism of toxicity are considered because low-level exposures to multiple chemicals causing a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any one of these individual chemicals. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by the EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

Unlike other pesticides for which EPA has considered cumulative risk based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding for 2,4-dichlorophenoxyacetic acid (2,4-D). Therefore, for the purposes of tolerance reassessment and a decision on reregistration eligibility, EPA is assuming that 2,4-D does not share a common mechanism of toxicity with other compounds. In the future, if information suggests 2,4-D shares a common mechanism of toxicity with other compounds, additional testing may be required and a cumulative assessment may be necessary.

This document presents summaries of EPA's revised human health and ecological risk assessments, tolerance reregistration decision, and the reregistration eligibility decision for 2,4-D. The document consists of six sections. Section I contains the regulatory framework for reregistration/tolerance reassessment. Section II provides a profile of the use and usage of the chemical. Section III gives an overview of the revised human health and environmental effects risk assessments based on data, public comments, and other information received in response to the preliminary risk assessments. Section IV presents the Agency's reregistration eligibility and risk management decisions. Section V summarizes label changes necessary to implement the risk mitigation measures outlined in Section IV. Finally, the Appendices list related information, supporting documents. The preliminary and revised risk assessments for 2,4-D are available in the Public Docket, under docket number OPP-2004-0167 and on the Agency's web page, http://www.epa.gov/edockets.

II. Chemical Overview

A. Regulatory History

2,4-D has been used as an herbicide since the mid-1940s. Currently over 600 end-use products are registered for use on over 300 distinct agricultural and residential sites, and there are over 100 tolerances for 2,4-D listed in the Code of Federal Regulations. 2,4-D was the subject of a Registration Standard and a Registration Standard Guidance Document dated February 16, 1988 and September 9, 1988, respectively. These documents summarized the regulatory conclusions based on available data, and specified the additional data required for reregistration purposes. Numerous data submissions have been received and evaluated since the Registration Standard Guidance Document was published.

Special Review

2,4-D has been in pre-Special Review status since September 22, 1986, because of carcinogenicity concerns. More specifically, there were concerns for epidemiological links of 2,4-D to non-Hodgkin's lymphoma from both occupational and residential exposure. A proposed decision not to initiate Special Review was published (53 FR 9590) on March 23, 1988 based on findings that such a link could not be established. The final decision was deferred until reregistration. In part to address these concerns, the 2,4-D Task Force agreed to risk reduction measures in September 1992 that included an exposure reduction plan effected through modifications of technical and manufacturing-use product labels and implementation of a user education program.

A Science Advisory Board/Scientific Advisory Panel Special Joint Committee reviewed available epidemiological and other data on 2,4-D in 1992 and concluded that "the data are not sufficient to conclude that there is a cause and effect relationship between exposure to 2,4-D and non-Hodgkin's lymphoma." 2,4-D was classified as a Group D, not classifiable as to human carcinogenicity. The Agency requested further histopathological examinations of rat brain tissues and mouse spleen tissues in question. These exams were submitted and reviewed, and on March 16, 1999, the Agency notified the 2,4-D Task Force that the Agency would continue to classify 2,4-D as a Group D carcinogen.

The Agency has twice recently reviewed epidemiological studies linking cancer to 2,4-D. In the first review, completed January 14, 2004, EPA concluded there is no additional evidence that would implicate 2,4-D as a cause of cancer (EPA, 2004). The second review of available epidemiological studies occurred in response to comments received during the Phase 3 Public Comment Period for the 2,4-D RED. EPA's report, dated December 8, 2004 and authored by EPA Scientist Jerry Blondell, Ph.D., found that none of the more recent epidemiological studies definitively linked human cancer cases to 2,4-D.

Final notice of the Agency's decision not to initiate Special Review will be issued at the completion of the reregistration process.

Residue Tolerances

Tolerances for residues of 2,4-D in/on plant and processed food/feed commodities, fish, and potable water are expressed in terms of 2,4-D *per se* [40 CFR §180.142(a)(1-6 and 9-12) and (b)]. There are currently approximately 110 tolerances for 2,4-D.

The Industry Task Force II on 2,4-D Research Data (Task Force II) is supporting the reregistration of 2,4-D. The members of the Task Force currently include Agro-Gor Corp (jointly owned by Atanor, S.A. and PBI-Gordon Corp.), Dow AgroSciences, and Nufarm USA. In addition, USDA's Interregional Project No. 4 (IR-4) is supporting the reregistration of a number of minor crop uses for 2,4-D, and the California Citrus Quality Council (CCQC) is supporting selected uses of 2,4-D isopropyl ester (IPE) on citrus fruits.

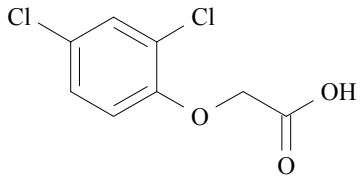
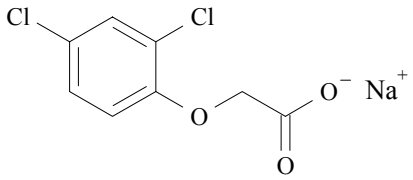
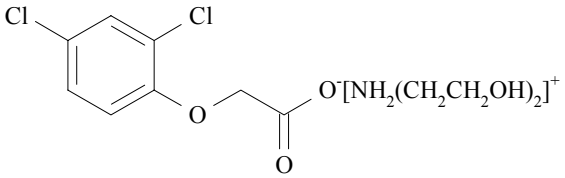
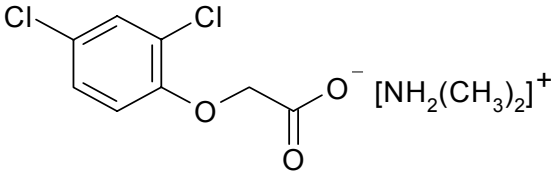
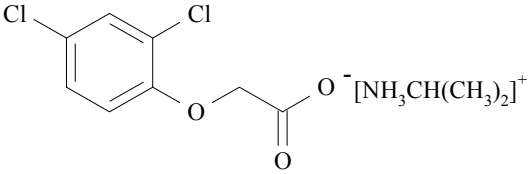
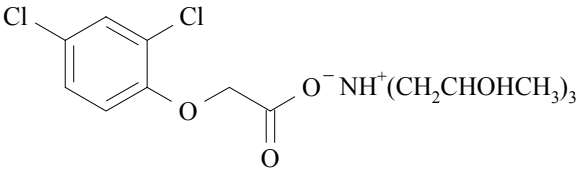
B. Chemical Identification

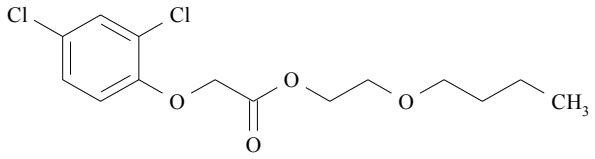
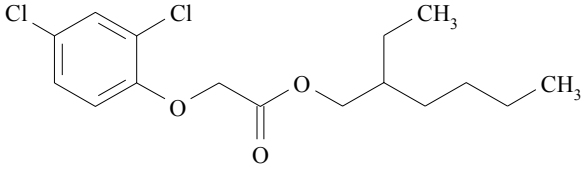
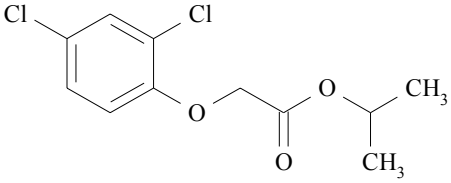
2,4-D [2,4-dichlorophenoxyacetic acid] is a List A pesticide active ingredient classified as an herbicide, a plant growth regulator, and a fungicide. It is, however, mainly used as a selective postemergence herbicide for the control of broadleaf weed species in a variety of food/feed sites including field, fruit, and vegetable crops. In addition to the acid form, there are numerous salts and esters of 2,4-D in Reregistration Case 0073, each with an assigned PC Code number, that are presently registered as active ingredients in end-use products (EPs). Nine forms of 2,4-D are currently supported; these forms are listed in Table 1 below. With regards to analytical methodology, the quantitative recovery of residues of concern are enhanced by the formation of the more polar acid form of 2,4-D. Given that results of 2,4-D analyses are typically expressed in terms of the quantified levels of the acid form, 2,4-D concentrations in product formulations are typically referred to in terms of acid equivalents (ae).

Chemical structures and information are presented in Tables 1 and 2 for 2,4-D acid and those salts and esters with registered manufacturing-use and/or end-use products (MPs/EPs) being supported by 2,4-D Task Force II and its member companies.

Table 1. Chemical Structures for Supported Forms of 2,4-D Acid, Amine Salts, and Esters

2,4-D active ingredients with registered MPs/EPs	
2,4-D acid Empirical Formula: $C_8H_6Cl_2O_3$ Molecular Weight: 221.0 CAS Registry No.: 94-75-7 PC Code: 030001	2,4-D sodium salt (Na) Empirical Formula: $C_8H_5Cl_2NaO_3$ Molecular Weight: 243.03 CAS Registry No.: 2702-72-9 PC Code: 030004

2,4-D active ingredients with registered MPs/EPs	
	
<u>2,4-D diethanolamine salt (DEA)</u> Empirical Formula: $C_{12}H_{17}Cl_2NO_5$ Molecular Weight: 326.18 CAS Registry No.: 5742-19-8 PC Code: 030016 	<u>2,4-D dimethylamine salt (DMA)</u> Empirical Formula: $C_{10}H_{13}Cl_2NO_3$ Molecular Weight: 266.13 CAS Registry No.: 2008-39-1 PC Code: 030019 
<u>2,4-D isopropylamine salt (IPA)</u> Empirical Formula: $C_{11}H_{15}Cl_2NO_3$ Molecular Weight: 280.04 CAS Registry No.: 5742-17-6 PC Code: 030025 	<u>2,4-D triisopropanolamine salt (TIPA)</u> Empirical Formula: $C_{17}H_{27}Cl_2NO_6$ Molecular Weight: 412.31 CAS Registry No.: 32341-80-3 PC Code: 030035 
<u>2,4-D 2-butoxyethyl ester (BEE)</u> Empirical Formula: $C_{14}H_{18}Cl_2O_4$ Molecular Weight: 321.20 CAS Registry No.: 1929-73-3 PC Code: 030053	<u>2,4-D 2-ethylhexyl ester (2-EHE)</u> [1] Empirical Formula: $C_{16}H_{22}Cl_2O_3$ Molecular Weight: 333.27 CAS Registry No.: 1928-43-4 PC Code: 030063

2,4-D active ingredients with registered MPs/EPs	
	
2,4-D isopropyl ester (IPE) Empirical Formula: $C_{11}H_{12}Cl_2O_3$ Molecular Weight: 263.12 CAS Registry No.: 94-11-1 PC Code: 030066 	

[1] Formerly identified as the isooctyl ester.

Available data concerning identification of the active ingredients are summarized in Table 2 for 2,4-D acid, salts, and esters with registered MPs/EPs.

Table 2. Available Data Concerning Identification of the Active Ingredient [1]

Active ingredient (PC Code)	Color	Physical State	Melting Point/ Boiling Point	Density/Specific Gravity	Octanol/Water Partition Coeff.	Vapor Pressure	Solubility
2,4-D acid (030001)	white	crystalline solid	m.p. 138-141 C	s.g.=1.416 at 25 C	Log $K_{O/W}$ 0.001 M sol'n pH 5 2.14 pH 7 0.177 pH 9 0.102	1.4×10^{-7} mm Hg at 25 C	water = 569 mg/L at 20 C
2,4-D Na salt (030004)	white	powder	m.p. 200 C	bulk = 42.2 lb/ft^3 at 25 C	N/A [2]; salt dissociates to acid in water		water = 4.5 g/100 mL at 25 C
2,4-D DEA salt (030016)	cream	powder	m.p. 83 C	bulk = 0.762 g/cm^3 at 25 C	2.24×10^{-2} at 25 C	$<1.33 \times 10^{-5}$ Pa at 25 C	mg/g at 25 C water = 806
2,4-D DMA salt (030019)	amber	aqueous liquid	m.p. 118-120 C (PAI)	s.g. = 1.23 at 20 C	N/A; salt dissociates to acid in water	$<1 \times 10^{-7}$ mm Hg at 26 C	g/100 mL at 20 C water = 72.9 (pH 7)
2,4-D IPA salt (030025)	amber	aqueous liquid	m.p. 121 C (PAI)	s.g. = 1.15 at 20 C	N/A; salt dissociates to acid in water		g/100 mL at 20 C water = 17.4 (pH 5.3)
2,4-D TIPA salt (030035)	amber	aqueous liquid	m.p. 87-110 C (PAI)	s.g. = 1.21 at 20 C	N/A; salt dissociates to acid in water		g/100 mL at 20 C water = 46.1 (pH 7)
2,4-D BEE (030053)	dark amber	liquid	b.p. 89 C	s.g. = 1.225 at 20 C	log = 4.13-4.17 at 25 C	2.4×10^{-6} mm Hg at 25 C	g/100 mL at 20 C water = insoluble
2,4-D 2-EHE (030063)	dark amber	liquid	b.p. 300 C	s.g. = 1.152 at 20 C	log = 5.78 (temp N/A)	3.6×10^{-6} mm Hg (temp N/A)	water = 86.7 ppb
2,4-D IPE (030066)	pale amber	liquid	b.p. 240 C	s.g. = 1.252 at 25 C	253.8 ± 44.4 (temp N/A)	5.3×10^{-6} mbar	water = 0.023 g/100 mL

[1] Data assembled from Agency memoranda and comprehensive review documents, including the 2,4-D Reregistration Standard.
[2] N/A = Not available.

C. Use Profile

2,4-D comes in multiple chemical forms and is found in numerous end-use products intended for use in a wide range of use patterns. 2,4-D is an ingredient in approximately 660 agricultural and home use products, as a sole active ingredient and in conjunction with other active ingredients. 2,4-D is formulated primarily as an amine salt in an aqueous solution or as an ester in an emulsifiable concentrate. Chemical forms covered by this risk assessment are as 2,4-D acid, 2,4-D DMAS, 2,4-D IPA, 2,4-D TIPA, 2,4-D EHE, 2,4-D BEE, 2,4-D DEA, 2,4-D IPE, and 2,4-D sodium salt. Copies of all labels may be found at http://www.cdpr.ca.gov/docs/epa/m2.htm. The following is information on the currently registered uses including an overview of use sites and application methods. A detailed table of the uses of 2,4-D eligible for reregistration is contained in Appendix A.

Type of Pesticide: Herbicide

Target organism(s): A wide variety of broadleaf weeds and aquatic weeds

Mode of action: 2,4-D is thought to increase cell-wall plasticity, biosynthesis of proteins and the production of ethylene. The abnormal increase in these processes is thought to result in uncontrolled cell division and growth which damages vascular tissue.

Use Sites: Table 3 presents a summary of the registered 2,4-D uses.

Use Classification: General use

Formulation Types: Formulation types registered include emulsifiable concentrate, granular, soluble concentrate/solid, water dispersible granules, and wettable powder.

Application Methods: 2,4-D may be applied with a wide range of application equipment including fixed-wing aircraft, backpack sprayer, band sprayer, boom sprayer, granule applicator, ground-directed sprayers, hand held sprayer, helicopter, injection equipment, tractor-mounted granule applicator, and tractor-mounted sprayers.

Application Rates: For 2,4-D, rates per application and rates per year are generally less than 1.5 pounds acid equivalent (ae) per acre per year and 2.0 pounds a.e. per acre per year (lbs ae/A), respectively. Maximum rates are 4.0 lbs ae/A per year for asparagus, forestry uses, and non-cropland uses, among others. The maximum rate for aquatic uses is 10.8 lbs ae/acre foot for submerged aquatic plants.

Application Timing: Timing of 2,4-D application can include at emergence, before bud break, during dormancy, to established plantings, foliar, post-emergence, pre-emergence, pre-harvest, and pre-plant.

Table 3. Registered 2,4-D Uses

Crop Grouping	Representative Crops
Terrestrial food crop	Pear, Pistachio, Stone fruits
Terrestrial food and feed crop	Agricultural fallow/idleland; Agricultural rights-of-way/fencerows/hedgerows; Agricultural uncultivated areas; Apple; Barley; Citrus fruits; Corn (unspecified);Corn, field; Corn, pop; Corn, sweet; Fruits (unspecified), Grapefruit, Lemon, Oats, Orange, Pome fruits, Rice, Rye, Small fruits, Soil, preplant/outdoor, Sorghum, Sorghum (unspecified), Soybeans (unspecified), Sugarcane, Tangelo, Tree nuts, Wheat
Terrestrial feed crop	Grass forage/fodder/hay, Pastures, Rangeland, Rye, Sorghum
Terrestrial non-food crop	Agricultural fallow/idleland, Agricultural rights-of-way/fencerows/hedgerows, Agricultural uncultivated areas, Airports/landing fields, Christmas tree plantations, Commercial/industrial lawns, Commercial/institutional/industrial, premises/equipment (outdoor), Forest nursery plantings (for transplant purposes), Golf course turf, Grasses grown for seed, Industrial areas (outdoor), Nonagricultural outdoor buildings/structures, Nonagricultural rights-of-way/fencerows/hedgerows, Nonagricultural uncultivated areas/soils, Ornamental and/or shade trees, Ornamental lawns and turf, Ornamental sod farm (turf), Ornamental woody shrubs and vines, Paved areas (private roads/sidewalks), Potting soil/topsoil, Recreation area lawns, Recreational areas, Soil, preplant/outdoor, Urban areas
Terrestrial non-food and outdoor residential	Fencerows/hedgerows, Nonagricultural rights-of-way/fencerows/hedgerows, Ornamental and/or shade trees, Ornamental lawns and turf, Ornamental woody shrubs and vines, Paths/patios, Paved areas (private roads/sidewalks), Urban areas
Aquatic food crop	Agricultural drainage systems, Aquatic areas/water, Commercial fishery water systems, Irrigation systems, Lakes/ponds/reservoirs (with human or wildlife use), Rice, Streams/rivers/channeled water, Swamps/marshes/wetlands/stagnant water
Aquatic non-food outdoor	Aquatic areas/water, Streams/rivers/channeled water, Swamps/marshes/wetlands/stagnant water
Aquatic non-food industrial	Drainage systems, Industrial waste disposal systems, Lakes/ponds/reservoirs (without human or wildlife use)
Forestry	Conifer release, Forest plantings (reforestation programs)(tree farms, tree plantations, etc.), Forest tree management/forest pest management, Forest trees (all or unspecified), Forest trees (hardwoods, broadleaf trees), Pine (forest/shelterbelt)
Outdoor residential	Residential lawns
Indoor non-food	Commercial transportation facilities-nonfeed/nonfood

D. Estimated Usage of Pesticide

Based primarily on pesticide usage information from 1992 through 2000 for agriculture and 1993 through 1999 for non-agriculture, total annual domestic usage of 2,4-D is approximately 46 million pounds, with 30 million pounds (66%) used by agriculture and 16 million pounds (34%) used by non-agriculture (see the OPP Biological and Economic Assessment Division [BEAD] quantitative use analysis [QUA] which is available on EPA's Pesticide Docket OPP-2004-0167 located at:

http://www.epa.gov/edockets). In terms of pounds, total 2,4-D usage is allocated mainly to pasture/rangeland (24%), lawn by homeowners with fertilizer (12%), spring wheat (8%), winter wheat (7%), lawn/garden by lawn care operators/landscape maintenance contractors (7%), lawn by homeowners alone (without fertilizer) (6%), field corn (6%), soybeans (4%), summer fallow (3%), hay other than alfalfa (3%), and roadways (3%).

Agricultural sites with at least 10% of U.S. acreage treated include spring wheat (51%), filberts (49%), sugarcane (36%), barley (36%), seed crops (29%), apples (20%), rye (16%), winter wheat (15%), cherries (15%), oats (15%), millet (15%), rice (13%), soybeans (12%) and pears (10%). For 2,4-D, rates per application and rates per year are generally less than 1.5 lbs ae/A per year and 2.0 lbs ae/A per year, respectively. 2,4-D is used predominantly in the Midwest, Great Plains, and Northwestern United States (Figure 1).

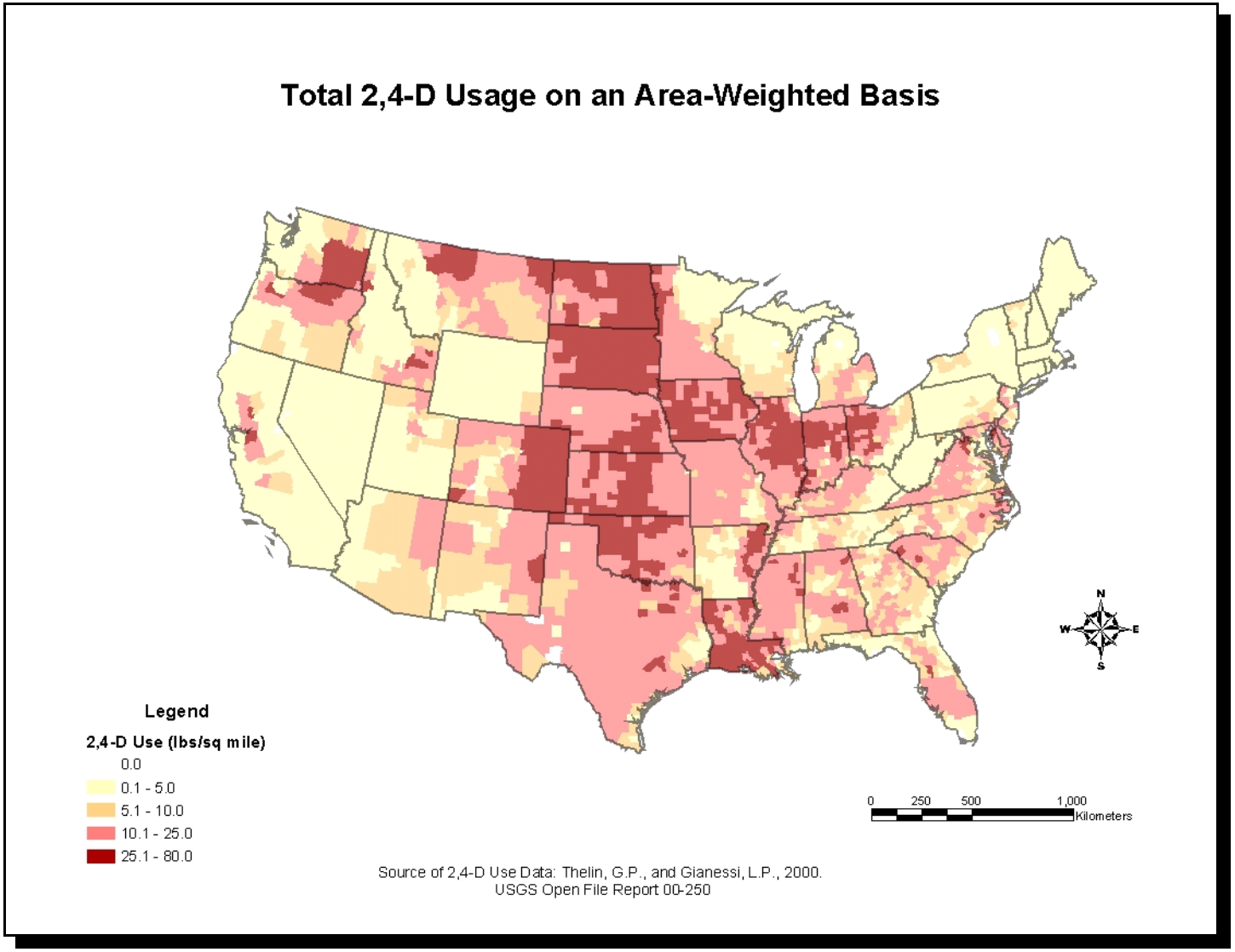


Figure 1. Estimated 2,4-D usage (lbs ae/square mile). The estimates are based on pesticide use rates compiled by the National Center for Food and Agricultural Policy (NCFAP) and modified by Thelin, G.P. and Gianessi, L.P., 2000 (USGS Open-File Report 00-250)

Application Rates, Timing and Frequency of Applications

The 2,4-D master label (available in EPA docket #OPP-2004-0167) has been developed by the 2,4-D Task Force and represents the maximum supported application rates for agricultural and non-agricultural uses. All end-use product manufacturers obtain 2,4-D starting material from companies represented by the 2,4-D Task Force. EPA used the master label rates in the 2,4-D human health and ecological risk assessments. Some master label rates are lower than the rates present on existing labels. The Agency and the task force have agreed that all of the 2,4-D labels will be updated with the new master label rates as part of the registration process. All of the registrants, including those that are not in the 2,4-D task force, will have to conform to the master label rates. The master label agreement is discussed in an internal Agency memo (EPA, March 18, 2003), which is available on EPA's Pesticide Docket OPP-2004-0167 located at: http://www.epa.gov/edockets.

Typically, one to three applications are made per growing season. Applications are made to the target weeds prior to crop emergence, after crop emergence, prior to harvest, and in the dormant season, depending upon the crop. The label required spray volumes for ground applications range from 0.0375 lbs ae/A for applications to low bush blueberries to 4.0 lbs ae/A for brush control. 2,4-D can be applied over the top to tolerant crops such as small grains and rice, but must be directed or shielded for the more sensitive crops such as fruits and berries.

The application rates on the master label are included in Table 4 for non-crop areas and Table 5 for agricultural crops. The average application rates from the 2,4-D QUA report (EPA BEAD 2001) are shown for comparison. With the exception of filberts, the QUA data indicate that only one application is made to most crops. The National Agricultural Pesticide Impact Assessment Program (NAPIAP) report on Phenoxy Herbicides indicates that on average one 2,4-D application is made annually to turfgrass.

Table 4. 2,4-D Application Rates for Non-Crop Areas

Aquatic Areas, Forestry, Non-Crop Areas and Turf	**Acid Equivalent lbs (ae) Application Rates Per Application/Per crop or Year**	
	Master Label	**Amount Used per QUA Report**
Aquatic Areas - Floating Weeds	2.0/4.0 per acre	512,000 lbs[A]
Aquatic Areas - Submerged Weeds	10.8 per acre foot	
Tree and Brush Control - Tree Injection	1 to 2 ml per inch of trunk diameter	136,000 lbs
Forestry - Weed and Brush Control	4.0/4.0 per acre	
Forestry - Conifer Release	4.0/4.0 per acre	
Irrigation Ditch Banks	2.0/4.0 per acre	
Rights of Way Areas	2.0/4.0 per acre	2.1 million lbs
Rangeland, Pastures	2.0/4.0 per acre	
Turf - Grass Grown for Seed or Sod	2.0/4.0 per acre	351,000 lbs

Aquatic Areas, Forestry, Non-Crop Areas and Turf	**Acid Equivalent lbs (ae) Application Rates Per Application/Per crop or Year**	
	Master Label	**Amount Used per QUA Report**
Turf - Ornamental	2.0/4.0 per acre [B]	11.6 million lbs
A. According to the NAPIAP report about 98,000 acres were treated for floating weeds and about 5,000 acres were treated for submerged weeds by state agencies in 1993. B. The registrants have agreed to reduce the ornamental turf rate from 2.0 to 1.5 lbs ae per acre. The new maximum yearly rate will be 3.0 lbs ae per acre.		

Table 5. 2,4-D Application Rates for Agricultural Crops

Agricultural Crops	Acid Equivalent lbs (ae) Application Rates per Acre Per Application/Per crop or Year	
	Master Label	Average Rate per QUA Report
Asparagus	2.0/4.0	1.1/1.3
Blueberries - Low Bush Wiper Bar	0.0375 lb/GA	0.46/0.51
Blueberries - High Bush	1.4/2.8	
Citrus (Growth Regulator)	0.1	No Data
Conifer Plantations	4.0/4.0	No Data
Corn (sweet) Corn (field and pop)	0.5 to 1.0/1.5 0.5 to 1.5/3.0	0.48/0.51 0.44/0.46
Cranberries - granular applications Cranberries - liquid applications	4.0/4.0 dormant season application 1.2/2.4 growing season application	1.8/2.0
Fallowland and Crop Stubble	2.0/4.0	0.69/0.89
Filberts	1.0 lb per 100 Ga/4 Apps per year	0.64/1.7
Grain Sorgum	0.5 to 1.0/1.0	0.46/0.50
Grapes	1.36/1.36	0.73/0.87
Orchard Floors (Pome and Stone Fruits, Tree Nuts)	2.0/4.0	Apples = 1.2/1.4 Pears = 1.1/1.5
Potatoes	0.07/0.14	0.10/0.17
Rice	1.0 or 1.5/1.5	0.92/0.94
Soybeans (Preplant burndown)	0.5 or 1.0/1.0	0.46/0.47
Strawberries (Except CA or FL)	1.5/1.5	1.2/1.3
Sugarcane	2.0/4.0	0.75/0.99
Cereal Grains (Wheat, Barley, Millet, Oats and Rye)	0.5 or 1.25/1.75	Wheat= 0.44/0.48 Barley =0.46/0.47 Oats = 0.46/0.46 Rye = 0.50/0.50 Millet= 0.44/0.44

Agricultural Crops	Acid Equivalent lbs (ae) Application Rates per Acre Per Application/Per crop or Year	
	Master Label	Average Rate per QUA Report
Wild Rice (MN only)	0.25/0.25	0.20/0.20

III. Summary of 2,4-D Risk Assessment

The following is a summary of EPA's human health and ecological risk findings and conclusions for 2,4-D, as presented fully in the documents "2,4-D. HED's Revised Human Health Risk Assessment for the Reregistration Eligibility Decision (RED) Revised to Reflect Public Comments" dated May 12, 2005, and the "Environmental Fate and Effects Division's Risk Assessment for the Reregistration Eligibility Decision for 2,4-D," dated October 28, 2004.

The purpose of this section is to summarize the key features and findings of the risk assessment in order to help the reader better understand the risk management decisions reached by the Agency. While the risk assessments and related addenda are not included in this document, they are available in the public docket OPP-2004-0167, and on the Agency's website at http://www.epa.gov/pesticides/reregistration/status.htm

A. Human Health Risk Assessment

EPA released its preliminary risk assessments for 2,4-D for public comment on June 23, 2004, thereby starting Phase 3 of a six phase public participation process. In response to comments received during Phase 3, the human health risk assessment was updated. EPA issued the revised risk assessments for 2,4-D for a second public comment period on January 12, 2005 (Phase 5 of the public participation process). The risk assessments were revised again in response to Phase 5 public comments, and are available for review.

The 2,4-D degradates detected in the various laboratory environmental fate studies were 1,2,4-benzenetriol, 2,4-dichlorophenol (2,4-DCP), 2,4-dichloroanisole (2,4-DCA), 4-chlorophenol, chlorohydroquinone (CHQ), volatile organics, bound residues, and carbon dioxide. The OPP Metabolism Assessment Review Committee (MARC) determined that all residues other than 2,4-D are not of risk concern due to low occurrence under environmental conditions, comparatively low toxicity, or a combination thereof. Therefore, the Agency assessed risks from 2,4-D *per se*.

1. Toxicity of 2,4-D

With very few exceptions, the effects and relative toxicities of the salt and ester forms of 2,4-D are quite similar to those of the acid form. Thus, the acid form was selected as being representative of all members of the 2,4-D reregistration case (Case No. 0073). The member chemicals in the 2,4-D case exhibit low to slight acute toxicity with the exception of the acid and salt forms being severe eye irritants. The Agency has reviewed all toxicity studies submitted for 2,4-D and has determined that the toxicological database is sufficient for reregistration. Further details on the toxicity of 2,4-D can be found in the technical support documents cited in Appendix C.

a. Toxicity Profile

Major features of the toxicology profile are presented below. In acute studies, 2,4-D generally has low acute toxicity (Toxicity Category III or IV) via the oral, dermal and inhalation routes of

exposure. 2,4-D is not a skin irritant (Toxicity Category III or IV), nor a skin sensitizer. Although the 2,4-D ester forms are not eye irritants (Toxicity Category III or IV), the acid and salt forms are considered to be severe eye irritants (Toxicity Category I). The acute toxicity of all 2,4-D forms is listed in Table 6.

Table 6. Acute Toxicity Data for 2,4-D acid, 2,4-D ester forms, and 2,4-D amine salts[1].

Guideline No.	Study Type	MRID Numbers	Results	Toxicity Category
870.1100	**Acute Oral**			
	2,4-D acid	00101605	rat LD_{50} = 639 mg/kg	III
	DEA salt	41920901	rat LD_{50} = 735 mg/kg	III
	DMA salt	00157512	rat LD_{50} = 949 mg/kg	III
	IPA salt	00252291	rat LD_{50} = 1646 mg/kg	III
	IPE ester	41709901	rat LD_{50} = 1250 mg/kg	III
	TIPA salt	41413501	rat LD_{50} = 1074 mg/kg	III
	BEE ester	40629801	rat LD_{50} = 866 mg/kg	III
	EHE ester	41209001	rat LD_{50} = 896 mg/kg	III
870.1200	**Acute Dermal**			
	2,4-D acid	00101596	rabbits LD_{50} >2000 mg/kg	III
	DEA salt	41920911	rabbits LD_{50} >2000 mg/kg	III
	DMA salt	00157513	rabbit LD_{50} 1829 mg/kg	III
	IPA salt	00252291	rabbits LD_{50} >2000 mg/kg	III
	IPE ester	41709902	rabbits LD_{50} >2000 mg/kg	III
	TIPA salt	41413502	rabbits LD_{50} >2000 mg/kg	III
	BEE ester	40629802	rabbits LD_{50} >2000 mg/kg	III
	EHE ester	41209002	rabbits LD_{50} >2000 mg/kg	III
870.1300	**Acute Inhalation**			
	2,4-D acid	00161660	rat LC_{50} >1.79 mg/L	III
	DEA salt	41986601	rat LC_{50} >3.5 mg/L	IV
	DMA salt	00157514	rat LC_{50} >3.5 mg/L	IV
	IPA salt	40085501	rat LC_{50} =3.1 mg/L	IV
	IPE ester	40352701	rat LC_{50} >4.97 mg/L	IV
	TIPA salt	41957601	rat LC_{50} =0.78 mg/L	III
	BEE ester	40629803	rat LC_{50} =4.6 mg/L	IV
	EHE ester	42605202	rat LC_{50} >5.4 mg/L	IV
870.2400	**Primary Eye Irritation**			
	2,4-D acid	41125302	severe eye irritant	I
	DEA salt	41920902	severe eye irritant	I
	DMA salt	00157515	severe eye irritant	I
	IPA salt	00252291	severe eye irritant	I
	IP ester	40352702	not an eye irritant	IV
	TIPA salt	41413504	severe eye irritant	I
	BEE ester	40629804	not an eye irritant	III
	EHE ester	44725303	not an eye irritant	III
870.2500	**Primary Skin Irritation**			
	2,4-D acid	42232701	unacceptable	N/A
	DEA salt	41920903	slight skin irritant	III
	DMA salt	00157516	slight skin irritant	IV
	IPA salt	00252291	slight skin irritant	IV
	IPE ester	40352703	slight skin irritant	IV
	TIPA salt	41413505	slight skin irritant	IV
	BEE ester	40629805	very mild irritant	IV
	EHE ester	41413505	not a skin irritant	IV

Guideline No.	Study Type	MRID Numbers	Results	Toxicity Category
870.2600	**Dermal Sensitization**			
	2,4-D acid	00161659	not a dermal sensitizer	N/A
	DEA salt	41920904	not a dermal sensitizer	
	DMA salt	41642805	unacceptable	
	IPA salt	41233701	unacceptable	
	IPE ester	40352704	not a dermal sensitizer	
	TIPA salt	41413506	not a dermal sensitizer	
	BEE ester	40629806	not a dermal sensitizer	
	EHE ester	41209006	unacceptable	

1. The technical acute toxicity values included in this document are for informational purposes only. The data supporting these values will be evaluated during reregistration and may or may not meet the current Agency acceptance criteria.

The mechanisms responsible for renal clearance of 2,4-D have been investigated in several species. 2,4-D is actively secreted by the proximal tubules. This mechanism of renal clearance is consistent with results seen with other phenoxy acids. It has been suggested that observed dose-dependent, non-linear, pharmacokinetics of 2,4-D are primarily due to the saturation of this renal secretory transport system. Due to a limited capacity to excrete organic acids, the dog is more sensitive to the effects of 2,4-D than the rat with respect to repeated dosing.

In laboratory animals, following subchronic, oral exposure at dose levels of 2,4-D above the threshold of saturation for renal clearance, the primary target organs are the eye, thyroid, kidney, adrenals, and ovaries/testes. Changes in these organs are also observed following exposure to the amine salts and esters of 2,4-D. Systemic toxicity was not observed following repeated dermal exposure to 2,4-D, EHE, and TIPA at or above the limit dose or following repeated dermal exposure to BEE and IPA at the highest dose tested. Liver toxicity was observed following repeated high-dose dermal exposure to DEA, and one death occurred following repeated high-dose dermal exposure to DMA.

There are no repeat-dose inhalation exposure data available on 2,4-D. The most reliable way to characterize inhalation toxicity and to quantify inhalation risk is through the use of inhalation toxicity studies. In general, chemicals tend to be more toxic by the inhalation route than by the oral route due to rapid absorption and distribution, bypassing of the liver's metabolic protection (portal circulation), and potentially serious portal-of-entry effects, such as irritation, edema, cellular transformation, degeneration, and necrosis. An inhalation risk assessment that is based on oral data generally underestimates the inhalation risk because it cannot account for these factors. However, in the case of 2,4-D, based on the limited metabolism of 2,4-D *via* the oral route, the moiety to which the body would be exposed would be the same for both routes of exposure. With regard to portal-of-entry effects, these can only be assessed in an inhalation study. Therefore, a subchronic (28-day) inhalation study is required for 2,4-D.

Developmental toxicity, characterized mainly as an increased incidence of skeletal abnormalities in the rat, was observed following exposure to 2,4-D and its amine salts and esters at dose levels that were at or above the threshold of saturation of renal clearance. Similarly, developmental toxicity was observed in the rabbit only following exposure to 2,4-D (abortions) and DEA (increased number of litters with fetuses having 7th cervical ribs) at or above the threshold of

renal clearance.

Reproductive toxicity, characterized as an increase in gestation length, was observed following exposure to 2,4-D at a dose level above the threshold of saturation of renal clearance. A repeat 2-generation reproduction study (using the revised EPA protocol) is required to address concerns for endocrine disruption.

Neurotoxicity was demonstrated following exposure to 2,4-D at relatively high dose levels. Clinical signs of neurotoxicity (ataxia, decreased motor activity, myotonia, prostration, lateral recumbency, impaired/loss of the righting reflex, and skin cold to the touch) were observed in pregnant rabbits following exposure to 2,4-D and its amine salts and esters. Neuropathology (retinal degeneration) was observed following 2,4-D exposure in several studies in female rats. Incoordination and slight gait abnormalities (forepaw flexing or knuckling) were observed following acute dosing and increased forelimb grip strength was observed following chronic exposure to 2,4-D at dose levels that exceeded the threshold of saturation of renal clearance. A developmental neurotoxicity study in the rat is required for 2,4-D.

2,4-D is classified as a Group D chemical (not classifiable as to human carcinogenicity). Based on the overall pattern of responses observed in both *in vitro* and *in vivo* genotoxicity tests, 2,4-D was not mutagenic, although some cytogenic effects were observed. 2,4-D acid is currently considered to be representative of all nine member chemicals of the 2,4-D case.

The toxicological endpoints that were used to complete the risk assessments are summarized in Table 7. These endpoints were selected by the Agency from animal studies. With respect to dermal exposures, the Agency previously selected a dermal absorption factor of 5.8 percent based on the average absorbed dose value from a human dermal absorption study. That factor (5.8 percent) was used in previous versions of the human health risk assessment. Based on comments received during the Phase 5 comment period, the dermal absorption study and resulting absorption factor were reconsidered. In order to account for the variability observed in the dermal absorption study, the dermal absorption factor was changed from 5.8 percent to 10 percent. In their "Re-evaluation of the Lawn and Turf Uses of 2,4-D," which was made available to the public for review, Health Canada also selected a factor of 10 percent based upon the weight of evidence from several published studies, taking into account the variability in the data and the limitations of the various studies. These studies include the Feldman and Maibach study discussed above and studies from Harris and Solomon 1992, Moody et. al. 1990, Wester et. al. 1996, and Pelletier et al. 1988.

b. Safety and Database Uncertainty Factors

The Food Quality Protection Act (FQPA) directs the Agency to use an additional tenfold (10X) safety factor to protect for special sensitivity of infants and children to specific pesticide residues in food, drinking water, or residential exposures, or to compensate for an incomplete database. FQPA authorizes the Agency to modify the tenfold safety factor only if reliable data demonstrate that another factor would be appropriate.

FQPA Special Safety Factor. After evaluating hazard and exposure data for 2,4-D, EPA

removed the default 10X FQPA special safety factor. The toxicity database for 2,4-D includes acceptable developmental and reproductive toxicity studies. Developmental toxicity studies were conducted in both rats and rabbits for most 2,4-D forms. There is qualitative evidence of susceptibility in the rat developmental toxicity study with 2,4-D acid and DEA salt where fetal effects (skeletal abnormalities) were observed at a dose level that produced less severe maternal toxicity (decreased body-weight gain and food consumption). There is no evidence of increased (quantitative or qualitative) susceptibility in the prenatal developmental toxicity study in rabbits or in the 2-generation reproduction study in rats on 2,4-D. Regarding the 2,4-D amine salt and ester forms, no evidence of increased susceptibility (quantitative or qualitative) was observed in the prenatal developmental toxicity study in rats and rabbits (except for 2,4-D DEA) dosed with any of the amine salts or esters of 2,4-D. There is evidence of increased susceptibility (qualitative) in the prenatal developmental study in rabbits for 2,4-D DEA salt.

After establishing developmental toxicity endpoints to be used in the risk assessment with traditional uncertainty factors (10x for interspecies variability and 10x for intraspecies variability), the Agency has no residual concerns for the effects seen in the developmental toxicity studies. Therefore, the 10X FQPA special safety factor was reduced to 1X.

Database Uncertainty Factor. On April 8, 2003, based on the weight of evidence presented, the Agency reaffirmed the previous conclusion that a developmental neurotoxicity (DNT) study in rats is required for 2,4-D because there is a concern for developmental neurotoxicity resulting from exposure to 2,4-D. There is evidence of neurotoxicity, including clinical signs such as ataxia and decreased motor activity in pregnant rabbits following dosing during gestation days 6-15 in studies on 2,4-D itself and 2,4-D amine salts and esters, and tremors in dogs that died on test following repeat exposure to 2,4-D. Incoordination and slight gait abnormalities (forepaw flexing or knuckling) were also observed following dosing in the acute neurotoxicity study with 2,4-D. There is also evidence of developmental toxicity, as discussed above in the FQPA Special Safety Factor section. In addition, the Agency determined that a repeat 2-generation reproduction study using the new protocol is required to address specific concerns for endocrine disruption (thyroid and immunotoxicity measures). Therefore, the Agency determined that a 10X database uncertainty factor (UF_{DB}) is needed to account for the lack of these studies.

c. Carcinogenicity

A Science Advisory Board/Scientific Advisory Panel Special Joint Committee reviewed available epidemiological and other data on 2,4-D in 1992 and concluded that "the data are not sufficient to conclude that there is a cause and effect relationship between exposure to 2,4-D and non-Hodgkin's lymphoma." 2,4-D has been classified as a Category D chemical (i.e., not classifiable as to human carcinogenicity), by the EPA/OPP Cancer Peer Review Committee in 1996. The Agency requested further histopathological examinations of rat brain tissues and mouse spleen tissues in question. These exams were submitted and reviewed and on March 16, 1999, the Agency notified the 2,4-D Task Force that the Agency would continue to classify 2,4-D as a Group D carcinogen.

The Agency has twice recently reviewed epidemiological studies linking cancer to 2,4-D. In the first review, completed January 14, 2004, EPA concluded there is no additional evidence that

would implicate 2,4-D as a cause of cancer (EPA, 2004). The second review of available epidemiological studies occurred in response to comments received during the Phase 3 Public Comment Period for the 2,4-D RED. This report, dated December 8, 2004 and authored by EPA Scientist Jerry Blondell, Ph.D., found that none of the more recent epidemiological studies definitively linked human cancer cases to 2,4-D.

2,4-D Diethanolamine (DEA). The Agency recently reviewed the available toxicology data on diethanolamine (DEA) and related compounds. The Agency concluded that it was not likely that exposure to the DEA salt of 2,4-D resulting from occupational use would pose a carcinogenic risk to humans. While liver tumors were observed in mice following dermal exposure to DEA, there was no evidence of carcinogenicity in rats following dermal exposure, and there was no evidence of a genotoxic or mutagenic concern. Although no formal assessment has been performed on the proposed mode of action (choline deficiency), this mode of action was considered plausible for the mouse hepatocellular tumors observed following dermal exposure to DEA, as were other confounding factors, including the use of ethanol as a vehicle for dose administration and the fact that humans are generally refractive to choline deficiency. Additionally, the low use pattern for 2,4-D DEA indicates that there is no potential long-term dermal exposure to the diethanolamine salt of 2,4-D in agricultural uses. The Agency also determined that, at this time, no carcinogenicity studies are required for the DEA salt of 2,4-D.

d. Cumulative Assessment

FQPA requires EPA to consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity" when considering whether to establish, modify, or revoke a tolerance. Potential cumulative effects of chemicals with a common mechanism of toxicity are considered because low-level exposures to multiple chemicals causing a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any one of these individual chemicals. 2,4-D is a member of the alkylphenoxy herbicide class of pesticides. A cumulative risk assessment has not been performed as part of this human health risk assessment because the Agency has not yet made a determination whether or not phenoxy herbicides have a common mechanism of toxicity. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by the EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/

e. Endocrine Effects

EPA is required under the Federal Food, Drug, and Cosmetic Act (FDCA), as amended by the Food Quality Protection Act (FQPA), to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate."

When the appropriate screening and/or testing protocols being considered under the Agency's Endocrine Disruption Screening Program (EDSP) have been developed, 2,4-D may be subject to additional screening and/or testing to better characterize effects related to endocrine disruption.

Based on currently available toxicity data, which demonstrate effects on the thyroid and gonads following exposure to 2,4-D, there is concern regarding its endocrine disruption potential. There have been no studies on 2,4-D that specifically assess its endocrine disruption potential. The Agency has determined that a repeat 2-generation reproduction study using the most recent protocol is required to address both the concern for thyroid effects (comparative assessment between the young and adult animals) and immunotoxicity, as well as a more thorough assessment of the gonads and reproductive/developmental endpoints.

f. Toxicological Endpoints for Risk Assessment

The toxicological endpoints used in the human health risk assessment for 2,4-D are listed in Table 7. The safety factors used to account for interspecies extrapolation, intraspecies variability, special susceptibility of infants and children, and database uncertainties are also described in Table 7 below. This table also describes any absorption factors used to extrapolate from one route of exposure to another (e.g., oral to dermal).

Table 7. Toxicity Endpoints for Human Health Risk Assessment for 2,4-D

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF and Level of Concern for Risk Assessment	Study and Toxicological Effects
Dietary Exposures			
Acute Dietary (Females 13-49 years of age) MRID 00130407, 00130408	NOAEL = 25 mg/kg/day UF = 1000 **Acute RfD** = 0.025 mg/kg/day	FQPA SF = 1X **aPAD** = acute RfD(0.025) / FQPA SF (1) = 0.025 mg/kg/day	Rat Developmental Toxicity Study, LOAEL = 75 mg/kg/day based on skeletal abnormalities
Acute Dietary (General population including infants and children) MRID 43115201	NOAEL = 67 mg/kg/day UF = 1000 **Acute RfD** = 0.067 mg/kg/day	FQPA SF = 1X **aPAD** = acute RfD (0.067) / FQPA SF (1) = 0.067mg/kg/day	Acute Neurotoxicity Study in Rats LOAEL = 227 mg/kg/day based on gait abnormalities
Chronic Dietary (All populations) MRID 43612001	NOAEL= 5 mg/kg/day UF = 1000 **Chronic RfD** = 0.005 mg/kg/day	FQPA SF = 1X **cPAD** = chronic RfD (0.005) / FQPA SF (1) = 0.005 mg/kg/day	Rat Chronic Toxicity Study LOAEL = 75 mg/kg/day based on decreased body-weight gain (females) and food consumption (females), alterations in hematology , and clinical chemistry parameters, decreased T4 (both sexes), glucose (females), cholesterol (both sexes), and triglycerides (females).
Occupational and Residential Non-Dietary Exposures			

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF and Level of Concern for Risk Assessment	Study and Toxicological Effects
Short-Term Incidental Oral (1-30 days) MRID 00130407, 00130408	NOAEL= 25 mg/kg/day	**Residential** LOC for MOE =1000 **Occupational** = NA	Rat developmental toxicity study LOAEL = 75 mg/kg/day based on decreased maternal body-weight gain
Intermediate-Term Incidental Oral (1-6 months) MRID 41991501	NOAEL = 15 mg/kg/day	**Residential** LOC for MOE = 1000 **Occupational** = NA	Rat Subchronic Oral Toxicity LOAEL = 100 mg/kg/day based on decreased body weight/body-weight gain, alterations in some hematology, and clinical chemistry parameters, and cataract formation.
Short-Term Dermal* MRID 00130407, 00130408	Oral study NOAEL= 25 mg/kg/day	**Residential** LOC for MOE = 1000 **Occupational** LOC for MOE = 100	Rat Developmental Toxicity Study LOAEL = 75 mg/kg/day based on decreased maternal body-weight gain and skeletal abnormalities
Intermediate-Term Dermal* MRID 00130407, 00130408	Oral study NOAEL = 15 mg/kg/day		Rat Subchronic Oral Toxicity (same as for intermediate-term incidental oral)
Long-Term Dermal* MRID 43612001	Oral study NOAEL= 5 mg/kg/day		Rat Chronic Toxicity Study (same as for chronic dietary)
Short-Term Inhalation* MRID 00130407, 00130408	Oral study NOAEL= 25 mg/kg/day		Rat Developmental Toxicity Study (same as for short-term dermal)
Intermediate-Term Inhalation* MRID 00130407, 00130408	Oral study NOAEL = 15 mg/kg/day		Rat Subchronic Oral Toxicity (same as intermediate-term incidental oral)
Long-Term Inhalation* MRID 43612001	Oral study NOAEL= **5** mg/kg/day		Rat Chronic Toxicity Study (same as for chronic dietary)
Cancer	**Classification**: Group D [not classifiable as to human carcinogenicity]		

The dermal absorption factor is 10 percent and the inhalation absorption factor is 100 percent.

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic), RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable

Dermal Absorption. A dermal absorption study utilizing human volunteers is available. Excretion following dermal application was 5.8 ± 2.4 percent (mean ± S.D.) of the administered dose and after intravenous administration was 100 ± 2.5 percent. The Agency previously selected a dermal

absorption factor of 5.8 percent based on the human dermal absorption study. This factor was used in previous versions of this risk assessment. Based on comments received during the Phase 5 comment period, this dermal absorption study and factor were reconsidered. In order to account for the variability observed in the dermal absorption study, the dermal absorption factor was changed from 5.8 percent to 10 percent. In their "Re-evaluation of the Lawn and Turf Uses of 2,4-D," which was made available to the public, Health Canada also selected a factor of 10 percent based upon the weight of evidence from several published studies, taking into account the variability in the data and the limitations of the various studies. These studies include the Feldman and Maibach study discussed above and studies from Harris and Solomon 1992, Moody et. al. 1990, Wester et. al. 1996, and Pelletier et al. 1988.

2. Dietary Exposure and Risk from Food

a. Exposure Assumptions

Acute and chronic dietary exposure and risk analyses for 2,4-D were conducted using the Lifeline ™ Model Version 2.0 and Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 1.33). DEEM incorporates consumption data from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. Lifeline ™ uses food consumption data from the United States Department of Agriculture's (USDA's) Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. Lifeline™ uses recipe files contained within the program to relate raw agricultural commodities (RACs) to foods "as-eaten." Lifeline™ converts the RAC residues into food residues by randomly selecting a RAC residue value from the "user defined" residue distribution (created from the residue, percent crop treated, and processing factors data), and calculating a net residue for that food based on the ingredients' mass contribution to that food item.

Lifeline™ models the individual's dietary exposures over a season by selecting a new CSFII diary each day from a set of similar individuals based on age and season attributes. Lifeline™ groups CSFII diaries based on the respondent's age and the season during which the food diary was recorded. Based on analysis of the 1994-96, and 1998 CSFII consumption data, which took into account dietary patterns and survey respondents, the Agency concluded that it is most appropriate to report risk for the following population subgroups: the general U.S. population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youths 13-19, adults 20-49, females 13-49, and adults 50+ years old. The most highly exposed population subgroup for 2,4-D using both DEEM and Lifeline was children 1-2 years of age.

The acute dietary assessment was only slightly refined as the following assumptions were made: tolerance-level exposure values for most commodities, the highest field trial residue value for citrus commodities, and 100% crop treated (%CT). Note that half of the average level of detection (LOD) from the United States Department of Agriculture (USDA) Pesticide Data Program (PDP) monitoring data was used as the milk residue value because no milk sample contained detectable 2,4-D residues over several years of PDP sampling.

The chronic dietary assessment was moderately refined, making use of the following assumptions: tolerance-level exposure values for most commodities; averages of field trial data and processing study factors for small grains, citrus, and sugarcane sugar and molasses; %CT information for all commodities; and the MCL (70 ppb) as well as the highest observed groundwater monitoring concentration (15 ppb) for drinking water in a forward calculation. As in the case of the acute assessment, half of the average LOD from PDP monitoring data was used for milk.

b. Population Adjusted Dose

A population adjusted dose, or PAD, is the reference dose (RfD) adjusted for the FQPA safety factor. A risk estimate that is less than 100% of the acute PAD (aPAD), the dose at which an individual could be exposed over the course of a single day and no adverse health effects would be expected, does not exceed EPA's level of concern. Likewise, a risk estimate that is less than 100% of the chronic PAD (cPAD), the dose at which an individual could be exposed over the course of a lifetime and no adverse health effects would be expected, does not exceed EPA's level of concern.

In the case of 2,4-D , the FQPA SF has been removed (equivalent to a factor of 1x), so the acute or chronic RfD is identical to the respective aPAD or cPAD. In addition, an uncertainty factor is determined for each chemical. In the acute and chronic dietary risk assessments for 2,4-D, the total uncertainty factor (UF) is 1000x; 10x for interspecies variability, 10x for intraspecies variability, and 10x for database uncertainty.

c. Food Risk Estimates

Acute: Risk to the general U.S. population was 18% and 17% of the aPAD using both DEEM and Lifeline, respectively. The most highly exposed population subgroup using both DEEM and Lifeline was children 1-2 years of age; risks were 33% and 32% of the aPAD, respectively. Risk to females 13-49 years of age was 31% of the aPAD using DEEM and 42% of the aPAD using Lifeline; these higher calculated risks for women of child-bearing age are due to the 2.7x lower toxicological point of departure for developmental effects applicable to Females 13-49 years of age. These acute dietary (food) risks are all less than the Agency's level of concern (100% of the aPAD).

Chronic: Risk to the general U.S. population was 4.1% and 3.8% of the cPAD, using DEEM and Lifeline, respectively. Risk to children 1-2 years of age, the most highly exposed population subgroup, was 8.5% of the cPAD using DEEM and Lifeline.

3. Dietary Exposure and Risk from Drinking Water

Drinking water exposure to pesticides can occur through surface and ground water contamination. EPA considers acute (one day) and chronic (lifetime) drinking water risks and uses either modeling or monitoring data, if available and of sufficient quality, to estimate those exposures. In assessing drinking water risks, EPA compares model results to concentrations that would be acceptable in drinking water from a human health perspective (e.g., DWLOCs). If the estimated drinking water concentrations (EDWCs) in water are less than the DWLOCs, EPA does not have

concern from consuming drinking water. If the EDWCs are greater than DWLOCs, EPA will conduct further analysis to characterize the potential dietary risk from drinking water. Risks from exposure to 2,4-D in drinking water are further discussed in the section III.A.5.

2,4-D is an herbicide used in a wide variety of environments. As the major route of degradation is aerobic microbial metabolism, 2,4-D is non-persistent ($t_{1/2}$=6.2 days) in terrestrial (aerobic) environments, moderately persistent ($t_{1/2}$=45 days) in aerobic aquatic environments, and highly persistent ($t_{1/2}$= 231 days) in anaerobic terrestrial and aquatic environments. Because 2,4-D will be anionic ($X\text{-}COO^- H^+$) under most environmental conditions, it is expected to be mobile (K_{oc}=61.7) in soil and aquatic environments.

The 2,4-D degradates detected in the various laboratory environmental fate studies were 1,2,4-benzenetriol, 2,4-dichlorophenol (2,4-DCP), 2,4-dichloroanisole (2,4-DCA), 4-chlorophenol, chlorohydroquinone (CHQ), volatile organics, bound residues, and carbon dioxide. The Agency has determined that residues other than 2,4-D are not of risk concern due to low occurrence under environmental conditions, comparatively low toxicity, or a combination thereof.

Estimated Environmental Concentrations (EEC) were derived through an evaluation of monitoring data and modeling. A number of different scenarios were assessed and EECs provided for each. Scenarios evaluated included the direct application of 2,4-D to water bodies for aquatic weed control, a rice use scenario, and terrestrial uses including food and nonfood uses.

a. Surface Water

Modeling: The Tier II screening models, Pesticide Root Zone Model and Exposure Analysis Modeling System (PRZM-EXAMS),with the Index Reservoir and Percent Crop Area adjustment (IR-PCA PRZM/EXAMS) were used to estimate 2,4-D residues in surface water used for drinking water.

The Index Reservoir represents a watershed that is more vulnerable than most watersheds used as drinking water sources. It was developed from a watershed in western Illinois that has been used for drinking water purposes. The Index Reservoir is used as a standard watershed that, in combination with local soils types, weather conditions, and cropping practices, represents a vulnerable watershed that could support a drinking water supply.

For terrestrial uses of 2,4-D, EECs were calculated from aquatic exposure modeling using PRZM/EXAMS with the Index Reservoir and a percent crop area treated (PCA) adjustment (Tier II). Fifteen scenarios were chosen for aquatic exposure modeling, including sugarcane in Florida; turf in Florida and Pennsylvania; spring wheat in North Dakota; winter wheat in Oregon; corn in Illinois and California; sorghum in Kansas and Texas; soybean in Mississippi; pasture in North Carolina; apples in North Carolina, Oregon, and Pennsylvania; and filberts in Oregon. Although this only represents a portion of the crops for which 2,4-D has a labeled use, it does represent crops with higher application rates and crops which have a large percentage of their total acreage treated with 2,4-D.

Surface water concentrations were modeled using PRZM version 3.12 and EXAMS version

2.98.04. Ground water concentrations were modeled using SCIGROW version 2.2. The 15 crop scenarios listed above were modeled using PRZM/EXAMS. Based on the maximum modeled values, (more specifically, the North Carolina apple model scenario), the model-estimated, surface-water-derived drinking water concentrations for the use of 2,4-D are:

118 ug/L for the 1 in 10 year annual peak concentration (acute)
64 ug/L for the 1 in 10 year 90-day average
23 ug/L for the 1 in 10 year annual mean concentration (chronic)

Monitoring: Monitoring data considered in the assessment were the United States Geological Survey's (USGS) National Water Quality Assessment Program (NAWQA) groundwater and surface water database, USGS/EPA reservoir monitoring database, National Drinking Water Contaminant Occurrence Database (NCOD), and US EPA's Storage and Retrieval environmental data system (STORET). Review of these databases was conducted to provide peak and median concentrations. Additionally, the quality of data was evaluated for targeting pesticide use areas, detection limits, and analytical recoveries. The monitoring data indicate that 2,4-D is detected in groundwater and surface water. Also, 2,4-D is detected in finished drinking water. Maximum concentrations of 2,4-D in surface source water and ambient groundwater are 58 ug/L and 14.8 ug/L, respectively. The highest median 2,4-D concentration of 1.18 ug/L was derived from finished water samples in the NCOD database. The highest time weighted annual mean (TWAM) concentration was 1.45 ug/L from the NAWQA database containing nontargeted data reflecting pesticide concentrations in flowing water as opposed to more stationary bodies of water such as ponds, lakes, and reservoirs.

The PRZM/EXAMS surface water-derived drinking water model estimate that would be appropriate for acute exposure (118 ug/L) is approximately two times the peak concentration of 58 ug/L detected in the surface water monitoring data evaluated as part of this assessment. However, since 70 ug/l is the current maximum contaminant level (MCL) established under the Safe Drinking Water Act, and is the label-prescribed 2,4-D concentration in treated water to be used for drinking water, this MCL limit is a reasonable and practical value to be used for the surface water concentration of 2,4-D for acute risk assessment purposes.

Note that the peak surface water concentration of 58 ug/L is consistent with the 70-ppb label instruction (also the MCL). Although the surface water monitoring was not specifically targeted to known 2,4-D- treated sites or even areas of high 2,4-D usage, this agreement suggests that, from a practical standpoint, the MCL is a reasonable regulatory limit.

Although of high quality, the available monitoring data is not targeted to 2,4-D use. However, the data provide context to model results and indicate that there is little evidence that concentrations are likely to be found exceeding these levels.

b. Ground Water

Monitoring: The maximum 2,4-D concentration detected in ground water is 14.89 ug/L based on the USGS NAWQA program and 8 ug/L based on the NCOD monitoring data. The next highest

concentration detected in the NAWQA groundwater data is 4.54 ug/L which is consistent with the NCOD-reported concentration. Therefore, the Agency is using 15 ug/L based on monitoring for the groundwater EDWC.

c. EDWCs Selected for Risk Assessment

The EDWCs for 2,4-D in surface and ground water are listed in Table 8 below. The EDWCs were selected from both modeling calculations and monitoring data.

Table 8. Surface and Ground Water Estimated Drinking Water Concentrations (EDWCs)

Drinking Water Source	Duration	EDWC (ppb) (ppb = ug/liter)	Data Source
Surface Water	Acute (Peak)	70 ug/liter (aquatic applications)	Maximum Contaminant Level (MCL)
		118 ug/liter (terrestrial applications)	Modeling - PRZM-EXAMS (NC apple scenario)
	Short and Intermediate	70 ug/liter (aquatic applications)	Maximum Contaminant Level (MCL)
		64 ug/liter (terrestrial applications)	Modeling - PRZM-EXAMS (NC apple 1 in 10 year annual average)
	Chronic	11 ug/liter (aquatic application)	Modeling - Dissipation modeling of aquatic application
		23 ug/liter (terrestrial application)	Modeling - PRZM-EXAMS worst case terrestrial use (NC apple scenario)
		1.5 ug/liter (terrestrial application)	Monitoring - Maximum time weighted annual mean from NAWQA database
Ground Water	All Duration	15 ug/liter	Monitoring - Highest monitored value from NAWQA database

4. Residential and Other Non-occupational Exposure

Residential exposure assessment considers all potential pesticide exposure, other than exposure due to residues in foods or in drinking water. Exposure may occur during and after application on lawns and turf, golf courses, parks, cemeteries, and other grass areas. Exposure may also occur to recreational swimmers while swimming in waters treated with 2,4-D for aquatic weeds. Each route

of exposure (oral, dermal, inhalation) is assessed, where appropriate, and risk is expressed as a Margin of Exposure (MOE), which is the ratio of estimated exposure to an appropriate NOAEL. 2,4-D products are marketed for homeowner use on residential lawns and turf. 2,4-D containing products are also marketed for use by professional applicators on residential turf, golf courses, and on other turf such as recreational or commercial areas. Based on these uses, 2,4-D has been assessed for the residential mixing/loading/applicator (or "handler") exposure for applications by homeowners to home lawns. For post-application exposure, 2,4-D has been assessed for toddlers playing on treated turf, adults performing yardwork on treated turf, adults playing golf on treated turf, and children and adults swimming in bodies of water treated with 2,4-D for aquatic weed control.

a. Toxicity

The toxicological endpoints, and associated uncertainty factors used for assessing the non-dietary risks for 2,4-D are listed in Table 9.

In a dermal absorption study utilizing human volunteers, excretion following dermal application was 5.8 ± 2.4% and after i.v. administration was 100 ± 2.5%. In previous risk assessments, the Agency selected a dermal absorption factor of 5.8 percent based on the human dermal absorption study. Based on comments received during the Phase 5 comment period, this dermal absorption study and factor were reconsidered. In order to account for the variability observed in the dermal absorption study, the dermal absorption factor was changed from 5.8 percent to 10 percent. In their "Re-evaluation of the Lawn and Turf Uses of 2,4-D," which was made available to the public, Health Canada also selected a factor of 10 percent based upon the weight of evidence from several published studies, taking into account the variability in the data and the limitations of the various studies. These studies include the Feldman and Maibach study discussed above and studies from Harris and Solomon 1992, Moody et. al. 1990, Wester et. al. 1996, and Pelletier et al. 1988.

Chronic endpoints were not used in the residential assessment because chronic occupational and residential exposures to 2,4-D are not expected to occur. Per the 2,4-D Master Label, the maximum label frequency for application of 2,4-D to turf is two times per year. 2,4-D also rapidly dissipates from foliage and is readily excreted from the human body.

A MOE greater than or equal to 1000 is considered adequately protective for the residential exposure assessment. The MOE of 1000 includes 10x for interspecies extrapolation, 10x for intraspecies variation, and 10x for a database uncertainty factor. Table 9 lists the toxicity endpoints selected for assessing residential risk for 2,4-D.

Table 9. Toxicity Endpoints Selected for Assessing Residential Risk for 2,4-D

Exposure Scenario	Dose Used in Risk Assessment, UF	Level of Concern for Risk Assessment	Study and Toxicological Effects
Occupational and Residential Non-Dietary Exposures			

Exposure Scenario	Dose Used in Risk Assessment, UF	Level of Concern for Risk Assessment	Study and Toxicological Effects
Short-Term Incidental Oral (1-30 days) MRID 00130407, 00130408	NOAEL= 25 mg/kg/day UF_{DB} = 10	**Residential** LOC for MOE =1000 **Occupational** = NA	rat developmental toxicity study LOAEL = 75 mg/kg/day based on decreased maternal body-weight gain
Intermediate-Term Incidental Oral (1- 6 months) MRID 41991501	NOAEL = 15 mg/kg/day	**Residential** LOC for MOE = 1000 **Occupational** = NA	subchronic oral toxicity - rat LOAEL = 100 mg/kg/day based on decreased body weight/body-weight gain, alterations in some hematology, and clinical chemistry parameters, and cataract formation.
Short-Term Dermal* MRID 00130407, 00130408	Oral study NOAEL= 25 mg/kg/day	**Residential** LOC for MOE = 1000 **Occupational** LOC for MOE = 100	rat developmental toxicity study LOAEL = 75 mg/kg/day based on decreased maternal body-weight gain and skeletal abnormalities
Intermediate-Term Dermal* MRID 00130407, 00130408	Oral study NOAEL = 15 mg/kg/day		subchronic oral toxicity - rat (same as for incidental oral)
Long-Term Dermal* MRID 43612001	Oral study NOAEL= 5 mg/kg/day		rat chronic toxicity study (same as for chronic dietary)
Short-Term Inhalation* MRID 00130407, 00130408	Oral study NOAEL= 25 mg/kg/day		rat developmental toxicity study (same as for short-term dermal)
Intermediate-Term Inhalation* MRID 00130407, 00130408	Oral study NOAEL = 15 mg/kg/day		subchronic oral toxicity - rat (same as incidental oral)
Long-Term Inhalation* MRID 43612001	Oral study NOAEL= **5** mg/kg/day		rat chronic toxicity study (same as for chronic dietary)
Cancer	**Classification**: Group D [not classifiable as to human carcinogenicity]		

*The dermal absorption factor is 10 percent and the inhalation absorption factor is 100 percent.

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic), RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable

b. Residential Handler

1) Exposure Scenarios, Data, and Assumptions

Homeowners (or others) may be exposed to 2,4-D while treating their lawns. All homeowner-use products are available in liquid or granular form. 2,4-D is applied using hose-end sprayers, pump sprayers, ready-to-use sprayers, broadcast spreaders, bellygrinders, and hand application, either before or after seasonal weed emergence, at a rate up to 1.5 lbs ae/A. A number of assumptions, or

estimates, such as adult body weight and area treated per application, are made by the Agency for residential risk assessment. Also, note that residential handlers are addressed somewhat differently than occupational handlers in that homeowners are assumed to complete all elements of an application (mix/load/apply) without use of personal protective equipment (assessments are based on an assumption that individuals will be wearing short pants and short-sleeved shirts).

The quantitative exposure/risk assessment developed for residential handlers is based on these scenarios:

1) Hand application of granules
2) Belly grinder application
3) Load/apply granules with a broadcast spreader
4) Mix/load/apply with a hose-end sprayer (mix your own)
5) Mix/load/apply with a hose-end sprayer (ready-to-use)
6) Mix/load/apply with hand held pump sprayer
7) Mix/load/apply with ready-to-use sprayer

Exposure estimates for these scenarios are taken from the Pesticide Handlers Exposure Database (PHED, Version 1.1 August 1998) which is used to assess handler exposures when chemical-specific monitoring data are not available. In addition to PHED data, the residential risk assessment relies on data from the Outdoor Residential Exposure Task Force (ORETF) and proprietary studies. Three turf transferable residue studies submitted by the Broadleaf Turf Herbicide Turf Transferable Residue (TTR) Task Force. These studies measured the dissipation of several phenoxy herbicides, including 2,4-D, using the ORETF roller technique. Scenarios #1 through #5 use ORETF or PHED data; scenarios #6 and #7 use exposure data from the Carbaryl Mixer/Loader/Applicator Exposure Study (EPA MRID 444598-01).

The results of a biomonitoring study (Harris and Solomon 1992) were also used to calculate dermal MOEs for post application exposure on turf. The study was conducted with adult volunteers who were exposed to 2,4-D while performing controlled activities for one hour on turf treated with 2,4-D. The controlled activities were conducted at 1 hour after treatment (HAT) and at 24 HAT. Ten volunteers participated in the study. Five volunteers wore long pants, a tee shirt, socks and closed footwear. The other five wore shorts and a tee shirt and were barefoot. The volunteers walked on the turf for a period of 5 minutes and then sat or lay on the area for 5 minutes and then continued in this fashion for 50 more minutes. Each volunteer collected all urine for the next 96 hours immediately following the exposure. The MOEs for the DAT 1 volunteers who wore shorts and no shoes ranged from 1000 to 26000 with the lowest MOE corresponding to a volunteer who removed his shirt during the exposure period. The MOEs for the remaining volunteers ranged from 17000 to 27000.

For more information, see "2,4-D. HED's Revised Human Health Risk Assessment for the Reregistration Eligibility Decision (RED) Revised to Reflect Public Comments. PC Code 030001; DP Barcode D316597" dated May 12, 2005, and the "2,4-D: 3rd Revised Occupational and Residential Exposure and Risk Assessment and Response to Public Comments for the Registration Eligibility Decision (RED) Document" dated May 4, 2005.

Assumptions Regarding Residential Handlers

- Clothing would consist of a short-sleeved shirt, short pants and no gloves.
- Broadcast spreaders and hose end sprayers would be used for broadcast treatments and the other application methods would be used for spot treatments only.
- An area of 0.023 acre (1000 square feet) would be treated per application during spot treatments and an area of 0.5 acre would be treated during broadcast applications.
- The application rate is 1.5 lb ae/acre representing the most recent revision to the master label.
- Average body weight of an adult handler is 70 kg.
- The duration of exposure is expected to be short-term (1-30 days) for residential handlers of 2,4-D. Intermediate- and long-term exposures of residential applicators are not anticipated based on 2,4-D's residential use pattern.

2) Residential Handler Risk Estimates

Based on toxicological criteria and potential for exposure, the Agency has conducted both a dermal and an inhalation exposure assessment. Risk assessment for short-term inhalation exposure is based on a rat developmental study. An assumption is made that 100% of the estimated inhalation dose will be absorbed. A dermal absorption factor of 10 percent was selected for converting dermal exposures to oral equivalent doses. An MOE greater than or equal to 1000 (10x for interspecies extrapolation, 10x for intraspecies variation, and 10x for database uncertainty) is considered adequately protective for this assessment. Since all residential handler MOEs are greater than 1000, risk to residential handlers is not of concern. The 2,4-D risk estimates are presented in Table 10 below.

In preliminary versions of the risk assessment, when considered alone, acute and short-term residential risks posed by the use of 2,4-D were not of concern to the Agency; however, when considered as part of an aggregate exposure with food and drinking water, exposures did exceed the Agency's level of concern. As a result, 2,4-D registrants agreed to reduce the maximum application rate to turf and residential lawns from 2.0 lbs ae/A to 1.5 lbs ae/A. The revised application rate (1.5 lbs ae/A) was used in the current risk assessment.

Table 10. 2,4-D Short Term Risk Estimates for Residential Handlers

Scenario	Application Rate (lbs ae/acre)	Treated Area (acres/day)	MOE
1. Hand Application of Granules	1.5	0.023	3,700
2. Belly Grinder Application	1.5	0.023	3,900
3. Load/Apply Granules with a Broadcast Spreader	1.5	0.5	29,000
4. Mix/Load/Apply with a Hose-end Sprayer (Mix your own)	1.5	0.5	1,800
5. Mix/Load/Apply with a Hose-end Sprayer (Ready to Use)	1.5	0.5	7,400
6. Mix/Load/Apply with Hand Held Pump Sprayer	1.5	0.023	11,000

Scenario	Application Rate (lbs ae/acre)	Treated Area (acres/day)	MOE
7. Mix/Load/Apply with Ready to Use Sprayer	1.5	0.023	7,900
Note: 1000 square feet equals 0.023 acres			

For more information, see Appendix F of "2,4-D: 3rd Revised Occupational and Residential Exposure and Risk Assessment and Response to Public Comments for the Reregistration Eligibility Decision (RED) Document (PC Code 030001, DP Barcode D316596)" dated May 4, 2005.

c. Residential Postapplication Risk

1) Exposure Scenarios, Data, and Assumptions

2,4-D uses in the residential setting include applications to home lawns. The following scenarios were assessed for residential post application risks:

1) Toddlers playing on treated turf
2) Adults performing yardwork on treated turf
3) Adults playing golf on treated turf

These scenarios chosen for risk assessment represent what the Agency considers the likely upper-end estimates of possible exposure. An MOE of 1000 (or more) is considered protective for this assessment.

<u>Assumptions Regarding Residential Postapplication Risk</u>

- An assumed initial turf transferable residue (TTR) value of 5.0% of the application rate is used for assessing hand to mouth exposures.
- An assumed initial TTR value of 20% of the application is used for assessing object to mouth exposures.
- Soil residues are contained in the top centimeter and soil density (i.e., the ratio of the mass of dry solids to the bulk volume of the soil occupied by those dry solids) is 0.67 gram/mL.
- Three year old toddlers are expected to weigh 15 kg.
- Hand-to-mouth exposures are based on a frequency of 20 events/hour and a surface area per event of 20 cm^2 representing the palmar surfaces of three fingers.
- Saliva extraction efficiency is 50 percent. Every time the hand goes in the mouth approximately half of the residues on the hand are removed.
- Adults are assessed using a transfer coefficient of 14,500 cm^2/hour.
- Toddlers are assessed using a transfer coefficient of 5,200 cm^2/hour.
- Golfers are assessed using a transfer coefficient of 500 cm^2/hour.
- An exposure duration of 2 hours per day is assumed for toddlers playing on turf or adults performing heavy yardwork.

The following assumptions that are specific to 2,4-D are used for assessing residential post application exposures.

- The master label application rate of 1.5 lbs ae/acre was used.
- The exposure following the application of granular formulations was not assessed because there were no TTR data submitted for granular formulations. It was assumed this exposure would be less than or equal to the exposure from liquid formulations.

Other residential exposure standard operating procedures (SOPs) may be viewed at the following website: http://www.epa.gov/oscpmont/sap/1997/september/sopindex.htm .

Calculation Method for Postapplication Exposure for Toddlers on Treated Turf

MOEs were calculated for acute toddler exposures using the maximum TTR value along with the acute dietary NOAEL of 67 mg/kg/day. This NOAEL was adapted to acute dermal exposures by using the dermal absorption factor of 10 percent to account for route to route extrapolation. The MOEs for toddler short term exposures were calculated using the seven day average TTR value because the short term NOAEL was based upon decreased body weight gain which occurred after several days of exposure. MOEs for acute and adult short term exposures were calculated using the maximum TTR value because the acute and short term NOAELs are the same and are based upon the developmental effects which could have occurred following one day of exposure.

The quantitative exposure/risk assessment for postapplication risk to children is based on these scenarios:

1) *Dermal activity from treated turf:* Postapplication exposure to children from the dermal exposure of pesticide residues from activity on treated turf.
2) *Hand-to-mouth activity from treated turf:* Postapplication exposure to children from the "incidental" ingestion of pesticide residues on treated turf from hand-to-mouth transfer (i.e., those residues that end up in the mouth from children touching turf and then putting their hands in their mouths).
3) *Object-to-mouth activity from treated turf:* Postapplication exposure to children from incidental ingestion of pesticide residues on treated turf from object-to-mouth transfer (i.e., those residues that end up in the mouth from a child mouthing a handful of treated turf).
4) *Soil ingestion activity:* Postapplication exposure to children from incidental ingestion of soil in a treated area.

For more information on formulas used for calculating occupational and residential exposures to 2,4-D, see Appendix A of "2,4-D: 3rd Revised Occupational and Residential Exposure and Risk Assessment and Response to Public Comments for the Reregistration Eligibility Decision (RED) Document" dated May 4, 2005.

2) Postapplication Risk Estimates

Risk assessment for children's postapplication exposure is based on a NOAEL of 67 mg/kg/day from an oral study of acute neurotoxicity study in rats. A Margin of Exposure (MOE) of 1000 (10x for interspecies extrapolation, 10x for intraspecies variation, and 10x for database uncertainty) is considered adequately protective for this assessment. Table 11 below presents the MOEs for Post-Application Exposure in Children. Since all MOEs meet or exceed 1000, postapplication exposure to children is not of concern.

Table 11. Children Post-Application Exposure to Turf Treated with 2,4-D

	Application Rate (lbs ae/acre)	Dermal MOE	Hand-to Mouth MOE	Object to Mouth MOE	Soil Ingestion MOE	Total MOE
Acute Toddler Risks Using the Maximum TTR (North Carolina Trial 1 using 2,4-D DMA)						
DAT 0	1.5	1,900	3000	12,000	>100,000	1,100
Short Term Toddlers Risks Using California TTR Data (DMA Mix, No Rain)						
DAT 0 to DAT 6	1.5	3,900	2,100	8,500	>100,000	1,200
Short Term Toddler Risks Using North Carolina TTR Data from Trial 1 (DMA and DMA Mix, No Rain)						
DAT 0 to DAT 6	1.5	5,100	4,400	18,000	>100000	2,100
Short Term Toddler Risks Using North Carolina TTR Data from Trial 2 (DMA Mix, Some Rain)						
DAT 0 to DAT 6	1.5	12,000	7,000	28,000	>100000	3,900
The acute NOAEL is 67 mg/kg/day for neurotoxic effects observed in the acute neurotoxicity study. The short term NOAEL is 25 mg/kg/day for maternal effects observed in the developmental study.						

Table 12 below lists the adult acute/short term MOEs for exposure to turf treated with 2,4-D. The acute/short term NOAEL is 25 mg/kg/day from the rat developmental toxicity study. The LOAEL was 75 mg/kg/day based on skeletal abnormalities from a developmental toxicity study in rats. All MOEs meet or exceed 1000, so postapplication exposure to adults is not of concern.

Table 12. Adult Acute/Short Term MOEs for Exposure to Turf Treated with 2,4-D

Exposure Scenario	Application Rate (lbs ae/acre)	TTR (ug/cm^2)	Acute/Short Term Dermal MOE[1] on Day 0
Heavy Yardwork Playing Golf	1.5	0.50	1000 15000
[1.] The acute/short term NOAEL is 25 mg/kg/day for developmental effects observed in the developmental study.			

d. Recreational Swimmer Risk

1) Exposure Scenarios, Data, and Assumptions

The master label indicates that 2,4-D can be used for aquatic weed control of surface weeds such as water hyacinth and submersed weeds such as Eurasian milfoil. Surface weeds are controlled by foliar applications at a maximum rate of 4.0 lb ae/acre. Submersed weeds are controlled by subsurface injection of liquids to achieve a target concentration of 2 to 4 ppm in the water column surrounding the weeds. This requires 5.4 to 10.8 lb ae per acre foot of water depth (e.g., 5.4 lbs ae would be required to achieve 2 ppm in a one acre pond that has an average depth of 1 foot). Granular formulations of BEE (Aquakleen and Navigate) are also used to control submersed weeds. The granular formulations resist rapid decomposition in water and release the herbicide into the root zone.

Although many herbicide treatments are applied to aquatic areas where recreational swimming is not likely to occur, some of the subsurface treatments are made at recreational lakes. These treatments are made because the Eurasian milfoil interferes with recreation and other activities. This problem is particularly prevalent in the northern states such as Minnesota and Washington and in the New England region.

The following exposure scenarios are assessed for recreational swimmers:

1) Adult Recreational Swimmer
2) Child Recreational Swimmer

<u>Assumptions Regarding Recreational Swimmer Risk</u>

The following assumptions were used for the assessment of swimmer risks. Many of these assumptions were taken from the Residential SOPs and are also used in the SWIMODEL.

- The skin surface area of adults is assumed to be 21,000 cm^2 (Residential SOPs). This is the 95th percentile value for females (EPA Exposure Factors Handbook, 1997).
- The body weight for children is assumed to be 22 kg as cited in the Residential SOPs. This is a mean value for 6 year old children.
- The skin surface area for children is assumed to be 9,000 cm^2 as cited in the Residential SOPs. This is the 90th percentile value for male and female children.
- The assumed mean ingestion rate is 0.05 liters per hour for both adults and children as cited in the Residential SOP. This value may be greater for young children playing in water and accidentally ingesting a remarkable quantity of water (U.S. EPA SAP, 1999).
- The exposure time is assumed to be 3 hours per day. This is the 90th percentile value for time spent swimming in a freshwater pool (EPA Child Specific Exposure Factors Handbook, 2002).
- The body weight for female adult acute exposures is assumed to be 60 kg.
- The body weight for male adult acute exposures is assumed to be 70 kg.
- The body weight for adult short term exposure is assumed to be 60 kg because the endpoint is gender specific.
- Risks were not calculated for foliar treatments because the application rate of 2.0 lb ae/acre would result in water concentration of only 0.25 ppm in a three foot water column

even if all of the spray were to run off the leaves into the water.

Calculation Method for Recreational Swimmer Exposure

The Agency used the Swimmer Exposure Assessment Model (SWIMODEL) to calculate exposures to swimmers in water treated with 2,4-D for aquatic weed control. The SWIMODEL estimates exposure for up to six exposure routes (i.e., oral ingestion, dermal absorption, inhalation, buccal/sublingual, nasal/orbital, and aural routes), or calculates exposure as a function of any one of the three major exposure routes (i.e., oral ingestion, dermal absorption, or inhalation). Other factors used in the SWIMODEL formulae for dermal and ingestion exposure which are described in Appendix A of "2,4-D: 3rd Revised Occupational and Residential Exposure and Risk Assessment and Response to Public Comments for the Reregistration Eligibility Decision (RED) Document" dated May 4, 2005.

The SWIMODEL formulas for the other dermal pathways (aural, buccal/sublingual and orbital/nasal) were not used in the 2,4-D human health risk assessment because these formulas are based upon recreational swimmers in swimming pools who swim with their heads partially immersed. It is anticipated that recreational swimmers in weed infested areas would be less likely to swim with their heads immersed than recreational swimmers in weed- free swimming pools. In addition, the formulas for the buccal/sublingual and orbital/nasal pathways contain a default absorption factor of 0.01 which is based upon the absorption of nitroglycerin. This factor would greatly overestimate the risk of 2,4-D exposure because 2,4-D is absorbed at a much lower rate.

Because the 2,4-D water concentrations can vary depending upon the application rate and site conditions the Maximum Swimming Water Concentration (MSWC) was calculated. The MSWC is the water concentration at which the combined dermal and ingestion MOE meets or exceeds the target MOE of 1000. The MSWCs were calculated for children's acute exposures using the acute NOAEL of 67 mg/kg/day and the MSWCs for children's short term exposures were calculated using the short term NOAEL of 25 mg/kg/day for maternal effects. The MSWCs for adult acute/short term exposures were calculated using a NOAEL of 25 mg/kg/day that is based upon developmental effects which could have occurred following one day of exposure.

2) Recreational Swimmer Risk Estimates

The MSWCs are summarized in Table 13 and the detailed calculations are included in Appendix H of the 3rd Revised Occupational and Residential Exposure Assessment for 2,4-D. The acute MSWCs range from 1.2 ppm for 2,4-D BEE to 9.8 ppm for 2,4-D acid while the short term MSWCs range from 0.9 ppm for 2,4-D BEE to 3.6 ppm for 2,4-D acid or amine. The MSWCs for 2,4-D BEE are lower because based on its chemical properties, 2,4-D BEE is expected to have a much higher dermal absorption value.

Table 13. Maximum Swimming Water Concentrations for 2,4-D Aquatic Applications

Exposure Duration	NOAEL (mg/kg/day)	2,4-D Form	2,4-D MSWC* (ppm)	Dermal MOE	Ingestion MOE	Combined MOE
Adults						
Acute/Short Term	25	Acid or Amine	9.8	97000	1000	1000
	25	BEE	1.2	1200	8300	1000
Children						
Acute	67	Acid or Amine	9.8	425000	1000	1000
Acute	67	BEE	2.4	1300	4100	1000
Short Term	25	Acid or Amine	3.6	230000	1000	1000
Short Term	25	BEE	0.90	1300	4100	1000

* The MSWC is the concentration below which the combined MOE would be above 1000 and the risks would not be of concern.

The Acute MSWC of 9.8 ppm for exposures to 2,4-D acid or amine is greater than the master label application rate of 4.0 ppm, therefore, acute exposures to 2,4-D acid or amine are not of concern. The MSWC of 3.6 ppm for short-term exposures to 2,4-D acid or amine is also not of concern because some dissipation or dispersion is likely to occur which would cause the 7-day average of 2,4-D concentrations to be less than 3.6 ppm. Dissipation studies submitted to EFED indicated that the half lives following pond and lake liquid treatments ranged from 3.2 days to 27.8 days which yield 7 day average concentrations of 1.9 ppm when the half life equals 3.2 days to 3.6 ppm when the half life equals 27.8 days.

The MSWCs for 2,4-D BEE are less than the master label application rate of 4 ppm, but they are unlikely to be of concern for the following reasons:

- 2,4-D BEE degrades rapidly by abiotic hydrolysis in sterile water to form 2,4-D acid particularly when the pH is 7.5 or above.

- 2,4-D BEE degrades to 2,4-D acid by microbial hydrolysis with an average half life of 2.6 ± 1.8 hours at a bacterial concentration of 5×10^{-8} organisms per liter. Therefore, degradation of 2,4-D BEE to 2,4-D under typical environmental conditions will be rapid leading to significantly lower risk estimates because the 2,4-D acid has a lower rate of dermal absorption.

- Modeling predicts direct water application of 2,4-D BEE will yield surface water concentrations of 2,4-D BEE concentrations in the Agency standard pond of 624 ug/L for peak (24 hour average), 30 ug/L for the 21-day average, and 10 ug/L for the 60-day average.

- The existing label rates for 2,4-D BEE products are also lower than the master label rate.

5. Aggregate Exposure and Risk

OPP has traditionally compared estimates of concentrations of a pesticide in drinking water to DWLOCs. A DWLOC is the portion of the acute PAD or chronic PAD remaining after estimated dietary (food only) exposures have been subtracted and the remaining exposure has been converted to a concentration (ug/L or ppb). This concentration value (DWLOC) represents the available or allowable exposure through drinking water. In an acute risk assessment, the remaining portion of the aPAD is based on dietary exposures at the percentile of exposure appropriate for a given risk assessment and depends on each relevant population subgroup considered. Estimated Drinking Water Concentrations (EDWCs) of 2,4-D in ground and surface water that are less than the DWLOCs do not exceed the Agency's level of concern. DWLOC values vary for population subgroups depending on dietary exposure through foods for each subgroup, assumptions made about the volume of drinking water consumed, and default body weights for each subgroup.

More recently, OPP has adopted the forward calculation approach for the assessment of aggregate risks. In this approach, food, drinking water and residential exposures are aggregated and compared to an appropriate endpoint.

In the case of 2,4-D, the DWLOCs were calculated for comparison to the MCL established by the EPA Office of Water and aggregate risks were calculated using the forward calculation approach for comparison to the appropriate endpoint. The respective DWLOCs and aggregate risks are shown for acute, chronic and short term exposures in the following sections.

a. Acute Aggregate Risk Assessment

<u>DWLOC Approach</u>

Acute DWLOCs were calculated based upon acute dietary exposures. Acute residential exposures from swimming in treated water bodies or playing on treated turf were not included because exposures are unlikely to co-occur with acute dietary exposures. The acute DWLOCs are summarized in Table 14 and are 432 ppb or greater with the most sensitive population being females 13-49 years old. The EDWCs of 118 ug/liter for surface water and 15 ug/liter for groundwater are substantially less than the DWLOCs which means that the risks are not of concern.

Table 14. Acute DWLOC Calculations

Population Subgroup	Body Weight (kg)	Water Consumption (liters/day)	aPAD (mg/kg/day)	Food Exp[1] (mg/kg/day)	Max Water Exposure (mg/kg/day[2])	DWLOC (µg/L)[3]
General U.S. Population	70	2.0	0.067	0.0118	0.0552	1932
All Infants (< 1 year old)	10	1.0		0.0132	0.0538	538
Children 1-2 years old	10	1.0		0.0221	0.0449	449
Children 3-5 years old	10	1.0		0.0206	0.0464	464
Children 6-12 years old	10	1.0		0.0147	0.0523	523
Females 13-49 years old	60	2.0	0.025	0.0106	0.0144	432

1. Food exposure values are the maximum of the acute DEEM or Lifeline values.
2 . Maximum water exposure (mg/kg/day) = [(acute PAD - food exposure)]
3. DWLOC (µg/L) = [maximum water exposure x body weight] ÷ [water consumption x 10^{-3} mg/µg].

Surface Water EDWC = 70 ug/liter (aquatic applications) or 118 ug/liter (terrestrial applications)
Ground Water EDWC = 15 ug/liter

Forward Calculation Approach

Acute aggregate risks were assessed by aggregating acute food exposures and acute water exposures. The acute aggregate risks are presented in Table 15 and are not of concern because they are less than 100 percent of the aPAD. The highest risks (58 percent of the aPAD) are for females 13-49 years old because these risks are based upon the lower NOAEL of 25 mg/kg/day.

Table 15. 2,4-D Aggregate Acute MOEs

Population Subgroup	Body Weight (kg)	Water Consumption (liters/day)	Food Exposure[1] (mg/kg/day)	Drinking Water Exposure[2] (mg/kg/day)	Aggregate Exposure[3] (mg/kg/day)	aPAD[4] (mg/kg/day)	Percent aPAD[5]
General U.S. Population	70	2.0	0.0118	0.00337	0.0152	0.067	23
Females 13-49 yrs old	60	2.0	0.0106	0.0039	0.015	0.025	58

Notes for Table X
1. Food exposure values are the maximum of the DEEM or Lifeline acute values.
2. Drinking Water Exposure = (EDWC * daily water consumption) / (1000 ug/mg * Body Weight); where the EDWC = 118 ug/liter
3. Aggregate Exposure = Food Exposure + Drinking Water Exposure
4. aPAD = NOAEL/1000; where the NOAEL is 25 mg/kg/day for females 13-49 and 67 mg/kg/day for all other population subgroups
5. Percent aPAD = (Aggregate Exposure/aPAD) * 100

b. Chronic Aggregate Risk Assessment

DWLOC Approach

Chronic DWLOCs were calculated based upon chronic dietary exposures. As there are no chronic residential exposures, residential exposures were not included in the chronic DWLOC calculations. The chronic DWLOCs are summarized in Table 16 and are 46 ug/liter or greater with the most sensitive population being children. The EDWCs, which range from 1.5 to 23 ug/liter, are less than the DWLOCs which means that the risks are not of concern. It should be noted that the master label indicates that potable water consumption from a treated water body cannot begin until the 2,4-D concentration is 70 ug/liter or below, therefore an annual average exposure at the MCL of 70 ug/liter would not occur because dissipation would reduce the initial concentration of 70 ug/liter to an annual average concentration of 11 ug/liter.

Table 16. Chronic DWLOC Calculations

Population Subgroup	Body Weight (kg)	Water Consumption (liters/day)	cPAD (mg/kg/day)	Food Exp[1] (mg/kg/day)	Max Water Exposure (mg/kg/day)[2]	DWLOC (µg/L)[3]
General U.S. Population	70	2.0	0.005	0.00020	0.0048	168
All Infants (< 1 year old)	10	1.0		0.00016	0.00484	48
Children 1-2 years old	10	1.0		0.00042	0.00458	46
Children 3-5 years old	10	1.0		0.00037	0.00463	46
Children 6-12 years old	10	1.0		0.00026	0.00474	47
Youth 13-19 years old	60	2.0		0.00019	0.00481	144
Adults 20-49 years old	70	2.0		0.00019	0.00481	168
Adults 50+ years old	70	2.0		0.00018	0.00482	169
Females 13-49 years old	60	2.0		0.00020	0.0048	144

1. Food exposure values are the maximum of the DEEM or Lifeline chronic dietary values.
2. Maximum water exposure (mg/kg/day) = [(chronic PAD - food exposure)]
3. DWLOC (µg/liter) = [maximum water exposure x body weight] ÷ [water consumption x 10^{-3} mg/µg].

Surface Water EDWC (maximum time weighted annual mean from the NAWQA database) = 1.5 ug/liter
Surface Water EDWC (dissipation modeling of aquatic application when 70 ppb occurs at time zero) = 11 ug/liter
Surface Water EDWC (worst case terrestrial use PRZM-EXAMs run) = 23 ug/liter
Ground Water EDWC (the highest monitored value from the NAWQA database) = 15 ug/liter

Forward Calculation Approach

Chronic aggregate risks were also assessed by aggregating chronic food exposures and chronic water exposures in a forward calculation approach. The chronic aggregate risks are presented as percent cPAD in Table 17 and are not of concern because they are less than 100 percent of the cPAD. The highest risks (38 percent of the cPAD) are for children 1-2 years old.

Table 17. 2,4-D Aggregate Chronic Risks

Population Subgroup	Body Weight (kg)	Water Consumption (liters/day)	Food Exposure[1] (mg/kg/day)	Drinking Water Exposure[2] (mg/kg/day)	Aggregate Exposure[3] (mg/kg/day)	cPAD[4] (mg/kg/day)	Percent cPAD[5]
General U.S. Population	70	2.0	0.00020	0.00043	0.0006	0.005	13
Children 1-2 yrs old	10	1.0	0.00042	0.0015	0.002	0.005	38

1. Food exposure values are from Table X and are the maximum of the DEEM or Lifeline chronic dietary values.
2. Drinking Water Exposure = (EDWC * daily water consumption) / (1000 ug/mg * Body Weight); where the EDWC = 15 ug/liter
3. Aggregate Exposure = Food Exposure + Drinking Water Exposure
4. cPAD = NOAEL of 5 mg/kg/day / 1000
5. Percent cPAD = (Aggregate Exposure/aPAD) * 100

c. Short-term Aggregate Risk Assessments

DWLOC Approach

Short-term aggregate risks assessments were conducted by calculating DWLOCs based upon short term turf exposures, chronic food exposures and short term endpoints. Short-term exposures from swimming in treated water bodies were not included because these exposures represent episodic scenarios that are unlikely to occur the same day as an acute dietary exposure. The short-term DWLOCs were calculated only for females 13-49 and children 1-6 because these population subgroups have the highest exposure and are protective of the other subgroups. The DWLOCS are listed in Table 18 and range from 24 to 54 ug/liter. These DWLOCs are all greater than the EDWCs, which range from 15 to 23 ug/liter, and indicate that short term risks are not of concern.

Table 18. Short-Term DWLOC Calculations for 2,4-D

Pop. Subgroup	Body Weight (kg)	Water Consumption (liters/day)	NOAEL/UF (mg/kg/day)	Turf Exposure (mg/kg/day)	Food Exp[1] (mg/kg/day)	Max Water Exposure (mg/kg/day)[2]	DWLOC (µg/L)[3]
Children 1-6	15	1.0	0.025	0.021	0.00042	0.00358	54
Females 13-49	60	2.0	0.025	0.024	0.00020	0.00080	24

1. Food exposure values are the maximum of the DEEM or Lifeline chronic dietary values.
2 Maximum water exposure (mg/kg/day) = [(NOAEL/UF) - (Turf exposure + food exposure)]
3. DWLOC (µg/liter) = [maximum water exposure x body weight] ÷ [water consumption x 10^{-3} mg/µg].

Surface Water EDWC (worst case terrestrial use PRZM-EXAMs run) = 23 ug/liter
Ground Water EDWC (based upon the highest monitored value) = 15 ug/liter

Forward Calculation Approach

Short-term aggregate risks were also assessed by directly aggregating short-term turf exposures, chronic food exposures and chronic water exposures. Short-term aggregate risks were calculated only for females 13-49 and children 1-6 because these population subgroups have the highest exposure and are protective of the other subgroups. The short term aggregate MOEs are presented in Table 19 and indicate that the short term risks are not of concern because the MOEs equal or exceed the target MOE of 1000.

Table 19. 2,4-D Aggregate Short-Term MOEs Including Turf Exposures

Population Subgroup[1]	Turf Application Rate (lbs ae/acre)	Chronic Food Exposure[2] (mg/kg/day)	Short-Term Turf Exposure[3] (mg/kg/day)	Chronic EDWC[4] (ug/liter)	Drinking Water Exposure[5] (mg/kg/day)	Aggregate Exposure[6] (mg/kg/day)	Aggregate MOE[7]
Females 13 - 49	1.5	0.000195	0.024	15	0.00050	0.0247	1000
Children 1 - 6	1.5	0.000424	0.021	15	0.0010	0.0224	1100
Females 13 - 49	1.5	0.000195	0.024	23	0.00077	0.0250	1000
Children 1 - 6	1.5	0.000424	0.021	23	0.0015	0.0230	1100

1. Body weights are 60 kg (females) and 15 kg (children). Water consumption values are 2 liter/day (females) and 1.0 liter/day (children).
2. The food exposure for females is from Lifeline. The food exposure for children is from DEEM and is for 1-2 year old children
3. Female's turf exposures are from the dermal route only. Children's turf exposures are from the dermal and incidental oral routes.
4. EDWC is 15 ug/liter for ground water and 23 ug/liter for surface water.
5. Drinking Water Exposure = (EDWC * daily water consumption) / (1000 ug/mg * Body Weight)
6. Aggregate Exposure = Turf Exposure + Food Exposure + Drinking Water Exposure
7. Aggregate MOE = NOAEL/Aggregate Exposure where the NOAEL is 25 mg/kg/day.

d. Cancer Aggregate Risk

2,4-D was classified as a Category D chemical, i.e., not classifiable as to human carcinogenicity, by the EPA/OPP Cancer Peer Review Committee in 1996. Thus, no aggregate cancer assessment is warranted.

e. Aggregate Risk Characterization

The highest aggregate risks are the short term risks that include the turf exposure scenarios. For the most sensitive subpopulation (females 13-49), these risks just meet the target MOE of 1000 and the turf exposure is the risk driver as it contributes 96 percent of the risk. It is important to note, however, that the turf exposure estimate is based upon modeling and is greater than exposure measurements obtained from biomonitoring. The results of a biomonitoring study (Harris and Solomon 1992) were also used to calculate dermal MOEs for post application exposure on turf. The study was conducted with adult volunteers who were exposed to 2,4-D while performing controlled activities for one hour on turf treated with 2,4-D. The controlled activities were conducted at 1 hour after treatment (HAT) and at 24 HAT. Ten volunteers participated in the study. Five volunteers wore long pants, a tee shirt, socks and closed footwear. The other five wore shorts and a tee shirt and were barefoot. The volunteers walked on the turf for a period of 5 minutes and then sat or lay on the area for 5 minutes and then continued in this fashion for 50 more minutes. Each volunteer collected all urine for the next 96 hours immediately following the exposure. The MOEs for the DAT 1 volunteers who wore shorts and no shoes ranged from 1000 to 26000 with the lowest MOE corresponding to a volunteer who removed his shirt during the exposure period. The MOEs for the remaining volunteers ranged from 17000 to 27000. If the calculated MOE of 1000 is considered in conjunction with the biomonitoring results, it is clear that the short term risks are upper bound estimates and not likely to be of concern.

6. Occupational Risk

Workers can be exposed to a pesticide through mixing, loading, and/or applying a pesticide, or re-entering treated sites. Occupational handlers of 2,4-D include workers in agricultural areas, workers in forest areas, workers in rights-of-way and non-cropland areas, workers in lawn and turf areas (including turf grown for seed or sod), and workers applying 2,4-D for aquatic weed control. Occupational risk for all of these potentially exposed populations is measured by an MOE which determines how close the occupational exposure comes to a NOAEL. In the case of 2,4-D, MOEs greater than 100 do not exceed the Agency's level of concern. For workers entering a treated site, MOEs are calculated for each day after application to determine the minimum length of time required before workers can safely reenter.

Occupational risk estimates are expressed as MOEs, which are the ratio of estimated exposure to an established dose level (NOAEL). 2,4-D MOEs are determined by a comparison of specific exposure scenario estimates to the NOAELs for short-term assessment and intermediate-term assessment, respectively. The NOAEL for short-term dermal and inhalation exposure is 25 mg/kg/day from a rat developmental toxicity study, and the NOAEL for intermediate-term dermal and inhalation exposure is 15 mg/kg/day from a rat subchronic oral toxicity study. The dermal absorption factor is 10 percent and the inhalation absorption factor is 100 percent. For 2,4-D users an MOE of 100 has been determined to be adequately protective (for both short- and intermediate-term exposure) based on the standard uncertainty factors of 10x for interspecies extrapolation and 10x for intraspecies variability. Long-term worker exposure is not expected for 2,4-D.

Occupational risk is assessed for exposure at the time of application (termed "handler" exposure) and assessed for exposure following application, or postapplication exposure. Application parameters are generally defined by the physical nature of the formulation (e.g., formula and packaging), by the equipment required to deliver the chemical to the use site, and by the application rate required to achieve an efficacious dose. Post-application risk is assessed for activities such as scouting, irrigating, pruning, and harvesting and is based primarily on dermal exposure estimates.

Occupational risk estimates are calculated based on assumptions concerning acres treated per day and the seasonal duration of exposure. For more information on the assumptions and calculations of potential risk of 2,4-D to workers, see the Occupational Exposure Assessment (Section 7.0) in "2,4-D: 3rd Revised Occupational and Residential Exposure and Risk Assessment and Response to Public Comments for the Reregistration Eligibility Decision (RED) Document," dated May 4, 2005.

a. Occupational Toxicity

Table 20 provides a listing of the toxicological endpoints used in the 2,4-D occupational risk assessment.

Table 20. Toxicological Endpoints for the Occupational Risk Assessment

Exposure Scenario	Dose Used in Risk Assessment, UF	Level of Concern for Risk Assessment	Study and Toxicological Effects
Short-Term Dermal*	Oral study NOAEL= **25** mg/kg/day	**Occupational** LOC for MOE = 100	Rat developmental toxicity study LOAEL = 75 mg/kg/day based on decreased maternal body-weight gain and skeletal abnormalities
Intermediate-Term Dermal*	Oral study NOAEL = **15** mg/kg/day		Subchronic oral toxicity - rat LOAEL = 100 mg/kg/day based on decreased body weight/body-weight gain, alterations in some hematology, and clinical chemistry parameters, and cataract formation.
Long-Term Dermal*	Oral study NOAEL= **5** mg/kg/day		Rat Chronic Toxicity Study LOAEL = 75 mg/kg/day based on decreased body-weight gain (females) and food consumption (females), alterations in hematology , and clinical chemistry parameters, decreased T4 (both sexes), glucose (females), cholesterol (both sexes), and triglycerides (females)].
Short-Term Inhalation*	Oral study NOAEL= **25** mg/kg/day		Rat developmental toxicity study (same as for dermal)
Intermediate-Term Inhalation*	Oral study NOAEL = **15** mg/kg/day		Subchronic oral toxicity - rat (same as incidental oral)
Long-Term Inhalation*	Oral study NOAEL= **5** mg/kg/day		Rat chronic toxicity study (same as for chronic dietary)
Cancer	**Classification**: Group D [not classifiable as to human carcinogenicity]		

*The dermal absorption factor is 10 percent and the inhalation absorption factor is 100 percent.

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic), RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable

For more occupational toxicity information, see "2,4-D: HED's Revised Human Health Risk Assessment for the Reregistration Eligibility Decision (RED) Revised to Reflect Public Comments," dated January 4, 2005.

b. Occupational Handler Exposure

Occupational handler risk estimates have been assessed for both short- and intermediate-term exposure durations. Because 2,4-D is typically applied only a few times per season and because the agricultural scenarios occur for only a few months per year, it is anticipated that 2,4-D exposures would primarily be short-term. Intermediate-term risk estimates are provided as an upper-bound assessment.

Occupational handler assessments are conducted using increasing levels of protection. The

Agency typically evaluates all exposures with minimal protection and then considers additional protective measures using a tiered approach (going from minimal to maximum levels of protection). The lowest tier is represented by the baseline clothing scenario (i.e., single layer clothing, socks, and shoes), followed by, if MOEs are of concern, increasing levels of risk mitigation such as personal protective equipment (PPE) and engineering controls (EC). With the exception of mixing and loading wettable powders, MOEs for most occupational exposure scenarios are above 100 at baseline PPE (long-sleeved shirt, long pants, socks, and shoes) or single layer PPE (long-sleeved shirt, long pants, socks, shoes, and gloves). The MOEs for handling wettable powder are acceptable with engineering controls (i.e. water soluble bags). While the generic assessment for 2,4-D as an active ingredient does not indicate a need for additional PPE, evaluation of end-use product toxicity data may. End-use product PPE will be assessed on a product-by-product basis.

c. Occupational Handler Risk Summary

The Agency has determined that there are potential exposures to individuals who mix, load, apply, and otherwise handle 2,4-D during the usual use patterns associated with the pesticide's use. Based on the use patterns, 18 major occupational handler exposure scenarios were identified as follows:

<u>Mixer/Loader</u>

(1a) Mix/Load Wettable Powder for Aerial Application
(1b) Mix/Load Wettable Powder for Groundboom Application
(1c) Mix/Load Wettable Powder for Aquatic Subsurface Application
(1e) Mix/Load Wettable Powder for 10 Man Crew Backpack Application
(1f) Mix/Load Wettable Powder for Row Sprayer
(1g) Mix/Load Wettable Powder for Aquatic Foliar Application
(1h) Mix/Load Wettable Powder for Turfgun Application
(2a) Mix/Load Liquids for Aerial Application
(2b) Mix/Load Liquids for Groundboom
(2c) Mix/Load Liquids for Aquatic Subsurface Application
(2d) Mix/Load Liquids for Airblast Application
(2e) Mix/Load Liquids for 10 Man Crew Backpack Application
(2f) Mix/Load Liquids for Row Sprayer
(2g) Mix/Load Liquids for Aquatic Foliar Application
(2h) Mix/Load Liquids for Turfgun Application
(3) Load Granules for Broadcast Spreader

<u>Applicator</u>

(4) Aerial Application
(5) Groundboom Application
(6) Subsurface Application of Liquids to Submersed Aquatic Weeds
(7) Airblast Application
(8) Backpack Application
(9) Rights of Way (ROW) Application

(10) Foliar Application of Liquids to Floating Aquatic Weeds
(11) Turfgun Application
(12) Broadcast Spreader Application

Mixer/Loader/Applicator
(13) Mix/Load/Apply Wettable Powder with a Turfgun
(14) Mix/Load/Apply Liquids with a Turfgun
(15) Mix/Load/Apply Water Dispersable Granules with a Turfgun
(16) Mix/Load/Apply Liquids with a Backpack Sprayer
(17) Load/Apply Granules with a Push Spreader

Flagger
(18) Flag Aerial Application

Occupational Handler Exposure Assumptions

When possible, the assumptions for daily areas treated are taken from the Health Effects Division Science Advisory Committee on Exposure Policy 9: Standard Values for Daily Acres Treated in Agriculture (July 5, 2000). In other instances, the daily areas treated were defined for each handler scenario by best scientific judgement, or the best information available, as footnoted below in Table 21.

Analyses were completed using acceptable surrogate exposure data for the scenario assessed. Several handler assessments were completed using data from the Pesticide Handler Exposure Database (PHED) (version 1.1). PHED data were used primarily for the large scale agricultural and forestry scenarios. Some handler assessments (i.e., handheld handgun equipment, push-type spreader, and other lawn care scenarios) were completed using data from the Outdoor Residential Exposure Task Force (ORETF). California Department of Pesticide Regulation (CA DPR) data were used for the backpack applicator forestry scenario where multiple applicators are supplied by a nurse tank.

The following assumptions and factors were used in order to complete the exposure and risk assessments for occupational handlers and applicators:

- The average work day was 8 hours.
- A listing of application methods and amounts of acreage treated per 8 hour day is included in Table 22 and Table 23.
- The application rate for submerged aquatic weeds is based upon the master label rate of 10.8 lbs a.e. per acre foot times an average lake depth of 5 feet.
- Maximum application rates and daily acreage were used to evaluate short term exposures.
- Average application rates were used to evaluate intermediate term exposures.
- A body weight of 60 kg was assumed for short-term exposures because the short-term endpoint relates to females 13-50 years of age.
- A body weight of 70 kg was assumed for intermediate-term exposures because the

intermediate-term endpoint is not gender-specific.

- The dermal absorption rate is 10%.
- The inhalation absorption rate is 100%.
- Baseline PPE includes long sleeve shirts, long pants and no gloves or respirator.
- Single Layer PPE includes baseline PPE with gloves.
- Double Layer PPE includes coveralls over single layer PPE.
- Double Layer PPE PF5 includes above with a PF5 respirator (i.e. a dustmask).
- Double Layer PPE PF10 includes above with a PF10 cartridge respirator.
- Only closed cockpit airplanes are used for aerial application.
- There are very little exposure data to evaluate the exposure in helicopters; therefore, the exposure data for fixed-wing aircraft are used as a surrogate.
- Airplane and helicopter pilots do not wear chemical resistant gloves.

Table 21. 2,4-D Application Methods and Assumptions

Application Method	Typical Crops Treated	Treated Area[1]
Aerial	Small Grain, Field Corn, Sugarcane Citrus Growth Regulation	1200 350
Groundboom	Small Grains, Field Corn, Sugarcane Orchard/Vineyard Floors Strawberries	200 80 80
Subsurface Application of Liquids	Submersed Aquatic Weeds	30[2]
Airblast	Citrus Growth Regulation	40
Backpack Sprayer - Mix/Load/Apply	Christmas Tree Plantations	2[3]
Backpack Sprayer - Apply Only	Conifer Release	4[4]
Right of Way (ROW) Sprayer	Weed Control - 20 gallons per acre Brush Control - 400 gallons per acre	50[5] 2.5[5]
Foliar Application of Liquids	Floating Aquatic Weeds	10[6]
Broadcast Spreader - Tractor Drawn or Boat Mounted	Turf Submersed Aquatic Weeds	40 50[7]
Turfgun	Turf	5
Broadcast Spreader - Push Type	Turf	5

1. Except as noted, the acres treated per day values are from ExpoSAC Policy #9 "Standard Values for Daily Acres Treated in Agriculture", Revised 7/5/2000.
2. The area treated for aquatic application of liquids to submersed aquatic weeds is based on information provided in an email of 12/11/03 from Dr. Kurt Getsinger of the US Army Corps of Engineers to Timothy C. Dole of the US EPA Office of Pesticide Programs.
3. The area treated for Backpack Sprayer (Mix/Load/Apply) is 40 gallons per day from ExpoSAC Policy #9 divided by the label recommended spray volume of 20 gallons per acre.
4. The area treated for Backpack Sprayer (Apply Only) is 4 acres per day based upon the acreage treated in CA DPR HS-1769 normalized to an 8 hour day.
5. The area treated for ROW sprayers was determined by the dividing the daily spray volume handled (1000 gallons per

day) from ExpoSAC Policy #9 by the label recommended spray volume of 20 gallons per acre for weed control and 400 gallons per acre for woody brush control.
6. The area treated for foliar application of liquids to floating aquatic weeds is based upon use information reported in the HED Memorandum "Occupational and Residential Exposure Characterization/Risk Assessment for Triclopyr Triethylamine for Aquatic Weed Control, DP Barcode D269448 of 7/22/2002.
7. The area treated for application of granules to submersed aquatic weeds is based upon information provided in an email of 11/22/2000 from Jim Kannenburg of Marine Biochemists/Applied Biochemists to Troy Swackhammer of the US EPA Office of Pesticide Programs.

Summary of Risk Concerns and Data Gaps for Handlers

The MOEs for handlers are summarized in Tables 22 and 23 below. With the exception of mixing/loading wettable powder, all of the short-term and intermediate-term MOEs exceed the target of 100 with baseline PPE (i.e., long-sleeved shirt, long pants, shoes plus socks, no respirator) or single layer PPE (i.e., long-sleeved shirt, long pants, shoes plus socks, gloves, no respirator) and are not of concern. The MOEs for handling wettable powder are adequate with engineering controls (i.e. water soluble bags).

Table 22. MOEs for Short-Term Risk to Occupational Handlers

Exposure Scenario	Crop Type	Application Rate (lb ae/acre)	Acres/ Day	Base-line	Single Layer	Eng. Control
Mixer/Loader (M/L)						
M/L WP	All Crops	0.25 to 4	5 to 1200	**≥1**	**≥5**	≥260
M/L Liquids	All Crops	0.25 to 4	5 to 1200	**≥1**	**≥89**	≥330
M/L Liquids	Submersed Weeds	54	30	**3.2**	260	980
Load Granulars for Broadcast Spreader	Golf Courses and Aquatic Areas	2 to 54	40 or 50	≥220	≥230	>1000
Applicator (APP)						
Aerial Application	All Crops	1.25 to 4.0	1200	ND	ND	>550
Groundboom Application	All Crops	1.25 to 4	40 to 200	>1000	>1000	>1000
Subsurface Aquatic Application of Liquids	Submersed Weeds	54	30	430	430	>1000
Airblast Application	Citrus	0.1	40	>1000	>1000	>1000
Backpack Application	Conifer Release	4	4	ND	140	ND
ROW Application	Weed Control	2	50	110	350	ND
Foliar Aquatic Application of Liquids	Floating Weeds	2	10	280	870	ND
Turfgun Application	turf	1.5	5	ND	>1000	>1000
Broadcast Spreader Application	Golf Courses and Aquatic Areas	1.5 or 54	40 or 50	>250	>290	>1000
Mixer/Loader/Applicator (M/L/A)						

Exposure Scenario	Crop Type	Application Rate (lb ae/acre)	Acres/ Day	Base-line	Single Layer	Eng. Control
M/L/A Liquids with Backpack Sprayer	Christmas Trees	4	2	ND	730	ND
M/L/A WD Granules with a Turfgun	turf	1.5	5	ND	>1000	ND
M/L/A Wettable Powder with a Turf Gun	turf	1.5	5	ND	>1000	>1000
M/L/A Liquid Flowables with a Turfgun	turf	1.5	5	ND	>1000	ND
Load/Apply Granules with a Push Spreader	turf	1.5	5	ND	710	ND
Flagger						
Flag Aerial Liquid Application	All Crops	1.25 to 4.0	1200	≥210	≥200	≥1000
MOEs in bold font do not exceed the target MOE of 100 and are of concern **ND** not determined						

Table 23. MOEs for Intermediate-Term Risk to Occupational Handlers

Exposure Scenario	Crop Type	Application Rate (lb ae/acre)	Acres/ Day	Base-line	Single Layer	Eng. Control
Mixer/Loader (M/L)						
M/L WP	All Crops	0.25 to 4	5 to 1200	**≥1.1**	**≥7.3**	≥360
M/L Liquids	All Crops	0.25 to 4	5 to 1200	**≥1.5**	≥130	≥460
M/L Liquids	Submersed Weeds	54	30	**2.2**	190	690
Load Granulars for Broadcast Spreader	Golf Courses or Aquatic Areas	1.5 or 54	40 or 50	≥150	≥160	>1000
Applicator (APP)						
Aerial Application	All Crops	0.5 to 2.0	1200	ND	ND	>770
Groundboom Application	All Crops	0.5 to 4	40 to 200	>1000	>1000	>1000
Subsurface Aquatic Application	Submersed Weeds	54	30	300	300	>1000
Airblast Application	Citrus	0.1	40	>1000	>1000	>1000
Backpack Application	Conifer Release	2	4	ND	200	ND
ROW Application	Weed Control	2	50	**78**	240	ND
Foliar Aquatic Application of Liquids	Floating Weeds and Wild Rice	4 or 0.25	10	≥200	≥610	ND
Turfgun Application	turf	1.5	5	ND	>1000	ND
Broadcast Spreader Application	Golf Courses and Aquatic Areas	1.5 or 54	40 or 50	≥180	≥200	ND
Mixer/Loader/Applicator (M/L/A)						

Exposure Scenario	Crop Type	Application Rate (lb ae/acre)	Acres/ Day	Base-line	Single Layer	Eng. Control
M/L/A Liquids with Backpack Sprayer	Conifer Plantations	4	2	ND	510	ND
M/L/A WD Granules with a Turfgun	turf	1.5	5	ND	>1000	ND
M/L/A Wettable Powder with a Turf Gun	turf	1.5	5	ND	>1000	>1000
M/L/A Liquid Flowables with a Turfgun	turf	1.5	5	ND	>1000	ND
Load/Apply Granules with a Push Spreader	turf	1.5	5	ND	500	ND
Flagger						
Flag Aerial Liquid Application	All Crops	0.50 to 2.0	1200	≥660	≥610	≥1000
MOEs in bold font do not exceed the target MOE of 100 and are of concern						

d. Occupational Postapplication Risk

Post application 2,4-D exposures can occur in the agricultural environment when workers enter fields recently treated with 2,4-D to conduct tasks such as scouting and irrigation. In the Worker Protection Standard (WPS), a restricted entry interval (REI) is defined as the duration of time which must elapse before residues decline to a level so entry into a previously treated area and engaging in a specific task or activity would not result in exposures that are of concern. The WPS REI for 2,4-D is 12 hours for the ester and sodium salt forms and is 48 hours for the acid and amine salt forms.

1) Exposure Scenarios, Data, and Assumptions

Postapplication dislodgeable foliar residue (DFR) data were submittted for 2,4-D as well as turf transferable residue (TTR) data from treated turf. Three turf transferable residue (TTR) studies were submitted by the Broadleaf Turf Herbicide TTR Task Force. These studies are described in "2,4-D: 3rd Revised Occupational and Residential Exposure (ORE) and Risk Assessment and Response to Public Comments for the Reregistration Eligibility Decision (RED) Document"dated May 4, 2005, and in Appendix F of that document. These data were used in the human health risk assessment along with standard transfer coefficients based on EPA Science Advisory Council guidance to assess potential exposures to workers reentering treated sites.

For all other postapplication activities, EPA used the EPA Science Advisory Council for Exposure (Exposure SAC) policy on agricultural transfer coefficients.

The following assumptions were made regarding postapplication occupational exposure:

- Short term risks were assessed using master label rates.
- Intermediate term risks were assessed using average application rates when available.

- The transfer coefficients are from an interim transfer coefficient policy developed by HED's Science Advisory Council for Exposure using proprietary data from the Agricultural Re-entry Task Force (ARTF) database (US EPA, August 7, 2001). This policy will be periodically updated to incorporate additional information about agricultural practices in crops and new data on transfer coefficients. Much of this information will originate from exposure studies currently being conducted by the ARTF, from further analysis of studies already submitted to the Agency, and from studies in the published scientific literature.
- The transfer coefficients for turf harvesting and maintenance are based upon recently conducted ARTF studies that are being reviewed by EPA.
- In cases where applications would be made in such a way as to minimize contact with crop foliage postapplication exposures are expected to be negligible and are not assessed. These cases are included in "2,4-D: 3rd Revised Occupational and Residential Exposure and Risk Assessment and Response to Public Comments for the Reregistration Eligibility Decision (RED) Document (PC Code 030001, DP Barcode D316596)", dated May 4, 2005.
- The initial percent of application rate as Dislodgeable Foliar Residue (DFR) was assumed to be 20% for all crops except turf. This is the standard value used in the absence of chemical specific data.

2) Occupational Postapplication Risk Estimates

All short- and intermediate-term MOEs are above 100 on day zero. All occupational postapplication risk scenarios are not of concern. Short-term and intermediate-term risk estimates are shown in Tables 24 and 25 below.

Table 24. 2,4-D Postapplication Short-Term Worker Risks

Crop Group	ShortTerm MOE on Day 0			
	Application Rate (lb a.e./acre)	Low Exposure Scenarios	Medium Exposure Scenarios	High Exposure Scenarios
Field/row crop, low/med (cereal grains)	1.25	6,700	450	NA
Field/row crop, low/med (rice)	1.5	5,600	370	NA
Field/row crop, tall (corn) Pre-harvest rate for field corn Post-emergence rate for sweet corn	 1.5 0.5	 5,600 17,000	 1,400 4,200	 560 NA
Field/row crop, tall (sorghum)	1.0	8,400	2,100	NA
Sugarcane	2.0	NA	420	210
Turf - California Turf - North Carolina	2.0 2.0	1,900 860	NA NA	950 430

Table 25. 2,4-D Postapplication Intermediate Term Worker Risks

Crop Group	Intermediate Term MOE on Day 0			
	Application Rate+ (lb a.e./acre)	Low Exposure Scenarios	Medium Exposure Scenarios	High Exposure Scenarios
Field/row crop, low/med (cereal grains)	0.5	12,000	780	NA
Field/row crop, low/med (rice)	0.92	6,400	420	NA
Field/row crop, tall (field corn)	0.44	13,000	3,300	1,300
Field/row crop, tall (sweet corn)	0.48	13,000	3,100	NA
Field/row crop, tall (sorghum)	0.46	13,000	3,100	NA
Sugarcane	0.75	NA	780	390
Turf - California Turf - North Carolina	2.0 2.0	1,600 610	NA NA	810 300
+ Average application rates as reported in the QUA report or NASS report were used when available.				

7. Human Incident Data

In evaluating incidents to humans, the Agency reviewed reports from the National Poison Control Centers, the EPA OPP's Incident Data System (IDS), the California Pesticide Illness Surveillance Program, and the National Pesticide Telecommunications Network (NPTN).

The Agency reviewed 2,4-D incident reports in January 2004. A total of 45 incidents were reported in the OPP Incident Data System and many of these incidents involved irritant effects to the eyes, skin and occasionally respiratory passages. Poison Control Center Incident Data (1993 to1998) indicated that 2,4-D is generally less likely than other pesticides to cause minor, moderate or life threatening symptoms. The most common symptoms were dermal irritation and ocular problems. Incident data from the California Pesticide Illness Surveillance Program indicated that the number of cases generally ranges from 0 to 3 per year and most of these cases were due to eye or skin effects. Incident data from the National Pesticide Information Center for the years 1996 to 2002 indicated that an average of 3 cases definitely or probably related to 2,4-D exposure were reported per year.

8. Cancer Epidemiology Studies

A Science Advisory Board/Scientific Advisory Panel Special Joint Committee reviewed available epidemiological and other data on 2,4-D in 1992 and concluded that "the data are not sufficient to conclude that there is a cause and effect relationship between exposure to 2,4-D and non-Hodgkin's lymphoma" and 2,4-D was classified as a Group D, not classifiable as to human carcinogenicity. The Agency has twice recently reviewed epidemiological studies linking cancer to 2,4-D. In the first review, completed January 14, 2004, EPA concluded there is no additional evidence that would implicate 2,4-D as a cause of cancer (EPA, 2004). The second recent review of available epidemiological studies occurred in response to comments received during the Phase 3 Public Comment Period during the reregistration process for 2,4-D. EPA's report, dated December 8,

2004 and authored by Jerry Blondell, Ph.D., found that none of the more recent epidemiological studies definitively linked human cancer cases to 2,4-D.

B. Environmental Risk Assessment

A summary of the Agency's environmental risk assessment for 2,4-D is presented below. The Agency has conducted an assessment of potential risks to aquatic and terrestrial organisms resulting from the use of 2,4-D and its associated chemical forms including 2,4-D dimethylamine salt (2,4-D DMAS), 2,4-D isopropylamine salt (2,4-D IPA), 2,4-D triisopropanolamine salt (2,4-D TIPA), 2,4-D ethylhexyl ester (2,4-D EHE), 2,4-D butoxyethyl ester (2,4-D BEE), 2,4-D-diethanolamine salt (2,4-D DEA), 2,4-D isopropyl ester (2,4-D IPE) and 2,4-D sodium salt. In this document, the term "chemical form" is used to refer to the supported technical formulations listed above, while the term "formulation" refers to the physical nature (e.g. granular or emulsifiable concentrate) of the applied product, and the term "end use product" is used to refer to any formulated product including mixtures of pesticide sold in the United States.

2,4-D has the following registered uses, which result in environmental exposures: pasture/rangeland, turf, wheat, corn, soybeans, fallowland, hay other than alfalfa, noncropland (roadways, rights-of-way, ditches, industrial sites, etc.), forestry, rice, sugarcane, pome fruits, stone fruits, nut orchards, filberts, grass grown for seed and sod, aquatic weed control, potatoes, asparagus, strawberries, blueberries, grapes, cranberries, and citrus.

This summary will present exposure estimates and hazard determinations associated with 2,4-D and its various chemical forms. In addition, risks of concern, as determined in the environmental assessment, will be identified and characterized. More detailed information associated with the potential environmental risk from the use of 2,4-D can be found in the Environmental Fate and Effects Division's Risk Assessment for the Reregistration Eligibility Document for 2,4-Dichlorphenoxyacetic Acid, (2,4-D), dated October 28, 2004. The complete environmental risk assessment is not included in this RED, but may be accessed in the OPP Public Docket (OPP-2004-0167) and on the Agency's website at http://www.epa.gov/pesticides/reregistration/status.htm.

1. Environmental Exposure

a. Environmental Fate and Transport

The environmental fate database is sufficient to characterize the environmental exposure associated with 2,4-D use. However, there are some studies that will be required as a result of the reregistration process. An aerobic aquatic metabolism study for 2,4-D BEE in acidic aquatic environments is required, along with several other dissipation studies. See section V.A.1 of this reregistration eligibility decision (RED) document for a complete list of all required studies. EPA intends to issue a DCI as part of this RED to require submission of additional data to address areas of uncertainty. These data are expected to confirm the conclusions of this environmental risk assessment.

Database

A complete database has been assembled for 2,4-D acid. The dissipation of 2,4-D appears to be dependent on oxidative microbial-mediated mineralization, photodegradation in water, and leaching. 2,4-D is stable to abiotic hydrolysis. Photodegradation of 2,4-D was observed [half life ($t_{1/2}$) =12.9 calendar days or 7.57 days of constant light] in pH 5 buffer solution. However, the 2,4-D photodegradation half-life on soil was 68 days.

Degradation Summary

The degradation of 2,4-D was rapid ($t_{1/2}$= 6.2 days) in aerobic mineral soils. The half-life of 2,4-D in aerobic aquatic environments was 15 days. 2,4-D was moderately persistent to persistent ($t_{1/2}$= 41 to 333 days) in anaerobic aquatic laboratory studies.

Several degradates were detected in the laboratory fate studies reviewed. The degradates detected were 1,2,4-benzenetriol, 2,4-DCP, 2,4-DCA, chlorohydroquinone (CHQ), 4-chlorophenol, volatile organics, bound residues, and carbon dioxide. For a complete listing of 2,4-D degradates for each route of degradation, please see the environmental risk assessment. No degradates were considered for further analysis in water or the terrestrial ecological assessment.

Mobility

2,4-D has a low binding affinity (K_{ad} < 3 and K_{de} < 1) in mineral soils and sediment. The mobility of 2,4-D in supplemental soil thin layer chromatography (TLC) studies was classified as intermediately mobile (R_f=0.41) to very mobile (R_f=1.00) in "sieved" mineral soils. Aged radiolabeled residues of 2,4-D appeared to be immobile in supplemental soil column studies. 2,4-D was studied in sandy loam, sand, silty clay loam and loam soil. Freundlich K_{ads} values were 0.17 for the sandy loam soil, 0.36 for the sand soil, 0.52 for the silty clay loam soil, and 0.28 for the loam soil. Corresponding K_{oc} values were 70, 76, 59 and 117 mL/g.

Bridging Strategy

The 1988 2,4-D Registration Standard proposed an environmental fate strategy for bridging the degradation of 2,4-D esters and 2,4-D amine salts to 2,4-D acid. The bridging provides information on the dissociation of 2,4-D amine salts and hydrolysis of 2,4-D esters is included in the ecological risk assessment. The bridging data indicate esters of 2,4-D are rapidly hydrolyzed in alkaline aquatic environments, soil/water slurries, and moist soils. The 2,4-D amine salts have been shown to dissociate rapidly in water. However, 2,4-D esters may persist under sterile acidic aquatic conditions and on dry soil. These bridging data indicate under most environmental conditions 2,4-D esters and 2,4-D amines will degrade rapidly to form 2,4-D acid.

2,4-D Amine Salts

Additional data submitted subsequent to establishment of the environmental fate bridging strategy generally support the strategy for the amine salts. Direct evidence of the stability of 2,4-D amine salts in soil and aquatic environments is difficult due to the lack of analytical methods. Based on maximum application rates for 2,4-D amine salts (at 4 lbs ae/A), 2,4-D amine salts are expected to fully dissociate in soil environments because their theoretical concentrations in soil solution does not exceed water solubilities. Additionally, dissociation studies indicate the time for complete

dissociation is rapid (less than 3 minutes). Although the analytical methods in the field studies for 2,4-D DMAS were not capable of separating and identifying 2,4-D DMAS from 2,4-D acid, the most conservative half-lives of 2,4-D DMAS would be equivalent to the 2,4-D acid half-lives in field studies. Half-lives of 2,4-D in 2,4-DMAS field studies ranged from 1.1 days to 30.5 days with a median half-life of 5.6 days.

2,4-D Esters

The conversion of 2,4-D esters to the acid and an associated alcohol moiety is more difficult to generalize. Unlike the physical dissociation mechanism of 2,4-D amine salts, the de-esterification of 2,4-D esters is dependent on abiotic and microbial-mediated processes. Any environmental variable influencing microbial populations or microbial activity could theoretically influence the persistence of the 2,4-D ester. Soil properties including clay mineralogy, organic carbon content, temperature, and moisture content are known to influence hydrolysis rates (Wolfe, et al, 1989 and Wolfe, 1990).

Registrant-sponsored research indicates the 2,4-D esters (ethylhexyl, isopropyl, butoxyethyl) degrade rapidly (half life less than 24 hours) in soil slurries, aerobic aquatic environments, and anaerobic, acidic aquatic environments. In terrestrial field dissipation studies for 2,4-D EHE, the half-lives for 2,4-D EHE ranged from 1 to 14 days with median half-life of 2.9 days. 2,4-D BEE, applied as a granule formulation, degraded rapidly in the water column in aquatic field dissipation studies under alkaline conditions. However, the 2,4-D BEE residues were detected in sediment samples from Day 0 (immediately posttreatment) to 186 days posttreatment. It is unclear whether 2,4-D BEE persistence in sediment is due to the slow release of the granule formulation or to slow de-esterification of sediment bound 2,4-D BEE. Available open-literature and registrant sponsored laboratory data would suggest slow granule dissolution prolonged the persistence of 2,4-D BEE. In forest dissipation studies, the 2,4-D EHE ester degraded slowly on foliage and in leaf litter.

Persistance of 2,4-D Amine Salts and 2,4-D Esters

The weight of evidence from open-literature and registrant sponsored data indicates that 2,4-D amine salts and 2,4-D esters are not persistent under most environmental conditions including those associated with most sustainable agricultural conditions. 2,4-D amine salt dissociation is expected to be instantaneous (< 3 minutes) under most environmental conditions. Although the available data on de-esterification of 2,4-D ester may not support instantaneous conversion from the 2,4-D ester to 2,4-D acid under all conditions, it does show 2,4-D esters in normal agriculture soil and natural water conditions are short lived compounds (< 2.9 days). Under these conditions, the environmental exposure from 2,4-D esters and 2,4-D amines is expected to be minimal in both terrestrial and aquatic environments.

b. Aquatic Organism Exposure

For exposure to aquatic fish and invertebrates, EPA considers surface water exposure only, since most aquatic organisms are not found in ground water. Surface water models are used to estimate exposure to freshwater aquatic animals. Unlike the drinking water assessment described in the human health risk assessment section of this document, the ecological water resource assessment does not include the Index Reservoir (IR) and Percent-Crop Area (PCA) factor refinements. The IR

and PCA factors represent a drinking water reservoir, not the variety of aquatic habitats, such as ponds adjacent to treated fields, relevant to a risk assessment for aquatic animals. Therefore, the EEC values used to assess exposure to aquatic animals are not the same as the values used to assess human dietary exposure from drinking water sources.

1) Exposure to 2,4-D Acid in Surface Water

The aquatic exposure assessment for 2,4-D has relied on a combination of monitoring data and modeling. Both Tier I (SCIGROW and screening level models for aquatic uses) and Tier II (PRZM/EXAMS) models have been used to estimate exposure to 2,4-D and its various chemical forms in a variety of exposure scenarios. Concentrations used for ecological assessment are 62.8 ug ae/L for peak, 55.1 ug ae/L for the 21-day average concentration, and 45.4 ug ae/L for the 60-day average. The predicted 2,4-D concentrations in surface water are slightly higher than reported monitoring data. The modeling predictions are expected to indicate upper bound concentration ranges for 2,4-D. Model input and output files for the ecological assessment may be found in the ecological risk assessment for 2,4-D.

2) Surface Water Modeling of 2,4-D Esters

The Agency's strategy for bridging the fate data requirements for the ester and amine salt forms of 2,4-D to the acid form was supported by laboratory data which indicated rapid conversion of the amine and ester forms of 2,4-D to the acid form. However, 2,4-D esters may persist under acidic aquatic conditions. In order to account for the potential impact of the spray application of 2,4-D esters to aquatic environments, and to account for runoff during the time in which 2,4-D EHE may remain in the field, the Agency conducted additional modeling with PRZM/EXAMS to assess the potential for aquatic organisms to be exposed to 2,4-D EHE through spray drift or runoff. The peak (acute) estimated environmental concentrations (EECs) for the 2,4-D esters were estimated for each scenario and range from 0.6 ug ae/L (CA citrus) to 7.4 ug ae/L (NC pasture). A chronic EEC was not provided in this scenario because the hydrolysis soil slurry data indicate that dissipation in a non-sterile water body will occur at all pHs and therefore long-term exposures are unlikely.

3) Modeling of Direct Application of 2,4-D for Control of Aquatic Weeds

Because there are no aquatic herbicide model scenarios, a first approximation of an aquatic ecological EEC was predicted assuming direct application to the standard pond. For this assessment, the Agency developed a simple spreadsheet model that incorporates degradation based on an acceptable aerobic aquatic metabolism study for the EFED standard pond with no flow. In this model, the 21-day average and 60-day average concentrations were calculated assuming first-order dissipation from aerobic aquatic degradation, but does not assume dissipation.

The interpretation of the label for aquatic weed control is that the target rate for 2,4-D amine (2,4-D DMAS) and ester (2,4-D BEE) use is based on concentration and not application rate. In order to account for this scenario it was assumed that 2,4-D would be applied at a rate to meet the target concentration of 4000 ug/l. This assumption would be applicable across all water bodies since

the target rate is based on a rate per acre foot of water (10.8 lbs ae/acre-foot) and would be independent of water body geometry/volume. This scenario included the assumption of uniform application across the entire water body; however, this application scenario will over-predict actual concentrations because 2,4-D is not applied to more than 50% of a water body in a single treatment. Treating more than 50% of a water body will result in oxygen depletion due to decaying plant material. Typically, 2,4-D is applied to control aquatic weeds in littoral zones that make up less than 50% of the water body. Modeling the 2,4-D concentration that results when 100% of the water body is treated predicts direct water application of 2,4-D will yield surface water concentrations of 2,4-D concentrations in the EFED standard pond of 4000 ug ae/L for peak, 3417 ug ae/L for the 21-day average, and 2610 ug ae/L for the 60-day average. Actual concentrations are expected to be less given the conservative treatment area assumption as described above, and the likely effects of dispersion on 2,4-D concentrations.

EFED evaluated the potential for exposure to 2,4-D BEE using a similar approach. Modeling predicts direct water application of 2,4-D BEE will yield surface water concentrations of 2,4-D BEE concentrations in the EFED standard pond of 624 ug/L for peak (24 hour average), 30 ug/L for the 21-day average, and 10 ug/L for the 60-day average.

4) Modeling of 2,4-D Use on Rice

Finally, the use of 2,4-D on rice was evaluated using a screening level model. 2,4-D is registered for use in rice paddies for the acid and amine salt forms of 2,4-D (esters are not registered for rice use) with a maximum seasonal application rate of 1.5 pounds ae per acre. Modeling of this use rate results in an estimated acute 2,4-D concentration in the rice paddy of 1431 ug ae/L. This value is expected to represent upper percentile concentrations for edge of paddy concentrations because of the lack of consideration for degradation, dilution and dispersion. EFED conducted a preliminary evaluation of the effect of degradation and holding times on EECs for the use of 2,4-D on rice. As with the previous rice model, this refined model provides a single EEC which represents both an acute and chronic exposure and is an approximation of the EEC at the point of release into a receiving water body. Modeling with all three scenarios predict initial concentrations in the paddy water between 678 ug ae/L (California) and 762 ug ae/L (Louisiana) and decreasing concentrations with holding times based on degradation due to aerobic aquatic metabolism.

c. Terrestrial Organism Exposure

The Agency assessed exposure to terrestrial organisms by first predicting the amount of 2,4-D residues found on animal food items and then by determining the amount of pesticide consumed by using information on typical food consumption by various species of birds and mammals. The amount of residues on animal feed items are based on the Fletcher nomogram (a model developed by Fletcher, Hoerger, Kenaga, et al.)[1] and the current maximum application rate as stated in the Master Label for 2,4-D. For terrestrial uses of 2,4-D, the Master Label allows a maximum single application of 4 lbs ae/A and up to two 2 lbs ae/A applications per season for a total seasonal maximum rate of 4

lbs ae/A. Therefore, for terrestrial uses, EPA modeled the maximum and mean residues of 2,4-D in various food items immediately after the 4 lb lbs ae/A application. The Agency assumed no dilution due to the growth of the plants or degradation of 2,4-D. EPA's estimates of 2,4-D residues on various wild animal food items are summarized in Table 26. EPA used these EECs and standard food consumption values to estimate dietary exposure levels for 2,4-D to birds and mammals.

Table 26. Estimated Environmental Concentrations on Avian and Mammalian Food Items (ppm) Following a Single Application at 1 lb ae/A

Food Items	EEC (ppm) Predicted Maximum Residue[1]	EEC (ppm) Predicted Mean Residue[1]
Short grass	240	85
Tall grass	110	36
Broadleaf/forage plants and small insects	135	45
Fruits, pods, seeds, and large insects	15	7

[1] Predicted maximum and mean residues are for a 1 lb ae/a application rate and are based on Hoerger and Kenaga (1972) as modified by Fletcher *et al.* (1994).

1) Birds and Mammals

The Agency expects exposure to birds and mammals from residues of 2,4-D on food items. Exposure is probable because 2,4-D is applied in many different environments that provide habitats rich in food sources attractive to various avian and mammalian species.

a) Exposure to Nongranular (Liquid) Formulations

Toxicant concentrations on food items following multiple applications are predicted based on a first-order residue decline using the Agency's FATE5 model. The FATE5 model allows determination of residue dissipation over time by incorporating degradation half-life. Predicted maximum and mean EECs resulting from multiple applications are calculated by taking into account the maximum or mean initial EEC from the first application, the total number of applications, the time interval between applications, and a first-order foliar degradation rate of 8.8 days.

b) Exposure to Granular Formulations

Birds and small mammals may be exposed to granular formulations through ingestion of granules. The number of lethal doses (LD_{50}) that are available within one square foot immediately after application (LD_{50}/ft^2) is used as the risk quotient (RQ) for granular products. RQs are calculated for three separate weight classes of birds (1000 g, 180 g, and 20 g) and mammals (15 g, 35 g, and 1000 g, 35 g, and 15 g).

2) Non-target Terrestrial Plants

Due to the differences in the solubilities of the acid and amine salts when compared to the solubilities of the esters, risks for these two groups were calculated separately for the non-target terrestrial plant risk assessment. The terrestrial plant toxicity data for the 2,4-D acid and amine salts were bridged as one group, while that of the esters were bridged as another group.

Terrestrial plants inhabiting dry and semi-aquatic areas may be exposed to pesticides from runoff, spray drift or volatilization. EPA's runoff exposure estimate assumes a 1-in-10 year rain event and is based on a pesticide's water solubility and the amount of pesticide present on the soil surface and its top one inch, characterized as "sheet runoff" (one treated acre to an adjacent acre) for dry areas, characterized as "channelized runoff" (10 treated acres to a distant low-lying acre) for semi-aquatic areas, and is based on percent runoff values of 0.01, 0.02, and 0.05 for water solubility of <10 ppm, 10-100 ppm, and >100 ppm, respectively. The modeled runoff exposure estimates likely over-estimate actual exposures from runoff, given the conservative 1-in-10 year rain event assumption, and also given that farming practices, intended to minimize soil loss from runoff, are not taken into account.

Spray drift exposure from ground and overhead chemigation applications is assumed to be 1% of the application rate. Spray drift from aerial, airblast, and forced-air applications is assumed to be 5% of the application rate with an application efficiency (i.e., the amount that lands on the target area) of 60%. The effects of multiple applications are addressed by summing the application rates from individual applications.

Applications of granular formulations may pose risks to terrestrial plants inhabiting dry and semi-aquatic areas. Exposure is assumed to be from runoff only, and drift is assumed not to occur with granular applications of pesticides. Therefore, the Agency's runoff scenario is essentially the same as that used in the non-granular scenario described above, with the exception that the drift component is removed.

The EECs for the acid and amine salts as well as the esters to dry and semi-aquatic areas are tabulated in Appendix F of the 2,4-D ecological risk assessment for single applications to the targeted use sites. The percent runoff value based on water solubility is assumed to be 5% for the acid and amines and 1% for the esters.

2. Environmental Effects (Toxicity)

a. Toxicity to Aquatic Organisms

<u>Freshwater and Estuarine/Marine Fish</u>

The available acute toxicity data on 2,4-D indicate that the acid and amine salts are practically non-toxic to freshwater or marine fish. The esters are highly to slightly toxic to marine or freshwater fish. Toxicities for the acid and amine salts range from a LC_{50} of >80.24 to 2244 milligrams acid equivalent per liter (mg ae/L). The ester toxicities range from a LC_{50} of >0.1564 to 14.5 mg ae/L.

Chronic toxicity, based on length and larval survival from the early life stage studies, range from a NOEC of 14.2 to 63.4 mg ae/L for 2,4-D acid, 2,4-D DEA and 2,4-D DMAS. The NOEC based on larval fish survival for the fish full life cycle studies ranged from 0.0555 to 0.0792 mg ae/L for 2,4-D BEE and 2,4-D EHE.

Amphibians

Although not currently required by the Agency, freshwater amphibian studies were conducted on frog tadpoles (Rana pipiens). Tests were conducted using the ASTM (American Society for Testing and Materials) Standard E729-88a. Tests indicate that 2,4-D acid, 2,4-D DMA, and 2,4-D EHE are practically non-toxic to tadpoles.

Freshwater and Estuarine/Marine Invertebrates

Acute toxicity of 2,4-D acid and amine salts to freshwater aquatic invertebrates ranges from a LC_{50} of 25 to 642.8 mg ae/L (slightly toxic to practically non-toxic). The freshwater toxicities of the esters range from 2.2 mg ae/L for the 2,4-D IPE to 11.88 mg ae/L for the 2,4-D EHE (moderately toxic to slightly toxic). Acute toxicity of 2,4-D acid and amine salts to marine invertebrates range from an LC_{50} of 49.6 for 2,4-D IPA to 830 mg ae/L for 2,4-D DMA (slightly toxic to practically non-toxic). The marine invertebrate LC_{50} s range from >0.092 to >66 mg ae/L for the 2,4-D esters (highly toxic to practically non-toxic). These toxicities indicate that the esters are more toxic than the acid and amine salts. Although acute data are missing for some of the amine salts, these studies will not be required because none of the RQs exceed the aquatic levels of concern for the acid amine salts.

Chronic toxicity tests for freshwater and estuarine/marine invertebrates were performed on 2,4-D acid, 2,4-D DEA, 2,4-D DMAS, and 2,4-D BEE. The toxicity ranged from a NOEC of 16.05 mg ae/l for 2,4-D DEA (survival and reproduction) and 79 mg ae/L for the 2,4-D acid (number of young). The chronic freshwater NOEC is 0.20 mg ae/L for the 2,4-D BEE (survival and reproduction). There are no freshwater or marine chronic toxicity data for any of the other 2,4-D esters.

Although an estuarine/marine invertebrate life-cycle toxicity test using the TGAI is required to establish the toxicity of products containing the 2,4-D acid, salts, and amines, a chronic study will not be required. The data from the freshwater invertebrate studies will be bridged to the estuarine/marine invertebrates for the 2,4-D acid and amine salts. The RQs for the freshwater chronic studies were well below the levels of concern, and the chronic risk for estuarine/marine invertebrates would be expected to be low. However, there is a risk concern for for estuarine/marine invertebrates for the 2,4-D esters. A chronic study will be required for 2,4-D BEE to reduce the uncertainty to estuarine/marine invertebrates.

Aquatic Plants

The vascular plant EC_{50} toxicity data for the acid and amine salts range from 0.29 mg ae/L for 2,4-D DEA to 1.28 mg ae/L for 2,4-D TIPA. The EC_{50} toxicity data for the more toxic esters range from 0.33 mg ae/L for 2,4-D EHE to 0.3974 mg ae/L for 2,4-D BEE. The same trend is shown for the

non-vascular plant EC_{50}. The nonvascular plant EC_{50} toxicity data range for the acid and amine salts is 3.88 to 156.5 mg ae/L for 2,4-D DMA. The range for the esters is 0.066 mg ae/L for 2,4-D EHE to 19.8 mg ae/L for 2,4-D EHE. In addition, based on the data available, it appears that the vascular plants are more than two orders of magnitude more sensitive than the non-vascular plants.

b. Toxicity to Terrestrial Organisms

The bird and mammal toxicity values of the 2,4-D acid, salts, amine salts, and esters were pooled because the toxicity values were within one to two orders of magnitude for all the chemical forms.

Birds

Toxicity ranges for birds do not show distinct differences between the acid, salts, amine salts, and esters, as indicated for aquatic animals. All studies have been conducted with the active ingredient, and have been converted to the acid equivalent since use rates on the master label are given in pounds acid equivalent per acre.

2,4-D is classified as moderately toxic to practically non-toxic to birds on an acute oral basis, since the oral LD_{50} ranges from 500 mg ai/kg (415 mg ae/kg) for 2,4-D DMAS to >1000 mg ae/kg for the 2,4-D acid.

The chronic NOEC of 962 ppm is based on the endpoints of eggs cracked and a decreased number of eggs laid for the 2,4-D acid. There is no comparable study for the mallard duck and no other avian chronic study was performed on any of the other active ingredients.

Mammals

The Agency expects exposure to mammals from residues of 2,4-D on food items, since 2,4-D is used in many different mammalian habitats, including pasture and rangeland, and turf lawns. Toxicity ranges for mammals do not show distinct differences between the acid, salts, amine salts, and esters as indicated for aquatic animals. All studies have been conducted with the active ingredient, and have been converted to the acid equivalent since all use rates on the master label are given in pounds acid equivalent per acre. The rat LD_{50} ranged from 579 to 1300 mg ae/kg.

Mammalian chronic toxicity values are from rat and rabbit developmental toxicity studies for the 2,4-D acid and all amine salts, and esters. In addition, the 2-generation rat study is also available for the 2,4-D acid. The NOAEL in the rat chronic toxicity study was 5 mg/kg/day, with a LOAEL of 75 mg/kg/day based on decreased body-weight gain and alterations in hematology. The NOAEL in the rabbit developmental toxicity study was 30 mg/kg/day, and the LOAEL was 90 mg/kg/day based on clinical signs, loss of righting reflex, and abortions.

Non-Target Insects

Available data from a honey bee acute toxicity study indicated that technical 2,4-D is practically non-toxic to the honey bee. The LD_{50} in the honey bee acute toxicity study is greater than 10 micrograms per bee; see MRID 445173-04 for 2,4-D DMA and MRID 445173-01 for 2,4-D EHE. Minimal risk is expected to non-target insects from 2,4-D use.

Terrestrial Plants

The terrestrial plant runoff exposure scenario is based on the solubility of the 2,4-D compound. The water solubilities differ greatly between 2,4-D esters and 2,4-D acid and amine salts. The terrestrial plant toxicity values for 2,4-D acid and amine salts is summarized in Table 27, and have been listed as the acid equivalent. The sensitivity ranges for the monocot and dicot species are listed for the seedling emergence and vegetative vigor studies.

Table 27. Terrestrial Plant Toxicity Summary for 2,4-D Acid and amine salts

Study Type		Most sensitive Crop / Active Ingredient	EC25 / NOEC (lb ae/A)
Seedling Emergence	Monocot	Sorghum / 2,4-D DMAS	0.026 / 0.015
	Dicot	Mustard /2,4-D DEA	0.045 / <0.045
Vegetative Vigor	Monocot	Onion / 2,4-D Acid	<0.0075 / <0.0075
	Dicot	Tomato / 2,4-D DEA	0.003 / 0.002

The terrestrial plant toxicity for the 2,4-D esters is summarized in Table 28. The sensitivity ranges for the monocot and dicot species are listed for the seedling emergence and vegetative vigor studies.

Table 28. Terrestrial Plant Toxicity Summary for 2,4-D Esters

Study Type		Most sensitive Crop / Active Ingredient	EC25 / NOEC (lb ae/A)
Seedling Emergence	Monocot	Onion / 2,4-D IPE	0.01 / 0.005628
	Dicot	Lettuce / 2,4-D IPE	0.00081 / 0.00047
Vegetative Vigor	Monocot	Corn /2,4-D IPE	0.2016 / 0.0252
	Dicot	Lettuce / 2,4-D IPE	0.00126 / 0.006132

3. Ecological Risk Estimation (RQs)

The Agency's ecological risk assessment compares toxicity endpoints from ecological toxicity studies to estimated environmental concentrations (EECs) based on environmental fate characteristics and pesticide use data. To evaluate the potential risk to non-target organisms from the use of 2,4-D

products, the Agency calculates a Risk Quotient (RQ), which is the ratio of the EEC to the most sensitive toxicity endpoint values. These RQ values are then compared to the Agency's levels of concern (LOCs), given in Table 29, which indicate whether a pesticide, when used as directed, has the potential to cause adverse effects on non-target organisms. When the RQ exceeds the LOC for a particular category (e.g., endangered species), the Agency presumes a risk of concern to that category. These risks of concern may be addressed by further refinements of the risk assessment or by mitigation. Use, toxicity, fate, exposure, and incidents are considered when characterizing the risk, as well as the levels of uncertainty in the assessment.

Table 29. EPA's Levels of Concern and Associated Risk Presumptions.

Risk Presumption	LOC terrestrial animals	LOC aquatic animals	LOC Plants
Acute Risk - there is potential for acute risk; regulatory action may be warranted in addition to restricted use classification.	0.5	0.5	1
Acute Restricted Use - there is potential for acute risk, but may be mitigated through restricted use classification.	0.2	0.1	N/A
Acute Endangered Species - endangered species may be adversely affected; regulatory action may be warranted.	0.1	0.05	1
Chronic Risk - there is potential for chronic risk; regulatory action may be warranted.	1	1	N/A

For a more detailed explanation of the ecological risks posed by the use of 2,4-D, refer to Environmental Fate and Effects Division's Risk Assessment for the Reregistration Eligibility Document for 2,4- Dichlorophenoxyacetic Acid (2,4-D), dated October 28, 2004.

a. Risk to Aquatic Organisms

The RQs for aquatic organisms are presented in detail in Appendix F of the ecological risk assessment for 2,4-D.

1) Fish and Aquatic Invertebrates

There were no acute or chronic Level of Concern (LOC) exceedances for aquatic organisms through use of 2,4-D acid and amine salts due to runoff/drift from use on terrestrial sites, no acute LOC exceedances for aquatic organisms due to drift-only of 2,4-D esters to water bodies from use on terrestrial sites, and, there were no acute LOC exceedances for aquatic organisms due to the runoff/drift of 2,4-D esters to water bodies from use on terrestrial sites. Chronic concerns were not evaluated for terrestrial uses of 2,4-D esters.

Estimated risk quotients (RQs) from use of 2,4-D acid and amine salts in aquatic weed control through direct subsurface application to water bodies exceed the restricted use LOCs for freshwater

invertebrates. There are no chronic LOC exceedances for this use. Estimated RQs for use of 2,4-D BEE in weed control through direct subsurface application to water bodies exceed the acute risk LOC for freshwater fish and invertebrates and chronic risk LOC for freshwater and estuarine fish and freshwater invertebrates when compared on an acid equivalent basis.

Additional characterization of the potential risk associated with the direct application of 2,4-D for aquatic weed control was completed by back-calculating the target concentration needed to reduce EECs below LOCs. This type of consideration provides context to the characterization of potential risk and indicates that for all 2,4-D chemical forms target concentration reduction of up to 10-fold still exceeds all LOCs for aquatic organisms.

While noting the potential risks identified above, it is important to note the benefits gained through the direct application of 2,4-D to aquatic bodies, for the control of invasive species. The U.S Army Corps of Engineers (USACE), among others, has identified 2,4-D as an important tool for protecting the nation's waters from the invasion and establishment of some of the world's worst species of exotic nuisance vegetation. 2,4-D has a reputation as a selective and economical means to remove invasive plants, enhance the growth and recovery of desirable native vegetation, restore water quality, reduce sedimentation rates in reservoirs, and improve fish and wildlife habitat. 2,4-D products are used to control invasive weeds, such as Eurasian watermilfoil (*Myriophyllum spicatum*) in the northern tier states and water hyacinth (*Eichhornia crassipes*) in the Gulf Coast states. Effective control of these plants can benefit public health with respect to reducing levels of mosquito habitat. In addition, according to USACE, no other product (or alternative technique) can control these plants in a more cost-effective manner (K. Getsinger, USACE, Public Comment; Docket ID# OPP-2004-0167-0053).

Estimated RQs for use of 2,4-D acid and amine salts in rice paddies exceed the acute endangered species LOCs for freshwater invertebrates. The rice model used to predict these EECs is a screening level model which predicts concentration in tailwater at the point of release from the paddy. It is anticipated that once released, the concentration will be reduced and subsequently is expected to decrease away from the point of release. Additional characterization was conducted by considering average application rates (average rates are presented in the quantitative usage analysis dated August 9, 2001 prepared by the Biological and Economic Affairs Division of EPA/OPP) versus maximum label rates and assuming a proportional reduction in EECs. Consideration of average application rates results in EECs below the endangered species LOC.

2) Aquatic Plants

For non-target, aquatic plants, estimated RQs resulting from the runoff/drift of 2,4-D acid and amine salts from use on terrestrial crops exceed the aquatic vascular plant endangered species LOCs for use of 2,4-D acid and amine salts on pasture and apples. Consideration of average application rates and assuming a proportional reduction in EECs results in RQs below the endangered species LOC. Likewise, there are no LOC exceedances from the drift of the ester forms to aquatic water bodies or from the runoff of the ester forms to water bodies from use on terrestrial sites.

Estimated RQs for the scenario of direct application to water for aquatic weed control for 2,4-D acid and amine salts indicate acute and endangered species LOC exceedances for aquatic vascular plants and acute LOC exceedances for non-vascular plants, while estimated RQs for the use of 2,4-D BEE for direct application to water to control aquatic weeds exceed all LOCs for vascular and one acute LOC exceedance for non-vascular plants. Risk to endangered non-vascular plants is not evaluated because at this time there are no listed endangered nonvascular plant species. Additional characterization of potential risk for the direct application of 2,4-D for aquatic weed control was completed by back-calculating the target concentration needed to reduce the RQs below LOCs. This type of consideration provides context to the characterization of potential risk and indicates that for all 2,4-D chemical forms target concentration reduction of up to 100-fold still exceeds all LOCs for aquatic plants.

While noting the potential risks identified above, it is important to note the benefits gained through the direct application of 2,4-D to aquatic bodies, for the control of invasive species. The U.S Army Corps of Engineers (USACE), among others, has identified 2,4-D as an important tool for protecting the nation's waters from the invasion and establishment of some of the world's worst species of exotic nuisance vegetation. 2,4-D has a reputation as a selective and economical means to remove invasive plants, enhance the growth and recovery of desirable native vegetation, restore water quality, reduce sedimentation rates in reservoirs, and improve fish and wildlife habitat. 2,4-D products are used to control invasive weeds, such as Eurasian watermilfoil (*Myriophyllum spicatum*) in the northern tier states and water hyacinth (*Eichhornia crassipes*) in the Gulf Coast states. Effective control of these plants can benefit public health with respect to reducing levels of mosquito habitat. In addition, according to USACE, no other product (or alternative technique) can control these plants in a more cost-effective manner (K. Getsinger, USACE, Public Comment; Docket ID# OPP-2004-0167-0053).

Estimated RQs for use of 2,4-D acid and amine salts in rice paddies exceed the acute and endangered species LOCs for aquatic vascular plants. Consideration of average application rates results in RQs below the endangered species LOCs.

b. Risk to Non-target Terrestrial Organisms

1) Birds

The RQs for birds are presented in detail in Appendix F of the ecological risk assessment for 2,4-D. Potential risks were evaluated for non-granular and granular formulations applied both as banded and broadcast applications.

EPA has relied on risk estimates from oral gavage studies on birds (LD_{50} of 415 mg ae/kg-bw) to assess risk because no definitive endpoint was determined from dietary studies. Therefore, it is likely that the risk estimates associated with the gavage studies overestimate the actual exposure of birds in the field. For predicted maximum exposures when compared with oral gavage data there are exceedances of acute LOCs for all use sites except potatoes and citrus for most small birds and some medium birds. There are also exceedances of acute restricted use and endangered species LOCs for medium and large birds feeding on short grass, tall grass, and broadleaf forage/small insects at all use sites except potatoes and citrus. However, comparison with the lowest dietary LC_{50} of >5620 mg

ae/kg-diet would result in no acute LOC exceedances. As noted previously, no definitive endpoint was available from the avian acute dietary studies and, hence, risk was not evaluated using this endpoint.

The RQs are presented below in Table 30 for the avian risk due to 2,4-D residues on various food items.

Table 30. Avian Risk Quotient Summaries for Non-granular Spray Applications of 2,4-D acid, amine salts and esters

Use Site (Acute & Chronic Risk)	Scenario			
	Short Grass	**Tall Grass**	**Broadleaf, forage, small insects**	**Fruit, large insects,**
Fallow areas and Crop Stubble; Turf (Golf courses, Residential Lawns, Grasses Grown for Seed, and Sod); Pastures, Rangeland, Perennial Grassland; Sugarcane (2 lbs ae/A/app, 2 app., ground/aerial, 30 day interval)				
Acute RQ Exceedance	0.1* - 1.91***	0.04 - 0.88***	0.04 - 0.78***	-
Non-Cropland (Fencerows, Hedgerows, Roadsides, Ditches, Rights-of-Way, Utility Power Lines, Railroads, Airports, Industrial Sites, etc.); Forest Uses, Cranberry (4.0 lbs ae/A/app, 1 app., ground/aerial,)				
Acute RQ Exceedance	0.18* - 3.5***	0.07 - 1.6***	0.07 - 1.43***	0.01 - 0.15*
Fruit, Small Grains (Except Corn), Asparagus (1.4 to 2.0 lbs ae/A/app)				
Acute RQ Exceedance	0.09 - 1.75***	0.04 - 0.81***	0.03 - 0.72***	-
Corn (1.5 lbs ae/A/app, 2 app., 7 day interval, ground or aerial)				
Acute RQ Exceedance	0.1* - 2.07***	0.04 - 0.81***	0.03 - 0.72***	-

* indicates an exceedance of Endangered Species Level of Concern (LOC).
** indicates an exceedance of Acute Restricted Use LOC.
*** indicates an exceedance of Acute Risk LOC.

Chronic risk calculations resulted in RQ's of 1.0 to 1.1 on birds which forage on short grass when the application rate of 2,4-D ranges from 2.0 to 4.0 lb ae/A such as seen with rights-of-way, cranberries or asparagus. The chronic risk LOC is 1.0.

Non-granular Banded Applications - According to the Master Label for 2,4-D, products that allow for banded applications of sprays to row crops require all formulators to adjust the application rates according to a formula provided. Many current labels do not advise applicators to adjust the application rates, and the resulting treatment can be interpreted to concentrate the per acre application rate into a narrow band. Birds, at least in theory, could be exposed to the higher concentration of toxicant by foraging or wandering into the treated band. EPA/OPP evaluated the banded risk by comparing the RQs from unadjusted band rates to those using the adjusted band rates to illustrate the increased risk. OPP assumed a 6 inch band and 30 inch row space as a typical banded application. The RQs indicate that levels of concern are not exceeded for 1000 g birds for rates adjusted due to band widths. LOCs are also not exceeded for these adjusted rates for potatoes for all weight classes of birds. The unadjusted band width rate, however, exceeds LOCs for all weight classes of birds for all uses with the exception of potatoes.

Granular Broadcast Applications - Acute RQs for granular products are calculated for three separate

weight classes of birds using the LD_{50}/ft^2: 1000 g (e.g., waterfowl), 180 g (e.g., upland gamebird), and 20 g (e.g., songbird). The acute RQs for broadcast applications of granular products are tabulated below for the use sites from the 2,4-D Master Label which support granular formulations.

Table 31: Avian Acute Risk Quotient Calculations for Granular Broadcast Applications

	Bird Body Weight (g)	Acute RQ (LD_{50} per ft^2) [a]
Non-Cropland (4.0 lbs ae/A/app, 1 app., ground/aerial,) Aquatic areas (4.0 lb ae/A/app. 3 wks between apps) Cranberry (4.0 lbs ae/A/app, 1 app., ground)	20	5.02***
	180	0.55***
	1000	0.1*
Turf (2.0 lbs ae/A/app, 2 app., ground/aerial, 30 day interval) Aquatic areas - Ditchbank applications (2.0 lb ae/A/app., 2 app., ground)	20	2.5***
	180	0.3**
	1000	0.05
Aquatic areas - Surface application or subsurface injection (10.8 lb ae/acre-foot to an average pond depth of 5 feet)	20	13.55***
	180	1.5***
	1000	0.27**

[a] $RQ = \frac{\text{App. Rate (lbs ae)}}{\text{Acre}} \times \frac{453{,}590\text{ mg}}{\text{Lb}} \times \frac{\text{Acre}}{43{,}560\text{ ft}^2} \times \frac{1}{\text{Animal weight (g)}} \times \frac{1000\text{ g}}{1\text{ kg}} \times \frac{\text{Kg}}{\text{LD50 mg}}$

* indicates an exceedance of Endangered Species Level of Concern (LOC).
** indicates an exceedance of Acute Restricted Use LOC.
*** indicates an exceedance of Acute Risk LOC.

Granular Banded Applications - In addition to broadcast applications of granular formulations, a number of labels instruct the applicators to apply unincorporated banded treatments of granular products to crops. As explained for banded spray treatments above, many labels adjust application rates according to band width and row spaces, but many others do not. If banded granular applications were used at the same sites as banded spray applications, the risk would be similar.

2) Mammals

Acute LOCs for mammals feeding on plants and insects were exceeded when considering non-granular formulations, for all uses assessed for small and medium size mammals, except potatoes and citrus. There were no exceedances for granivores. Banded applications result in exceedances of acute LOCs at all use sites.

Mammalian chronic RQs range from 0.05 to 200 and chronic LOCs were exceeded in all cases with the exception of potatoes and citrus (large insects, seeds). Consideration of average application rates results in EECs below the LOCs for non-granular, granular, or banded applications. However, consideration of average application rates for non-granular, granular and banded applications did not result in exposure below the chronic LOC.

Acute Exposure from Nongranular 2,4-D Products The acute RQs for broadcast applications of nongranular products are tabulated for herbivores/insectivores and granivores in Appendix F of the ecological risk assessment for 2,4-D. When the LD_{50} of 1072 mg ai/kg (579 mg ae/kg) is used for in herbivore/insectivore RQ calculations, endangered species LOCs are exceeded at many sites for mammals foraging on short and tall grass, broadleaf plants, and small insects. The RQs range from 1.72 for asparagus to < 0.01 for potatoes. There are no LOC exceedances for granivorous mammals.

As described above for avian risk, in addition to broadcast spray, a number of labels instruct the applicators to apply unincorporated banded treatments of sprays to row crops. Using the same assumptions as described above for birds, the RQs for mammals are presented in Table 32. Again, for purposes of comparison, the unadjusted rates that appear on many of the current labels have been included. Using the mammalian LD50 of 579 mg ae/kg, acute levels of concern are exceeded at all use sites and for 15, 35, and 1000 g mammals when banded rates are not adjusted. When the banded rates are adjusted, LOCs are not exceeded for 1000 g mammals. The results of these calculations are tabulated in Appendix F of the ecological risk assessment for 2,4-D.

Acute Exposure to Granular 2,4-D Products - Mammalian species also may be exposed to granular pesticides by ingesting granules. The number of lethal doses (LD_{50}) that are available within one square foot immediately after application can be used as a RQ ($LD_{50}/ft^{2)}$ for the various types of exposure to pesticides. RQs are calculated for three separate weight classes of mammals: 15 g, 35 g, and 1000 g. The LOCs are exceeded for all sites with the following exceptions: no LOCs are exceeded for 1000 g mammals in turf, aquatic areas (ditchbanks and surface applications), or cranberries.

The acute RQs for broadcast applications of granular products are tabulated below for the use sites from the master label which support granular formulations.

Table 32: Mammalian Acute Risk Quotient Calculations for Granular Broadcast Applications

Animal Body Weight (g)		Acute RQ (LD_{50} per ft^2) [1]
Non-Cropland (4.0 lbs ae/A/app, 1 app., ground/aerial,) Aquatic areas (4.0 lb ae/acre/app. 3 weeks between applications) Cranberry (4.0 lbs ae/A/app, 1 app., ground)	15	4.8 ***
	35	2.1 ***
	1000	0.1 *
Turf (2.0 lbs ae/A/app, 2 app., ground/aerial, 30 day interval) Aquatic areas - Ditchbank applications (2.0 lb ae/acre/app., 2 app., ground	15	2.4 ***
	35	1.0 ***
	1000	??
Aquatic areas - Surface application or subsurface injection (10.8 lb ae/acre foot to an average pond depth of 5 feet)	15	12.9 ***
	35	5.5 ***
	1000	0.2 **

[1] $RQ = \frac{\text{App. Rate (lbs ae)}}{\text{Acre}} \times \frac{453{,}590\text{ mg}}{\text{Lb}} \times \frac{\text{Acre}}{43{,}560\text{ ft}^2} \times \frac{1}{\text{Animal weight (g)}} \times \frac{1000\text{ g}}{1\text{ kg}} \times \frac{\text{Kg}}{\text{LD50 mg}}$

* indicates an exceedence of Endangered Species Level of Concern (LOC).
** indicates an exceedence of Acute Restricted Use LOC.
*** indicates an exceedence of Acute Risk LOC.

Chronic Exposure to Mammals - The chronic RQs for broadcast applications of nongranular products are tabulated in Appendix F of the 2,4-D ecological risk assessment for all classes of mammals. The parental toxicity NOAELs ranged from 5 mg/kg/day based on female body weight gain and male renal tubule alteration for the 2,4-D acid. The FATE program was used to determine the maximum and 56-day average residues that occur in a one year time period. The application rate, minimum number of applications, and the interval between applications were determined from the 2,4-D Master Label and represent the highest single application rates. Levels of concern were exceeded in all cases with the exception of potatoes and citrus (large insects, seeds) and RQs ranged from 0.1 to 200.

3) Non-Target Insects

The Agency currently does not quantify risks to terrestrial non-target insects. RQs are therefore not calculated for these organisms. Since the test results from one of the salts (2,4-D DMAS) and 2,4-D EHE was practically non-toxic to honey bees (LD_{50} of >100 µg/bee), the potential for 2,4-D and its salts and esters is predicted to pose minimal risk to pollinators and other beneficial insects.

4) Non-target Terrestrial Plants

Acute LOCs for both non-endangered and endangered terrestrial plants were exceeded for non-granular and granular uses at many use sites. Consideration of average application rates did not result in exposure below LOCs.

RQs for terrestrial plants in dry and semi-aquatic areas are calculated for multiple and single spray applications for endangered and non-endangered species. As mentioned above in the exposure section, the runoff scenarios are based on solubility, and as a consequence, the environmental concentrations must be calculated separately for the esters and the acid and amine salts. The environmental concentrations for the esters were calculated separately at a percent runoff value of 0.01, while that of the acid and amine salts were calculated at a value of 0.05. A 60% efficiency factor is also included for aerial applications. In addition, banded applications granular and non-granular formulations are also calculated. The detailed calculations for terrestrial plants are tabulated in Appendix F of the ecological risk assessment.

Risk Quotient (RQ) Calculations - To calculate the RQs for non-endangered plants the EC_{25} value of the most sensitive species in the seedling emergence study is compared to runoff and drift exposure to determine the RQ (EEC/toxicity value). The EC_{25} value of the most sensitive species in the vegetative vigor study is compared to the drift exposure to determine the acute RQ. RQs are calculated for the most sensitive monocot and dicot species.

RQs for Endangered Plants - To calculate the RQs for endangered plants the NOEC or EC_{05} value of the most sensitive species in the seedling emergence study is compared to runoff and drift exposure (EEC/toxicity value). The NOEC or EC_{05} value of the most sensitive species in the vegetative vigor study is compared to the drift exposure to determine the acute RQ. RQs are calculated for the most sensitive monocot and dicot species. The RQ ranges for single and multiple applications are summarized below for non-endangered and endangered plants for the acid and amine salts, and

separately for the esters.

- **Single Spray Applications** - Most use sites on the 2,4-D Master Label allow multiple applications. However, the following use sites are labeled for maximum application rate for a single application.

Table 33. 2,4-D Use Sites With Maximum Labeling for a Single Application

Use Site	Application Rate/Method
Non-crop [1], Forest Uses, Cranberry	Ground & Aerial Applications (4.0 lbs ae/A/app.,)
Strawberry, Rice	Ground & Aerial Applications (1.5 lbs ae/ac/app.)
Grapes	Ground Applications (1.36 lbs ae/A/app.)
Sorghum, Soybean	Ground and Aerial Applications (1.0 lbs ae/A/app.)
Soybean	Ground & Aerial Applications (1.0 lbs ae/A/app.)
Citrus	Ground or Aerial Applications (0.1 lbs ae/A/app.)

[1] Woody plants in rights-of-way. Other non-crop sites may have up to 2 applications of 2 lbs each.

The detailed RQ calculations for single applications are tabulated in detail in Appendix F of the ecological assessment for 2,4-D, and a summary is presented below.

Table 34. Terrestrial Plant Risk Quotients for Single Applications

Chemical Group (acid / ester)	Plant Group (non-endangered / endangered)	Risk Quotient Range
2,4-D Acid and Amine Salt	non-endangered	0.18 - 67
	endangered	0.13 - 136
2,4-D Ester	non-endangered	<0.01 - 543.21
	endangered	0.04 - 936.17

Multiple spray applications - Most of the 2,4-D products on the 2,4-D Master Label allow second applications at prescribed intervals ranging from 7 to 30 days with the exception of pome fruit which allows a 75 day interval. The RQs for multiple applications follow a linear pattern for changes in application rates, and since a maximum of two applications is allowed, the RQ doubles for these applications. The detailed calculations are tabulated in detail in Appendix F of the 2,4-D ecological risk assessment, and a summary is presented below.

Table 35. Terrestrial Plant Risk Quotients for Multiple Applications

Chemical Group (acid / ester)	Plant Group (non-endangered / endangered)	Risk Quotient Range
2,4-D Acid and Amine Salt	non-endangered	0.19 - 157
	endangered	0.19 - 272

Chemical Group (acid / ester)	Plant Group (non-endangered / endangered)	Risk Quotient Range
2,4-D Ester	non-endangered	0.01 - 12
	endangered	0.01 - 33

Banded Spray Applications - Banded spray applications are allowed on a number of labels and instruct the applicators to apply unincorporated banded treatments of sprays to row crops. Many labels adjust application rates according to band width and row spaces, but others do not. For the labels which do not adjust the application rates, the treatments could be more concentrated in the bands. Since non-target plants do not migrate from treated to untreated bands as is the case with birds and mammals, exposure to plants is characterized as "sheet runoff" (one treated acre to an adjacent acre) for dry areas and "channelized runoff" (10 treated acres to a distant low-lying acre) for semi-aquatic areas. Therefore, the higher per acre rates in the concentrated bands do not affect the exposure to non-target plants when label rates are not adjusted.

The 2,4-D Task Force proposal to require all formulators to adjust the application rates for banded applications will reduce the exposure to non-target plants. If we assume use of the same 6 inch band and 30 inch row space that we used for the analysis of birds and mammals, the per acre banded application rate would be reduced by 1/5 of the broadcast application rate. The RQs are detailed in Appendix F of the ecological risk assessment for 2,4-D, and summarized for multiple and single applications in the following table.

Table 36. Non-target Plant Risk Quotient Summary of Adjusted Band Applications to Selected Row Crops.

Chemical Group (acid / ester)	Plant Group (non-endangered / endangered)	Risk Quotient Range (Single Applications)	Risk Quotient Range (Multiple Applications)
2,4-D Acid and Amine Salt	non-endangered	0.02 - 60	0.04 - 120
	endangered	0.02 - 439	0.04 - 878
2,4-D Ester	non-endangered	<0.01 - 27	<0.01 - 54
	endangered	<0.01 - 47	<0.01 - 94

Granular Applications **-** The only currently approved granular applications which are currently allowed on the master label are on grass grown for seed or sod, turf, cranberries, non-crop land, and aquatic weed control sites. The non-target terrestrial plant RQ summaries for the acid and amine salts for the esters are presented below. Detailed RQs are presented in Appendix F of the ecological risk assessment for 2,4-D.

Table 37. Non-target Plant Risk Quotient Summary of Granular Applications to Selected Uses.

Chemical Group (acid / ester)	Plant Group (non-endangered / endangered)	Risk Quotient Range (Single Applications)	Risk Quotient Range (Multiple Applications)[1]
2,4-D Acid and Amine Salt	non-endangered	2.2 - 77	4.4 - 154
	endangered	2.2 - 133	4.4 - 266
2,4-D Ester	non-endangered	2.0- 494	4.0 - 987.62
	endangered	3.57 - 851	7.14 - 1702.12

[1] Turf is only site for multiple applications of granular products.

4. Ecological Incidents

Aquatic Incidents

The EFED Ecological Incident Information System (EIIS) database reports pesticide incidents that have been voluntarily submitted to EPA by state agencies. The report assigns a certainty index of 0 (unrelated), 1 (unlikely), 2 (possible) 3 (probable) or 4 (highly probable) to each incident. In addition, a judgement of registered use, accidental misuse, intentional misuse, or undetermined is assigned. There were 227 incidents reported for 2,4-D, and 24 of these incidents were reported as aquatic incidents under the 2,4-D acid only.

The two "highly probable" registered use incidents occurred when 2,4-D was applied to corn and a railroad right-of-way. The corn application resulted in bluegill and largemouth bass mortalities in Missouri, while the right-of-way application resulted in a kill of 23,000 (presumably) fish.

The corn incident affected bluegill, catfish, crappie, fox squirrel, greengill, largemouth bass, silver minnow, smallmouth bass, sunfish and watersnake. This incident was determined to be "highly probable" and was not listed as a misuse, however, no residue analysis was obtained. Another incident was recorded as "possible" and the use was "undetermined." The species affected included bass, catfish, crappie, grass carp, and perch.

Results from these incidents should be regarded with caution since it is not clear exactly which products or tank mixes might be involved. In addition, residue analysis was not available in almost all instances.

Terrestrial Incidents

There were 227 terrestrial incidents reported for 2,4-D, and 155 of these incidents were reported as plant incidents under the acid form only. Two incidents were reported as both terrestrial and aquatic.

Eighty-four incidents to plants were listed as registered uses and most were considered "probable." Crop damage was reported to have occurred on numerous crops, but most common non-target plant damages occurred on grass and corn. However, most of these incidents resulted from applications to lawns/turf and corn, respectively.

Results from the incident reports should be regarded with caution since it is not clear exactly which products or tank mixes might be involved. In addition, residue analysis was not available in almost all instances.

5. Endangered Species Concerns

The Agency has developed the Endangered Species Protection Program to identify pesticides whose use may cause adverse impacts on endangered and threatened species, and to implement mitigation measures that address these impacts. The Endangered Species Act requires federal agencies to ensure that their actions are not likely to jeopardize listed species or adversely modify designated critical habitat. To analyze the potential of registered pesticide uses to affect any particular species, EPA puts basic toxicity and exposure data developed for REDs into context for individual listed species and their locations by evaluating important ecological parameters, pesticide use information, the geographic relationship between specific pesticide uses and species locations, and biological requirements and behavioral aspects of the particular species. This analysis will take into consideration any regulatory changes recommended in the RED that are being implemented at this time. A determination that there is a likelihood of potential impact to a listed species may result in limitations on use of the pesticide, other measures to mitigate any potential impact, or consultations with the Fish and Wildlife Service and/or the National Marine Fisheries Service as necessary.

The Endangered Species Protection Program as described in a Federal Register notice (54 FR 27984-28008, July 3, 1989) is currently being implemented on an interim basis. As part of the interim program, the Agency has developed County Specific Pamphlets that articulate many of the specific measures outlined in the Biological Opinions issued to date. The Pamphlets are available for voluntary use by pesticide applicators on EPA's website at www.epa.gov/espp.

The preliminary risk assessment for endangered species indicates that 2,4-D exceeds the endangered species LOCs for the following combinations of analyzed uses and species:

- Estimated risk quotients (RQs) from use of 2,4-D DMAS in weed control through direct subsurface application to water bodies exceed the endangered species LOC for freshwater and estuarine fish, and estuarine invertebrates. However, there are currently no endangered estuarine/marine invertebrates.
- Estimated RQs from use of 2,4-D BEE in weed control through direct subsurface application to water bodies exceed the endangered species LOC for freshwater fish and invertebrates and estuarine fish.
- Estimated RQs from use of 2,4-D acid and amine salts in rice paddies exceed endangered species LOCs for freshwater invertebrates. The rice model used to predict these EECs is a screening level model which predicts concentration in tailwater at the point of release from the paddy. It is anticipated that once released, the concentration will be reduced and subsequently, RQs will decrease.
- The scenario of the direct application to water for weed control for the acid and amine salts indicates a endangered species concern for aquatic vascular plants. Estimated RQs from use of 2,4-D BEE for direct application to water for weed control exceed all LOCs for both vascular and non-vascular plants. Potential risk to endangered non-vascular plants is not evaluated because at this time there are no listed endangered non-vascular plant species.
- Target acute RQs for birds and mammals were exceeded for endangered species risks for multiple crops and multiple animal weights. Banded and granular applications result in higher RQs at more use sites.
- Target acute LOCs for both non-endangered and endangered plants were exceeded for non-granular and granular for multiple uses, based on predicted EECs.

In December 2004, EPA completed a refined assessment for 2,4-D's potential effects to 26 environmentally significant units (ESUs) of Pacific Salmonids (salmon and steelhead). That refined assessment concluded that 2,4-D has "no effect" on these species when used according to label directions on terrestrial sites. Further, that assessment concluded that use of 2,4-D on rice "may affect but is not likely to adversely affect" 4 ESU's and will have "no effect" on 22 ESU's. That same analysis concluded that use of 2,4-D "may affect" each of the 26 ESU's when used for aquatic weed control purposes. As a result of that assessment, EPA is currently engaged in consultation with the National Marine Fisheries Service regarding those scenarios that resulted in a determination that 2,4-D "may affect but is not likely to adversely affect" the species, or "may affect" the species.

The Agency's level of concern for endangered and threatened freshwater fish and invertebrates, estuarine invertebrates, birds, mammals, aquatic vascular plants, and terrestrial non-target plants is exceeded for the use of 2,4-D. The Agency recognizes that there are no Federally listed estuarine/marine invertebrates. The registrant must provide information on the proximity of Federally listed freshwater vascular plants, birds, mammals, and non-target terrestrial plants (there are no listed estuarine/marine invertebrates) to the 2,4-D use sites. This requirement may be satisfied in one of three ways: 1) having membership in the FIFRA Endangered Species Task Force (Pesticide Registration [PR] Notice 2000-2); 2) citing FIFRA Endangered Species Task Force data; or 3) independently producing these data, provided the information is of sufficient quality to meet FIFRA requirements. The information will be used by the OPP Endangered Species Protection Program to develop recommendations to avoid adverse effects to listed species.

6. Risk Characterization

The Agency has considered available information on 2,4-D's toxicity, use areas, usage, fate properties, and application methods and formulations in characterizing ecological risks related to normal use. Upon review and synthesis of this information, the Agency concludes use of 2,4-D for aquatic weed control presents risk to aquatic organisms, while 2,4-D use on terrestrial sites presents the greatest potential risks to small mammals, birds, and non-target terrestrial plants.

a. Characterization of risk to aquatic organisms from direct aquatic application

Whereas the maximum labeled target concentration for control of aquatic weeds is 4 ppm, the typical target concentration is 2 ppm. Moreover, the risks to aquatic organisms were estimated based on a 2,4-D application that resulted in a whole-reservoir concentration of 4 ppm. Treating 100% of the water body would result in a large amount of decaying plant life, thereby creating an oxygen-depleted environment that would most likely result in fish kills. To avoid that scenario, the 2,4-D label advises the applicator to avoid treating more than 50% of a water body in a single application. In actual practice, aquatic weeds that 2,4-D controls tend to grow in littoral zones. As a result, generally a maximum of 20-30% of a water body is treated in a single application. Applying the typical rate of 2 ppm, and taking into account a typical maximum treated area of 30% would decrease calculated RQs by approximately 6-fold.

While noting the potential risks to aquatic organisms from the direct application of 2,4-D for the control of aquatic weeds identified above, it is important to note the benefits gained through the direct application of 2,4-D to aquatic bodies, for the control of invasive species. The U.S Army Corps of

Engineers (USACE), among others, has identified 2,4-D as an important tool for protecting the nation's waters from the invasion and establishment of some of the world's worst species of exotic nuisance vegetation. 2,4-D has a reputation as a selective and economical means to remove invasive plants, enhance the growth and recovery of desirable native vegetation, restore water quality, reduce sedimentation rates in reservoirs, and improve fish and wildlife habitat. 2,4-D products are used to control invasive weeds, such as Eurasian watermilfoil (*Myriophyllum spicatum*) in the northern tier states and water hyacinth (*Eichhornia crassipes*) in the Gulf Coast states. Effective control of these plants can benefit public health with respect to reducing levels of mosquito habitat. In addition, according to USACE, no other product (or alternative technique) can control these plants in a more cost-effective manner (K. Getsinger, USACE, Public Comment; Docket ID# OPP-2004-0167-0053).

b. Characterization of risk to mammals from terrestrial use

All of the calculated RQs for mammalian acute risk for the non-granular use of 2,4-D were based on maximum labeled application rates. The QUA from BEAD (Quantitative Usage Analysis for 2,4-D, Case Number: 0073, Date: 8-9-01, A. Halvorson) suggests that the average application rates for many crops are considerably less than the modeled maximum application rates. For non-granular spray application mammalian acute concerns, the highest RQ was 1.72 for use on asparagus for small mammals feeding on short grass based on a maximum application rate of 4 lbs ae/acre; however, the average application rate was only 1.10 lbs ae/acre (BEAD QUA). If the modeled application rate was reduced to the reported average application rate of 1.10 lbs ae/acre for asparagus, the RQ would be 1.08 which is still above the acute LOC of 0.5. However, asparagus is representative of a minor 2,4-D use, and risk to mammals from use of 2,4-D on asparagus would be minimal, given that fact.

To add context to the acute mammalian assessment, the effect of assuming an average application rate was determined. Major 2,4-D crops include pasture/rangeland, turf, wheat, corn, and soybeans. For pasture/rangeland, the highest acute RQ was 0.86 for small mammals feeding on short grass based on a maximum application rate of 4 lbs ae/acre. However, the average application rate was only 0.62 lbs ae/acre (BEAD QUA). If the modeled application rate was reduced to 0.62 lbs ae/acre for pasture/rangeland, the resulting RQ is 0.31 which is below the acute LOC, but above the restricted use LOC of 0.2. Similar trends are noted for other major use sites.

Calculated chronic risks to mammals were greatest for small herbivores/insectivores. For 15 g mammalian herbivores/insectivores, chronic RQs based on maximum residues and mean residues ranged from <1 to 200 and <1 to 70, respectively. For major use sites, including rangeland/pasture, RQs were approximately 100. These chronic risk estimates are likely conservative as described below.

<u>Exposure</u>

The chronic RQs calculated for mammalian herbivores/insectivores are based on conservative estimates of exposure that are not likely to occur in nature. In the example of pasture/rangeland, the chronic RQ of approximately 100 for maximum residues (35 for mean residues) was calculated based on an application rate of 4 lbs ae/A. This maximum application rate was determined based on the knowledge that the maximum rate of 2 lbs ae/A may be applied twice per year, at a 30 day interval. However, the Biological and Economic Analysis Division within OPP has determined that the average application rate on pasture/rangeland is only 0.62 lbs ae/acre (BEAD QUA). Moreover, information from several state contacts indicate that a once per year application of less than 1 lb ae/A

is typical (personal communications). As the typical rate is approximately 25% of the assessed rate, use of the typical rate would be expected to decrease the RQ for the pasture/rangeland scenario to approximately 25 for maximum residues and 9 for mean residues.

A second example of the conservative assumptions included in the assessment of exposure to mammalian herbivores/insectivores is the assumption that 100% of the long term diet is limited to single food types foraged only from treated fields. The assumption of 100% diet from a single food type may be realistic for acute exposures, but diets are likely to be more variable over longer periods of time. Moreover, currently Agency models do not account for the uptake of 2,4-D by plants and therefore assume that all non-dissipated pesticide applied to the field is present for exposure to organisms. In fact, many pesticides, including 2,4-D, are systemic and are absorbed by plants in the field so that the current approach may overestimate the amount of 2,4-D available for exposure in terrestrial systems. Therefore, the percent of diet assumption is likely to be conservative and will tend to overestimate potential risks for chronic exposure, especially for larger organisms that have larger home ranges.

Hazard

The mammalian chronic risk assessment utilized a toxicity endpoint from a rat two-generation reproduction test. This endpoint was the NOAEL of 5 mg/kg-bw/day for growth rate reductions in F1b offspring. The agency considers that reduced growth (reductions in pup body weight gains relative to controls) in offspring as a potentially important effect with implications for the survivability of offspring and therefore a potential impact on fecundity. Because the endpoint is the no effect level for this measured parameter, evaluations of the significance of any exposures above this endpoint were conducted. From the same two-generation rat reproduction study, the LOAEL associated with F1b pup growth rate reduction was 20 mg/kg-bw/day. This LOAEL corresponds with body-weight gain reductions of 15 to 17 % (males and females) relative to controls. The 20 mg/kg-bw/day dose level also represents a NOAEL for increased gestational length and incidents of skeletal anomalies and reduced ossification in F1b pups. The LOAEL for these gestational and skeletal effects is 80 mg/kg-bw/day.

In addition to the available rat two generation reproduction study, a number of developmental toxicity studies are available in rats and rabbits for the acid, amine salts and esters. These data are from studies involving short-term exposures during critical periods of fetal development and are useful to determine if long-term or short-term exposure events are necessary for the types of effects observed in the two-generation reproduction study. MRID 41747601, developmental toxicity in rabbits with the acid, shows a NOAEL of 30 mg/kg-bw/day for increased rate of fetal abortions, with a LOAEL 90 mg/kg-day. Similar NOAEL and LOAEL thresholds were observed in studies in rabbits with the amine salts and esters of 2,4-D. MRID 000251031, developmental toxicity in rats with the acid, showed a NOAEL of 25 mg/kg-bw/day and a LOAEL of 75 mg/kg-bw/day for increased incidence of skeletal malformations. Similar results are reported in other studies with rats involving the amine salt and esters of 2,4-D.

c. Characterization of risk to birds from terrestrial use

The assessment of risk to birds from exposure to 2,4-D is likely conservative as follows. Currently, Agency models do not account for the uptake of 2,4-D by plants and therefore assume that

all non-dissipated pesticide applied to the field is present for exposure to organisms. In fact, many pesticides, including 2,4-D, are systemic and are absorbed by plants in the field and therefore, the current approach may overestimate the amount of 2,4-D available for exposure in terrestrial and aquatic systems.

For non-granular spray application, the highest acute avian RQ (3.50) was from the cranberry scenario, for birds feeding on short grass. That assessment was based on a maximum application rate of 4 lbs ae/acre; however, the average application rate is 1.83 lbs ae/acre (see the BEAD QUA). If the modeled application rate was reduced to 1.83 lbs ae/acre for cranberries, and an assumption made that the resulting EEC will be reduced linearly, the RQ would be 1.60.

To determine the hazard associated with acute exposures to birds, the assessment has considered two types of data, a suite of dietary studies and a suite of gavage studies. For avian acute exposures, the dietary studies result in non-definitive endpoints which are not appropriate for estimating risk. Therefore, the assessment has relied on the gavage studies to estimate avian acute risks. The Agency recognizes that this approach may overestimate risk to birds due to the fact that birds would not typically be expected to consume 2,4-D in this manner.

Given the conservative assumptions in both exposure scenarios and hazard determinations, the Agency finds that the acute risk to birds from 2,4-D exposure does not exceed the Agency's level of concern.

Potential chronic risks to birds is limited to a few use sites. These include non-cropland, forest, asparagus, and cranberry. The RQs for these sites range from 1 -1.09. Further characterization of these use sites by evaluating average application rates versus maximum application rates lower these RQs to below the LOCs.

d. Characterization of risk to non-target plants from terrestrial use

Acute LOCs for both non-endangered and endangered terrestrial plants were exceeded for non-granular and granular uses at many use sites. Consideration of average application rates did not result in exposure below LOCs. However, the exposure estimates used to develop the RQs were likely conservative, as follows.

In the exposure calculation for non-target plants, the major contributor is run-off from the application site. The runoff and leaching vulnerability schemes used in this assessment were adapted from a vulnerability scheme developed by the USDA (Kellogg et al, 1998), and incorporate several conservative assumptions. For example, a 1-in-10 year rain event is modeled, resulting in 3 cm of runoff water. USDA identified several caveats to be considered when using this vulnerability scheme which could contribute to the uncertainty associated with this assessment. Among these are that estimates of runoff and leaching vulnerability are estimated through the use of algorithms (i.e. they represent estimates of vulnerability and not actual field measurements), fate and transport processes (i.e. dilution and recharge) are not included, farm management practices are not considered, and some watershed estimates are based on major crops only. The effect of these factors on the vulnerability assessment is unknown, however, there is a low probability that a 1-in-10 year rain event will coincide with the first few days following a 2,4-D application at the maximum application rate. Also, it is likely that farm management practices would be in place to limit run-off, as run-off events are detrimental to the farm as a whole for reasons other than pesticide damage.

Currently Agency models do not account for the uptake of 2,4-D by plants and therefore assume that all non-dissipated pesticide applied to the field is present for exposure to organisms. In fact, many pesticides, including 2,4-D, are systemic and are absorbed by plants in the field and

therefore, the current approach may overestimate the amount of 2,4-D available for exposure in terrestrial and aquatic systems.

IV. Risk Management, Reregistration, and Tolerance Reassessment Decision

A. Determination of Reregistration Eligibility

Section 4(g)(2)(A) of FIFRA calls for the Agency to determine, after submission of relevant data concerning an active ingredient, whether or not products containing the active ingredient are eligible for reregistration. The Agency has previously identified and required the submission of the generic (i.e., active ingredient-specific) data to support reregistration of products containing 2,4-D as an active ingredient. The Agency has completed its review of these generic data, and has determined that the data are sufficient to support reregistration of all products containing 2,4-D .

The Agency has completed its assessment of the dietary, occupational, residential, and ecological risk associated with the use of pesticide products containing the active ingredient 2,4-D . Based on a review of these data and on public comments on the Agency's assessments for the active ingredient 2,4-D , the Agency has sufficient information on the human health and ecological effects of 2,4-D to make decisions as part of the tolerance reassessment process under FFDCA and reregistration process under FIFRA, as amended by FQPA. The Agency has determined that 2,4-D containing products are eligible for reregistration provided that: (i) current data gaps and confirmatory data needs are addressed; (ii) the risk mitigation measures outlined in this document are adopted; and (iii) label amendments are made to implement these measures. Label changes are described in Section V. Appendix A summarizes the uses of 2,4-D that are eligible for reregistration. Appendix B identifies the generic data requirements that the Agency reviewed as part of its determination of reregistration eligibility of 2,4-D, and lists the submitted studies that the Agency found acceptable. Data gaps are identified as generic data requirements that have not been satisfied with acceptable data.

Based on its evaluation of 2,4-D, the Agency has determined that 2,4-D products, unless labeled and used as specified in this document, would present risks inconsistent with FIFRA. Accordingly, should a registrant fail to implement any of the risk mitigation measures identified in this document, the Agency may take regulatory action to address the risk concerns from the use of 2,4-D . If all changes outlined in this document are incorporated into the product labels, then all current risks for 2,4-D will be adequately mitigated for the purposes of this determination.

B. Public Comments and Responses

Through the Agency's public participation process, EPA worked extensively with stakeholders and the public to reach the regulatory decisions for 2,4-D . During the public comment period on the revised risk assessments, which closed on March 14, 2005, the Agency received comments from numerous parties. These comments in their entirety are available in the public docket (OPP-2004-0167) at http://www.epa.gov/edockets. Individual responses to these comments are also available in the public docket (OPP-2004-0167).

The RED and technical supporting documents for 2,4-D are available to the public through EPA's electronic public docket and comment system, EPA Dockets, under docket identification number OPP-2004-0167. The public may access EPA Dockets at http://www.epa.gov/edockets. In

addition, the 2,4-D RED may be downloaded or viewed through the Agency's website at http://www.epa.gov/pesticides/reregistration/status.htm.

C. Regulatory Position

1. Food Quality Protection Act Findings

a. "Risk Cup" Determination

As part of the FQPA tolerance reassessment process, EPA assessed the risks associated with this pesticide. EPA has determined that risk from dietary (food sources only) exposure to 2,4-D is within its own "risk cup." An aggregate assessment was conducted for exposures through food, drinking water, and residential uses. The Agency has determined that the aggregate human health risks from these combined exposures are within the risk cup. In other words, EPA has concluded that the tolerances for 2,4-D meet FQPA safety standards. In reaching this determination, EPA has considered the available information on the special sensitivity of infants and children, as well as aggregate exposure from food, water, and residential uses.

b. Determination of Safety to U.S. Population

The Agency has determined that the established tolerances for 2,4-D , with amendments and changes as specified in this document, meet the safety standards under the FQPA amendments to section 408(b)(2)(D) of the FFDCA, and that there is a reasonable certainty no harm will result to the general population or any subgroup from the use of 2,4-D. In reaching this conclusion, the Agency has considered all available information on the toxicity, use practices and exposure scenarios, and the environmental behavior of 2,4-D . Both the acute dietary (food alone) and chronic dietary risk from 2,4-D are not of concern.

Acute and chronic risks from drinking water exposures are not of concern. Models have been used to estimate surface water concentrations. The surface water EECs are below the DWLOCs for all population subgroups. Drinking water monitoring data from the USGS NAWQA Program confirm that concentrations of 2,4-D are less than modeled estimates for surface water. The maximum concentration detected in ground water monitoring (from USGS NAWQA) has been used as the ground water EEC. The ground water EEC is below the DWLOCs for all populations subgroups.

EPA has determined that the established tolerances for 2,4-D, with amendments and changes as specified in this document, meet the safety standards under the FQPA amendments to section 408(b)(2)(C) of the FFDCA, that there is a reasonable certainty of no harm for infants and children. The safety determination for infants and children considers the factors noted above for the general population, but also takes into account the possibility of increased dietary exposure due to the specific consumption patterns of infants and children, as well as the possibility of increased susceptibility to the toxic effects of 2,4-D residues in this population subgroup. FQPA directs EPA, in setting pesticide tolerances, to use an additional tenfold margin of safety to protect infants and children, taking into account the potential for pre- and postnatal toxicity and the completeness of the toxicology and exposure databases. The statute authorizes EPA to replace this tenfold FQPA safety factor with a

different FQPA factor only if reliable data demonstrate that the resulting level of exposure would be safe for infants and children.

FQPA Special Safety Factor

EPA concludes that the toxicology database for 2,4-D is substantially complete since all required studies have been submitted. After evaluating hazard and exposure data for 2,4-D, EPA removed the default 10X FQPA special safety factor. The toxicity database for 2,4-D includes acceptable developmental and reproductive toxicity studies. Developmental toxicity studies were conducted in both rats and rabbits for most 2,4-D forms. There is qualitative evidence of susceptibility in the rat developmental toxicity study with 2,4-D acid and DEA salt where fetal effects (skeletal abnormalities) were observed at a dose level that produced less severe maternal toxicity (decreased body-weight gain and food consumption). There is no evidence of increased (quantitative or qualitative) susceptibility in the prenatal developmental toxicity study in rabbits or in the 2-generation reproduction study in rats on 2,4-D. Regarding the 2,4-D amine salt and ester forms, no evidence of increased susceptibility (quantitative or qualitative) was observed in the prenatal developmental toxicity study in rat and rabbits (except for 2,4-D DEA) dosed with any of the amine salts or esters of 2,4-D. There is evidence of increased susceptibility (qualitative) in the prenatal developmental study in rabbits for 2,4-D DEA salt.

After establishing developmental toxicity endpoints to be used in the risk assessment with traditional uncertainty factors (10x for interspecies variability and 10x for intraspecies variability), the Agency has no residual concerns for the effects seen in the developmental toxicity studies. Therefore, the 10X FQPA special safety factor was reduced to 1X.

Database Uncertainty Factor

The EPA has concluded that there is a concern for developmental neurotoxicity resulting from exposure to 2,4-D, and that a developmental neurotoxicity (DNT) study in rats is required for 2,4-D. The Agency has also concluded that a 2-generation reproduction study is required to address both the concern for thyroid effects and immunotoxicity, as well as a more thorough assessment of the gonads and reproductive/developmental endpoints. EPA has determined that a 10X database uncertainty factor (UF_{DB}) is needed to account for the lack of these studies. This Uncertainty Factor is applied only to exposure scenarios that are expected for children or pregnant women, and thus is not applied to occupational exposure scenarios.

2. Endocrine Disruptor Effects

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other endocrine effects as the Administrator may designate." When the appropriate screening and/or testing protocols being considered under the EDSP have been developed, 2,4-D may be subject to additional screening and/or testing to better characterize effects related to endocrine disruption.

3. Cumulative Risks

The Food Quality Protection Act (FQPA) requires EPA to consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity" when considering whether to establish, modify, or revoke a tolerance. Potential cumulative effects of chemicals with a common mechanism of toxicity are considered because low-level exposures to multiple chemicals causing a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any one of these individual chemicals. 2,4-D is a member of the alkylphenoxy herbicide class of pesticides. A cumulative risk assessment has not been performed as part of this human health risk assessment because the Agency has not yet made a determination of whether 2,4-D and other alkylphenoxy compounds have a common mechanism of toxicity. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements by the EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://epa.gov/pesticides/cumulative/.]

4. Special Review Disposition

2,4-D has been in pre-Special Review status since September 22, 1986, because of carcinogenicity concerns. In 1994 a Science Advisory Panel/Scientific Advisory Board classified 2,4-D as a Group D carcinogen (not classifiable to human carcinogenicity). The Agency requested further histopathological examinations of rat brain tissues and mouse spleen tissues in question. These exams were submitted and reviewed, and on March 16, 1999, The Agency notified the 2,4-D Task Force that the Agency would continue to classify 2,4-D as a Group D carcinogen. Also, in a 1994 review of all relevant epidemiological studies, EPA found that none of the more recent epidemiological studies definitively linked human cancer cases to 2,4-D. A final notice of the Agency's intent not to initiate Special Review will be published in concert with the release of this RED document.

5. Dioxin Contaminants

Exposure

In 1987, a DCI titled "Data Call-In Notice for Product Chemistry Relating to Potential Formation of Halogenated Dibenzo-p-dioxin or Dibenzofuran Contaminants in Certain Active Ingredients," was issued to identify pesticides that may contain halogenated dibenzo-p-dioxin and dibenzofuran contaminants. A second DCI in 1987, "Data Call-In for Analytical Chemistry Data on Polyhalogenated Dibenzo-p-Dioxins/Dibenzofurans (HDDs and HDFs)," was issued, under which registrants whose products did not qualify for an exemption or waiver were required to generate and submit analytical methods and certification limits of dioxins and furans.

The specific results of analysis of multiple 2,4-D technical products, submitted to EPA in response to both DCIs, are considered confidential business information (CBI) and cannot be released by EPA to the public. In summary, two of eight technical products had concentrations of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD; dioxin) greater than the limit of quantitation (LOQ; LOQ = 0.1 ppb) and three of eight had concentrations of 1,2,3,7,8-pentachlorodibenzo-p-dioxin (PCDD) greater than the LOQ (LOQ = 0.5 ppb).

In 1991, the EPA's Office of Research and Development (EPA/ORD) began an assessment of

the health risks of exposure to dioxins. The most recent revision of that assessment has recently been submitted to the National Academies of Science (NAS) for review. In that document and elsewhere, a source inventory of dioxin was published. As a result of the 1987 DCI data, and the amount of 2,4-D applied to agricultural and residential settings (approximately 50 million pounds per year), the current draft dioxin source inventory (see The Inventory of Sources and Environmental Releases of Dioxin-Like Compounds in the United States: The Year 2000 Update, EPA/600/P-03/002A, External Review Draft, March 2005) identifies 2,4-D as a source of dioxin emissions (28.9 g TEQDF-WHO98; TEQ = Toxic EQuivalent amount, or an amount of total dioxin equivalent to 28.9 g of the most toxic dioxin congener, 2,3,7,8-TCDD). It should be noted that this estimate of dioxin release assumes all products are contaminated and does not take into account manufacturing changes since the DCI. Moreover, that estimate is specific for the year 1995, and therefore should not be considered the current estimate of dioxin release.

The 1995 estimate for dioxin emissions from 2,4-D, taken together with NAS estimates for 2002/2004 releases from other sources of dioxin in the U.S., suggest that 2,4-D applications to land ranks seventh (2.6% of all dioxin sources) behind backyard burning (57%), sewage sludge application (6.9%), residential wood burning (5.7%), coal-fired utilities (5.4%), diesel trucks (3.2%), and secondary aluminum smelting (2.6%) in terms of dioxin emissions (see The Inventory of Sources and Environmental Releases of Dioxin-Like Compounds in the United States: The Year 2000 Update, EPA/600/P-03/002A, External Review Draft, March 2005). According to 2,4-D registrants, since the 1990's, the manufacturing processes for 2,4-D and its chemical intermediate, dichlorophenol, have been modified, and those modifications decrease the chance that TCDD and PCDD are formed during the manufacturing process. The following description of the current 2,4-D manufacturing process summarizes information submitted by the 2,4-D Task Force II.

A key chemical intermediate in the manufacture of 2,4-D is 2,4-dichlorophenol (2,4-DCP) and the purity of this intermediate has a strong correlation to the purity of 2,4-D acid produced from it. In the manufacture of 2,4-DCP, multiple positions around the phenyl ring structure may be chlorinated. The desired positions for chlorination are carbons two and four of the phenyl ring, but the reaction may yield small quantities of compounds chlorinated at different positions. Certain combinations of these chlorinated structures may form precursors to the dioxin 2,3,7,8-TCDD.

Manufacture of the 2,4-DCP intermediate has been optimized by controlling processing conditions necessary to drive the chlorination reaction to the preferred two and four carbon positions, thereby limiting the formation of impurities that can lead to dioxin formation. Controlled temperature and residence time during the chlorination reaction, programmed addition of the chlorinating agent, and efficient agitation in the reaction vessel are processing factors that contribute to the purity of 2,4-DCP. Additionally, distillation of 2,4-DCP is a technique that may be employed post-chlorination to increase purity. Moreover, quality control sampling and analytical procedures are also utilized to verify product quality at various steps of the 2,4-DCP process. According to Results of testing of 2,4-DCP, performed in response to the Toxic Substances Control Act (TSCA) Dioxin/Furan Test Rule, showed no detectable concentrations of 2,3,7,8-substituted tetra- through hepta-CDD/CDFs.

In the manufacture of 2,4-D acid *per se*, there are additional process conditions and procedures that must be controlled to maximize yield and purity. Details regarding these measures are dependent on specific manufacturing methodologies and, as such, are protected under FIFRA Section 10 as Confidential Business Information.

Anticipated Residues

The Agency's most recent evaluations of anticipated dioxin and furan residues resulting from 2,4-D applications are based on the concentrations of dioxins and furans present in technical grade 2,4-D as determined by review of analytical data submitted in response to the 1987 DCI. In those evaluations, completed in the early 1990's, the ratios of individual chlorodibenzo-p-dioxin (CDD; dioxin) or chlorodibenzo-p-furan (CDF; furan) contaminant concentrations to 2,4-D acid concentrations were calculated, and those ratios were used with 2,4-D tolerance expressions to calculate an anticipated residue in eggs, fruits, grains, kidney (hogs), meat (hogs), milk, nuts, poultry, and sugarcane, for each detected dioxin or furan. For each technical 2,4-D formulation for which the Agency received data, calculation of an anticipated dietary exposure was based on a worst-case scenario in which the highest anticipated residue was used, and an assumption was made that 100% of the diet consisted of the food item with the highest anticipated residue.

Toxicological Significance

Based on the calculation of dietary exposures, using the worst-case scenario described above, both the cancer and non-cancer risks from dietary exposure to dioxins and furans as contaminants of 2,4-D acid were considered to be of no toxicological concern at the time of the assessment.

Risk Management

Members of the 2,4-D Task Force II have submitted information about the current manufacturing process for the 2,4-D intermediate, 2,4-DCP, as well as for 2,4-D acid itself, and have included in their submissions explanatory text on how current manufacturing processes minimize the chance of dioxin and furan formation. To confirm that the changes to the manufacturing processes since the time of the 1987 DCI have resulted in lower concentrations of dioxin congeners in technical 2,4-D products, the Agency is requiring that five recent batches of all technical products be analyzed for 2,3,7,8-TCDD, 2,3,7,8-TCDF and their respective higher substituted chlorinated congeners using validated analytical methods. The Agency is specifying that the manufacturers use the most current state-of-the art laboratory methods for measuring 2,3,7,8-TCDD and TCDF at levels less than 1 part per trillion (EPA Method 1613, Tetra- through Octa-Chlorinated Dioxins and Furans by Isotope Dilution HRGC/HRMS). Because 1,2,3,7,8-PeCDD is equi-potent to 2,3,7,8-TCDD in the TEF scheme, the Agency is adding this compound to our testing requirements. The pentachloro-congener was reported as present in 2,4-D in the 1987 Data Call-in. Registrants are encouraged to submit their analytical methods and sampling plans to the Agency for review prior to commencing these studies.

D. Tolerance Reassessment Summary

1. Tolerances Currently Listed Under 40 CFR §180.142

Tolerances for residues of 2,4-D in/on plant RACs and processed commodities, fish, and potable water are currently expressed in terms of 2,4-D *per se* [40 CFR §180.142(a)(1-6 and 9-12) and (b)]. Tolerances for residues in livestock commodities are currently expressed in terms of 2,4-D and/or its metabolite 2,4-dichlorophenol (2,4-DCP) [40 CFR §180.142(a)(8)]. EPA has concluded that 2,4-D is the residue of concern and that tolerances listed in 40 CFR §180.142 are to be defined as residues of 2,4-D, both free and conjugated, determined as the acid.

The listing for 2,4-D tolerances in 40 CFR §180.142 should be recodified into parts (a), (b), (c), and (d). Part (a) should be reserved for commodities with permanent tolerances reflecting at least a

preharvest (field) or postharvest use, part (b) for Section 18 emergency exemptions, part (c) for tolerances with regional use registrations, and part (d) for commodities bearing 2,4-D residues solely inadvertently, including irrigated crops. A summary of 2,4-D tolerance reassessments and recommended recodifications is presented in Table 37 along with any recommended changes in commodity definitions.

Note that some commodities currently are the subject of two or more separate tolerances depending on the use pattern, the 2,4-D form applied, timing of treatment (preharvest or postharvest), or degree of intent to deposit residues (direct treatment or inadvertent). Direct treatment involves intentional field treatment of crop sites or postharvest treatment of harvested commodities on registered labels. Inadvertent deposition involves the incidental exposure of crops when water passing through 2,4-D-treated irrigation ditchbanks or diverted from 2,4-D-treated bodies of water is used to irrigate crops. EPA is proposing to remove most such use-pattern or FIFRA-related language at 180.142. Due to the complicated nature of the routes of residue deposition, we are proposing to subsume the lower tolerances in the highest existing or reassessed tolerance established in the same commodity - even if that results in 180.142(a) containing some tolerances that reflect 2,4-D residues that could potentially result from two or more exposure routes. An example is citrus which has tolerances for 2,4-D in the RAC resulting from preharvest use + postharvest use, irrigation ditchbank treatment (inadvertent), and direct water body treatment (also inadvertent). If there are no registered uses on a given commodity and residues are likely to occur on that commodity solely inadvertently, i.e., via irrigation, then the tolerance in that commodity will be located under 180.142(d). In most cases, residues, and hence the tolerance, resulting from a direct, registered use are higher than the residues (and the tolerance) resulting inadvertently. EPA proposes these revisions because we know that an enforcement agency, having detected 2,4-D residues in a commodity, would: (i) not be able to distinguish which form of 2,4-D had been applied; (ii) rarely be able to determine who applied the pesticide, when, or for what purpose; and (iii) not know whether a sample is violative if the 2,4-D concentration falls between two tolerance levels.

Tolerances Listed Under 40 CFR §180.142(a)(1):

Adequate data are available to reassess the established tolerances for the following commodities: apple, apricot, citrus fruit, pear, potato and quince.

The available apple and pear residue data will support a crop group tolerance at 0.05 ppm for pome fruits under the redesignated section 180.142(a). The separate tolerances on apple, pear, and quince should be revoked concomitant with establishing a new pome fruit crop group tolerance.

The 5 ppm tolerance on citrus fruits should be reassessed to 3.0 ppm to reflect any combination of the preharvest use on citrus, the postharvest use of 2,4-D on lemons in the U.S., a similar postharvest use on oranges imported into the U.S., and any inadvertent (irrigation) residues that may be incurred as a result of 2,4-D use in aquatic sites. The tolerances in citrus fruit of 0.1 ppm at 180.142(a)(3) and 1.0 ppm at 180.142(a)(6), both reflecting inadvertent residues, should be revoked as they will be subsumed by the reassessed tolerance of 3.0 ppm at 180.142(a).

The tolerance for residues in/on apricots should be revoked as residues in/on apricots will be covered by the tolerance in stone fruits.

Tolerances Listed Under 40 CFR §180.142(a)(2):

Adequate data are available to reassess all the tolerances listed under 180.142(a)(2). All reassessed tolerances should be recodified under the revised section 180.142(a).

Based on the available residue data, the current tolerances on grass hay and tree nuts are adequate. However, tolerances can be lowered on the following commodities: blueberry, sweet corn (kernel plus cob with husks removed), corn forage and grain, cranberry, stone fruits, grape, grass forage, pistachio, rice straw, sorghum forage, grain and stover, and sugarcane. Tolerances should be increased on the following commodities: corn stover, rice grain, and wheat grain and forage.

The available residue data for wheat commodities will be used to reassess tolerances on similar commodities from barley, millet, oats, and rye. Tolerances should be increased accordingly on: barley grain; millet grain, forage and straw; oat forage and grain; and rye forage and grain.

The tolerance for residues in sugarcane forage should be revoked because it is no longer considered a significant livestock feed item (OPPTS GLN 860.1000).

Tolerances Listed Under 40 CFR §180.142(a)(3):

Tolerances listed in 40 CFR §180.142(a)(3) are established for negligible residues of 2,4-D in irrigated crops from application of its dimethylamine salt to irrigation ditch banks in the Western United States in programs of the Bureau of Reclamation, U.S. Department of Interior; cooperating water user organizations; the Bureau of Sport Fisheries, U.S. Department of Interior; Agricultural Research Service, U.S. Department of Agriculture; and the Corps of Engineers, U.S. Department of Defense. Where tolerances are established at higher levels resulting from other uses of 2,4-D, the higher tolerance applies also to residues in crops from the irrigation ditch bank use cited in this paragraph.

The tolerances in crops or crop groups listed under 40 CFR §180.142(a)(3) that do not have a direct treatment tolerance under 180.142(a) should be recodified as 180.142(d), i.e., inadvertent residue tolerances.

The available irrigated crop data support tolerances for inadvertent residues at 0.2 ppm in foliage of legume vegetables (group 7) and non-grass animal feed (group 18) and at 0.05 ppm in/on the following crops groups: bulb vegetables (group 3), legume vegetables (group 6), cucurbit vegetables (group 9), and fruiting vegetables (group 8).

In addition, tolerances resulting from the primary use of 2,4-D on grasses, citrus fruits, and tree nuts are high enough to cover any inadvertent residues in these crops that may result from the use of 2,4-D treated irrigation water. Therefore, separate tolerances for inadvertent residues in/on these crops are not required.

Separate tolerances for inadvertent residues are unnecessary in pome fruits, stone fruits, pistachios, grapes, blueberry, and strawberry as these crops all have tolerances resulting from the direct use of 2,4-D. However, the tolerances in all of these commodities have been reassessed at 0.05 ppm, the limit of quantitation of the enforcement method, to reflect only direct treatment at this time. It is reasonably possible that inadvertent residues resulting from irrigation with treated water could contribute concentrations of 2,4-D in the commodities necessitating tolerances higher than 0.05 ppm. Therefore, confirmatory irrigated crop residue data are required for a representative perennial crop (strawberry). Also, additional residue data on sugar beets and tops irrigated with water containing 2,4-D at 0.1 ppm are required to permit reassessment of the tolerances in the Root and Tuber Vegetables Group and the Leaves of Root and Tuber Vegetables Group resulting inadvertently due to

irrigation with 2,4-D-treated water. These data may also be used to reassess inadvertent tolerances established at 180.142(d) as a result of the 2,4-D RED.

Tolerance Listed Under 40 CFR §180.142(a)(4):

The established tolerance for residues in/on asparagus is reassessed at the current level under the revised tolerance expression and is to be recodified as 40 CFR §180.142(a).

Tolerance Listed Under 40 CFR §180.142(a)(5)

The established tolerance for residues in/on strawberry is reassessed at the current level under the revised tolerance expression and is to be recodified as 40 CFR §180.142(a).

Tolerances Listed Under 40 CFR §180.142(a)(6):

Tolerances listed in 40 CFR §180.142(a)(6) are established for residues of 2,4-D from application of its dimethylamine salt for water hyacinth control in ponds, lakes, reservoirs, marshes, bayous, drainage ditches, canals, rivers, and streams that are quiescent or slow moving in programs conducted by the Army Corps of Engineers or other Federal, State, or local public agencies. Where tolerances are established at higher levels from other uses of the dimethylamine salt of 2,4-D on crops included within these commodity groups, the higher tolerances also apply to residues from the aquatic uses cited in this paragraph.

Based on the available residue data, the current tolerance in shellfish is adequate and the tolerance in fish can be reduced to 0.1 ppm. Both tolerances should be recodified under the revised section 180.142(a).

Tolerances for residues in/on the irrigated crops and crop groups at the current §180.142(a)(6) are set at 1.0 ppm whereas the tolerances in/on the identical crops/crop groups at §180.142(a)(3) are at 0.1 ppm for the irrigation ditchbank use. The recommended/reassessed tolerances from §180.142(a)(3) to be recodified under sections §180.142(a) or §180.142(d) concomitantly address the reassessments/recodifications recommended for tolerances at §180.142(a)(6), depending on whether residues are incurred directly and/or inadvertently, as explained above.

Tolerances Listed Under 40 CFR §180.142(a)(8):

Tolerances listed in 40 CFR §180.142(a)(8) are established for residues of 2,4-D and/or its metabolite 2,4-DCP in livestock commodities. As indicated by the Agency, the regulated residue in animal commodities is 2,4-D (free and conjugated). As a result of this residue definition change, all reassessed livestock tolerances should be recodified to §180.142(a).

Based upon the available livestock feeding study, the 0.1 ppm tolerance in milk is reassessed at 0.05 ppm and the tolerances in cattle, goat, horse, and sheep commodities are reassessed at: 0.3 ppm in fat, meat, and meat byproducts except kidney and 4.0 ppm in kidney.

The established tolerances for 2,4-D residues in hog commodities may be revoked. Based on the MTDB for swine (1.6 ppm) and the results of the ruminant feeding study, there is no reasonable expectation of finite 2,4-D residues occurring in hog commodities [Category 3 of 40 CFR §180.6(a)(3)].

In addition, the established tolerances for 2,4-D residues in eggs and poultry tissues may be revoked. Based on the results of the 2,4-D poultry metabolism study, there is no reasonable expectation of finite residues in poultry tissues and eggs [Category 3 of 40 CFR §180.6(a)(3)].

Tolerance Listed Under 40 CFR §180.142(a)(9):

Tolerances listed in 40 CFR §180.142(a)(9) are established for residues of 2,4-D from applications of its dimethylamine salt or its butoxyethanol ester for Eurasian water milfoil control in programs conducted by the Tennessee Valley Authority in dams and reservoirs of the TVA system.

The tolerance for 2,4-D residues in fish at 40 CFR §180.142(a)(9) should be revoked and this section deleted. There is no need for two 2,4-D tolerances in fish. It has already been recommended that the 1.0 ppm tolerance in fish currently at §180.142(a)(6) be reassessed at 0.1 ppm and that this reassessed tolerance be recodified at the new 40 CFR §180.142(a).

Tolerance Listed Under 40 CFR §180.142(a)(10):

The tolerance listed in 40 CFR §180.142(a)(10) is a regional registration as defined in Sec. 180.1(n) and is established for the residues of 2,4-D in raspberries. The tolerance includes residues from the application of 2,4-D and its N-oleyl-1,3-propylenediamine salt.

As the members of Task Force II are not supporting 2,4-D use on this commodity, the tolerance for residues in/on raspberries should be revoked unless another party wishes to support a use on this crop. 40 CFR §180.142(a)(10) should be deleted and any tolerances with regional use registration should be established under the revised section 40 CFR §180.142(c).

Tolerance Listed Under 40 CFR §180.142(a)(11):

A time-limited tolerance of 0.02 ppm has been established for residues of 2,4-D resulting from the preplant use of 2,4-D ester or amine in/on soybean seed [40 CFR §180.142(a)(11)], expired on December 31, 2004. Adequate residue data are available to support permanent tolerances on soybean commodities. Section 180.142(a)(11) should be deleted, and permanent tolerances for 2,4-D residues in/on soybean seed, forage, and hay are recommended to be established under the revised section 180.142(a).

Tolerances Listed Under 40 CFR §180.142(a)(12):

Tolerances listed at 40 CFR §180.142(a)(12) are established for residues of 2,4-D in processed feeds. Such residues may be present therein only as a result of application to the growing crop of the herbicides identified in this section. Tolerances formerly listed at 40 CFR §180.1450 were moved to 40 CFR §180.142(a)(12) (63 FR 34829, 6/26/98).

The tolerance for residues in sugarcane bagasse should be revoked because it is no longer considered a significant livestock feed item and has been deleted from Table 1 (OPPTS GLN 860.1000).

40 CFR §180.142(a)(12) should be deleted. The tolerance for 2,4-D residues in milled fractions derived from barley, oats, rye, and wheat should be revoked as the commodity definition will change and the tolerances will be increased and recodified at the revised 40 CFR §180.142(a) for residues in barley bran, rye bran, and wheat bran. No tolerances in other processed products of small grains are necessary because concentration of residues does not occur in them.

Tolerances Listed Under 40 CFR §180.142(a)(13):

Tolerances listed at CFR §180.142(a)(13) are established for residues of 2,4-D in processed foods and potable water.

40 CFR §180.142(a)(13) should be deleted. The tolerances for 2,4-D residues in sugarcane molasses and in milled fractions derived from barley, oats, rye, and wheat should be revoked as tolerances will be recodified under the revised 40 CFR §180.142(a) for residues in sugarcane molasses, barley bran, rye bran, and wheat bran.

The established tolerance for residues of 2,4-D in potable water should be revoked as EPA/OPPTS/OPP no longer establishes pesticide tolerances in potable water. Instead, the EPA Office of Water establishes Maximum Contaminant Levels (MCLs). An MCL of 0.07 ppm has been established for 2,4-D in drinking water.

Tolerances Listed Under 40 CFR §180.142(b):

The tolerance listed in 40 CFR §180.142(b) is a time-limited tolerance established for 2,4-D in/on wild rice in connection with use of 2,4-D in MN under a Section 18 emergency exemption granted by EPA. The tolerance is set to expire on December 31, 2005. As adequate residue data are available on wild rice grown in MN, a permanent tolerance for rice, wild, grain should be established at 0.05 ppm under 40 CFR §180.142(c).

2. Tolerances to Be Proposed Under 40 CFR §180.142

Tolerances Needed Under 40 CFR §180.142(a):

The revised section will include all permanent tolerances for residues of 2,4-D, defined as residues of 2,4-D, both free and conjugated, determined as the acid. The section will include all plant commodities (excluding crop commodities exposed solely inadvertently), livestock commodities, fish, and shellfish at reassessed levels.

In addition, the available residue data indicate that new tolerances should be established for 2,4-D residues in/on the following commodities: almond hulls; aspirated grain fractions; barley bran and straw; oat straw; rice hulls; rye bran and straw; soybean forage, hay, and seeds; and wheat bran and straw.

Once adequate residue data become available, new tolerances should also be established for wheat hay. Wheat hay data will be translated to barley hay, millet hay, and oat hay.

Tolerances Needed Under 40 CFR §180.142(c):

Based on the available residue data, tolerances with regional use registrations should be established for wild rice grain at 0.05 ppm, reflecting the use of 2,4-D on wild rice grown in MN.

Tolerances Needed Under 40 CFR §180.142(d):

Tolerances for inadvertent 2,4-D residues in irrigated crops that have no registered, direct uses will be moved from paragraph §180.142(a)(3) to paragraph §180.142(d) and the commodity and crop group listings will be revised to the current EPA definitions.

Table 38. Tolerance Reassessment Summary for 2,4-D.

Commodity	Tolerance Listed Under 40 CFR §180.142 (ppm)	Reassessed Tolerance (ppm)	Comment *[Corrected Commodity Definition]*
Tolerances Listed Under 40 CFR §180.142 (a) (1) [2]			

Commodity	Tolerance Listed Under 40 CFR §180.142 (ppm)	Reassessed Tolerance (ppm)	Comment *[Corrected Commodity Definition]*
Apple	5	Revoke	A single tolerance should be established at 0.05 ppm under 180.142(a) for direct and inadvertent residues in/on the *Fruit, pome, group 11*.
Apricot	5	Revoke	Residues in/on apricots will be covered by the tolerance for direct and inadvertent residues in stone fruits at 180.142(a).
Fruit, citrus	5	3.0	A tolerance should be established in Fruit, citrus, group 10, recodified as 180.142(a), that will cover the preharvest use on citrus, the postharvest use on lemons in the U.S., the postharvest use on citrus imported into the U.S., and the inadvertent residues due to irrigation with treated water.
Pear	5	Revoke	A single tolerance should be established at 0.05 ppm under 180.142(a) for direct and inadvertent residues in/on the *Fruit, pome, group 11*.
Potato	0.2	0.40	Includes direct and inadvertent (irrigation) residues. Recodify as 180.142(a).
Quince	5	Revoke	Residues in/on quince will be included under the 0.05 ppm tolerance at 180.142(a) for direct and inadvertent residues in/on the *Fruit, pome, group 11*.
Tolerances Listed Under 40 CFR §180.142 (a) (2) [2]			
Barley, grain	0.5	2.0	The submitted data for wheat grain may be translated to barley grain. Recodify as 180.142(a).
Blueberry	0.1	Revoke	To be included under the 0.2 ppm *Berries group 13* tolerance to be recodified as 180.142(a).
Corn, fodder	20	50.0	Residue data from the 7-day PHI. Recodify as 180.142(a). *Corn, stover*
Corn, forage	20	6.0	Residue data from the 7-day PHI. Recodify as 180.142(a).
Corn, fresh, sweet, kernel plus cob with husks removed	0.5	0.05	Recodify as 180.142(a).
Corn, grain	0.5	0.05	Residue data from 7-day PHI. Recodify as 180.142(a).
Cranberry	0.5	Revoke	To be included under the 0.2 ppm *Berries group 13* tolerance to be recodified as 180.142(a).
Fruit, stone	0.2	0.05	Recodify as 180.142(a). This tolerance will now cover both direct and inadvertent residues. *Fruit, stone, group 12*
Grape	0.5	0.05	Residue data on grape are available for the entire U.S. Recodify as 180.142(a).
Grass, hay	300	300	Residue data from the 7-day posttreatment interval (PTI) for *Grass, hay*. Recodify as 180.142(a).

Commodity	Tolerance Listed Under 40 CFR §180.142 (ppm)	Reassessed Tolerance (ppm)	Comment *[Corrected Commodity Definition]*
Grass, pasture	1,000	360	Recodify as 180.142(a). Residue data from the 0-day PTI. This new tolerance will now cover both direct and inadvertent residues. *Grass, forage*
Grass, rangeland	1,000		
Millet, forage	20	25	The data for wheat forage, grain, and straw may be translated to millet forage, grain, and straw. The required wheat hay data will be translated to millet hay. Recodify as 180.142(a). This new tolerance will now cover both direct and inadvertent residues.
Millet, grain	0.5	2.0	
Millet, straw	20	50	
Nut	0.2	0.2	Recodify as 180.142(a). This new tolerance will now cover both direct and inadvertent residues. *Nut, tree, group 14*
Oat, forage	20	25	The data for wheat forage may be translated to oat forage. Recodify as 180.142(a). This new tolerance will now cover both direct and inadvertent residues.
Oat, grain	0.5	2.0	The data for wheat grain may be translated to oat grain. Recodify as 180.142(a). This new tolerance will now cover both direct and inadvertent residues.
Pistachio	0.2	0.05	Recodify as 180.142(a). This new tolerance will now cover both direct and inadvertent residues.
Rice	0.1	0.5	Recodify as 180.142(a). This new tolerance will now cover both direct and inadvertent residues. *Rice, grain*
Rice, straw	20	10	Recodify as 180.142(a). This new tolerance will now cover both direct and inadvertent residues.
Rye, forage	20	25	Recodify as 180.142(a). This new tolerance will now cover both direct and inadvertent residues. The data for wheat forage may be translated to rye forage.
Rye, grain	0.5	2.0	Recodify as 180.142(a). This new tolerance will now cover both direct and inadvertent residues. The data for wheat grain may be translated to rye grain.
Sorghum, fodder	20	0.2	Recodify as 180.142(a). This new tolerance will now cover both direct and inadvertent residues. *Sorghum, stover*
Sorghum, forage	20	0.2	Recodify as 180.142(a). This new tolerance will now cover both direct and inadvertent residues.
Sorghum, grain	0.5	0.2	Recodify as 180.142(a). This new tolerance will now cover both direct and inadvertent residues.
Sugarcane	2	0.05	Recodify as 180.142(a). *Sugarcane, cane*
Sugarcane, forage	20	Revoke	Sugarcane forage is no longer considered a significant livestock feed item.

Commodity	Tolerance Listed Under 40 CFR §180.142 (ppm)	Reassessed Tolerance (ppm)	Comment *[Corrected Commodity Definition]*
Wheat, forage	20	25	Recodify as 180.142(a). This new tolerance will now cover both direct and inadvertent residues. The 14-day PHI residue data on wheat forage and grain will be used to support tolerances for residues in/on similar commodities of barley, millet, oats, and rye.
Wheat, grain	0.5	2.0	
Tolerance Listed Under 40 CFR §180.142 (a)(3) [4]			
Avocado	0.1(N)	0.05	Recodify as 180.142(d).
Cottonseed	0.1(N)	0.05	Recodify as 180.142(d). *Cotton, undelinted seed*
Cucurbits	0.1(N)	0.05	Recodify as 180.142(d). *Vegetable, cucurbit, group 9*
Fruit, citrus	0.1(N)	Revoke	Inadvertent residues will be covered by the crop group tolerance on citrus fruit at 180.142(a).
Fruit, pome	0.1(N)	Revoke	Inadvertent residues will be covered by the crop group tolerance on pome fruit at 180.142(a).
Fruit, stone	0.1(N)	Revoke	Revocation of one strone fruit tolerance is necessary to avoid duplication. Inadvertent residues will be covered by the stone fruit group tolerance at 180.142(a)(2) to be recodified as 180.142(a).
Grain, crop	0.1(N)	Revoke	Separate tolerances in RACs of each grain will be individually established and recodified as 180.142(a) in/on grain, forage, fodder, stover, or hay, as applicable, to cover both direct and inadvertent residues. Upon formal Agency approval, a small grains subgroup tolerance may be established.
Grass, forage	0.1(N)	Revoke	Inadvertent residues will be covered by the grass forage tolerance for direct residues to be recodified as 180.142(a).
Hop	0.1(N)	0.2	Inadvertent residues will be covered by the hop tolerance for direct residues upon establishment at 180.142(a) in response to PP#2E6352.
Leafy vegetables	0.1(N)	0.4	Establish separate tolerances for inadvertent residues in the *Vegetable, leafy, except brassica, group 4* and *Vegetable, brassica, leafy, group 5* at 0.4 ppm under the revised 180.142(d)
Legume, forage	0.1(N)	Group 7 - 0.2 Group 18 - 0.2	Establish separate tolerances for the *Vegetable, foliage of legume, group 7* and *Animal feed, nongrass, group 18* for inadvertent residues under 180.142(d).
Nut	0.1(N)	Revoke	Inadvertent residues will be covered by the tolerance in the tree nuts crop group at 180.142(a)

Commodity	Tolerance Listed Under 40 CFR §180.142 (ppm)	Reassessed Tolerance (ppm)	Comment *[Corrected Commodity Definition]*
Root crop vegetables	0.1(N)	Group 1 - TBD Group 2 - TBD Group 3 - 0.05	Additional data are required to determine inadvertent residues in sugar beet roots and tops to represent root and tuber vegetables. Establish separate tolerances in the *Vegetable, bulb, group 3*. When sugar beet data are received, establish separate tolerances in the *Vegetable, root and tuber, group 1* and *Vegetable, leaves of root and tuber, group 2*. Recodify as 180.142(a).
Seed and pod vegetables	0.1(N)	0.05	Establish tolerance for inadvertent residues at 180.142(d) in the *Vegetable, legume, group 6*.
Small fruit	0.1(N)	0.2	The 0.2 ppm tolerance in the *Berries group 13*, to be recodified at §180.142(a), will also cover inadvertent residues. Inadvertent residues in/on blueberry and cranberry will also be covered by this group tolerance. Inadvertent residues in/on grape and strawberry will be covered by separate tolerances for direct uses on these crops §180.142(a).
Vegetable, fruiting	0.1(N)	0.05	Establish tolerance for inadvertent residues at 0.05 ppm in the *Vegetable, fruiting, group 8* recodified under §180.142(d).
Tolerance Listed Under 40 CFR §180.142 (a)(4) [2]			
Asparagus	5	5.0	Recodify as §180.142(a).
Tolerance Listed Under 40 CFR §180.142 (a)(5) [2]			
Strawberry	0.05	0.05	Recodify as §180.142(a). This tolerance will cover direct and inadvertent residues.
Tolerance Listed Under 40 CFR §180.142 (a)(6) [2]			
Crops in paragraph (c) of this section	1.0	Revoke	The tolerances to be established under paragraphs §180.142(a) and §180.142(d) will be sufficient to cover inadvertent residues in irrigated crops under the recodified §180.142(a)(6).
Crop groupings in paragraph (c) of this section	1.0	Revoke	The tolerances to be established under paragraphs §180.142(a) and §180.142(d) will be sufficient to cover inadvertent residues in irrigated crops under the recodified §180.142(a)(6).
Fish	1.0	0.10	Residue data for fish and shellfish are from recent tests where fish and shellfish were exposed to 2,4-D under static conditions at 6.0 ppm (1.5x). Recodify to §180.142(a).
Shellfish	1.0	1.0	
Tolerance Listed Under 40 CFR §180.142 (a)(8) [2]			
Cattle, fat	0.2	0.3	Recodify as §180.142(a).
Cattle, kidney	2	4.0	Recodify as §180.142(a).
Cattle, meat	0.2	0.3	Recodify as §180.142(a).

Commodity	Tolerance Listed Under 40 CFR §180.142 (ppm)	Reassessed Tolerance (ppm)	Comment *[Corrected Commodity Definition]*
Cattle, meat byproducts, except kidney	0.2	0.3	Recodify as §180.142(a).
Egg	0.05	Revoke	Category 3 of 40 CFR §180.6(a)(3) applies.
Goat, fat	0.2	0.3	Recodify as §180.142(a).
Goat, kidney	2	4.0	Recodify as §180.142(a).
Goat, meat	0.2	0.3	Recodify as §180.142(a).
Goat, meat byproducts, except kidney	0.2	0.3	Recodify as §180.142(a).
Hog, fat	0.2	Revoke	Category 3 of 40 CFR §180.6(a)(3) applies.
Hog, kidney	2		
Hog, meat	0.2		
Hog, meat byproducts, except kidney	0.2		
Horse, fat	0.2	0.3	Recodify as §180.142(a).
Horse, kidney	2	4.0	Recodify as §180.142(a).
Horse, meat	0.2	0.3	Recodify as §180.142(a).
Horse, meat byproducts, except kidney	0.2	0.3	Recodify as §180.142(a).
Milk	0.1	0.05	Residues in milk increased linearly with dose; therefore, the 0.05 ppm tolerance will be adequate for the 1x dose level. Recodify as §180.142(a).
Poultry	0.05	Revoke	Category 3 of 40 CFR §180.6(a)(3) applies.
Sheep, fat	0.2	0.2	Recodify as §180.142(a).
Sheep, kidney	2	2.0	Recodify as §180.142(a).
Sheep, meat	0.2	0.2	Recodify as §180.142(a).
Sheep, meat byproducts, except kidney	0.2	0.2	Recodify as §180.142(a).
Tolerance Listed Under 40 CFR §180.142 (a)(9) [2]			
Fish	1.0	Revoke	The reassessed tolerance of 0.1 ppm at §180.142(a)(6) will be recodified as §180.142(a). There is no need for duplication of tolerances.
Tolerance Listed Under 40 CFR §180.142 (a)(10) [2]			
Raspberry	1.0	Revoke	Although there is no indication that IR-4 or the Task Force II is supporting a use on raspberries, it would be covered by the 0.2 ppm tolerance in the Berries group 13 at §180.142(a).

Commodity	Tolerance Listed Under 40 CFR §180.142 (ppm)	Reassessed Tolerance (ppm)	Comment *[Corrected Commodity Definition]*
Tolerance Listed Under 40 CFR §180.142 (a)(11) [3]			
Soybean, seed	0.02	0.02	Tolerance expired on 12/31/04. Residue data support a permanent tolerance. If established, recodify as §180.142(a).
Tolerance Listed Under 40 CFR §180.142 (a)(12) [2]			
Sugarcane bagasse	5	Revoke	Sugarcane bagasse is no longer considered a significant livestock feed item.
Sugarcane molasses	5	0.20	Maximum residue value is based on HAFT residues of 0.015 ppm in/on sugarcane and a 7x concentration factor for molasses. Recodify as §180.142(a). *Sugarcane, molasses*
Milled fractions derived from barley, oats, rye, and wheat to be ingested as animal feed or converted into animal feed	2	Revoke	Tolerances for direct and inadvertent residues of 2,4-D in barley, bran; rye, bran; and wheat, bran are to be established under revised 40 CFR 180.142(a). Tolerances in other small grain processed products are not necessary as residues do not concentrate upon processing.
Tolerance Listed Under 40 CFR §180.142 (a)(13) [2]			
Sugarcane molasses	5	Revoke	The sugarcane molasses reassessed tolerance at §180.142(a)(12) will be recodifed as §180.142(a). Duplication of tolerances is not necessary.
Milled fractions derived from barley, oats, rye, and wheat to be ingested as animal feed or converted into animal feed	2	Revoke	Tolerances for direct and inadvertent residues of 2,4-D in barley, bran; rye, bran; and wheat, bran are to be established under revised 40 CFR 180.142(a). Tolerances in other small grain processed products are not necessary as residues do not concentrate upon processing.
Potable water	0.1 (N)	Revoke	OPP no longer establishes tolerances in drinking water. EPA's Office of Water has established an MCL for 2,4-D at 0.07 ppm.
Tolerances Needed Under 40 CFR §180.142 (a); this list does not include recodifications, etc. from above			
Almond hulls	None	0.10	*Almond, hulls*
Aspirated grain fractions	None	40	Based on HAFT residues of 0.038 ppm for corn grain and a 39x concentration factor, maximum expected residues would be 1.48 ppm in aspirated grain fractions (AGF) derived from corn grain. Based on HAFT residues of 3.24 ppm for wheat grain and a 11.2x concentration factor, maximum expected residues would be 36.3 ppm in AGF derived from wheat grain. As sorghum and soybeans uses are early-season uses, residue data on AGF were not generated for these crops. Establish tolerance in AGF at 40 ppm.

Commodity	Tolerance Listed Under 40 CFR §180.142 (ppm)	Reassessed Tolerance (ppm)	Comment *[Corrected Commodity Definition]*
Barley, hay	None	TBD	Data for wheat straw were translated to barley straw. Required wheat wheat hay data will be translated to barley hay.
Barley, straw	None	50	
Barley, bran	None	4.0	Data for wheat bran were translated to barley bran.
Millet, hay	None	TBD	Required wheat wheat hay data will be translated to millet hay.
Oat, hay	None	TBD	Data for wheat straw were translated to oat straw. Required wheat wheat hay data will be translated to oat hay.
Oat, straw	--	50	
Rice, hulls	None	2.0	Maximum residue value is based on HAFT residues of 0.425 ppm in/on rice grain and a 3.3x concentration factor for hulls.
Rye, straw	None	50	Data for wheat straw were translated to rye straw.
Rye, bran	None	4.0	Data for wheat bran were translated to rye bran.
Soybean, forage	None	0.02	Adequate residue data are available to support permanent tolerances on soybean commodities.
Soybean, hay	None	2.0	
Soybean, seed	None	0.02	
Wheat, hay	None	TBD	Data are required on wheat hay
Wheat, straw	None	50	
Wheat, bran	None	4.0	Maximum residue value is based on HAFT residues of 1.08 ppm in/on wheat grain (14-day PHI) and a 3.6x concentration factor for bran.
Tolerance Listed Under 40 CFR §180.142 (b) [5]			
Wild rice	0.1	0.05	Tolerance expires 12/31/05. Adequate data are available to establish a permanent tolerance with a regional registration to be recodified as §180.142(c) for *Rice, wild, grain* at 0.05 ppm.
Tolerance Needed Under 40 CFR §180.142 (c) [6]			
Rice, wild, grain	None	0.05	regional tolerance with use restricted to MN
Tolerances Needed Under 40 CFR §180.142 (d) [7]			
Commodities and crop groups currently listed under paragraph (a)(3)	0.1 (N)	NA	See comments listed under §180.142(a)(3)

[1] Maximum residue of treated RAC sample(s) following application of 2,4-D formulations according to use patterns the Task Force II registrants intend to support for reregistration.

[2] This subparagraph will be deleted and tolerances recodified under revised paragraph (a).

[3] TBD = To be determined. Reassessment of tolerances(s) cannot be made at this time because additional data are required.

[4] Tolerances listed under §180.142 (a)(3) for inadvertent residues will be recodified as either §180.142(a) or §180.142(d).

[5] This paragraph will be reserved for future time-limited tolerances under Section 18 Emergency Exemptions.

[6] Tolerances with regional use registration.

[7] Paragraph (d) will contain tolerances for inadvertent residues (e.g., residues in irrigated crops) only, i.e., there is no registration for direct use in the U.S. If residues may result inadvertently as well as intentionally (direct, labeled treatment), the tolerance is codified at §180.142(a)

3. Codex Harmonization

The Codex Alimentarius Commission has established several maximum residue limits (MRLs) for residues of 2,4-D in/on various plant and animal commodities. The Codex MRLs are expressed in terms of 2,4-D *per se*. The expression of residues for Codex MRLs and U.S. tolerances is harmonized. A numerical comparison of the Codex MRLs and the corresponding reassessed U.S. tolerances is presented in Table 39.

Table 39. Codex MRLs and applicable U.S. tolerances for 2,4-D. Recommendations for compatibility are based on conclusions following reassessment of U.S. tolerances

Codex		Reassessed U.S. Tolerance, ppm	Recommendation And Comments
Commodity, As Defined	MRL (mg/kg)		
Barley	0.5	2.0	
Blackberries	0.1	0.20	U.S. tolerance for Berries group 13
Citrus fruits	2.0	3.0	
Eggs	0.05 (*)	Revoked	
Maize	0.05 (*)	0.05	
Meat (from mammals other than marine mammals)	0.05 (*)	0.30	Meat, fat, and mbyp except kidney
		4.0	Kidney
Milk products	0.05 (*)	0.05	
Milks	0.05 (*)	0.05	
Oats	0.5	2.0	
Potato	0.2	0.40	
Raspberries, Red, Black	0.1	0.20	U.S. tolerance for Berries group 13
Rice	0.05 (*)	0.50	
Rye	0.5	2.0	
Sorghum	0.05 (*)	0.20	Forage, grain, and stover=0.2
Vaccinium berries, including Bearberry	0.1	0.20	U.S. tolerance for Berries group 13
Wheat	0.5	2.0	

(*) = At or about the limit of detection.

4. Residue Analytical Methods - Plants and Livestock (GLN 860.1340)

For the purpose of reregistration, adequate methods are available for data collection and the enforcement of plant commodity tolerances. The Pesticide Analytical Manual (PAM) Vol. II lists three GC methods (designated as Methods A, B, and C) with microcoulometric detection and one GC

method (designated as Method D) with electron capture detection (ECD). In a letter dated September 3, 1993 (CBRS No. 12270, DP Barcode D193335, 9/3/93, W. Smith), Task Force II indicated that the enforcement methods currently listed in PAM Vol. II are unsuitable for determining residues of 2,4-D in wheat and poultry commodities.

Plant Commodities: Task Force II submitted an adequate proposed GC/ECD enforcement method for plants (designated as EN-CAS Method No. ENC-2/93) which has been independently validated. Adequate radiovalidation data have been submitted and evaluated for the proposed enforcement method using samples from the wheat metabolism study. The proposed enforcement method or modifications of the enforcement method were used for data collection purposes.

Livestock Commodities: Task Force II submitted two separate (but essentially comparable) proposed enforcement methods (GC/ECD) for determination of 2,4-D in livestock commodities. Adequate radiovalidation data have been submitted for the method using samples of fat, kidney, and milk from the goat metabolism study and samples of eggs from the poultry metabolism study. The Agency concluded that the methods are adequate provided the registrants satisfy the following requests: (i) submit a revised method which combines the two methods into a single method; (ii) delete from the method all references to the use of diazomethane as a derivatizing agent; and (iii) provide complete raw data and sample calculations (including chromatograms showing peak areas, external standard linearity curves and associated data, standard calculations, etc.). Once an adequate revised method is submitted, the Agency will evaluate the tolerance method validation. Recently, it has been determined that the technology to generate diazomethane has advanced such that it is no longer considered to be a dangerous procedure; as a result, the use of diazomethane as a derivatizing agent is now considered acceptable.

E. Regulatory Rationale

The following is a summary of the rationale for managing risks associated with the use of 2,4-D. Where labeling revisions are warranted, specific language is set forth in the summary tables of Section V of this document.

1. Human Health Risk Management

a. Residential Risk

1) Residential risk summary

A Margin of Exposure (MOE) of 1000 (10x for interspecies extrapolation, 10x for intraspecies variation, and 10x database uncertainty factor) is considered adequately protective for this assessment of residential risks. Residential handler risks are not of concern. All MOEs for post-application, oral exposure to children from playing on treated lawns meet or exceed 1000; therefore, post-application exposure to children is not of concern. Likewise, all adult acute/short term MOEs meet or exceed 1000, so post-application exposure is not of concern for adults.

As discussed below, potential risks were identified to individuals who swim in water treated with 2,4-D. Although the risk assessment is likely to be conservative, mitigation measures will be required.

2) Residential Post-application Mitigation

For residential, post-application exposures, when the calculated MOE of 1000 based on modeling is considered in conjunction with biomonitoring results, it is clear that the modeled short-term risks from post-application exposure are upper bound estimates. At one day post-treatment, the MOEs for the volunteers who wore shorts and no shoes ranged from 1400 to 35000 with the lowest MOE corresponding to the volunteer who removed his shirt during the exposure period. The MOEs for the remaining volunteers ranged from 24000 to 37000. The Agency has concluded that no further mitigation is needed for residential post-application exposures.

3) Residential Swimmer Mitigation

The acute MSWC of 9.8 ppm for exposures to 2,4-D acid or amine is greater than the proposed maximum application rate of 4.0 ppm, therefore, acute exposures to acid or amine are not of concern. The MSWC of 3.6 ppm for short-term exposures to acid or amine is also not of concern because some dissipation or dispersion is likely to occur which would cause the 7-day average of 2,4-D concentrations to be less than 3.6 ppm. Dissipation studies submitted to the Agency indicated that the half lives following pond and lake liquid treatments ranged from 3.2 days to 27.8 days which yield 7 day average concentrations of 1.9 ppm when the half life equals 3.2 days, to 3.6 ppm when the half life equals 27.8 days.

The MSWCs for 2,4-D BEE are less than the master label application rate of 4 ppm, but they are unlikely to be of concern for the following reasons:

- 2,4-D BEE degrades rapidly by abiotic hydrolysis in sterile water to form 2,4-D acid particularly when the pH is 7.5 or above.

- 2,4-D BEE degrades to 2,4-D acid by microbial hydrolysis with an average half life of 2.6 ± 1.8 hours at a bacterial concentration of 5×10^{-8} organisms per liter. Therefore, degradation of 2,4-D BEE to 2,4-D under typical environmental conditions will be rapid leading to significantly lower risk estimates because the 2,4-D acid has a lower rate of dermal absorption.

- Modeling predicts direct water application of 2,4-D BEE will yield surface water concentrations of 2,4-D BEE concentrations in the Agency standard pond of 624 ug/L for peak (24 hour average), 30 ug/L for the 21-day average, and 10 ug/L for the 60-day average.

- The existing label rates for 2,4-D BEE products are also lower than the master label rate.

Although the risk characterization above suggests that the risk estimates are conservative, a 24 hour post-application restriction on swimming is necessary to ensure the safety of children swimming in water treated with 2,4-D BEE.

b. Aggregate Risk

The Food Quality Protection Act amendments to the Federal Food, Drug, and Cosmetic Act (FFDCA, Section 408(b)(2)(A)(ii)) require "that there is a reasonable certainty that no harm will result from aggregate exposure to pesticide chemical residue, including all anticipated dietary exposures and other exposures for which there is reliable information." Aggregate exposure will typically include exposures from food, drinking water, residential uses of a pesticide, and other non-occupational sources of exposure.

1) Aggregate Risk Summary

For 2,4-D, EPA conducted acute, short-term, and chronic aggregate risk assessments using the reduced maximum application rate for residential turf (1.5 lbs ae/A). The aggregate risk assessment compares the Drinking Water Level of Comparison (DWLOC) for each scenario with the appropriate Estimated Drinking Water Concentration (EDWC) for the pesticide. The DWLOC is the maximum concentration in drinking water which, when considered together with food, and, if appropriate, residential exposure, does not exceed EPA's level of concern. Generally, EDWCs that are less than the corresponding DWLOC are not of concern to the Agency.

It is important to note that the MCL for 2,4-D, established by EPA's Office of Water under the Safe Drinking Water Act (SDWA), is 70 ug/L. To minimize the possibility that direct aquatic applications will result in drinking water concentrations in excess of the MCL, the Agency has worked with the 2,4-D Task Force and water quality specialists to develop appropriate label requirements for 2,4-D products registered for use to control aquatic weeds.

2) Acute Aggregate Risk

<u>DWLOC Approach</u>

Acute DWLOCs were calculated based upon acute dietary exposures. Acute residential exposures from swimming in treated water bodies or playing on treated turf were not included because exposures are unlikely to co-occur with acute dietary exposures. The acute DWLOCs are range from 432 to 1932 with the most sensitive population being females 13 to 49 years old. The EDWCs of 118 ug/liter for surface water and 15 ug/liter for groundwater are substantially less than the DWLOCs which means that the risks are not of concern.

<u>Forward Calculation Approach</u>

Acute aggregate risks were assessed by directly combining acute food exposures and estimates of acute water exposures. The acute aggregate risks and are not of concern because they are less than 100 percent of the aPAD. The highest risks (58 percent of the aPAD) are for females 13-49 years old because these risks are based upon the lower NOAEL of 25 mg/kg/day from a developmental study in

rats. Whereas, estimates of other population groups are based on a NOAEL of 67 mg/kg/day from an acute neurotoxicity study in rats.

3) Short-term Aggregate Risk

DWLOC Approach

Short-term aggregate risks assessments were conducted by calculating DWLOCs based upon short-term turf exposures, chronic food exposures and short-term endpoints. Short-term exposures from swimming in treated water bodies were not included because these exposures represent high-end unlikely scenarios. The short-term DWLOCs were calculated only for females 13-49 and children 1-6 because these population subgroups have the highest exposure and estimates calculated for these groups are protective of the other subgroups. The DWLOCs range from 24 to 36 ug/liter. The EDWCs range from 15 to 23 ug/liter. Since the DWLOCs are all greater than the EDWCs, the short term risks are not of concern.

Forward Calculation Approach

Short-term aggregate risks were assessed by aggregating short-term turf exposures, chronic food exposures and chronic water exposures. Short-term aggregate risk were calculated only for females 13-49 and children 1-6 because these population subgroups have the highest exposure and estimates calculated for these groups are protective of the other subgroups. The short-term aggregate MOEs indicate that the short term risks are not of concern because the MOEs equal or exceed the target MOE of 1000.

4) Chronic (Non-Cancer) Aggregate Risk

DWLOC Approach

Chronic DWLOCs were calculated based upon chronic dietary exposures. As there are no chronic residential exposures, residential exposures were not included in the chronic DWLOC calculations. The chronic DWLOCs are 46 ug/L or greater with the most sensitive populations being infants and children. The EDWCs, which range from 1.5 to 23 ug/L, are less than the DWLOCs which means that the risks are not of concern. It should be noted that the master label indicates that potable water consumption from a treated water body cannot begin until the 2,4-D concentration is 70 ug/L or below, therefore an annual average exposure at the MCL of 70 ug/L would not occur because dissipation would reduce the initial concentration of 70 ug/L to an annual average concentration of 11 ug/L.

Forward Calculation Approach

Chronic aggregate risks were assessed by aggregating chronic food exposures and chronic water exposures. The chronic aggregate risks are not of concern because they are less than 100 percent of the cPAD. The highest risks (38 percent of the cPAD) are for children 1-2 years old.

5) Aggregate Risk Mitigation

Given the reduced maximum application rate to residential lawns (1.5 lbs ae/A), the highest aggregate risks are the risks from short-term exposures, which include the turf exposure scenarios. For the most sensitive subpopulation (females 13-49) these risks meet the target MOE of 1000 and the turf exposure is the risk driver as it contributes 96 percent of the risk.

Whereas calculated risks just meet the Agency's target MOE, it is important to note that the turf exposure estimate is based upon modeling and is greater than exposure measurements obtained from biomonitoring. As described in the human health assessment, the results of a biomonitoring study were used to calculated MOEs by assuming that all of the urinary 2,4-D measured in the 96 hours after the exposure period was the result of the turf exposure. This assumption is protective because 2,4-D exposures due to inhalation and due to food and water ingestion would be counted as dermal exposure. The biomonitoring results were adjusted by a factor of two to account for the SOP assumption of two hours of daily exposure vs one hour of exposure during the study, and a factor of 1.7 to account for an application rate of 1.5 lbs ae/acre vs 0.88 lb ae/acre applied during the study. At one day post-treatment, the MOEs for the volunteers who wore shorts and no shoes ranged from 1400 to 35000 with the lowest MOE corresponding to the volunteer who removed his shirt during the exposure period. The MOEs for the remaining volunteers ranged from 24000 to 37000. If the calculated MOE of 1000 based on modeling is considered in conjunction with the MOE calculated based on biomonitoring results, it is clear that the modeled short-term risks are upper bound estimates. The Agency has concluded that aggregate risks from acute, short-term and chronic exposures are not of concern. No further mitigation beyond reducing the maximum application rate from 2.0 to 1.5 lbs/ae per acre is needed.

c. Occupational Risk Mitigation

1) Handler Risk Mitigation

With the exception of mixing/loading wettable powder, the short-term and intermediate-term Margin of Exposure estimates (MOEs) exceed 100 with baseline attire (i.e., long-sleeved shirt, long pants, shoes plus socks) or single layer attire (i.e., long-sleeved shirt, long pants, shoes plus socks, gloves) and are not of concern. The MOEs for handling wettable powder are acceptable with engineering controls (i.e. water soluble bags). Water soluble bags will be required for wettable powder formulations.

2) Post-application Risk Mitigation

All short- and intermediate-term MOEs are above 100 on day zero. All occupational postapplication risk scenarios are below EPA's level of concern. Products containing 2,4-D salt and ester forms as active ingredient with Worker Protection Standard (WPS) uses will require a re-entry interval (REI) of 12 hours. Because of acute eye irritation concerns, products containing 2,4-D acid and amine forms with WPS uses will require a REI of 48 hours and protective eyewear. The requirements for individual products will be finalized based on product-specific chemistry and acute

toxicity review. The exposure reduction program implemented in 1992 will be replaced with the personal protective equipment described in section V.D. of this document.

2. Environmental Risk Mitigation

The Agency has considered available information on 2,4-D's toxicity, use areas, usage, fate properties, application methods, and formulations in calculating ecological risks. The resulting assessment suggests that the use of 2,4-D for aquatic weed control presents risk to aquatic organisms, while 2,4-D use on terrestrial sites presents greater potential risks to small mammals, birds, and non-target terrestrial plants, than to other plants and animals.

a. Birds

Acute Risk

Whereas the assessment of risk to birds from the terrestrial use of 2,4-D suggests risks of concern, the assessed exposures to 2,4-D are likely conservative in the following ways. Currently, Agency models do not account for the uptake of 2,4-D by plants and therefore assume that all non-dissipated pesticide applied to the field is present for exposure to organisms. In fact, many pesticides, including 2,4-D, are systemic and are absorbed by plants in the field and therefore, the current approach may overestimate the amount of 2,4-D available for exposure in terrestrial and aquatic systems.

For non-granular spray application, the highest acute avian RQ (3.5) was from the cranberry use-site scenario, for birds feeding on short grass. That assessment was based on a maximum application rate of 4 lbs ae/acre; however, the average application rate is 1.83 lbs ae/acre (see the Agency's quantitative use assessment). If the modeled application rate was reduced to 1.83 lbs ae/acre for cranberries, and an assumption made that the resulting EEC will be reduced linearly, the RQ would be 1.6.

To determine the hazard associated with acute exposures to birds, the assessment has relied on two types of data, a suite of dietary studies and a suite of gavage studies. For avian acute exposures, the dietary studies result in non-definitive endpoints which are not appropriate for estimating risk. Therefore, the assessment has relied on the gavage studies to estimate avian acute risks. The Agency recognizes that this approach may overestimate risk to birds due to the fact that birds would not typically be expected to consume 2,4-D in this manner.

Chronic Risk

Potential chronic risks to birds is limited to the following use sites: non-cropland, forest, asparagus, and cranberry. The RQs for these sites range from one to slightly above one. Further characterization of these use sites by evaluating average application rates versus maximum application rates lower these RQs to below the LOCs.

Given the conservative assumptions in both exposure scenarios and hazard determinations, the Agency finds that the acute and chronic risks to birds from 2,4-D exposure are not of concern.

b. Mammals

Acute risk

All of the calculated RQs for mammalian acute risk for the non-granular use of 2,4-D were based on maximum labeled application rates. The EPA's quantitative use assessment (EPA QUA) suggests that the average application rates for many crops are considerably less than the modeled maximum application rates. For non-granular spray application mammalian acute concerns, the highest RQ was 1.72 for use on asparagus for small mammals feeding on short grass based on a maximum application rate of 2 lbs ae/A applied two times a year; however, the average application rate was only 1.10 lbs ae/A (EPA QUA). If the modeled application rate was reduced to the reported average application rate of 1.10 lbs ae/A for asparagus, the RQ would be 1.08 which is still above the acute LOC of 0.5. However, asparagus is representative of a minor 2,4-D use, and risk to mammals from use of 2,4-D on asparagus would be minimal, given that fact.

To add context to the acute mammalian assessment, the effect of assuming an average application rate was determined. Major 2,4-D crops include pasture/rangeland, turf, wheat, corn, and soybeans. For pasture/rangeland, the highest acute RQ was 0.86 for small mammals feeding on short grass based on a maximum application rate of 4 lbs ae/A. However, the average application rate was only 0.62 lbs ae/A (BEAD QUA). If the modeled application rate was reduced to 0.62 lbs ae/A for pasture/rangeland, the resulting RQ is 0.31 which is below the acute LOC, but above the restricted use LOC of 0.2. Similar trends are noted for other major use sites.

Although the calculated RQ values still exceed the Agency's level of concern when average applications rates are considered, the Agency has concluded that the benefits from 2,4-D use (including control of invasive and noxious weed species), taken together with the low toxicity of 2,4-D to humans, outweigh the concerns of toxicity to small mammals. No additional mitigation steps will be taken.

Chronic risk

Calculated chronic risks to mammals were greatest for small herbivores/insectivores. For 15 g mammalian herbivores/insectivores, chronic RQs based on maximum residues and mean residues ranged from <1 to 200 and <1 to 70, respectively. For major use sites, including rangeland/pasture, RQs were approximately 100. These chronic risk estimates are likely conservative as described below.

The chronic RQs calculated for mammalian herbivores/insectivores are based on conservative estimates of exposure that are not likely to occur in nature. In the example of pasture/rangeland, the chronic RQ of approximately 100 for maximum residues (35 for mean residues) was calculated based on an application rate of 2 lbs ae/A applied twice per year, at a 30 day interval. However, the EPA has determined that the average application rate on pasture/rangeland is only 0.62 lbs ae/A (EPA QUA). Moreover, information from several of the Agency's state contacts indicate that a once per year application of less than 1 lb ae/A is typical (personal communications). As the typical rate is approximately 25% of the assessed rate, use of the typical rate would be expected to decrease the RQ for the pasture/rangeland scenario approximately four-fold, to approximately 25 for maximum residues and 9 for mean residues.

A second example of the conservative assumptions included in the assessment of exposure to mammalian herbivores/insectivores is the assumption that 100% of the long term diet is relegated to

single food types foraged only from treated fields. The assumption of 100% diet from a single food type may be realistic for acute exposures, but diets are likely to be more variable over longer periods of time. The risk assessment assumed that 100% of the small mammals' diet consists of short grasses. Several published reports suggest that actual diets of small mammals are more varied, and would likely include invertebrates, worms, fungi, and seeds, in addition to plant matter.

Given the conservative assumptions in the exposure scenarios, the Agency finds that the risks identified in the risk assessment are likely to overestimate actual risks to mammals from 2,4-D applications. Based on information about average application rates and dietary patterns as described above, the Agency has concluded that actual 2,4-D exposures to mammals are likely to be significantly lower than those assessed but may still be above the chronic LOC for this screening level assessment. However, the Agency has concluded that the benefits from 2,4-D use (including control of invasive and noxious weed species), taken together with the low toxicity of 2,4-D to humans, outweigh the concerns of toxicity to small mammals. No additional mitigation is being required at this time.

c. Aquatic Organisms

Whereas the assessment of risk to aquatic organisms suggests risks of concern, the assessed exposures to 2,4-D are likely conservative as follows. Whereas the maximum labeled target concentration for control of aquatic weeds is 4 ppm, the typical target concentration is 2 ppm. A rate of 4 ppm is reserved for spot-treating new aquatic weed stands and hybrid weed species that tend to be less susceptible to 2,4-D. Per the product label, re-application of 2,4-D can occur after 21 days.

In the current assessment, the risks to aquatic organisms were estimated based on a 2,4-D application that resulted in a whole-reservoir concentration of 4 ppm. Treating 100% of the water body would likely result in a large amount of decaying plant life, thereby creating an oxygen-depleted environment that would most likely result in fish kills. To avoid that scenario, the current 2,4-D label advises that the applicator avoid treating more than 50% of a water body in a 21-day period. In actual practice, aquatic weeds that 2,4-D controls tend to grow near the shore of lakes, ponds, and reservoirs. As a result, generally a maximum of 20-30% of a water body is treated in a single application. Applying the typical rate of 2 ppm, and taking into account a typical maximum treated area of 30%, would decrease calculated RQs by approximately 6-fold.

While noting the potential risks to aquatic organisms from the direct application of 2,4-D for the control of aquatic weeds identified above, it is important to note the benefits gained through the direct application of 2,4-D to aquatic bodies, for the control of invasive species. The U.S Army Corps of Engineers (USACE) and state agencies have identified 2,4-D as an important tool for protecting water bodies from the invasion and establishment of some species of exotic nuisance vegetation. 2,4-D has a reputation as a selective and economical means to remove invasive plants, enhance the growth and recovery of desirable native vegetation, restore water quality, reduce sedimentation rates in reservoirs, and improve fish and wildlife habitat. 2,4-D products are used to control invasive weeds, such as Eurasian water milfoil (*Myriophyllum spicatum*) in the northern tier states and water hyacinth (*Eichhornia crassipes*) in the Gulf Coast states. Effective control of these plants can benefit public health with respect to reducing levels of mosquito habitat. In addition, according to USACE, no other product (or alternative technique) can control these plants in a more cost-effective manner (K. Getsinger, USACE, Public Comment; Docket ID# OPP-2004-0167-0053).

Given the typical application rates and treatment areas, and considering the beneficial aspects of using 2,4-D to control invasive plant species, the Agency concludes that the benefits from direct aquatic use of 2,4-D outweigh the risk concerns for aquatic organisms. No additional mitigation measures will be required at this time to address risk to aquatic organisms.

d. Non-target Insects

Risk to non-target insects do not exceed the Agency's level of concern. Available data from a honey bee acute toxicity study indicated that technical 2,4-D is practically non-toxic to the honey bee. The potential for 2,4-D and its salts and esters to pose risk to pollinators and other beneficial insects is expected to be minimal.

e. Non-target Terrestrial Plants

Estimated RQs exceeded acute LOCs for both non-endangered and endangered terrestrial plants for non-granular and granular uses at many use sites. Consideration of average application rates did not result in exposure below LOCs. However, the exposure estimates used to develop the RQs were likely conservative, as follows.

In the exposure calculation for non-target aquatic plants and terrestrial plants in intermittently flooded areas, the major contributor is run-off from the application site. The run-off and leaching vulnerability schemes used in this assessment incorporate several conservative assumptions which are fully discussed in the ecological risk assessment. Also, it is likely that farm management practices would be in place to limit run-off, as run-off events are detrimental to the farm as a whole for reasons other than pesticide damage.

Whereas the risk assessments are likely conservative as described above, the Agency is concerned about the risk to non-target terrestrial plants from drift of 2,4-D during application. To address that concern, the Agency is implementing spray drift controls that will decrease the risk that 2,4-D will drift onto non-target plants.

f. Summary of Environmental Risk Mitigation

Characterization of the risks identified in the Agency's screening level risk assessment suggests that risks from drift onto non-target plants exceeds the Agency's level of concern. The Agency is implementing spray drift controls that will decrease the risk that 2,4-D will drift onto non-target plants.

F. Other Labeling Requirements

In order to be eligible for reregistration, various use and safety information will be included in the labeling of all end-use products containing 2,4-D. For the specific labeling statements and a list of outstanding data, refer to Section V of this RED document.

1. Endangered Species Considerations

The Agency has developed the Endangered Species Protection Program to identify pesticides whose use may cause adverse impacts on endangered and threatened species, and to implement mitigation measures that address these impacts. The Endangered Species Act requires federal agencies to ensure that their actions are not likely to jeopardize listed species or adversely modify designated critical habitat. To analyze the potential of registered pesticide uses that may affect any particular species, EPA uses basic toxicity and exposure data and considers ecological parameters, pesticide use information, geographic relationship between specific pesticide uses and species locations, and biological requirements and behavioral aspects of the particular species. Based on EPA's screening level assessment for 2,4-D, RQs exceed levels of concern for mammals, birds, aquatic plants, and terrestrial plants. However, these findings are based solely on EPA's screening level assessment and do not constitute "may affect" findings under the ESA. The Agency is requiring additional data to further characterize and refine its ecological and endangered species risk assessments. The 2,4-D Task Force has submitted a limited endangered species assessment on several crops for the Agency's consideration. This assessment was generated using the FIFRA Endangered Species Task Force (FESTF) integrated management system (IMS).

2. Spray Drift Management

The Agency has been working closely with stakeholders to develop improved approaches for mitigating risks to human health and the environment from pesticide spray and dust drift. As part of the reregistration process, we will continue to work with all interested parties on this important issue.

From its assessment of 2,4-D, as summarized in this document, the Agency concludes that certain drift mitigation measures are needed to address the risks from off-target drift for 2,4-D. Label statements implementing these measures are listed in the "spray drift management" section of the Labeling Changes Summary Table in section V.D. of this RED document. In the future, 2,4-D product labels may need to be revised to include additional or different drift label statements.

3. Consumer Labeling Initiative

The Consumer Labeling Initiative (CLI) is an effort among federal, state, and local government agencies, industry, environmental groups, and other interested parties working to improve product labels on residential pesticides in order to improve consumer understanding and compliance of consumer labels. The CLI Work Group of the Pesticide Program Dialogue Committee (PPDC) is working to revise consumer labels. In addition to the labeling changes presented in this RED, the Agency will leave open the possibility that changes to residential product labeling may occur as the result of the PPDC CLI.

V. What Registrants Need To Do

<u>For 2,4-D technical grade active ingredient products,</u> registrants need to submit the following items.

Within 90 days from receipt of the generic data call-in (DCI):

(1) completed response forms to the generic DCI (i.e., DCI response form and requirements status and registrant's response form); and

(2) submit any time extension and/or waiver requests with a full written justification.

Within the time limit specified in the generic DCI:

(1) cite any existing generic data which address data requirements or submit new generic data responding to the DCI.

Please contact Katie Hall at (703) 308-0166 with questions regarding generic reregistration and/or the DCI. All materials submitted in response to the generic DCI should be addressed:

<u>By US mail:</u>
Document Processing Desk (DCI/SRRD)
Katie Hall
US EPA (7508C)
1200 Pennsylvania Ave., NW
Washington, DC 20460

<u>By express or courier service:</u>
Document Processing Desk (DCI/SRRD)
Katie Hall
Office of Pesticide Programs (7508C)
Room 604, Crystal Mall 2
1801 S. Bell Street
Arlington, VA 22202 -4501

<u>For products containing the active ingredient 2,4-D</u> registrants need to submit the following items for each product.

Within 90 days from the receipt of the product-specific data call-in (PDCI):

(1) completed response forms to the PDCI (i.e., PDCI response form and requirements status and registrant's response form); and

(2) submit any time extension or waiver requests with a full written justification.

Within eight months from the receipt of the PDCI:

(1) two copies of the confidential statement of formula (EPA Form 8570-4);

(2) a completed original application for reregistration (EPA Form 8570-1). Indicate on the form that it is an "application for reregistration";

(3) five copies of the draft label incorporating all label amendments outlined in Table 40 of this document;

(4) a completed form certifying compliance with data compensation requirements (EPA Form 8570-34);

(5) if applicable, a completed form certifying compliance with cost share offer requirements (EPA Form 8570-32); and

(6) the product-specific data responding to the PDCI.

Please contact Moana Appleyard at (703) 308-8175 with questions regarding product reregistration and/or the PDCI. All materials submitted in response to the PDCI should be addressed:

By US mail:
Document Processing Desk (PDCI/PRB)
Moana Appleyard
US EPA (7508C)
1200 Pennsylvania Ave., NW
Washington, DC 20460

By express or courier service only:
Document Processing Desk (PDCI/PRB)
Moana Appleyard
Office of Pesticide Programs (7508C)
Room 266A, Crystal Mall 2
1801 Bell Street
Arlington, VA 22202

A. Manufacturing Use Products

1. Additional Generic Data Requirements

The generic data base supporting the reregistration of 2,4-D for eligible uses has been reviewed and determined to be substantially complete. However the following data requirements are necessary to confirm the reregistration eligibility decision documented in this RED.

Table 40. Data Requirements for the Reregistration Eligibility Decision for 2,4-D

Guideline Study Name	New OPPTS Guideline No.	Old Guideline No.
Environmental Fate and Effects Data Requirements		
Aquatic field dissipation studies (Behavior of 2,4-D BEE under acidic to neutral aquatic conditions in a water/sediment system)	835.6200	164-2
Laboratory volatility study (2,4-D IPE)	835.1410	163-2
Terrestrial field dissipation studies (2,4-D IPA, 2,4-D TIPA, 2,4-D DEA, 2,4-D BEE)	835.6100	164-1

Guideline Study Name	New OPPTS Guideline No.	Old Guideline No.
Aquatic field dissipation studies in a rice use scenario (2,4-D IPA, 2,4-D TIPA, 2-4-D DEA)	835.6200	164-2
Aquatic field dissipation studies in an aquatic weed control scenario (2,4-D IPA, 2,4-D TIPA, 2-4-D DEA)	835.6200	164-2
Forest field dissipation studies (2,4-D IPA, 2,4-D TIPA, 2,4-D BEE, and 2,4-D DEA)	835.6300	164-3
Fish acute toxicity test, freshwater and marine with typical end-use product (TEP) (2,4-D BEE)	850.1075	72-1
Oyster acute toxicity test with TEP (2,4-D BEE)	850.1025	72-3
Mysid acute toxicity test with TEP (2,4-D BEE)	850.1035	72-3
Penaid acute toxicity test with TEP (2,4-D BEE)	850.1045	72-3
Sediment and soil adsorption/desorption (2,4-D BEE granular formulation)	835.1230	163-1
Seedling Germination/Seedling Emergence Vegetative Vigor Non-target terrestrial plants - TEP representative testing from the acid and amine salts group, and representative testing from the ester group. The test products should include the most common and most active surfactants and adjuvants which affect the toxicity of the product. The registrants should consult with the Agency before finalizing which products to test.	850.4225 850.4250	123-1(a) 123-1(b)
The registrant must provide information on the proximity of Federally listed freshwater vascular plants, birds, mammals, and non-target terrestrial plants (there are no listed estuarine/marine invertebrates) to the 2,4-D use sites. This requirement may be satisfied in one of three ways: 1) having membership in the FIFRA Endangered Species Task Force (Pesticide Registration [PR] Notice 2000-2); 2) citing FIFRA Endangered Species Task Force data; or 3) independently producing these data, provided the information is of sufficient quality to meet FIFRA requirements. Registrants should consult with the Agency prior to fulfilling this data requirement.	-	-
Human Health Effects Data Requirements		
Developmental neurotoxicity study	870.6300	83-6
Subchronic inhalation toxicity study (28-day)	870.3465	82-4
Repeat two-generation reproduction study (using the most recent Agency protocol) addressing concerns for endocrine disruption (thyroid and immunotoxicity measures)	870.3800	83-4
Product and Residue Chemistry Data Requirements		
Crop field trials - wheat hay	860.1500	171-4k

Guideline Study Name	New OPPTS Guideline No.	Old Guideline No.
Water, fish, and irrigated crops - irrigated crop studies in strawberries and sugar beet roots and tops	860.1400	171-4f
Residue analytical method - revised enforcement method for determination of 2,4-D in livestock commodities	860.1340	171-4c
Directions for Use	860.1200	171-3
Other Data Requirements		
UV/Visible Absorption	830.7050	None
Droplet Size Spectrum	840.1100	201-1
Drift Field Evaluation	840.1200	202-1
The Agency is requiring that five recent batches of all technical products be analyzed for 2,3,7,8-TCDD, 2,3,7,8-TCDF and their respective higher substituted chlorinated congeners using validated analytical methods. The Agency specifies that the manufacturers use the most current state-of-the art laboratory methods for measuring 2,3,7,8-TCDD and TCDF at levels less than 1 part per trillion (EPA Method 1613, Tetra- through Octa-Chlorinated Dioxins and Furans by Isotope Dilution HRGC/HRMS). Because 1,2,3,7,8-PeCDD is equi-potent to 2,3,7,8-TCDD in the TEF scheme, the Agency is adding this compound to our testing requirements.	-	-

B. End-Use Products

1. Additional Product-Specific Data Requirements

Section 4(g)(2)(B) of FIFRA calls for the Agency to obtain any needed product-specific data regarding the pesticide after a determination of eligibility has been made. Registrants must review previous data submissions to ensure that they meet current EPA acceptance criteria and if not, commit to conduct new studies. If a registrant believes that previously submitted data meet current testing standards, then the study MRID numbers should be cited according to the instructions in the Requirement Status and Registrants Response Form provided for each product.

2. Labeling for End-Use Products

Labeling changes are necessary to implement the mitigation measures outlined in Section IV above. Specific language to incorporate these changes is specified in Table 40.

C. Existing Stocks

Registrants may generally distribute and sell products bearing old labels/labeling for 12 months from the date of the issuance of this Reregistration Eligibility Decision document. Persons

other than the registrant may generally distribute or sell such products for 24 months from the date of the issuance of this RED. However, existing stocks time frames will be established case-by-case, depending on the number of products involved, the number of label changes, and other factors. Refer to "Existing Stocks of Pesticide Products; Statement of Policy"; *Federal Register*, Volume 56, No. 123, June 26, 1991.

D. Required Labeling Changes Summary Table

In order to be eligible for reregistration, all product labels must be amended to incorporate the risk mitigation measures outlined in Section IV. The following table describes how language on the labels should be amended.

Table 41: Summary of Labeling Changes for 2,4-D

Description	Amended Labeling Language	Placement on Label
For all Manufacturing Use Products	"Only for formulation into an *herbicide or plant growth regulator* for the following use(s) [fill blank only with those uses that are being supported by MP registrant]." "Wettable powder formulations must be packaged in water-soluble packages."	Directions for Use
One of these statements may be added to a label to allow reformulation of the product for a specific use or all additional uses supported by a formulator or user group	"This product may be used to formulate products for specific use(s) not listed on the MP label if the formulator, user group, or grower has complied with U.S. EPA submission requirements regarding support of such use(s)." "This product may be used to formulate products for any additional use(s) not listed on the MP label if the formulator, user group, or grower has complied with U.S. EPA submission requirements regarding support of such use(s)."	Directions for Use
Environmental Hazards Statements Required by the RED and Agency Label Policies	"This chemical is toxic to fish and aquatic invertebrates. Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans, or other waters unless in accordance with the requirements of a National Pollution Discharge Elimination System (NPDES) permit and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product to sewer systems without previously notifying the local sewage treatment plant authority. For guidance contact your State Water Board or Regional Office of the EPA."	Precautionary Statements
End Use Products Intended for Occupational Use		

PPE Requirements Established by the RED[1] for liquids, wettable powders formulated in water-soluble packages, and water-dispersible granules	"Personal Protective Equipment (PPE) "Some materials that are chemical-resistant to this product are" (*registrant inserts correct chemical-resistant material*). "If you want more options, follow the instructions for category" *[registrant inserts A,B,C,D,E,F,G,or H]* "on an EPA chemical-resistance category selection chart." "All mixers, loaders, applicators, flaggers, and other handlers must wear: - long-sleeved shirt and long pants, - shoes and socks, plus - chemical resistant gloves, when applying postharvest dips or sprays to citrus, applying with any handheld nozzle or equipment, mixing or loading, cleaning up spills or equipment, or otherwise exposed to the concentrate. - chemical resistant apron when applying postharvest dips or sprays to citrus, mixing or loading, cleaning up spills or equipment, or otherwise exposed to the concentrate. See engineering controls for additional requirements."	Immediately following/below Precautionary Statements: Hazards to Humans and Domestic Animals
PPE Requirements Established by the RED[1] for granular formulations	"Personal Protective Equipment (PPE) All loaders, applicators, and other handlers must wear: - long-sleeved shirt and long pants, - shoes plus socks."	Immediately following/below Precautionary Statements: Hazards to Humans and Domestic Animals
User Safety Requirements	"Follow manufacturer's instructions for cleaning/maintaining PPE. If no such instructions for washables exist, use detergent and hot water. Keep and wash PPE separately from other laundry."	Precautionary Statements: Hazards to Humans and Domestic Animals immediately following the PPE requirements

Engineering Controls for aerial applications	Enclosed Cockpits "Engineering Controls: Pilots must use an enclosed cockpit that meets the requirements listed in the WPS for agricultural pesticides [40 CFR 170.240(d)(6)]"	Precautionary Statements: Hazards to Humans and Domestic Animals (Immediately following PPE and User Safety Requirements.)
Engineering Controls for wettable powder formulations packaged in water-soluble packages	"Engineering Controls" "Water-soluble packets when used correctly qualify as a closed loading system under the WPS. Mixers and loaders using water-soluble packets (1) must wear the PPE specified above for mixers and loaders and (2) must be provided, have immediately available for use in an emergency, such as a broken package, spill, or equipment breakdown a NIOSH-approved dust mist filtering respirator with MSHA/NIOSH approval number prefix TC-21C *or* a NIOSH-approved respirator with any N [2], R, P, or HE filter."	Precautionary Statements: Hazards to Humans and Domestic Animals (Immediately following PPE and User Safety Requirements.)
User Safety Recommendations	"User Safety Recommendations Users should wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet. Users should remove clothing/PPE immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing. If pesticide gets on skin, wash immediately with soap and water. Users should remove PPE immediately after handling this product. Wash the outside of gloves before removing. As soon as possible, wash thoroughly and change into clean clothing."	Precautionary Statements under: Hazards to Humans and Domestic Animals immediately following Engineering Controls (Must be placed in a box.)

Environmental Hazard Statement for Terrestrial Uses	"This pesticide may be toxic to fish and aquatic invertebrates. Do not apply directly to water, to areas where surface water is present, or to intertidal areas below the mean high water mark except as noted on appropriate labels. Drift and runoff may be hazardous to aquatic organisms in water adjacent to treated areas. Do not contaminate water when disposing of equipment wash waters or rinsate. This chemical has properties and characteristics associated with chemicals detected in groundwater. The use of this chemical in areas where soils are permeable, particularly where the water table is shallow, may result in groundwater contamination. Application around a cistern or well may result in contamination of drinking water or groundwater."	Precautionary Statements immediately following the User Safety Recommendations
Environmental Hazard Statement for products used for aquatic weed control	"Fish breathe dissolved oxygen in the water and decaying weeds also use oxygen. When treating continuous, dense weed masses, it may be appropriate to treat only part of the infestation at a time. For example, apply the product in lanes separated by untreated strips that can be treated after vegetation in treated lanes has disintegrated. During the growing season, weeds decompose in a 2 to 3 week period following treatment. Begin treatment along the shore and proceed outwards in bands to allow fish to move into untreated areas. Waters having limited and less dense weed infestations may not require partial treatments."	Precautionary Statements immediately following the User Safety Recommendations
Restricted-Entry Interval for products containing with directions for use within the scope of the WPS and containing 2,4-D acid or amine forms	"Do not enter or allow worker entry into treated areas during the restricted entry interval (REI) of 48 hours."	Directions for Use, Under Agricultural Use Requirements Box
Restricted-Entry Interval for products containing with directions for use within the scope of the WPS and containing 2,4-D salt or ester forms	"Do not enter or allow worker entry into treated areas during the restricted entry interval (REI) of 12 hours."	Directions for Use, Under Agricultural Use Requirements Box

Early Entry Personal Protective Equipment established by the RED for products containing 2,4-D acid or amine forms and with WPS uses	"PPE required for early entry to treated areas that is permitted under the Worker Protection Standard and that involves contact with anything that has been treated, such as plants, soil, or water is: - coveralls, - chemical-resistant gloves made of any water-proof material, - shoes plus socks, - protective eyewear."	Directions for Use, Agricultural Use Requirements Box
Early Entry Personal Protective Equipment established by the RED for products containing 2,4-D salt or ester forms and with WPS uses	"PPE required for early entry to treated areas that is permitted under the Worker Protection Standard and that involves contact with anything that has been treated, such as plants, soil, or water is: - coveralls, - chemical-resistant gloves made of any water-proof material, - shoes plus socks."	Directions for Use, Agricultural Use Requirements Box
Entry Restrictions for Granular Formulations with directions for use outside the scope of the WPS	"Do not enter or allow people (or pets) to enter the treated area until dusts have settled."	If no WPS uses on the product, place the appropriate statement in the Directions for Use Under General Precautions and Restrictions. If the product also contains WPS uses, then create a NonAgricultural Use Requirements box as directed in PR Notice 93-7 and place the appropriate statement inside that box.

Entry Restrictions for liquids, water-dispersible granules, and wettable powders formulated in water-soluble packages with directions for use outside the scope of the WPS	"Do not enter or allow people (or pets) to enter the treated area until sprays have dried."	If no WPS uses on the product, place the appropriate statement in the Directions for Use Under General Precautions and Restrictions. If the product also contains WPS uses, then create a NonAgricultural Use Requirements box as directed in PR Notice 93-7 and place the appropriate statement inside that box.
General Application Restrictions for products primarily intended for occupational (professional) use	"Do not apply this product in a way that will contact workers or other persons, either directly or through drift. Only protected handlers may be in the area during application."	Directions for Use under General Precautions and Restrictions

Use-Specific Application Restrictions (Note: The maximum allowable application rate must be listed as pounds or gallons of formulated product per surface acre, not just as pounds acid equivalent per surface acre.)	**"Aquatic weed control"** For all acids, salts, amines, and butoxyethanol ester forms used for aquatic weed control, the following statements must appear on the product label: **> "Ditchbank application** Postemergence: Limited to 2 applications per season. Maximum of 2.0 lbs ae/acre per application. Minimum of 30 days between applications. Spot treatment permitted. Do not use on small canals with a flow rate less than 10 cubic feet per second (CFS) where water will be used for drinking purposes. CFS may be estimated by using the formula below. The approximate velocity needed for the calculation can be determined by observing the length of time that it takes a floating object to travel a defined distance. Divide the distance (ft.) by the time (sec.) to estimate velocity (ft. per sec.). Repeat 3 times and use the average to calculate CFS. Average Width (ft.) x Average Depth (ft.) x Average Velocity (ft. per sec.) = CFS For ditchbank weeds: Do not allow boom spray to be directed onto water surface. Do not spray across stream to opposite bank.	Directions for Use Associated with the Specific Use Pattern

Use-Specific Application Restrictions (Note: The maximum allowable application rate must be listed as pounds or gallons of formulated product per surface acre, not just as pounds acid equivalent per surface acre.)	For shoreline weeds: Allow no more than 2 foot overspray onto water." **> "Floating and Emergent Weeds** Maximum of 4.0 lbs ae/surface acre per application. Limited to 2 applications per season. Minimum of 21 days between applications. Spot treatments are permitted. Apply to emergent aquatic weeds in ponds, lakes, reservoirs, marshes, bayous, drainage ditches, non-irrigation canals, rivers, and streams that are quiescent or slow moving. Coordination and approval of local and state authorities may be required, either by letter of agreement or issuance of special permits for aquatic applications. **<u>Water Use</u>** **1. Water for irrigation or sprays:** **A.** If treated water is intended to be used only for crops or non-crop areas that are labled for direct treatment with 2,4-D such as pastures, turf, or cereal grains, the treated water may be used to irrigate and/or mix sprays for these sites at anytime after the 2,4-D aquatic application.	Directions for Use Associated with the Specific Use Pattern

Use-Specific Application Restrictions	**B.** Due to potential phytotoxicity considerations, the following restrictions are applicable: If treated water is intended to be used to irrigate or mix sprays for plants grown in commercial nurseries and greenhouses; and other plants or crops that are not labeled for direct treatment with 2,4-D, the water must not be used unless one of the following restrictions has been observed: **i.** A setback distance from functional water intake(s) of greater than or equal to 600 ft. was used for the application, or, **ii.** A waiting period of 7 days from the time of application has elapsed, or, **iii.** An approved assay indicates that the 2,4-D concentration is 100 ppb (0.1 ppm) or less at the water intake. Wait at least 3 days after application before initial sampling at water intake. **2. Drinking water (potable water):** **A.** Consult with appropriate state or local water authorities before applying this product to public waters. State or local agencies may require permits. The potable water use restrictions on this label are to ensure that consumption of water by the public is allowed only when the concentration of 2,4-D in the water is less than the MCL (Maximum Contaminant Level) of 70 ppb. Applicators should consider the unique characteristics of the treated waters to assure that 2,4-D concentrations in potable water do not exceed 70 ppb at the time of consumption.	Directions for Use Associated with the Specific Use Pattern

Use-Specific Application Restrictions	**B.** For floating and emergent weed applications, the drinking water setback distance from functioning potable water intakes is greater than or equal to 600 ft. **C.** If no setback distance of greater than or equal to 600 ft. is used for application, applicators or the authorizing organization must provide a drinking water notification prior to a 2,4-D application to the party responsible for public water supply or to individual private water uses. Notification to the party responsible for a public water supply or to individual private water users must be done in a manner to assure that the party is aware of the water use restrictions when this product is applied to potable water. The following is an example of a notification via posting, but other methods of notification which convey the above restrictions may be used and may be required in some cases under state or local law or as a condition of a permit. **Example:** Posting notification should be located every 250 feet including the shoreline of the treated area and up to 250 feet of shoreline past the application site to include immediate public access points. Posting must include the day and time of application. Posting may be removed if analysis of a sample collected at the intake 3 or more days following application shows that the concentration in the water is less than 70 ppb (100 ppb for irrigation or sprays), or after 7 days following application, whichever occurs first.	Directions for Use Associated with the Specific Use Pattern

Use-Specific Application Restrictions	**Text of notification:** Wait 7 days before diverting functioning surface water intakes from the treated aquatic site to use as drinking water, irrigation, or sprays, unless water at functioning drinking water intakes is tested at least 3 days after application and is demonstrated by assay to contain not more than 70 ppb 2,4-D (100 ppb for irrigation or sprays). Application Date:_____ Time:_____ **D.** Following each application of this product, treated water must not be used for drinking water unless one of the following restrictions has been observed: **i.** A setback distance from functional water intake(s) of greater than or equal to 600 ft. was used for the application, or, **ii.** A waiting period of at least 7 days from the time of application has elapsed, or, **iii.** An approved assay indicates that the 2,4-D concentration is 70 ppb (0.07 ppm) or less at the water intake. Sampling for drinking water analysis should occur no sooner than 3 days after 2,4-D application. Analysis of samples must be completed by a laboratory that is certified under the Safe Drinking Water Act to perform drinking water analysis using a currently approved version of analytical Method Number 515, 555, other methods for 2,4-D as may be listed in Title 40 CFR, Part 141.24, or Method Number 4015 (immunoassay of 2,4-D) from U.S. EPA Test Methods for Evaluating Solid Waste SW-846. **E.** Note: Existing potable water intakes that are no longer in use, such as those replaced by a connection to a municipal water system or a potable water well, are not considered to be functioning potable water intakes.	Directions for Use Associated with the Specific Use Pattern

Use-Specific Application Restrictions	**F.** Drinking water setback distances do not apply to terrestrial applications of 2,4-D adjacent to water bodies with potable water intakes. **3. Swimming (2,4-D butoxyethanol ester only):** **A.** Do not swim in treated water for a minimum of 24 hours after application. **B.** Users must provide notification prior to performing a 2,4-D BEE application. Notification to the party responsible for the public swimming area or to individual private users must be done in a manner to assure that the party is aware of the water use swimming restrictions when this product is applied to water. The following is an example of a notification via posting, but other methods of notification which convey the above restrictions may be used and may be required in some cases under state or local law or as a condition of a permit. **Example:** Posting notification should be located every 250 feet including the shoreline of the treated area and up to 250 feet of shoreline past the application site to include immediate public access points. **Text of Notification:** Do not swim in treated water for a minimum of 24 hours after application. Application Date: _____ Time: _____ . **4.** Except as stated above, there are no restrictions on using water from treated areas for swimming, fishing, watering livestock or domestic purposes."	Directions for Use Associated with the Specific Use Pattern

Use-Specific Application Restrictions (Note: The maximum allowable application rate must be listed as pounds or gallons of formulated product per acre-foot, not just as pounds acid equivalent per acre-foot.)	**> "Submersed Weeds** Maximum of 10.8 lbs ae/per acre-foot per application. Limited to 2 applications per season. Apply to aquatic weeds in ponds, lakes, reservoirs, marshes, bayous, drainage ditches, non-irrigation canals, rivers, and streams that are quiescent or slow moving. Do not apply within 21 days of previous application. When treating moving bodies of water, applications must be made while traveling upstream to prevent concentration of 2,4-D downstream from the application. Coordination and approval of local and state authorities may be required, either by letter of agreement or issuance of special permits for such use.				Directions for Use Associated with the Specific Use Pattern
	Table 1. Amount of 2,4-D to Apply for a Target Subsurface Concentration				
	Surface Area	Average Depth	For typical conditions - 2 ppm 2,4-D ae/acre-foot	For difficult conditions* - 4 ppm 2,4-D ae/acre-foot	
	1 acre	1 ft.	5.4 lbs	10.8 lbs	
		2 ft.	10.8 lbs	21.6 lbs	
		3 ft.	16.2 lbs	32.4 lbs	
		4 ft.	21.6 lbs	43.2 lbs	
		5 ft.	27.0 lbs	54.0 lbs	
	* Examples include spot treatment of pioneer colonies of Eurasian Water Milfoil and certain difficult to control aquatic species.				

Use-Specific Application Restrictions	**<u>Water Use:</u>** **1. Water for irrigation or sprays:** **A.** If treated water is intended to be used only for crops or non-crop areas that are labeled for direct treatment with 2,4-D such as pastures, turf, or cereal grains, the treated water may be used to irrigate and/or mix sprays for these sites at anytime after the 2,4-D aquatic application. **B.** Due to potential phytotoxicity and/or residue considerations, the following restrictions are applicable: If treated water is intended to be used to irrigate or mix sprays for unlabeled crops, non-crop areas or other plants not labeled for direct treatment with 2,4-D, the water must not be used unless one of the following restrictions has been observed: **i.** A setback distance described in the Drinking Water Setback Table was used for the application, or, **ii.** A waiting period of 21 days from the time of application has elapsed, or, **iii.** An approved assay indicates that the 2,4-D concentration is 100 ppb (0.1 ppm) or less at the water intake. See Table 3 for the waiting period after application but before taking the initial sampling at water intake. **2. Drinking water (potable water):** **A.** Consult with appropriate state or local water authorities before applying this product to public waters. State or local agencies may require permits.	Directions for Use Associated with the Specific Use Pattern

Use-Specific Application Restrictions	The potable water use restrictions on this label are to ensure that consumption of water by the public is allowed only when the concentration of 2,4-D in the water is less than the MCL (Maximum Contaminant Level) of 70 ppb. Applicators should consider the unique characteristics of the treated waters to assure that 2,4-D concentrations in potable water do not exceed 70 ppb at the time of consumption. **B.** For submersed weed applications, the drinking water setback distances from functioning potable water intakes are provided in Table 2. Drinking Water Setback Distance (below). **C.** If no setback distance from the Drinking Water Setback Table (Table 2) is to be used for the application, applicators or the authorizing organization must provide a drinking water notification and an advisory to shut off all potable water intakes prior to a 2,4-D application. Notification to the party responsible for a public water supply or to individual private water users must be done in a manner to assure that the party is aware of the water use restrictions when this product is applied to potable water. The following is an example of a notification via posting, but other methods of notification which convey the above restrictions may be used and may be required in some cases under state or local law or as a condition of a permit.	Directions for Use Associated with the Specific Use Pattern

Use-Specific Application Restrictions	**Example:** Posting notification should be located every 250 feet including the shoreline of the treated area and up to 250 feet of shoreline past the application site to include immediate public access points. Posting should include the day and time of application. Posting may be removed if analysis of a sample collected at the intake no sooner than stated in Table 3 (below) shows that the concentration in the water is less than 70 ppb (100 ppb for irrigation or sprays), or after 21 days following application, whichever occurs first. **Text of notification:** Wait 21 days before diverting functioning surface water intakes from the treated aquatic site to use as drinking water, irrigation, or sprays, unless water at functioning drinking water intakes is tested no sooner than (insert days from Table 3) and is demonstrated by assay to contain not more than 70 ppb 2,4-D (100 ppb for irrigation or sprays). Application Date: _____ Time: _____ . **D.** Following each application of this product, treated water must not be used for drinking water unless one of the following restrictions has been observed: **i.** A setback distance described in the Drinking Water Setback Distance Table was used for the application, or, **ii.** A waiting period of at least 21 days from the time of application has elapsed, or,	Directions for Use Associated with the Specific Use Pattern

Use-Specific Application Restrictions	**iii.** An approved assay indicates that the 2,4-D concentration is 70 ppb (0.07 ppm) or less at the water intake. Sampling for drinking water analysis should occur no sooner than stated in Table 3. Analysis of samples must be completed by a laboratory that is certified under the Safe Drinking Water Act to perform drinking water analysis using a currently approved version of analytical Method Number 515, 555, other methods for 2,4-D as may be listed in Title 40 CFR, Part 141.24, or Method Number 4015 (immunoassay of 2,4-D) from U.S. EPA Test Methods for Evaluating Solid Waste SW-846. **E.** Note: Existing potable water intakes that are no longer in use, such as those replaced by a connection to a municipal water system or a potable water well, are not considered to be functioning potable water intakes. **F.** Drinking water setback distances do not apply to terrestrial applications of 2,4-D adjacent to water bodies with potable water intakes.	Directions for Use Associated with the Specific Use Pattern

Use-Specific Application Restrictions	**3. Swimming (2,4-D butoxyethanol ester only):** **A.** Do not swim in treated water for a minimum of 24 hours after application. **B.** Users must provide the following notification prior to performing a 2,4-D BEE application. Notification to the party responsible for the public swimming area or to individual private users must be done in a manner to assure that the party is aware of the water use swimming restrictions when this product is applied to water. The following is an example of a notification via posting, but other methods of notification which convey the above restrictions may be used and may be required in some cases under state or local law or as a condition of a permit. Example: Posting notification should be located every 250 feet including the shoreline of the treated area and up to 250 feet of shoreline past the application site to include immediate public access points. **Text of Notification:** Do not swim in treated water for a minimum of 24 hours after application. Application Date: _____ Time: _____ . **4.** Except as stated above, there are no restrictions on using water from treated areas for swimming, fishing, watering livestock or domestic purposes."	Directions for Use Associated with the Specific Use Pattern
Use-Specific Application Restrictions	**Table 2. Drinking Water Setback Distance for Submersed Weed Applications** Application Rate and Minimum Setback Distance (feet) From Functioning Potable Water Intake	Directions for Use Associated with the Specific Use Pattern

	1 ppm*	2 ppm*	3 ppm*	4 ppm*
	600	1200	1800	2400
	* ppm acid equivalent target water concentration			
	Table 3. Sampling for Drinking Water Analysis After 2,4-D Application for Submersed Weed Applications			
	Minimum Days After Application Before Initial Water Sampling at the Functioning Potable Water Intake			
	1 ppm*	2 ppm*	3 ppm*	4 ppm*
	5	10	10	14
	* ppm acid equivalent target water concentration”			

Use-Specific Application Restrictions (Note: The maximum allowable application rate must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.	**"Asparagus**" Permitted forms of 2,4-D include acid, salts, and amines. "The preharvest interval (PHI) is 3 days. Limited to 2 applications per crop cycle. Maximum of 2.0 lb ae/acre per application Minimum of 30 days between applications." **"Blueberry, low bush"** Permitted forms of 2,4-D include acid, salts, and amines. "Postemergence: Limited to one postemergence application per year. Maximum of 0.0375 lbs ae/gallons of spray solution per application. Postharvest: Limited to one postharvest application per year. Maximum of 1.0 lbs ae/gallon spray solution per application. For spot or directed wipe treatment only. Apply only in non-bearing years."	Directions for Use Associated with the Specific Use Pattern

Use-Specific Application Restrictions (Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.)	"**Blueberry, high bush"** Permitted forms of 2,4-D include acid, salts, and amines. "The preharvest interval (PHI) is 30 days. Postemergence and postharvest: Limited to 2 applications per year. Maximum of 1.4 lbs ae/acre per application." **"Cereal Grains (wheat, barley, millet, oats, and rye)"** Permitted forms of 2,4-D include acid, salts, amines, and esters. "The preharvest interval (PHI) is 14 days. Postemergence: Limited to one postemergence application per crop cycle. Maximum of 1.25 lbs ae/acre per application. Preharvest: Limited to one preharvest application per crop cycle. Maximum of 0.5 lbs ae/acre per application. Limited to 1.75 lbs ae/acre per crop cycle."	Directions for Use Associated with the Specific Use Pattern

Other Application Restrictions (Risk Mitigation) (Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.)	**"Citrus (growing fruit)** Permitted form of 2,4-D is isopropyl ester. "The preharvest interval (PHI) is 7 days. -<u>To increase fruit size on growing Navel oranges, Valencia oranges, and grapefruit</u>: Limited to one application per crop cycle. Maximum of 45 grams ae per acre (0.1 lbs ae/acre). -<u>To reduce pre-harvest fruit drop on growing Navel oranges, Valencia oranges, and grapefruit</u>: Limited to one application per crop cycle. Maximum rate of 200 ppm per application. -<u>To prevent pre-harvest drop of mature fruit and leaves on lemons, Navel oranges, Valencia oranges, and Tangelos</u>: Limited to one application per crop cycle. Maximum rate of 24 ppm per application."	Directions for Use Associated with the Specific Use Pattern

Other Application Restrictions (Risk Mitigation) (Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.)	**Postharvest Citrus Treatment** Permitted form of 2,4-D is isopropyl ester. "Permitted application methods include dip or spray. <u>Postharvest packing house application to lemons:</u> Limited to one application per crop. Maximum rate of 500 ppm per application."	Directions for Use Associated with the Specific Use Pattern

Other Application Restrictions (Risk Mitigation) (Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.)	**"Corn, field and pop"** Permitted forms of 2,4-D include acid, salts, amines, and esters. "Do not use treated crop as fodder for 7 days following application. The preharvest interval (PHI) is 7 days. Maximum of 3 lbs ae/acre per crop cycle. <u>Preplant or preemergence</u>: Limited to one preplant or preemergence application per crop cycle. Maximum of 1.0 lb ae/acre per application. <u>Postemergence</u>: Limited to one postemergence application per crop cycle. Maximum of 0.5 lb ae/acre per application. <u>Preharvest</u>: Limited to one preharvest application per crop cycle. Maximum of 1.5 lbs ae/acre per application."	Directions for Use Associated with the Specific Use Pattern

Other Application Restrictions (Risk Mitigation) (Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.)	**"Corn, sweet"** Permitted forms of 2,4-D include acid, salts, amines, and esters. "Do not use treated crop as fodder for 7 days following application. The preharvest interval (PHI) is 45 days. Minimum of 21 days between applications. Maximum of 1.5 lbs ae/acre per crop cycle. <u>Preplant or preemergence</u>: Limited to one preplant or preemergence application per crop cycle. Maximim of 1.0 lb ae/acre per application. <u>Postemergence</u>: Limited to one postemergence application per crop cycle. Maximum of to 0.5 lb ae/acre per application."	Directions for Use Associated with the Specific Use Pattern

Other Application Restrictions (Risk Mitigation) (Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.)	"**Cranberries"** Permitted forms of 2,4-D include acid, salts, amines, and esters. "The preharvest interval (PHI) is 30 days. <u>Dormant Season</u>: Limited to one application per crop cycle. Maximum of 4.0 lbs ae/acre per dormant season <u>Postemergence</u>: Limited to 2 applications per crop cycle. Maximum of 1.2 lbs ae/acre per postemergence application." **"Filberts"** Permitted forms of 2,4-D include acid, salts, and amines. "The preharvest interval (PHI) is 45 days. Minimum of 30 days between applications. Limited to 4 applications per year. Maximum of 1.0 lbs ae per 100 gallons of spray solution per application. "**Fallowland (crop stubble on idle land, or postharvest to crops, or between crops)**" Permitted forms of 2,4-D include acid, salts, amines, and esters. "Plant only labeled crops within 29 days following application. Limited to 2 applications per year. Maximum of 2.0 lbs ae/acre per application. Minimum of 30 days between applications."	Directions for Use Associated with the Specific Use Pattern

Other Application Restrictions (Risk Mitigation) (Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.)	"**Forestry (forest site preparation, forest roadsides, brush control, established conifer release, Chrismas trees, reforestation areas)"** Permitted forms of 2,4-D include acid, salts, amines, and esters. Broadcast application: Limited to 1 broadcast application per year. Maximum of 4.0 lbs ae/acre per broadcast application. Basal spray, Cut Surface - Stumps, and Frill: Limit of one basal spray or cut surface application per year. Maximum of 8.0 lbs ae per 100 gallons of spray solution. Injection: Limit to one injection application per year. Maximum of 2 ml of 4.0 lbs ae formulation per injection site." "**Grapes"** Permitted forms of 2,4-D include acid, salts, and amines. "For use only in California. The preharvest interval (PHI) is 100 days. Limited to 1 application per crop cycle. Maximum of 1.36 lbs ae/acre per application."	Directions for Use Associated with the Specific Use Pattern

Other Application Restrictions (Risk Mitigation) (Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.)	"**Grasses (pastures and rangeland not in agricultural production)**" Permitted forms of 2.4-D include acid, salts, amines, and esters. "The preharvest interval (PHI) is 7 days (cut forage for hay). <u>Postemergence</u>: Limited to 2 applications per year. Maximum of 2.0 lbs ae/acre per application. Minimum of 30 days between applications. If grass is to be cut for hay, Agricultural Use Requirements for the Worker Protection Standard are applicable. For program lands, such as Conservation Reserve Program, consult program rules to determine whether grass or hay may be used. The more restrictive requirements of the program rules or this label must be followed." **"Hops"** Permitted forms of 2,4-D include acid and amines. "The preharvest interval (PHI) is 28 days. Postemergence: Limited to 3 applications per crop cycle. Maximum of 0.5 lb ae/acre per application. Maximum of 1.5 lbs ae/acre per crop cycle. Minimum of 30 days between applications."	Directions for Use Associated with the Specific Use Pattern

Other Application Restrictions (Risk Mitigation) (Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.)	**"Non-Cropland (fencerows, hedgerows, roadsides, ditches, rights-of-way, utility power lines, railroads, airports, and industrial sites)"** Permitted forms of 2,4-D include acid, salts, amines, and esters. "Postemergence (annual and perennial weeds): Limited to 2 applications per year. Maximum of 2.0 lbs ae/acre per application. Minimum of 30 days between applications. Postemergence (woody plants): Limited to 1 application per year. Maximum of 4.0 lbs ae/acre per year. Applications to non-cropland areas are not applicable to treatment of commercial timber or other plants being grown for sale or other commercial use, or for commercial seed production, or for research purposes."	Directions for Use Associated with the Specific Use Pattern

Other Application Restrictions (Risk Mitigation) (Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.)	**"Pasture and Rangeland (established grass pastures, rangeland, and perennial grasslands not in agricultural production)"** Permitted forms of 2,4-D include acid, salt, amines, and esters. "Do not cut forage for hay within 7 days of application. <u>Postemergence</u>: For susceptible annual and biennial broadleaf weeds: Use 1.0 lbs ae/acre per application. For moderately susceptible biennial and perennial broadleaf weeds: Use 1.0 to 2.0 lbs ae/acre per application. For difficult to control weeds and woody plants: Use 2.0 lbs ae/acre per application. Spot treatment: Use 2.0 lbs ae/acre. Maximum of two applications per year. Maximum of 4.0 lbs ae/acre per year. Minimum of 30 days between applications. If grass is to be cut for hay, Agricultural Use Requirements for the Worker Protection Standard are applicable." **"Pistachios"** Permitted forms of 2,4-D include acid, salts, and amines. "Do not cut orchard floor forage for hay within 7 days of application. The preharvest interval (PHI) is 60 days. <u>Postemergence</u>: Limited to 2 applications per year. Maximum of 2.0 lbs ae/acre per application. Minimum of 30 days between applications."	Directions for Use Associated with the Specific Use Pattern

Other Application Restrictions (Risk Mitigation) (Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.)	**"Pome Fruits"** Permitted forms of 2,4-D include acid, salts, and amines. "The preharvest interval (PHI) is 14 days. Do not cut orchard floor forage for hay within 7 days of application. <u>Postemergence</u>: Limited to 2 applications per crop cycle. Maximum of 2.0 lbs ae/acre per application. Minimum of 75 days between applications." **"Potatoes"** Permitted forms of 2,4-D include acid, salts, amines, and esters. "Only for use on potatoes intended for fresh market. The preharvest interval (PHI) is 45 days. <u>Postemergence</u>: Limited to 2 applications per crop cycle. Maximum of 0.07 lb ae/acre per application. Minimum of 10 days between applications."	Directions for Use Associated with the Specific Use Pattern

Other Application Restrictions (Risk Mitigation) (Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.)	**"Rice"** Permitted forms of 2,4-D include acid, salts, and amines. "The preharvest interval (PHI) is 60 days. Maximum of 1.5 lbs ae/acre per crop cycle." <u>Preplant</u>: Limited to one preplant application per crop cycle. Maximum of 1.0 lbs ae/acre per preplant application.. <u>Postemergence</u>: Limited to one postemergence application per crop cycle. Maximum of 1.5 lbs ae/acre per postemergence application. "**Rice, wild"** Permitted forms of 2,4-D include acid, salts, and amines. "For use in Minnesota only. The preharvest interval (PHI) is 60 days. <u>Postemergence</u>: Limited to 1 application per crop cycle . Maximum of 0.25 lb ae/acre per application."	Directions for Use Associated with the Specific Use Pattern

Other Application Restrictions (Risk Mitigation) (Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.)	"**Sorghum"** Permitted forms of 2,4-D include acid, salts, amines, and esters. "The preharvest interval (PHI) is 30 days. Do not permit meat or dairy animals to consume treated crop as fodder or forage for 30 days following application. <u>Postemergence (acid, salts, and amines)</u>: Limited to 1 application per crop cycle. Maximum of 1.0 lb ae/acre per application. <u>Postemergence (esters)</u>: Limited to 1 application per crop cycle. Maximum of 0.5 lb ae/acre per application."	Directions for Use Associated with the Specific Use Pattern

Other Application Restrictions (Risk Mitigation) (Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.)	**"Soybeans**" Permitted forms of 2,4-D include acid, salts, amines, and esters. "The maximum rate per crop cycle is 1.0 lb ae/acre. <u>Preplant</u>: Limited to 2 preplant applications per crop cycle. Maximum of 0.5 lb ae/acre per preplant application. > Esters: Apply not less than 7 days prior to planting soybeans. >Amines, acid, salts: Apply not less than 15 days prior to planting soybeans." or "<u>Preplant</u>: Limited to 1 application per crop cycle. Maximum of 1.0 ae/acre per preplant application. >Esters: Apply not less than 15 days prior to planting soybeans. >Amines, acid, salts: Apply not less than 30 days prior to planting soybeans." **"Stone Fruits"** Permitted forms of 2,4-D include acid, salts, and amines. "The preharvest interval (PHI) is 40 days. Do not cut orchard floor forage for hay within 7 days of application. <u>Postemergence</u>: Limited to 2 applications per crop cycle. Maximum of 2.0 lb ae/acre per application. Minimum of 75 days between applications."	Directions for Use Associated with the Specific Use Pattern

Other Application Restrictions (Risk Mitigation) (Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.)	**"Strawberry"** Permitted forms of 2,4-D include acid, salts, and amines. "Do not apply in California or Florida. <u>Dormant or after last picking</u>: Limited to 1 application per crop cycle. Maximum of 1.5 lbs ae/acre per application." **"Sugarcane"** Permitted forms of 2,4-D include acid, salts, and amines. "Do not harvest cane prior to crop maturity. Do not apply more than 4 lbs ae/acre per crop cycle. <u>Preemergence</u>: Limited to one application per crop cycle. Maximum of 2.0 lbs ae/acre per application. <u>Postemergence</u>: Limited to one application per crop cycle. Maximum of 2.0 lbs ae/acre per application.."	Directions for Use Associated with the Specific Use Pattern

Other Application Restrictions (Risk Mitigation) (Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.)	**"Tree Nuts"** Permitted forms of 2,4-D include acid, salts, and amines. "The preharvest interval (PHI) is 60 days. Do not cut orchard floor forage for harvest within 7 days of application. <u>Postemergence</u>: Limited to 2 applications per crop cycle Maximum of 2.0 lbs ae/acre per application. Minimum of 30 days between applications." **"Turf, ornamental (golf courses, cemetaries, parks, sports fields, turfgrass, lawns and other grass areas)"** Permitted forms of 2,4-D include acid, salts, amines, and esters. "<u>Postemergence</u>: Limited to 2 applications per year. Maximum of 1.5 lbs ae/acre per application. The maximum seasonal rate is 3.0 lbs ae/acre, excluding spot treatments." **"Turf, grown for seed or sod"** Permitted forms of 2,4-d include acid, salts, amines, and esters. "Limited to 2 applications per year. Maximum of 2.0 lbs ae/acre per application. Minimum of 21 days between applications."	Directions for Use Associated with the Specific Use Pattern

Spray Drift	"SPRAY DRIFT MANAGEMENT" "A variety of factors including weather conditions (e.g., wind direction, wind speed, temperature, relative humidity) and method of application (e.g., ground, aerial, airblast, chemigation) can influence pesticide drift. The applicator must evaluate all factors and make appropriate adjustments when applying this product." **Droplet Size** "When applying sprays that contain 2,4-D as the sole active ingredient, or when applying sprays that contain 2,4-D mixed with active ingredients that require a Coarse or coarser spray, apply only as a Coarse or coarser spray (ASAE standard 572) or a volume mean diameter of 385 microns or greater for spinning atomizer nozzles." "When applying sprays that contain 2,4-D mixed with other active ingredients that require a Medium or more fine spray, apply only as a Medium or coarser spray (ASAE standard 572) or a volume mean diameter of 300 microns or greater for spinning atomizer nozzles." **Wind Speed** "Do not apply at wind speeds greater than 15 mph. Only apply this product if the wind direction favors on-target deposition and there are not sensitive areas (including, but not limited to, residential areas, bodies of water, known habitat for nontarget species, nontarget crops) within 250 feet downwind. If applying a Medium spray, leave one swath unsprayed at the downwind edge of the treated field."	*Directions for Use*

	Temperature Inversions "If applying at wind speeds less than 3 mph, the applicator must determine if: a) conditions of temperature inversion exist, or b) stable atmospheric conditions exist at or below nozzle height. Do not make applications into areas of temperature inversions or stable atmospheric conditions." **Susceptible Plants** "Do not apply under circumstances where spray drift may occur to food, forage, or other plantings that might be damaged or crops thereof rendered unfit for sale, use or consumption. Susceptible crops include, but are not limited to, cotton, okra, flowers, grapes (in growing stage), fruit trees (foliage), soybeans (vegetative stage), ornamentals, sunflowers, tomatoes, beans, and other vegetables, or tobacco. Small amounts of spray drift that might not be visible may injure susceptible broadleaf plants." **Other State and Local Requirements** "Applicators must follow all state and local pesticide drift requirements regarding application of 2,4-D herbicides. Where states have more stringent regulations, they must be observed." **Equipment** "All aerial and ground application equipment must be properly maintained and calibrated using appropriate carriers or surrogates." *Additional requirements for aerial applications:* "The boom length must not exceed 75% of the wingspan or 90% of the rotor blade diameter."	

	"Release spray at the lowest height consistent with efficacy and flight safety. Do not release spray at a height greater than 10 feet above the crop canopy unless a greater height is required for aircraft safety. This requirement does not apply to forestry or rights-of-way applications." "When applications are made with a crosswind, the swath will be displaced downwind. The applicator must compensate for this by adjusting the path of the aircraft upwind." *Additional requirements for ground boom application:* "Do not apply with a nozzle height greater than 4 feet above the crop canopy." *Additional requirements for liquid products applied as a spray and containing an ester form of 2,4-D (e.g. 2,4-D butoxyethyl ester, 2,4-D ethylhexyl ester, 2,4-D isopropyl ester):* "2,4-D esters may volatilize during conditions of low humidity and high temperatures. Do not apply during conditions of low humidity and high temperatures."	
End Use Products Intended for Residential Use		
Application Restrictions	"Do not apply this product in a way that will contact any person or pet, either directly or through drift. Keep people and pets out of the area during application."	Directions for Use under General Precautions and Restrictions
Entry Restrictions for liquids, water-dispersible granules, and wettable powders formulated in water-soluble packages	"Do not allow people or pets to enter the treated area until sprays have dried."	Directions for use under General Precautions and Restrictions

Entry Restrictions for granular formulations	"Do not allow people or pets to enter the treated area until dusts have settled."	Directions for use under General Precautions and Restrictions
Environmental Hazard Statement for Residential Use labels	"This pesticide is toxic to fish and aquatic invertebrates. Do not apply directly to water, to areas where surface water is present, or to intertidal areas below the mean high water mark except as noted on appropriate labels. Drift and runoff may be hazardous to aquatic organisms in water adjacent to treated areas. Do not contaminate water when disposing of equipment wash waters or rinsate.[2] This chemical has properties and characteristics associated with chemicals detected in groundwater. The use of this chemical in areas where soils are permeable, particularly where the water table is shallow, may result in groundwater contamination. Application around a cistern or well may result in contamination of drinking water or groundwater."	Precautionary Statements immediately following the User Safety Recommendations

[1] PPE that is established on the basis of Acute Toxicity of the end-use product must be compared to the active ingredient PPE in this document. The more protective PPE must be placed in the product labeling. For guidance on which PPE is considered more protective, see PR Notice 93-7.

[2] May be deleted for ready-to-use products.

VI. Appendicies

Appendix A. Table of 2,4-D Use Patterns Eligible for Reregistration (Case 0073)

Appendix A. Use Patterns Subject to Reregistration for 2,4-D (Case 0073)

Use Site	Formulation	Max. Single App. Rate	Unit	Max. # App. Per Crop Cycle/Year	Max. App. Rate Per Crop Cycle/Year	Min. Retreatment Interval (days)	Reentry Interval (REI)	Preharvest Interval (PHI) Pregrazing Interval (PGI) Preslaughtering Interval (PSI)	Restrictions/Comments
Aquatic weed control - Ditchbank application	Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid, Granular	2.0	Lbs ae/acre	2 per season	4.0 lbs ae/acre	30	NA	NA	See Label Changes Summary Table in 2,4-D RED.
Aquatic weed control - floating and emergent weeds	Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid, Granular	4.0	Lbs ae/surface acre	2 per season	8.0 lbs ae/surface acre	21	NA	NA	Apply to aquatic weeds in ponds, lakes, reservoirs, marshes, bayous, drainage ditches, non-irrigation canals, rivers, and streams that are quiescent or slow moving. Coordination and approval of local and state authorities may be required, either by letter of agreement or issuance of special permits for such use. See Label Changes Summary Table in 2,4-D RED.

Use Site	Formulation	Max. Single App. Rate	Unit	Max. # App. Per Crop Cycle/Year	Max. App. Rate Per Crop Cycle/Year	Min. Retreatment Interval (days)	Reentry Interval (REI)	Preharvest Interval (PHI) Pregrazing Interval (PGI) Preslaughtering Interval (PSI)	Restrictions/Comments
Aquatic weed control - submersed weeds	Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid, Granular	10.8	Lbs ae per acre-foot	2 per season	21.6 lbs ae per acre-foot per season	21	24 hour swimming restriction for 2,4-D BEE form	NA	Apply to aquatic weeds in ponds, lakes, reservoirs, marshes, bayous, drainage ditches, non-irrigation canals, rivers, and streams that are quiescent or slow moving. When treating moving bodies of water, applications must be made while traveling upstream to prevent concentration of 2,4-D downstream of the application. Coordination and approval of local and state authorities may be required, either by letter of agreement or issuance of special permits for such use. See Label Changes Summary Table in 2,4-D RED.
Asparagus	Wettable powder, Emulsifiable concentrate, soluble concentrate - liquid, soluble concentrate - solid	2.0	Lbs ae/acre	2 per crop cycle	4.0 lbs ae/acre	30	2,4-D acid and amines -48 hours; 2,4-D salt and esters - 12 hours	NA	See Label Changes Summary Table in 2,4-D RED.

Use Site	Formulation	Max. Single App. Rate	Unit	Max. # App. Per Crop Cycle/Year	Max. App. Rate Per Crop Cycle/Year	Min. Retreatment Interval (days)	Reentry Interval (REI)	Preharvest Interval (PHI) Pregrazing Interval (PGI) Preslaughtering Interval (PSI)	Restrictions/Comments
Blueberry, low bush	Wettable powder, Emulsifiable concentrate, soluble concentrate - liquid, soluble concentrate - solid	Postemergence: 0.0375 Postharvest: 1.0	lbs ae per gallon spray solution per application	Postemergence: 1 Postharvest: 1	0.0375 lbs ae per gallon spray solution	NA	2,4-D acid and amines -48 hours; 2,4-D salt and esters - 12 hours	NA	Postharvest: For spot or directed wipe treatment only. Apply only in non-bearing years. See Label Changes Summary Table in 2,4-D RED.
Blueberry, high bush	Wettable powder, Emulsifiable concentrate, soluble concentrate - liquid, soluble concentrate - solid	1.4	Lbs ae/acre	2 per year	2.8 lbs ae/acre	NS	2,4-D acid and amines -48 hours; 2,4-D salt and esters - 12 hours	PHI - 30 days	See Label Changes Summary Table in 2,4-D RED

Use Site	Formulation	Max. Single App. Rate	Unit	Max. # App. Per Crop Cycle/Year	Max. App. Rate Per Crop Cycle/Year	Min. Retreatment Interval (days)	Reentry Interval (REI)	Preharvest Interval (PHI) Pregrazing Interval (PGI) Preslaughtering Interval (PSI)	Restrictions/Comments
Citrus, growing fruit	Emulsifiable concentrate	To increase fruit size on growing Navel oranges, Valencia oranges, and grapefruit: 0.1 To reduce pre-harvest fruit drop on growing Navel oranges, Valencia oranges, and grapefruit: 200	To increase fruit size on growing Navel oranges, Valencia oranges, and grapefruit: lbs ae/acre To reduce pre-harvest fruit drop on growing Navel oranges, Valencia oranges, and grapefruit: ppm	1 per crop cycle	same as max. single app. rate	NA	12 hours	PHI - 7 days	See Label Changes Summary Table in 2,4-D RED

Use Site	Formulation	Max. Single App. Rate	Unit	Max. # App. Per Crop Cycle/Year	Max. App. Rate Per Crop Cycle/Year	Min. Retreatment Interval (days)	Reentry Interval (REI)	Preharvest Interval (PHI) Pregrazing Interval (PGI) Preslaughtering Interval (PSI)	Restrictions/Comments
		To prevent pre-harvest drop of mature fruit and leaves on lemons, Navel oranges, Valencia oranges, and Tangelos: 24	To prevent pre-harvest drop of mature fruit and leaves on lemons, Navel oranges, Valencia oranges, and Tangelos: ppm	1	same as max. single app. rate				
Citrus, postharvest treatement	Emulsifiable concentrate	500	ppm	1	500 ppm	NA	NA	NA	Application methods include dip or spray See Label Changes Summary Table in 2,4-D RED
Corn, field and pop	Wettable powder, Emulsifiable concentrate, Granular, Soluble concentrate - liquid, Soluble concentrate - solid	Preplant or preemergence: 1.0 Postemergence: 0.5 Preharvest: 1.5	Lbs ae/acre	Preplant or preemergence: 1 Postemergence: 1 Preharvest: 1	3.0 lbs ae/acre	NA	2,4-D acid and amines - 48 hours; 2,4-D salt and esters - 12 hours	PHI - 7 days PGI - 7 days	See Label Changes Summary Table in 2,4-D RED

Use Site	Formulation	Max. Single App. Rate	Unit	Max. # App. Per Crop Cycle/Year	Max. App. Rate Per Crop Cycle/Year	Min. Retreatment Interval (days)	Reentry Interval (REI)	Preharvest Interval (PHI) Pregrazing Interval (PGI) Preslaughtering Interval (PSI)	Restrictions/Comments
Corn, sweet	Wettable powder, Emulsifiable concentrate, Granular, Soluble concentrate - liquid, Soluble concentrate - solid	Preplant or preemergence: 1.0 Postemergence: 0.5	Lbs ae/acre	Preplant or preemergence: 1 Postemergence: 1	1.5 lbs ae/acre per crop cycle	21	2,4-D acid and amines - 48 hours; 2,4-D salt and esters - 12 hours	PHI - 45 days PGI - 7 days	See Label Changes Summary Table in 2,4-D RED
Cranberries	Wettable powder, Emulsifiable concentrate, Granular, Soluble concentrate - liquid, Soluble concentrate - solid	Dormant season: 4.0 Postemergence: 1.2	Dormant season: lbs ae/acre per dormant season Postemergence: lbs ae/acre per postemergence application	Dormant season: 1 Postemergence: 2	Dormant season: 4 lbs ae/acre per dormant season Postemergence: 2.4 lbs ae/acre per postemergence application	NS	2,4-D acid and amines - 48 hours; 2,4-D salt and esters - 12 hours	PHI - 30 days	See Label Changes Summary Table in 2,4-D RED
Filberts	Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid	1.0	lbs ae per 100 gallons of spray solution	4	4.0 lbs ae per 100 gallons of spray solution per year	30	2,4-D acid and amines - 48 hours; 2,4-D salt and esters - 12 hours	PHI - 45 days	See Label Changes Summary Table in 2,4-D RED

Use Site	Formulation	Max. Single App. Rate	Unit	Max. # App. Per Crop Cycle/Year	Max. App. Rate Per Crop Cycle/Year	Min. Retreatment Interval (days)	Reentry Interval (REI)	Preharvest Interval (PHI) Pregrazing Interval (PGI) Preslaughtering Interval (PSI)	Restrictions/Comments
Fallowland (crop stubble on idle land, or postharvest to crops, or between crops)	Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid	2.0	Lbs ae/acre	2 per year	4.0 lbs ae/acre per year	30	2,4-D acid and amines - 48 hours; 2,4-D salt and esters - 12 hours	NS	Plant only label crops within 29 days following application. See Label Changes Summary Table in 2,4-D RED
Forestry (forest site preparation, forest roadsides, brush control, established conifer release, Christmas trees, reforestation areas)	Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid	Broadcast: 4.0 Basal spray, cut surface - stumps, frill: 8.0 Injection: 2	Broadcast: lbs ae/acre Basal spray, cut surface - stumps, frill: lbs ae per 100 gallons of spray solution Injection: ml of 4.0 lbs ae formulation per injection site	1 per year	Broadcast: 4.0 lbs ae/acre per year Basal spray, cut surface - stumps, frill: lbs ae per 100 gallons of spray solution Injection: ml of 4.0 lbs ae formulation per injection site	NA	2,4-D acid and amines - 48 hours; 2,4-D salt and esters - 12 hours	NA	See Label Changes Summary Table in 2,4-D RED
Grapes	Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid	1.36	lbs ae/acre	1 per crop cycle	1.36 lbs ae/acre per year	NA	2,4-D acid and amines - 48 hours; 2,4-D salt and esters - 12 hours	PHI - 100 days	For use in California only. Do not apply to grape foliage, shoots, or stems. See Label Changes Summary Table in 2,4-D RED

Use Site	Formulation	Max. Single App. Rate	Unit	Max. # App. Per Crop Cycle/Year	Max. App. Rate Per Crop Cycle/Year	Min. Retreatment Interval (days)	Reentry Interval (REI)	Preharvest Interval (PHI) Pregrazing Interval (PGI) Preslaughtering Interval (PSI)	Restrictions/Comments
Grasses (pastures and rangeland not in agricultural production)	Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid	2.0	Lbs ae/acre	2 per year	4.0 lbs ae/acre per year	30	2,4-D acid and amines - 48 hours; 2,4-D salt and esters - 12 hours	PHI - 7 days	Do not cut forage for hay within 7 days of application. If grass is to be cut for hay, Agricultural Use Requirements for the Worker Protection Standard are applicable. For program lands, such as Conservation Reserve Program, consult program rules to determine whether grass or hay may be used. The more restrictive requirements of the program rules or this label must be followed. See Label Changes Summary Table in 2,4-D RED
Hops	Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid	0.5	Lbs ae/acre	3 per crop cycle	1.5 lbs ae/acre per crop cycle	NS	2,4-D acid and amines - 48 hours	PHI - 28 days	See Label Changes Summary Table in 2,4-D RED

Use Site	Formulation	Max. Single App. Rate	Unit	Max. # App. Per Crop Cycle/Year	Max. App. Rate Per Crop Cycle/Year	Min. Retreatment Interval (days)	Reentry Interval (REI)	Preharvest Interval (PHI) Pregrazing Interval (PGI) Preslaughtering Interval (PSI)	Restrictions/Comments
Non-Cropland (fenecrows, hedgerows, roadsides, ditches, rights-of-way, utility power lines, railroads, airports, and industrial sites)	Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid, Granular	Postemergence (annual and perennial plants): 2 Postemergence (woody plants): 4	lbs ae/acre	Postemergence (annual and perennial plants): 2 Postemergence (woody plants): 1	4.0 lbs ae/acre	Postemergence (annual and perennial plants): 30 days Postemergence (woody plants): NA	2,4-D acid and amines - 48 hours; 2,4-D salt and esters - 12 hours	NA	Applications to non-cropland areas are not applicable to treatment of commercial timber or other plants being grown for sale or other commercial use, or for commercial seed production, or for research purposes. See Label Changes Summary Table in 2,4-D RED.
Nut Orchards	Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid	2.0	Lbs ae/acre	2 per year	4.0 lbs ae/acre per year	30	2,4-D acid and amines - 48 hours; 2,4-D salt - 12 hours	NS	Do not cut forage for hay within 7 days of application. See Label Changes Summary Table in 2,4-D RED.

Use Site	Formulation	Max. Single App. Rate	Unit	Max. # App. Per Crop Cycle/Year	Max. App. Rate Per Crop Cycle/Year	Min. Retreatment Interval (days)	Reentry Interval (REI)	Preharvest Interval (PHI) Pregrazing Interval (PGI) Preslaughtering Interval (PSI)	Restrictions/Comments
Pasture and Rangeland (established grass pastures, rangeland, and perennial grasslands not in agricultural production)	Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid	Susceptible annual and biennial broadleaf weeds: 1.0 Moderately susceptible biennial and perennial broadleaf weeds: 1.0 to 2.0 Difficult to control weeds and woody plants: 2.0 Spot treatment: 2.0	Lbs ae/acre	2 per year	4.0 lbs ae/acre	30	2,4-D acid and amines - 48 hours; 2,4-D salt and esters - 12 hours		Do not forage for hay within 7 days of application. For program lands, such as Conservation Reserve Program, consult program rules to determine whether grass or hay may be used. The more restrictive requirements of the program rules or this label must be followed. If grass is to be cut for hay, Agricultural Use Requirements for the Worker Protection Standard are applicable. See Label Changes Summary Table in 2,4-D RED.
Pome fruits	Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid	2.0	Lbs ae/acre	2 per crop cycle	4.0 lbs ae/acre	75	2,4-D acid and amines - 48 hours; 2,4-D salt - 12 hours	PHI - 14 days	Do not cut orchard floor forage for hay within 7 days of application. See Label Changes Summary Table in 2,4-D RED.

Use Site	Formulation	Max. Single App. Rate	Unit	Max. # App. Per Crop Cycle/Year	Max. App. Rate Per Crop Cycle/Year	Min. Retreatment Interval (days)	Reentry Interval (REI)	Preharvest Interval (PHI) Pregrazing Interval (PGI) Preslaughtering Interval (PSI)	Restrictions/Comments
Potatoes	Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid	0.07	Lbs ae/acre	2 per crop cycle	0.14 per crop cycle	10	2,4-D acid and amines - 48 hours; 2,4-D salt and esters - 12 hours	PHI - 45 days	Only for use on potatoes intended for fresh market. See Label Changes Summary Table in 2,4-D RED.
Rice	Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid	Preplant: 1.0 Postemergence: 1.5	Lbs ae/acre	Preplant: 1 per crop cycle Postemergence: 1 per crop cycle	1.5 lbs ae/acre per crop cycle	NA	2,4-D acid and amines - 48 hours; 2,4-D salt - 12 hours	PHI - 60 days	See Label Changes Summary Table in 2,4-D RED.
Rice, wild	Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid	0.25	Lbs ae/acre	1 per crop cycle	0.25 lbs ae/acre per crop cycle	NA	2,4-D acid and amines - 48 hours; 2,4-D salt - 12 hours	PHI - 60 days	For use in Minnesota only. See Label Changes Summary Table in 2,4-D RED.

Use Site	Formulation	Max. Single App. Rate	Unit	Max. # App. Per Crop Cycle/Year	Max. App. Rate Per Crop Cycle/Year	Min. Retreatment Interval (days)	Reentry Interval (REI)	Preharvest Interval (PHI) Pregrazing Interval (PGI) Preslaughtering Interval (PSI)	Restrictions/Comments
Sorghum	Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid	Postemergence (acid, salts, and amines): 1.0 Postemergence (esters): 0.5	Lbs ae/acre	1 per crop cycle	Postemergence (acid, salts, and amines): 1.0 lbs ae/acre per crop cycle Postemergence (esters): 0.5 lbs ae/acre per crop cycle	NA	2,4-D acid and amines - 48 hours; 2,4-D salt and esters - 12 hours	PHI - 30 days	Do not permit meat or dairy animals to consume treated crop as fodder or forage for 30 days following application. See Label Changes Summary Table in 2,4-D RED.
Soybean	Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid	1.0	Lbs ae/acre	1 app. of 1.0 lbs ae/acre per crop cycle OR 2 apps. Of 0.5 lbs ae/acre per crop cycle	1.0 lbs ae/acre per crop cycle	NS	2,4-D acid and amines - 48 hours; 2,4-D salt and esters - 12 hours	-	0.5 lbs ae/acre rate: >Esters: Apply not less than 7 days prior to planting soybeans. >Amines, acid, salts: Apply not less than 15 days prior to planting soybeans. 1.0 lb ae/acre rate: >Esters: Apply not less than 15 days prior to planting soybeans. >Amines, acid, salts: Apply not less than 30 days prior to planting soybeans. See Label Changes Summary Table in 2,4-D RED.

Use Site	Formulation	Max. Single App. Rate	Unit	Max. # App. Per Crop Cycle/Year	Max. App. Rate Per Crop Cycle/Year	Min. Retreatment Interval (days)	Reentry Interval (REI)	Preharvest Interval (PHI) Pregrazing Interval (PGI) Preslaughtering Interval (PSI)	Restrictions/Comments
Stone fruits	Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid	2.0	Lbs ae/acre	2	4.0 lbs ae/acre per crop cycle	75	2,4-D acid and amines - 48 hours; 2,4-D salt - 12 hours	PHI - 40 days	Do not cut orchard floor forage for hay within 7 days of application. See Label Changes Summary Table in 2,4-D RED.
Strawberry	Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid	1.5	Lbs ae/acre	1	1.5 lbs ae/acre per cop cycle	NA	2,4-D acid and amines - 48 hours; 2,4-D salt - 12 hours	-	Do not apply in California or Florida. Apply in dormant stage or after last picking. See Label Changes Summary Table in 2,4-D RED.
Sugarcane	Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid	Preemergence: 2.0 Postemergence: 2.0	Lbs ae/acre	Preemergence: 1 Postemergence: 1	4 lbs ae/acre per crop cycle	NS	2,4-D acid and amines - 48 hours; 2,4-D salt - 12 hours	-	Do not harvest cane prior to crop maturity. See Label Changes Summary Table in 2,4-D RED.

Use Site	Formulation	Max. Single App. Rate	Unit	Max. # App. Per Crop Cycle/Year	Max. App. Rate Per Crop Cycle/Year	Min. Retreatment Interval (days)	Reentry Interval (REI)	Preharvest Interval (PHI) Pregrazing Interval (PGI) Preslaughtering Interval (PSI)	Restrictions/Comments
Turf, ornamental (golf courses, cemetaries, parks, sports fields, turfgrass, lawns, and other grass areas)	Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid, Granular	1.5	Lbs ae/acre	2	3.0 lbs ae/acre per year, excluding spot treatments	NS	NS	-	See Label Changes Summary Table in 2,4-D RED.
Turf, grown for seed or sod	Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid, Granular	2.0	Lbs ae/acre	2	4.0 lbs ae/acre per crop cycle	21	2,4-D acid and amines - 48 hours; 2,4-D salt and esters - 12 hours	-	See Label Changes Summary Table in 2,4-D RED.

Appendix B. Data Supporting Guideline Requirements for the Reregistration of 2,4-D

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Data Supporting Guideline Requirements for the Reregistration of 2,4-D

REQUIREMENT			Use Patterns	CITATION(S)
PRODUCT CHEMISTRY				
New Guideline Number	**Old Guideline Number**			
830.1550	**61-1**	**Product Identity and Composition**	All	41219701, 41223801, 41926201, 43516401, 43516402, 43981801, 40808301, 41219601, 41055804, 41055805, 41220101, 41973501, 41055801, 41055802, 41220101, 41973501, 41067001, 41203301, 41123601, 41055809, 41055810, 41964401, 41055815, 41055816, 41978001, 44807001, 41055818, 41055819, 41055812, 41055813, 41961301, 41055806, 41055807, 41968301, 41015001, 42188601, 42786501, 40443301, 41224201
830.1600	**61-2A**	**Description of materials used to produce the product**	All	41223801, 41637501, 41790601, 44149301, 44547901, 43516401, 40808301, 41246701, 41681901, 41796201, 41055804, 41496701, 41055801, 41496701, 41973501, 41067001, 41599401, 42537501, 44184201, 41055809, 41055815, 41055818, 41055812, 44584501, 44963803, 41055806, 44982101, 41015001, 42188601, 41376701, 40443301, 41224201
830.1620	**61-2B**	**Description of production process**		41223801, 41790601, 44149301, 44547901, 43516401, 40808301, 41246701, 41796201, 41496701, 41055801, 41973501, 41067001, 41599401, 41789901, 42537501, 44184201, 41055809, 41055815, 44727101, 44807001, 41055818, 44228301, 41055812, 44584501, 44963803, 41055806, 44982101, 41015001, 42188601, 41376701, 40443301, 41224201

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Data Supporting Guideline Requirements for the Reregistration of 2,4-D

REQUIREMENT			Use Patterns	CITATION(S)
830.1670	**61-2B**	**Formation of Impurities**	All	41223801, 41790601, 44149301, 44547901, 43516401, 40808301, 41246701, 41496701, 41055801, 41973501, 41067001, 41599401, 41789901, 41789902, 41123601, 42537501, 44184201, 41055809, 41964401, 42798101, 41055815, 41978001, 42798301, 44727101, 44807001, 41055818, 42798201, 44228301, 41055812, 41961301, 44584501, 44963803, 41055806, 41968301, 44982101, 41015001, 42188601, 42786501, 40443301
830.1700	**62-1**	**Preliminary Analysis**	All	41219701, 41926201, 41790602, 44149302, 44543502, 44543503, 44932701, 43516401, 43516402, 43981801, 40808301, 41724201, 41724202, 41349001, 41796201, 41796202, 41219601, 41796202, 41055805, 41220101, 41496701, 41973501, 43777501, 44287101, 41055802, 41220101, 41496701, 41973501, 43777502, 44228601, 41067001, 41203301, 41735701, 41123601, 41055810, 41964401, 43314701, 41055816, 41055819, 44620501, 41055813, 44963801, 41349002, 41724201, 41724203, 41055807, 45014801, 41015002, 42188601, 40443301, 41206901
830.1750	**62-2**	**Certification of limits**	All	41219701, 41223801, 41926201, 43516401, 43516402, 43981801, 40808301, 41219601, 41055804, 41055805, 41220101, 41496701, 41973501, 41055801, 41055802, 41220101, 41496701, 41973501, 41067001, 41203301, 41599401, 41123601, 41055809, 41055810, 41964401, 41055815, 41055816, 41978001, 44807001, 41055818, 41055819, 41055812, 41055813, 41961301, 44963804, 41055806, 41055807, 41968301, 41015001, 42188601, 40443301, 41206901

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REQUIREMENT			Use Patterns	CITATION(S)
830.1800	**62-3**	**Analytical Method**	All	41219701, 41223801, 41637501, 41926201, 44543502, 44543503, 43516401, 43516402, 43981801, 40808301, 41219601, 41796202, 41055802, 41220101, 41496701, 41055802, 41220101, 41496701, 41067001, 41203301, 41599401, 41789902, 41123601, 41055810, 41055816, 41055819, 41055813, 449638034, 44963804, 41055807, 44982102, 41015002, 42188601, 42786501, 40443301, 41206901
830.6302	**63-2**	**Color**	All	41223801, 44543504, 43516403, 43516404, 40808301, 41055803, 41067001, 41123601, 42857203, 41055811, 41055817, 41055820, 41055814, 44963802, 41055808, 41015003, 40443301, 41224201
830.6303	**63-3**	**Physical State**	All	41223801, 44543504, 43516403, 43516404, 40808301, 41055803, 41067001, 41123601, 42857203, 41055811, 41055817, 41055820, 41055814, 44963802, 41055808, 41015003, 40443301, 41224201
830.6304	**63-4**	**Odor**	All	41223801, 44543504, 43516403, 43516404, 40808301, 41055803, 41067001, 41123601, 42857203, 41055811, 41055817, 41055820, 41055814, 44963802, 41055808, 41015003, 40443301, 41224201
830.6313	**63-13**	**Stability to normal and elevated temperatures, metals, and metal ions**	All	41223801, 41745301, 42023601, 44543504, 41055803, 41855701, 42023601, 42795401, 43516403, 43516404, 40808301, 41055803, 41855701, 42023601, 42795401, 41055803, 42795401, 41973502, 41067001, 41855701, 42857209, 41978002, 42487901, 41968303, 44963802, 41015003, 42116702, 42786501, 40443301, 41224201
830.6314		**Oxidation/Reduction: Chemical Incompatibility**	All	42023601, 43516403, 43516404, 40808301, 41973501, 41067001, 41055811, 41055817, 41055820, 41055814, 41968303, 44963802, 41055808, 40443301, 41224201

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REQUIREMENT			Use Patterns	CITATION(S)
830.6315		**Flammability**	All	41055811, 41055817, 41055820, 41055814, 41055808, 41015003, 40443301, 41224201
830.6316		**Explodability**	All	41745302, 43516403, 43516404, 40808301, 41973501, 41067001, 42537501, 41055811, 41055817, 41055820, 41055814, 41055808, 41015003, 40443301, 41224201
830.6317		**Storage stability**	All	41745301, 41926203, 43516403, 43516404, 40808301, 43260501, 41067001, 41123601, 42227501, 41055811, 45642701, 41055817, 43874601, 41055820, 41055814, 41055808, 41015003, 42786501, 40443301, 41224201
830.6319		**Miscibility**	All	40443301, 41224201
830.6320		**Corrosion characteristics**		42023601, 43516403, 43516404, 40808301, 43260501, 41973501, 41067001, 41123601, 42227501, 41055811, 45642701, 41055817, 41055820, 41055814, 41055808, 41015003, 40443301, 41224201
830.7000	**63-12**	**pH**	All	41926202, 44543504, 43516403, 43516404, 40808301, 41123601, 42857208, 41055811, 41055817, 41055820, 41015003, 40443301, 41224201
830.7050	**None**	**UV/Visable Absorption**	All	44543504, **Datagap**
830.7100		**Viscosity**	All	41055811, 41055817, 41055820, 41055814, 41055808, 41015003, 40443301, 41224201
830.7200	**63-5**	**Melting Point**	All	41223801, 44543504, 41055803, 41067001, 41223801, 43516403, 43516404, 40808301, 41055803, 41067001, 42537501, 42857209, 42829901, 42831001, 43325003,
830.7220	**63-6**	**Boiling Point**	All	43325001, 42830901, 43325001, 44963802, 43325002, 44963802, 42831101, 41015003, 40443301, 41224201

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Data Supporting Guideline Requirements for the Reregistration of 2,4-D

REQUIREMENT			Use Patterns	CITATION(S)
830.7300	**63-7**	**Density**	All	41223801, 44543504, 43516403, 43516404, 40808301, 41055803, 41973501, 41067001, 41855701, 41123601, 42857204, 41055811, 41055817, 41055820, 41055814, 44963802, 41055808, 41015003, 40443301, 41224201
830.7370	**63-10**	**Dissociation constants in water**	All	41223801, 41308901, 44543504, 41055803, 41067001, 41972501, 44543504, 43516403, 43516404, 40808301, 41055803, 41067001, 41332009, 41015003, 41224201
830.7550	**63-11**	**Partition coefficient, shake flask method**	All	41332004, 44543504, 41332004, 43516403, 43516404, 40808301, 41055803, 41067001, 42537501, 42857207, 41647001, 44963802, 41055808, 44963802, 41055808, 41015003, 42116702, 40443301, 41224201
830.7840	**63-8**	**Solubility**	All	41223801, 42023601, 41332002, 44543504, 45692501, 41055803, 45692501, 43516403, 43516404, 40808301, 45692501, 41055803, 41067001, 41332002, 41880601, 42537501, 42857205, 43358801, 41055811, 42021002, 41978001, 43358802, 41669501, 42830901, 42831101, 44963802, 41055808, 41968302, 41015003, 42116702 [3], 42786501, 43302001, 40443301, 41224201
830.7950	**63-9**	**Vapor Pressure**	All	41223801, 44543504, 41055803, 41067001, 44543504, 43516403, 43516404, 40808301, 41055803, 41067001, 42537501, 42857206, 42021001, 41431101, 41431301, 44963802, 41055808, 44963802, 41055808, 41015003, 40443301, 41224201
ECOLOGICAL FATE AND EFFECTS				
835.2120	**161-1**	**Hydrolysis**	A, B	410073-01, 413537-01, 414831-01, 413496-01, 434412-01, 427354-01, 427705-02, 427705-01
835.2240	**161-2**	**Photodegradation in Water**	A, B	411253-06, 414831-02, 427497-02
835.2410	**161-3**	**Photodegradation on Soil**	A, B	411253-05, 427497-02

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REQUIREMENT			Use Patterns	CITATION(S)
835.2370	**161-4**	**Photodegradation in Air**	A, B	414831-03
835.4100	**162-1**	**Aerobic Soil Metabolism**	A, B	431675-01, 437991-01, 431496-01, 434159-01, 436859-01, 437991-02, 438215-01
835.4200	**162-2**	**Anaerobic Soil Metabolism**	A, B	433560-01, 434159-01,
835.4400	**162-3**	**Anaerobic Aquatic Metabolism**	A, B	415579-01, 433560-01, 425747-01, 437991-03, 436063-01, 438829-01, 439083-01, 437991-05, 437991-04
835.4300	**162-4**	**Aerobic Aquatic Metabolism**	A, B	420453-01, 429792-01, 441886-01, 437991-06, 431496-01, 436910-01, 436859-02, 444394-01, 437796-01, 437991-08, 437991-07
835.1230	**163-1**	**Leaching-Adsorption/Desorption**	A, B	420253-02, 441179-01, 441585-01, 441052-01, **Datgap**
835.1410	**163-2**	**Laboratory Volatility**	A, B	417180-01, 420596-01, **Datagap**
835.8100	**163-3**	**Field Volatility**	A, B	
835.6100	**164-1**	**Terrestrial Field Dissipation**	A, B	435146-01, 435334-01, 435428-01, 436406-01, 437052-02, 437624-04, 437624-03, 437624-01, 438317-02, 438317-01, 438491-02, 438640-01, 439147-01, 438727-03, 437634-02 446031-01, 434704-01, 436697-02, 435003-01, 436697-01, 435928-02, 436121-01, 436768-03, 437052-01, 437979-02, 438107-01, 438317-03, 438343-01, 438491-01, 438640-02, 438727-02, 438727-01, 438724-01, 446031-02, **Datagap**
835.6200	**164-2**	**Aquatic Field Dissipation**	A, B	445250-01, 439083-02, 439547-01, 434916-01, 458971-01, 439083-02, 439547-01, **Datagap**
835.6300	**164-3**	**Forestry Dissipation**	A, B	439083-03, 439271-01, 439547-02, **Datagap**
840.1100	**201-1**	**Droplet Size Spectrum**	A, B	**Datagap**
840.1200	**202-1**	**Drift Field Evaluation**	A, B	**Datagap**
850.2100	**71-1A**	**Avian Acute Oral Toxicity**	A, B	415462-02, 419751-01, 415462-01, 233351, 00138871, 416444-01, 414541-01, 411583-03, 72472, 226397, 439350-01

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REQUIREMENT			Use Patterns	CITATION(S)
850.2200	**71-2A** **71-2B**	**Avian Dietary Toxicity**	A, B	415861-01, 415462-02, 419751-02, 419751-03, 417495-01, 233351, 417495-02, 00138870, 00138872, 416444-02, 416444-03, 414484-01, 414290-07, 411583-05, 45070, 411583-04, 226397, 439349-01, 439352-01
850.2300	**71-4A** **71-4B**	**Avian Reproduction**	A, B	453364-01
850.1075	**72-1**	**Fish Toxicity Bluegill**	A, B	411583-01, 53986, 419751-05, 419751-04, 0073-091-01, 233350, 411583-11, 419751-04, 234027, 419751-04, 01338869, 413538-03, 413538-04, 413538-01, 00050674, 00053988, 417373-03, 45068, 45069, 439331-01, 439332-01, 439307-01 439103-01, **Datagap**
850.1010	**72-2A**	**Invertebrate Toxicity**	A, B	411583-01, 419751-06, 232630, 413538-03, 413538-01, 67328
850.1075	**72-3A**	**Estuarine/Marine Toxicity - Fish**	A, B	429797-01, 417373-06, 420183-02, 419751-07, 411583-10, 419734-01, 411583-11, 418252-08, 232630, 414290-03, 414290-02, 414290-06, 411583-10, 418352-04, 418352-01, 411583-11, 418352-06, 418352-03
850.1025	**72-3B**	**Estuarine/Marine Toxicity - Mollusk**	A, B	429797-01, 420183-02, 411583-11, 419734-01, 414290-03, 414290-06, 411583-10, 418352-04, 418352-01, **Datagap**
850.1035	**72-3C**	**Estuarine/Marine Toxicity - Shrimp**	A, B	417373-06, 419751-07, 411583-11, 419252-08, 232630, 414290-02, 414290-05, 418352-06, 418352-03, **Datagap**
850.1045	**72-3**	**Estuarine/Marine Toxicity - Penaid**	A, B	**Datagap**
850.1300	**72-4A**	**Fish Early Life Stage - Daphnid**	A, B	417373-04, 420183-04, 417677-01
850.1350	**72-4B**	**Estuarine/Marine Invertebrate Life Cycle**	A, B	418352-11, 420183-03, 418352-10, 413583-02
850.1400	**72-4C**	**Freshwater Fish- Acute Toxicity**	A, B	
850.1500	**72-5**	**Life Cycle Fish**	A, B	413457-01, 417373–05
850.4100	**122-1A**	**Terrestrial Plant Toxicity, Seedling Emergence**	A, B	

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REQUIREMENT			Use Patterns	CITATION(S)
850.5400	**122-2**	**Aquatic Plant Growth**	A, B	
850.4225	**123-1A**	**Seedling Germination and Seedling Emergence**	A, B	424168-02, 426091-1, 442756-01, 430167-02, 423895-01, 431970-03, 431970-02, 431970-01, 424492-01, 439821-01, **Datagap**
850.4250	**123-1B**	**Vegetative Vigor**	A, B	424168-01, 426091-02, 423439-02, 437882-01, 426693-04, 439821-01, **Datagap**
850.4400	**123-2**	**Aquatic Plant Growth**	A, B	442951-01, 427122-04, 427122-05, 427122-01, 427122-02, 427122-03, 415059-04, 414200-02, 415059-01, 415059-03, 415059-02, 417321-02, 434886-02, 417321-01, 434886-03, 434886-04, 434886-01, 420684-04, 417321-02, 420684-04, 420684-03, 417352-03, 417352-06, 417352-04, 417352-05, 417352-02
850.3020	**141-1**	**Honey Bee Acute Contact**	A, B	445173-04, 445173-01
TOXICOLOGY				
870.1100	**81-1**	**Acute Oral Toxicity-Rat**	A, B	00101605, 41920901, 00157512, 00252291, 41709901, 41413501, 40629801, 41209001
870.1200	**81-2**	**Acute Dermal Toxicity-Rabbit/Rat**	A, B	00101596, 41920911, 00157513, 00252291, 41709902, 41413502, 40629802, 41209002
870.1300	**81-3**	**Acute Inhalation Toxicity-Rat**	A, B	00161660, 41986601, 00157514, 40085501, 40352701, 41957601, 40629803, 42605202
870.2400	**81-4**	**Primary Eye Irritation-Rabbit**	A, B	41125302, 41920902, 00157515, 00252291, 40352702, 41413504, 40629804, 44725303
870.2500	**81-5**	**Primary Skin Irritation**	A, B	42232701, 41920903, 00157516, 00252291, 40352703, 41413505, 40629805, 41413505
870.2600	**81-6**	**Dermal Sensitization**	A, B	00161659, 41920904, 41642805, 41233701, 40352704, 41413506, 40629806, 41209006
870.3100	**82-1A**	**Subchronic Oral Toxicity: 90-Day Study Rodent**	A, B	41991501, 41928101, 41994001, 41896701, 41896702, 42021401, 43515901, 42021402

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REQUIREMENT			Use Patterns	CITATION(S)
870.3150	**82-1B**	**Subchronic Oral Toxicity: 90-Day Study Non-rodent**	A, B	41737301, 42780001, 42780003, 43515501, 42780002
870.3200	**82-2**	**21-Day Dermal - Rabbit/Rat**	A, B	41735304, 41735301, 41407901, 41920905, 41735303, 41735306, 41735302, 41735305, 41407903, 41407902
870.3465	**82-4**	**90-Day Inhalation-Rat**	A, B	**Datagap**
870.4100	**83-1B**	**Chronic Feeding Toxicity**	A, B	43612001, 430490001
870.3700	**83-3A**	**Developmental Toxicity - Rat**	A, B	00130407, 00130408, 41527101, 41527104, 41920906, 41986602, 41735201, 42304601, 42304602, 43523101, 43523001, 41527103; 41527106, 41527102; 41527105
870.3700	**83-3B**	**Developmental Toxicity - Rabbit**	A, B	41747601, 42158703, 42158706, 42055501, 42013501, 42224001, 42304603, 42304604, 42158702; 42158704, 42158701, 42158705
870.3800	**83-4**	**2-Generation Reproduction - Rat**	A, B	00150557, 00163996, **Repeat Study Required**
870.4300	**83-5**	**Combined Chronic Toxicity/ Carcinogenicity: Rats**	A, B	43879801, 43597201
870.4200	**83-2B**	**Carcinogenicity Mice**	A, B	43612001
870.5265	**84-2**	**Gene Mutation**	A, B	41409801, 41388204, 41797903, 41409802, 41409803, 41388203, 41797902, 42015701, 43935101, 41388202, 41797901
870.5300	**84-2**	***In vitro* Mammalian Cell Gene Mutation Test**	A, B	43394201, 43327304, 43327302
870.5375	**84-2**	***In vitro* Chromosome Aberration**	A, B	43327305, 43327303, 43327301
870.5385	**84-2B**	***In vivo* chromosome aberration**	A, B	Mustonen, *et al.*, 41478301, 42015704, 42015701, 42015707, 41409805, 41870102, 41409806, 41870103, 41478303, 42015701, 42015703, 42015706, 43930801, 41478302, 42015701, 42015702, 42015705
870.5395	**84-2**	**Micronucleus Assay**	A, B	41409804, 41870101

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Data Supporting Guideline Requirements for the Reregistration of 2,4-D

REQUIREMENT			Use Patterns	CITATION(S)
870.5450	**84-2**	**Rodent Dominant Lethal Assay**	A, B	41409807, 41498101, 41409808, 41409809, 41498103, 43930501, 41498102
870.6200	**81-8, 82-7, 83-1**	**Neurotoxicity Screening Battery**	A, B	43115201, 43293901
870.6300	**83-6**	**Developmental Neurotoxicity**	A, B	**Datagap**
870.7485	**85-1**	**General Metabolism**	A, B	41737302
870.7600	**85-3**	**Dermal Penetration and Absorption**	A, B	Feldman. R. J. And Maibach, H. I. (1974)
OCCUPATIONAL/RESIDENTIAL EXPOSURE				
875.1100	**231**	**Estimation of Dermal Exposure at Outdoor Sites**	A, B	449722-01, 444598-01
875.1300	**232**	**Estimation of Inhalation Exposure at Outdoor Sites**	A, B	449722-01, 444598-01
875.2200	**132-1b**	**Soil Residue Dissipation**	A, B	446557-01, 446557-04, 446557-03, 450331-01
RESIDUE CHEMISTRY				
860.1200		**Directions for Use**	A, B	**Datagap**
860.1300	**171-4A**	**Plant Metabolism**	A, B	00004666, 00004667, 00004669, 00004675, 00004676, 00004677, 00004680, 00004681, 00004682, 00004683, 00004689, 00004693, 00004698, 00004699, 00004715, 00004723, 00004960, 00004996, 00074214, 00074215, 00074216, 00074217, 00102675, 00102676, 00102679 00102717, 00123973, Blacktop and Linscott. (1968), Feung, et al. (1972), 41991503, 42423101, 42439701 42615601, 43290501, 43496101
860.1300	**171-4B**	**Livestock Metabolism**	A, B	00004705, 00068891, 42605201, 42749701, 43160201

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Data Supporting Guideline Requirements for the Reregistration of 2,4-D

REQUIREMENT			Use Patterns	CITATION(S)
860.1340	**171-4C**	**Residue Analytical Method - Plant commodities**	A, B	00004720, 00033119, 00036171, 00037169, 00042288, 00045364, 00045365, 00046125, 00059025, 00059026, 00059027, 00059033, 00060113, 00060120, 00060870, 00060872, 00060880, 00061012, 00061014, 00061016, 00061017, 00061018, 00061645, 00074219, 00075198, 00075715, 00075716, 00075719, 00088176, 00102605, 00102710, 00102717, 00102719, 00102737, 00102815, 00102862, 00102865, 00109535, 00115499, 00115509, 00120057, 00121733, 00123269, 00126684, 00127273, 00133938, 00136845, 00138635, 00139511, 00139951, 00140092, 00156264, PP#6E2606 (1979), Aly and Faust (1964), Bontoyan (1985), Freed (1948), 43289301, 43691101, 43893701
860.1340	**171-4C**	**Residue Analytical Method - Livestock commodities**	A, B	00004701, 00004707, 00004719, 00037169, 00043759, 00055485, 00066156, 00068011, 00068892, 00068893, 00071787, 00078237, 00102713, 00102714, 00102760, 00102816, 00102821, 00115509, 00115515, 00120057 Otto et al (1982), 44016501, 44016502, **Datagap**
860.1340	**171-4C**	**Residue Analytical Method - Water**	A, B	00035913, 00115509, 00121711, 00136848, 00140032, Otto et al (1982)
860.1380	**171-4E**	**Storage Stability - Plant commodities**	A, B	00136845, 00140092, 00145248, 43809901, 43870301, 43879901, 43879902, 43879903, 43879904, 43879905, 43886401, 43886402, 43886403, 43886404, 43886405, 43886406, 43943101, 43963801, 43963802, 44211901, 45245601
860.1380	**171-4E**	**Storage Stability - Livestock commodities**	A, B	44024801, 44967401
860.1380	**171-4E**	**Storage Stability - Water**	A, B	00035913, 00139511
860.1400	**171-4F**	**Water, Fish, and Irrigated Crops - Irrigated Crops**	A, B	00052597, 00139511, **Datagap**

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REQUIREMENT			Use Patterns	CITATION(S)
860.1400	**171-4F**	**Water, Fish, and Irrigated Crops - Fish and Shellfish**	A, B	00028443, 00035913, 00043759, 00052597, 00102760, 00115741, 43378801, 44135201, 44577801
860.1400	**171-4F**	**Water, Fish, and Irrigated Crops - Water**	A, B	00035913, 00038429, 00052597, 00102788, 00115741, 00118549, 42968501, 42968502
860.1480	**171-4J**	**Meat, Milk, Poultry, Eggs - Milk and the Fat, Meat, and Meat Byproducts of Cattle, Goats, Hogs, Horses, and Sheep**	A, B	00004701, 00004707, 00004719, 00059034, 00068892, 00068893, 00102714, 44024801
860.1480	**171-4J**	**Meat, Milk, Poultry, Eggs - Eggs and the Fat, Meat, and Meat Byproducts of Poultry**	A, B	00102719
860.1500	**171-4K**	**Crop Field Trials (Root and Tuber Vegetables Group - Potatoes)**	A, B	00060876, 00102814, 00102862, 00136845, 43886401
860.1500	**171-4K**	**Crop Field Trials (Legume Vegetables (Succulent or Dried) Group - Soybean seed)**	A, B	43356301, 43356302, 43356303, 43669801
860.1500	**171-4K**	**Crop Field Trials (Foliage of Legume Vegetables Group - Soybean forage and hay)**	A, B	43356301, 43356302, 43356303, 43669801
860.1500	**171-4K**	**Crop Field Trials (Citrus - Grapefruits, Lemons, Oranges)**	A, B	00102605, 43870303, 00102879, 00115509, 43870303, 45462201, 00042526, 00102605, 00102737, 00139059, 00163903, 43870303, 45462201, 45672201
860.1500	**171-4K**	**Crop Field Trials (Pome Fruits Group - Apples, Pears, Quinces)**	A, B	00102824, 43943101, 00102824, 43886405
860.1500	**171-4K**	**Crop Field Trials (Stone Fruits Group - Cherry, Peach, Plum/Fresh Prune)**	A, B	00088176, 43879902, 43879901, 43879903
860.1500	**171-4K**	**Crop Field Trials (Berries Group - Blueberries, Raspberries)**	A, B	00061010, 00061012, 43886403, 44268501, 40881401

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REQUIREMENT			Use Patterns	CITATION(S)
860.1500	**171-4K**	**Crop Field Trials (Tree Nut Group - Almond, Filbert, Pecan, Walnut)**	A, B	00088176, 44211901, 43963801, 43963802, 00115509
860.1500	**171-4K**	**Crop Field Trials (Cereal Grains Group - Barley, grain; Corn, field, grain; Corn, sweet (K+CWHR); Millet, grain; Oats, grain; Rice, grain; Rice, wild, grain; Rye, grain; Sorghum, grain; Wheat, grain)**	A, B	00004610, 00036168, 00036169, 00036171, 00036169, 00059025, 00059027, 00059029, 00060117, 00061010, 00021755, 00022329, 00025383, 00028385, 00030697, 43676801, 43686001, 43693702, 00102865, 43886406, 00025330, 00161187, 00036169, 00059028, 00102816, 00004594, 00120057, 43747901, 43785901, 43853601, 00102719, 00102889, 00120057, 43697801, 43718001, 43718002, 00022622, 00036168, 00036170, 00036171, 00045369, 00046127, 00059029, 00060111, 00061010, 00078482, 00090361, 00127226, 00128778, 43665201, 43665202, 43676802, 43797901, 43797903, 44190301, 44190302, **Datagap**
860.1500	**171-4K**	**Crop Field Trials (Forage, Fodder, and Straw of Cereal Grains Group - Barley, haw and straw; Corn, field, forage, and stover; Corn, sweet, forage and stover; Millet, forage, hay, and straw; Oat, forage, hay, and straw; Rice, straw; Rye, forage and straw; Sorghum, forage and stover; Wheat, forage, hay, and straw)**	A, B	00036168, 00036171, 00059025, 00059027, 00021755, 00022622, 00025383, 00028385, 00030697, 00073273, 00075715, 00075724, 00102865, 00127273, 00139511, 43676801, 43686001, 43693702, 00059028, 00120057, 43747901, 43785901, 00102719, 00102889, 00120057, 43697801, 43718001, 43718002, 00004485, 00028173, 00028200, 00042288, 00061010, 00063507, 00090360, 00102712, 00120057, 00138635, 00144791, 00147047, 43665201, 43665202, 43676802, 43797901, 43797903, 44190301, 44190302, **Datagap**
860.1500	**171-4K**	**Crop Field Trials (Grass Forage, Fodder, and Hay Group - Grass (pastures and rangeland) forage and hay)**	A, B	00004485, 00028173, 00028200, 00042288, 00061010, 00063507, 00090360, 00102712, 00120057, 00138635, 00144791, 00147047, 43592101, 43610801, 43610802, 43665203, 43665204, 43665205, 43779501, 43779502, 43779503, 43779504

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REQUIREMENT			Use Patterns	CITATION(S)
860.1500	**171-4K**	**Crop Field Trials (Miscellaneous Commodities - Asparagus; Aspirated Grain Fractions; Cranberries; Grapes; Hops; Pistachios; Strawberries; Sugarcane)**	A, B	00025338, 00060870, 43879905, 43693701, 43709701, 00061010, 00061012, 43886402, 00061012, 00102833, 43947901, 45245601, 45647101, 45665801, 45512701, 43879904, 00102717, 00102812, 43886404, 00030701, 00079738, 00102640, 00102794, 00115793, 00127823, 43736101, 43736102
860.1520	**171-4L**	**Processed Food/Feed (Apples; Barley; Citrus; Corn, field; Grape; Oats; Potato; Prunes; Rice; Rye; Sorghum; Soybean; Sugarcane; Wheat)**	A, B	43943101, 43870302, 43709701, 45245601, 45647101, 43879903, 43755402, 43709702, 00030701, 00068889, 43755401, 43693701
860.1850	**165-1**	**Confined Rotational Crops**	A, B	43356002
OTHER				
840.1100	**201-1**	**Droplet Size Spectrum**	A, B	Reserved
840.1200	**202-1**	**Drift Field Deposition Evaluation**	A, B	Reserved

Appendix C. Technical Support Documents

Appendix C. TECHNICAL SUPPORT DOCUMENTS

Additional documentation in support of this RED is maintained in the OPP docket, located in Room 119, Crystal Mall #2, 1801 South Bell Street, Arlington, VA. It is open Monday through Friday, excluding legal holidays, from 8:30 am to 4 pm.

The docket initially contained preliminary risk assessments and related documents as of June 23, 2004. Sixty days later the first public comment period closed. The EPA then considered comments, revised the risk assessment, and added the response to comments documents, preliminary mitigation strategies, and the revised risk assessments to the docket on January 12, 2005. The second sixty day public comment period closed on March 14, 2005. The 2,4-D Reregistration Eligibility Decision (RED), revised risk assessments, and response to comments documents were made available in the summer of 2005.

All documents, in hard copy form, may be viewed in the OPP docket room or downloaded or viewed via the Internet at the following site:

www.epa.gov/pesticides/reregistration

These documents include:

HED Documents:

1. 2,4-D. HED's Revised Human Health Risk Assessment for the Reregistration Eligibility Decision (RED) Revised to Reflect Public Comments. PC Code 030001; DP Barcode D316597. May 12, 2005.

2. 2,4-D. Revised Acute and Chronic Dietary Exposure Assessments Including Proposed New Uses Hops and Potatoes for the Reregistration Eligibility Decision. April 18, 2005.

3. 2,4-D: 3rd Revised Occupational and Residential Exposure and Risk Assessment and Response to Public Comments for the Registration Eligibility Decision (RED) Document (PC Code 030001, DP Barcode D316596). May 4, 2005.

4. 2,4-D: Response to Phase 5 Public Comments (PC Code 030001, DP Barcode D315562). June 7, 2005.

5. 2,4-D. Revised Acute and Chronic Dietary Exposure Assessments for the Reregisration Eligibility Decision. October 13, 2004.

6. 2,4-D: Health Effects Division (HED) Metabolism Assessment Review Committee (MARC) Decision Document-Revised. DP Barcodes D309452 Chemical I.D. No. 030001. Case No. 0073. Meeting date 9/3/03. October 13. 2004.

7. 2,4-D. Revisions to the Product and Residue Chemistry Chatpers of the Reregistration Eligibility Decision; Reregistration Case no. 0073. Chemical I. D. No. 030001; DP Barcode No. D309450 and D309451. October 12, 2004.

8. 2,4-D PC Code 030001, Case No. 0073 DP Barcode D309450 Reregistration Eligibility Decision Revised Chemistry Considerations. October 12, 2004.

9. 2,4-D Case 0073 Reregistration Eligibility Decision: Revised Product Chemistry Considerations (DP Barcode D309451). October 12, 2004.

10. 2,4-D - Phase 3 Toxicology Chapter Revision. December 9, 2004.

11. 2,4-D: Response to Public Comments [PC Code 030001, DP Barcode D307717]. December 16, 2004.

EFED Documents:

1. Revised Environmental Fate and Effects Division Revised Preliminary Risk Assessment for the 2,4-Dichlorophenoxyacetic acid (2,4-D) Reregistration Eligibility Decision Document. October 28, 2004.

2. Revised EFED Revised Preliminary Risk Assesssment for the 2,4-D Reregistration Eligibility Document. October 28, 2004.

3. 2,4-D - Response to Public Comments on the Revised EFED Science Chapter for the Reregistration Eligibility Decision Document. October 28, 2004.

4. 2,4-D - Response to Public Comments from the San Francisco Department of the Environment on the EFED Science Chapter for the Reregistration Eligibility Decision Document. November 1, 2004.

Appendix D. Citations Considered to be Part of the Data Base Supporting the Reregistration Eligibility Decision (Bibliography) for 2,4-D

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Appendix E. Generic Data Call-In

Appendix E.

The generic data call-in will be posted at a later date.

Appendix F. Product Specific Data Call-In

Appendix F.

The product specific data call-in will be posted at a later date.

Appendix G. EPA's Batching of 2,4-D Products for Meeting Acute Toxicity Data Requirements for Reregistration

Appendix G.

The batching of 2,4-D products for meeting acute toxicity data requirements for reregistration will be posted at a later date.

Appendix H. List of Registrants Sent This Data Call-In

Appendix H.

A list of registrants sent this data call-in will be posted at a later date.

Appendix I. List Of Available Related Documents And Electronically Available Forms

Appendix I. LIST OF AVAILABLE RELATED DOCUMENTS AND ELECTRONICALLY AVAILABLE FORMS

Pesticide Registration Forms are available at the following EPA internet site:

http://www.epa.gov/opprd001/forms/

Pesticide Registration Forms (These forms are in PDF format and require the Acrobat reader)

Instructions

1. Print out and complete the forms. (Note: Form numbers that are bolded can be filled out on your computer then printed.)
2. The completed form(s) should be submitted in hardcopy in accord with the existing policy.
3. Mail the forms, along with any additional documents necessary to comply with EPA regulations covering your request, to the address below for the Document Processing Desk.

DO NOT fax or e-mail any form containing 'Confidential Business Information' or 'Sensitive Information.'

If you have any problems accessing these forms, please contact Nicole Williams at (703) 308-5551 or by e-mail at williams.nicole@epa.gov.

The following Agency Pesticide Registration Forms are currently available via the internet: at the following locations:

8570-1	Application for Pesticide Registration/Amendment	http://www.epa.gov/opprd001/forms/8570-1.pdf
8570-4	Confidential Statement of Formula	http://www.epa.gov/opprd001/forms/8570-4.pdf
8570-5	Notice of Supplemental Registration of Distribution of a Registered Pesticide Product	http://www.epa.gov/opprd001/forms/8570-5.pdf
8570-17	Application for an Experimental Use Permit	http://www.epa.gov/opprd001/forms/8570-17.pdf
8570-25	Application for/Notification of State Registration of a Pesticide To Meet a Special Local Need	http://www.epa.gov/opprd001/forms/8570-25.pdf
8570-27	Formulator's Exemption Statement	http://www.epa.gov/opprd001/forms/8570-27.pdf
8570-28	Certification of Compliance with Data Gap Procedures	http://www.epa.gov/opprd001/forms/8570-28.pdf
8570-30	Pesticide Registration Maintenance Fee Filing	http://www.epa.gov/opprd001/forms/8570-30.pdf
8570-32	Certification of Attempt to Enter into an Agreement with other Registrants for Development of Data	http://www.epa.gov/opprd001/forms/8570-32.pdf
8570-34	Certification with Respect to Citations of Data (PR Notice 98-5)	http://www.epa.gov/opppmsd1/PR_Notices/pr98-5.pdf

8570-35	Data Matrix (PR Notice 98-5)	http://www.epa.gov/opppmsd1/PR_Notices/pr98-5.pdf
8570-36	Summary of the Physical/Chemical Properties (PR Notice 98-1)	http://www.epa.gov/opppmsd1/PR_Notices/pr98-1.pdf
8570-37	Self-Certification Statement for the Physical/Chemical Properties (PR Notice 98-1)	http://www.epa.gov/opppmsd1/PR_Notices/pr98-1.pdf

Pesticide Registration Kit www.epa.gov/pesticides/registrationkit/

Dear Registrant:

For your convenience, we have assembled an online registration kit which contains the following pertinent forms and information needed to register a pesticide product with the U.S. Environmental Protection Agency's Office of Pesticide Programs (OPP):

1. The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA) as Amended by the Food Quality Protection Act (FQPA) of 1996.

2. Pesticide Registration (PR) Notices

   a. 83-3 Label Improvement Program--Storage and Disposal Statements
   b. 84-1 Clarification of Label Improvement Program
   c. 86-5 Standard Format for Data Submitted under FIFRA
   d. 87-1 Label Improvement Program for Pesticides Applied through Irrigation Systems (Chemigation)
   e. 87-6 Inert Ingredients in Pesticide Products Policy Statement
   f. 90-1 Inert Ingredients in Pesticide Products; Revised Policy Statement
   g. 95-2 Notifications, Non-notifications, and Minor Formulation Amendments
   h. 98-1 Self Certification of Product Chemistry Data with Attachments (This document is in PDF format and requires the Acrobat reader.)

   Other PR Notices can be found at http://www.epa.gov/opppmsd1/PR_Notices

3. Pesticide Product Registration Application Forms (These forms are in PDF format and will require the Acrobat reader).

   a. EPA Form No. 8570-1, Application for Pesticide Registration/Amendment
   b. EPA Form No. 8570-4, Confidential Statement of Formula
   c. EPA Form No. 8570-27, Formulator's Exemption Statement
   d. EPA Form No. 8570-34, Certification with Respect to Citations of Data
   e. EPA Form No. 8570-35, Data Matrix

4. General Pesticide Information (Some of these forms are in PDF format and will require the Acrobat reader).

   a. Registration Division Personnel Contact List
   b. Biopesticides and Pollution Prevention Division (BPPD) Contacts
   c. Antimicrobials Division Organizational Structure/Contact List
   d. 53 F.R. 15952, Pesticide Registration Procedures; Pesticide Data Requirements (PDF format)
   e. 40 CFR Part 156, Labeling Requirements for Pesticides and Devices (PDF format)

   f. 40 CFR Part 158, Data Requirements for Registration (PDF format)
   g. 50 F.R. 48833, Disclosure of Reviews of Pesticide Data (November 27, 1985)

Before submitting your application for registration, you may wish to consult some additional sources of information. These include:

1. The Office of Pesticide Programs' website.

2. The booklet "General Information on Applying for Registration of Pesticides in the United States", PB92-221811, available through the National Technical Information Service (NTIS) at the following address:

   National Technical Information Service (NTIS)
   5285 Port Royal Road
   Springfield, VA 22161

   The telephone number for NTIS is (703) 605-6000.

3. The National Pesticide Information Retrieval System (NPIRS) of Purdue University's Center for Environmental and Regulatory Information Systems. This service does charge a fee for subscriptions and custom searches. You can contact NPIRS by telephone at (765) 494-6614 or through their website.

4. The National Pesticide Telecommunications Network (NPTN) can provide information on active ingredients, uses, toxicology, and chemistry of pesticides. You can contact NPTN by telephone at (800) 858-7378 or through their website: ace.orst.edu/info/nptn.

   The Agency will return a notice of receipt of an application for registration or amended registration, experimental use permit, or amendment to a petition if the applicant or petitioner encloses with his submission a stamped, self-addressed postcard. The postcard must contain the following entries to be completed by OPP:

   - Date of receipt;
   - EPA identifying number; and
   - Product Manager assignment.

   Other identifying information may be included by the applicant to link the acknowledgment of receipt to the specific application submitted. EPA will stamp the date of receipt and provide the EPA identifying file symbol or petition number for the new submission. The identifying number should be used whenever you contact the Agency concerning an application for registration, experimental use permit, or tolerance petition.

   To assist us in ensuring that all data you have submitted for the chemical are properly coded and assigned to your company, please include a list of all synonyms, common and trade names, company experimental codes, and other names which identify the chemical (including "blind" codes used when a sample was submitted for testing by commercial or academic facilities). Please provide a chemical abstract system (CAS) number if one has been assigned.

Documents Associated with this RED

The following documents are part of the Administrative Record for this RED document and may be included in the EPA's Office of Pesticide Programs Public Docket. Copies of these documents are not available electronically, but may be obtained by contacting the person listed on the respective Chemical Status Sheet.

1. Detailed Label Usage Information System (LUIS) Report.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PREVENTION, PESTICIDES, AND TOXIC SUBSTANCES
WASHINGTON, D.C. 20460

May 27, 2004

MEMORANDUM

SUBJECT: **2,4-D:** Revised Occupational and Residential Exposure and Risk Assessment and Response to Phase one Comments for the Registration Eligibility Decision (RED) Document [PC Code 030001, DP Barcode D302261]

FROM: Timothy C. Dole, CIH, Industrial Hygienist
Reregistration Branch I
Health Effects Division (7509C)

THROUGH: Jeff Dawson, Chemist
And
Whang Phang, PhD, Branch Senior Scientist
Reregistration Branch I
Health Effects Division (7509C)

TO: Bill Hazel, Risk Assessor
Reregistration Branch I
Health Effects Division (7509C)

Mark Seaton, Ph.D., Chemical Review Manager
Reregistration Branch II
Special Review and Reregistration Division (SRRD), 7508C

The following is in reference to the Occupational and Residential (ORE) Aspects of the "Error Only Response to Health Effects Division's Risk Assessment for the Reregistration Eligibility Decision (RED) for 2,4-Dichlorophenoxy acetic acid (2,4-D)" that was prepared by the Industry Task Force II on 2,4-D Research Data on April 21, 2004. This response was submitted following the Phase 1 review period. The ORE Risk Assessment has been revised as appropriate and responses to the Task Force comments are included in Appendix J.

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H - 2,4-D Swimmer Exposures
I - 2,4-D Aquatic Dissipation Data
J - Response to the Phase One Comments from the 2,4-D Task Force

Executive Summary

2,4-D Product Descriptions, Uses and Application Methods:

There are registered products of 2,4-D for both occupational and residential site applications. The registered agricultural uses include field/row crops, orchard floors, vineyard floors, and sod farm turf. Residential uses include broadcast and spot treatment on turf. The acid, dimethylamine and ethylhexyl ester forms of 2,4-D account for the most products. Most of the 2,4-D products are formulated as liquids or granules, although a few of the acid and salt forms are also formulated as water soluble powders. The residential products are typically formulated as dry weed and feed products or as liquids in concentrates or ready to use sprays. The 2,4-D master label has been developed by the 2,4-D task force and represents the maximum application rates for agricultural and non-agricultural uses. Some of the rates are lower than the rates present on existing labels, however, the agency and the task force have agreed that the existing labels will be updated with the new rates as part of the re-registration process.

Typically one to three applications are made per growing season. Applications are made to the target weeds prior to crop emergence, after crop emergence, prior to harvest and in the dormant season, depending upon the crop. The 2,4-D labels allow ground and aerial application, however, they do not allow chemigation. Ground applications are made whenever possible due to cost and convenience while aerial applications are primarily made to rice fields that are flooded or to rangeland areas where woody weeds are too tall for a tractor (2,4-D Smart Meeting, 2001). Aquatic areas can treated from boats either by spraying the floating weeds or by applying liquid or granular materials to submerged weeds. Forestry applications can be made by rotary winged aircraft (i.e. helicopters) for large scale conifer release programs or by backpack for smaller areas such as Christmas tree plantations.

Toxicology Endpoints:

The following endpoints as selected by the HIARC (US EPA, May 1, 2003) were used for assessing 2,4-D risks:

- A NOAEL of 67 mg/kg/day was selected from an acute neurotoxicity study in rats during which in-coordination and slight gait abnormalities were observed. This NOAEL is applicable to acute incidental oral and dermal exposures.

- A NOAEL of 25 mg/kg/day was selected from a developmental oral study in rats during which developmental (skeletal variations) and maternal (decreased body weight gain) effects were observed. This NOAEL is applicable to short term incidental oral, dermal and inhalation exposures.

- A NOAEL of 15 mg/kg/day was selected from a sub-chronic oral study in rats during which decreased body weight/body weight gain, alterations in hematology and clinical chemistry parameters and cataract formation were observed. This NOAEL is applicable to intermediate term incidental oral, dermal and inhalation exposures.

- A dermal absorption factor of 5.8 percent was selected for converting dermal exposures to oral equivalent doses. An inhalation absorption factor of 100 percent was selected for converting inhalation exposures to oral equivalent doses.

Endpoints were also selected by the HIARC for chronic exposures, however, these endpoints were not used in this assessment because chronic occupational and residential exposures to 2,4-D are not expected to occur. 2,4-D is only applied a couple of times each year during the growing season, rapidly dissipates from the foliage and is readily excreted from the human body.

The target MOE for occupational populations is 100 which includes the standard uncertainty factors of 10X for intraspecies variability (i.e. differences among humans) and 10X for interspecies variability (differences between humans and animals). The target MOE for residential populations is 1000 because it also includes a database uncertainty factor of 10X. The HIARC determined that this factor is needed due the lack of certain studies since the available data provide no basis to support reduction or removal of the default 10X factor.

Occupational Handler/Applicator Exposure and Risk Estimates:

The non-cancer risks (i.e. MOEs) for occupational exposures were calculated for short and intermediate term dermal and inhalation exposures using standard assumptions and unit exposure data for a wide range of application methods and equipment. The standard assumptions, such as acres treated per day, were taken from ExpoSAC SOPs. The unit exposure data were taken from PHED, the ORETF studies for professional lawn care operators and a California DPR study for backpack applicators. With the exception of mixing/loading wettable powder, most of the MOEs exceed the target of 100 with baseline or single layer PPE and are not of concern. This level of PPE is generally consistent with the labels which typically require coveralls and gloves. The MOEs for handling wettable powder are acceptable with engineering controls (i.e. water soluble bags). Only a few 2,4-D products are formulated as wettable powders and almost all of these products are packaged in water soluble bags.

Post-Application Occupational Exposure and Risk Estimates:

2,4-D, which is highly selective for broadleaf weeds, can cause leaf damage to some of the labeled broadleaf crops and the labels specify that it should be applied to the ground in such a manner as to minimize crop damage. To provide weed control without damaging the crops, applications are made in the dormant season or prior to planting, sprays are directed to the row middles or orchard floors and drop booms and/or shields are used to prevent crop contact. Broadcast applications can be made to grass crops such cereal grains, rice and sugarcane which

are tolerant of 2,4-D. Given the above characteristics of 2,4-D, it is anticipated that post application exposures would primarily occur following treatment of the grass crops.

MOEs were calculated for short and intermediate term post application exposures using standard assumptions, standard transfer coefficients and the TTR data. All of the MOEs are above 100 on day zero which indicates that the risks are not of concern. The WPS REI ranges from 12 to 48 hours depending upon the form of 2,4-D.

Residential Applicator Exposure and Risk Estimates:

The residential products are typically formulated as dry weed and feed products or as liquids in concentrates or ready to use sprays. Many of these formulations include other phenoxy herbicides such as MCPP-p and MCPA. Both spot and broadcast treatments are included on the labels. Exposures are expected to be short term in duration for broadcast treatments because the label allows only two broadcast treatments per year. Exposures are also expected to be short term in duration for spot treatments because the labels recommend repeat applications for hard to kill weeds in two to three weeks.

The MOEs for residential handlers exposures were calculated using standard assumptions, master label rates and PHED and ORETF unit exposure data. All of the MOEs exceed the target MOE of 1000 and are not of concern.

Data Used for Turf Post Application Exposure Assessment

There are three turf transferable residue studies that were submitted by the Broadleaf Turf Herbicide TTR Task Force. These studies measured the dissipation of several phenoxy herbicides, including 2,4-D, using the ORETF roller technique (which is also called the modified California Roller). The studies have been reviewed by HED and were found to meet all of the series 875 guidelines for postapplication exposure monitoring.

The purpose of the first study was to assess the effects of the different chemical forms upon the day zero turf transferable residues (TTR) and dissipation rates of phenoxy herbicides including 2,4-D. This study indicated that the DMA form of 2,4-D had the highest transferability of 2.9 percent. The half lives ranged from 0.53 days to 1.2 days and no rain occurred.

The purpose of the second study was to assess the effects of different spray volumes upon the day zero TTRs and dissipation rates of phenoxy herbicides. The day zero TTRs ranged from 0.87 to 1.3 percent and were generally greater than the DAY 1 TTRs. The half lives were fairly consistent and were short (0.30 days) because rain occurred on Day 2 and 3.

The purpose of third study was to assess the effects of two additional sites (California and Wisconsin) upon the day zero TTRs and dissipation rates. The TTRs declined to the LOQ by

DAT 1 in Wisconsin due to rain. The TTRs remained above the LOQ at the California site because no rain occurred and the halflife was 2.7 days.

Residential Turf Post Application Exposure and Risk Estimates

The MOEs for residential turf exposures were calculated using the TTR data, master label rates and the Residential SOPs. MOEs were calculated for acute exposures using the maximum TTR value of 2.9 percent of the application rate along with the acute NOAEL. MOEs for toddler short term exposures were calculated using the seven day average TTR values because the short term NOAEL was based upon decreased body weight gain which occurred after several days of exposure. MOEs for adult short term exposures were calculated using the maximum TTR value because the short term NOAEL is based upon developmental effects that could have occurred following one day of exposure. All of the MOEs meet or exceed the target MOE of 1000.

The results of a biomonitoring study (Harris and Solomon 1992) were also used to calculate dermal MOEs for post application exposure on turf. The study was conducted with adult volunteers who were exposed to 2,4-D while performing controlled activities for one hour on turf treated with 2,4-D. The controlled activities were conducted at 1 hour after treatment (HAT) and at 24 HAT. Ten volunteers participated in the study. Five volunteers wore long pants, a tee shirt, socks and closed footwear. The other five wore shorts and a tee shirt and were barefoot. The volunteers walked on the turf for a period of 5 minutes and then sat or lay on the area for 5 minutes and then continued in this fashion for 50 more minutes. Each volunteer collected all urine for the next 96 hours immediately following the exposure. The MOEs for the DAT 1 volunteers who wore shorts and no shoes ranged from 1000 to 26000 with the lowest MOE corresponding to the volunteer who removed his shirt during the exposure period. The MOEs for the remaining volunteers ranged from 17000 to 27000.

Recreational Swimmer Post Application Exposure and Risk Estimates

The master label indicates that 2,4-D can be used for aquatic weed control of surface weeds such as Water Hyacinth and submersed weeds such as Eurasian Milfoil. Surface weeds are controlled by foliar applications at a maximum rate of 2.0 lbs ae/acre. Submersed weeds are controlled by the subsurface injection of liquids or the application of slow dissolving granules. Although many herbicide treatments are applied to aquatic areas where recreational swimming is not likely to occur, some of the subsurface treatments are made at recreational lakes because the Eurasian Milfoil interferes with swimming, fishing and boating.

The MOEs for recreational swimmers were calculated using master label target water concentrations, standard exposure factors and the dermal and ingestion exposure formulae from the SWIMODEL. MOEs were calculated for acute exposures using the maximum target concentration value along with the appropriate acute NOAELs. MOEs for toddler short term exposures were calculated using the seven day average water concentration because the short

term NOAEL was based upon decreased body weight gain which occurred after several days of exposure. MOEs for adult short term exposures were calculated using the maximum water concentrations value because the short term NOAEL is based upon developmental effects that could have occurred following one day of exposure.

All of the dermal MOEs meet or exceed the target MOE of 1000 when the 2,4-D acid or 2,4-D DMA are used because these forms have very low skin permeability coefficients. The dermal MOEs are of concern when 2,4-D BEE is used because 2,4-D BEE has a relatively high skin permeability coefficient. The ingestion MOEs are of concern for short term children's exposure and is not dependent on the form used. If a lower target concentration of 2 ppm is used, the MOEs for ingestion rise to above 1000, however, the dermal MOEs remain below 1000 for 2,4-D BEE exposures.

Incident Reports

The incident report was prepared by the HED Chemistry and Exposure Branch (US EPA, 2004). A total of 45 incidents were reported in the OPP Incident Data System and many of these incidents involved irritant effects to the eyes, skin and occasionally respiratory passages. Poison Control Center Incident Data (1993 to1998) indicated that 2,4-D is generally less likely than other pesticides to cause minor, moderate or life threatening symptoms. The most common symptoms were dermal irritation and ocular problems. Incident data from CA DPR indicated that the number of cases generally ranges from 0 to 3 per year and most of these cases were due to eye or skin effects. Incident data from the National Pesticide Information center for the years 1996 to 2002 indicated that an average of 3 cases definitely or probably related to 2,4-D exposure were reported per year.

Risk Characterization

The occupational handler risks are mainly of concern when handling 2,4-D as a wettable powder without engineering controls (i.e. the powder is not in water soluble bags). Only a few 2,4-D products are formulated as wettable powders and most of these products are packaged in water soluble bags.

The occupational post application MOEs are above the target MOE of 100 on day zero and many are greater than 1000 which means that the risks are generally low.

The master label application rate of 2.0 lb ae/acre was used for the residential handler and post application turf assessments. Many of the labels have application rates in the range of 0.5 to 1.5 lb ae/acre because 2,4-D is formulated with other phenoxy herbicides such as MCPP-p and MCPA.

The probability that a person would swim in an area recently treated for milfoil is low because the presence of milfoil makes swimming difficult and unpleasant. The dermal exposures from 2,4-D BEE might be less than calculated because 2,4-D BEE degrades rapidly to form 2,4-D acid. According to EFED, the average half life of BEE is 2.6 hours based upon several literature studies that cover a wide range of field conditions.

The acute MOEs may underestimate risk in cases where swimming occurs immediately after application before mixing has occurred. Field dissipation studies reviewed by EFED indicated that 2,4-D concentrations sometimes exceeded the target concentration in parts of the treated area shortly after application. The short term MOEs from water ingestion are an upper bound estimate of risk because dissipation was not taken into account. Field dissipation studies indicated that the 2,4-D half lives following the subsurface injection of 2,4-D to lakes and ponds ranged from 2.9 to 29.5 days with an average of 11.4 days and a geometric mean of 7.3 days.

1.0 Background Information

1.1 Purpose and Criteria for Conducting Exposure Assessments

Occupational and residential exposure and risk assessments are required for an active ingredient if: (1) certain toxicological criteria are triggered **and** (2) there is potential exposure to handlers (i.e., mixers, loaders, applicators, etc.) during use or to persons entering treated areas after application is completed. 2,4-D (2,4-dichlorophenoxy acetic acid; CAS # 94-75-7) meets both criteria. There is potential exposure to private growers and custom applicators from agricultural site applications of 2,4-D. In addition, the general public may be exposed to 2,4-D during or after application to residential lawns.

2,4-D is produced in various forms including acid, sodium salt, amine salts and esters. A listing of these forms is included in Table 1.

Table 1 - 2,4-D Forms

2,4-D Form	PC CODE
2,4-D Acid	030001
2,4-D Sodium Salt	030004
2,4-D diethanolamine salt (DEA)	030016
2,4-D dimethylamine salt (DMA)	030019
2,4-D isopropylamine salt (IPA)	030025
2,4-D trisisopropanolamine (TIPA)	030035
2,4-D 2-butoxyethyl ester (BEE)	030053
2,4-D 2-ethylhexyl ester (2-EHE)	030063
2,4-D isopropyl ester (IPE)	030066

Many of the 2,4-D products also contain other phenoxy herbicides such as MCPA and MCPP-p. These herbicides are not addressed in this risk assessment.

1.2 Acute Toxicity and Endpoints Used for Risk Assessment

Acute Toxicity

The results of acute toxicity testing are summarized in Table 2. The sodium salt, IPE, BEE and EHE forms of 2,4-D are mild to moderate eye irritants (i.e. Toxicity Category III) while all of the other forms are severe eye irritants (i.e. Toxicity Category I). All of the forms are of moderate toxicity (Tox III) via oral and dermal exposure. With the exception of the BEE ester, all of the forms are of low toxicity (Tox IV) for primary skin irritation. None of the forms are dermal sensitizers.

Table 2 - Acute Toxicity Categories for the Various Forms of 2,4-D									
	2 ,4-D Form								
Guideline (Number)	**Acid**	**Sodium Salt**	**DEA**	**DMA**	**IPA**	**IPE**	**TIPA**	**BEE**	**2-EHE**
Acute Oral (870.1100)	III	III	III	III	III	III	III	III	III
Acute Dermal (870.1200)	III	III	III	III	III	III	III	III	III
Acute Inhalation (870.1300)	III	No Data	IV	IV	IV	IV	IV	IV	IV
Primary Eye Irritation (870.2400)	I	III	I	I	I	III	I	III	III
Primary Skin Irritation (870.2500)	IV	IV	IV	IV	IV	IV	IV	III	IV
Dermal Sensitization (870.2600)	Not a dermal sensitizer - all forms								
Note: The acute toxicity categories range from I which is the most toxic to IV which is the least toxic.									

Toxicological Endpoints Used for ORE Risk Assessment

The toxicological endpoints that were used to complete occupational and residential exposure assessments are summarized in Table 3. These endpoints were selected from animal studies by the HIARC and are discussed in detail in HED Document #0051866 of May 1, 2003.

The combined uncertainty factor which defines the target MOE for occupational populations is 100 which includes the standard safety factors of 10X for intraspecies variability (i.e. differences among humans) and 10X for interspecies variability (differences between humans and animals). The target MOE for residential populations is 1000 because it also includes a database uncertainty factor of 10X. The HIARC determined that this factor is needed due the lack of certain studies since the available data provide no basis to support reduction or removal of the default 10X factor. These studies include a developmental neurotoxicity study and a repeat of 2-generation reproduction study using the new protocol.

Table 3 - 2,4-D Toxicology Endpoints Used for ORE Assessment				
EXPOSURE SCENARIO	**DOSE (mg/kg/day)**	**ENDPOINT (NOAEL/LOAEL = mg/kg/day)**	**TARGET MOE**	**STUDY**
Acute Dietary (Females 13-50 years of age)	NOAEL= 25 Developmental toxicity	Skeletal malformations and variations with a LOAEL of 75.	100 = O 1000 = R	Developmental rat study
Acute Dietary General Population	NOAEL = 67	Gait abnormalities with a LOAEL of 227. The NOAEL for systemic toxicity was 227[the highest dose tested].	1000 = R	Acute Nuerotoxicity in rats
Short Term Dermal, Inhalation and Incidental Oral	NOAEL= 25 Maternal and Developmental toxicity	Developmental - skeletal malformations and variations with a LOAEL of 75. Maternal - Decreased weight gain with a LOAEL of 75.	100 = O 1000 = R	Developmental rat study
Intermediate Term Dermal, Inhalation and Incidental Oral	NOAEL = 15	Decreased body weight/body-weight gain, alterations in some hematology [decreased platelets] and clinical chemistry [decreased T_3 and T_4] parameters, and cataract formation with a LOAEL of 100.	100 = O 1000 = R	Sub-chronic oral study in rats
Long Term Dermal, Inhalation and Incidental Oral	NOAEL = 5.0	Decreased body weight/body-weight gain, alterations in hematology, clinical chemistry parameters, increased kidney weights, degeneration of the descending proximal tubules, hepatocellular hypertrophy, lung inflammation and adipose tissue atrophy with a LOAEL of 75. At the high-dose level, there also were microscopic lesions in the eyes, liver, testes, thyroid, and lungs.	100 = O 1000 = R	Chronic oral toxicity study in rats

Notes

1. Oral endpoint were used for dermal exposure, therefore a dermal absorption factor of 5.8% of oral exposure was used.
2. Oral endpoints were used for inhalation exposure, therefore inhalation exposure was assumed to be equivalent to oral exposure.
3. The target MOE is 100 for occupational populations (O) and 1000 for residential populations (R).

Carcinogenicity of 2,4-D

The HED Carcinogenicity Assessment Review Committee (CARC) concluded that 2,4-D "should remain classified as a group D - Not Classifiable as to Human Carcinogenicity. That is, the evidence is inadequate and cannot be interpreted as showing either the presence or absence of a carcinogenic effect." This conclusion is discussed in the EPA/OPP Memorandum "Carcinogenicity Peer Review (4th) of 2,4-Dichlorophenoxyacetic acid", TXR #005017 of January 29, 1997. This memo also states that "Overall, the pattern of responses observed in both in vitro and in vivo tests indicated that 2,4-D was not mutagenic (although some cytogenic effects were observed)".

1.3 Incident Report

The incident report was prepared by the HED Chemistry and Exposure Branch (US EPA, 2004). A total of 45 incidents were reported in the OPP Incident Data System. Many of these incidents involved irritant effects to the eyes, skin and occasionally respiratory passages. Poison Control Center Incident Data (1993 to1998) indicated that 2,4-D is generally less likely than other pesticides to cause minor, moderate or life threatening symptoms. The most common symptoms were dermal irritation and ocular problems.

There were 33 cases reported in the California Pesticide Illness Surveillance Program for the years 1982-2001 where 2,4-D was used alone or was judged to be responsible for the health effects. With the exception of 1989 when seven cases were reported, the number of cases per year ranged from 0 to 3. Of the 33 cases, 13 were due to systemic effects, 18 were due to eye or skin effects, 1 was due to respiratory effects and 1 was due a combination of effects. Seven of the 13 systemic cases occurred in 1989. Twenty two of the cases involved pesticide handling (mixing, loading, application or storage), seven involved drift, one case involved field worker exposure and 3 cases involved unspecified exposures. Many of the handler cases occurred during equipment cleaning or repair or when a hose broke. Six of the seven drift cases involved a helicopter application that violated label instructions.

According to the National Pesticide Information center, 2,4-D was number 8 in terms of calls received with a total of 429 incidents reported in humans and 108 incidents reported in animals (mostly pets) during the years 1984 to 1991. A similar pattern was also observed during the years 1996 to 2002 when a total of 368 incidents were reported in humans and 206 incidents were reported in animals. Of the incidents reported from 1996 to 2002, 19 incidents in humans and 3 incidents in animals were considered to be definite or probable.

The incident report includes a review of the incidents reported in the literature. Many of these incidents were the result of accidental or intentional ingestion of relatively large amounts of 2,4-D and some resulted in death due to renal failure, acidosis and electrolyte imbalance. Single doses of 5 mg/kg/day have been administered to human subjects without adverse affects and one subject consumed 500 mg per day for 3 week without experiencing symptoms or signs of illness. Neurotoxic effects such as peripheral neuropathy have been observed following dermal exposures, however, it is not certain that exposures to other neurotoxicants, such as solvents, were entirely excluded.

The incident report concludes with the following recommendations: (1) Dermal PPE may be important not only to prevent minor dermal irritant effects, but also long term effects of the muscles. Labels should clearly warn that significant amounts of 2,4-D spilled on the skin should be rinsed off with copious amounts of soap and water immediately after exposure. (2) Eye protection for both occupational and residential users is warranted because a large number of problems have occurred among workers and residential users who got 2,4-D in their eyes.

1.4. Summary of Use Patterns, Formulations and Application Methods

Uses

The 2,4-D Task Force has developed a Master Label for Reregistration of 2,4-D Uses (2,4-D Master Label, 2003) and SRRD has determined that this label will be used for risk assessment (EPA, 2003). There are registered, supported products of 2,4-D intended for both occupational and residential site applications. The registered agricultural uses include field /row crops, orchard floors, vineyard floors, and sod farm turf. Residential uses include broadcast and spot treatment on turf.

Based upon available pesticide survey usage information for the years 1992-2000, the Biological and Economic Effects Division (BEAD) of EPA estimates that total annual domestic usage for agricultural applications of 2,4-D is approximately 30 million pounds active ingredient (ai). Based upon information for the years 1993-1999, BEAD estimates that total annual domestic usage for non-agricultural applications of 2,4-D is approximately 16 million pounds ai. A listing of the use sites with the largest amounts of 2,4-D used and/or the highest percent crop treated is given in Table 4.

Table 4 - Qualitative Usage Analysis Summary for 2,4-D

Use Site	Amount Used (pounds)	Percent of Total Amount Used	Percent Crop Treated
Pasture/Rangeland	11 million	37%	3%
Spring Wheat	3.8 million	13%	51%
Winter Wheat	3.3 million	11%	15%
Field Corn	2.9 million	9.7%	9%
Soybeans	1.7 million	5.7%	5%
Fallow, Summer	1.4 million	4.7%	7%
Filberts	26,000	0.087%	49%
Sugar cane	335,000	1.1%	36%
Barley	1 million	3.3%	36%
Total Agriculture	30 million		
Lawns by Homeowner	8.3 million	52%	
Lawns by PCO	3.2 million	20%	
Roadways/Rights of Way	1.4 million	7.0%	
Total Non-Agriculture	16 million		

Source: QUA Report for 2,4-D, EPA BEAD, 8/9/01.

Mode of Action and Targets Controlled

2,4-D is a highly selective herbicide that is used mainly for post emergence control of certain broadleaf weeds and woody plants. It is translocated throughout the weed plant and has a complex mechanism of action resembling those of auxins (growth hormones) and affects cellular division, activates phosphate metabolism, and modifies nucleic acid metabolism (Ware 2000). It is well tolerated by grass crops such as small grains, however, it can be highly damaging to broadleaf crops.

Formulation Types and Percent Active Ingredient

According to EPA OPP REFS label tracking system, as of 01/29/03 there are approximately 600 active products of 2,4-D formulated from 9 different forms. A listing of these forms is included in Table 5. The acid, DMA and 2-EHE forms of 2,4-D have the most products. Most of the 2,4-D products are formulated as liquids or granules, although a few of the acid and salt forms are also formulated as wettable powders. The residential products are typically formulated as dry weed and feed products or as liquids in concentrates or ready to use sprays.

Table 5 - 2,4-D Forms and Number of Labels

2,4-D Form	PC CODE	Number of Labels	Predominant Formulations	Other Formulations
Acid	030001	100	Liquids and granulars	Wettable Powder (8 labels)
Sodium Salt	030004	7	granular	Wettable Powder (1 label)
DEA	030016	3	Liquids	None
DMA	030019	342	Liquids and granulars	Wettable Powder (4 labels)
IPA	030025	8	Liquids	None
TIPA	030035	20	Liquids and granulars	None
BEE	030053	14	Liquids and granulars	None
2-EHE	030063	111	Liquids and granulars	None
IPE	030066	5	Liquids	None

Application Rates, Timing and Frequency of Applications

The 2,4-D master label has been developed by the 2,4-D task force and represents the maximum application rates for agricultural and non-agricultural uses. Some of the rates are lower than the rates present on existing labels, however, the agency and the task force have agreed that all of the 2,4-D the labels will be updated with the new rates as part of the registration process. It was also decided that all of the registrants, including those that are not in the 2,4-D

task force, will have to conform to the master label rates. The master label agreement is discussed in a memo from SRRD to EFED and HED (EPA, March 18, 2003).

Typically one to three applications are made per growing season. Applications are made to the target weeds prior to crop emergence, after crop emergence, prior to harvest and in the dormant season, depending upon the crop. The label required spray volumes for ground applications range from 20 gallons for most crops to 400 gallons per acre for brush control. 2,4-D can be applied over the top to tolerant crops such as small grains and rice, but must be directed or shielded for the more sensitive crops such as fruits and berries.

The application rates as taken from the master label are included in Table 6 for non-crop areas and Table 7 for agricultural crops. The average application rates from the 2,4-D QUA report (EPA BEAD 2001) are shown for comparison. With the exception of filberts, the QUA data indicate that only one application is made to most crops. The National Agricultural Pesticide Impact Assessment Program (NAPIAP) report on Phenoxy Herbicides indicates that one 2,4-D application is made annually to turfgrass.

Table 6 - 2,4-D Application Rates for Non-Crop Areas

Aquatic Areas, Forestry, Non-Crop Areas and Turf	**Acid Equivalent (ae) Application Rates Per Application/Per crop or Year**	
	Master Label	**Amount Used per QUA Report**
Aquatic Areas - Floating Weeds	2.0/4.0 per acre	512,000 lbs[1]
Aquatic Areas - Submerged Weeds	10.8 per acre foot	
Tree and Brush Control - Tree Injection	1 to 2 ml per inch of trunk diameter	136,000 lbs
Forestry - Weed and Brush Control	4.0/4.0 per acre	
Forestry - Conifer Release	4.0/4.0 per acre	
Irrigation Ditch Banks	2.0/4.0 per acre	
Rights of Way Areas	2.0/4.0 per acre	2.1 million lbs
Rangeland, Pastures	2.0/4.0 per acre	
Turf - Grass Grown for Seed or Sod	2.0/4.0 per acre	351,000 lbs
Turf - Ornamental	2.0/4.0 per acre	11.6 million lbs

1. According to the NAPIAP report 97789 acres were treated for floating weeds and 4652 acres were treated for submerged weeds by state agencies in 1993.

Table 7 - 2,4-D Application Rates for Agricultural Crops		
Agricultural Crops	**Acid Equivalent (ae) Application Rates per Acre Per Application/Per crop or Year**	
	Master Label	**Average Rate per QUA Report**
Asparagus	2.0/4.0	1.1/1.3
Blueberries - Low Bush Wiper Bar	0.0375 lb/GA	0.46/0.51
Blueberries - High Bush	1.4	
Citrus (Growth Regulator)	0.1	No Data
Conifer Plantations	4.0	No Data
Corn (sweet) Corn (field and pop)	0.5 to 1.0/1.5 0.5 to 1.5/3.0	0.48/0.51 0.44/0.46
Cranberries - granular applications Cranberries - liquid applications	4.0 1.2	1.8/2.0
Fallowland and Crop Stubble	2.0/NS	0.69/0.89
Filberts	1.0 lb per 100 Ga/4 Apps per year	0.64/1.7
Grain Sorgum	0.5 to 1.0/NS	0.46/0.50
Grapes	1.36	0.73/0.87
Orchard Floors (Pome and Stone Fruits, Tree Nuts)	2.0/4.0	Apples = 1.2/1.4 Pears = 1.1/1.5
Potatoes	0.07/0.14	0.10/0.17
Rice	1.0 or 1.5/1.5	0.92/0.94
Soybeans (Preplant burndown)	0.5 or 1.0/1.0	0.46/0.47
Strawberries (Except CA or FL)	1.5	1.2/1.3
Sugarcane	2.0/4.0	0.75/0.99
Cereal Grains (Wheat, Barley, Millet, Oats and Rye)	0.5 or 1.25/1.75	Wheat= 0.44/0.48 Barley =0.46/0.47 Oats = 0.46/0.46 Rye = 0.50/0.50 Millet= 0.44/0.44
Wild Rice (MN only)	0.25/0.25	0.20/0.20

Other Sources of Use Information

The Phenoxy Herbicide NAPIAP report (Burnside et. al. 1996) has a great deal of information regarding the use of 2,4-D on a wide variety of crops. Selected information that is relevant for 2,4-D occupational exposure assessment is summarized in Table 8.

The USDA Forest Service 2,4-D Risk Assessment (USFS, 1998) has useful information about 2,4-D applications in forests and rights of way areas. This information is summarized below:

- The most commonly used ground application method is backpack (selective) foliar applications and a worker can treat approximately 0.5 acre per hour.
- Hack and squirt applications are used to eliminate large trees during site preparation, conifer release or rights of way maintenance. The worker usually treats 0.5 acres per hour.
- Boom spray or roadside hydraulic spraying is used primarily for roadside rights of way management. Usually 8 acres are treated in a 45 minute period with 200 gallons of spray solution, however, some special truck mounted spray systems may be used to treat 12 acres in a 35 minute period with 300 gallons.
- Aerial application is currently not used by the Forest Service.
- The typical application rate is 1.0 lb ae/acre with a range of 0.5 to 2.0 lbs ae/acre.

Table 8 - 2,4-D Use Information in the Phenoxy Herbicide NAPIAP Report	
Use Site	**NIPIAP Findings**
Aquatic Weed Control	2,4-D accounted for 56% of aquatic acreage treated. 97789 acres were treated for water hyacinth and 4652 acres were treated for Eurasian water milfoil by state agencies in 1993. 2,4-D provides control for at least one season. Liquid formulations are primarily used for hyacinth while granular formulations are primarily used for milfoil. State agencies want to use liquid formulations for milfoil because this would significantly reduce costs.
Asparagus	Used on 27% of the crop. Only use amine. Broadcast applied before spears emerge in the spring or between cuttings. Directed spray is applied after harvest with drop nozzles to keep 2,4-D off of ferns.
Citrus	IPE form is applied as a growth regulator to delay harvest.
Conifer Release	Most herbicides are applied by helicopter in western regions. In the south, skidder mounted broadcast systems with boomless nozzles are also in extensive use. The typical application rate is 2.0 lbs ae per acre.
Conifer Plantations	Many growers selective spray with 2,4-D in backpack sprayers in June.
Corn (field)	Preharvest applications are not commonly made because the weeds are too large, yield reduction has already occurred, crop is too tall for ground application and drift may occur from aerial application.
Corn (sweet)	Similar to field corn though sweet corn is more sensitive and drop nozzles are used. Normally only one application is made per season.
Fallow land	Approximately 20% of the 72 million acres in fallow was treated once with 2,4-D at a rate of 0.5 lb ae/acre. 70% of fallow acreage in Kansas was treated with 2,4-D.
Grain Sorgum	Major use is post emergence control of broadleaf weeds.
Grapes	2,4-D is important for the control of annual broadleaf weeds.
Orchard Floors	Used for selective control of broadleaf weeds in a grass cover.
Rice (except CA)	18.5% of crop treated nationally with 45% crop treated in Louisiana. One treatment per year.
Rights of Way	Most products are applied by truck mounted sprayers and spray trains. Treatments are applied by backpack for ornamental plantings and around facilities such as pump stations. Generally applied in the spring but also applied in the fall in the south. Rates range from 1 to 2 lb/A.
Soybeans	Is used to control existing vegetation prior to planting no-till soybeans.
Strawberries	In the northeastern states where straw berries are a perennial crop, 70-90% of the acreage is treated with 2,4-D after harvest. Use is insignificant in CA because of methyl bromide fumigation.
Sugarcane	In some states multiple applications are made.
Small Grains	Use of 2,4-D is greater on spring wheat than on winter wheat because winter wheat is higher yielding and more competitive against weeds.
Wild Rice (MN only)	About 10% of crop is treated at a rate of 0.25 lb ae/acre.

Application Methods

The 2,4-D labels allow ground and aerial application, however, they do not allow chemigation. Ground applications are made whenever possible due to cost and convenience while aerial applications are made primarily to rice fields that are flooded or rangeland areas where woody weeds are too tall for a tractor (2,4-D Smart Meeting, 2001). Wiper bar applications can be made to crops such as blueberries and cranberries. Aquatic weeds can treated from boats either by foliar applications to floating weeds or by subsurface application of liquids or granular materials to submersed weeds. Forestry applications can be made by rotary winged aircraft (i.e. helicopters) for large scale conifer release programs or by backpack for smaller areas such as christmas tree plantations. Forestry applications can also be made to unwanted trees by injection or frill treatment.

2.0 Occupational and Residential Exposures and Risks

As discussed above, 2,4-D is used both in the agricultural and residential environment. The risks of mixing, loading and applying 2,4-D in the agricultural environment are discussed in section 2.1. Occupational post application exposures and risks are discussed in section 2.2. Residential applicator exposures and risk are discussed in section 2.3 and residential turf post application exposures and risks are discussed in section 2.4. Recreational swimmer post application exposure and risks are discussed in section 2.5.

2.1 Occupational Handler/Applicator Exposures & Risks

2.1.1 Exposure Scenarios

The following exposure scenarios were assessed based upon the application methods listed in Table 9.

Mixer/Loader
Mix/Load Wettable Powder
Mix/Load Liquid Formulations
Load Granules

Applicator
Aerial Application
Groundboom Application
Subsurface Application of Liquids to Submersed Aquatic Weeds
Airblast Application
Backpack Application
Rights of Way (ROW) Application
Foliar Application of Liquids to Floating Aquatic Weeds
Turfgun Application
Broadcast Spreader Application

Mixer/Loader/Applicator
Mix/Load/Apply Wettable Powder with a Turfgun
Mix/Load/Apply Liquids with a Turfgun
Mix/Load/Apply Water Dispersable Granules with a Turfgun
Mix/Load/Apply Liquids with a Backpack Sprayer
Load/Apply Granules with a Push Spreader

Flagger
Flag Aerial Application

2.1.2 Exposure Assumptions and Data Sources

The following assumptions and factors were used in order to complete the exposure and risk assessments for occupational handlers/applicators:

- The average work day was 8 hours.
- A listing of application methods and amounts of acreage treated per 8 hour day is included in Table 9.
- The application rate for submerged aquatic weeds is based upon the master label rate of 10.8 lbs a.i. per acre foot times an average lake depth of 5 feet.
- Maximum application rates and daily acreage were used to evaluate short term exposures.
- Average application rates were used to evaluate intermediate term exposures.
- A body weight of 60 kg was assumed for short term exposures because the short term endpoint relates to females 13-50 years of age.
- A body weight of 70 kg was assumed for intermediate term exposures because the intermediate term endpoint is not gender specific.
- The dermal absorption rate is 5.8%.
- The inhalation absorption rate is 100%.
- Baseline PPE includes long sleeve shirts, long pants and no gloves or respirator.
- Single Layer PPE includes baseline PPE with gloves.
- Double Layer PPE includes coveralls over single layer PPE
- Double Layer PPE PF5 includes above with a PF5 respirator (i.e. a dustmask)
- Double Layer PPE PF10 includes above with a PF10 cartridge respirator
- Only closed cockpit airplanes are used for aerial application.
- There are very little exposure data to evaluate the exposure in rotary winged aircraft, therefore, the exposure data for fixed wing aircraft are used as a surrogate.
- Airplane and helicopter pilots do not wear chemical resistant gloves.

Table 9 - 2,4-D Application Methods		
Application Method	**Typical Crops Treated**	**Treated Area[a]**
Aerial	Small Grain, Field Corn, Sugarcane Citrus Growth Regulation	1200 350
Groundboom	Small Grains, Field Corn, Sugarcane Orchard/Vineyard Floors Strawberries	200 80 80
Subsurface Application of Liquids	Submersed Aquatic Weeds	30[b]
Airblast	Citrus Growth Regulation	40
Backpack Sprayer - Mix/Load/Apply	Christmas Tree Plantations	2[c]
Backpack Sprayer - Apply Only	Conifer Release	4[d]
Right of Way (ROW) Sprayer	Weed Control - 20 gallons per acre Brush Control - 400 gallons per acre	50[e] 2.5[e]
Foliar Application of Liquids	Floating Aquatic Weeds	10[f]
Broadcast Spreader - Tractor Drawn or Boat Mounted	Turf Submersed Aquatic Weeds	40 50[g]
Turfgun	Turf	5
Broadcast Spreader - Push Type	Turf	5

Notes

a. Except as noted, the acres treated per day values are from ExpoSAC Policy #9 "Standard Values for Daily Acres Treated in Agriculture", Revised 7/5/2000.

b. The area treated for aquatic application of liquids to submersed aquatic weeds is based information provided in an email of 12/11/03 from Dr. Kurt Getsinger of the US Army Corps of Engineers to Timothy C. Dole of the US EPA Office of Pesticide Programs.

c. The area treated for Backpack Sprayer (Mix/Load/Apply) is 40 gallons per day from ExpoSAC Policy #9 divided by the label recommended spray volume of 20 gallons per acre.

d. The area treated for Backpack Sprayer (Apply Only) is 4 acres per day based upon the acreage treated in CA DPR HS-1769 normalized to an 8 hour day.

e. The area treated for ROW sprayers was determined by the dividing the daily spray volume handled (1000 gallons per day) from ExpoSAC Policy #9 by the label recommended spray volume of 20 gallons per acre for weed control and 400 gallons per acre for woody brush control.

f. The area treated for foliar application of liquids to floating aquatic weeds is based upon use information reported in the HED Memorandum "Occupational and Residential Exposure Characterization/Risk Assessment for Triclopyr Triethylamine for Aquatic Weed Control, DP Barcode D269448 of 7/22/2002.

g. The area treated for application of granules to submersed aquatic weeds is based upon information provided in an email of 11/22/2000 from Jim Kannenburg of Marine Biochemists/Applied Biochemists to Troy Swackhammer of the US EPA Office of Pesticide Programs.

Handler Exposure Data Sources

The handler exposure data were taken from the Pesticide Handler Exposure Database (PHED), the Outdoor Residential Exposure Task Force (ORETF) and the California Department of Pesticide Regulation (CA DPR). The PHED data were used primarily for the large scale agricultural and forestry scenarios and the ORETF data were used for lawn care scenarios. The CA DPR data were used for the backpack applicator forestry scenario where multiple applicators are supplied by a nurse tank. A summary of each data source is provided below.

PHED Data

PHED was designed by a task force of representatives from the US EPA, Health Canada, the California Department of Pesticide Regulation, and member companies of the American Crop Protection Association. PHED is a software system consisting of two parts – a database of measured exposure values for workers involved in the handling of pesticides under actual field conditions and a set of computer algorithms used to subset and statistically summarize the selected data. Currently, the database contains values for over 1,700 monitored individuals (i.e., replicates). The distribution of exposure values for each body part (e.g., chest, upper arm) is categorized as normal, lognormal, or "other" (i.e., neither normal nor lognormal). A central tendency value is then selected from the distribution of the exposure values for each body part. These values are the arithmetic mean for normal distributions, the geometric mean for lognormal distributions, and the median for all "other" distributions. Once selected, the central tendency values for each body part are composited into a "best fit" exposure value representing the entire body.

The unit exposure values calculated by PHED generally range from the geometric mean to the median of the selected data set. To add consistency and quality control to the values produced from this system, the PHED Task Force has evaluated all data within the system and has developed a set of grading criteria to characterize the quality of the original study data. The assessment of data quality is based upon the number of observations and the available quality control data. These evaluation criteria and the caveats specific to each exposure scenario are summarized in Table B1 of Appendix B. While data from PHED provide the best available information on handler exposures, it should be noted that some aspects of the included studies (e.g., duration, acres treated, pounds of active ingredient handled) may not accurately represent labeled uses in all cases. HED has developed a series of tables of standard unit exposures for many occupational scenarios that can be used to ensure consistency in exposure assessments.

Unit exposure values were calculated in PHED using the following protection factors for PPE: second layer of clothing = 50% PF for dermal exposure to the body, chemically resistant gloves 90% PF for dermal exposure to the hands, dust mask 80% PF for inhalation exposure and half face cartridge respirator = 90% PF for inhalation. Engineering controls are assigned a protection factor of 90% to 98% depending upon the type of engineering controls selected.

ORETF Data

Handler exposure data generated by the Outdoor Residential Exposure Task Force (ORETF) were used for assessing the lawn care operator scenarios. These studies are summarized in the HED Memorandum "Summary of HED's Reviews of ORETF Chemical Handler Exposure Studies; MRID 449722-01", DP Barcode D261948 of April 30, 2001. These studies used Dacthal as a surrogate compound with a target application rate of 2.0 lbs/ae acre. These studies were conducted in accordance with current Agency guidelines and the data generated were of high quality. These studies have been reviewed by HED and Health Canada.

California Department of Pesticide Regulation Exposure Data

The study HS-1769 "Exposure of Hand Applicators to Triclopyr in Forest Settings, 1995 " was used to assess the exposure of backpack application for conifer release. This study was conducted by the California Environmental Protection Agency, Department of Pesticide Regulation, Worker Health and Safety Branch.

Ten applicators were monitored for two days for a total of 20 replicates as they applied Garlon using Solo Backpack Sprayers which were filled from a 300 gallon mixing tank. The workers treated an average of 3.2 acres during each 9 hour day with a spray volume of 25 gallons per acre and an application rate of 1.0 lb triclopyr ae per acre. The actual spraying time was 360 minutes per day with the remainder of time spent placing plastic bags over the seedlings at the start of the workday, removing the bags at the end of the day, pulling hose, lunch/rest breaks and donning monitoring clothing and equipment.

Dermal exposures were monitored using long sleeve t-shirt and knee length socks, hand and face/neck exposures were monitored using Chubbs baby wipes and inhalation exposures were monitored using glass fiber filters. The workers typically wore coveralls over the dosimeters. The results of the socks were extrapolated to rest of the leg by the Agency using a factor of 2.04 to account for the thighs. This factor is based upon the surface area of the thighs, lower legs and feet (7510 cm^2) divided by the surface area of the lower legs and feet (3690 cm^2).

The field recovery was 60 $\pm$ 21% for the air filters at 100 ug/sample, 95.9 $\pm$ 8.7% for the wipes at 100 ug/sample, 85.6 $\pm$ 8.0% for the sock dosimeters at 100 ug/sample and 98.2 $\pm$ 5.1% at 5000 ug/sample for the t-shirt dosimeters. The measured results were above the fortification levels for the dermal media and were approximately one tenth the fortification level for the air filters. The minimum storage stability sample recoveries were 81 $\pm$ 40% for the air filters at week 31, 88% $\pm$ 7.3% for the socks at week 16, 93.2 $\pm$ 2.4% for the T-shirt at week 10 and 93.2 $\pm$ 6.5% for the wipes at week 16. Method validation data were also provided and substantiated the LOQs of 150 ug/sample for the T-shirts, 40.1 ug/sample for the socks, 10 ug/sample for the wipes and 1.5 ug/sample for the air filters. All of the results were above the LOQs.

This study meets Agency guidelines and is acceptable for use in risk assessment. The major limitation is the use of knee length socks to estimate exposures to the thighs. This could be significant because the majority of the exposure (53%) was measured on the legs, while lessor amounts were measured on the torso (33%), hands (13%) and head/face (2.3%). In a backpack

applicator study on grasslands in England, however, 86% of the leg exposure occurred to the lower legs, 11% occurred on the thighs and 3.5% occurred on the feet (Abbot et. al. 1983) . This study was conducted with whole body dosimeters. Another limitation is that 4 of the 20 inhalation replicates were not valid because the sampling pump flowrate decreased by more than 25 percent by the end of the sampling period. The data from this study are summarized in Table 10. In accordance with ExpoSAC Policy the geometric mean values will be used as the appropriate measure of central tendency for exposure assessment because the data have a lognormal distribution.

Table 10 - Unit Exposure Values for Backpack Application in Forest Settings (CA DPR HS-1769)

Unit Exposures per lb ae handled	N	Mean	SD	Geo. Mean[1]	Median	90th Percentile	Maximum	W-test Result for Normality
Dermal (mg/lb ae)	20	8.1	7.1	**6.1**	6.9	15.1	30.9	Lognormal
Inhalation (ug/lb ae)	16	56	17	**54**	56	78	91.1	Lognormal
Note 1 - The values in bold font are used for risk assessment in accordance with ExpoSAC Policy.								

2.1.3 Exposure and Risk Estimates

Calculation Methodology and Equations

Daily dermal and inhalation exposures, absorbed doses and MOEs are calculated as described in Appendix A. The basic rationale for these calculations is that the daily exposure is the product of the amount of ai handled per day times a unit exposure value. The target MOEs are 100 for both short and intermediate term exposures. Scenarios with MOEs greater than the target MOEs are not of concern for the occupational population.

Results and Comparison to Target MOE

The MOEs for Handlers are summarized in Tables 11 and 12 and a detailed listing of these MOEs is also included in Appendix B. With the exception of mixing/loading wettable powder, most of the MOEs exceed the target of 100 with baseline or single layer PPE and are not of concern. The MOEs for handling wettable powder are acceptable with engineering controls (i.e. water soluble bags). The labels typically require single layer PPE for applicators and handlers and that a probe and pump mechanical transfer system or spigot be used for containers of 5 gallons or more. The mechanical transfer system or spigot is not required for 1 to 5 gallon containers, however, additional PPE (coveralls or a chemical resistant apron) are required if the mechanical system or spigot are not used. Most of the wettable powder products are packaged in water soluble bags.

Table 11 - Summary of 2,4-D Short Term MOEs for Occupational Handlers									
Exposure Scenario	**Crop Type**	**Application Rate (lb ae/acre)**	**Acres/ Day**	**Base-line**	**Single Layer**	**Single Layer PF5**	**Single Layer PF10**	**Double Layer PF10**	**Eng. Control**
Mixer/Loader (M/L)									
M/L WP	All Crops	0.25 to 4	5 to 1200	**≥1.4**	**≥6**	**≥17**	**≥22**	**≥26**	≥390
M/L Liquids	All Crops	0.25 to 4	5 to 1200	**≥1.8**	≥130	≥200	≥220	≥270	≥550
M/L Liquids	Submersed Weeds	54	30	**5.5**	370	580	630	820	1600
Load Granulars for Broadcast Spreader	Golf Courses and Aquatic Areas	2 to 54	40 or 50	>1000	>1000	>1000	>1000	>1000	>1000
Applicator (APP)									
Aerial Application	All Crops	1.25 to 4.0	1200	ND	ND	ND	ND	ND	>850
Groundboom Application	All Crops	1.25 to 4	40 to 200	>1000	>1000	>1000	>1000	>1000	>1000
Subsurface Aquatic Application of Liquids	Submersed Weeds	54	30	600	600	970	1050	1300	2800
Airblast Application	Citrus	0.1	40	>1000	>1000	>1000	>1000	>1000	>1000
Backpack Application	Conifer Release	4	4	ND	230	260	260	ND	ND
ROW Application	Weed Control	2	50	190	570	640	650	870	ND
Foliar Aquatic Application of Liquids	Floating Weeds	2	10	950	>1000	>1000	>1000	>1000	>1000
Turfgun Application	turf	2	5	ND	>1000	>1000	>1000	>1000	>1000
Broadcast Spreader Application	Golf Courses and Aquatic Areas	2 or 54	40 or 50	>1000	>1000	>1000	>1000	>1000	>1000
Mixer/Loader/Applicator (M/L/A)									
M/L/A Liquids with Backpack Sprayer	Christmas Trees	4	2	ND	>1000	>1000	>1000	>1000	ND
M/L/A WD Granules with a Turfgun	turf	2	5	ND	>1000	>1000	>1000	>1000	ND
M/L/A Wettable Powder with a Turf Gun	turf	2	5	ND	>1000	>1000	>1000	>1000	>1000
M/L/A Liquid Flowables with a Turfgun	turf	2	5	ND	>1000	>1000	>1000	>1000	ND
Load/Apply Granules with a Push Spreader	turf	2	5	ND	>1000	>1000	>1000	>1000	ND
Flagger									
Flag Aerial Liquid Application	All Crops	1.25 to 4.0	1200	≥320	≥300	≥410	≥430	≥470	≥16000
MOEs in bold font do not exceed the target MOE of 100 and are of concern									

Table 12 - Summary of 2,4-D Intermediate Term MOEs for Occupational Handlers									
Exposure Scenario	**Crop Type**	**Application Rate (lb ae/acre)**	**Acres/ Day**	**Base-line**	**Single Layer**	**Single Layer PF5**	**Single Layer PF10**	**Double Layer PF10**	**Eng. Control**
Mixer/Loader (M/L)									
M/L WP	All Crops	0.25 to 4	5 to 1200	**≥1.7**	**≥8.3**	**≥24**	**≥31**	**≥37**	≥540
M/L Liquids	All Crops	0.25 to 4	5 to 1200	**≥2.6**	≥170	≥280	≥300	≥390	≥750
M/L Liquids	Submersed Weeds	54	30	**3.8**	250	420	450	570	1100
Load Granulars for Broadcast Spreader	Golf Courses or Aquatic Areas	2 or 54	40 or 50	≥180	≥190	≥530	≥680	>1000	>1000
Applicator (APP)									
Aerial Application	All Crops	0.5 to 2.0	1200	ND	ND	ND	ND	ND	>1200
Groundboom Application	All Crops	0.5 to 4	40 to 200	>1000	>1000	>1000	>1000	>1000	>1000
Subsurface Aquatic Application	Submersed Weeds	54	30	420	420	680	730	920	2000
Airblast Application	Citrus	0.1	40	>1000	>1000	>1000	>1000	>1000	>1000
Backpack Application	Conifer Release	2	4	ND	320	360	370	ND	ND
ROW Application	Weed Control	2	50	130	390	450	460	610	ND
Foliar Aquatic Application of Liquids	Floating Weeds and Wild Rice	4 or 0.25	10	≥330	≥990	>1000	>1000	>1000	>1000
Turfgun Application	turf	2	5	ND	>1000	>1000	>1000	>1000	>1000
Broadcast Spreader Application	Golf Courses and Aquatic Areas	2 or 54	40 or 50	≥220	≥240	≥590	≥720	>1000	>1000
Mixer/Loader/Applicator (M/L/A)									
M/L/A Liquids with Backpack Sprayer	Conifer Plantations	4	2	ND	720	860	880	1400	ND
M/L/A WD Granules with a Turfgun	turf	2	5	ND	>1000	>1000	>1000	>1000	ND
M/L/A Wettable Powder with a Turf Gun	turf	2	5	ND	>1000	>1000	>1000	>1000	>1000
M/L/A Liquid Flowables with a Turfgun	turf	2	5	ND	>1000	>1000	>1000	>1000	ND
Load/Apply Granules with a Push Spreader	turf	2	5	ND	>1000	>1000	>1000	>1000	ND
Flagger									
Flag Aerial Liquid Application	All Crops	0.50 to 2.0	1200	≥910	≥860	≥1200	≥1300	≥1400	≥32000
MOEs in bold font do not exceed the target MOE of 100 and are of concern									

2.1.4 Risk Characterization

Only a few 2,4-D products are formulated as wettable powders and most of these products are packaged in water soluble bags. These products are labeled primarily for use on turf.

2.2 Occupational Post Application Exposure and Risks

Post application 2,4-D exposures can occur in the agricultural environment when workers enter fields recently treated with 2,4-D to conduct tasks such as scouting and irrigation.

2.2.1 Post Application Exposure Scenarios

2,4-D, which is highly selective for broadleaf weeds, can cause leaf damage to some of the labeled broadleaf crops and the labels specify that it should be applied to the ground in such a manner as to minimize foliar residues and crop damage. This is particularly true for crops such as berries, grapes and tree fruits. To provide weed control without damaging the crops, applications are made during the dormant season or prior to planting, sprays are directed to the row middles or orchard floors and drop booms and/or shields are used to prevent crop foliar contact. These techniques also prevent post application exposures because they minimize the amount of residue on the crop foliar surfaces. Broadcast applications can be made to grass crops such cereal grains, rice and sugarcane which are tolerant of 2,4-D.

Given the above characteristics of 2,4-D, it is anticipated that post application exposures would primarily occur following treatment of the grass crops. Because 2,4-D is typically applied one to three times per season and because the agricultural scenarios occur for only a few months per year, it is anticipated that 2,4-D exposures would primarily be short term and secondarily intermediate term.

Potential inhalation exposures are not anticipated for the post-application worker scenarios because of the low vapor pressure of 2,4-D (2.0e-07 torr at 20° C).

In the Worker Protection Standard (WPS) a restricted entry interval (REI) is defined as the duration of time which must elapse before residues decline to a level so entry into a previously treated area and engaging in a specific task or activity would not result in exposures which are of concern. The WPS Restricted Entry Interval (REI) for 2,4-D is 12 hours for the ester and sodium salt forms and is 48 hours for the acid and amine salt forms.

2.2.2 - Exposure Data Sources, Assumptions and Transfer Coefficients

Data Sources:

There are three turf transferable residue studies that were submitted by the Broadleaf Turf Herbicide TTR Task Force. The field portion of the studies were conducted by Grayson Research LLC of Creedmore, North Carolina, AGSTAT of Verona, Wisconsin, and Research for Hire of Porterville California. The laboratory analysis for all three studies was conducted by Covance Laboratories of Madison, Wisconsin. These studies measured the dissipation of several phenoxy herbicides, including 2,4-D, using the OREFT roller technique (which is also called the modified California Roller). The studies have been reviewed by HED and were found to meet all of the series 875 guidelines for postapplication exposure monitoring. The studies are summarized on the following pages.

Determination of Transferable Turf Residues on Turf Treated with 2,4-D, 2,4-D-p, MCPA, MCPP-p and Dicamba, MRID 446557-01(Phase 1 - Effect of Form)

The purpose of this study was to assess the effects of different forms of phenoxy herbicides including 2,4-D upon the day zero turf transferable residues (TTR) and dissipation rates. In two cases 2,4-D was applied by itself while in one case it was applied as a tank mixture with the other herbicides. All of the applications were made to cool season fescue turf plots in North Carolina using a ground-boom sprayer. The plots were mowed to a height of two inches prior to the application and were not mowed again until after the seventh day of sampling. No irrigation was performed. Significant rainfall (i.e. greater than 0.05 inches) did not occur until DAT 10 when 0.17 inches occurred prior to the DAT 10 sample.

Sampling was conducted with a ORETF roller using a 27" X 39" percale cotton cloth in accordance with the SOP developed by the ORETF. Samples were collected after the sprays had dried and at 0.5, 1, 2, 3, 4, 5, 6, 7, 10 and 14 days after treatment (DAT). The samples were analyzed using Method 1 as described and validated in MRID 446557-04 and the LOQ was 0.879 ng/cm^2. The concurrent laboratory recoveries were 108 $\pm$ 11.3 (n=8) for 2,4-D 2-EHE and 108 $\pm$ 15.4 (n=15) for 2,4-D DMA. These recoveries did not vary significantly with respect to the fortification levels which ranged from 1 to 900X LOQ. Field recovery samples were prepared at DAT 0 and DAT 6 using fortification levels of 0.004 and 0.04 ug/cm^2. The recoveries for 2,4-D EHE were 110 $\pm$ 8.4 (n=12) and did not vary with respect to fortification level or day of preparation. The recovery for 2,4-D DMA was 99.1 $\pm$ 7.7 (n=6) and did not vary with respect to fortification level. Only the DAT 0 samples were used for 2,4-D DMA, however, because the evaporation of the extraction solvent caused high recoveries on the DAT 6 samples. The raw data were not corrected for field recovery because the recoveries were greater than 90 percent.

A summary of the results are shown in Table 13 and a more detailed listing is included in Appendix F. The highest TTR levels occurred on DAT 1 for the single ingredient application and were greater for the DMA form of 2,4-D. The highest TTR level for 2,4-D DMA applied as part of a combination occurred on DAT 0.5. The TTR levels declined to the LOQ in 10 days for the

EHE treatment, 7 days for the DMA treatment and 5 days for the DMA combination treatment.

Table 13 - Dissipation of 2,4-D Applied to Turf Using Various Forms (Phase 1)					
2,4-D Form	**Application Rate (lb ae/acre)**	**Maximum TTR[2] (ug/cm^2)**	**Percent Applied as TTR**	**Correlation Coefficient**	**Half Life (days)**
EHE	1.7	0.34 ± 0.87 (n=3)	1.8	0.96 (n=30)	1.2
DMA	1.7	0.56 ± 0.20 (n=3)	2.9	0.90 (n=27)	0.83
DMA Comb[1]	1.6	0.31 ± 0.066(n=3)	1.7	0.91 (n=21)	0.53

1. The combination included 2,4-D DMA, MCPP-p and dicamba.
2. The maximum TTR occurred on DAT 1 for EHE and DMA. The maximum TTR for the DMA combination occurred on DAT 0.5.

Determination of Transferable Turf Residues on Turf Treated with 2,4-D DMA + MCPP-p DMA + Dicamba DMA in Various Spray Volumes, - MRID 446557-03
(Phase 2 - Effect of Spray Volume)

The purpose of this study was to assess the effects of different spray volumes upon the day zero TTRs and dissipation rates of phenoxy herbicides. In all cases 2,4-D was applied in combination with MCPP-p DMA and dicamba DMA All of the applications were made to cool season fescue/blue grass turf plots in North Carolina using a ground-boom sprayer. The plots were mowed to a height of two inches prior to the application and were not mowed again until after the seventh day of sampling.

No irrigation was performed. No rain occurred on DAT 0 or DAT 1 and 0.17 inches of rain occurred prior to the DAT 2 sample, 0.46 inches occurred prior to the DAT 3 sample and 0.03 inches occurred prior to the DAT 4 and 5 samples.

Sampling was conducted in the same manner as for Phase 1 using an ORETF roller with cotton cloth. Samples were collected at 3 and12 hours after treatment (HAT) and at 1, 2, 3, 4, 5, 6, 7, 10 and 14 DAT. The samples were analyzed using Method 2 as described and validated in MRID 446557-04 and the LOQ was 0.879 ng/cm^2. The concurrent laboratory recovery was 82.8 ± 11.5 (n=28) and did not vary significantly with respect to the fortification levels which ranged from 1 to 400X LOQ. Field recovery samples were prepared at DAT 0 and DAT 6 using fortification levels of 0.004 and 0.04 ug/cm^2. The recoveries were 89.7 ± 7.2 (n=6) at 0.004 ug/cm^2 and 78.8 ± 5.9 (n=6) at 0.040 ug/cm^2. When considered by DAT, the recoveries were 82.0 ± 5.8 (n=6) for the DAT 0 samples and 86.5 ± 10.6 (n=6) for the DAT 6 samples. The raw data were corrected for field recovery by using 0.788 for data greater than 0.040 ug/cm^2 and 0.897 for data less than 0.040 ug/cm^2.

A summary of the results are shown in Table 14 and a more detailed listing is included in Appendix F. The half lives ranged from 0.29 to 0.32 days and were calculated based upon the first three days of dissipation because the TTRs reached the LOQ by DAT 3.

Table 14 - Dissipation of 2,4-D Applied to Turf at Various Spray Volumes (Phase 2)					
Spray Volume (GA/acre)	**Application Rate (lb ae/acre)**	**Maximum TTR[1] (ug/cm^2)**	**Percent Applied as TTR**	**Correlation Coefficient**	**Half Life (days)**
2	1.76	0.23 ± 0.035 (n=3)	1.0	0.79 (n=15)	0.31
5	1.76	0.25 ± 0.064 (n=3)	1.3	0.90 (n=15)	0.29
20	1.76	0.17 ± 0.025 (n=3)	0.87	0.95 (n=15)	0.32
1. The maximum average TTR occurred on DAT 1.0, DAT 0.0 and DAT 0.5 for the 2, 5 and 20 GPA applications, respectively.					

Determination of Transferable Turf Residues on Turf Treated with 2,4-D DMA, MCPA DMA, 2,4-D DMA + MCPP-p DMA + Dicamba DMA and MCPA DMA + MCPP-p DMA + 2,4-DP-p-DMA - MRID 450331-01 (Two Additional Sites)

The purpose of this study was to assess the effects of two additional sites upon the day zero TTRs and dissipation rates of phenoxy herbicides. The 2,4-D DMA was applied either by itself (Treatment 2) or in combination with MCPP-p DMA and dicamba DMA (Treatment 4). The applications were made to Kentucky Bluegrass turf plots in Wisconsin and to Dwarf Fescue turf plots in California using ground-boom sprayers with a spray volume of 9.4 to 9.9 gallons per acre. The plots were mowed to a height of two inches prior to the application and were not mowed again until after the seventh day of sampling. No irrigation was performed. No rain occurred at the California site, however, the grass was wet with dew during the DAT 0.5 sampling which occurred at night. The following rainfall occurred at the Wisconsin site: 0.025 inches prior to the HAT 8 sample, 0.145 inches prior to the HAT 12 sample and 0.19 inches prior to the HAT 24 sample.

Sampling was conducted in the same manner as for Phases 1 and 2 using the ORETF roller with cotton cloth. Samples were collected at 1, 4, 8, 12 and 24 HAT and 2, 3, 4 and 7 DAT. The samples were analyzed using Method 2 as described and validated in MRID 446557-04 and the LOQ was 0.879 ng/cm^2. The concurrent laboratory recovery for the California site data was 104 ± 11.5 percent (n=17) and did not vary significantly with respect to the fortification levels which ranged from 1 to 1600X LOQ. The concurrent laboratory recovery for the Wisconsin site data was 87.1 ± 12.7 percent (n=17) and did not vary significantly with respect to the fortification levels which ranged from 1 to 600X LOQ. Field recovery samples were prepared in the same manner as for Phases 1 and 2 with the exception that a different fortification solution was used. In Phases 1 and 2, the fortification solution contained only acetone as the solvent, while in this study 0.1 M phosphoric acid was added to the acetone. The recoveries obtained were very low and were not reported. These low recoveries were thought to be the result of interference caused by the acid interaction with the cotton during storage.

A summary of the results are shown in Table 15 and a more detailed listing is included in Appendix F. The TTR values declined to the LOQ by DAT 1 in Wisconsin and to 40X LOQ by DAT 7 in California. The California TTRs declined steeply during DAT 1 and at a much slower rate during DAT 1 through 7. The data for DAT 0.5 at the California site are not included

because these samples were collected at night when there was dew.

Table 15 - Dissipation of 2,4-D Applied to Turf at Sites in California and Wisconsin					
Site - Treatment[1]	**Application Rate (lb ae/acre)**	**Maximum TTR[2] (ug/cm^2)**	**Percent Applied as TTR**	**Correlation Coefficient**	**Half Life (days)**
CA-2	1.67	0.24 ± 0.030 (n=3)	1.3	0.78 (n=24)	2.8
CA-4	1.66	0.20 ± 0.020 (n=3)	1.1	0.91(n=24)	2.6
WI-2	1.65	0.21 ± 0.031 (n=3)	1.1	0.92 (n=15)	0.12
WI-4	1.64	0.21 ± 0.021(n=3)	1.1	0.89 (n=15)	0.11

1. Treatment 2 consisted of 2,4-D by itself. Treatment 4 consisted of 2,4-D with MCPP-p and dicamba
2. The maximum TTR occurred on HAT 1 for the both CA sites, on HAT 1 for the WI-2 and on HAT 8 for the WI-4 site.

Overall Summary and Application of the TTR Data

A detailed listing of the TTR data is included in Appendix F and a summary of the data used for occupational exposure assessment is included in Table 16. The maximum TTR values of 2.9% of the application rate in North Carolina and 1.3% of the application rate in California were used for assessing exposures in humid and dry regions, respectively. The Wisconsin data were not used because the rain occurred on DAT 1 which caused the TTRs to decline to the LOQ by the end of DAT 1. The dissipation rates were not used because the MOEs on day zero were greater than 100.

Table 16 - Summary of TTR Data Used for Occupational Post Application Exposure Assessment			
	NC - Phase 1	**NC - Phase 2**	**CA**
Conditions	No Rain	Some Rain After DAT 2	No Rain
Application Rate (lbs ae/acre)	1.72	1.76	1.67
Maximum TTR (ug/cm^2)	0.56	0.25	0.24
Maximum TTR (percent of applied)	2.9 - Note 1	1.3	1.3

Assumptions

The following assumptions were made regarding occupational post application:

- Short term risks were assessed using master label rates.
- Intermediate term risks were assessed using average application rates when available.
- The transfer coefficients as listed in Table 17 are from an interim transfer coefficient policy developed by HED's Science Advisory Council for Exposure using proprietary data from the Agricultural Re-entry Task Force (ARTF) database (US EPA, August 7, 2001). This policy will be periodically updated to incorporate additional information about agricultural practices in crops and new data on transfer coefficients. Much of this information will originate from exposure studies currently being conducted by the ARTF, from further analysis of studies already submitted to the Agency, and from studies in the published scientific literature.
- The transfer coefficients for turf harvesting and maintenance are based upon recently conducted ARTF studies that are being reviewed by HED.
- In cases where applications would be made in such a way as to minimize contact with crop foliage post application exposures are expected to be negligible and are not assessed. These cases are included in Table 17.
- The initial percent of application rate as Dislodgeable Foliar Residue (DFR) was assumed to be 20% for all crops except turf. This is the standard value used in the absence of chemical specific data.

Calculation Methodology for Post Application Exposures

The calculations used to estimate the exposures for the post-application scenarios are similar to those described previously for the handler/applicator scenarios and are described in Appendix A. Daily dermal exposure is calculated by multiplying the residue level (ug/cm^2 of leaf area) times a transfer coefficient (amount of leaf area contacted per unit time) time the duration worked (hr). Inhalation exposures were not calculated for the post-application scenarios because inhalation exposures have been shown to account for a negligible percentage of the overall body burden, particularly when the pesticide is applied outdoors and has a low vapor pressure. The vapor pressure of 2,4-D is 2.0e-07 torr at 20° C.

Table 17 - Post Application Exposure Scenarios and Transfer Coefficients for 2,4-D		
Crop	**Label Directions** **Post Application Exposure Scenarios**	**Transfer Coefficient (cm^2/hr)**
Asparagus	Apply immediately after cutting before regrowth of new spears or post harvest. Spears contacted the spray may be malformed and off flavor. Do not exceed two applications per crop. Do not apply within 30 days of previous application. Pre Harvest Interval (PHI) = 3 days	None[1,2]
Blueberries - High Bush	Make directed or shielded applications in the spring. Make directed applications to row middles in summer or fall after harvest.	None[1]
Blueberries - Low Bush	Make directed wipe or spot applications when weed tops are above crop. Make directed application to cut hardwoods in row middles in summer or fall after harvest. Avoid contact with blueberry foliage and apply only in the non-bearing year.	None[1]
Cereal Grains	Apply Post-emergence rate (1.25 lb ae/acre) after grain is fully tillered (4-8" high). Apply Pre-harvest rate (0.5 lb ae/acre) at the dough stage. PHI = 14 days Low Exposure Scenarios - Irrigation, scouting, immature plants Medium Exposure Scenarios - Same as above on mature plants	 100 1500
Citrus	Applied to trees to prevent fruit drop and increase fruit size. PHI = 7 days.	None[3]
Conifer Plantations	Apply over the top to firs prior to bud break or after complete bud set and hardening in the late summer or fall. Avoid treatment during the year of harvest. Directed sprays may be made to weeds in Christmas tree plantations of all conifer species, but the spray must not contact tree foliage as injury may occur.	None[1]
Corn, Field and Popcorn	Apply Preemergence rate (1.0) before corn emerges. Apply Post Emergence rate (0.5) when corn is less than 8" tall or by using drop nozzles. Apply Preharvest rate (1.5) after dough or at denting stage. Not applied in tassel to dent stage. PHI = 7 days. Low Exposure Scenarios - Scouting, weeding immature plants Medium Exposure Scenarios - Scouting, weeding more mature plants High Exposure Scenarios - Scouting, weeding, irrigation mature plants Very High Exposure Scenarios - Detasseling	 100 400 1000 NA[4]
Corn, Sweet	Apply Preemergence rate (1.0) before corn emerges. Apply Post Emergence rate (0.5) when corn is less than 8" tall or by using drop nozzles. Preharvest rate not used. PHI = 45 days. Low Exposure Scenarios - Scouting, immature plants	 100
Cranberries	Make broadcast applications at dormant rate (4.0) in the dormant season. Make directed wipe or spot applications at the postemergence rate (1.2) when weed tops are above crop. PHI = 30 days.	None[1]
Filberts	Spray on suckers that arise from the base of the trees.	None[1]
Grapes	Use hooded boom sprayer or equivalent to direct coarse spray to weeds and minimize potential contact with grape foliage, shoots or stems..	None[1]
Orchard Floors	For control of weeds on orchard floors. PHIs are 14 days for pome fruits, 40 days for stone fruits and 60 days for nuts.	None[1]
Pasture, Rangeland, Grassland	PHI = 7 days	None[1]
Potatoes	Make first application when potatoes are in the pre-bud stage (7 to 10" high) and second application is made 10 to 14 days later. PHI = 45 days.	None[3]
Rice, Wild	Applied to rice in the 1 to 2 aerial leaf through early tillering stage. Not applied after boot stage. PHI = 60 days.	See Below

Table 17 - Post Application Exposure Scenarios and Transfer Coefficients for 2,4-D		
Crop	**Label Directions** **Post Application Exposure Scenarios**	**Transfer Coefficient (cm^2/hr)**
Rice, Conventional	Apply Preplant rate (1.0) 2 to 4 weeks prior to planting. Apply Postemergence rate (1.5) at the late tillering stage usually 6 to 9 weeks after emergence. Do not apply after panicle initiation. PHI = 60 days. Low Exposure Scenarios - Irrigation, scouting, immature plants Medium Exposure Scenarios - Same as above on mature plants	 100 1500
Sorghum, Grain or Forage	Apply when sorghum is 6 to 15" tall. If sorghum is taller than 8" use drop nozzles and keep spray off the foliage. Low Exposure Scenarios - Scouting immature plants High Exposure Scenarios - Irrigation and scouting mature plants	 100 NA[5]
Soybeans	Apply for preplant burndown not less than 7 to 30 days prior to planting.	None[1]
Strawberries	Apply when strawberries have gone into dormancy or after last picking.	None[1]
Sugarcane	Apply before canes appear for control of emerged weeds. Apply after canes emerge and through canopy closure. Medium Exposure Scenarios - scouting immature plants High Exposure Scenarios - scouting mature plants	 1000 2000
Turf, Sod Farm and Golf Course	Treat when weeds are young and actively growing. Do not apply more than 4.0 lb per season. Low Exposure Scenarios - Mowing High Exposure Scenarios - Transplanting, hand weeding	 3400 6800

1. Post application exposures are expected to be minimal due to application timing or method.

2. Asparagus plants do not have foliage (i.e. ferns) when the spears are harvested.

3. The application rates are extremely low (0.1 lb ae/acre for citrus and 0.07 lb ae/acre for potatoes).

4. Detasselling TC does not apply to field corn because label prohibits application during tassel to dent stage.

5. This TC does not apply because 2,4-D is applied when the plants are immature.

2.2.3 Exposure and Risk Estimates

A summary of the worker risks for short term post application exposures is given in Table 18 and the calculations are included in Appendix C. All of the short term MOEs are above 100 on day zero which indicates that the risks are not of concern. The intermediate term MOEs as shown in Table 19 and Appendix D are also all above 100 on day zero.

Table 18 - 2,4-D Postapplication Short Term Worker Risks				
Crop Group	**ShortTerm MOE on Day 0**			
	Application Rate (lb a.e./acre)	**Low Exposure Scenarios***	**Medium Exposure Scenarios***	**High Exposure Scenarios***
Field/row crop, low/med (cereal grains)	1.25	12,000	770	NA
Field/row crop, low/med (rice)	1.5	9,600	640	NA
Field/row crop, tall (corn) Pre-harvest rate for field corn Post-emergence rate for sweet corn	 1.5 0.5	 9,600 28,000	 2,400 7,200	 960 NA
Field/row crop, tall (sorghum)	1.0	14,000	3,600	NA
Sugarcane	2.0	NA	720	360
Turf - California Turf - North Carolina	2.0 2.0	3,300 1,500	NA NA	1,600 750
*Task descriptions for each crop and exposure scenario are included in Table 17.				

Table 19 - 2,4-D Postapplication Intermediate Term Worker Risks				
Crop Group	**Intermediate Term MOE on Day 0**			
	Application Rate+ (lb a.e./acre)	**Low Exposure Scenarios***	**Medium Exposure Scenarios***	**High Exposure Scenarios***
Field/row crop, low/med (cereal grains)	0.5	20,000	1,300	NA
Field/row crop, low/med (rice)	0.92	11,000	730	NA
Field/row crop, tall (field corn)	0.44	23,000	5,700	2,300
Field/row crop, tall (sweet corn)	0.48	22,000	5,500	NA
Field/row crop, tall (sorghum)	0.46	22,000	5,500	NA
Sugarcane	0.75	NA	1,300	670
Turf - California Turf - North Carolina	2.0 2.0	2,800 1,000	NA NA	1400 520
+ Average application rates as reported in the QUA report or NASS report were used when available. *Task descriptions for each crop and exposure scenario are included in Table 17.				

2.2.4 Risk Characterization

All of the post application MOEs are substantially greater than 100 which means that the risks are not of concern.

2.3 - Residential Applicator Exposures and Risks

According to the EPA Pesticide Sales and Usage Report for 1998/1999, 2,4-D is the most commonly used conventional pesticide active ingredient in the home and garden market sector with 7 to 9 million pounds applied per year. It is also the most commonly used conventional active ingredient in the Industry/Commercial/Government market section with 17 to 20 million pound applied per year. This segment includes applications to homes and gardens by professional applicators.

The residential products are typically formulated as dry weed and feed products or as liquids in concentrates or ready to use sprays. Many of these formulations include other phenoxy herbicides such as MCPP-p and MCPA. Both spot and broadcast treatments are included on the labels. Exposures are expected to be short term in duration for broadcast treatments because the label allows only two broadcast treatments per year. Exposures are also expected to be short term in duration for spot treatments because the labels recommend repeat applications for hard to kill weeds in two to three weeks.

2.3.1 - Scenarios, Data Sources and Assumptions

Scenarios

The following scenarios were assessed.

1 Hand Application of Granules
2 Belly Grinder Application
3. Load/Apply Granules with a Broadcast Spreader
4. Mix/Load/Apply with a Hose-end Sprayer (Mix your own)
5. Mix/Load/Apply with a Hose-end Sprayer (Ready to Use)
6. Mix/Load/Apply with Hand Held Pump Sprayer
7. Mix/Load/Apply with Ready to Use Sprayer

Data Sources

Exposure data for scenarios #1 and #2 were taken from PHED. Exposure data for scenarios #3, #4 and #5 were taken from the residential portion of the ORETF Handler Study (this study was discussed in Section 2.1.2.)

Exposure data for scenarios #6 and #7 were taken from the following study which has recently been purchased by the ORETF:

- **Carbaryl Mixer/Loader/Applicator Exposure Study during Application of RP-2 Liquid (21%) Sevin (r) Ready to Use Insect Spray or Sevin 10 Dust to Home Garden Vegetables.** Agrisearch Study No. 1519. EPA MRID 444598-01. Report dated August 22, 1998, Author; Thomas C. Mester, PhD., Sponser: Rhone Poulenc Ag Company

This study involved low pressure handwand and RTU trigger sprayer application of Sevin(R)

which contains 21% carbaryl to home vegetable plants. Applications were made by volunteers to two 18 foot rows of tomatoes and one 18 foot row of cucumbers at a test field in Florida. A total of 40 replicates were conducted. Latex gloves were worn for twenty of the replicates and no gloves were worn for the other twenty replicates. Each replicate opened the end use product and applied it to the vegetable rows, after which the dosimeters were collected. Inhalation exposure was monitored in the breathing zone with personal air sampling pumps and OVS sampling tubes. Dermal exposure was monitored by the extraction of carbaryl from inner and outer cotton full body dosimeters, face neck wipes, and glove and hand washes.

The average field fortification recoveries for the full body dosimeters were 84.3% for the inner and 77.7 % for the outer. Face/neck wipe field recoveries were 84.8% and handwash and OVS tube field recoveries were greater than 90 %. Laboratory method validation for each sampling matrix fell within the acceptable range of 70 % to 120%. The limit of quantitation (LOQ) was 1.0 ug/sample for all media except the OVS tubes where the LOQ was 0.01 ug/sample.

Dermal exposure was determined by adding the values from the bare hand rinses, face/neck wipes, outer dosimeter lower legs and arms, inner dosimeter torso and inner dosimeter upper legs and upper arms. This accounts for the residential applicator wearing a short sleeved shirt and short pants. The unit exposures are presented in Table 20.

Table 20 - Unit Exposure Values For Trigger and Pump Sprayer Application (MRID 444598-01)

Scenario	Dermal Unit Exposure (mg/lb ai handled)			Inhalation Unit Exposure (ug/lb ai handled)		
	Average	Geo. Mean	Median	Average	Geo. Mean	Median
Trigger Sprayer	80	53	53	0.096	0.067	0.034
Hand Held Pump Sprayer	56	38	35	0.012	0.030	0.011

Assumptions regarding Residential Applicators

- Clothing would consist of a short-sleeved shirt, short pants and no gloves.
- Broadcast spreaders and hose end sprayers would be used for broadcast treatments and the other application methods would be used for spot treatments only.
- An area of 0.023 acre (1000 square feet) would be treated per application during spot treatments and an area of 0.5 acre would be treated during broadcast applications.
- The application rate is 2.0 lb ae/acre as listed on the master label.

2.3.2 Exposure and Risk Estimates

The MOE calculations are included in Appendix E and a summary is included in Table 21. All of the MOEs exceed the target MOE of 1000 and are not of concern.

Table 21 - 2,4-D Short Term MOEs for Homeowner Applications to Lawns			
Scenario	**Application Rate (lbs ae/acre)**	**Treated Area (acres/day)**	**MOE**
1 Hand Application of Granules	2.0	0.023	4,600
2 Belly Grinder Application	2.0	0.023	5,100
3. Load/Apply Granules with a Broadcast Spreader	2.0	0.5	38,000
4. Mix/Load/Apply with a Hose-end Sprayer (Mix your own)	2.0	0.5	2,300
5. Mix/Load/Apply with a Hose-end Sprayer (Ready to Use)	2.0	0.5	9,300
6. Mix/Load/Apply with Hand Held Pump Sprayer	2.0	0.023	15,000
7. Mix/Load/Apply with Ready to Use Sprayer	2.0	0.023	10,000
Note: 1000 square feet equals 0.023 acres			

2.3.3 Risk Characterization

The master label application rate of 2.0 lb ae/acre was used for all assessments. Many of the labels have application rates in the range of 0.5 to 1.5 lb ae/acre because 2,4-D is formulated with other phenoxy herbicides such as MCPP-p and MCPA.

The 2,4-D Task force is in the process of completing probabilistic assessments of residential handler scenarios using the CARES model, which has been reviewed by the FIFRA Science Advisory Panel. The Agency will evaluate the inputs and analysis of the CARES model when they are submitted and if all appropriate criteria for submission have been met. For example, the public availability of any model used for probabilistic assessments is required.

2.4 - Residential Turf Post Application Exposure and Risks

2.4.1 Exposure Scenarios, Data Sources and Assumptions

The following exposure scenarios are assessed for residential post application risks

Toddlers Playing on Treated Turf
Adults Performing Yardwork on Treated Turf
Adults Playing Golf on Treated Turf

Data Sources:

There are three turf transferable residue studies that were submitted by the Broadleaf Turf Herbicide TTR Task Force. These studies were described in Section 2.2.2.

Overall Summary and Application of the TTR Data

Regression analysis of the TTR data is included in Appendix F and a summary of the data used for exposure assessment is included in Table 22. The maximum TTR value of 2.9% percent of the application rate is used for assessing acute exposures. The dissipation rate for humid regions without rain is derived from the North Carolina Phase 1 study in which the DMA form of 2,4-D was applied by itself. This dissipation rate is similar to the rates observed when the EHE form of 2,4-D was applied or when the DMA form of 2,4-D is applied with MCPP-p and dicamba. The dissipation rate for the dry regions is derived from the California TTR site data in which the DMA form of 2,4-D was applied with MCPP-p and dicamba. The dissipation rate for humid regions with rain is derived from the North Carolina Phase 2 data in which the DMA form of 2,4-D was applied with MCPP-p and dicamba.

Table 22 - Summary of TTR Data Used for Residential Post Application Exposure Assessment

	NC - Phase 1	**NC - Phase 2**	**CA**
Conditions	No Rain	Some Rain After DAT 2	No Rain
Application Rate (lbs ae/acre)	1.72	1.76	1.67
Maximum TTR (ug/cm^2)	0.56	0.25	0.24
Maximum TTR (% of applied)	2.9 - Note 1	1.3	1.3
Initial TTR (ug/cm^2)	0.31	0.20	0.20
Initial TTR (% of applied)	1.6 - Note 2	1.0 - Note 2	1.1 - Note 2
Semi-log Slope Factor	-0.83	-2.3	-0.26
Seven Day Average TTR (ug/cm^2)	0.080	0.034	0.10
Seven Day Average TTR (% of applied)	0.41 - Note 2	0.18 - Note 2	0.56 - Note 2
Days to LOQ	7	3	greater than 7

Note 1 - This value was used to assess 1 day acute and one day short term exposures.
Note 2 - These values were used to assess seven day average short term exposures.

General Assumptions

The following assumptions and standard values are taken from the Standard Operating Procedure (SOPs) of December 18, 1997 and ExpoSAC Policy #12 "Recommended Revisions to the Standard Operating Procedures for Residential Exposure Assessments of February 22, 2001.

- An assumed initial TTR value of 5.0% of the application rate is used for assessing hand to mouth exposures.
- An assumed initial TTR value of 20% of the application is used for assessing object to mouth exposures.
- Soil residues are contained in the top centimeter and soil density is 0.67 mL/gram.
- Three year old toddlers are expected to weigh 15 kg.
- Hand-to-mouth exposures are based on a frequency of 20 events/hour and a surface area per event of 20 cm^2 representing the palmar surfaces of three fingers.
- Saliva extraction efficiency is 50 percent meaning that every time the hand goes in the mouth approximately ½ of the residues on the hand are removed.
- Adults are assessed using a transfer coefficient of 14,500 cm^2/hour.
- Toddlers are assessed using a transfer coefficient of 5,200 cm^2/hour.
- Golfers are assessed using a transfer coefficient of 500 cm^2/hour.
- An exposure duration of 2 hours per day is assumed for toddlers playing on turf or adults performing heavy yardwork.
- An exposure duration of 4 hours is assumed for playing golf.

Assumptions Specific to 2,4-D

The following assumptions that are specific to 2,4-D are used for assessing residential post application exposures.

- The master label application rate of 2.0 lbs ae/acre was used.
- The exposure following the application of granular formulations was not assessed because there were no TTR data submitted for granular formulations. It was assumed this exposure would be less than or equal to the exposure from liquid formulations.

Calculation Methods

The above factors were used in the standard SOP formulae to calculate the exposures. These formulas are described in Appendix A. MOEs were calculated for acute toddler exposures using the maximum TTR value along with the acute dietary NOAEL of 67 mg/kg/day as selected by the HIARC (see Table 3). This NOAEL was adapted to acute dermal exposures by using the dermal absorption factor of 5.8 percent to account for route to route extrapolation. The MOEs for toddler short term exposures were calculated using the seven day average TTR value because the short term NOAEL was based upon decreased body weight gain which occurred after several days of exposure. MOEs for acute and adult short term exposures were calculated using the maximum TTR value because the acute and short term NOAELs are the same and are based upon the developmental effects which could have occurred following one day of exposure.

2.4.2 Exposure and Risk Estimates

The MOEs are summarized in Table 23 and 24 and the detailed calculations are included in Appendix G. All of the MOEs meet or exceed the target MOE of 1000.

Table 23 - Toddler MOEs for Exposure to Turf Treated with 2,4-D

	Application Rate (lbs ae/acre)	TTR (ug/cm^2)	Semilog Slope	R^2	Dermal MOE	Hand-to Mouth MOE	Object to Mouth MOE	Soil Ingestion MOE	Total MOE
Acute Toddler Risks Using the Maximum TTR (North Carolina Trial 1 using 2,4-D DMA)									
DAT 0	2.0	0.67 (MAX)	N/A	N/A	2,500	2,200	9,000	>100,000	1,040
Short Term Toddlers Risks Using California TTR Data (DMA Mix, No Rain)									
DAT 0 to DAT 6	2.0	0.12 (AVG)	-0.26	0.83	5,000	1,600	6,400	>100,000	1,000
Short Term Toddler Risks Using North Carolina TTR Data from Trial 1 (DMA and DMA Mix, No Rain)									
DAT 0 to DAT 6	2.0	0.093 (AVG)	-0.83	0.81	6,700	3,300	13,000	>100000	1,900
Short Term Toddler Risks Using North Carolina TTR Data from Trial 2 (DMA Mix, Some Rain)									
DAT 0 to DAT 6	2.0	0.039 (AVG)	-2.3	0.87	16,000	5,200	21,000	>100000	3,300

The acute NOAEL is 67 mg/kg/day for neurotoxic effects observed in acute neurotoxicity study.
The short term NOAEL is 25 mg/kg/day for maternal effects observed in the developmental study.

Table 24: Adult Acute/Short Term MOEs for Exposure to Turf Treated with 2,4-D			
Exposure Scenario	**Application Rate (lbs ae/acre)**	**TTR (ug/cm^2)**	**Acute/Short Term Dermal MOE[A] on Day 0**
Heavy Yardwork Playing Golf	2.0	0.67	1300 19000
A. The acute/short term NOAEL is 25 mg/kg/day for developmental effects observed in the developmental study.			

2.4.3 Risk Characterization and Comparison to Biomonitoring Data

Risk Characterization

The calculation of acute MOEs using maximum TTR value for toddler turf post application exposure represents a policy change because the maximum TTR values were previously only used to calculate short term MOEs. The 2,4-D risk assessment team decided that the previous approach would greatly overestimate the short term toddler risk because the short term endpoint was based upon maternal effects that would only occur after several days of exposure. The team also decided that the single day toddler exposures as represented by the maximum TTR values would be more appropriately assessed using the acute endpoint. The short term toddler exposures were assessed using the seven day average TTR values because the endpoint occurred after following several days of exposure and because the TTR data were collected during a seven day time period. The acute/short term adult exposures were assessed using the maximum TTR value because the acute/short term endpoint was a development effect that could have occurred following a single day of exposure. Although the developmental effect only applies to females of reproductive age, the Agency currently does not calculate separate MOEs for male and females because it not practical to exclude females from residential exposures.

The master label application rate of 2.0 lb ae/acre was used for all assessments. Many of the labels have application rates in the range of 0.5 to 1.5 lb ae/acre because 2,4-D is formulated with other phenoxy herbicides such as MCPP-p and MCPA.

The 2,4-D Task force is also in the process of completing probabilistic assessments of residential turf post application scenarios using the CARES model.

Comparison to Biomonitoring Data

Researchers at the Canadian Centre for Toxicology conducted 2,4-D biomonitoring on adult volunteers who were exposed to 2,4-D while performing controlled activities for one hour on turf treated with 0.88 lb ae/acre 2,4-D (Harris and Solomon 1992). The controlled activities were conducted at 1 hour after treatment (HAT) and at 24 HAT. Ten volunteers participated in

the study. Five volunteers wore long pants, a tee shirt, socks and closed footwear. The other five wore shorts and a tee shirt and were barefoot. The volunteers walked on the turf for a period of 5 minutes and then sat or lay on the area for 5 minutes and then continued in this fashion for 50 more minutes. At the end of the exposure period the volunteers were allowed to wash their hands and were served a picnic lunch on an adjacent unsprayed area. Each volunteer collected all urine for the next 96 hours immediately following the exposure. A baseline urine sample was also collected on morning of the exposure day to account for previous 2,4-D exposures and to use for spike samples. The spike samples were prepared by adding 22 ug of 2,4-D to 100 ml subsamples of the baseline urine samples and were stored by the volunteers in the same manner as the daily urine samples. The results indicated that detectable levels of 2,4-D were found only in the volunteers who wore shorts without shoes and who were exposed at 1 HAT. The highest exposure of 426 ug was detected in a HAT 1 volunteer who removed his shirt during the exposure period. The 1 HAT volunteers who wore long pants and shoes and all of the 24 HAT volunteers had urinary 2,4-D levels that were below the limit of detection of 5 ug/liter. The creatinine values, which were in the normal range and showed little daily variation, indicated that the urine collection was complete. The spike samples indicated an average recovery of 92.5 $\pm$ 14.5 percent. One of the 1 HAT volunteers and one of the 24 HAT volunteers had detectable levels of 2,4-D in the baseline sample.

As discussed in a recent review of pesticide biomonitoring (Maroni et al. 2000) most of the phenoxy herbicide dose is excreted in the urine as unmodified compounds or conjugate derivatives. As part of the skin absorption study of various pesticides including 2,4-D (Maibach and Feldmann, 1974) intravenous dosing was conducted to measure urinary excretion. One hundred percent (n=6) of the administered 2,4-D dose was recovered within 120 hours of administration and 98 percent of the dose was recovered within 96 hours. The dermal absorption portion of this study indicated that 5.8 $\pm$ 2.4 percent of the topical dose was recovered within 120 hours and 5.2 percent of the topical dose was recovered within 96 hours. In a more recent study of 2,4-D skin absorption (Harris and Solomon, 1992) 80.8 $\pm$ 13.3 percent (n=10) of the urinary excretion of a topically applied dose occurred during the first 96 hours and urinary 2,4-D was approaching the limit of detection at 144 hours. It should be noted that the applied dose (ug/cm^2) in the Harris and Solomon study was 280 times that of the applied dose in the Maibach and Feldmann study. The applied dose of in the Maibach study (4 ug/cm^2) is also closer to the estimated dermal exposure of 1.8 ug/cm^2 for a 70 kg adult with an exposed skin surface area of 11000 cm^2. The dermal exposure in ug = 0.672 ug/cm^2 * 2 hours exposure * 14500 cm^2/hr and the dermal exposure in ug/cm^2 = 19500 ug/11000 cm$^{2.}$

The results of the biomonitoring study were used to calculated MOEs by assuming that all of the urinary 2,4-D measured in the 96 hours after the exposure period was the result of the turf exposure. This assumption is protective because 2,4-D exposures due to inhalation and due to food and water ingestion would be counted as dermal exposure. The biomonitoring results were adjusted by a factor of two to account the SOP assumption of two hours of daily exposure vs one hour of exposure during the study and factor of 2.3 to account for an application rate of 2.0 lbs ae/acre vs 0.88 lb ae/acre applied during the study.

The MOEs for the DAT 1 volunteers who wore shorts and no shoes ranged from 1000 to 26000 with the lowest MOE corresponding to the volunteer who removed his shirt during the exposure period. The MOEs for the remaining volunteers ranged from 17000 to 27000. The MOEs are listed in Table 25.

Table 25 - Residential Post Application MOES on 2,4-D Treated Turf Based Upon Biomonitoring Data

Volunteer	Clothing	BW	Measured 2,4-D Dose[A]	Adjusted 2,4-D Dose[B]	Adjusted 2,4-D dose	MOE[C]
Exposure Beginning at One Hour Post Application						
1	shorts/barefoot	100 kg	0.153 mg	0.70 mg	0.0070 mg/kg/day	3600
2	shorts/barefoot	95.5	0.020 (Note D)	0.091	0.00095	26000
3	shorts/barefoot	63.6	0.020	0.091	0.0014	17000
4	shorts/barefoot	45.5	0.103	0.47	0.0103	2400
5	shorts/barefoot[E]	79.5	0.426	1.9	0.0244	1000
Avg						10000
GM						5300
6	pants/shoes	77.3 kg	0.020 mg	0.091mg	0.0012 mg/kg/day	21000
7	pants/shoes	68.2	0.020	0.091	0.0013	19000
8	pants/shoes	72.7	0.020	0.091	0.0013	19000
10	pants/shoes	79.5	0.020	0.091	0.0011	23000
Avg						20000
GM						20000
Exposure Beginning at 24 Hours Post Application						
Volunteer	Clothing	BW	Measured 2,4-D Dose[A]	Adjusted 2,4-D Dose[B]	Adjusted 2,4-D dose	MOE[C]
1	shorts/barefoot	100 kg	0.020 mg	0.091mg	0.00091 mg/kg/day	27000
2	shorts/barefoot	77.3	0.020	0.091	0.0012	21000
3	shorts/barefoot	63.6	0.020	0.091	0.0014	17000
4	shorts/barefoot	79.5	0.020	0.091	0.0011	22000
5	shorts/barefoot	72.7	0.020	0.091	0.0013	20000
Avg						22000
6	pants/shoes	75 kg	0.020 mg	0.091mg	0.0012 mg/kg/day	21000
7	pants/shoes	67.3	0.020	0.091mg	0.0014	18000
8	pants/shoes	65.9	0.020	0.091mg	0.0014	18000
10	pants/shoes	100	0.020	0.091mg	0.00091	27000
Avg						21000

Notes
A. Study conditions included one hour of exposure on turf treated with 0.88 lb ae/acre
B. Adjusted to account for two hours of exposure and an application rate of 2.0 lb ae/acre.
C. MOEs were calculated using a NOAEL of 25 mg/kg/day.
D. Measured doses of 0.02 mg represent non-detect values where the LOD is 5 ug/liter and the sample volume is 4 litres. The sample volume of 4 litres is based upon an average urinary output of 1 litre per day times 4 days.
E. This volunteer removed his shirt during the exposure period.

2.5 - Recreational Swimmer Post Application Exposure and Risks

The master label indicates that 2,4-D can be used for aquatic weed control of surface weeds such as Water Hyacinth and submersed weeds such as Eurasian Milfoil. Surface weeds are controlled by foliar applications at a maximum rate of 2.0 lb ae/acre. Submersed weeds are controlled by subsurface injection of liquids to achieve a target concentration of 2 to 4 ppm in the water column surrounding the weeds. This requires 5.4 to 10.8 lb ae per acre foot of water depth (i.e. 5.4 lbs ae would be required to achieve 2 ppm in a one acre pond that has an average depth of 1 foot). Granular formulations of BEE (Aquakleen and Navigate) are also used to control submersed weeds. The granular formulations are made with heat treated attaclay granules that resists rapid decomposition in water and release the herbicide into the root zone.

Although many herbicide treatments are applied to aquatic areas where recreational swimming is not likely to occur, some of the subsurface treatments are made at recreational lakes. These treatments are made because the Eurasian Milfoil interferes with recreation and other activities. This problem is particularly prevalent in the northern states such as Minnesota and Washington and in the New England region.

2.5.1 Exposure Scenarios, Data Sources and Assumptions

Scenarios

The following exposure scenarios are assessed for recreational swimmers.

Adult Recreational Swimmer
Child Recreational Swimmer

Assumptions

The following assumptions were used for the assessment of swimmer risks. Many of these assumptions were taken from the Residential SOPs and are also used in the SWIMODEL.

- The skin surface area of adults is assumed to be 21,000 cm^2 as cited in the Residential SOPs. This is the 95th percentile value for females (EPA Exposure Factors Handbook, 1997).
- The body weight for children is assumed to be 22 kg as cited in the Residential SOPs. This is a mean value for 6 year old children.
- The skin surface area for children is assumed to be 9,000 cm^2 as cited in the Residential SOPs. This is the 90th percentile value for male and female children.
- The assumed mean ingestion rate is 0.05 liters per hour for both adults and children as cited in the Residential SOP. This value may be greater for young children playing in water and accidentally ingesting a remarkable quantity of water (U.S. EPA SAP, 1999).

- The exposure time is assumed to be 3 hours per day. This is the 90th percentile value for time spent swimming in a freshwater pool. (EPA Child Specific Exposure Factors Handbook, 2002).
- The body weight for female adult acute exposures is assumed to be 60 kg.
- The body weight for male adult acute exposures is assumed to be 70 kg.
- The body weight for adult short term exposure is assumed to be 60 kg because the endpoint is gender specific.
- The target concentration of 4 mg/liter (4 ppm) is from the master label.
- The target concentration of 2 mg/liter (2 ppm) is from use information.
- Risks were not calculated for foliar treatments because the application rate of 2.0 lb ae/acre would result in water concentration of only 0.25 ppm in a three foot water column even if all of the spray were to run off the leaves into the water.

Calculation Methods

The above factors were used in the SWIMODEL formulae for dermal and ingestion exposure which are described in Appendix A. The SWIMODEL formulas for the other dermal pathways (aural, buccal/sublingual and orbital/nasal) were not used because these formulas are based upon recreational swimmers in swimming pools who swim with their heads partially immersed. It is anticipated that recreational swimmers in weed infested areas would be less likely to swim with their heads immersed than recreational swimmers in weed- free swimming pools. In addition, the formulas for the buccal/sublingual and orbital/nasal pathways contain a default absorption factor of 0.01 which is based upon the absorption of nitroglycerin. This factor would greatly overestimate the risk of 2,4-D exposure because 2,4-D is absorbed at a much lower rate.

MOEs were calculated for children's acute exposures using the target water concentration (i.e. the maximum water concentration) along with the acute NOAEL of 67 mg/kg/day. MOEs for children's short term exposures were calculated using the target water concentration (because there was insufficient data to define a dissipation rate) along with the short term NOAEL of 25 mg/kg/day for maternal effects. MOEs for adult acute/short term exposures were calculated using the target water concentration because the acute/short term NOAEL is based upon the developmental effects which could have occurred following one day of exposure.

2.4.2 Exposure and Risk Estimates

The MOEs are summarized in Table 26 and the detailed calculations are included in Appendix H. All of the dermal MOEs meet or exceed the target MOE of 1000 when 2,4-D acid or 2,4-D DMA are used because these forms have very low skin permeability coefficients. The dermal MOEs are of concern when 2,4-D BEE is used because 2,4-D BEE has a relatively high skin permeability coefficient. The ingestion MOEs are of concern for short term children's exposure and are not dependent on the form used. If a lower target concentration of 2 ppm is used, the MOEs for ingestion rise to above 1000, however, the dermal MOEs remain below 1000 for 2,4-D BEE exposures.

Table 26 - MOEs for Recreational Swimmers in Water Bodies Treated with 2,4-D							
	2,4-D Form	**Acute Dermal MOE**	**Acute Ingestion MOE**	**Acute Combined MOE**	**Short Term Dermal MOE**	**Short Term Ingestion MOE**	**Short Term Combined MOE**
2,4-D Concentration = 4 mg/liter							
Adult - 60 kg	Acid	240000	2500	2500	Short Term MOEs are the same as acute MOEs because the same NOAEL applies to both acute and short term exposures.		
Adult	DMA	450000	2500	2500			
Adult	BEE	**350**	2500	**310**			
Child - 22 kg	Acid	550000	2500	2400	200000	**920**	**920**
Child	DMA	1000000	2500	2500	380000	**920**	**920**
Child	BEE	**800**	2500	**600**	**300**	**920**	**220**
2,4-D Concentration = 2 mg/liter							
Adult - 60 kg	Acid	470000	5000	5000	Short Term MOEs are the same as acute MOEs because the same NOAEL applies to both acute and short term exposures.		
Adult	DMA	900000	5000	5000			
Adult	BEE	**700**	5000	**620**			
Child - 22 kg	Acid	1300000	5000	4800	400000	1800	1800
Child	DMA	2400000	5000	5000	760000	1800	1800
Child	BEE	2000	5000	1200	**600**	1800	**440**
Note - MOEs in bold font do not exceed the target MOE of 1000 and are of concern to the Agency.							

2.5.3 Risk Characterization

The probability that a person would swim in an area recently treated for milfoil is low because milfoil forms dense mats of vegetation on the surface of the water which makes swimming difficult and unpleasant. This situation would occur prior to mid summer treatments when the milfoil has had time to grow. Early season treatments are recommended to prevent milfoil growth because milfoil is tolerant of cold water and will grow fast in the early spring when the lake water is still cold. In the case of early season treatments, the cold water would also reduce the time spent swimming.

The acute MOEs may underestimate risk in cases where swimming occurs immediately after subsurface liquid applications before mixing has occurred. Field dissipation studies reviewed by EFED indicated that 2,4-D concentrations sometimes exceeded the target concentration in parts of the treated area shortly after application. In the Minnesota lake study (MRID 458971-01), a maximum concentration of 13.2 ppm was measured at 1 HAT at one of the three sampling stations that were within the treated area while the average of the three stations

was 4.5 ppm. By DAT 1, the maximum and average concentrations had declined to 2.7 ppm and 1.8 ppm. Many of the states require or recommend that a 24 hour swimming restriction be imposed following the aquatic application of 2,4-D for milfoil control.

The short term MOEs from water ingestion are an upper bound estimate of risk because dissipation was not taken into account. Field dissipation studies reviewed by EFED indicated that the 2,4-D half lives following the subsurface injection of 2,4-D liquid DMA to lakes and ponds (application rate 8.4 to 13.6 lbs ae/acre foot) ranged from 2.9 to 29.5 days with an average of 12.9 days and a geometric mean of 8.7 days. The longest half life occurred following the second application to a 14 acre pond in North Dakota. The half life after the first application was 10.1 days. The diagram for this pond indicates that it had an inlet but no outlet and the water flow was not recorded. Summary data from these studies is included in Table 27.

The dermal exposures from BEE might be less than calculated because BEE degrades rapidly to form 2,4-D acid. This is particularly true when the PH is approximately 8.0 as was observed in a the BEE farm pond study (MRID 445250-01) that was reviewed by EFED . The majority of 2,4-D detected after the application of granular BEE was the acid form. The maximum 2,4-D BEE concentration was 71.1 ppb while the maximum 2,4-D acid concentration was 3370 ppb. According literature cited by EFED, the average half life of BEE is 2.6 hours.

The BEE farm pond study indicated that the maximum 2,4-D acid concentration of 3.4 ppm was measured on Day 14 in the North Carolina pond which was characterized as being stagnant with opaque water. The maximum 2,4-D acid concentrations in the other two ponds included in this study were 0.38 ppm in the Minnesota pond and 0.15 ppm in the Washington pond. These two ponds were characterized as having some flow out of the pond as well as clear water. The 2,4-D concentration in the Minnesota and Washington ponds declined to the LOQ of 0.002 ppm in 122 and 30 days, respectively, while the 2,4-D concentration in the North Carolina pond was 0.13 ppm at 189 days post application.

The skin surface area of 21,000 cm^2 for females as listed in the SOPs is a 95th percentile value. The median value for this parameter is 16,900 cm^2.

The EPA/ORD has recently completed the pilot phase of a study that will determine the ingestion rate of recreational swimmers. These rates are being obtained by measuring urinary cyanuric acid levels in swimmers after they swan in a cyanuric acid treated pool. The results for the 12 adult swimmers indicated that the average ingestion rate was 16 ml/hour and the maximum rate was 50 ml/hour. The results for the 41 children indicated that the average rate was 37 ml/hr, the 70th percentile rate was 50 ml/hr and the maximum rate was 154 ml/hr. These rates might be overestimates because the other pathways, such as dermal and buccal, were not considered. The full study will include 600 swimmers.

In testing the use of 2,4-D for use in managing Eurasian Watermilfoil in Minnesota, most treatments were done with 2,4-D BEE (i.e. Aqua-Kleen$^{(R)}$ or Navigate) an application rate of 100 lbs per acre. (Crowell, 1999). Practical experience from local applicators in Washington state has

indicated than an application rate of 90 to 100 pounds/acre may be more effective than rates of 200 pounds per acre due to a change in the plants physiology at higher rates (Washington State Dept of Ecology, 1998).

Table 27 - Dissipation Studies Following the Subsurface Injection of 2,4-D DMAS

MRID	Location	Water Body Type	Size in Acres	Acres Treated	Application Rate (lb ae)	Treated Area Depth (feet)	Max 2,4-D Concentration (ppm)	Half Life (days)
458971-01	MN	Lake	1700	4.5	10.8 acre/foot	8.25	13.2	3.2
439083-02	ND - 1st App	Pond	14	14	41.8/acre	4 to 6	6.1	10.1
	ND - 2nd App			14	41.8/acre	4 to 6	4.2	29.5[A]
439547-01	NC - 1st App	Pond - Stream Fed	2.4	2.4	41/acre	3	2.5[B]	20.5[C]
	NC - 2nd App			2.4	41/acre	3	3.0	2.9
Avg GM Max								12.9 8.7 29.5

A. This half life is based upon Day After Application (DAA) 0 to 30.
B. This maximum concentration occurred on DAA 3.
C. This half life is based upon DAA 3 to 30.

3.0 - Data Compensation Issues

The TTR studies were submitted by the Broadleaf Turf Herbicide TFR Task Force. This task force includes many, but not all, of the 2,4-D registrants. There are data compensation issues regarding the use of the TTR data to support reregistration of products belonging to the 2,4-D registrants that are not members of the Broadleaf Turf Herbicide TFR Task Force.

Many of the occupational and residential handler scenarios were evaluated using unit exposure data that was submitted by the Outdoor Residential Exposure Task Force (ORETF). This task force includes many, but not all, of the 2,4-D registrants. There are data compensation issues regarding the use of the ORETF data to support reregistration of products belonging to the 2,4-D registrants that are not members of the ORETF.

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5.0 Glossary of Terms Used in Occupational/Residential Exposure Assessment

TERM	DEFINITION
Absorbed Dose	The amount of pesticide that is absorbed into the body.
AE - Acid Equivalent	The weight of 2,4-D excluding the weight of the ester or salt groups
AI	Active ingredient
DAT	Day after treatment
DFR - Dislodgeable Foliar Residue	The amount of residue that can transfer from treated crop foliage to human skin.
ExpoSac - Scientific Advisory Committee for Exposure	A committee within the EPA Health Effects Division that reviews pesticide exposure assessments and develops policy.
Exposure	The amount of pesticide that impinges upon the skin, is inhaled or is ingested.
Handler/Applicator	A worker who mixes, loads and/or applies pesticides
Intermediate Term	31 days to six months
LOAEL	Lowest Observed Adverse Effect Level
MOE - Margin of Exposure	The ratio of the "safe" dose (usually the NOAEL or the LOAEL) divided by the estimated exposure. Formerly called the Margin of Safety.
NOAEL	No Observed Adverse Effect Level
ORETF	Outdoor Residential Exposure Task Force
PCO	Pest Control Operator
PF5 Respirator	A filtering facepiece respirator (i.e. dustmask) that has a protection factor of 5 when properly fitted.
PF10 Respirator	A half face respirator with appropriate cartridges that has a protection factor of 10 when properly fitted.
Re-entry Worker	One who works in fields that have been treated with pesticides
REI - Restricted Entry Interval	The period of time that must pass following pesticide application before workers are re-enter the treated area.
PPE	Personal Protective Equipment
Short Term	One to thirty days
TTR - Turf Transferable Residue	The amount of residue that can transfer from treated turf to human skin.